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Research Article

SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 1,3-DIONE DERIVATIVES OF 1-CYCLOPROPYL-7-[4-(2,6-DIMETHYL/ DIMETHOXY-PYRIMIDIN-2-YL-DIAZENYL) PIPERZIN-1-YL]-6-FLUORO-4-OXO-1,4-DIHYDRO-QUINOLINE-3-CARBOXYLIC ACID

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ABSTRACT

Object: To synthesise a series of 1-cyclopropyl-7-[4-(2,6-dimethyl-pyrimidin-2-yl-diazenyl)-piperzin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid and 1-cyclopropyl-7-[4-(2,6 dimethoxy-pyrimidin-2-yl-diazenyl)-piperzin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid and their dione derivatives and evaluate for their antibacterial activity.

Method: A series of 1-cyclopropyl-7-[4-(2,6-dimethyl-pyrimidin-2-yl-diazenyl)-piperzin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid and 1-cyclopropyl-7-[4-(2,6 dimethoxy-pyrimidin-2-yl-diazenyl)-piperzin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3- carboxylic acid and their dione derivatives were synthesized in moderate yield and characterized by IR, ^{1}H NMR spectra and elemental analysis. The compounds were evaluated for their in-vitro antibacterial activity against some Gram-positive and Gram-negative bacteria using conventional agar-dilution method.

Result and Discussion: The antibacterial data's of the newly synthesized compounds indicate that some of them show better antibacterial activity than compared to their reference drug Ciprofloxacin.

Conclusion: Ten (6a-j) new biologically active diketones were synthesized for the first time. Synthesized compounds exihibited good antibacterial activity against the tested bacteria.

Keywords: Dimethyl-pyrimidine, Dimethoxy-pyrimidine, Ciprofloxacin, Diketones.

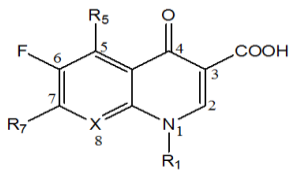
INTRODUCTION

Quinolone antibacterial are compounds of profound interest because of their broad antibacterial spectrum both to Gram-positive and Gram-negative and their in vitro chemotherapeutic efficacy[1]. Many quinolone antibacterial agents have been introduced into clinical use and significant improvements in antibacterial spectrum and activity have been achieved[2-4]. The most intensive structural variation has been carried out at the 7-position, partially due to the ease of their introduction through a nucleophilic aromatic-substitution reaction on the corresponding halide[5]. Piperazine, aminopyrrolidine and their substituted derivatives have been the most successfully employed side chains, as evidenced by the compounds currently on the market[5]. Originally, the newer fluoroquinolones arose with the development of 7-piperazinyl quinolones, such as norfloxacin 1 and ciprofloxacin 2, (**Fig. 1**), which combined structural features of flumequine (C-6 fluorine atom) and pipemidic acid (C-7 piperazine side chain)[6-8].

According to the inhibition mechanisms of the quinolones, proposed by Shen et al. [9-11], the site near the C-7 substituent is regarded as drug–enzyme interaction domain. The piperazine moiety of 7-piperazinyl quinolones possesses enough structural flexibility to allow product optimization.

In addition, the C-7 substituent affects with the target, and both the activity spectrum and kinetic profile can be controlled at C-7[12].

In continuation to an ongoing research program [13] to find potent and broad-spectrum antibacterial agents that display strong Gram-positive activity, in this paper we have focused our attention on modification of the C-7 basic group and C-3 acidic group of the quinolone [14-15].



Norfloxacin (1) R_1 = ethyl, R_5 = H, R_7 = piperazin-1-yl, X = CH
Ciprofloxacin (2) R_1 = cyclopropoyl, R_5 = H, R_7 = piperazin-1-yl, X =CH

Fig. 1:

MATERIALS AND METHODS

Microanalysis for C, H and N was performed using Perkin-Elmer analyzer 2400. Infrared (IR) spectra were recorded using KBr disk on a Nicolet-Megna FT-IR spectrometer. Melting points were determined using open capillary tube method and are uncorrected. ^{1}H NMR spectra were recorded at model DRX-300 at 300.13 MHz, using TMS as an internal standard. Purity of the compounds were tested by pre coated Silica Gel 60 F254 TLC plates from E. Merck.

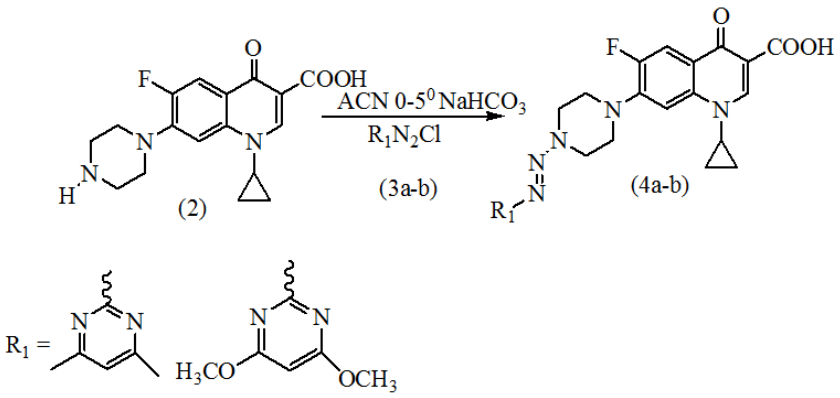
Experimental procedure

Synthesis of 1-cyclopropyle-7-[4-(2,6-dimethyl-pyrimidin-2-yl-diazenyl)-piperzin-1-yl] 6-fluoro -4-oxo-1,4- dihydro-quinoline-3-carboxylic acid (4a)

A mixture of ciprofloxacin (**2**) (1.65 g, 5.0 mmol) and sodium bicarbonate (1.0 g, excess) in acetonitrile (10ml) was stirred at 50°C for 2 hrs. Reaction mixture was cooled to 0°C and diazonium chloride salt of 4,6-dimethylpyrimidine-2-ylamine (5.0 mmol) was added. The mixture was stirred at 0-5 °C for 5 hrs. Volatiles were removed under reduced pressure and the residue was partitioned between chloroform/water. The organic layer was separated, washed with water, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography, recrystallised by 95% ethanol and obtained light yellow crystal in 48% yield. m.p.174°C, IR (KBr): 3510, 3100, 2942, 2830, 1710, 1625, 1595, 1252, 1039 cm^{-1}. ^{1}H NMR (300 MHz , DMSO-D6,) : δ= 1.73 (m, 4H, CH_2-CH_2), 2.15 (s, 6H, CH_3), 3.5-3.8 (m, 9H, piperzine ring, CH-cyclopropyle), 5.93 (s, 1H, CH), 7.03 (d, 1H, C_8-H), 7.2 (d, 1H, C_5-H), 7.5 (s, 1H, C_2-H), 15.07 (s, 1H, COOH) Anal. calcd. (Molecular formula) $C_{23}H_{24}FN_7O_3$: C, 59.35; H, 5.20; N, 21.06; found C, 59.33; H, 5.18; N,21.00.

Synthesis of 1-cyclopropyle-7-[4-(2,6-dimethoxy-pyrimidin-2-yl-diazenyl)-piperzin-1-yl] 6-fluoro -4-oxo-1,4- dihydro-quinoline-3-carboxylic acid (4b)

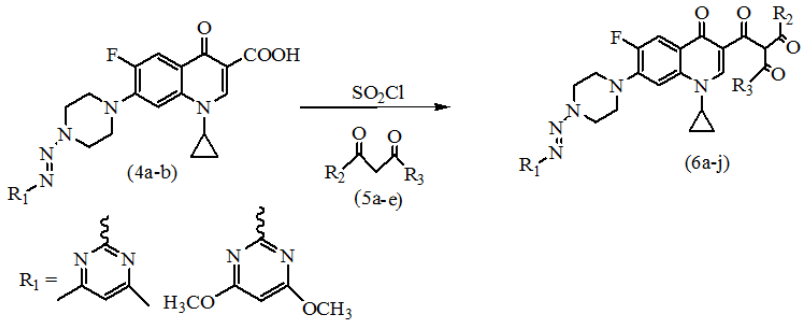
This was synthesized by the same procedure as 4a and obtained yellowish white crystal in 52% yield**.** m.p.183°C, IR (KBr): 3515, 3110, 2945, 2832, 1705, 1615, 1598, 1255, 1040 cm^{-1}. ^{1}H NMR (300 MHz , DMSO-D_6) :δ = 1.74 (m, 4H, CH_2-CH_2), 3.4 (s, 6H, CH_3), 3.6-3.8 (m, 9H, piperzine ring, CH-cyclopropyle), 5.95 (s, 1H, CH), 7.02 (d, 1H, C_8-H), 7.3 (d, 1H, C_5-H), 7.5 (s, 1H, C_2-H), 15.09 (s, 1H, COOH) Anal. calcd. (Molecular formula) $C_{23}H_{24}FN_7O_5$: C, 55.53; H, 4.86; N, 19.71; found C, 55.50; H, 4.85; N, 19.70.



Scheme 1

General method of preparation of 1-cyclopropyle-7-[4-(2,6-dimethyl-pyrimidin-2-yl- diazenyl)-piperzin-1-yl] 6-fluoro -4-oxo-1,4- dihydro-quinoline-3-carboxylic acid derivatives 6a-e

A solution of (**4a**) in $SOCl_2$ was refluxed for 10 hrs. The solvent was removed in vacuo to obtain acid chloride derivative of (**4a**) as dark foam. Now sodium salt of β-diketone (prepared by using NaOMe and β-diketone (**5a-e**) in dry methanol) was added and stirred at room temperature for 4 hrs. The solvent was removed and the residue was dissolved in 20 ml 95% ethanol. After concentration of the reaction mixture under reduced pressure, the residue was recrystallised from 95% ethanol to give (**6a-e**).



5a : $R_2 = R_3$ =Me
5b : R_2 = Me, R_3 = Ph
5c : $R_2 = R_3$ = Ph
5d : R_2 = Me, R_3 = OEt
5e : $R_2 = R_3$ = OEt

Scheme 2

3-{-1-cyclopropyle-7-[4-(2,6-dimethyl-pyrimidin-2-yl-diazenyl)-piperzin-1-yl] 6-fluoro -4-oxo-1,4- dihydro-quinoline-3-carbonyl}-pentane-2,4-dione (6a)

Compound 6a was obtained as yellowish red crystals in 47% yield. m.p.165°C, IR (KBr): 3100, 2950, 2838, 1715, 1620, 1589, 1250, 1039 cm^{-1}. ^{1}H NMR (300 MHz , DMSO-D_6) : δ = 1.75 (m, 4H, CH_2-CH_2), 2.09 (s, 6H, $COCH_3$), 2.18 (s, 6H, CH_3), 3.5-3.7 (m, 9H, piperzine ring, CH-cyclopropyle), 4.2 (s, 1H,CH-$COCH_3$), 6.01 (s,1H, CH), 7.04 (d, 1H, C_8-H), 7.3 (d, 1H, C_5-H), 7.48 (s, 1H, C_2-H). Anal. calcd. (Molecular formula) $C_{28}H_{30}FN_7O_4$: C, 61.42; H, 5.52; N, 17.91; found C, 61.40; H, 5.50; N, 17.90.

2-Benzoyl-1-{1-cyclopropyl-7-[4-(4,6-dimethyl-pyrimidin-2-yl-diazenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinolin-3-yl}-butane-1,3-dione (6b)

Compound 6b was obtained as yellowish crystals in 45% yield. m.p. 160°C, IR (KBr) 3090, 2970, 2840, 1718, 1619, 1591, 1251, 1037 cm^{-1}. ^{1}H NMR (300 MHz , DMSO-D_6) : δ = 1.73 (m, 4H, CH_2-CH_2), 2.08 (s, 3H, $COCH_3$), 2.18 (s, 6H, CH_3), 3.6-3.7 (m, 9H, piperzine ring, CH-cyclopropyle), 4.4 (s, 1H, $CHCOCH_3$), 6.3 (s, 1H, CH), 7.04 (d, 1H, C_8-H), 7.3 (d, 1H, C_5-H), 7.48 (s, 1H, C_2-H), 7.6-7.7 (m,5H, C_6H_5) Anal. calcd. (Molecular formula) $C_{33}H_{32}FN_7O_4$: C, 65.01; H, 5.29; N, 16.08; found: C, 65.00; H, 5.25; N, 16.05.

2-Benzoyl-1- {1-cyclopropyl-7- [4-(4,6-dimethyl-pyrimidin-2-yl-diazenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinolin-3-yl}-3-phenyl-propane-1,3-dione (6c)

Compound 6c was obtained as light reddish crystals in 40% yield. m.p. 163°C, IR (KBr): 3095, 2976, 2835, 1720,1615, 1589, 1259, 1036 cm^{-1}. ^{1}H NMR (300 MHz , DMSO-D_6) : δ = 1.75 (m, 4H, CH_2-CH_2), 2.20 (s, 6H, CH_3), 3.5-3.7 (m, 9H, piperzine ring, CH-cyclopropyle), 5.30 (s, 1H, CH-CO), 6.8 (s, 1H, CH) 7.05 (d, 1H, C_8-H), 7.25(d, 1H, C_5-H), 7.49 (s, 1H, C_2-H), 7.6-7.7 (m, 10H, C_6H_5). Anal. calcd. (Molecular formula) $C_{38}H_{34}FN_7O_4$: C, 67.95; H, 5.10; N, 14.60; found C, 67.93; H,5.12; N, 14.55.

2-{1-Cyclopropyl-7-[4-(4,6-dimethyl-pyrimidin-2-yl-diazenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carbonyl}-3-oxo-butyric acid ethyl ester (6d)

Compound 6d was obtained as reddish brown crystals in 56% yield. m.p. 170°C, IR (KBr) 3100, 2973, 2836, 1721, 1619, 1586, 1257, 1034 cm^{-1}. ^{1}H NMR (DMSO-D_6, 300 MHz): δ =1.30 (t, 3H, CH_2-CH_3), 1.68 (m, 4H, CH_2-CH_2), 2.10 (s, 3H, $COCH_3$), 2.35 (s, 6H, CH_3), 3.6-3.8 (m, 9H, piperzine ring, CH-cyclopropyle), 4.2 (q, 2H, CH_2-CH_3), 5.35 (s, 1H, CH-CO), 6.9 (s, 1H, CH), 7.03 (d, 1H, C_8-H), 7.2 (d, 1H, C_5-H), 7.46 (s, 1H, C_2-H), Anal. calcd. (Molecular formula) $C_{29}H_{32}FN_7O_5$: C, 60.30; H, 5.58; N, 16.97; found C, 60.28; H, 5.55; N, 16.95.

2-{1-Cyclopropyl-7-[4-(4,6-dimethyl-pyrimidin-2-yl-diazenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carbonyl}-malonic acid diethyl ester (6e)

Compound 6e was obtained as light pink crystals in 60% yield. m.p. 166°C, IR (KBr) 3098, 2980, 2840, 1718, 1617, 1587, 1252, 1030 cm^{-1}. ^1H NMR (300 MHz , DMSO-D_6) : δ = 1.31(t, 6H, CH_2-CH_3), 1.70 (m, 4H, CH_2-CH_2), 2.33 (s, 6H, CH_3), 3.5-3.8 (m, 9H, piperzine ring, CH cyclopropyle), 4.4 (q, 4H, CH_2-CH_3), 5.25 (s, 1H, CH-CO) 6.8 (s, 1H, CH), 7.05 (d, 1H, C_8-H),7.22 (d, 1H, C_5-H), 7.44 (s, 1H, C_2-H), Anal. calcd. (Molecular formula) $C_{30}H_{34}FN_7O_6$: C, 59.30;H, 5.64; N, 16.14; found C, 59.30; H, 5.62; N, 16.12.

General method of preparation of 1-cyclopropyle-7-[4-(2,6-dimethoxy-pyrimidin-2-yldiazenyl)-piperzin-1-yl] 6-fluoro -4-oxo-1,4- dihydro-quinoline-3-carboxylic acid derivatives (6f-j)

A solution of (**4b**) in SOCl2 was refluxed for 10 hrs. The solvent was removed in vacuo to obtain acid chloride derivative of (**4b**) as dark foam. Now sodium salt of β-diketone (prepared by using NaOMe and β-diketone (**5a-e**) in dry methanol) was added and stirred at room temperature for 4 hrs. The solvent was removed and the residue was dissolved in 20 ml 95% ethanol. After concentration of the reaction mixture under reduced pressure, the residue was recrystallised from 95% ethanol to give (**6f-j**).

3-{1-Cyclopropyl-7-[4-(4,6-dimethoxy-pyrimidin-2-yl-diazenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carbonyl}-pentane-2,4-dione (6f)

Compound 5f was obtained as reddish crystals in 52% yield. m.p. 171°C, IR (KBr) 3090, 2945, 2842, 1718, 1620, 1592, 1248, 1041 cm^{-1}. ^1H NMR (300 MHz , DMSO-D_6): δ=1.69 (m, 4H, CH_2-CH_2), 2.2 (s, 6H, $COCH_3$),3.60 (s, 6H, OCH_3), 3.7-3.8 (m, 9H, piperzine ring, CH-cyclopropyle), 5.25 (s, 1H, CH-CO),6.01 (s, 1H, CH), 7.04 (d, 1H, C_8-H), 7.32 (d, 1H, C_5-H), 7.55(s, 1H, C_2-H), Anal. calcd. (Molecular formula) $C_{28}H_{30}FN_7O_6$: C, 58.02; H, 5.22; N, 16.92 found C, 58.00; H, 5.20; N, 16.90.

2-Benzoyl-1-{1-cyclopropyl-7-[4-(4,6-dimethoxy-pyrimidin-2-yl-diazenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinolin-3-yl}-butane-1,3-dione (6g)

Compound 6g was obtained as pink crystals in 53% yield. m.p. 162°C, IR (KBr) 3095, 2952, 2841, 1720, 1621, 1587, 1242, 1032 cm^{-1}. ^1H NMR (300 MHz , DMSO-D_6): δ=1.70 (m, 4H, CH_2-CH_2), 2.3 (s, 3H, $COCH_3$), 3.58 (s, 6H, OCH_3), 3.6-3.8 (m, 9H, piperzine ring, CH-cyclopropyle), 5.52 (s, 1H, CH-CO), 6.2 (s, 1H, CH), 7.02 (d, 1H, C_8-H), 7.35 (d, 1H, C_5-H), 7.65 (s, 1H, C_2-H), 7.8 (m, 5H, C_6H_5). Anal. calcd. (Molecular formula) $C_{33}H_{32}FN_7O_6$ C, 61.77; H, 5.03; N, 15.28; found C, 61.75; H, 5.00; N, 15.25.

2-Benzoyl-1-{1-cyclopropyl-7-[4-(4,6-dimethoxy-pyrimidin-2-yl-diazenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinolin-3-yl}-3-phenyl-propane-1,3-dione (6h)

Compound 6h was obtained as yellowish crystals in 53% yield. m.p. 177°C, IR (KBr) 3093, 2950, 2844, 1719, 1616, 1585, 1245, 1035 cm^{-1}. ^1H NMR (300 MHz , DMSO-D_6) δ:1.71 (m, 4H, CH_2-CH_2), 3.60 (s, 6H, OCH_3), 3.65-3.8 (m, 9H, piperzine ring, CH-cyclopropyle), 6.1 (s, 1H, CH-CO), 6.3 (s,1H, CH), 7.01 (d, 1H, C_8-H), 7.45 (d, 1H, C_5-H), 7.70 (s, 1H, C_2-H), 7.8-7.9 (m, 10H, C_6H_5). Anal. calcd. (Molecular formula) $C_{38}H_{34}FN_7O_6$: C, 64.86; H, 4.87; N, 13.93; found C, 64.85; H,4.85; N, 13.90.

2-{1-Cyclopropyl-7-[4-(4,6-dimethoxy-pyrimidin-2-yl-diazenyl)-piperazin-1-yl]-6 fluoro-4-oxo-1,4-dihydro-quinoline-3-carbonyl}-3-oxo-butyric acid ethyl ester (6i)

Compound 6i was obtained as yellow red crystals in 49% yield. m.p. 174°C, IR (KBr) 3095, 2945, 2840, 1722, 1619, 1586, 1251, 1033 cm^{-1}. ^1H NMR (300 MHz , DMSO-D_6) : δ = 1.32(t, 3H, CH_2-CH_3), 1.73 (m, 4H, CH_2-CH_2), 2.10 (s, 3H, $COCH_3$) 3.63 (s, 6H, OCH_3), 3.7-3.85 (m, 9H, piperzine ring, CH-cyclopropyle), 4.2 (q, 2H, CH_2-CH_3), 6.1 (s, 1H, CH-CO), 6.3 (s, 1H, CH), 7.01 (d, 1H, C_8-H), 7.45 (d, 1H, C_5-H), 7.70 (s, 1H, C_2-H), Anal. calcd. (Molecular formula) $C_{29}H_{32}FN_7O_7$: C,57.14; H, 5.29; N, 16.08; found C, 57.10; H, 5.25; N, 16.00.

2-{1-Cyclopropyl-7-[4-(4,6-dimethoxy-pyrimidin-2-yl-diazenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carbonyl}-malonic acid diethyl ester (6j)

Compound 6j was obtained as red crystals in 53% yield. m.p. 175°C, IR (KBr) 3090, 2943, 2842, 1721, 1618, 1585, 1252, 1031 cm^{-1}. ^1H NMR (300 MHz , DMSO-D_6) δ:1.33 (t, 6H, CH_2-CH_3), 1.70 (m, 4H, CH_2-CH_2), 3.58 (s, 6H, OCH_3), 3.7-3.85 (m, 9H, piperzine ring, CHcyclopropyle), 4.2 (q, 4H, CH_2-CH_3), 6.2 (s, 1H, CH-CO), 6.3 (s, 1H, CH), 7.03 (d, 1H, C_8-H), 7.40 (d, 1H, C_5-H), 7.68 (s, 1H, C_2-H), Anal. calcd. (Molecular formula) $C_{30}H_{34}FN_7O_8$: C, 56.33;H, 5.36; N, 15.33; found C, 56.30; H, 5.35; N, 15.30.

RESULT AND DISCUSSION

A series of 1-cyclopropyl-7-[4-(2,6-dimethyl-pyrimidin-2-yl-diazenyl)-piperzin-1-yl]-6-fluoro-4- oxo-1,4-dihydro-quinoline-3-carboxylic acid (4a) and 1-cyclopropyl-7-[4-(2,6-dimethoxypyrimidin-2-yl-diazenyl)-piperzin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid(4b) and their dione derivatives were synthesized in moderate yields using the synthetic route outlined in **Figure 1**. Structures of the synthesized compounds were established on the basis of IR, ^1H NMR spectral data's and elemental analysis. Ciprofloxacin was treated with diazoniumchloride derivative of 4,6-dimethyl-pyrimidine-2-ylamine / 4,6-dimethoxy-pyrimidine-2-ylamine in presence of base to give piperazine substituted ciprofloxacin derivatives (**4a-b**). The acid part of these derivatives was converted to acid chloride using thionyl chloride, which further condensed with various diketone (**5a-e**) to obtain (**6a-j**). Table 1 summarizes the in vitro antibacterial data of the newly synthesized compound (**6a-j)** against three Gram-positive bacteria (Staphylococcus aureus ATCC 6538p, Staphylococcus epidermidis ATCC 12228 and Bacillus subtilis PTCC 1023) and three Gram-negative organisms.(Escherichia coli ATCC 8739, Klebsiella pneumoniae ATCC 10031 and Enterobacter cloacae PTCC 1003). The data of ciprofloxacin are included for comparison.

Activity

Compounds (6a-j) were evaluated for their antibacterial activity against Gram-positive (Staphylococcus aureus ATCC 6538p, Staphylococcus epidermidis ATCC 12228 and Bacillus subtilis PTCC 1023) and Gram-negative (Escherichia coli ATCC 8739, Klebsiella pneumonia ATCC 10031 and Enterobacter cloacae PTCC 1003) bacteria using conventional agar-dilution method [16]. The minimum inhibitory concentration (MIC) values were determined in comparison to ciprofloxacin as reference drugs.

Table 1: Antibacterial activity data in Minimum Inhibitory Concentration (MIC)

Compounds	Gram-positive			Gram-negative		
	S. aureus	S. epidermidis	B. sublitis	K. pneumonia	E. coli	E. cloace
6a	0.25	0.25	0.015	2	0.25	0.5
6b	1.0	0.5	0.125	8	16	8
6c	2.0	0.5	0.5	>8	32	4
6d	0.5	0.125	0.03	4	4	1
6e	0.5	0.125	0.015	1	2	4
6f	0.125	0.5	0.5	2	1.0	8
6g	2.0	1.0	0.125	4	2	2
6h	2.0	0.5	0.5	>8	>32	>32
6i	0.25	1.0	0.5	8	8	16
6j	0.125	0.125	0.03	2	2	4
Ciprofloxacin	0.5	0.25	0.015	0.03	0.125	0.06

As noted in Table 1, the MIC values of the tested compounds indicated that some compounds exhibited high activity against Gram-positive bacteria and mild activity against Gram-negative bacteria.

CONCLUSION

In conclusion, ten (6a-j) new biologically active diketones were synthesized for the first time in this study. The structures of novel compounds were determined by FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopic techniques and analytical methods.

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