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

ANUJ SINGHAI1*, M. K. GUPTA2

1Department of Pharmaceutical Chemistry, Oriental College of Pharmacy and Research, Oriental University, Indore, Madhya Pradesh, India. 2Department of Pharmacognosy, Oriental College of Pharmacy and Research, Oriental University, Indore, Madhya Pradesh, India. Email: anujsinghail1989@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 IVh showed enhanced activities then ciprofloxacin against all Gram-positive and Gram-negative organisms. Compound IVe showed the highest activity against Staphylococcus aureus and compound IVd 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.

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 amount of research has accumulated to demonstrate the efficiency of 1,3,4-oxadiazole including antimicrobial [3,4], antifungal [5], anti-HIV [6], antihelmintic [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 carbonyl 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. These second-generation antibiotics, now called fluoroquinolones, have excellent activity against many Gram-negative bacteria. Fluoroquinolones constitute 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], antitum or 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 Themmonik melting point apparatus and are uncorrected; IR spectra were recorded on Thermo Nicolet Spectrophotometer using KBr pellets. The proton nuclear magnetic resonance (1H 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). 1H NMR chemical shift at (CDCl3, 8 ppm) 8.45 (s, 1H, 2nd ary H), 8.05 (d, 1H, 5th ary H), 6.84 (s, 1H, 2nd ary H), 3.78 (s, 3H, CH3), 3.76–2.32 (m, 9H, piperznyl) H, 2.55 (m, 1H of cyclopropane), and 1.78–1.44 (m, 4H of cyclopropane).
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_{6}O_{3}S   |
| IVb      |            | 216–218   | 69.9      | 0.41 | C_{24}H_{29}FN_{6}O_{2}S   |
| IVc      |            | 202–204   | 70.7      | 0.29 | C_{25}H_{31}FN_{6}O_{2}S   |
| IVd      |            | 184–186   | 70.7      | 0.44 | C_{23}H_{28}FN_{7}O_{2}S   |
| IVe      |            | 194–196   | 71.4      | 0.53 | C_{24}H_{30}FN_{7}O_{2}S   |
| IVf      |            | 215–217   | 68.2      | 0.24 | C_{23}H_{28}FN_{6}O_{2}S   |
| IVg      |            | 242–244   | 75.5      | 0.43 | C_{24}H_{30}FN_{6}O_{2}S   |
| IVh      |            | 178–180   | 72.8      | 0.64 | C_{25}H_{31}FN_{6}O_{2}S   |

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). ¹H NMR chemical shift at (CDCl₃, 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, NH₂).

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). M.p 238–240°C,
yield: 72%. IR spectra showed bands at 3373 cm⁻¹, 1576 (C-N), 1571 (C=C), 1456 (C-N), 1312 (C-S), 1300 (C-F), and 1249 (C-O-C). ¹H NMR chemical shift at (CDCl₃, 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, piperzyln 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 N-methylpiperazine (0.015 mol) as described in general procedure. Mp 242–244°C, yield: 75.50%. IR spectra showed bands at 3080 (C-H), 1566 (C=C), 1460 (C-N), 1322 (C-S), 1310 (C-F), and 1249 (C-O-C). ¹H NMR chemical shift at (CDCl₃, 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, piperzyln H). 3.52 (s, 2H, N-CH₃), 2.62–2.56 (m, 9H, piperzyln H), 3.02 (s, 2H, N-CH₂-N), 2.52–2.37 (t, 8H, piperazine), 2.23 (s, 3H, CH₃), 2.51 (m, 1H of cyclopropane), and 1.26–1.08 (m, 4H of cyclopropane).
Compounds IVb and IVc showed less activity than 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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