

Microwave-assisted synthesis and biological activity of ester, carbothioate and carbonylhydrazone derivative compounds of the drug Ciprofloxacin

Nadhir N. A. Jafar^{*1}, Nadia Sadiq Majeed²

¹Department of Chemistry, College of science, University of Babylon, Iraq P.O. Box Babil 4

²Department of Chemistry, College of women education, University of Kufa, Iraq

*Corresponding author: E-Mail: nathernajim1@gmail.com

ABSTRACT

Our work aimed to organic synthesis and biological investigation of newly ciprofloxacin derivative as ester, thioester and hydrazine form by using microwave irradiation. The synthesis compounds were identified and confirmed by IR, ¹HNMR, ¹³CNMR and elemental analysis. All these derivatives were tested against different bacteria. The result found that all compounds have better biological activity comparable with Ciprofloxacin itself.

KEY WORDS: Ciprofloxacin, Ester, Carbothioate, Carbonylhydrazone, Fluroquinolone.

1. INTRODUCTION

Ciprofloxacin is regards a second generation fluoroquinolone with a wide spectrum of antibacterial activity. It has an excellent bioavailability after oral administration, excellent tissue penetration and is some extent safe. Ciprofloxacin exerts its function by closing bacterial DNA synthesis through inhibition of bacterial topoisomerase II (DNA gyrase) and topoisomerase IV. Inhibition of DNA gyrase enzymes necessary to separate bacterial DNA so inhibiting cell division (Crumplin and Smith, 1976; Wang, 1985). Inhibition of topoisomerase IV interferes with separation of replicated chromosomal DNA into respective daughter cells during cell division (Lester and Zwerink, 2003). A many compounds of benzoquinolizine-2-carboxylic acid arginine salt of nadifloxacin have been synthesized and evaluated as an excellent activity against infections of multi-drug-resistance vancomycin resistant *Staphylococcus aureus* (de Souza, 2005). Some of ciprofloxacin derivatives gave antifungal and cytotoxic activities have been observed and described (Siddiqui, 2007). Ciprofloxacin have been introduced to new different of Schiff base of 1, 2, 4-triazole *via* Mannich reaction and got good antibacterial results than ciprofloxacin. (Jubie, 2010). In recent years the antibiotic resistance is a great interest all over the world in health sector. Major scientists are prime interest to find out the desirable antibacterial agent, so we undertook the present study with the aim of substitution the alcohol, thiol and hydrazine in 4-position to synthesis ester, carbothioate and carbonylhydrazone derivatives respectively to continuous of previous work by used of microwave irradiation (Nadhir, 2016; 2015).

2. MATERIAL AND METHODS

Reagents, and reactants are used as procured from commercial suppliers without further purification. Solvents were purified before use. The purity of compounds, and course of reaction were monitored using thin layer chromatography on silica gel-G (Merck grade), with ethyl acetate and hexane mixture as mobile phase, and plates were viewed under UV lamp at 254- 366 nm. The melting points were measured in open capillaries, with the help of (Stuart) melting point (SMP30, England) melting point apparatus, are expressed in °C and are uncorrected. Infrared spectra (IR) were recorded on Shimadzu Prestige-21 Spectrophotometer in Kufa University using potassium bromide (KBr pellets) and the values are expressed in cm⁻¹, ¹H NMR and ¹³C NMR spectra of the compounds were recorded on Bruker (Avance III, Bruker 300 MHz NMR spectrophotometer using TMS as an internal standard and the values are expressed in δ ppm in university of Toronto and elemental analyses were performed on a Flash EA1112 CHN analyzer (Thermo Electron Corporation). Microwave oven LG MOD MH7947S 1450- 1150 W.

General procedure for preparation of esters: In 250 ml round bottomed flask put ciprofloxacin (0.5gm, 0.001moles) then added (30ml) of absolute methanol, ethanol, propanol, butanol and pentanol. (1 ml) of sulphuric acid was added to the flask and the reaction was irradiated to refluxed for about 20 min in the microwave oven. After the depletion of ciprofloxacin and forming ciprofloxacin ester (followed by TLC and monitor reactions). The volume of the reaction mixture was then reduced by rotary-evaporator. The precipitates were filtrated off, washed with methanol, ethanol, propanol, butanol and pentanol depending on the type of prepared ester.

General procedure for preparation of thioesters: In 250 ml around bottom flask dissolved ciprofloxacin (0.5gm, 0.001moles) and (0.1g of KI in small quantity of water) in dimethyl formaldehyde (DMF). Thiol compounds (Mercaptobenzothiazol, sodium thiophenolate, ethane thiolate, Thio glycolic acid, sodium diethyl dithiocarbamate) were added to the flask and the reaction was irradiated to refluxed for about 20 min in the microwave oven. After the depletion of ciprofloxacin and forming ciprofloxacin ester (followed by TLC and monitor reactions). The volume of the reaction mixture was then reduced by rotary-evaporator. The precipitates were filtrated off, washed by DMF.

General procedure for preparation of carbonylhydrazone: In 250 ml around bottomed flask dissolved ethyl-1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate (0.2gm, 0.0005moles) hydrazide compounds (hydrazine hydrate, phenyl hydrazine, 2,4-dinitrophenyl hydrazine and N,N-di isopropyl

hydrazine hydrochloride in ethanol 10 ml) were added to the flask and the reaction was irradiated to refluxed for about 20 min in the microwave oven. After the depletion of ciprofloxacin and forming ciprofloxacin ester (followed by TLC and monitor reactions). The volume of the reaction mixture was then reduced by rotary-evaporator. The precipitates were filtrated off, washed by ethanol.

Table.1. Spectral data, CHNS analysis and physical properties

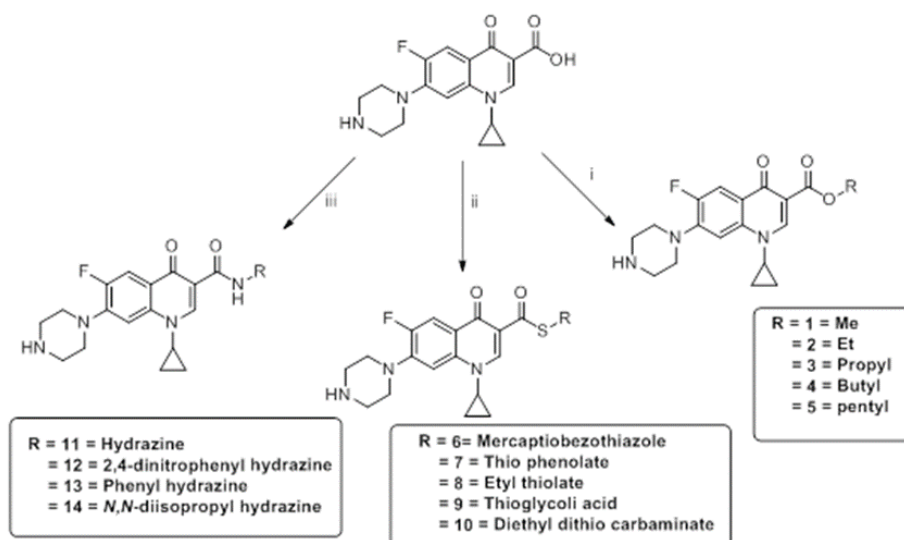
No.	Name	Color	Yield %	m.p. °C	Spectral data & CHNS analysis
1	methyl-1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate	Yellow	65	236	FT- IR $\nu = \text{cm}^{-1}$: 3431 (-NH secondary amine), 3026 (C-H aromatic), 2839 (C-H aliphatic), 1722 (C=O ester), 1629 (C=O pyridine), 1273 (C-O-C ester), 1002 (C-F aryl halide), 0.8 (s, 1H, H Cyclopropane), 1.2-1.6 (d, 4H, H Cyclopropane), 3.3-3.7 (m, 8H, Hpiperazin), 5.2 (s, 1H, CH ₃ ester), 6.5- 7.2 (m, 4H, Ar -H), 13C-NMR (DMSO-d ₆ , ppm) δ : 200 (1C, Cpyridone), 186 (1C, C=O ester), 175 (1C, C=O, OCH ₃), 116-124 (6C, Caromatic), 108 (2C, C=C), 40 (DMSO-d ₆ solvent), 35-38 (4C, Cpiperazin), 22-26 (3C, Ccyclopropane), Anal. Calcd. for C ₁₈ H ₂₀ FN ₃ O (345.37): C, 62.60; H, 5.84; N, 12.17; Found: C, 62.28; H, 5.75; N 12.07
2	Eethyl-1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate	White	70	240	FT- IR $\nu = \text{cm}^{-1}$, 3435 (-NH secondary amine), 2985 (C-H aromatic), 2839 (C-H aliphatic), 1718 (C=O ester), 1631 (C=O pyrdone), 1274 (C-O-C ester), 1012 (C-F aryl halide); 1H-NMR (DMSO-d ₆ , ppm) δ : 1.3 (s, 1H, H Cyclopropane), 1.5-2.3 (d, 4H, H Cyclopropane), 3.0-3.5 (m, 8H, H piperazin), 3.7-3.9 (m, 6H, -CH ₂ -ester), 5.1-5.3 (m, 3H, -CH ₃), 6.2-6.3 (s, 3H, -OCH ₂), 7.2- 7.7 (m, 3H, Ar -H), 13C-NMR (DMSO-d ₆ , ppm) δ : 213 (1C, C quinolone), 192 (1C, C=O-ester), 183 (1C, C=O, OCH ₂), 170 (1C, C=O, -CH ₃), 115-122 (6C, C aromatic), 100-110 (2C, C=C), 40 (DMSO-d ₆ solvent), 30-38 (4C, C piperazin), 10-15 (3C, C cyclopropane), Anal. Calcd. for C ₁₉ H ₂₂ FN ₃ O ₃ : (359.40) C, 63.50; H, 6.17; N, 11.69; Found: C, 63.20; H, 6.07; N, 11.19
3	Propyl-1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate	White	83	244	FT- IR $\nu = \text{cm}^{-1}$, 3433 (-NH secondary amine), 3051 (C-H aromatic), 2839 (C-H aliphatic), 1718 (C=O ester), 1629 (C=O pyridon), 1274 (C-O-C ester), 1010 (C-F aryl halide); 1H-NMR (DMSO- d ₆ , ppm) δ : 0.8 (s, 1H, H Cyclopropane), 1.2-1.5 (d, 4H, H Cylopropane), 3.0-3.5 (m, 8H, H piperazin), 3.5-3.8 (s, 4H, -CH ₂ -ester), 4.5 (m, 3H, -CH ₃), 7.0- 7.8 (m, 3H, Ar -H), 13C-NMR (DMSO-d ₆ ppm) δ : 222 (1C, C pyridone), 185 (1C, C=O-ester), 168 (1C, C=O, OCH ₂), 115-122 (6C, C aromatic), 100-110 (2C, C=C) , 40 (DMSO-d ₆ solvent), 28-34 (4C, C piperazin), 20-24 (2C, -CH ₂ CH ₃), 15-18 (3C, Ccyclopropane), Anal. Calcd. for C ₂₀ H ₂₄ FN ₃ O ₃ : (373.43) C, 64.33; H, 6.48; N, 11.25; Found: C, 64.20; H, 6.27; N, 11.19
4	Butyl-1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate	Yellow	82	246	FT- IR $\nu = \text{cm}^{-1}$, 3427 (-NH secondary amine), 3053 (C-H aromatic), 2839 (C-H aliphatic), 1720 (C=O ester), 1629 (C=O pyridone), 1274 (C-O-C ester), 1045 (C-F aryl halide); 1H-NMR (DMSO- d ₆ ppm) δ : 1.0 (s, 1H, H Cyclopropane), 1.2-1.4 (d, 4H, H Cyclopropane), 2.3-2.8 (m, 3H, -CH ₃), 3.2-3.6 (m, 8H, H piperazin), 3.5-3.8 (s, 2H, -CH ₂ - ester), 6.0 (d, 2H, -CH ₂ -ester), 6.5-6.8 (m, 2H, -OCH ₂ -), 7.3- 7.8 (m, 3H, Ar-H), 13C-NMR (DMSO-d ₆ ppm) δ : 232 (1C, C pyridone), 196 (1C, C=O-ester), 168 (1C, C=O, OCH ₂), 115-124 (6C, C aromatic), 104-110 (2C, C=C), 40 (DMSO-d ₆ solvent), 32-36 (4C, C piperazin), 22-26 (3C, -CH ₂ CH ₂ CH ₃), 18-21 (3C, C cyclopropane). Anal. Calcd. for C ₂₁ H ₂₆ FN ₃ O ₃ : (387.46) C, 65.10; H, 6.76; N, 10.85; Found: C, 64.98; H, 6.27; N, 10.19
5	Pentyl-1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate	Yellow	78	250	FT- IR $\nu = \text{cm}^{-1}$, 3433 (-NH secondary amine), 3051 (C-H aromatic), 2846 (C-H aliphatic), 1720 (C=O ester), 1629 (C=O pyridone), 1273 (C-O-C ester), 1043 (C-F aryl halide); 1H-NMR(DMSO-d ₆ ppm) δ : 1.0 (s, 1H, H Cyclopropane), 1.2-1.4 (m, 4H, H Cyclopropane), 2.3-3.0 (s, 3H, -CH ₃), 3.2-

					3.6 (m, 8H, H piperazin), 4.0-4.3 (s, 2H, -CH ₂ - ester), 5.2-5.6 (m, 4H, -CH ₂ CH ₂ -ester), 6.5-6.8 (m, 2H, -OCH ₂ -), 7.1-7.6 (m, 3H, Ar -H), ¹³ C-NMR (DMSO-d ₆ ppm) δ: 210 (1C, C pyridone), 188 (1C, C=O-ester), 174 (1C, C=O, OCH ₂), 115-130 (6C, C aromatic), 100-110 (2C, C=C), 40 (DMSO-d ₆ solvent), 26-34 (4C, C piperazin), 15-22 (4C, -CH ₂ CH ₂ CH ₂ CH ₃), 9.0-12 (3C, C cyclopropane). Anal. Calcd. for C ₂₂ H ₂₈ N ₃ O ₃ : (401.48) C, 65.82; H, 7.03; N, 10.47; Found: C, 65.38; H, 6.97; N, 10.39
6	S-(benzo[d]thiazol-2-yl)1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carbothioate	Light brown	73	228	FT- IR ν = cm ⁻¹ , 3437 (-NH secondary amine), 3049 (C-H aromatic), 2837 (C-H aliphatic), 1722 (C=O thioester), 1672 (C=N thiazol ring), 1627 (C=O pyridone), 1010 (C-F aryl halide); ¹ H-NMR (DMSO-d ₆ ppm) δ: 0.8 (s, 1H, H Cyclopropane), 1.0-2.3 (s, 4H, H Cyclopropane), 2.8-3.7 (m, 8H, H piperazin), 4.4-4.6 (s, 1H, -NH piperazin), 6.4-7.5 (m, 7H, Ar -H), ¹³ C-NMR (DMSO-d ₆ ppm) δ: 215 (1C, C pyridone), 180 (1C, C=O-thioester), 160 (1C, C=N thiazol ring), 116-132 (12C, C aromatic), 102-104 (2C, C=C), 40 (DMSO-d ₆ solvent), 30-36 (4C, C piperazin), 12-15 (3C, C cyclopropane), Anal. Calcd. for C ₂₄ H ₂₁ N ₄ O ₂ S ₂ : (480.58) C, 59.98; H, 4.40; N, 11.66; S, 13.34; Found: C, 59.78; H, 4.10; N, 11.16; S, 13.24
7	S-phenyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carbothioate	Yellow	76	232	FT- IR ν = cm ⁻¹ , 3415 (-NH secondary amine), 3022 (C-H aromatic), 2845 (C-H aliphatic), 1716 (C=O thioester), 1622 (C=O pyridone), 1575 (C=C aromatic), 1029 (C-F aryl halide); ¹ H-NMR (DMSO-d ₆ ppm) δ: 0.8 (s, 1H, H Cyclopropane), 1.0-1.6 (d, 4H, H Cyclopropane), 2.7-3.6 (m, 8H, H piperazin), 4.7-5.5 (s, 1H, -NH piperazin), 6.8-7.8 (m, 8H, Ar-H), ¹³ C-NMR (DMSO-d ₆ ppm) δ: 235 (1C, C pyridone), 179 (1C, C=O thioester), 118-130 (12C, C aromatic), 100-104 (2C, C=C), 40 (DMSO-d ₆ solvent), 34-38 (4C, C piperazin), 10-15 (3C, C cyclopropane), Anal. Calcd. for C ₂₃ H ₂₂ N ₃ O ₂ S: (423.51) C, 65.23; H, 5.24; N, 9.92; S, 7.57; Found: C, 65.13; H, 5.14; N, 9.90; S, 7.50
8	S-ethyl-1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carbothioate	Brown	80	231	FT- IR ν = cm ⁻¹ , 3421 (-NH secondary amine), 3053 (C-H aromatic), 2843 (C-H aliphatic), 1718 (C=O thioester), 1624 (C=O pyridone), 1581 (C=C aromatic), 1029 (C-F aryl halide); ¹ H-NMR(DMSO-d ₆ ppm) δ: 0.8-1.5 (m, 5H, H Cyclopropane), 3.0-3.6 (s, 8H, H piperazin), 4.0 (s, 1H, -NH piperazin), 4.5-5.0 (m, 3H, -CH ₃), 5.2-5.6 (m, 2H, -CH ₂), 7.0-7.5 (s, 3H, Ar -H), ¹³ C-NMR (DMSO-d ₆ ppm) δ: 218 (1C, C pyridone), 182 (1C, C=O-thioester), 116-132 (6C, C aromatic), 100-102 (2C, C=C), 40 (DMSO-d ₆ solvent), 34-38 (4C, C piperazin), 22-24 (2C ethyl group), 10-14 (3C, C cyclopropane). Anal. Calcd. for C ₁₉ H ₂₂ N ₃ O ₂ S: (375.46) C, 60.78; H, 5.91; N, 11.19; S, 8.54; Found: C, 60.74; H, 5.81; N, 11.10; S, 8.50
9	2-((1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carbonyl)thio)acetic acid	White	85	221	FT- IR ν = cm ⁻¹ , 3412 (-NH secondary amine + OH Carboxylic acid), 3047 (C-H aromatic), 2872 (C-H aliphatic), 1718 (C=O carboxylic acid), 1668 (C=O thio ester), 1625 (C=O pyridone), 1481 (C=C aromatic), 1186 (C-C aliphatic), 1008 (C-F aryl halide); ¹ H-NMR(DMSO-d ₆ ppm) δ: 0.9 (m, 5H, H Cyclopropane), 2.0 (d, 2H, -CH ₂), 3.0-4.0 (m, 8H, H piperazin), 4.6-4.8 (s, 1H, -NH piperazin), 7.2-7.8 (s, 3H, Ar -H), 13.0 (s, 1H, COOH), ¹³ C-NMR (DMSO-d ₆ ppm) δ: 220 (1C, C pyridone), 218 (1C, C=O, COOH), 186 (1C, C=O thioester), 122-132 (6C, C aromatic), 100 (2C, C=C), 40 (DMSO-d ₆ solvent), 32-36 (4C, C piperazin), 22.0 (1C, -CH ₂), 10-14 (3C, C cyclopropane). Anal. Calcd. for C ₁₉ H ₂₀ N ₃ O ₄ S: (405.44) C, 56.29; H, 4.97; N, 10.36; S, 7.91; Found: C, 56.19; H, 4.87; N, 10.26; S, 7.90

10	1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic diethylcarbamothioic thioanhydride	Orange	78	218	FT-IR $\nu = \text{cm}^{-1}$, 3410 (-NH secondary amine), 3053 (C-H aromatic), 2870 (C-H aliphatic), 1724 (C=O thioester), 1672 (C=S), 1627 (C=O pyridone), 1012 (C-F aryl halide); ¹ H-NMR(DMSO-d ₆ ppm) δ : 0.8-1.4 (m, 5H, H Cyclopropane), 2.6-3.6 (m, 8H, H piperazin) 4.0 (s, 1H, -NH piperazin), 4.5-5.0 (m, 6H, 2CH ₃), 5.2-5.6 (m, 4H, 2CH ₂) 7.0-7.4 (s, 3H, Ar-H), ¹³ C-NMR (DMSO-d ₆ ppm) δ : 220 (1C, C pyridone), 178 (1C, C=O, thioester), 175 (1C, C=S), 124-136 (6C, C aromatic), 106 (2C, C=C), 40 (DMSO-d ₆ solvent), 32-38 (4C, C piperazin), 20-25 (4C, 2 CH ₂ CH ₃), 10-14 (3C, C cyclopropane). Anal. Calcd. for C ₂₂ H ₂₇ FN ₄ O ₂ S ₂ : (462.60) C, 57.12; H, 5.88; N, 12.11; S, 13.86: Found: C, 57.14; H, 5.89; N, 12.04; S, 13.80
11	1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carbohydrazide	Light green	68	169	FT-IR $\nu = \text{cm}^{-1}$, 3450 (NH ₂ free amine), 3344 (NH secondary amine +OH tautomerism), 1731 (C=O amide), 1610 (C=O pyridone), 1577 (C=N imine tautomerism), 1029 (C-F aryl halide); ¹ H-NMR(DMSO-d ₆ ppm) δ : 0.9-1.5 (m, 4H, H cyclopropane), 2.6-3.7 (m, 8H, H piperazin), 4.0 (s, 1H, NH piperazin), 5.2-5.7 (m, 2H, -NH ₂), 6.5-7.5 (s, 3H, Ar-H), 9.1 (s, 1H, C=O-NH); ¹³ C-NMR(DMSO-d ₆ ppm) δ : 232 (1C, C pyridone), 160 (1C, C=O-NH), 118-128 (6C, C aromatic), 106 (1C, C=C), 35-38 (4C, C piperazin), 10-14 (3C, C Cyclopropane). Anal. Calcd. for C ₁₇ H ₂₀ FN ₅ O ₂ : (345.38) C, 59.12; H, 5.84; N, 20.28: Found: C, 59.02; H, 5.80; N, 20.26
12	1-cyclopropyl-N'-(2,4-dinitrophenyl)-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carbohydrazide	Brown	73	215	FT-IR $\nu = \text{cm}^{-1}$, 3427 OH (tautomerism + secondary amine), 1722 (C=O amide), 1670 (C=N tautomerism), 1627 (C=O pyridone), 1519 (C=C aromatic), 1344 (-NO ₂), 1022 (C-F aryl halide); ¹ H-NMR(DMSO-d ₆ ppm) δ : 0.9-1.8 (s, 4H, H cyclopropane), 3.8 (s, 1H, -NH hydrazide), 4.2-4.6 (m, 8H, H piperazin), 5.5 (s, 1H, NH piperazin), 7.2-7.8 (s, 6H, Ar-H), 9.1 (s, 1H, C=O-NH); ¹³ C-NMR(DMSO-d ₆ ppm) δ : 198 (1C, C quinolone), 160 (1C, C=O-NH), 111-128 (12C, C aromatic), 104-110 (1C, C=C), 30-38 (4C, C piperazin), 20-24 (3C, C Cyclopropane). Anal. Calcd. for C ₂₃ H ₂₂ FN ₇ O ₆ : (511.47) C, 54.01; H, 4.34; N, 19.17: Found: C, 54.00; H, 4.31; N, 19.10
13	1-cyclopropyl-6-fluoro-4-oxo-N'-phenyl-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carbohydrazide	Orange	79	195	FT-IR $\nu = \text{cm}^{-1}$, 3421 OH (tautomerism), 3282 N-H (secondary amine), 1720 (C=O amide), 1629 (C=O pyridone), 1610 (C=tautomerism), 1581 (C=C aromatic), 1043 (C-F aryl halide); ¹ H-NMR (DMSO-d ₆ ppm) δ : 0.8-1.2 (s, 4H, H Cyclopropane), 3.0 (s, 1H, -NH hydrazide), 3.4-4.2 (m, 8H, H piperazin), 5.8 (s, 1H, NH piperazin), 7.0-7.6 (s, 8H, Ar-H), 9.0 (s, 1H, C=O-NH); ¹³ C-NMR(DMSO-d ₆ ppm) δ : 212 (1C, C pyridone), 168 (1C, C=O-NH), 115-132 (12C, C aromatic), 106 (1C, C=C), 32-36 (4C, C piperazin), 9.0-12 (3C, C Cyclopropane). Anal. Calcd. for C ₂₃ H ₂₄ FN ₅ O ₂ : (421.48) C, 65.54; H, 5.74; N, 16.62: Found: C, 65.34; H, 5.54; N, 16.51
14	1-cyclopropyl-6-fluoro-N', N'-diisopropyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carbohydrazide	White	77	243	FT-IR $\nu = \text{cm}^{-1}$, 3466 (-NH secondary amine), 1722 (C=O amide), 1629 (C=O pyridone), 1012 (C-F aryl halide); ¹ H-NMR(DMSO-d ₆ ppm) δ : 0.8-1.2 (s, 4H, H cyclopropane), 2.2-2.6 (m, 8H, H piperazin), 3.0-3.8 (m, 12H, 4CH ₃), 4.3(s, 2H, 2CH-), 5.2 (s, 1H, NH piperazin), 7.0-7.5 (m, 3H, Ar-H), 9.2 (s, 1H, C=O-NH); ¹³ C-NMR (DMSO-d ₆ ppm) δ : 200 (1C, C pyridone), 159 (1C, C=O-NH amide), 115-128 (6C, C aromatic), 105 (1C, C=C), 22-36 (4C, C piperazin), 12-22 (6C, C iso propyl) 5.0-10 (3C, C cyclopropane). Anal. Calcd. for C ₂₃ H ₃₂ FN ₅ O ₂ : (429.54) C, 64.31; H, 7.51; N, 16.30: Found: C, 64.11; H, 7.47; N, 16.33

3. RESULTS AND DISCUSSION

Chemistry: Ciprofloxacin were treatment with different reagents aiming to synthesis new potential activity against wide range of bacteria, so we success to enter three functional groups like ester, carbothioate and carbohydrazide with different examples as in scheme.1. Therefore, treatment of ciprofloxacin with different drying alcohol (methanol, ethanol, propanol, butanol and pentanol) with catalytic amount of concentration.



Scheme 1. Reagents and conditions: (i) alcohol, 1ml Con. H_2SO_4 (ii) KI, DMF, Thiols (iii) Hydrazides in ethanol for all reaction MWI for 18-20 min.

Scheme 1. reagents and conditions

sulphuric acid to synthesis appropriated ester 1-5 after 20 minutes irradiated by microwave with continuous removed of generated water. The reactions mixture was monitored and followed by (TLC). The IR spectra of all compounds 1-5 exhibited absorption bands for C=O ester $\nu = 1718-1722\text{ cm}^{-1}$, the C=O group in pyridone still constant at $\nu = 1229\text{ cm}^{-1}$ and $\nu = 1274\text{ cm}^{-1}$ for C-O-C bond and the absence of absorption band of OH group for all compounds that means there is no reaction occur in these groups of the structure of molecules except of OH group. The 1H NMR of these compounds different only of positions of different groups from $\delta = 3.5-4.3$ ppm for each methylene groups and $\delta = 5.1-6.0$ ppm for methyl groups. In ^{13}C NMR the presence new bands for different R groups in positions $\delta = 15-170$ ppm means presence new methylene groups that confirmed the structure of proposed synthesis compounds as in figure 1.

R	1H NMR= δ	R	^{13}C NMR= δ
1 = Me	5.2	1 = Me	175
2 = Et	3.9, 5.1-5.3	2 = Et	170, 183
3 = Propyl	3.5-3.8, 4.5	3 = Propyl	20-24, 168
4 = Butyl	3.5-3.8, 6.0	4 = Butyl	22-26, 168
5 = pentyl	4.0-4.3, 5.2-5.6	5 = pentyl	15-22, 188

Figure.1. Chemical shifts of 1H NMR and ^{13}C NMR of ester derivatives

The type carbothioate compounds 6-10 exhibited absorption band at $\nu = 1716-1724\text{ cm}^{-1}$ for C=O_{thioester}, but compound 6 shown up absorption band at $\nu = 1672\text{ cm}^{-1}$ back to C=N band in thiazole heterocyclic ring. Compound 9 show the characteristic band of OH Integrated with N-H for secondary amine of piperazinyl in the region about $\nu = 3412\text{ cm}^{-1}$. Finally, the IR spectrum of compound 10 exhibited clear band for C=S at $\nu = 1672\text{ cm}^{-1}$. The structures of compounds 6-10 were identified by the 1HNMR and ^{13}C NMR spectra, which showed rather similar patterns for the ciprofloxacin scaffold. The spectra were characterized by the presence of additional aromatic proton and carbon atoms, in the $\delta = 2.0-5.6$ ppm in 1H NMR and $\delta = 22-26$ ppm attributed to new methylene groups, indicative for alkylation of the original molecule (ciprofloxacin).

But carbohydrazide compounds 11-14 show tautomerism skeletal due to the presences absorption bands in IR spectra attributed to OH group at $\nu = 3344$ and $\nu = 1577-1670\text{ cm}^{-1}$ back to C=N so, all compounds tautomerism to imine structures formation shown in figure 2, It has been confirmed by resonated in 1H NMR around $\delta = 9.0-9.2$

ppm for NH in carbohydrazone compounds and presences bands in $\delta = 160, 160, 168$ and 169 ppm attributed to compounds 11, 12, 13 and 14 respectively in ^{13}C NMR spectra. Recently (Nadhir and Nadia, 2016) have synthesized a series of amide derivatives shown tautomerism property.

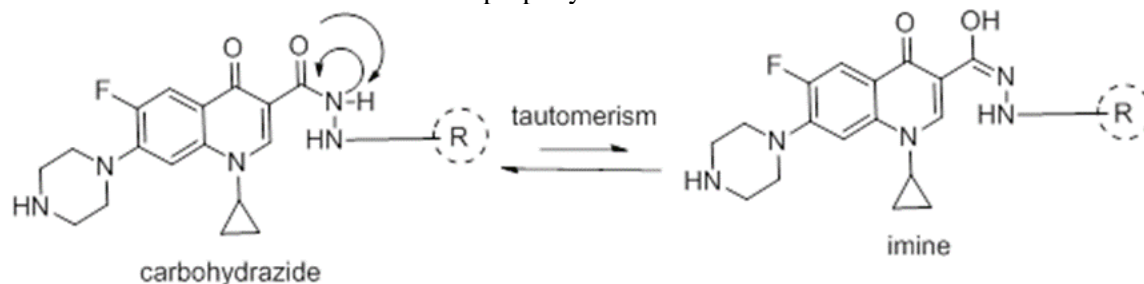


Figure.2. Tautomerism between carbohydrazone and imine in compounds 11-14

Antibacterial activity: An antibacterial activity has been conducted according to piercing method, all ciprofloxacin derivatives 1-14 were tested by this method against four types of bacteria gram negative such as *Escherichia coli*, *Proteus mirabilis* and gram positive such as *Staphylococcus aureus*, *Granutice tella adiacens*. All derivatives were dissolved in three dissimilar concentrations 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. 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 types of bacteria table (1). The results showed that compounds 1-5 showed high activity against all types of bacteria because converted ester group instead of carboxylic groups in these compounds. The derivative 6 exhibited excellent activities against all types of bacteria because this compound including a thiazole heterocyclic ring as well as sulphure atom, compound 8 and 9 showed decrease in their activity towards all tested bacteria. Moreover, compounds 7 and 10 exhibited better activity against *staphylococcus aureus* and *Grantice tella adiaceus* bacteria but showed lower activity against *E.coli* and *proteus mirabilis*. The compound 11 was found to be respectable activity against gram-negative (*E.coli* and *proteus mirabilis*) because it contains free amine group but compound 12 showed better activity because the compound containing two nitro groups ($-\text{NO}_2$) in the phenyl ring. The derivatives 13 and 14 exhibited high activity towards all types of bacteria because these compounds include phenyl ring and amine group that can exhibits hydrogen bonds. 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.

Table.2. Zone inhibition (mm) of ciprofloxacin and their derivatives (1-14) against various microorganisms

NO	Concentrations $\mu\text{g/L}$			Inhibition zone (mm)											
				<i>Staphylococcus Aureus</i>			<i>Granutice tella adiacens</i>			<i>Escherichia Coli</i>			<i>Proteus mirabilis</i>		
1	1	0.5	0.1	20	16	12	18	16	14	25	22	16	22	18	14
2	1	0.5	0.1	22	18	14	21	18	14	23	16	14	20	16	13
3	1	0.5	0.1	24	18	15	18	14	12	22	18	14	22	19	14
4	1	0.5	0.1	18	16	12	20	16	12	18	17	15	21	18	15
5	1	0.5	0.1	20	19	13	18	16	12	20	17	13	18	15	13
6	1	0.5	0.1	30	24	22	32	26	22	28	25	20	30	24	21
7	1	0.5	0.1	24	20	16	22	18	14	17	13	11	18	14	10
8	1	0.5	0.1	17	12	9	18	14	12	16	14	10	17	13	10
9	1	0.5	0.1	18	14	12	16	14	12	17	14	10	16	12	10
10	1	0.5	0.1	25	22	18	23	20	18	15	12	10	16	13	11
11	1	0.5	0.1	18	17	13	18	14	11	20	17	14	21	18	14
12	1	0.5	0.1	27	22	18	25	20	19	23	17	15	22	21	18
13	1	0.5	0.1	28	23	20	24	21	18	22	20	17	22	20	18
14	1	0.5	0.1	26	23	21	23	20	18	25	22	18	23	21	19
Cip	1	0.5	0.1	13	10	8	12	10	9	14	11	8	17	13	11

4. CONCLUSION

In summary, we have synthesized and evaluated a new series of drug ciprofloxacin derivatives with evaluation of their anti-bacterial activity against various microorganisms (*Staphylococcus Aureus*, *Granutice telladiacens*, *Escherichia Coli*, *Proteus mirabilis*). 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 itself. Many compounds like 6, 12, 13 and 14 are a promising agent for further structural modification and pharmacological evaluation as target treatment of infections caused by these types of bacteria.

REFERENCES

- Crumplin GC, Smith JT, Nalidixic acid bacterial chromosome replication, *Nature*, 260, 1976, 643-45.
- de Souza NJ, Gupte SV, Deshpande PK, Desai VN, Bhawsar SB, Yeole RD, Shukla MC, Strahilevitz J, Hooper DC, Bozdogan B, Appelbaum PC, Jacobs MR, Shetty N, Patel MV, Jha R, Khorakiwala HF, A chiral benzoquinolizine-2-carboxylic acid arginine salt active against vancomycin resistant *Staphylococcus aureus*, *J Med Chem*, 48, 2005, 5232-5242.
- Jubie S, Sikdar P, Kalirajan R, Gowramma B, Gomaathy S, Sankar S, Elanga K, Synthesis and antimicrobial activity of some novel ciprofloxacin analogues, *J Pharma Res*, 3, 2010, 511-513.
- Lester M and Zwerink M, Structure Activity Relationships of Quinolones in Fluoroquinolones Antibiotics, In, A.R. Ronald and D.E. Low, Eds, Birkhauser Based, 2003, 11-48.
- Nadhir N.A, Jafar, Abbas N M, and Ammar K.M, Synthesis of New Analogues of drug 'Monastrol' via Biginelli Reaction, *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, 6 (5), 2015, 906-915.
- Nadhir N.A, Jafar, Nadia S.M, Microwave assisted synthesis of amide derivatives of the drug ciprofloxacin and screening the biological properties, *International Journal of Chem Tech Research*, 9 (7), 2016, 387-395.
- Peter B and Glenn T, Tolerability of Fluoroquinolones Antibiotics Past Present and Future, *Drug Safe*, 13, 1995, 345-358.
- Siddiqui R, Sultana N, Khan KM, Akbar N, Ali M, Arayne S, Effects of skeletal modifications of ciprofloxacin on antibacterial, antifungal and cytotoxic activities, *J Chinese Clin Med*, 21, 2007, 188-195.
- Wang JC, DNA topoisomerases, *Annu Rev Biochem*, 54, 1985, 665-697.