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# SYNTHESIS AND *IN-VITRO* ANTIBACTERIAL ACTIVITY OF SOME NOVEL N-NICOTINOYL-1-ETHYL-6-FLUORO-1,4-DIHYDRO-7-PIPERAZIN-1-YL-4-OXOQUINOLINE-3-CARBOXYLATES

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**Abstract**: A series of N-nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxylates has been synthesized and evaluated for antibacterial activity. Norfloxacin was reacted with thionyl chloride, to yield norfloxacin acid chloride which was used immediately in next step by reacting with respective alcohols to furnish the corresponding esters i.e. 1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxylates (**III**). Nicotinoyl chloride (**IV**) was prepared by adopting reported procedures and was reacted appropriately with previously synthesized esters (**III**) to yield the title compounds (**V**). The structures of synthesized compounds were established on the basis of analytical and spectral studies. All the synthesized compounds were evaluated for antibacterial activity against four different strains of bacteria. Compounds exhibited moderate to significant minimum inhibitory concentration (MIC) values ranging from 0.19 to 0.37 against *E. coli*, 0.17 to 0.37 against *S. dysentry*. The MIC values against Gram positive bacteria were slightly more that Gram negative ones and ranged from 1.9 to 3.5 against *S. aureus* and 2.0 to 3.1 against *B. subtilis*.

**Keywords:** fluoroquinolones, norfloxacin, antibacterial activity

Fluoroquinolones are broad spectrum antibiotics widely used for the treatment of numerous diseases (1). Norfloxacin is a fluoroquinolone and it is chemically named as 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl)-quinoline-3-carboxylic acid. It is the first choice drug for the treatment of diseases caused by *Campylobacter* spp., *E. coli*, *Salmonella enteridis*, *Shigella* spp. and *V. colera*. It is used for the treatment of gonorrhea as well as eye and urinary tract infections (2, 3). The mechanism of action of norfloxacin involves inhibition of bacterial DNA gyrase which is essential for DNA replication (4, 5). Since the development of norfloxacin, fluoroquinolones have gained prominence in the therapy of bacterial infections owing to their broad antibacterial spectrum and excellent bioavailability. However, the emergence of quinolone resistance has been steadily rising. This emergence of resistance has been associated with the use of quinolones both in humans and animals (6-8).

Despite of many significant developments in the antimicrobial therapy, many problems remain to be solved for most of the antimicrobial drugs available. Hence, discovery of novel antimicrobial agents with better pharmacological profile is still highly desirable (9). The development of new antibiotics can be achieved from derivatives of known antimicrobial agents or by identification of novel agents active against previously unexploited targets (10). Without doubt, modification at C-3 position results in loss of activity, however, incorporation of an aldehyde group as well as certain labile carboxylate esters have afforded derivatives which display antibacterial activity *in vivo* (11). Moreover, substitution by bulky groups at position 7 of piperazinyl quinolone molecule is permitted for good activity (12). Also, 1,3-diketones have been reported to be of immense importance in medicinal chemistry (13). Therefore, it was felt worthwhile to synthesize some new derivatives of norfloxacin and evaluate them for their antibacterial potential.

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## EXPERIMENTAL

The entire chemicals were supplied by E. Merck (Germany) and S.D. Fine Chemicals (India).The melting points of synthesized compounds were determined in open capillary tubes using Veego VMP-1 melting point apparatus, expressed in $^{o}$C and are uncorrected. The IR spectra of compounds were recorded on Perkin Elmer Infra Red Spectrophotometer in KBr discs and absorption bands are expressed in $cm^{-1}$. $^{1}$H NMR spectra were recorded on Brucker Avance 700 MHz NMR Spectrometer (chemical shifts in δ ppm) using TMS as internal standard.

### General method

The title compounds were prepared in the following steps:

Synthesis of norfloxacin esters (**IIIa-IIIj**)

Norfloxacin (I) (0.01 mol) was heated under reflux with thionyl chloride (10 mL) for 6 h, yielding norfloxacin acid chloride (**II**). Excess of thionyl chloride was distilled off under vacuum. Pale yellow crystals of acid chloride (**II**) thus obtained were used immediately in next step by reacting under reflux with respective alcohols for 4 to 6 h to yield 1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxylates, the corresponding esters (**III**). After completion of the reaction (monitored by TLC), an excess of solvent was removed by distillation and the resultant viscous mass was poured into ice water (100 mL) with vigorous stirring and left overnight for complete precipitation. The resultant solid product was neutralized with sodium bicarbonate, filtered, washed with cold water, dried and recrystallized.

Synthesis of nicotinoyl chloride (**IV**)

Nicotinic acid (0.01 mol) was heated under reflux with thionyl chloride (10 mL) for 6 h. The solvent was evaporated under reduced pressure. Needle shaped, pale yellow crystals were formed and the product was used immediately for the next step.

Synthesis of title compounds (**Va-Vj**)

Norfloxacin esters (0.01 mol) (**III**) were dissolved in anhydrous pyridine (20 mL). The resulting suspension was reacted with nicotinoyl chloride (**IV**) in anhydrous pyridine by adding it drop by drop at 0$^{o}$C. The mixture was first, stirred at room temperature for 6 h on magnetic stirrer followed by heating under reflux for 3 h. Afterwards, the reaction mixture was poured in 250 mL of distilled ice cold water and kept overnight. The precipitates of N-nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxylates (**Va-Vj**) thus formed, were filtered off. Subsequent washing with cold water was done in order to remove the pyridine from the product. The product was collected, dried in vacuum desiccator and was recrystallized using appropriate solvents.

N-Nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxy methyl ester **(Va)**

IR (KBr, $cm^{-1}$): 3150, 1645, 1710, 1735, 1550, 1220, 1158; $^{1}$H-NMR (300 MHz, $CDCl_3$, δ, ppm): 9.17 (s, 1H, pyridine), 8.88 (d, 1H, pyridine), 8.12 (d, 1H, pyridine), 7.69 (s, 1H, pyridinone), 7.40 (t, 1H, pyridine), 7.11 (s, 1H, aromatic), 5.69 (s, 1H, aromatic), 4.59 (q, 2H, $CH_2$, ethyl), 3.77 (s, 3H, $CH_3$), 3.48 (t, 4H, 2 $CH_2$, piperazine), 3.19 (t, 4H, 2 $CH_2$, piperazine), 1.40 (t, 3H, $CH_3$, ethyl).

N-Nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxy ethyl ester **(Vb)**

IR (KBr, $cm^{-1}$): 3125, 1656, 1710, 1738, 1545, 1236, 1152; $^{1}$H-NMR (300 MHz, $CDCl_3$, δ, ppm): 9.11 (s, 1H, pyridine), 8.78 (d, 1H, pyridine), 8.17 (d, 1H, pyridine), 7.63 (s, 1H, pyridinone), 7.42 (t, 1H- pyridine), 7.10 (s, 1H aromatic), 5.60 (s, 1H, aromatic), 4.65 (q, 2H, $CH_2$ ethyl), 4.19 (q, 2H, $CH_2$ ethyl), 3.75 (s, 3H, $CH_3$), 3.45 (t, 4H, 2 $CH_2$, piperazine), 3.21 (t, 4H, 2 $CH_2$, piperazine), 1.40 (t, 3H, $CH_3$ ethyl).

N-Nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxy-n-propyl ester **(Vc)**

IR (KBr, $cm^{-1}$): 3146, 1655, 1716, 1729, 1545, 1215, 1133. $^{1}$H-NMR (300 MHz, $CDCl_3$, δ, ppm): 9.45 (s, 1H, pyridine), 8.34 (d, 1H, pyridine), 8.02 (d, 1H, pyridine), 7.63 (s, 1H, pyridinone), 7.39 (t, 1H, pyridine), 7.01 (s, 1H, aromatic) 5.67 (s, 1H, aromatic), 4.40 (t, 2H, $CH_2$), 4.25 (q, 2H, $CH_2$, ethyl), 3.61 (t, 4H, 2 $CH_2$, piperazine): 3.19 (t, 4H, 2 $CH_2$, piperazine); 1.57 (m, 2H, $CH_2$); 1.51 (t, 3H, $CH_3$ ethyl); 0.96 (t, 3H, $CH_3$).

N-Nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxy isopropyl ester **(Vd)**

IR (KBr, $cm^{-1}$): 3135, 1665, 1708, 1545, 1212, 1150. $^{1}$H-NMR (300 MHz, $CDCl_3$, δ, ppm): 9.39 (s, 1H, pyridine), 8.60 (d, 1H, pyridine), 8.13 (d, 1H, pyridine), 7.58 (s, 1H, pyridinone), 7.41 (t, 1H, pyridine), 7.12 (s, 1H, aromatic), 5.86 (s, 1H, aromatic), 4.40 (q, 2H, $CH_2$, ethyl), 4.21 (m, 1H, CH), 3.77 (t, 4H, 2 $CH_2$, piperazine), 3.64 (t, 4H, 2 $CH_2$, piperazine), 1.56 (t, 3H, $CH_3$, ethyl), 1.50 (d, 6H, 2 $CH_3$).

N-Nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxy isobutyl ester **(Ve)**

IR (KBr, $cm^{-1}$): 3144, 1666, 1712, 1735, 1555, 1225, 1155.

N-Nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxy *tert* butyl ester **(Vf)**

IR (KBr, $cm^{-1}$): 3142, 1663, 1732, 1551, 1229. $^1$H-NMR (300 MHz, $CDCl_3$, δ, ppm): 9.22 (s, 1H, pyridine) 8.72 (d, 1H, pyridine), 8.36 (d, 1H, pyridine) 7.87 (s, 1H, pyridinone), 7.69 (t, 1H, pyridine), 7.20 (s, 1H, aromatic), 5.63 (s, 1H, aromatic), 4.25 (q, 2H, $CH_2$, ethyl); 3.43 (t, 4H, 2 $CH_2$-piperazine): 3.23 (t, 4H, 2 $CH_2$-piperazine); 1.51 (t, 3H, $CH_3$ ethyl); 1.40 (s, 9H, 3 $CH_3$)

N-Nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxy pentyl ester **(Vg)**

IR (KBr, $cm^{-1}$): 3160, 1655, 1715, 1742, 1550, 1235, 1129. $^1$H-NMR (300 MHz, $CDCl_3$, δ, ppm): 9.45 (s, 1H, pyridine), 8.34 (d, 1H, pyridine), 8.02 (d, 1H, pyridine), 7.63 (s, 1H, pyridinone), 7.39 (t, 1H, pyridine), 7.01 (s, 1H, aromatic), 5.67 (s, 1H, aromatic), 4.40 (t, 2H, $CH_2$), 4.25 (q, 2H, $CH_2$, ethyl), 3.61 (t, 4H, 2 $CH_2$, piperazine), 3.19 (t, 4H, 2 $CH_2$, piperazine), 1.57 (m, 2H, $CH_2$), 1.51 (t, 3H, $CH_3$, ethyl), 1.33 (m, 2H, $CH_2$), 1.29 (m, 2H, $CH_2$); 0.96 (t, 3H, $CH_3$).

N-Nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxy hexyl ester **(Vh)**

IR (KBr, $cm^{-1}$): 3135, 1655, 1719, 1737, 1520, 1228, 1136. $^1$H-NMR (300 MHz, $CDCl_3$, δ, ppm): 9.11 (s, 1H, pyridine), 8.39 (d, 1H, pyridine), 8.20 (d, 1H, pyridine), 7.81 (s, 1H, pyridinone), 7.43 (t, 1H, pyridine), 7.21 (s, 1H, aromatic), 5.66 (s, 1H, aromatic), 4.30 (q, 2H, $CH_2$, ethyl); 4.01 (t, 2H, $CH_2$); 3.61 (t, 4H, 2 $CH_2$, piperazine), 3.19 (t, 4H, 2 $CH_2$, piperazine), 1.68 (m, 2H, $CH_2$), 1.48 (m, 2H, $CH_2$), 1.40 (t, 3H, $CH_3$, ethyl), 1.30 (m, 4H, 2 $CH_2$), 0.91 (t, 3H, $CH_3$).

N-Nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxy heptyl ester **(Vi)**

IR (KBr, $cm^{-1}$): 3155, 1670, 1720, 1710, 1545, 1234, 1145. $^1$H-NMR (300 MHz, $CDCl_3$, δ, ppm): 9.11 (s, 1H, pyridine), 8.39 (d, 1H, pyridine); 8.20 (d, 1H, pyridine), 7.81 (s, 1H, pyridinone), 7.43 (t, 1H, pyridine), 7.21 (s, 1H, aromatic), 5.66 (s, 1H, aromatic), 4.30 (q, 2H, $CH_2$, ethyl), 4.01 (t, 2H, $CH_2$), 3.61 (t, 4H, 2 $CH_2$, piperazine), 3.19 (t, 4H, 2 $CH_2$, piperazine), 1.68 (m, 2H, $CH_2$); 1.48 (m, 2H, $CH_2$); 1.40 (t, 3H, $CH_3$ ethyl), 1.30 (m, 6H, 3 $CH_2$), 0.91 (t, 3H, $CH_3$).

N-Nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxy octyl ester **(Vj)**

IR (KBr, $cm^{-1}$): 3166, 1667, 1709, 1720, 1535, 1263, 1125. $^1$H-NMR (300 MHz, $CDCl_3$, δ, ppm): 9.21 (s, 1H, pyridine), 8.67 (d, 1H, pyridine), 8.12 (d, 1H, pyridine), 7.79 (s, 1H, pyridinone), 7.43 (t, 1H, pyridine), 7.01 (s, 1H, aromatic), 5.83 (s, 1H, aromatic), 4.30 (q, 2H, ethyl), 4.26 (t, 2H, $CH_2$), 3.55 (t, 4H, 2 $CH_2$, piperazine), 3.08 (t, 4H, 2 $CH_2$, piperazine), 1.72 (m. 2H, $CH_2$), 1.49 (m, 8H, 4 $CH_2$), 1.40 (t, 3H, $CH_3$ ethyl), 1.28 (m, 2H, $CH_2$), 0.88 (t, 3H, $CH_3$).

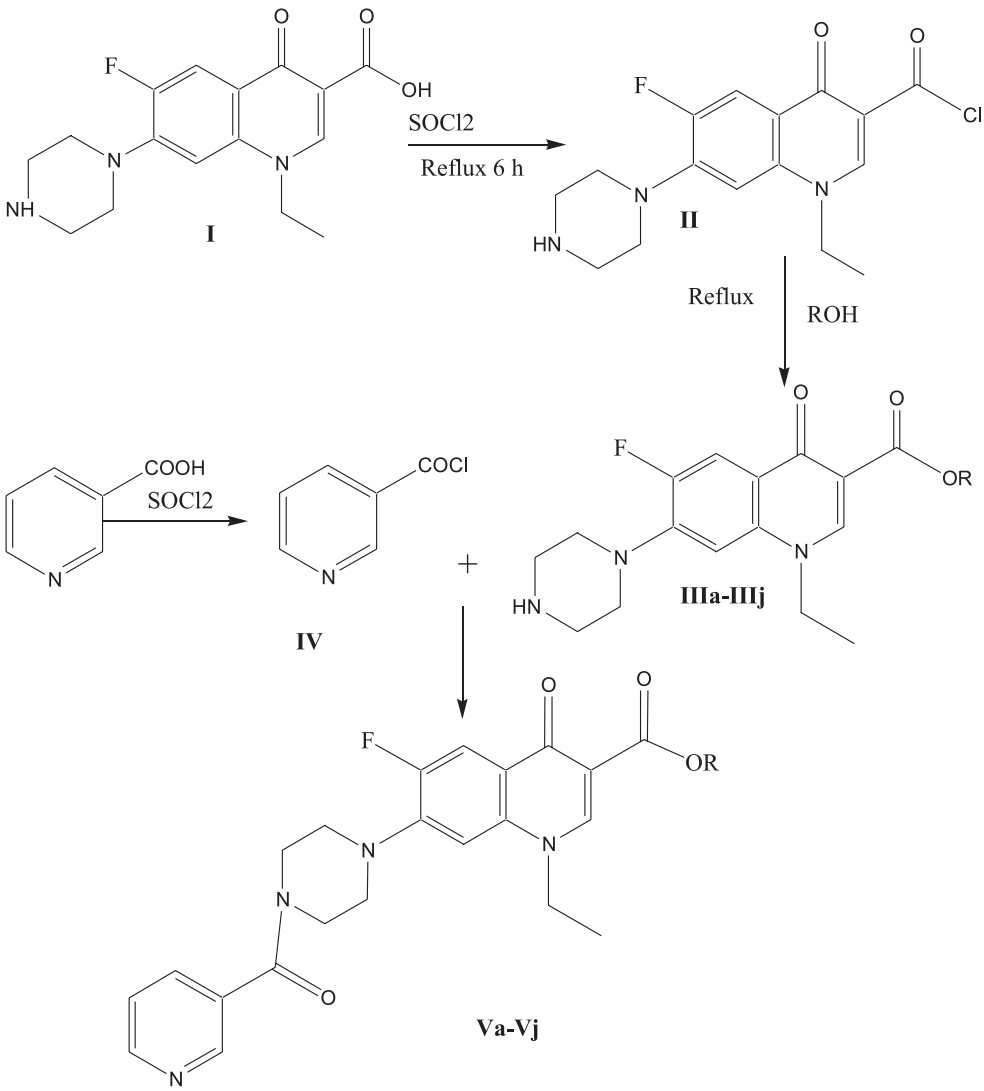
**Antibacterial screening**

All the compounds were screened for their antibacterial activity against two Gram-negative strains (*Escherichia coli* and *Staphylococcus dysentry*) and two Gram-positive strains (*Bacillus subtilis* and *Staphylococcus aureus*). Norfloxacin was used as a standard drug for antibacterial activity. The MIC values of the compounds tested in this study were determined according to the method of Goto et al by a serial dilution technique (14). The inoculum size was approximately $10^6$ colony-forming units (CFU/mL). The reference standard norfloxacin inhibited Gram-negative bacteria viz., *E. coli* and *S. dysentry* at a MIC of 0.1 µg/mL and 0.12 µg /mL, respectively, whereas against Gram positive bacteria viz., *S. aureus* and *B. subtilis* MIC was found to be 1.5 µg/mL and 1.4 µg/mL, respectively. All synthesized compounds exhibited moderate to significant antibacterial activities against all selected bacterial strains. Each experiment was done in triplicate and the average reading was taken.

## RESULTS AND DISCUSSION

**Chemistry**

N-susbstituted-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxylates (**Va-Vj**) described in this study are shown in Table 1 and the reaction sequence for their preparation is outlined in Scheme 1. First, norfloxacin esters, i.e. 1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxylates (**IIIa-IIIj**) were synthesized by reaction of norfloxacin acid chloride with respective alcohols. Reaction of norfloxacin with nicotinoyl chloride afforded the title compounds in 46-67% yield. Reactions were monitored by thin layer chromatography on pre-coated silica gel G plates using different solvent systems. The purity of synthesized compounds was ascertained by TLC, using iodine vapors as visualizing agent. Both analytical and spectral data (IR and $^1$H-NMR) of all the




Scheme 1. Synthesis of N-nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxymethyl esters.

synthesized compounds were in full agreement with proposed structures.

**Antibacterial activity**

The synthesized compounds (**Va**-**Vj**) were tested *in vitro* for their antibacterial activity against two Gram-negative strains and two Gram-positive strains by serial two-fold dilution technique. All the compounds exhibited moderate to significant activities. In general, the derivatives with smaller substituent groups were found to be more potent than the derivatives with larger substituent groups. Compound **Va** with methyl substitution was the most active against Gram negative bacteria whereas compound **Vc** with isopropyl substitution was the most active against Gram positive bacteria. The results of antibacterial screening are summarized in Table 2.

## CONCLUSION

Among the newly synthesized derivatives, N-nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxy methyl ester (**Va**) was found to be the most active against Gram negative bacteria while N-nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxy-n-propyl ester (**Vc**) was the most active

Table 1. Physical and analytical data of the synthesized compounds

| Comp. no. | R | m.p. (°C) | Yield (%) | Mol. formula | Mol. Wt. | C H N Analysis calculated (found) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | %C | %H | %N |
| **$V_a$** | Methyl | 155-157 | 57 | $C_{23}H_{23}FN_4O_4$ | 438 | 63.00 (62.88) | 5.29 (5.26) | 12.78 (12.76) |
| **$V_b$** | Ethyl | 165-167 | 49 | $C_{24}H_{25}FN_4O_4$ | 452 | 63.71 (63.73) | 5.57 (5.52) | 12.38 (12.34) |
| **$V_c$** | n-Propyl | 145-146 | 52 | $C_{25}H_{27}FN_4O_4$ | 466 | 64.37 (63.35) | 5.83 (5.85) | 12.01 (12.04) |
| **$V_d$** | Isopropyl | 168-170 | 48 | $C_{25}H_{27}FN_4O_4$ | 466 | 64.37 (63.36) | 5.83 (5.87) | 12.01 (12.06) |
| **$V_e$** | Isobutyl | 159-161 | 46 | $C_{26}H_{29}FN_4O_4$ | 480 | 64.99 (64.96) | 6.08 (6.05) | 11.66 (11.64) |
| **$V_f$** | *tert* butyl | 165-167 | 48 | $C_{26}H_{29}FN_4O_4$ | 480 | 64.99 (64.97) | 6.08 (6.07) | 11.66 (11.67) |
| **$V_g$** | Pentyl | 151-153 | 52 | $C_{27}H_{31}FN_4O_4$ | 494 | 65.57 (65.55) | 6.32 (6.31) | 11.33 (11.29) |
| **$V_h$** | Hexyl | 143-145 | 67 | $C_{28}H_{33}FN_4O_4$ | 508 | 66.12 (66.16) | 6.54 (6.51) | 11.02 (11.04) |
| **$V_i$** | Heptyl | 161-162 | 51 | $C_{29}H_{35}FN_4O_4$ | 522 | 66.65 (66.62) | 6.75 (6.71) | 10.72 (10.70) |
| **$V_j$** | Octyl | 155-157 | 49 | $C_{30}H_{37}FN_4O_4$ | 537 | 67.14 (67.16) | 6.95 (6.92) | 10.44 (10.41) |

Table 2. *In vitro* antibacterial activity of compounds $V_a$-$V_j$ (MIC µg /mL)

| Compound | Gram negative bacteria | | Gram positive bacteria | |
|---|---|---|---|---|
| | *E. coli* | *S. dysentry* | *S. aureus* | *B. subtilis* |
| **$V_a$** | 0.19 | 0.17 | 1.9 | 2.0 |
| **$V_b$** | 0.27 | 0.29 | 2.2 | 2.6 |
| **$V_c$** | o.26 | 0.23 | 1.9 | 2.1 |
| **$V_d$** | 0.29 | 0.28 | 2.9 | 3.1 |
| **$V_e$** | 0.31 | 0.19 | 2.7 | 2.7 |
| **$V_f$** | 0.22 | 0.20 | 3.1 | 2.8 |
| **$V_g$** | 0.29 | 0.26 | 3.2 | 2.1 |
| **$V_h$** | 0.33 | 0.29 | 3.5 | 2.4 |
| **$V_i$** | 0.32 | 0.37 | 2.6 | 2.1 |
| **$V_j$** | 0.37 | 0.33 | 2.8 | 2.9 |
| Norfloxacin (Standard drug) | 0.1 | 0.12 | 1.5 | 1.4 |

against Gram positive bacteria. Further studies are required to generate more information about structure activity relationship of these derivatives. In conclusion, a series of N-nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxy methyl esters has been synthesized and evaluated for antibacterial activity. The compounds exhibited moderate activities.

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