CHAPTER - 2

SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL 7-(N-ALKYLAMINOINDENYL)-8-METHOXY FLUOROQUINOLONES

2.1. INTRODUCTION

Review of literature reveals that the fluorinated quinolones are extensively used in the field of medicinal chemistry. The ability of bacteria to develop resistance to the antibiotics currently used warrants novel research into modern fluoroquinolone antibacterial. The present chapter deals with the synthesis and biological evaluation of novel N-substituted cyclopropyl-7-((2,3-dihydro-1H-inden-2-yl)amino)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid compounds 155(a-k) in the light of discovering new anti-bacterial agents.

2.2. EXPERIMENTAL

Melting points were determined using Thermonik melting point apparatus (Campbell Electronics, India) by open capillary method and are uncorrected. Reactions were monitored by thin layer chromatography (TLC) using aluminium sheets coated with silica gel 60 F254 (Merck) in UV chambers. IR spectra were recorded on a Perkin-Elmer 1700 spectrometer in KBr discs. $^1$H NMR and $^{13}$C NMR were recorded at 300MHz in DMSO-d$_6$ using Joel instrument (Joel, Japan) and avance BRUKER 300MHz. Chemical shifts were measured in δ units (ppm) relative to tetramethylsilane (TMS). Electrospray ionization mass spectra (ES-MS) were recorded on Varian 300 MS-spectrometer. Elemental analysis data were obtained by employing a Perkin-Elmer 240c analyzer. Solvents were of reagent grade and were purified and dried by standard procedure.
2.2.1. Preparation of 1-cyclopropyl-7-((2,3-dihydro-1H-inden-2-yl)amino)-6-fluoro-8-methoxy-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid (155a) from 115

To a mixture of acetic anhydride (500 ml), zinc chloride (2.5g, 2.5 % w/w) and boric acid (27.4 g, 443 mmol), 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 115 (100 g, 338 mmol) was added and heated the reaction mass to 120-125°C. After maintaining the reaction mass between 120 and 125°C for 5h, the reaction mass was cooled and the excess of acetic anhydride was distilled under reduced pressure. Toluene (300 ml) was added and stirred for 1h at 25-30°C. The precipitated compound was filtered to get borate complex as wet solid. The borate complex was immediately dissolved in acetonitrile and N,N-dimethylformamide (DMF) mixture (500:50 ml), added aminooindane (67.6 g, 507 mmol) followed by triethylamine (102.4 g, 1014 mmol) and the reaction mass was maintained for 8h at 25-30°C. The progress of the reaction was monitored by TLC. The reaction mixture was added to crushed ice (500.0 g) and the pH was adjusted to 1.0-2.0 using dilute hydrochloric acid. The precipitated solid was filtered and dried. The obtained product was recrystallized from methanol to get the pure compound 155a.

Yield: 89%; White solid; mp: 213.3-217.2°C; IR (KBr, cm\(^{-1}\)): 2957 (C-H), 1729 (C=O), 1622 (C=O); \(^1\)H NMR (DMSO-d\(_6\)): \(\delta\) 1.02-1.10 (m, 4H, 2 × CH\(_2\), cyclopropyl), 3.03-3.57 (m, 4H, 2 × CH\(_2\), indane), 4.12 (m, 1H, indane), 3.78 (1S, 3H, OCH\(_3\)), 4.77 (m, 1H, CH of cyclopropyl), 6.07 (1H, exchangeable proton), 7.13-7.23 (m,
4H, Ar-H), 7.71-7.75 (d, 1H, Ar-H), 8.62 (S, 1H, olefinic); $^{13}$C NMR (DMSO-d$_6$): 8.98 (2 × CH$_2$, cyclopropyl), 38.58 (CH), 39.4 (2 × CH$_2$), 55.57 (CH-N), 61.20 (OCH$_3$), 105.94 (CH), 106.84 (CH), 107.15 (2 × CH), 115.88 (CH), 124.47 (2 × CH-Ar), 126.38 (2 × CH-Ar), 137.82 (C), 140.89 (2 × C), 150.04 (CH), 151.95 (C-F), 165.79 (C=O, acid), 176.06 (C=O, ketone); Mass (ES): m/z 409 [M+H]$^+$; Anal. Calcd. for C$_{23}$H$_{21}$FN$_2$O$_4$: C, 67.64; H, 5.18; F, 4.65; N, 6.86; O, 15.67% Found: C, 67.6; H, 5.21; F, 4.62; N, 6.82; O, 15.62%.

2.2.2. **Preparation of 1-cyclopropyl-7-((2,3-dihydro-1H-inden-2-yl)(methyl)amino)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (155b)**

Methyl-4-methyl benzene sulfonate 153a (4.55 g, 24.46 mmol) was dissolved in DMF (15 ml), added powdered potassium hydroxide (36.69 mmol) and the mixture was heated to 40-45°C. The compound 155a (5.0 g, 12.23 mmol) was added portion wise to above reaction mass and maintained for 4h at the same temperature. The progress of the reaction was monitored by TLC. The reaction mixture was quenched into crushed ice (50g) and pH was adjusted to 6-7 using dilute hydrochloric acid. The compound was extracted into dichloromethane (DCM). The organic layer was washed with water, 5% sodium chloride solution, again with water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the obtained solid was recrystallized from methanol to afford pure title compound 155b.
Yield: 80%; Pale yellow solid; mp: 180.1-181.8°C; IR (KBr, cm\(^{-1}\)): 3053 (C-H), 2940 (C-H), 1611 (C=O), 1731 (C=O). \(^1\)H NMR (DMSO-d\(_6\)): \(\delta\) 0.92-1.04 (m, 4H, 2\(\times\)CH\(_2\) of cyclopropyl), 2.98-3.32 (m, 4H, indane), 3.54 (1S, 3H, N-methyl), 3.78 (1S, 3H, OCH\(_3\)), 3.95-4.02 (m, 1H, CH of indane), 4.69-4.71 (m, 1H, CH of cyclopropyl), 7.12-7.23 (m, 4H, Ar-H), 7.57-7.62 (d, 1H, Ar-H), 8.42 (S, 1H, olefinic); \(^13\)C NMR (DMSO-d\(_6\)): \(\delta\) 8.99 (2 \(\times\) CH\(_2\) cyclopropyl), 38.68 (CH), 39.5 (CH), 55.56 (CH-N), 61.05 (OCH\(_3\)), 107.67 (CH), 108.28 (CH), 119.41 (C), 124.58 (2 \(\times\) CH-Ar)), 126.44 (2 \(\times\)CH-N), 138.15 (CH), 141.05 (2 \(\times\) C), 150.49 (C-F), 164.87 (C=O, acid), 171.24 (C=O, ketone); Mass (S): \(m/z\) 423 [M+H]+; Anal. Calcd. for C\(_{24}\)H\(_{23}\)FN\(_2\)O\(_4\): C, 68.23; H, 5.49; F, 4.50; N, 6.63, O 15.15%; Found: C, 68.25; H, 5.48; N, 6.68; O, 15.12%.

2.2.3. Preparation of 1-cyclopropyl-7-((2,3-dihydro-1H-inden-2-yl)(ethyl)amino)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (155c)

Ethyl-4-methyl benzene sulfonate 153b (4.91 g, 24.46 mmol) was dissolved in DMF (15 ml), added powdered potassium hydroxide (42.23 mmol) and the mixture was heated to 40-45°C. The compound 155a (5.0 g, 12.23 mmol) was added portion wise to above reaction mass and maintained for 4h at the same. The progress of the reaction was monitored by TLC. The reaction mixture was quenched into crushed ice (50g) and pH was adjusted to 6-7 using dilute hydrochloric acid. The compound was
extracted into dichloromethane (DCM). The organic layer was washed with water, 5% sodium chloride solution, again with water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the obtained solid was recrystallized from methanol to afford pure title compound 155c.

Yield: 82%; White solid; mp: 167.1-169.4°C; IR (KBr, cm⁻¹): 3364 (N-H), 2941 (C-H), 1726 (C=O), 1611 (C=O); ¹H NMR (DMSO-d₆): δ 0.92-1.04 (m, 4H, 2 × CH₂ of cyclopropyl), 1.23-2.28 (t, 3H, CH₃), 2.98-3.32 (m, 4H, 2 × CH₂, indane), 3.54 (S, 3H, OCH₃), 3.95-4.03 (m, 1H, indane), 4.15-4.22 (m, CH₂ of ethyl), 4.71-4.78 (m, 1H, CH of cyclopropyl), 7.12-7.23 (m, 4H, Ar-H), 7.57-7.62 (d, 1H, Ar-H), 8.40 (S, 1H, olefinic); ¹³C NMR (DMSO-d₆): δ 8.98 (2 × CH₂, cyclopropyl), 14.29 (CH₃-CH₂) 38.7 (CH), 40.66 (2 × CH₂), 55.55 (CH-N), 59.65 (CH₂-CH₃), 61.04 (OCH₃), 107.36 (2×CH), 107.66 (CH), 108.56 (CH), 119.52 (CH), 124.58 (2 × CH-Ar), 126.43 (2×CH-Ar), 132.31 (C), 141.05 (C), 150.28 (C-F), 164.31 (C=O, acid), 171.32 (C=O, ketone); Mass (ES): m/z 437 [M+H]⁺; Anal. Calcd. for C₂₅H₂₅FN₂O₄: C, 68.79; H, 5.77; F, 4.35; N, 6.42; O, 14.66%. Found: C, 68.72; H, 5.73; F, 4.38; N, 6.82; O, 14.69%.

2.2.4. Preparation of 1-cyclopropyl-7-((2,3-dihydro-1H-inden-2-yl)(propyl)amino)-6-fluoro-8-methoxy-4-oxo1,4-dihydroquinoline-3-carboxylic acid (155d)
Propyl-4-methyl benzene sulfonate 153c (5.25 g, 24.46 mmol) was dissolved in N,N-dimethylformamide (25 ml), added powdered potassium hydroxide (36.69 mmol) and the mixture was heated to 40-45°C. The compound 155a (5.0 g, 12.23 mmol) was added portion wise to above reaction mass and maintained for 4h at the same temperature. The progress of the reaction was monitored by TLC. The reaction mixture was quenched into crushed ice (50g) and pH was adjusted to 6-7 with dilute hydrochloric acid. The compound was extracted into dichloromethane. The organic layer was washed with water, 5% sodium chloride solution, again with water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the obtained solid was recrystallized from methanol to afford pure title compound 155d.

Yield: 74%; Pale yellow solid; mp: 155.4-157.0°C; IR (KBr, cm\(^{-1}\)): 2963 (C-H), 1726 (C=O), 1614 (C=O); \(^1\)H NMR (DMSO-d\(_6\)): \(\delta\) 0.92-1.04 (m, 7H, 2 × CH\(_2\) of cyclopropyl and CH\(_3\) of N-alkyl), 1.62-1.69 (m, 2H, CH\(_2\), N-alkyl), 2.98-3.32 (m, 4H, 2 × CH\(_2\) of indane), 3.54 (S, 3H, OCH\(_3\)), 3.95-3.97 (m, 1H, CH of indane), 4.08-4.12 (m, 2H, CH\(_2\) of N-alkyl), 4.71-4.76 (m, 1H, CH of cyclopropyl), 7.15-7.21 (m, 4H, Ar-H), 7.58-7.62 (d, 1H, Ar-H), 8.40 (s, 1H, olefinic); \(^13\)C NMR (DMSO-d\(_6\)): \(\delta\) 8.69 (2 × CH\(_2\), cyclopropyl), 10.14 (CH\(_3\), alkyl chain), 21.41 (CH\(_2\), alkyl chain), 25.28 (C-alkyl chain), 38.4 (CH), 39.5 (2 × CH\(_2\)), 55.28 (C-alkyl chain), 60.77 (OCH\(_3\)), 64.88 (CH-N), 107.12 (2 × CH), 107.41 (CH), 108.31 (CH), 134.56 (CH), 124.30 (2 × CH-Ar), 124.3 (C), 126.16 (2 × CH-Ar), 132.04 (C), 134.56 (CH), 140.78 (2 × C), 150 (C-F), 151.30 (C), 164.14 (C=O, acid), 171.01 (C=O, ketone); Mass (ES): m/z 451 [M+H]\(^+\); Anal. Calcd. for C\(_{26}\)H\(_{27}\)FN\(_2\)O\(_4\): C, 69.32; H, 6.04; F, 4.22; N, 6.22; O, 14.21%; Found: C, 69.35; H, 6.08; N, 6.28; O, 14.23%.
2.2.5. Preparation of 7-(butyl(2,3-dihydro-1H-inden-2-yl)amino)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (155e)

n-Butyl-4-methyl benzene sulfonate 153d (5.59 g, 24.46 mmol) was dissolved in DMF (25 ml), added powdered potassium hydroxide (36.69 mmol) and the mixture was heated to 40-45°C. The compound 155a (5.0 g, 12.23 mmol) was added portion wise to above reaction mass and maintained for 4h at the same temperature. The progress of the reaction was monitored by TLC. The reaction mixture was quenched into crushed ice (50g) and pH was adjusted to 6-7 with dilute hydrochloric acid. The compound was extracted into dichloromethane. The organic layer was washed with water, 5% sodium chloride solution, again with water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and obtained solid was recrystallized from methanol to afford pure title compound 155e.

Yield: 72%; Pale yellow solid; mp: 165.8-168.3°C; IR (KBr, cm\(^{-1}\)): 2955 (C-H), 1721 (C=O), 1612 (C=O); \(^1\)H NMR (DMSO-d\(_6\)): \(\delta\) 0.89-1.04 (m, 7H, 2 \times CH\(_2\) of cyclopropyl and CH\(_3\) of N-alkyl), 1.36-1.44 (m, 2H, CH\(_2\), N-alkyl), 1.57-1.64 (m, 2H, CH\(_2\) of N-alkyl), 2.98-3.25 (m, 4H, 2 \times CH\(_2\) of indane), 3.54 (S, 3H, OCH\(_3\)), 3.95-3.98 (m, 1H, CH of indane), 4.12-4.17 (m, 2H, CH\(_2\) of N-alkyl), 4.71-4.76 (m, 1H, CH of cyclopropyl), 7.12-7.23 (m, 4H, Ar-H), 7.58-7.62 (d, 1H, Ar-H), 8.40
(s, 1H, olefinic); $^{13}$C NMR (DMSO-d$_6$): $\delta$ 8.94 (2 $\times$ CH$_2$, cyclopropyl), 13.6 (CH$_3$-alkyl chain), 18.72 (CH$_2$-alkyl chain), 30.3 (CH$_2$-alkyl chain), 30.3 (CH$_2$-alkyl chain), 38.3 (2 $\times$ CH$_2$), 38.66 (CH), 55.5 (CH$_3$-alkyl chain), 61.02 (OCH$_3$), 63.36 (CH-N), 107.39 (CH), 107.68 (CH), 119.54 (CH), 124.57 (2 $\times$ CH-Ar), 126.43 (2 $\times$ CH-Ar), 132.29 (CH), 138.12 (C), 141.04 (2 $\times$ C), 150.25 (CH), 151.56 (C-F), 164.0 (C=O, acid), 171.30 (C=O, ketone); Mass (ES): $m/z$ 465.51 [M+H]$^+$; Anal. Calcd. for C$_{27}$H$_{29}$FN$_2$O$_4$: C, 69.81; H, 6.29; F, 4.09; N, 6.03; O, 13.78%. Found: C, 69.84; H, 6.31; F, 4.07; N, 6.04; O, 13.71%.

2.2.6. Preparation of 1-cyclopropyl-7-((2,3-dihydro-1H-inden-2-yl)(pentyl)amino)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (155f)

n-Pentyl-4-methyl benzene sulfonate 153e (5.92 g, 24.46 mmol) was dissolved in dimethylformamide (DMF) (25 ml), added powdered potassium hydroxide (36.69 mmol) and the mixture was heated to 40-45°C. The compound 155a (5.0 g, 12.23 mmol) was added portion wise to above reaction mass and maintained for 4h at the same temperature. The progress of the reaction was monitored by TLC. The reaction mixture was quenched into crushed ice (50 g) and pH was adjusted to 6-7 with dilute hydrochloric acid. The compound was extracted into dichloromethane. The organic
layer was washed with water, 5% sodium chloride solution, again with water and
dried over anhydrous sodium sulphate. The solvent was evaporated under reduced
pressure and obtained solid was recrystallized from methanol to afford pure title
compound 155f.

Yield: 88%; Pale yellow solid; mp: 127.9-131.8°C; IR (KBr, cm\(^{-1}\)): 2960 (C-H),
1725 (C=O), 1614 (C=O); \(^1\)H NMR (DMSO-d\(_6\)): \(\delta\) 0.86-1.04 (m, 7H, 2 × CH\(_2\) of
cyclopropyl and CH\(_3\) of N-alkyl), 1.62-1.66 (m, 2H, CH\(_2\) of N-alkyl), 2.98-3.31
(m, 4H, 2 × CH\(_2\) of indane), 3.54 (s, 3H, OCH\(_3\)), 3.93-3.97 (m, 1H, CH of indane),
4.03-4.13 (m, 1H, CH of cyclopropyl), 7.12-7.21 (m, 4H, Ar-H), 7.58-7.62 (d, 1H, Ar-H),
8.40 (s, 1H, olefinic); \(^13\)C NMR (DMSO-d\(_6\)): \(\delta\) 8.95 (2 × CH\(_2\), cyclopropyl), 11.79
(CH\(_2\)-alkyl), 13.88 (CH-alkyl chain), 13.88 (CH\(_3\)-alkyl chain), 27.68 (CH\(_2\)- alkyl
chain), 27.95 (CH\(_2\)-alkyl chain), 38.68 (CH), 38.95 (2 × CH\(_2\)), 52.80 (CH\(_2\)-alkyl chain),
55.66 (OCH\(_3\)), 63.65 (CH-N), 107.39 (CH), 108.54 (CH), 119.54 (CH), 121.02 (CH),
124.57 (2 × CH-Ar), 126.43 (2 × CH-Ar), 141.05 (C), 142.47 (2 × C), .41 (CH), 159.33
(C-F), 164.35 (C=O, acid), 171.31 (C=O, ketone); Mass (ES): \(m/z\) 479 [M+H]\(^+\); Anal.
Calcd. for C\(_{28}\)H\(_{31}\)FN\(_2\)O\(_4\): C, 70.27; H, 6.53; F, 3.97; N, 5.85; O, 13.37%. Found: C,
70.32; H, 6.54; N, 5.87; O, 13.34%.

2.2.7. Preparation of 1-cyclopropyl-7-((2,3-dihydro-1H-inden-2-yl)(isopropyl)amino)-
6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (155g)
Isopropyl-4-methyl benzene sulfonate \textbf{153f} (5.25 g, 24.46 mmol) was dissolved in dichloroformamide (DMF) (25 ml), added powdered potassium hydroxide (45.69 mmol) and the mixture was heated to 40-45°C. The compound \textbf{155g} (5.0 g, 12.23 mmol) was added portion wise to above reaction mass and maintained for 4h at the same temperature. The progress of the reaction was monitored by TLC. The reaction mixture was quenched into crushed ice (50g) and pH was adjusted to 6-7 with dilute hydrochloric acid. The compound was extracted into dichloromethane. The organic layer was washed with water, 5% sodium chloride solution, again with water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and obtained solid was recrystallized from methanol to afford pure title compound \textbf{155g}.

Yield: 72%; Pale yellow solid; mp: 75.2-77°C; IR (KBr, cm\(^{-1}\)): 2977 (C-H), 1724 (C=O), 1684 (C=O); \(^1\)H NMR (DMSO-d\(_6\)): \(\delta\) 0.91-1.03 (m, 4H, 2 \(\times\) CH\(_2\) of cyclopropyl), 1.24-1.26 (2S, 6H, 2 \(\times\) CH\(_3\) of \textit{N-alkyl}), 2.98-3.25 (m, 4H, 2 \(\times\) CH\(_2\) of indane), 3.14 (S, 3H, OCH\(_3\)), 3.95-3.98 (m, 1H, CH of indane), 4.71-4.74 (m, 1H, CH of cyclopropyl), 5.0-5.05 (m, 1H, CH of N-alkyl), 7.12-7.23 (m, 4H, Ar-H), 7.57-7.61 (d, 1H, Ar-H), 8.37 (s, 1H, olefinic); \(^{13}\)C NMR (DMSO-d\(_6\)): \(\delta\) 9.65 (2 \(\times\) CH\(_2\) cyclopropyl), 22.43 (2 \(\times\) CH), 39.29 (CH), 39.35 (2 \(\times\) CH), 56.25 (CH-N), 61.70 (OCH\(_3\)), 67.53 (N-CH-alkyl chain), 108.04 (CH), 108.33(CH),120.13(CH), 120.22 (CH), 125.26 (2 \(\times\) CH-Ar), 127.11 (2 \(\times\) CH-Ar), 132.99 (CH), 141.67 (2 \(\times\) CH-Ar), 141.73 (C), 149.02 (CH), 152.23 (C-F), 164.52 (C=O, acid), 172.03 (C=O, ketone); Mass (ES): \(m/z\) 451.50 [M+H]\(^+\); Anal. Calcd. for C\(_{26}\)H\(_{27}\)FN\(_2\)O\(_4\): C, 69.32; H, 6.04; F, 4.22; N, 6.22, O, 14.21%. Found: C, 69.6; H, 6.08; F, 4.33; N, 6.28%.
2.2.8. Preparation of 1-cyclopropyl-7-((2,3-dihydro-1H-inden-2-yl)(isobutyl)amino)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (155h)

Isobutyl-4-methyl benzene sulfonate 153g (5.59 g, 24.46 mmol) was dissolved in DMF (25 ml), added powdered potassium hydroxide (36.69 mmol) and the mixture was heated to 40-45°C. The compound 155h (5.0 g, 12.23 mmol) was added portion wise to above reaction mass and maintained for 4h at the same temperature. The progress of the reaction was monitored by TLC. The reaction mixture was quenched into crushed ice (50g) and pH was adjusted to 6-7 with dilute hydrochloric acid. The compound was extracted into dichloromethane. The organic layer was washed with water, 5% sodium chloride solution, again with water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and obtained solid was recrystallized from methanol to afford pure title compound 155h.

Yield: 83%; White solid; mp: 164.8-167.8°C; IR (KBr, cm\(^{-1}\)): 2933 (C-H), 1726 (C=O), 1614 (C=O); \(^1\)H NMR (DMSO-d\(_6\)): \(\delta\) 0.92-2.04 (m, 10H, 2 \(\times\) CH\(_3\) of N-alkyl and 2 \(\times\) CH\(_2\) of cyclopropyl), 1.48-1.52 (t, 3H, CH\(_3\)), 1.90-1.99 (m, 1H, CH of N-Alkyl), 2.98-3.25 (m, 4H, 2 \(\times\) CH\(_2\) of indane), 3.54 (s, 3H, OCH\(_3\)), 3.9-3.95 (m, 3H, CH\(_2\) of N-alkyl and CH of indane), 4.69-4.71 (m, 1H, CH of cyclopropyl), 7.12-7.23 (m, 4H, Ar-H), 7.59-7.63 (d, 1H, Ar-H), 8.41 (s, 1H, olefinic); \(^13\)C NMR (DMSO-d\(_6\)): 
δ 8.48 (2 × CH₂, cyclopropyl), 18.55 (2 × CH₃ alkyl chain), 26.95 (CH-alkyl chain), 38.13 (2 × CH), 60.59 (N-CH₂ of Alkyl chain), 61.02 (OCH₃), 64.12 (C-N), 105.92 (CH), 106.84 (CH), 107.15 (CH), 107.28 (CH), 124.12 (2 × CH-Ar), 125.98 (2 × CH-Ar), 134.38 (CH), 137.02 (C), 140.59 (2 × C), 149.82 (C-F), 163.96 (C=O, acid), 170.9 (C=O, ketone); Mass (ES): m/z 465 [M+H]⁺; Anal. Calcd. for C₂₇H₂₉FN₂O₄: C, 69.81; H, 6.29; F, 4.09; N, 6.03; O, 13.78%. Found: C, 69.86; H, 6.31; F, 4.11; N, 6.08; O, 13.76%.

2.2.9. Preparation of 1-cyclopropyl-7-((2,3-dihydro-1H-inden-2-yl)(2-ethoxyethyl)amino)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (155i)

2-Ethoxy ethyl-4-methyl benzene sulfonate 153h (6.0 g, 24.46 mmol) was dissolved in DMF (25 ml), added powdered potassium hydroxide (36.69 mmol) and the mixture was heated to 40-45°C. The compound 155i (5.0 g, 12.23 mmol) was added portion wise to above reaction mass and maintained for 4h at the same temperature. The progress of the reaction was monitored by TLC. The reaction mixture was quenched into crushed ice (50g) and pH was adjusted to 6-7 with dilute hydrochloric acid. The compound was extracted into dichloromethane. The organic layer was washed with water, 5% sodium chloride solution, again with water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced
pressure and obtained solid was recrystallized from methanol to afford pure title compound 155i.

Yield: 80%; White solid; mp: 121.1-123.9°C; IR (KBr, cm\(^{-1}\)): 2939 (C-H), 1728 (C=O), 1565 (C=O); \(^1\)H NMR (DMSO- \(d_6\)): \(\delta \) 0.92-1.04 (m, 4H, 2 \(\times\) CH\(_2\) of cyclopropyl), 1.09-1.14 (t, 3H, CH\(_3\) of N-alkyl), 2.98-3.26 (m, 2H, 2 \(\times\) CH\(_2\) of indane), 3.41-3.50 (m, 2H, CH\(_2\)), 3.61-3.64 (m, 2H, CH\(_2\) of N-Alkyl), 3.54 (s, 3H, OCH\(_3\) ), 3.61-3.64 (m, 2H, CH\(_2\) of N-alkyl), 3.96-3.98 (m, 1H, CH of indane), 4.23-4.27 (m, 2H, CH\(_2\)), 4.69-4.71 (m, 1H, CH of cyclopropyl), 7.12-7.23 (m, 4H, Ar-H), 7.58-7.62 (d, 1H, Ar-H), 8.41 (S, 1H, olefinic); \(^1^3\)CNMR (DMSO-\(d_6\)): \(\delta \) 8.91 (2 \(\times\) CH\(_2\), cyclopropyl), 15.07 (C-alkyl chain), 38.63 (CH), 38.67 (2 \(\times\) CH), 59.62 (N-CH\(_2\) alkyl chain), 64.59 (C-alkyl chain), 65.56 (CH-N), 67.75 (CH\(_2\)-alkyl chain), 107.5 (CH), 107.66 (CH), 108.28 (CH), 119.02 (CH), 125.02 (2 \(\times\) CH-Ar), 132.25 (CH), 133.19 (C), 141.01 (2 \(\times\) C), 150.31 (CH), 155.03 (C-F), 163.98 (C=O, acid), 181.22 (C=O, ketone);

Mass (ES): \(m/z\) 481 [M+H]\(^+\); Anal. Calcd. for C\(_{27}\)H\(_{29}\)FN\(_2\)O\(_5\): C, 67.49; H, 6.08; F, 3.95; N, 5.83; O, 16.65%. Found: C, 67.41; H, 6.12; F, 3.98; N, 5.88; O, 16.72%.

**2.2.10. Preparation of 1-cyclopropyl-7-((2,3-dihydro-1H-inden-2-yl)(2-propoxyethyl)amino)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (155j)**
2-Propoxy ethyl-4-methyl benzene sulfonate 153i (6.32 g, 24.46 mmol) was dissolved in DMF (15 ml), added powdered potassium hydroxide (36.69 mmol) and the mixture was heated to 40-45°C. The compound 155a (5.0 g, 12.23 mmol) was added portion wise to above reaction mass and maintained for 4h at the same temperature. The progress of the reaction was monitored by TLC. The reaction mixture was quenched into crushed ice (50g) and pH was adjusted to 6-7 with dilute hydrochloric acid. The compound was extracted into dichloromethane. The organic layer was washed with water, 5% sodium chloride solution, again with water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and obtained solid was recrystallized from methanol to afford pure title compound 155j.

Yield: 87%; Off white color; mp: 118.8-119.6°C; IR (KBr, cm\(^{-1}\)): 2961 (C-H), 1615 (C=O), 1730 (C=O); \(^1\)H NMR (DMSO-d\(_6\)): \(\delta\) 0.84-1.03 (m, 7H, 2×CH\(_2\) of cyclopropyl, CH\(_3\) of N-alkyl), 1.47-1.54 (CH\(_2\)-CH\(_3\), 2H, CH\(_2\) of N-alkyl), 2.98-3.26 (m, 4H, 2×CH\(_2\)), 3.40-3.42 (m, 2H, CH\(_2\) of N-alkyl), 3.61-3.65 (m, 2H, CH\(_2\) of N-alkyl, 3.54 (s, 3H, OCH\(_3\)), 3.61-3.65 (m, 2H, CH\(_2\) of N-alkyl), 4.23-4.25 (m, 2H, CH\(_2\) of indane), 4.71-4.76 (m, 1H, CH of cyclopropyl), 7.12-7.20 (m, 4H, Ar-H), 7.58-7.63 (dd, 1H, Ar-H), 8.41 (S, 1H, olefinic); \(^13\)C NMR (DMSO-d\(_6\)): \(\delta\) 8.98 (2×CH\(_2\), cyclopropyl), 10.49 (CH\(_3\)-alkyl chain), 22.43 (CH\(_2\)-alkyl chain, 38.69 (2×CH), 38.6 (CH), 55.68 (N-CH\(_2\)-alkyl chain), 61.07 (OCH\(_3\)), 63.07 (CH-N), 68.00 (CH\(_2\)-Alkyl), 71.91 (CH\(_2\)-alkyl chain), 107.8 (CH), 108.32 (CH), 123.8(CH), 124.61 (2×CH-Ar), 125.9 (C), 128.32 (CH), 126.46 (2×CH-Ar), 134.91 (CH), 146.9 (CH), 150.33 (C), 163.92 (C=O, acid), 175.02 (C=O, ketone); Mass (ES): \(m/z\) 495.5 [M+H]\(^+\); Anal.
Calcd. for C\textsubscript{28}H\textsubscript{31}FN\textsubscript{2}O\textsubscript{6}: C, 65.87; H, 6.12; F, 3.72; N, 5.49; O, 18.80%. Found: C, 65.88; H, 6.16; F, 3.76; N, 5.52; O, 18.72%.

2.2.11. Preparation of 7-(benzyl(2,3-dihydro-1H-inden-2-yl)amino)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid(155k)

Benzyl-4-methyl benzene sulfonate 153j (6.41 g, 24.50 mmol) was dissolved in DMF (25 ml), added powdered potassium hydroxide (42.18 mmol) and the mixture was heated to 40-45°C. The compound 155a (5.0 g, 12.23 mmol) was added portion wise to above reaction mass and maintained for 4h at the same temperature. The progress of the reaction was monitored by TLC. The reaction mixture was quenched into crushed ice (50g) and pH was adjusted to 6-7 with dilute hydrochloric acid. The compound was extracted into dichloromethane. The organic layer was washed with water, 5% sodium chloride solution, again with water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and obtained solid was recrystallized from methanol to afford pure title compound 155k.

Yield: 69%; White solid; mp: 142.8-146.8°C; IR (KBr, cm\textsuperscript{-1}): 2961 (C-H), 1724 (C=O), 1614 (C=O); \textsuperscript{1}H NMR (DMSO- d\textsubscript{6}): \delta 0.93-1.03 (m,4H, 2\times CH\textsubscript{2} of cyclopropyl), 2.98-3.25 (m, 4H, CH\textsubscript{2} of indane), 3.54 (s, 3H, OCH\textsubscript{3}), 3.96-3.97 (m, 2H, CH\textsubscript{2} of indane), 4.69-4.71 (m, 1H, CH of cyclopropyl), 5.62 (S, 2H, CH\textsubscript{2} of cyclopropyl),...
7.12-7.23 (m, 4H, Ar-H), 7.29-7.48 (m, 5H, Ar-H of N-alkyl), 7.58-7.63 (d, 1H, Ar-H), 8.46 (S, 1H, olefinic); $^{13}$C NMR (DMSO-d$_6$): $\delta$ 9.43 (2xCH$_2$, cyclopropyl), 39.14 (CH), 39.23 (2xCH), 56.02 (CH$_2$), 61.51 (OCH$_3$), 65.54 (CH-N), 107.91 (CH), 108.2 (CH), 125.04 (CH), 126.89 (2xCH-Ar), 127.9 (CH), 128.5 (2xCH), 128.17 (CH), 128.80 (2xCH-Ar), 132.76 (CH), 138.52 (C), 141.51 (CH), 148.84 (C), 152.06 (C-F), 164.82 (C=O, acid), 171.80 (C=O, ketone); Mass (ES): m/z 499 [M+H]$^+$; Anal. Calcd. for C$_{30}$H$_{27}$FN$_2$O$_4$: C, 72.27; H, 5.46; F, 3.81; N, 5.62; O, 12.84%. Found: C, 72.29; H, 5.41; F, 3.78; N, 5.65; O, 12.82%.

2.3. RESULTS AND DISCUSSION

The focus of the present investigation is on the development of a few N-substituted 1-cyclopropyl-7-((2,3-dihydro-1H-inden-2-yl)amino)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid compounds 155(a-k) starting from 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 115 which was prepared as per the following route of synthesis$^{112}$ (Scheme 39).
Initially, the conversion of 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 115 to 1-cyclopropyl-7-((2,3-dihydro-1H-inden-2-yl)amino)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 155a was tried by the reaction of 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 115 with 2-aminoindane (2,3-dihydro-1H-inden-2-amine) 159 in presence of a base. The reaction of 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 115 with 2,3-dihydro-1H-inden-2-amine 159 was carried out in various solvents like acetonitrile, N,N-dimethylformamide or dimethyl sulfoxide by deploying bases like pyridine, triethylamine, potassium carbonate and sodium hydroxide. Almost all attempts failed to give the complete conversion of starting material into the desired products with acceptable quality and quantity. This might be due to the poor solubility of starting compound 115. It was observed that the reaction did not go to completion even after the usage of excess base and prolonged reaction time.

Later, the above condensation reaction was performed using the borate complex protocol\textsuperscript{113} which furnished desired product 155a with excellent yields. 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro quinoline-3-carboxylic acid 115 was reacted with boric acid in acetic anhydride in presence of zinc chloride to get the corresponding borate complex 158. Further, compound 158 on reaction with 2-aminoindane 159 in presence of triethylamine in acetonitrile resulted 155a regioselectively with good yield (Scheme 40).
During the course of reaction, it was observed that the borate complex is quite unstable and should be used immediately.

The structure of the compound 155a was assigned on the basis of its elemental analysis, IR (KBr) spectrum (Fig. 20), $^1$H NMR Spectrum (Fig. 21), $^{13}$C-NMR spectrum (DMSO-d$_6$) (Fig. 22) and mass spectrum (Fig. 23).

The IR spectrum of compound 155a has shown absorption at 1729 cm$^{-1}$ and 1622 cm$^{-1}$ assignable to two carbonyl groups as diagnostic absorptions. Its $^1$H NMR spectrum (DMSO-d$_6$) showed signals at $\delta$ 1.02-1.10 (m, 4H, aliphatic protons of cyclopropyl ring for two CH$_2$ groups), 3.03-3.57 (m, 4H, 2CH$_2$, indane), 3.78 (1S, 3H, OCH$_3$), 4.12 (m, 1H, indane), 4.77 (m, 1H, CH of cyclopropyl), 6.07 (1H, exchangeable proton), 7.13-7.23 (m, 4H, Ar-H), 7.71-7.75 (d, 1H, Ar-H), 8.62 (S, 1H, olefinic).

Its $^{13}$C NMR (DMSO-d$_6$) spectrum showed signals at 8.98 (2×CH$_2$, cyclopropyl), 38.58 (CH), 39.4 (2×CH$_2$), 55.57 (CH-N), 61.20 (OCH$_3$), 105.94 (CH), 106.84 (CH), 107.15 (2×CH), 115.88 (CH), 124.47 (2×CH-Ar), 126.38 (2×CH-Ar), 137.82 (C), 140.89 (2×C), 150.04 (CH), 151.95 (C-F), 159.79 (C=O, acid) and 176.06 (C=O, ketone).

A mass spectrum of compound 155a when recorded in the ES technique, showed the molecular ion peak [M+H]$^+$ at 409.34 corresponding to a molecular mass of 408.15.
Fig. 20. IR (KBr) spectrum of 155a
Fig. 21. $^1$H NMR (DMSO-$d_6$) spectrum of 155a
Fig. 22. $^1$H NMR (DMSO-$d_6$) spectrum of 155a
Fig. 23. Mass spectrum of 155a
In order to add other pharmacophore on compound 155a, previously reported alkyl/aryl tosylates 153(a-j)\textsuperscript{114, 115} were used for N-alkylation on position 7 to get N-substituted indinyl amino fluoroquinolone carboxylic acid compounds 155(b-k) (Scheme 41).

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme41.png}
\caption{Scheme 41}
\end{figure}
\end{center}

Wherein R is defined as below:

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
</tr>
</thead>
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<td>155b</td>
<td>CH\textsubscript{3}</td>
</tr>
<tr>
<td>155c</td>
<td>CH\textsubscript{2}CH\textsubscript{3}</td>
</tr>
<tr>
<td>155d</td>
<td>CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}</td>
</tr>
<tr>
<td>155e</td>
<td>CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}</td>
</tr>
<tr>
<td>155f</td>
<td>CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}</td>
</tr>
<tr>
<td>155g</td>
<td>CH(CH\textsubscript{3})\textsubscript{2}</td>
</tr>
<tr>
<td>155h</td>
<td>CH\textsubscript{2}CH(CH\textsubscript{3})\textsubscript{2}</td>
</tr>
<tr>
<td>155i</td>
<td>CH\textsubscript{2}CH\textsubscript{2}OCH\textsubscript{2}CH\textsubscript{3}</td>
</tr>
<tr>
<td>155j</td>
<td>CH\textsubscript{2}CH\textsubscript{2}OCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}</td>
</tr>
<tr>
<td>155k</td>
<td>CH\textsubscript{2}Ph</td>
</tr>
</tbody>
</table>

The structure of the compound 155b was assigned on the basis of its elemental analysis, IR (KBr) spectrum (Fig. 24), \textsuperscript{1}H NMR Spectrum (Fig. 25), \textsuperscript{13}C-NMR spectrum (DMSO-d\textsubscript{6}) (Fig. 26) and mass spectrum (Fig. 27).

The IR spectrum of compound 155b has shown absorption at 1731 cm\textsuperscript{-1} and 1611 cm\textsuperscript{-1} assignable to two carbonyl groups as diagnostic absorptions. Its \textsuperscript{1}H NMR
spectrum (DMSO-d$_6$) showed signals at $\delta$ 0.92-1.04 (m, 4H, 2 × CH$_2$ of cyclopropyl), 2.98-3.32 (m, 4H, indane), 3.54 (1S, 3H, N-methyl), 3.78 (1S, 3H, OCH$_3$), 3.95-4.02 (m, 1H, CH of indane), 4.69-4.71 (m, 1H, CH of cyclopropyl), 7.12-7.23 (m, 4H, Ar-H), 7.57-7.62 (d, 1H, Ar-H), 8.42 (S, 1H, olefinic). Its $^{13}$C NMR (DMSO-d$_6$) showed signals at $\delta$ 8.99 (2×CH$_2$, cyclopropyl), 38.68 (CH), 39.5 (CH), 55.56 (CH-N), 61.05 (OCH$_3$), 107.67 (CH), 108.28 (CH), 119.41 (C), 124.58 (2×CH-Ar), 126.44 (2×CH-N), 138.15 (CH), 141.05 (2×C), 150.49 (C-F), 164.87 (C=O, acid), 171.24 (C=O, ketone). Its mass spectrum, when recorded in the ES technique, showed the molecular ion peak [M+H]$^+$ at 423 corresponding to a molecular mass of 422.16.

In same manner other compounds 155(c–k) were prepared and confirmed based on their elemental analysis, IR (KBr) spectrum, $^1$H and $^{13}$C-NMR spectrum (DMSO-d$_6$) and mass spectrum. The respective IR, $^1$H and $^{13}$C-NMR and mass spectrum were shown in Fig. 28 to Fig. 63.
Fig. 24. IR (KBr) spectrum of 155b
Fig. 25. $^1$H NMR (DMSO-d$_6$) spectrum of 155b
Fig. 26. $^{13}$C NMR (DMSO-$d_6$) spectrum of 155b
Fig. 27. Mass spectrum of 155b
Fig. 28. IR spectrum of 155c
Fig. 29. $^1$H NMR (DMSO-d$_6$) spectrum of 155c
Fig. 30. $^{13}$C NMR (DMSO-d$_6$) spectrum of 155c
Fig. 32. IR (KBr) spectrum of 155d
Fig. 33. $^1$H NMR (DMSO-d$_6$) spectrum of 155d
Fig. 34. $^{13}$C NMR (DMSO-$d_6$) spectrum of 155d
Fig. 35. Mass spectrum of 155d
Fig. 36. IR (KBr) spectrum of 155e
Fig. 37. $^1$H NMR (DMSO-$d_6$) spectrum of 155e
Fig. 38. $^{13}$C NMR (DMSO-$d_6$) spectrum of 155e
Fig. 39. Mass spectrum of 155e
Fig. 40. IR (KBr) spectrum of 155f
Fig. 41. $^1$H NMR (DMSO-$d_6$) spectrum of 155f
Fig. 42. $^{13}$C NMR (DMSO-d$_6$) spectrum of 155f
Fig. 43. Mass spectrum of 155f
Fig. 44. IR (KBr) spectrum of 155g
Fig. 45. $^1$H NMR (DMSO-$d_6$) spectrum of 155g
Fig. 46. $^{13}$C NMR (DMSO-d$_6$) spectrum of 155g
Fig. 47. Mass spectrum of 155g
Fig. 48. IR (KBr) spectrum of 155h
Fig. 49. $^1$H NMR (DMSO-d$_6$) spectrum of 155h
Fig. 50. $^{13}$C NMR (DMSO-d$_6$) spectrum of 155h
Fig. 51. Mass spectrum of 155h
Fig. 52. IR (KBr) spectrum of 155i
Fig. 53. $^1$H NMR (DMSO-$d_6$) spectrum of 155i
Fig. 54. $^{13}$C NMR (DMSO-d$_6$) spectrum of 155i
Fig. 55. Mass spectrum of 155i
Fig. 56. IR (KBr) spectrum of 155j
Fig. 57. $^1H$ NMR (DMSO-$d_6$) spectrum of 155j
Fig. 58. $^{13}$C NMR (DMSO-d$_6$) spectrum of 155j
Fig. 59. Mass spectrum of 155j
Fig. 60. IR (KBr) spectrum of 155k
Fig. 61. $^1$H NMR (DMSO-d$_6$) spectrum of 155k
Fig. 62. $^{13}$C NMR (DMSO-$d_6$) spectrum of 155k
Fig. 63. Mass spectrum of 155k
2.4. BIOLOGICAL ACTIVITY

2.4.1. Antibacterial activity

*In vitro* antimicrobial activity was carried out using disc diffusion assay. Whatman no.1 filter paper discs of 5mm diameter were sterilised by autoclaving for 15 min at 121°C. The sterile discs were impregnated with the test compounds (100µg and 500µg/disc). The agar plates were then inoculated with standard inoculum (10^5 cells/mL broth) of the test organisms namely, *Staphylococcus aureus* (NCIM 2079), *Escherichia coli* (NCIM 2065), *Pseudomonas aeruginosa* (NCIM 2036), *Bacillus subtilis* (NCIM 2063), *Aspergillus niger* (NCIM 105) and *Candida albicans* (NCIM 3102). They were all obtained from National Chemical Laboratory (NCL), Pune and maintained by periodical sub culturing on nutrient agar and sabouraud dextrose agar medium. The impregnated discs were inoculated at 5°C for 1h to permit good diffusion and then transferred to an incubator at 37°C for 24h. The diameter of inhibition zone was measured using a calibre to the nearest mm. and were compared with moxifloxacin and levofloxacin 5µg/disc for bacteria and nystatin 100µg/disc for fungi.

The synthesized compounds 155(a-k) were tested for antibacterial activity against two representative Gram-positive organisms viz. *Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96), and two Gram-negative organisms viz., *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 741) by disc diffusion method recommended by National Committee for Clinical Laboratory (NCCL) standards. Minimum inhibitory concentration (MIC) values are presented in Table 1.
Table 1: Minimum inhibitory concentration (MIC) values of compounds 155(a-k)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>S.aureus 500 µg/mL</th>
<th>S.aureus 1000 µg/mL</th>
<th>B.subtilis 500 µg/mL</th>
<th>B.subtilis 1000 µg/mL</th>
<th>P.aeruginosa 500 µg/mL</th>
<th>P.aeruginosa 1000 µg/mL</th>
<th>E.coli 500 µg/mL</th>
<th>E.coli 1000 µg/mL</th>
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<td>155b</td>
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<td>18</td>
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<tr>
<td>Standard</td>
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<td>25</td>
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<td>28</td>
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</table>

Newly synthesized compounds 155a, 155f and 155k exhibited excellent antibacterial activity and compounds 155g and 155h exhibited good to moderate antibacterial activity. Especially, the compounds 155j and 155k displayed remarkable activity compared with moxifloxacin.

2.4.2. Antifungal activity

In vitro antifungal activity of newly synthesized compounds was studied against the fungal strains Candida albicans (MTCC 227) and Aspergillus niger (MTCC 282) by disc diffusion method in 500 and 1000µg/mL concentrations. The results of the activity against Candida albicans and Aspergillus niger (MTCC 282) are tabulated in Table 2. All the compounds 155(a-k) were found to have an excellent antifungal activity against A.niger and C.albicans.
Table 2: Minimum inhibitory concentration (MIC) values 155(a-k)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>500µg/mL</th>
<th>1000µg/mL</th>
<th>500µg/mL</th>
<th>1000 µg/mL</th>
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<tbody>
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<td>155a</td>
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<td>Standard Levo</td>
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<td>23</td>
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</tbody>
</table>

The zone of inhibition for compounds 155(a-k) along with standards Moxifloxacin and Levofloxacin are given in the Fig. 64 to Fig. 76.
Fig. 64. Zone of inhibition for compound 155a
Fig. 65. Zone of inhibition for compound 155b
Fig. 66. Zone of inhibition for compound 155c
Fig. 67. Zone of inhibition for compound 155d
Fig. 68. Zone of inhibition for compound 155e
Fig. 69. Zone of inhibition for compound 155f
Fig. 70. Zone of inhibition for compound 155g
Fig. 71. Zone of inhibition for compound 155h

#
Fig. 72. Zone of inhibition for compound 155i
Fig. 73. Zone of inhibition for compound 155j
Fig. 74. Zone of inhibition for compound 155k
Fig. 75. Zone of inhibition for standard moxifloxacin
Fig. 76. Zone of inhibition for standard levofloxacin
2.4. MOLECULAR DOCKING STUDIES

2.4.1. Materials and Methods

Materials

The Structure of the target protein 4GOV – Human Topoisomerase II in complex with DNA and mitoxantrone was downloaded from PDB. The structures of the different compounds were drawn using Marvinsketch software and the files were saved as MOL files. PASS (Prediction of Activity Spectra for Substances) is a software product designed as a tool for evaluating the general biological potential of an organic drug-like molecule. PASS provides simultaneous predictions of many types of biological activity based on the structure of organic compounds. Pa (probability “to be active”) estimates the chance of the compound under study is belonging to the sub-class of active compounds. Pi (probability “to be inactive”) estimates the chance of the compound under study is belonging to the sub-class of inactive compounds. Docking studies were done using iGEMDOCK\textsuperscript{118,119} which is a Graphical-Automatic Drug Design System for Docking, Screening and Post-Analysis. Absorption Distribution Metabolism Excretion (ADME) properties of the best docked compounds were predicted using the MEDCHEM DESIGNER software.

Methodology

1. The structure of compounds were drawn and prepared by fixing Hydrogen atoms.
2. The prepared compounds were then analyzed for the Activity spectra using the tool PASS Online. The Pa and Pi values of the various activities of the compound were predicted.
3. To carry out molecular docking studies, the PDB structure of the target (ID 4GOV) was loaded into the iGEMDOCK software.

4. The binding site for the target was prepared with the radius of 4 Å.

5. The following parameters were set:- Population size: 100; Generations: 50; Number of solutions: 2.

6. ‘Start Docking’ option was clicked and when docking was complete post analysis of the docked ligands were done.

7. The predicted poses and the energy list of these poses were outputted into the “best_Pose” and “fitness.txt” of the output location respectively. The predicted poses and scores of ligands are saved in the user defined output path.

8. Fitness is the total energy of a predicted pose in the binding site. The empirical scoring function of iGEMDOCK is estimated as: Fitness = vDW + Hbond + Elec.

   Here, the vdw term is van der Waal’s energy. Hbond and Elect terms are hydrogen bonding energy and electrostatic energy respectively\textsuperscript{120,121}.

2.4.2. Results and Discussion

Docking was done for all the compounds with the target 4GOV and the results of docking study and Lipinski’s properties are presented in the tables 3, 4 and 5 respectively.

The Interaction of compounds 155a-k (red) with active site residues of the target are given in Fig. 77 to Fig. 84.
Table 3: Predicted values of Pa and Pi for various activities of the compounds 155(a-k)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compound</th>
<th>Pa</th>
<th>Pi</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>155a</td>
<td>0.545</td>
<td>0.013</td>
<td>Antibacterial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.515</td>
<td>0.004</td>
<td>Topoisomerase II inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.500</td>
<td>0.011</td>
<td>RELA expression inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.490</td>
<td>0.021</td>
<td>Rhinitis treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.485</td>
<td>0.019</td>
<td>DNA synthesis inhibitor</td>
</tr>
<tr>
<td>2.</td>
<td>155b</td>
<td>0.643</td>
<td>0.052</td>
<td>CYP2H substrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.566</td>
<td>0.005</td>
<td>Antineoplastic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.516</td>
<td>0.004</td>
<td>Topoisomerase II inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.519</td>
<td>0.015</td>
<td>Antibacterial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.485</td>
<td>0.013</td>
<td>RELA expression inhibitor</td>
</tr>
<tr>
<td>3.</td>
<td>155c</td>
<td>0.694</td>
<td>0.060</td>
<td>Gluconate 2 dehydrogenase inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.490</td>
<td>0.004</td>
<td>Topoisomerase II inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.567</td>
<td>0.083</td>
<td>CYP2H substrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.504</td>
<td>0.022</td>
<td>Anti-infective</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.479</td>
<td>0.023</td>
<td>Rhinitis treatment</td>
</tr>
<tr>
<td>4.</td>
<td>155d</td>
<td>0.626</td>
<td>0.104</td>
<td>Gluconate 2 dehydrogenase inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.455</td>
<td>0.005</td>
<td>Topoisomerase II inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.541</td>
<td>0.097</td>
<td>CYP2H substrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.444</td>
<td>0.023</td>
<td>Antibacterial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.428</td>
<td>0.025</td>
<td>RELA expression inhibitor</td>
</tr>
<tr>
<td>5.</td>
<td>155e</td>
<td>0.661</td>
<td>0.080</td>
<td>Gluconate 2 dehydrogenase inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.465</td>
<td>0.020</td>
<td>Antibacterial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.444</td>
<td>0.005</td>
<td>Topoisomerase II inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.529</td>
<td>0.105</td>
<td>CYP2H substrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.415</td>
<td>0.002</td>
<td>Ophthalmic – Antibacterial</td>
</tr>
<tr>
<td></td>
<td>155f</td>
<td></td>
<td>155g</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-------</td>
<td>---</td>
<td>-------</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.648</td>
<td>0.089</td>
<td>Gluconate 2 dehydrogenase inhibitor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.686</td>
<td>0.040</td>
<td>CYP2H substrate</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.527</td>
<td>0.019</td>
<td>Antipsoriatic</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.434</td>
<td>0.005</td>
<td>Topoisomerase II inhibitor</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.413</td>
<td>0.006</td>
<td>Topoisomerase II inhibitor</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.665</td>
<td>0.045</td>
<td>CYP2H substrate</td>
<td></td>
</tr>
</tbody>
</table>
Table 4: Predicted values of Energy and interacting residues of the compounds 155(a-k) with the target Topoisomerase II

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compounds</th>
<th>Energy Kcal/mol</th>
<th>Interacting Residues</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ligand-MIX</td>
<td>-53.26</td>
<td>Gln 778, Asn 520, Glu 522</td>
</tr>
<tr>
<td>1.</td>
<td>155a</td>
<td>-50.24</td>
<td>Gln 778, Asn 520, Glu 522, Trp 467</td>
</tr>
<tr>
<td>2.</td>
<td>155b</td>
<td>-47.83</td>
<td>Asn 520</td>
</tr>
<tr>
<td>3.</td>
<td>155c</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>4.</td>
<td>155d</td>
<td>-42.60</td>
<td>Gln 778, Glu 522</td>
</tr>
<tr>
<td>5.</td>
<td>155e</td>
<td>-51.59</td>
<td>Gln 778, Asn 520, Glu 522</td>
</tr>
<tr>
<td>6.</td>
<td>155f</td>
<td>-72.26</td>
<td>Gln 778, Asn 520, Glu 522</td>
</tr>
<tr>
<td>7.</td>
<td>155g</td>
<td>2.520</td>
<td>464.540</td>
</tr>
<tr>
<td>8.</td>
<td>155h</td>
<td>1.760</td>
<td>480.540</td>
</tr>
<tr>
<td>9.</td>
<td>155i</td>
<td>-2.64</td>
<td>0</td>
</tr>
<tr>
<td>10.</td>
<td>155j</td>
<td>-47.86</td>
<td>Gln 778, Asn 520</td>
</tr>
<tr>
<td>11.</td>
<td>155k</td>
<td>0.0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 5: Predicted ADME properties of the compounds 155(a-k)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compound</th>
<th>MLogP</th>
<th>Mol.Wt.</th>
<th>HBDH</th>
<th>T_PSA</th>
<th>M_No</th>
<th>Rule of 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>155a</td>
<td>1.702</td>
<td>408.432</td>
<td>2</td>
<td>80.500</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>2.</td>
<td>155b</td>
<td>1.911</td>
<td>422.459</td>
<td>1</td>
<td>71.770</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>3.</td>
<td>155c</td>
<td>2.147</td>
<td>436.486</td>
<td>1</td>
<td>71.70</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>4.</td>
<td>155d</td>
<td>2.320</td>
<td>450.513</td>
<td>1</td>
<td>71.770</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>5.</td>
<td>155e</td>
<td>2.520</td>
<td>464.540</td>
<td>1</td>
<td>71.70</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>6.</td>
<td>155f</td>
<td>2.716</td>
<td>478.567</td>
<td>1</td>
<td>71.770</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>7.</td>
<td>155g</td>
<td>2.320</td>
<td>450.513</td>
<td>1</td>
<td>71.70</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>8.</td>
<td>155h</td>
<td>2.520</td>
<td>464.540</td>
<td>1</td>
<td>71.70</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>9.</td>
<td>155i</td>
<td>1.760</td>
<td>480.540</td>
<td>1</td>
<td>81.00</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>10.</td>
<td>155j</td>
<td>1.957</td>
<td>494.56</td>
<td>1</td>
<td>81.00</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>11.</td>
<td>155k</td>
<td>2.888</td>
<td>498.558</td>
<td>1</td>
<td>71.770</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Mol. Wt. – molecular weight (< 500); Log P-Partition Coefficient (< 5.00); HBDH- Number of Hydrogen bond donor protons (< 5.00); M_No.-Total number of Nitrogen and Oxygen atoms (< 10); T_PSA-Topological polar surface area in square angstroms; Rule of Five.- Lipinski’s Rule of Five, a score indicating the number of potential problems a structure might have with passive oral absorption.
### Table 6: Energy values and the interacting residues of the compounds with the active sites of the target, Elastase of Pseudomonas aeruginosa with an inhibitor

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compounds/Ligands</th>
<th>Energy</th>
<th>Interacting Residues</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>155a</td>
<td>-50.57</td>
<td>Arg198, Asn112, His223</td>
</tr>
<tr>
<td>2.</td>
<td>155b</td>
<td>-44.69</td>
<td>Glu115, Ala113, Glu41, His223</td>
</tr>
<tr>
<td>3.</td>
<td>155d</td>
<td>-49.45</td>
<td>Glu115, Ala113, Glu41, Asn112</td>
</tr>
<tr>
<td>4.</td>
<td>155e</td>
<td>-38.20</td>
<td>Ala113, Glu41, Arg198, Asn112</td>
</tr>
<tr>
<td>5.</td>
<td>155f</td>
<td>-71.75</td>
<td>Ala113, Glu41, Arg198, Asn112</td>
</tr>
<tr>
<td>6.</td>
<td>155g</td>
<td>-39.90</td>
<td>Glu115, Ala113, Glu41</td>
</tr>
<tr>
<td>7.</td>
<td>155k</td>
<td>-68.48</td>
<td>Glu115, Ala113, Glu41, Arg198, Asn112</td>
</tr>
</tbody>
</table>

### Table 7: The Glide score

<table>
<thead>
<tr>
<th>Molecule ID</th>
<th>Glide Score</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>155a</td>
<td>-6.691</td>
<td>H-Bonding with DC11, ASP 1083</td>
</tr>
<tr>
<td>155b</td>
<td>-4.950</td>
<td>NO H-Bonding, good receptor contacts (DG 10, ARG 1122, ASP 1083, MET 1075, TYR 1087, SER 1084)</td>
</tr>
<tr>
<td>155c</td>
<td>-5.212</td>
<td>H-Bonding with DG 09, SER 1084, good receptor contacts (SER 438, ASP 1083, ALA 1068, ALA 1120)</td>
</tr>
<tr>
<td>155d</td>
<td>-4.768</td>
<td>No H-Bonding, good receptor contacts (DG 10, ARG 1122, MET 1122, MET 1121, TYR 1087)</td>
</tr>
<tr>
<td>155e</td>
<td>-5.575</td>
<td>H-Bonding with DC 11, good receptor contacts</td>
</tr>
<tr>
<td>155f</td>
<td>-5.776</td>
<td>NO H-Bonds, good receptor contacts (DG 10, ASP 1083, TYR 1087)</td>
</tr>
<tr>
<td>155g</td>
<td>-5.228</td>
<td>H-Bonding with DG 09, SER 1084, good receptor contacts (ARG 1122, TYR 1087, ALA 1068, SER 1067, SER 1084)</td>
</tr>
<tr>
<td>155h</td>
<td>-6.249</td>
<td>H-Bonding with DC11, ASP 1083</td>
</tr>
<tr>
<td>155i</td>
<td>-5.554</td>
<td>H-Bonding with DC 11, good receptor contacts (DG 10, DG 11, ARG 1122, ALA 1118, ARG 1122, TYR 1087)</td>
</tr>
<tr>
<td>155j</td>
<td>-7.598</td>
<td>H-Bonding with DG10, good receptor contacts (ASP 1083, SER 1084, TYR 1087)</td>
</tr>
<tr>
<td>155k</td>
<td>-6.152</td>
<td>NO H-Bonds, good receptor contacts (DG10, MET 1121, ARG 1122, ASP 1083, SER 1084)</td>
</tr>
</tbody>
</table>
Fig. 77. Active site residues of target with Ligand Mitoxantrone (Green)

Fig. 78. Interaction of compound 155f (red) with active site residues of the target

155f: 1-cyclopropyl-7-[(2,3-dihydro-11H-inden-2-yl)isopropyl]amine)-6-fluoro-8-methoxy-4-oxo-1,4-dihydropyridine-3-carboxylic acid
1-cyclopropyl-7-((2,3-dihydro-1H-inden-2-yl)(methyl)amino)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (155b).

Fig. 79. Interaction of compound 155b (red) with active site residues of the target
7-(butyl(2,3-dihydro-1H-inden-2-yl)amino)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (155d)

Fig. 80. Interaction of compound 155d (red) with active site residues of the target
155a-1-cyclopropyl-7-((2,3-dihydro-1H-inden-2-yl)amino)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

Fig. 81. Interaction of compound 155a with active site residues of the target
Fig. 82. Interaction of compound 155e (red) with active site residues of the target
155g- 1-cyclopropyl-7-((2,3-dihydro-1H-inden-2-yl)(isobutyl)amino)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

Fig. 83. Interaction of compound 155g(red) with active site residues of the target
Fig. 84. Interaction of compound 155d (red) with active site residues of the target
From docking analysis, the energy and binding site residues of the original ligand MIX were compared with the compounds of interest and were found to be good. All the compounds except 155h, 155j and 155b were found to fit well with the binding sites of the target protein. It was found that the compounds, 155g, 155f and 155e have minimum energy than the ligand and also found to interact with Gln 778, Asn 520 and Glu 522 residues of active site similar to the ligand.

The predicted ADME properties proved that all the compounds obey Lipinski’s rule of 5. The results of docking suggest that all the compounds were efficient enough to inhibit the target protein and hence satisfy the characteristic features of drug likeliness.

Hence, the compounds can suppress the growth of cancer cells by inhibiting the topoisomerase II which is involved in cell division. But further research is needed to formulate them as drugs.

Also all these compounds were docked against the target DNA gyrase of Staphylococcus aureus using GLIDE software (Schrodinger). The GLIDE score, H- Bonds and interacting residues of the compounds 155a-k with the target were predicted. The results suggest that, among the eleven compounds, 155a, 155c, 155e, 155h, 155g, 155i and 155j were found to interact with the active site residues ASP1083 and SER 1084 of the target by forming hydrogen bonds. 155a, 155h and 155j had good GLIDE Score and better interactions with the receptor. Hence, these three compounds have enhanced inhibitory activity against the target (Fig. 86 to Fig. 93).

The crystal structure of the catalytic core (B'A' Region) Staphylococcus aureus DNA gyrase complexed with GSK299423 and DNA is given in Fig. 87 and the used are - Resolution [Å] : 3.50, R-Value : 0.210, R-Free : 0.259.
Fig. 85. The crystal structure of the catalytic core of *Staphylococcus aureus* DNA gyrase complexed with GSK299423 and DNA.
Fig. 86. 155j-Docking poses superimposed and H-Bond interactions
Fig. 87. 155a-Docking poses superimposed and H-Bond interactions
Fig. 88. 155h-Docking poses superimposed and H-Bond interactions
Fig. 89. 155k-Docking poses superimposed and H-Bond interactions

155k
Docking Score: 6.152
No Significant H-bonds
Fig. 90. 155e- Docking poses superimposed and H-Bond interactions
Fig. 91. 155i & 155f Docking poses superimposed and H-Bond interactions
Fig. 92. 155c-Docking poses superimposed and H-Bond interactions
Fig. 93. 155b and 155d-Docking poses superimposed and H-Bond interactions
2.5. CONCLUSION

In conclusion, series of novel antibacterial agents 155(a-k) were synthesized. All the synthesized compounds were evaluated for their antimicrobial activity against bacteria and fungi. Among all the newly synthesized compounds, compounds 155a and 155k exhibited excellent antibacterial activity as compared to levofloxacin. Similarly, compounds 155j and 155k exhibited excellent antifungal activity.

Docking studies were conducted for all the compounds with 4GOV using iGEMDOCK and DNA gyrase of *Staphylococcus aureus* using Glide software. From Docking analysis it was found that all these compounds were efficient enough to inhibit the target protein and hence satisfy the characteristic features of drug likeliness.