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Research Article

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SUBSTITUTED 1,3,4-OXADIAZOLE DERIVATIVE: DERIVED FROM CIPROFLOXACIN

ANUJ SINGHAI[1]*, M. K. GUPTA[2]

[1]Department of Pharmaceutical Chemistry, Oriental College of Pharmacy and Research, Oriental University, Indore, Madhya Pradesh, India. [2]Department of Pharmacognosy, Oriental College of Pharmacy and Research, Oriental University, Indore, Madhya Pradesh, India. Email: anujsinghai1989@gmail.com

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ABSTRACT

Objective: The purpose of this research is synthesized and evaluates different derivatives of oxadiazole.

Methods: A novel series of substituted 1,3,4-oxadiazole derivative were synthesized by condensing different amine with 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)quinolin-4(1H)-one (III) in the presence of formaldehyde. The structure of these novel synthesized compounds was characterized on the bases of physicochemical and spectral analysis. The title compounds (IVa-h) were screened for antibacterial activity by disc diffusion method.

Results: Substituted 1,3,4-oxadiazole derivative was synthesized, characterized, and evaluated for antibacterial activity. Compounds IVa, IVd, IVe, IVf, and IV h showed enhance activities then ciprofloxacin against all Gram-positive and Gram-negative organisms. Compound IVe showed the highest activity against *Staphylococcus aureus* and compound IV showed the highest activity against *Escherichia coli.*

Conclusion: The present study demonstrates the synthesis and characterization of 1,3,4-oxadiazole derivatives derived from ciprofloxacin. These compounds were evaluated for antibacterial activity against different Gram-positive and Gram-negative organism. In some cases, antibacterial activity is found to be enhanced as compared to standard drug ciprofloxacin.

Keywords: 1,3,4-Oxadiazole, Ciprofloxacin, Antimicrobial.

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INTRODUCTION

Chemical modification of bioactive components is one of the most common approaches in drug discovery and development with an improved therapeutic effect. As resistance to antimicrobial drugs is widespread, there is an increasing need for the identification of novel structure leads that may be of use in designing new, potent, and less toxic antimicrobial agents.

1,3,4-Oxadiazole is an important class of heterocyclic compounds containing one oxygen and two nitrogen atoms in five-member ring with a broad spectrum of biological activities [1,2]. During the past year, considerable evidence have accumulated to demonstrate the efficiency of 1,3,4-oxadiazole including antimicrobial [3,4], antifungal [5], anti-HIV [6], anthelmintic [7], anticancer [2], anticonvulsant [8], antiviral [9], antimalarial [10], hypoglycemic [11], anti-inflammatory [12], analgesic [13], antitubercular [14], and other biological properties such as genotoxic studies and lipid peroxidation inhibitor [15].

In this paper, we have focused on the incorporation of 1,3,4-oxadiazole with ciprofloxacin in one framework. Oxadiazole ring was introduced to the carboxylic side chain and different amines were attached to oxadiazole. In some cases, antibacterial activity is found to be enhanced as compared to standard drug ciprofloxacin.

Ciprofloxacin is the first widely used quinolone with advanced systemic activity, marketed in 1987. The second-generation antibiotics, now called fluoroquinolones, have excellent activity against many Gram-negative bacteria. Fluoroquinolones constituted a significant advancement in the management of infectious diseases [16]. Ciprofloxacin is used for the treatment of urinary tract infection [17], prostatitis [18], continuous ambulatory peritoneal dialysis infection [19], antitumor activity [20], etc. Ciprofloxacin is found to be an important antibacterial agent. Keeping this in view, it was thought worthwhile to design the synthesis of title compounds, wherein the biological activity of ciprofloxacin is enhanced by 1,3,4-oxadiazole.

METHODS

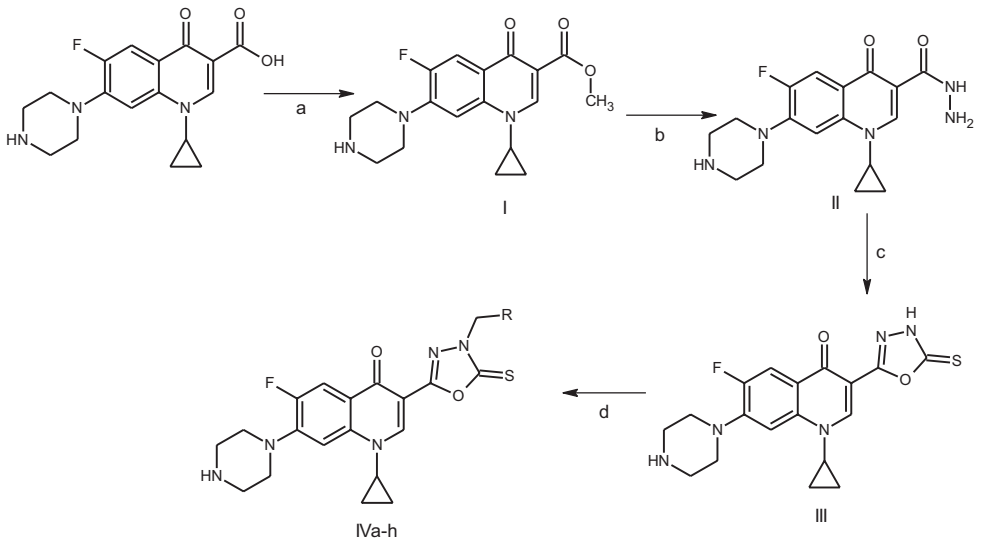
Chemicals used in this synthetic work were purchased from S.D. Fine-Chem Ltd., Mumbai, and Sigma-Aldrich, India (Merck). Solvents except laboratory reagent grade were dried and purified according to the literature when necessary. The purity of the compounds was checked on thin-layer chromatography (TLC) plates using silica gel G as stationary phase and iodine vapors as a visualizing agent. Melting points of synthesized compounds were determined using Thermonik melting point apparatus and are uncorrected; IR spectra were recorded on Thermo Nicolet Spectrophotometer using KBr pellets. The proton nuclear magnetic resonance (^{1}H NMR) was recorded on Bruker Avance II NMR 500 MHz instruments using appropriated solvent and TMS as internal standard, chemical shifts are expressed as δ values (ppm).

Synthesis and spectral studies

The title compounds were synthesized as given in Scheme 1.

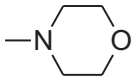
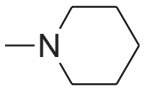
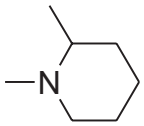
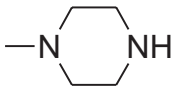
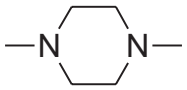
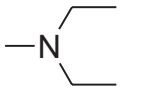
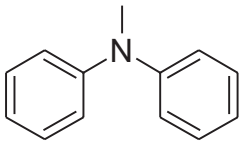
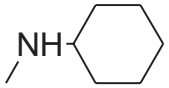
Synthesis of methyl ester of ciprofloxacin (I)

The methyl ester was prepared as per procedure reported in literature [21]. M.p. 244–246°C, yield: 78.43%. IR spectra showed bands at 3088 (C-H), 1745 (C=O), 1531 (C=C), 1476 (C-N), and 1330 (C-F). ^{1}H NMR chemical shift at ($CDCl_3$, δ ppm) 8.45 (s, 1H, 2nd aryl H), 8.05 (d, 1H, 5th aryl H), 6.84 (s, 1H, 8th aryl H), 3.78 (s, 3H, CH_3), 3.76–2.32 (m, 9H, piperznyl H), 2.55 (m, 1H of cyclopropane), and 1.78–1.44 (m, 4H of cyclopropane).



Scheme 1: a- CH3OH/ H2SO4, b- CH3OH/ NH2NH2H2O, c- CH3OH/CS2 / KOH, d- CH3OH/HCHO/ Amine, R- Different amines Synthesis of 1,3,4-oxadiazole derivatives

Table 1: Physicochemical data of the different synthesized title compounds (IVa-h)

Compound	R	M.P. (°C)	Yield (%)	Rf*	Molecular formula
IVa		232–234	74.5	0.30	$C_{23}H_{27}FN_6O_3S$
IVb		216–218	69.9	0.41	$C_{24}H_{29}FN_6O_2S$
IVc		202–204	70.7	0.29	$C_{25}H_{31}FN_6O_2S$
IVd		184–186	70.7	0.44	$C_{23}H_{28}FN_7O_2S$
IVe		194–196	71.4	0.53	$C_{24}H_{30}FN_7O_2S$
IVf		215–217	68.2	0.24	$C_{23}H_{29}FN_6O_2S$
IVg		242–244	75.5	0.43	$C_{31}H_{41}FN_6O_2S$
IVh		178–180	72.8	0.64	$C_{25}H_{31}FN_6O_2S$

All compounds were recrystallized by methanol. Stationary phase* – silica gel G. Mobile phase – ethyl acetate: chloroform (4:1). Visualizing agent – iodine vapors

Synthesis of 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carbohydrazide (II)

Compound I (0.01 mol) and hydrazine hydrate (99%) (0.02 mol) were refluxed in absolute methanol (50 ml) for 20 h (monitored by TLC). The mixture was concentrated, cooled, and poured in ice-cold water. The solid thus separated, filtered, dried, and recrystallized from ethanol:water (4:1). M.p. 256–258°C, yield: 75%. IR spectra showed bands at N-H at 3325 cm^{-1} 3058 (C-H), 1645 (C=O), 1511 (C=C), 1466 (C-N), and 1320 (C-F).^{1}H NMR chemical shift at ($CDCl_3$, δ ppm) 8.96 (s, 1H, 2nd aryl H), 8.15 (d, 1H, 5th aryl H), 6.14 (s, 1H, 8th aryl H), 3.66–2.12 (m, 9H, piperazinyl H), 2.65 (m, 1H of cyclopropane), 1.88–1.44 (m, 4H of cyclopropane), and 7.90 (s, 1H, NH), 2.15 (s, 2H, NH_2).

Synthesis of 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)quinolin-4(1H)-one (III)

A mixture of II (0.005 mol) KOH (0.005 mol) and carbon disulfide (5 ml) in methanol (50 ml) were refluxed on a steam bath for 12 h (monitored by TLC). The solution was then concentrated, cooled, and acidified with dil. HCl. The solid mass that separated, filtered, washed with ethanol, dried, and recrystallized from ethanol:water (4:1). Mp 238–240°C,

Table 2: Zone of inhibition (mm) of ciprofloxacin and their derivatives against various microorganism

Organism	Ciprofloxacin (50 ug/ml)	IVa	IVb	IVc	IVd	IVe	IVf	IVg	IVh
Staphylococcus aureus	24	26	22	23	26	28	25	21	27
Bacillus subtilis	18	22	16	16	21	25	19	17	23
Staphylococcus pneumoniae	19	20	18	19	24	22	19	17	21
Escherichia coli	21	28	22	20	24	24	22	16	22
Pseudomonas aeruginosa	22	23	21	20	26	27	23	19	24
Klebsiella pneumonia	16	15	12	15	18	18	15	15	18
Salmonella typhi	15	14	11	10	16	16	16	15	17

yield: 72%. IR spectra showed bands at N-H at 3373 cm^{-1} 3068 (C-H), 1576 (C=N), 1511 (C=C), 1456 (C-N), 1312 (C=S), 1300 (C-F), and 1249 (C-O-C). ^{1}H NMR chemical shift at ($CDCl_3$, δ ppm) 8.90 (s, 1H, NH), 8.66 (s, 1H, 2nd aryl H), 8.35 (d, 1H, 5th aryl H), 6.54 (s, 1H, 8th aryl H), 3.16–2.02 (m, 9H, piperznyl H), 3.65 (m, 1H of cyclopropane), and 1.78–1.34 (m, 4H of cyclopropane).

General procedure for the synthesis of derivatives (IVa-h)

To a solution of III (0.01 mol) in ethanol, a mixture of formaldehyde (0.015 mol) and a secondary amine (0.01 mol) in ethanol was added with stirring. After complete addition, the stirring was continued overnight at room temperature. The precipitated solids were filtered, washed with water, and recrystallized from methanol.

1-cyclopropyl-6-fluoro-3-(4-(morpholinomethyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2yl)-7-(piperazin-1yl)quinolin-4(1H)-one (IVa)

This was obtained by reacting 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) quinolin-4(1H)-one (III, 0.01 mol) and morpholine (0.015 mol) as described in general procedure. Mp 232–234°C, yield: 74.5%. IR spectra showed bands at 3068 (C-H), 1576 (C=N), 1511 (C=C), 1456 (C-N), 1312 (C=S), 1300 (C-F), and 1249 (C-O-C). ^{1}H NMR chemical shift at ($CDCl_3$, δ ppm) 8.14 (s, 1H, 2nd aryl H), 7.95 (d, 1H, 5th aryl H), 6.14 (s, 1H, 8th aryl H), 3.46–2.10 (m, 9H, piperznyl H), 3.72 (s, 2H, N-CH_2-N), 3.68–3.65 (t, 4H, morpholine), 2.79–2.76 (t, 4H, morpholine), 2.65 (m,1H of cyclopropane), and 1.88–1.44 (m, 4H of cyclopropane).

1-cyclopropyl-6-fluoro-7-(piperazin-1yl)-3-(4-(piperidin-1-ylmethyl)-5-thioxo-4,5 dihydro-1,3,4-oxadiazol-2yl)-quinolin-4(1H)-one (IVb)

This was obtained by reacting 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)quinolin-4(1H)-one (III, 0.01 mol) and piperidine (0.015 mol) as described in general procedure. Mp 216–218°C, yield: 69.6%. IR spectra showed bands at 3075 (C-H), 1540 (C=N), 1525 (C=C), 1460 (C-N), 1320 (C=S), 1310 (C-F), and 1230 (C-O-C). ^{1}H NMR chemical shift at ($CDCl_3$, δ ppm) 8.24 (s, 1H, 2nd aryl H), 7.85 (d, 1H, 5th aryl H), 6.18 (s,1H, 8th aryl H), 3.66–2.20 (m, 9H, piperznyl H), 3.42 (s, 2H,N-CH_2-N), 2.80–2.72 (t, 4H, piperidine), 1.64 (m, 2H, piperidine), 1.51–1.24 (m, 4H, piperidine), 2.55 (m, 1H of cyclopropane), and 1.28–1.04 (m, 4H of cyclopropane).

1-cyclopropyl-6-fluoro-3-(4-((2-methylpiperidin-1-ylmethyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2yl)-7-(piperazin-1yl) quinolin-4(1H)-one (IVc)

This was obtained by reacting 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) quinolin-4(1H)-one (III, 0.01 mol) and 2-methyl piperidine (0.015 mol) as described in general procedure. Mp 202–204°C, yield: 70.7%. IR spectra showed bands at 3078 (C-H), 1563 (C=N), 1512 (C=C), 1474 (C-N), 1355 (C=S), 1313 (C-F), and 1263 (C-O-C). ^{1}H NMR chemical shift at ($CDCl_3$, δ ppm) 8.04 (s, 1H, 2nd aryl H), 7.65 (d, 1H, 5th aryl H), 6.66 (s, 1H, 8th aryl H), 3.16–2.16 (m, 9H, piperznyl H), 3.92 (s, 2H,N-CH_2-N), 2.80–2.72 (m, 1H, piperidine), 1.74–1.55 (m, 6H, piperidine), 1.37–1.35 (d, 3H, 2-methyl piperidine), 1.25 (m, 2H, piperidine), 2.51 (m, 1H of cyclopropane), and 1.26–1.08 (m, 4H of cyclopropane).

1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(4-(piperazin-1-ylmethyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)quinolin-4(1H)-one (IVd)

This was obtained by reacting 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) quinolin-4(1H)-one (III, 0.01 mol) and piperazine (0.015 mol) as described in general procedure. Mp 184–186°C, yield: 70.7%. IR spectra showed bands at 3080 (C-H), 1566 (C=N), 1520 (C=C), 1466 (C-N), 1322 (C=S), 1310 (C-F), and 1239 (C-O-C). ^{1}H NMR chemical shift at ($CDCl_3$, δ ppm) 8.17 (s, 1H, 2nd aryl H), 7.45 (d, 1H, 5th aryl H), 6.75 (s, 1H, 8th aryl H), 3.66–2.36 (m, 9H, piperznyl H), 3.52 (s, 2H, N-CH_2-N), 2.62–2.47 (t, 4H, piperazine), 2.39–2.32 (t, 4H, piperazine), 1.91 (m, 1H, piperazine), 2.51 (m, 1H of cyclopropane), and 1.26–1.08 (m, 4H of cyclopropane).

1-cyclopropyl-6-fluoro-3-(4-((4-methylpiperazin-1-yl)methyl)-5-thioxo-4,5-dihydro-1,3,4 -oxadiazol-2-yl)-7-(piperazin-1-yl) quinolin-4(1H)-one (IVe)

This was obtained by reacting 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)quinolin-4(1H)-one (III, 0.01 mol) and N-methylpiperazine (0.015 mol) as described in general procedure. Mp 194–196°C, yield: 71.4%. IR spectra showed bands at 3065 (C-H), 1545 (C=N), 1521 (C=C), 1446 (C-N), 1332 (C=S), 1314 (C-F), and 1239 (C-O-C). ^{1}H NMR chemical shift at ($CDCl_3$, δ ppm) 8.17 (s, 1H, 2nd aryl H), 7.85 (d, 1H, 5th aryl H), 6.15 (s, 1H, 8th aryl H), 3.26–2.56 (m, 9H, piperznyl H), 3.02 (s, 2H,N-CH_2-N), 2.52-2.37(t, 8H, piperazine), 2.23 (s, 3H, CH_3), 2.51 (m, 1H of cyclopropane), and 1.26–1.08 (m, 4H of cyclopropane).

1-cyclopropyl-3-(4-((diethyl amino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)6-fluoro-7-(piperazin-1-yl)quinolin-4(1H)-one (IVf)

This was obtained by reacting 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) quinolin-4(1H)-one (III, 0.01 mol) and diethyl amine (0.015 mol) as described in general procedure. Mp 215–217°C, yield: 68.20%. IR spectra showed bands at 3045 (C-H), 1546 (C=N), 1530 (C=C), 1470 (C-N), 1325 (C=S), 1322 (C-F), and 1242 (C-O-C). ^{1}H NMR chemical shift at ($CDCl_3$, δ ppm) 8.02 (s, 1H, 2nd aryl H), 7.55 (d, 1H, 5th aryl H), 6.05 (s, 1H, 8th aryl H), 3.16–2.36 (m, 9H, piperznyl H), 3.08 (s, 2H, N-CH_2-N), 3.06–2.70 (m, 4H, CH_2, CH_2), 1.49–1.08 (t, 6H, CH_3, CH_3), 2.61 (m, 1H of cyclopropane), and 1.16–1.06 (m, 4H of cyclopropane).

1-cyclopropyl-3-(4-((dicyclohrxylamino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)6-fluoro-7-(piperazin-1-yl)quinolin-4(1H)-one (IVg)

This was obtained by reacting 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) quinolin-4(1H)-one (III, 0.01 mol) and diphenyl amine(0.015 mol) as described in general procedure. Mp 242–244°C, yield: 75.50%. IR spectra showed bands 3075 (C-H), 1570 (C=N), 1520 (C=C), 1470 (C-N), 1305 (C=S), 1290 (C-F), and 1244 (C-O-C).^{1}H NMR chemical shift at ($CDCl_3$, δ ppm) 7.82 (s, 1H, 2nd aryl H), 7.25 (d, 1H, 5th aryl H), 6.16 (s, 1H, 8th aryl H), 7.12–6.95 (m, 10H of diphenyl amine) 3.76–2.66 (m, 9H, piperznyl H), 3.58 (s, 2H, N-CH_2-N), 2.61 (m, 1H of cyclopropane), and 1.16–1.06 (m, 4H of cyclopropane).

3-(4((cyclohexylamino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-1-cyclopropyl-6-fluoro-7-(piperazin-1-yl) quinolin-4(1H)-one (IVh)

This was obtained by reacting 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) quinolin-4(1H)-one (III, 0.01 mol) and cyclohexyl amine(0.015 mol) as described in general procedure. Mp 178–180°C, yield: 72.80%. IR spectra showed bands 3090 (C-H), 1580 (C=N), 1536 (C=C), 1476 (C-N), 1322 (C=S), 1316 (C-F), and 1245 (C-O-C). ^{1}H NMR chemical shift at ($CDCl_3$, δ ppm) 8.23 (s, 1H, 2nd aryl H), 7.15 (d, 1H, 5th aryl H), 6.55 (s, 1H, 8th aryl H), 3.96–2.86 (m, 9H, piperznyl H), 3.75 (s, 2H,N-CH_2-N), 2.57–1.25 (m, 11H cyclohexyl amine), 2.02 (s, 1H NH) 2.61 (m, 1H of cyclopropane), and 1.16–1.06 (m, 4H of cyclopropane).

Antibacterial activities [22-24]: The antibacterial activity of all newly synthesized derivatives was performed by disc diffusion method. For this activity, 50 µg/mL stock solution of ciprofloxacin and its derivatives were prepared. This method is based on the determination of an inhibited zone proportion to the bacterial susceptibility to the antimicrobial present in the disc.

The result was compared with ciprofloxacin against seven different Gram-positive and Gram-negative organisms, i.e., *Staphylococcus aureus*, *Bacillus subtilis*, *Staphylococcus pneumonia*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, and *Salmonella typhi.*

RESULTS AND DISCUSSION

The ciprofloxacin was converted to its methyl esters (I) by esterification. This methyl ester was reacted with hydrazine hydrate, gave carbohydrazide (II). This carbohydrazide was treated with CS_2/ KOH in methanol gave 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)quinolin-4(1H)-one) (III). The purity of the compounds was confirmed by melting point; TLC and structure were confirmed by IR and ^{1}H NMR spectral data.

Treatment of 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)quinolin-4(1H)-one) (III) with various amines in the presence of formaldehyde gave the title compounds IVa-h. The purity of these compounds was assessed by melting point; TLC and structure were confirmed by IR and^{1}H NMR. Physicochemical data of the different synthesized title compounds (IVa-h) are given in Table 1.

The result of antibacterial activity is collected in Table 2. The antibacterial activity of all newly synthesized derivatives was performed by disc diffusion method. The result was compared with ciprofloxacin against seven different Gram-positive and Gram-negative organisms and observed that compounds IVa, IVd, IVe, IVf, and IVh showed enhance activities then ciprofloxacin against all Gram-positive and Gram-negative organism. Compound IVg showed less potent activity than ciprofloxacin against all Gram-positive and Gram-negative organisms. Compounds IVb and IVc showed similar activity as ciprofloxacin against Gram-positive and Gram-negative organism. Compound IVe showed the highest activity against *S. aureus* and compound IV showed the highest activity against *E. coli.* Compounds IVb and IVc showed less active against *S. typhi.* In general, we can say that a total of five derivatives showed enhanced activities out of eight derivatives.

It was observed that when oxadiazole ring was introduced to the carboxylic side chain, significant enhancement of potency against the organism attached to ciprofloxacin.

CONCLUSION

A series of substituted 1,3,4-oxadiazole were synthesized according to Scheme 1 and the identity of the compounds was confirmed based on their melting point, TLC, IR, and 1H-NMR data. Antibacterial activity was carried out for all the synthesized compounds using disc diffusion method against various Gram-positive and Gram-negative organisms and ciprofloxacin was used as standard. Compounds IVa, IVd, IVe, IVf, and IV h showed enhance activities then ciprofloxacin against all Gram-positive and Gram-negative organisms. A total of five derivatives showed enhanced activities out of eight derivatives.

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AUTHORS' CONTRIBUTIONS

Equal.

CONFLICTS OF INTEREST

None.

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