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SYNTHESIS AND EVALUATION OF ANTIMICROBIAL & ANTIFUNGAL ACTIVITY OF NOVEL 1-CYCLOPROPYL-6 -FLUORO-7-(SUBSTITUTED AZOLE AND FUSED AZOLE)-1, 4-DIHYDRO-8-METHOXY-4-OXOQUINOLINE-3-CARBOXAMIDE DERIVATIVES

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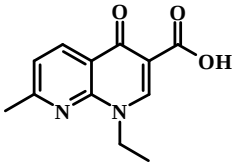
ABSTRACT

One pot synthesis of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxamide was carried out by reacting 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid with simple reagent and condition. Different novel derivatives of 7-substituted 1-cyclopropyl-6 -fluoro-1, 4-dihydro-8-methoxy-4-oxoquinoline-3-carboxamide were synthesized by substituting fluoro group at C-7 position with different azoles and fused azoles. These novel compounds were examined for their antibacterial and antifungal activities.

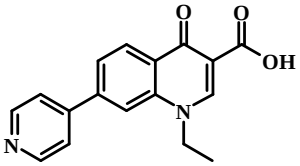
KEYWORDS: Quinolones, Nalidixic acid, Carbonyldi imidazole, Antimicrobial.

INTRODUCTION

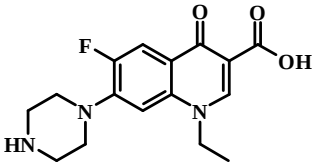
4-quinolones are synthetic anti-bacterial agents. Nalidixic acid [1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8 naphthyridine-3-carboxylic acid **(Ia)** was first quinolones drug introduced in 1962.[1][2]. It was observed that number of organisms developed resistance to it rapidly.[3] Different derivatives were synthesized to increase the activity against Gram-negative bacteria and Gram-positive bacteria but having similar drug activity as that of nalidixic acid.[4] It was observed that substitution at C-7 position with nitrogen containing heterocycles (aliphatic or aromatic amine) play a very important role in increasing antimicrobial activity such as 4-pyridyl group in Rosoxazine.[5] **(Ib)** etc.



Nalidaxic acid
Ia

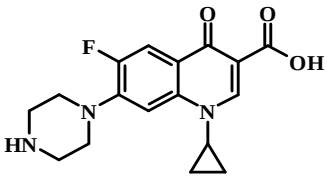


Rosoxacin
Ib

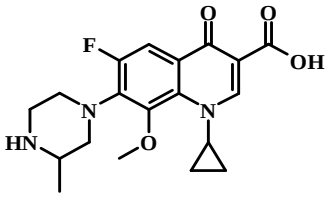


Norfloxacin
Ic

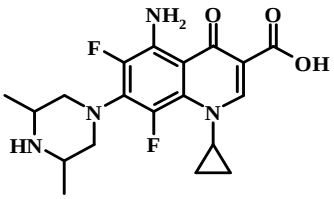
In 1980 first fluoroquinolone drug was introduced in market having fluoro group at C-6 position was Norfloxacine.[6] **(Ic)**. Then Ciprofloxacin.[7] **(II)**, Sparfloxacin **(IV)** and Trovafloxacin **(V)** were introduced which will changed the landscape of antibacterial chemotherapy, and were active against both Gram- negative and Gram-positive bacterial pathogens.



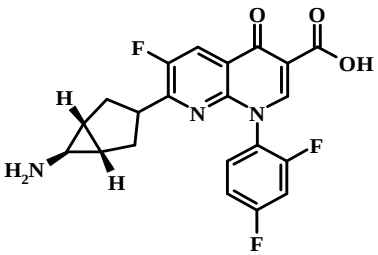
Ciprofloxacin
II



Gatifloxacin
III



Sparfloxacine
IV



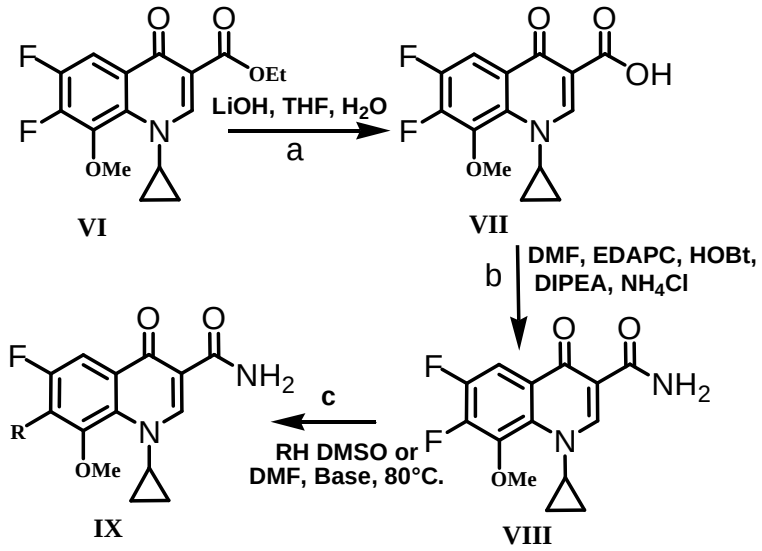
Trovafloxacin
V

Then Gatifloxacin [1-cyclopropyl-8-methoxy-7-(3-methyl-piperazin-1-yl)-6-fluoro-4oxo-1,4-dihydro-quinoline-3-carboxylic acid] **(III)**.[8] was synthetic broad-spectrum fourth-generation quinolone antibacterial agent and it has an inhibitory effect on the production of inflammatory cytokines by macrophages. It suppresses bacterial infection which induced inflammation.[9] 4-quinolones having five member heterocyclic substituent at C- 7 position such as thiophenes, isoxazole, pyrazoles, imidazole, pyrrole etc. are very less reported.[10] In this paper we describe the synthesis of 7-substituted 1-cyclopropyl-6 -fluoro-1, 4-dihydro-8-methoxy-4-oxoquinoline-3-carboxamide by substituting fluoro group at C-7 position with different azoles and fused azoles.[11][12]

MATERIALS AND METHODS

All the raw materials used for synthesis were obtained from commercial suppliers and was purified as per requirement. Mass spectra were recorded on 'LCMS-Qp2010s' instrument by direct injection method. Nuclear Magnetic Resonance spectra (^{1}HNMR) were recorded on Bruker advance spectrometer (400 MHz) using DMSO-d6 or CDCl3 solvents. Tetramethylsilane was used as internal standard. Chemical shift (δ) are reported in parts per million. Reactions were monitored and its purity was checked by Merck pre-coated plate (silica gel 60 F254) Thin Layer Chromatography was visualized with UV light. Melting points were determined in open capillary tube and are uncorrected.

Reaction scheme-1



R= azole, substituted azole and fused azole.

PROCEDURE

Synthesis of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid (*VII*)

To the suspension of ethyl 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylate (**VI**) (15.4mmol) in THF (50 ml) was added the lithium hydroxide (16.94mmol) solution (25ml water) drop wise at 0^{o}C in 30 minutes. Reaction mass was stirred at room temperature for 4 hour. Solvent was removed under the reduced pressure at 35^{o}C. Cool the reaction mass to 0^{o}C and pH was adjusted (between 5 to 6) by 2 N HCl solution. Reaction mass was filtered and obtained cake was washed with water (3 x 20ml) and dried under reduced pressure at 35^{o}C. Compound (VII) obtained yield 85%; mp 188-190°C**;** ^{1}H NMR ($CDCl_3$) (400 MHz) δ: 14.39 (s, 1H), 8.875 (s, 1H), 8.075-8.029 (t, 1H, J=

8.4 Hz), 4.151 (s, 3H), 4-145-4.127(m, 1H), 1.303-1.284 (m, 2H), 1.144-1.129 (m, 2H); MS (ESI) m/z 296 (M^{+1}).

Synthesis of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxamide (*VIII*)

To the suspension of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid (*VII*) (16.9mmol) in N,N-Dimethylformamide (50mL) were added 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide HCl (25.4mmol) and 1-Hydroxybenzotriazole (18.6 mmol) at 0°C and stirred for 1h. Ammonium chloride (119mmol) and N,N-Diisopropylethylamine (169mmol) were added, After stirring the reaction mixture for 1h at 0°C, allow the mixture to stir at room temperature for 16 h, the reaction was quenched to 500mL chilled water, filter and wash the cake with 50mL water. Dry the solid mass under reduced pressure at 40°C. The crude product was further purified and dried. Yield 63%; mp >220 °C; ^{1}H NMR (DMSO-d6, 400 MHz) δ: 8.974 (s, 1H), 8.710 (s, 1H), 7.939 (t, 1H), 7.584 (s, 1H), 4.145-4.111 (m, 1H), 4.067 (s, 3H), 1.178-1.076 (m, 4H), MS (ESI): *m/z* 295 (M^{+1}).

Synthesis of 1-cyclopropyl-6-fluoro-7-(heterocyclic amino)-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxamide (*IXa-h*).

To a suspension of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxamide (***VIII***) (1.53mmol) in N,N Dimethylformamide (5ml), azole or fused azole (1.688 mmole), and cesium carbonate (Cs_2CO_3) (1.688mmol) was added. Reaction mass was stirred at 80°C for 16 h. Concentrate the reaction mass under reduced pressure. Ice water was added and reaction mass was stirred for 1h. Reaction mass was filtered and dried.

Preparation of 1-cyclopropyl-6-fluoro-1,4-dihydro-7-(1H-imidazol-1-yl)-8-methoxy-4-oxoquinoline-3-carboxamide (IXa)

A off white colour solid isolated from crystallized from methanol; Yield 43%; Mol Formula: $C_{17}H_{15}FN_4O_3$; MW: 342.33; mp= 208-210°C; ES-MS: m/z 343 (M^{+1}). ^{1}H NMR ($CDCl_3$)(400 MHz) δ: 9.417 (s, 1H), 8.950 (s, 1H), 8.162-8.138 (d, 1H, J=9.6Hz), 7.854 (s, 1H), 7.331(s, 1H), 7.298 (s, 1H), 5.782 (s, 1H), 4.019-4.002 (m, 1H), 3.409 (s, 3H),1.114-0.863 (m, 4H).

1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-7-(1H-1,2,4-triazol-1-yl)quinoline-3-carboxamide (IXb)

A off white colour solid isolated from crystallized from methanol; Yield 73%; Mol Formula: $C_{16}H_{14}FN_5O_3$; MW: 343.32; mp=228-230°C; ES-MS: m/z 344 (M^{+1}). ^{1}H NMR (DMSO-

D_6)(400 MHz) δ: 9.019 (s, 1H), 8.950 (s, 1H), 8.770 (s, 1H), 8.416 (s, 1H), 8.015-7.991 (d, 1H, J=9.6 Hz), 7.627(s, 1H), 4.116-4.106 (m, 1H), 3.44 7 (s, 3H), 1.133-1.054 (m, 4H).

1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-7-(1H-pyrazol-1-yl)quinoline-3-carboxamide (IXc)

A off white colour solid isolated from crystallized from methanol; Yield 86%; Mol Formula: $C_{17}H_{15}FN_4O_3$; MW: 342.33; mp=>230^oC; ES-MS: m/z 343 (M^{+1}). ^1H NMR (DMSO-D_6) (400 MHz) δ: 8.994 (s, 1H), 8.774 (s, 1H), 8.130 (s, 1H), 7.965-7.940 (d, 1H, J=10 Hz), 7.898 (s, 1H), 7.616 (s, 1H), 6.651 (s, 1H), 4.148 -4.113 (s, 1H), 3.317 (s, 3H), 1.147-1.075 (m, 4H).

1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-7-(1H-pyrrol-1-yl)quinoline-3-carboxamide (IXd)

A off white colour solid isolated from crystallized from methanol; Yield 88%; Mol Formula: $C_{18}H_{16}FN_3O_3$; MW: 341.34; mp= >230^oC; ES-MS: m/z 342 (M^{+1}). ^1H NMR (DMSO-D_6) (400 MHz) δ: 8.991 (s, 1H), 8.735 (s, 1H), 7.930-7.905 (d, 1H, J=10), 7.576 (s, 1H), 7.051-7.046 (d, 2H, J=2Hz), 6.362-6.357 (d, 2H, J=2 Hz), 4.115 (m, 1H), 3.300 (s, 3H), 1.137-1.054 (m, 4H).

1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-7-(1H-1,2,3-triazol-1-yl)quinoline-3-carboxamide (IXe)

A off white colour solid isolated from crystallized from methanol; Yield 50%; Mol Formula: $C_{16}H_{14}FN_5O_3$; MW: 343; mp=238-240^oC; ES-MS: m/z 344 (M^{+1}). ^1H NMR (DMSO-D_6) (400 MHz) δ: 8.967 (s, 1H), 8.799 (s, 1H), 8.664 (s, 1H), 8.118 (s, 1H), 8.064-8.041 (d, 1H, J=9.2Hz), 7.653 (s, 1H), 4.148-4.120 (m, 1H), 3.426 (s, 3H), 1.169-1.080 (m, 4H).

1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(5-methyl-1H-imidazol-1-yl)-4-oxoquinoline-3-carboxamide (IXf)

A off white colour solid isolated from crystallized from methanol; Yield 62%; Mol Formula: $C_{18}H_{17}FN_4O_3$; MW: 356.36; mp=226-228^oC; ES-MS: m/z 357 (M^{+1}). ^1H NMR ($CDCl_3$) (400 MHz) δ: 9.94 (s, 1H), 8.95 (s, 1H), 8.137-8.113 (d, 1H, J= 9.6 Hz), 7.182 (s, 1H), 7.049 (s, 1H), 5.753(s, 1H), 4.044-4.018(m, 1H), 3.418 (s, 3H), 2.355(s, 3H), 1.118-1.036 (m, 4H).

1-Cyclopropyl-6-fluoro-7-indol-1-yl-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid amide (IXg)

A off white colour solid isolated by purifying by passing through 60-120 mesh silica gel and chloroform-methanol was used to elute it; Yield 65%; Mol Formula: $C_{22}H_{18}FN_3O_3$; MW: 391; mp= 216-218^oC; ES-MS: m/z 392 (M^{+1}). ^1H NMR ($CDCl_3$) (400 MHz) δ: 9.052 (s, 1H), 8.80 (s, 1H), 8.038-8.013 (d, 1H, J=10 Hz), 7.719-7.699 (d, 1H, J= 8 Hz), 7.639-7.598 (m, 2H), 7.234-7.166 (m, 3H), 6.856-6.847 (m, 1H), 4.168-4.137 (m, 1H), 3.152 (s, 3H), 1.156-1.098 (m, 4H).

7-(1H-benzo[d]imidazol-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxamide (IXh)

A off white colour solid isolated by purifying by passing through 60-120 mesh silica gel and chloroform-methanol was used to elute it; Yield 52%; Mol Formula: $C_{21}H_{17}FN_4O_3$; MW: 392.39; mp= 222-224^oC; ES-MS: m/z 393 (M^{+1}). ^1H NMR ($CDCl_3$) (400 MHz) δ: 9.017 (s, 1H), 8.812 (s, 1H), 8.572 (s, 1H), 8.094-8.071 (d, 1H, J=9.2 Hz), 7.848-7.829 (m, 1H), 7.652 (s, 1H), 7.372-7.347 (m, 3H), 4.160-4.135 (m, 1H), 3.269 (s, 3H), 1.176-1.126 (m, 4H).

Antimicrobial testing (Disc diffusion assay):

Various bacterial strains - *Staphylococcus aureus* (NCIM 2079), *Escherichia coli* (NCIM 2109) and fungal strain *Candida albicans* (NCIM 3471) were used as test microorganism to evaluate the antimicrobial testing of newly synthesized compounds (Table-2) IX (a-n), IIIV and compound X (a-b).

Pure culture of test bacterial strain was picked with a loop and the growth was transferred into a tube containing 5 ml of a nutrient broth medium, while pure culture of test fungal strain was transferred into a tube containing 5 ml of a MGYP medium. The broth culture was incubated at 37°C until it achieves or exceeds the turbidity of the 0.5 McFarland standards (usually to 6 hours). The turbidity of the actively growing broth culture is adjusted with sterile saline or broth to obtain turbidity optically comparable to that of the 0.5 McFarland standards. This result in a suspension contains 2 x 10^8 CFU/ml of microbial cells.

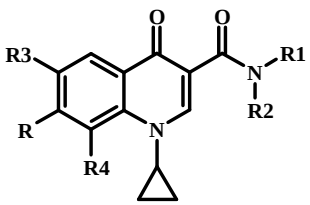
Within 15 minutes after adjusting the turbidity of the inoculum suspension, a sterile cotton swab was dipped into the adjusted suspension. The swab was rotated several times and pressed firmly on the inside wall of the tube above the fluid level. The surface of a nutrient agar plate was inoculated by streaking the swab over the entire sterile agar surface. This procedure is repeated

by streaking several times, rotating the plate approximately 60° each time to ensure an even distribution of inoculum.

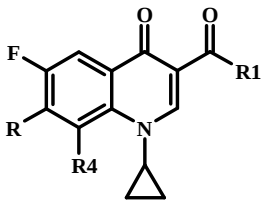
Stock solution [1000 microgram per ml] of each newly synthesized compounds were prepared in dimethylsulfoxide (DMSO). The sterile discs of 6 mm diameter were used in this assay. The disc diffusion assay was carried out by taking concentration 100 microorganism per disc. The discs immersed with compounds were dispensed onto the surface of the inoculated agar plate. Also, Ciprofloxacin (10 microgram/disk, Amphotericin-B (100 units/disk) [Hi-media, Mumbai, disc diameter 6 mm] moistened with DMSO were placed on agar plate as standard. Each disc was pressed down to ensure complete contact with the agar surface. The plates were placed in a refrigerator at to 8°C for 30 minutes after the discs are applied. Then the plates were incubated in incubator at 37°C for 24 hours.

After 24 hours of incubation, each plate was examined. The diameters of the zones of complete inhibition including the diameter of the disc were measured using Vernier caliper, which is held on the back of the inverted petri plate. The results were summarized in Table 1.

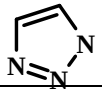
Table: 1-Antibacterial and Antifungal activity data of compounds (IXa - IXh).

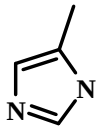
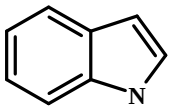
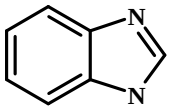
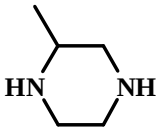


(IX a-h)



(X a-b)

	R	R1	R2	R3	R4	*S.aureus*	*E. coli*	*C.albicans*
IXa		**H**	**H**	**F**	**OMe**	**9.38**	**-**	**-**
IXb		**H**	**H**	**F**	**OMe**	**-**	**-**	**-**
IXc		**H**	**H**	**F**	**OMe**	**13.68**	**-**	**-**
IXd		**H**	**H**	**F**	**OMe**	**20.81**	**11.90**	**-**
IXe		**H**	**H**	**F**	**OMe**	**9.98**	**11.80**	**-**

IXf		**H**	**H**	**F**	**OMe**	**-**	**-**	**-**
IXg		**H**	**H**	**F**	**OMe**	**-**	**-**	**-**
IXh		**H**	**H**	**F**	**OMe**	**-**	**-**	**-**
VIII	**F**	**H**	**H**	**F**	**OMe**	**12.88**	**16.88**	**-**
Xa	**F**	**OH**	**-**	**F**	**OMe**	**16.23**	**21.00**	**-**
Xb		**OH**	**-**	**F**	**OMe**	**33.32**	**32.10**	**-**
Ciprofloxacin						**26.94**	**32.70**	**NA**
Amphotericin						**NA**	**NA**	**9.59**

Diameter in mm calculated by Vernier Caliper '-' means no zone of inhibition, NA Not applicable

Microbial Cultures Used to test antimicrobial Activity, Fungi (Yeast), *Candida albicans, Gram Positive Bacteria: Staphylococcus aureus. Gram Negative Bacteria: Escherichia coli.*

BIOLOGICAL ACTIVITY

Antifungal studies. The antifungal activity was studied against with *Candida albicans* pathogenic fungi. Amphotericin was used as reference for inhibitory activity against fungi. Compounds (**Table-1**) IX (**a-h)**, **VIII** and compound **X** (**a-b**) show no activity against *Candida albicans* pathogenic fungi.

The compound synthesized (Table-1) **IX** (**a-h**), **VIII** and compound **X** (**a-b**) were tested against *Staphylococcus aureus* (Gram-positive bacteria) and *Escherichia coli* (Gram-negative bacteria). Ciprofloxacine used as a reference standard. It was observed that carboxylic acid at C-3 and Carbonyl at C-4 position is necessary for antimicrobial activity. So compound (**Xa**) have slightly better activity as compared to compound **VIII** (Table-1) which have fluoro group at C-7 position and carboxamide at C-3 position against *Staphylococcus aureus* and *Escherichia coli* pathogens. So compound **IX** (**a-h**) **(Table-1)** were synthesized to increase the activity against both pathogens by substituting different azole, substituted azole or fused

azoles at C-7 position. Antibacterial screening data in **Table-1** shows that all the tested compounds depict moderate to good bacterial inhibition capabilities.

It was observed compound **IXd** shows good activity against *Staphylococcus aureus* pathogen but show moderate activity against *Escherichia coli* pathogens. Compound **IXa & IXc** shows moderate activity against *S. aureus* but no activity against *E. coli* pathogens. Compound **IXe** shows moderate activity against *S. aureus* & *E. coli* pathogens. Compound **IXf, IXg and IXh** shows no activity against *S. aureus* & *E. coli* pathogens.

CONCLUSION

The 1-cyclopropyl-6, 7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxamide derivative were synthesized by novel method which is simple, cheaper and safe. These compounds were synthesized by using EDPC and HOBt as coupling reagent, DIPEA as base and ammonium chloride was used for amidation which is easy to handle. This reaction is carried at low temperature therefore chances of forming side product are very less and yield is high.

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