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Synthesis of novel quinazolino-quinolones as potential antibacterial agents

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ABSTRACT

Synthesis of novel quinozolono-quinolones from 3-quinazolinones coupled with N-1 position of 6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate with a two carbon chain linker and to evaluate the biological activities.

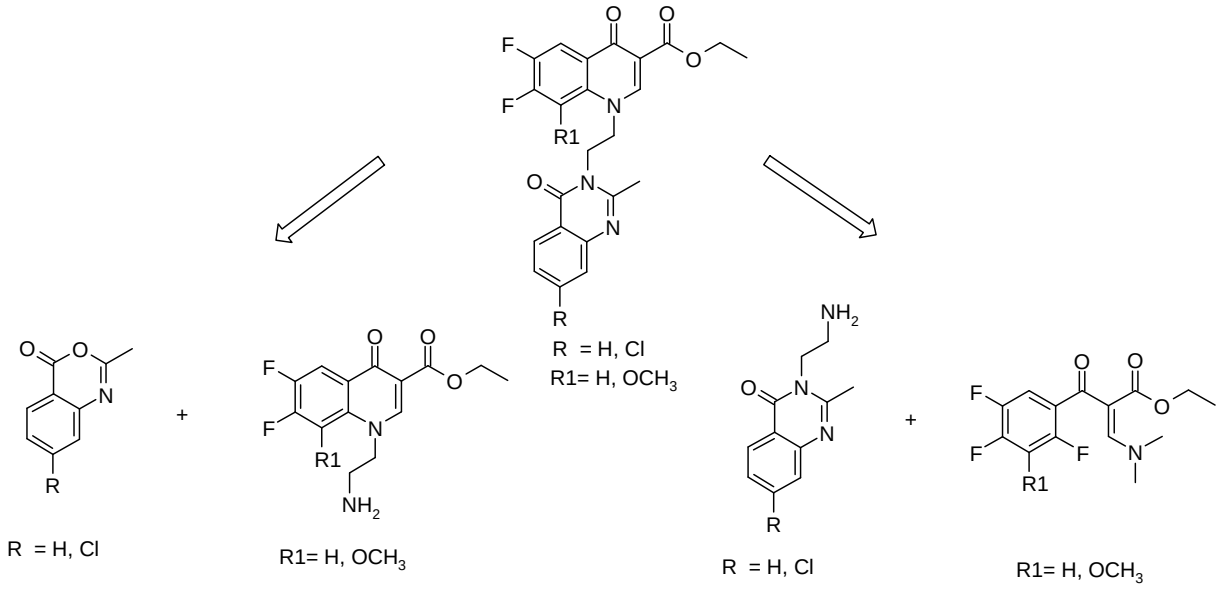
Key words: Quinazolono-quinolones, quinazolinone, quinolone, fluoro benzoic acids, anti bacterial activity.

INTRODUCTION

1, 4-dihydro-4-oxo-6-fluoroquinoline-3-carboxylic acid derivatives are quinolone class of anti-bacterial agents [1], which are effective against a variety of gram-negative microorganisms. A number of fluoroquinolone subclass of antibacterial agents such as norfloxacin, ofloxacin, ciprofloxacin are in clinical use. Similarly quinazolinones and its derivatives, a class of quinazolone heterocyclic compounds are widely used as anti microbial agents. Among other pharmacological activities, quinazolinones are extensively used as hypnotic/sedatives that contain a 4-quinazolinone core. Their use has also been proposed in the treatment of cancer. Examples include afloqualone, cloroqualone and diproqualone [2]. Quinazolinone derivatives show remarkable antimicrobial properties against microorganism associated with death in patients carrying immune compromised diseases [3]. Quinazolinones and condensed quinozolinones are reported to show antimicrobial activities, such as antibacterial [4] antifungal [5], antibacterial [6] and anti HIV [7]. Since there is continuous demand for new antibacterial agents, many researchers [8] have been working on modified quinolones to potentiate them further. In view of above wide variety of pharmaceutical applications with quinazolinone and quinolones, we have designed and synthesized a novel series of quinazolino-quinolone derivatives (**Fig-1**) to study the antibacterial activity.

We have prepared N-1-quinolone dimers with a two carbon chain linker to fulfill the STERIMOL length [9]. Here, we wish to report the synthesis of 3-quinazolinones coupled with N-1 position of 6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate with a two carbon chain linker to evaluate the biological activities. Interestingly these compounds have two core

components viz. quinazolinone (core component 1) and quinolone (core component 2) which are biologically very active on its own. Quinazolinones (core component 1) were prepared from 2-amino benzoic acid as shown in Scheme **1**. Quinolones (core component 2) were prepared from fluoro benzoic acid as shown in Scheme **2**.



Figrure-1

MATERIALS AND METHODS

2.1 Chemistry

Melting points were determined on a polmon capillary melting point apparatus. IR spectra were recorded on Perkin-Elmer FTIR spectrometer and the v_{max} are expressed in cm^{-1}. ^1H NMR and ^{13}C NMR were recorded in CDCl3, DMSO and D_2O solvent on on Bruker 300 spectrophotometer (300MHz) at ambient temperature. Chemical shifts δ are given in ppm, coupling constant *J* are in Hz. The chemical shifts are reported in ppm on scale downfield from TMS as internal standard. All the reagents and solvents were reagent grade and used without further purification unless specified otherwise. Technical grade dichloromethane, ethyl acetate, methanol and petroleum ether used for column chromatography were distilled prior to use. Column chromatography was carried out using silica gel (100-200 mesh) packed in glass columns. All reactions were performed under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring.

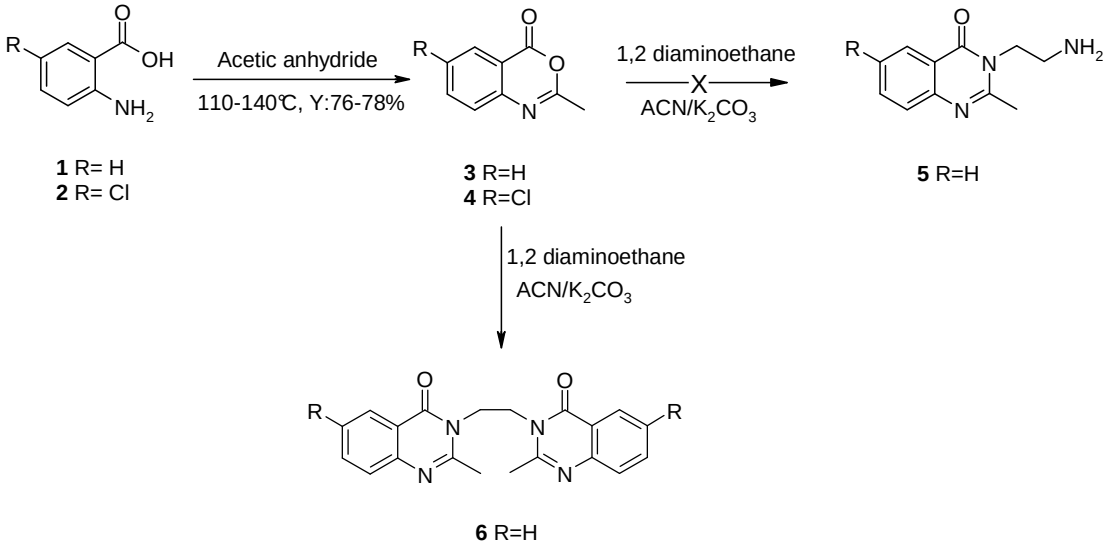
General procedure for the synthesis of lactone

Anthranilic acid (**1, 2**) (0.02187 moles, 1 eq.) was dissolved in acetic anhydride (0.2187 mol., 10 eq.) and reaction mass was heated to reflux for 1 h at 110°C-140°C. After completion of starting material acetic anhydride was distilled completely, and obtained residue was co -distilled with heptanes and added heptanes to precipitate out and stirred at 0-5°C for 30 minutes and filtered under nitrogen to get corresponding product (**3**, **4**) as a solid.

2-methyl-4*H*-3,1-benzoxazin-4-one (**3**)

Wt: 2.7 g, Y: 76.7%, Mp: 75-79°C. IR (KBr): 3479, 3070, 2933, 1756, 1645, 1606, 1572, 1472, 1380, 1265, 1195, 1053, 961, 779 cm^{-1}**.** ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 2.46 (s, 3H, CH_3), 7.46-7.54 (m, 2H, aromatic), 7.75-7.81 (m, 1H, aromatic), 8.16-8.19 (m, 1H, aromatic). MS (ESI): *m/z (%)* = 162 ($[M+H]^+$, 100), 120 (15)

6-chloro-2-methyl-4*H*-3,1-benzoxazin-4-one (4)
Wt: 1.8 g, Y: 78.9%. Mp: 114-117°C. IR (KBr): 3504, 3081, 3068, 2934, 1761, 1649, 1601, 1470, 1306, 1253, 1187, 1055, 968, 840 cm^{-1}**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.45 (s, 3H, CH_3), 7.46 (d, *J*= 8.6 Hz, 1H, aromatic), 7.69-7.73 (m, 1H, aromatic), 8.12-8.13 (m, 1H, aromatic). MS (ESI): *m/z (%)* = 196 ($[M+H]^+$, 100)



1 R= H
2 R= Cl

3 R=H
4 R=Cl

5 R=H

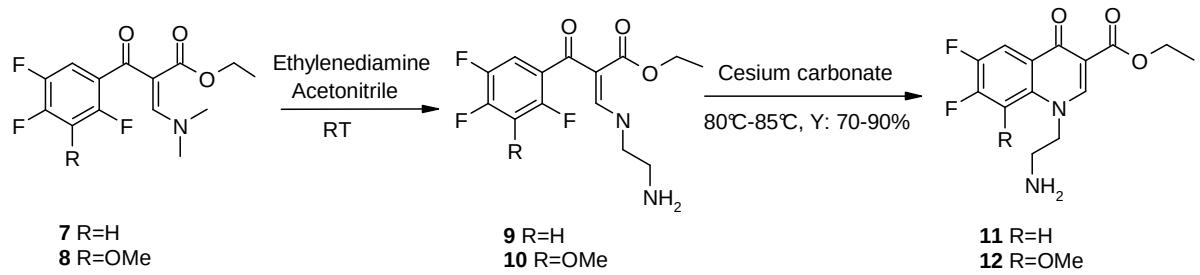
6 R=H

Scheme 1 Synthesis of quinazolinone core component

2-methyl-3-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl)ethyl]-4--3,4-dihydro-3-quinazolinone (**6**)
To a stirred solution of 2-methyl-4*H*-3,1-benzoxazin-4-one (**3**) (0.5 g, 0.0031 mol., 1 eq.) in acetonitrile (20 ml), 1,2 diamino ethane (0.074 g, 0.00155 mol, 0.5 eq.) was added at ambient temperature and stirred for 3 h. While stirring potassium carbonate (0.835 g, 0.00605 mol,1.95 eq.) was added to the reaction mass and refluxed for 4 h. After completion of reaction resulting mixture was cooled to ambient temperature and diluted with water. Obtained solid was filtered and washed with acetonitrile and dried under reduced pressure to afford compound **6** as white solid.

Mp: 172-185°C. IR (KBr): 3388, 3052, 1683, 1595, 1475, 1371, 1245, 1175, 1061, 918, 779 cm^{-1}**.** ^{1}H NMR (300 MHz, DMSO) δ ppm: 2.68 (s, 6H, CH_3), 4.33 (s, 4H, *N*-CH_2, *N*'-CH_2), 7.41-7.46 (m, 2H, aromatic), 7.55-7.58 (m, 2H, aromatic), 7.74-7.78 (m, 2H, aromatic), 8.00-8.034 (m, 2H, aromatic). MS (ESI): *m/z (%)* = 347 ($[M+H]^+$, 100), 274 (60), 187 (80).

General procedure for the synthesis quinolone core moieties
A mixture of fluoro acrylate (**7**, **8**) (0.00990 mol.) in acetonitrile (20 mL) was taken in round bottom flask, and while stirring ethylene diamine (0.0296 mol., 3.0 eq.) was added drop wise in to reaction mass at RT. After formation of intermediate (**9, 10**), cesium carbonate (0.0494 mol., 5.0 eq.) was added in to reaction mass and heated to reflux for about 2 h. After completion of reaction, mass was filtered and washed with acetonitrile and concentrated to get crude product. Product was precipitated in dichloromethane /heptanes (**11, 12)**

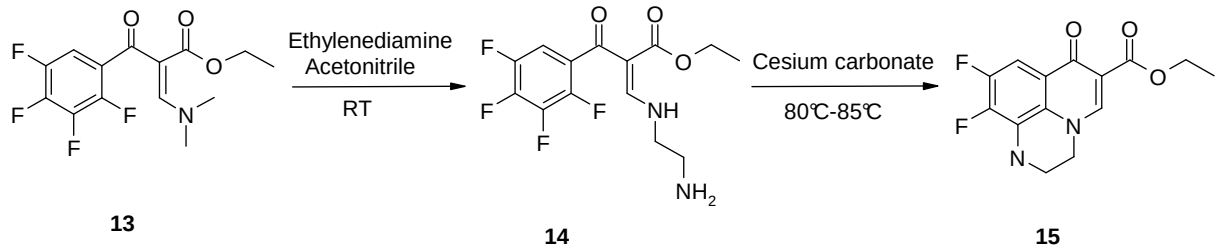


Scheme 2. Synthesis of N-ethyl amino quinoline carboxylic acids

Ethyl 1-(2-aminoethyl)-6,7-difluoro-4-oxo-1,4-dihydro-3-quinoline carboxylate (**11**)
Wt: 2.7 g, Y: 91.5%, Mp: 128-135°C. IR (KBr): 3364, 3299, 2925, 1721, 1676, 1619, 1497, 1393, 1315, 1290, 1233, 1158, 1087, 908, 872, 802 cm^{-1}**.** ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.25 (t, *J*= 7.1 Hz, 3H, CH_3), 2.84-2.88 (q, 2H, OCH_2), 4.16-4.27 (m, 4H, *N*-CH_2), 8.01-8.10 (m, 2H, aromatic), 8.60 (s, 1H, =CH). MS (ESI): *m/z (%)* = 297 ($[M+H]^+$, 100)

Ethyl-1-(2-aminoethyl)-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate (**12**)
Wt: 0.70 g, Y: 71.4%. Mp: 172-210°C. IR (KBr): 3387, 3056, 2985, 1718, 1676, 1644, 1567, 1476, 1387, 1321, 1285, 1197, 1099, 934, 883, 800 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.37 (t, *J*= 7.1 Hz, 3H, CH_3), 3.11 (q, *J*= 6.0 Hz, 2H, OCH_2), 4.06 (s, 3H, OCH_3), 4.34-4.45 (m, 4H, *N*-CH_2), 8.09-8.15 (m, 1H, aromatic), 8.42 (s, 1H, =CH). MS (ESI): *m/z (%)* = 327 ($[M+H]^+$, 100)

Ethyl 1-(2-aminoethyl)-6,7-difluoro-4-oxo-1,4-dihydro-3-quinoline carboxylate (**15**)
Tetrafluorobenzoic acrylate (**13**) (0.5 g, 0.00156 mol.) was dissolved in acetonitrile (20 mL), while stirring ethylene diamine (0.28 g, 0.00469 mol., 3.0 eq) was added in to reaction mass and stirred for 1 h at room temperature, after formation of intermediate (**14**) was confirmed, then cesium carbonate (2.55 g, 0.0078 mol., 5.0 eq) was added and refluxed for about 2 h. Reaction mass was filtered and washed with acetonitrile and concentrated to get crude product. Crude product was recrystallized in ethyl acetate in heptanes to give a pure product **15** (Wt: 0.25 g, Y: 54.3%)

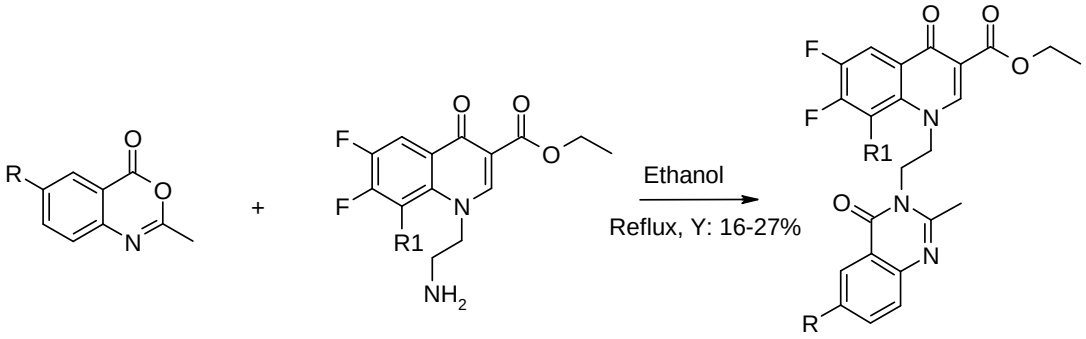


Scheme 3. Synthesis of tricyclic difluoro quinoline carboxylic acid

Mp: 270-292°C. IR (KBr): 3282, 3052, 2975, 1668, 1606, 1570, 1494, 1386, 1366, 1261, 1173, 1088, 965, 799 cm^{-1}**.** ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.22 (t, *J*= 7.0 Hz, 3H, CH_3), 3.48 (bs, 2H, CH_2), 4.14 (q, *J*= 7.0 Hz, 3H, OCH_2), 4.28 (t, *J*= 5.1 Hz, 2H, *N*-CH_2), 6.99 (bs, 1H, aromatic), 7.13-7.20 (m, 1H, aromatic), 8.48 (s, 1H, =CH). MS (ESI): *m/z (%)* = 295 ($[M+H]^+$, 100), 249 (25)

General procedure for the synthesis of quinazolino-quinolones
Mixture of compounds (**3**, **4**) (1.6 g, 0.0099 mol., 1.0 eq.) and compound (**11**, **12**) (0.010 mol., 1.0 eq.) in ethanol (30 mL) was heated to reflux for 3-4 h. After 1 h solid was precipitated out.

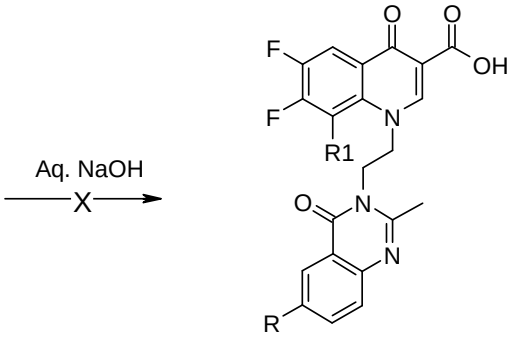
After completion of reaction, reaction mass was cooled to ambient temperature and obtained solid was filtered, and washed with heptanes. Crude product was purified by flash column chromatography on triethylamine impregnated silicagel (100-200 mesh), column was eluted with 1.5% methanol in dichloromethane to get the corresponding pure product (**16, 17, 18, 19**) as a off-white solid



3 R=H
4 R=Cl

11 R1=H
12 R1=OCH_3

16 R=H, R1=H
17 R=Cl, R1=H
18 R=H, R1=OCH_3
19 R=Cl, R1=OCH_3



20 R=H, R1=H
21 R=Cl, R1=H
22 R=H, R1=OCH_3
23 R=Cl, R1=OCH_3

Scheme 4 Synthesis of quinazolino-quinolones

Ethyl 6,7-difluoro-1-[2-(2-methyl-4-oxo-3,4-dihydro-3-quinazolin- -yl)ethyl]-4-oxo-1,4-dihydro-3-quinolinecarboxylate (16)

Wt: 1.2 g, Y: 27.2%. Mp: 243-247°C. IR (KBr): 3599, 3460, 3066, 2987, 1698, 1674, 1615, 1504, 1479, 1390, 1364, 1296, 1235, 1093, 862, 805 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 1.05 (t, *J*= 7.0 Hz, 3H, CH_3), 2.57 (s, 3H, CH_3), 4.02 (q, *J*= 7.1 Hz, 2H, OCH_2), 4.43-4.45 (m, 2H, N-CH_2), 4.67-4.69 (m, 2H, N-CH_2), 7.41-7.43 (m, 1H, aromatic), 7.54-7.57 (m, 1H, aromatic), 7.74-7.79 (m, 1H, aromatic), 8.03-8.09 (m, 2H, aromatic), 8.25-8.32 (m, 1H, aromatic), 8.53 (s, 1H,=CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 14.41, 23.23, 42.74, 50.90, 60.12, 106.96 (d, J_{C-F} = 23.2 Hz), 110.58, 114.18 (d, J_{C-F} = 18.0 Hz), 119.90, 126.48, 134.89, 147.29, 150.36, 154.94, 161.98, 164.33, 171.71. MS (ESI): *m/z (%)* = 440 ($[M+H]^+$, 100), 187 (18). Anal. Calcd. for $C_{23}H_{19}F_2N_3O_4$ (%): C, 62.87; H, 4.36; N, 9.56. Found: C, 62.84; H, 4.21; N, 9.60.

Ethyl-1-[2-(6-chloro-2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl) ethyl]-6,7-difluoro-4-oxo-1,4-dihydro-3 quinolinecarboxylate (**17**)
Wt: 0.8 g, Y: 20 %. Mp: 253-261°C. IR (KBr): 3381, 3046, 2926, 1729, 1682, 1621, 1594, 1505, 1472, 1384, 1358, 1292, 1164, 1050, 931, 803 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 1.08 (t, *J*= 7.1 Hz, 3H, CH_3), 2.57 (s, 3H, CH_3), 4.05 (q, *J*= 7.0 Hz, 2H, OCH_2), 4.45 (m, 2H, N-CH_2), 4.69 (m, 2H, N-CH_2), 7.58 (d, *J*= 8.6 Hz, 1H, aromatic), 7.78-7.89 (m, 2H, aromatic), 8.03-8.10 (m, 1H, aromatic), 8.23-8.29 (m, 1H, aromatic), 8.50 (s, 1H,=CH). ^{13}C NMR (75 MHz, CDCl3) δ ppm: 14.17, 23.13, 43.30, 50.63, 61.17, 104.78 (d, J_{C-F} = 22.5 Hz), 111.75, 115.77 (d, J_{C-F} = 18.7 Hz), 120.82, 125.91 (d, J_{C-F} =16.5 Hz), 128.73, 132.98, 135.41, 145.48, 148.77, 152.52, 161.47, 164.84, 172.34. MS (ESI): *m/z (%)* = 474 ($[M+H]^+$, 100). Anal. Calcd. for $C_{23}H_{18}ClF_2N_3O_4$ (%): C, 58.30; H, 3.83; N, 8.87. Found: C, 58.28; H, 3.80; N, 8.82

Ethyl 6,7-difluoro-8-methoxy-1-[2-(2-methyl-4-oxo-3,4-dihydro-quinazolinyl)ethyl]-4-oxo-1,4-dihydro-3-quinolinecarboxylate (**18**)
Wt: 0.3 g, Y: 21 %**.** Mp: 211-224°C. IR (KBr): 3428, 3067, 2983, 1725, 1673, 1601, 1570, 1476, 1383, 1350, 1285, 1166, 1066, 931, 861, 804 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 1.01 (t, *J*= 7.1 Hz, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.92 (q, *J*= 7.1 Hz, 2H, OCH_2), 4.05 (s, 3H, OCH_3), 4.46 (m, 2H, N-CH_2), 4.88 (m, 2H, N-CH_2), 7.34-7.39 (m, 1H, aromatic), 7.49 (d, *J*= 7.7 Hz, 1H, quinolone aromatic), 7.69-7.85 (m, 3H, aromatic), 8.29 (s, 1H,=CH). ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 14.30, 23.23, 44.24, 55.39, 60.04, 63.39, 107.83 (d, J_{C-F} =18.7 Hz), 109.54, 119.77, 126.36, 126.69, 130.91, 134.69, 139.97 (d, J_{C-F} =12 Hz), 147.22, 152.43, 154.97, 161.73, 163.99, 171.21. MS (ESI): *m/z (%)* = 470 ($[M+H]^+$, 100), 492 (5). Anal. Calcd. for $C_{24}H_{21}F_2N_3O_5$ (%): C, 61.45; H, 4.51; N, 8.09. Found: C, 61.45; H, 4.45; N, 8.10

Ethyl-1-[2-(6-chloro-2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl) ethyl]-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate (**19**)
Wt: 0.5 g, Y: 16.2 %. Mp: 195-211°C. IR (KBr): 3394, 2928, 1728, 1677, 1593, 1474, 1378, 1321, 1286, 1165, 1068, 936, 835, 803 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 1.03 (t, *J*= 6.9 Hz, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.97 (q, *J*= 7.0 Hz, 2H, OCH_2), 4.04 (s, 3H, OCH_3), 4.46 (s, 2H, N-CH_2), 4.88 (s, 2H, N-CH_2), 7.53 (d, *J*= 8.5 Hz, 1H, quinolone aromatic), 7.70-7.85 (m, 3H, aromatic), 8.29 (s, 1H,=CH). ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 14.30, 23.29, 44.40, 55.27, 60.09, 63.47, 107.83 (d, J_{C-F} =16.5 Hz), 109.54, 125.19, 129.06, 134.86, 140.10, 145.94, 152.39, 155.75, 160.79, 164.08, 171.21. MS (ESI): *m/z (%)* = 504 ($[M+H]^+$, 100), 221 (55) Anal. Calcd. for $C_{24}H_{20}ClF_2N_3O_5$ (%): C, 57.21; H, 4.00; N, 8.34. Found: C, 57.10; H, 4.15; N, 8.31.

2.2 *In vitro* antibacterial activity testing by agar diffusion method

In our current study, the antimicrobial activity was carried out by the agar diffusion method. 100µL (50 µg conc.) of each diluted extract were added into wells of 6 mm diameter formed into Muller Hinton agar plates. **Ciprofloxacin** (50 µg/100 µL) was used as control positive broad spectrum antibiotic. DMSO was used as control negative. Here responses of microorganisms to the synthesized compounds were measured and compared with the response of the standard reference drug (i.e Ciprofloxacin). The two microorganisms used were *Escherichia coli ATCC 8739* (Gram negative) and *Staphylococcus aureus ATCC 6538* (Gram positive).Mueller Hinton agar composition as Beef infusion 300 g , casein acid hydrolysate 17.5 g , starch 1.5 g , agar 17 g , purified water 1000 mL, final pH 7.3.

Each test compound **(16-19)** was dissolved in DMSO to get a concentration of 50 µg/mL. This concentration was used for testing antibacterial activity. The suspensions of all the organisms were prepared as per standard procedure. ATCC Culture was used for the preparation of bacterial suspension. Suspensions of organisms were made in sterile. Buffered Sodium Chloride-Peptone Solution pH 7.0.

Testing procedure: Weighed and transferred 11.4 g of Mueller Hinton agar media in to a 500 mL volumetric flask containing 300 mL of purified water. The pH was measured and found to be 7.3. The media was sterilized by autoclaving at 121 ºC for 15 minutes at 15 psi pressure. Afterwards the mixture was cooled to 45 ºC and then *Escherichia coli ATCC 8739* inoculums is added to the above cooled media, mixed properly and poured into the 18 sterile Petri dishes for solidifying. In the same way as mentioned above 18 No's *Staphylococcus aureus ATCC 6538* inoculated plates were also prepared. Bores were made on the medium using sterile borer. 100µL of test solution and standard solution (i.e Ciprofloxacin) at a concentration of 50 µg/100 µL were taken. A standard (Ciprofloxacin) was maintained with same concentration in each plate and a control having only DMSO in one plate. Then the petri dishes were incubated at 37 ºC for 24 hours and zones of inhibition were observed and measured in mm using a ruler.

RESULTS AND DISCUSSION

4.1 Synthesis of N-ethylamino quinazolinone core component

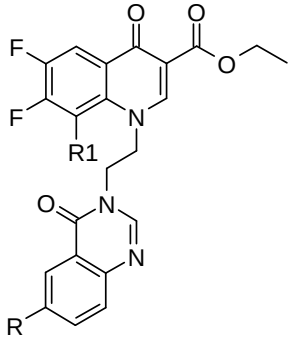
Anthranilic acid (**1**) was treated with acetic anhydride at 110-140°C to afford lactone (**3**). In the same manner chloro anthranilic acid (**2**) was treated with acetic anhydride at 110-140°C to result lactone (**4**) in quantitative yields. The obtained lactone **3** was treated with 1 eq of 1,2-diaminoethane in acetonitrile in the presence of base such as potassium carbonate at reflux temperature which resulted in formation of quinazolinone dimer (**6**) instead of N-ethylamino quinazolinone (**5**) as shown in scheme 1. An alternate route was proposed for the synthesis of quinazolinono-quinolones as shown in scheme 2.

4.2 Synthesis of N-ethyl amino quinolone core component

N-ethyl amino quinolones (core component 2) were prepared from a key intermediate acrylates (**7** and **8**) which were synthesized from corresponding commercially available fluorobenzoic acids [10]. Compound **7** and **8** were reacted with three equivalents of 1,2 diamino ethane in acetonitrile at ambient temperature which resulted in formation of corresponding enamine ketoesters **9** and **10.** Regiospecific cyclisation in acetonitrile in the presence of base like cesium carbonate resulted in N-etyl amino quinolones **11** and **12** as shown in scheme-2**.** In case of tetrafluorobenzoic acrylate (**13**) the reaction with 1,2 diamino ethane resulted in enamine ketoesters (**14**) followed by a step wise substitution of fluorines at second and third positions resulted a trycyclic product **15** as shown in scheme-3. **Synthesis of quinazolino- quinolone**

Substituted fluoroquinoline carboxylate **11** and **12** were treated with substituted lactones **3** and **4** in ethanol which resulted in corresponding products **16 to 19** in moderate to good yields as shown in scheme-4. The esters **16** to **19** were tried to hydrolyze using basic and acidic media and found that these compounds are decomposing, and could not isolate corresponding acids.

Table 1. Chemical structures and yields of fluoro quinazolino-quinolones



S. No	Compound	R	R1	Yield
1	**16**	H	H	27.2
2	**17**	Cl	H	20
3	**18**	H	OCH_3	21
4	**19**	Cl	OCH_3	16.2

4.3 Antibacterial activity of quinazolino- quinolone

The in vitro antibacterial activity of the compounds were tested in comparison with ciprofloxacin and determined by conventional agar dilution procedure. Dimethylsulfoxide (DMSO) was used as control negative. Here responses (Zone of inhibition) of microorganisms to the synthesized compounds were measured in mm and compared with the standard reference drug (i.e Ciprofloxacin). All compounds (**16-19**) were shown approximately half of the anti bacterial activity when compared with standard (Ciprofloxacin)

Table 2. In vitro antibacterial activity of quinazolinono- quinolone (16-19)

Compound No	Zone of inhibition in mm	
	Escherichia coli	Staphylococcus aureus
16	14	16
17	14	14
18	15	14
19	15	15
Ciprofloxacin	36	35

CONCLUSION

Quinazolinone derivatives are well known antimicrobial agents such as antibacterial, antifungal, antimalarial and anticancer agents. In view of high importance of these analogues we have synthesized a new series of quinazolinono-quinolones with a two carbon chain linker to increase their antibacterial activity. Captivatingly these compounds have two cores anti bacterial active components, such as quinolone core component and quinazolinono core components bridged with linker. The biological data of these targets show half of the antibacterial activity when compared to ciprofloxacin.

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