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Synthesis and antimicrobial evaluation of substituted fluoroquinolones under conventional and microwave irradiation conditions

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ABSTRACT

A series of new fluoroquinolones analogs (3a-i) were prepared under conventional and microwave irradiation technique. Ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (1) on reaction with boric acid and acetic anhydride in the presence of catalytic amount of zinc chloride under reflux, resulted in an unstable borate complex. Which was instantaneously treated with morpholine, piperidine, thiomorpholine, 2,6-dimethylmorpholine, 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride, 5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4*H*)-one hydrochloride, 2,3-dichlorophenylpiperazine hydrochloride, 3-(piperidin-4-yl)benzo[d]isoxazole hydrochloride and 5,6,7,8-tetrahydro-[1,2,4] triazolo[4,3-a]pyrazine, in the presence of triethylamine to yield compounds 3a-i. The same compounds on the other hand synthesized using a microwave irradiation technique in the presence of triethylamine and adsorbed neutral alumina. The structures of the synthesized compounds were established on the basis of spectral and analytical data. The antimicrobial activity of newly synthesized compounds were evaluated against different microorganisms and found the compounds exhibited significant activity.

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1. Introduction

Fluoroquinolones belong to broad spectrum antibiotics, therapeutically used in the treatment of variety of Gram-positive and Gram-negative bacteria with minimum toxic side-effects [1,2]. Fluoroquinolone derivatives exhibit various pharmacological properties such as antimicrobial [3], anti-inflammatory [4], analgesic [5] and antiviral [6]. The structure activity relationship (SAR) studies of the fluoroquinolone pharmacophore led to synthesize new class of compounds with superior bactericidal activity. These derivatives inhibit two bacterial enzymes namely DNA gyrase and topoisomerase IV due to presence of fluorine atom at 6th position and modification at 7th position fluoroquinolones have also been incurporated in a variety of therapeutically interesting anti-bacterial drugs such as ciprofloxacin, levofloxacin and moxifloxacin. On the other hand, heterocyclic compounds substituted with various compounds **2a-i**, morpholine, piperidine, thiomorpholine, 2, 6-dimethyl morpholine, 4,5,6-tetrahydro thieno[3,2-c]pyridine hydrochloride, 5,6,7,7a-tetra-hydro thieno[3,2-*c*]pyridin-2(*4H*)-one hydrochloride, 2,3-dichloro phenyl piperazine hydrochloride, 3-(piperidin-4-yl)benzo[d] isoxazole hydrochloride and 5,6,7,8-tetrahydro-[1,2,4]triazolo [4,3-a]pyrazine are a promising class of bioactive heterocyclic compounds, exhibit a wide range of medicinal applications. These include anti-cancer [7], anti-microbial [8], anti-fungal [9] and anti-viral [10] activity.

A survey of the literature indicates that chemical substitution at C-7 position of fluoroquinolone ring system possess improved antibacterial activities. The pharmacological importance of substituted fluoroquinolones has motivated us to prepare a class of new fluoroquinolone derivatives (**3a-i**) [11-13]. Herein, we reported the facile synthesis of 1-cyclo propyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylates (**3a-i**) employing conventional and micro wave irradiation methods.

2. Experimental

2.1. Instrumentation

All the reagents and solvents used were of analytical grade and were used without further purification unless otherwise mentioned.

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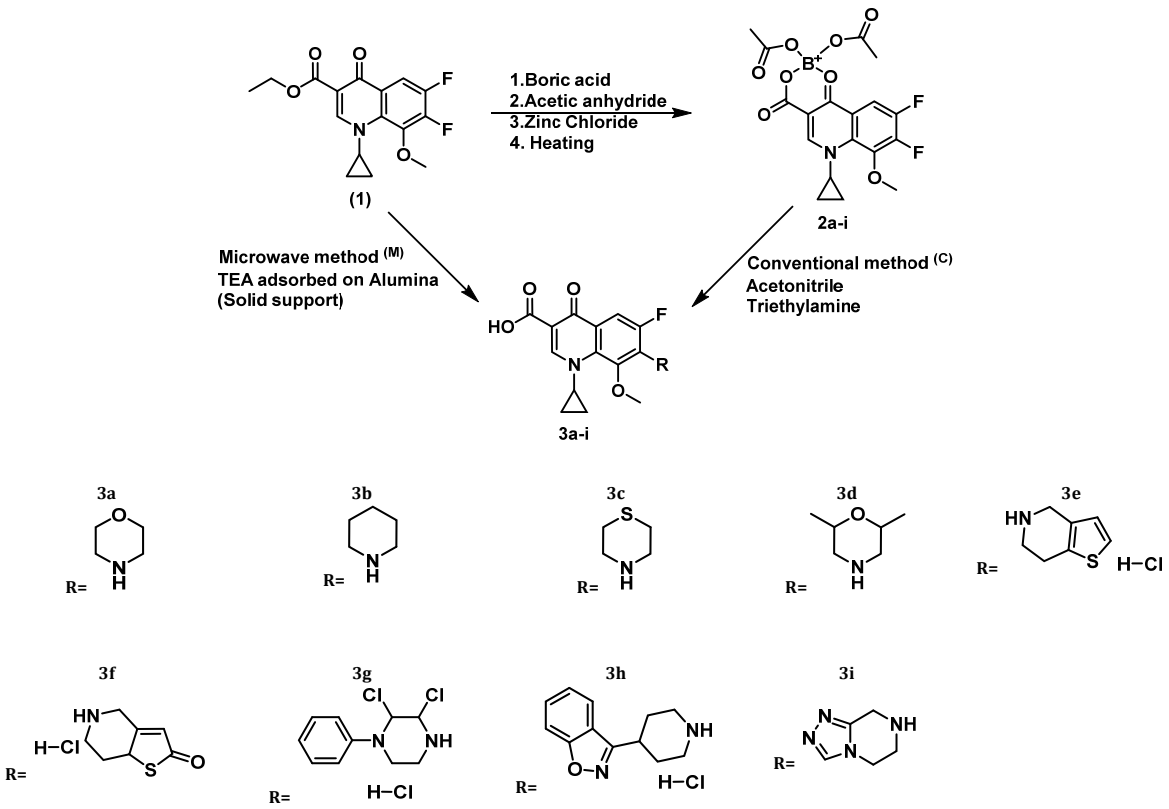

Scheme 1

Thin layer chromatography (TLC) was carried out on aluminium sheets coated with silica gel $60F_{254}$ (Merck, Darmstadt, Germany). TLC plates were inspected under UV light. Elemental analyses data were obtained by employing a Perkin-Elmer 240c analyser (Waltham, MA). IR spectra (KBr pellets) were recorded with a Perkin-Elmer 1700 spectrophotometer (Waltham, MA). ^{1}H NMR and ^{13}C NMR spectra were measured on BRUKER Avance 300 MHz spectrometer (Bruker, Bremen, Germany). Mass was recorded on Varian 300-MS spectrometer (Apeldoorn, Netherlands) and melting points were recorded on a Polmon MP96.

2.2. Synthesis

2.2.1. Microwave method

Ethyl-1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-di hydroquinoline-3-carboxylate (**1**) (5 g, 17.6 mmol) was treated with morpholine, piperidine, thiomorpholine, 2,6-dimethyl morpholine, 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride, 5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4*H*)-one hydrochloride, 2,3-dichlorophenyl piperazine hydro chloride, 3-(piperidin-4-yl)benzo[d]isoxazole hydrochloride, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (**2a-i**) (21.2 mmol) in the presence of triethyl amine adsorbed on alumina (10 mol%) and tranfered into a microwave vial. The vial was sealed and placed in microwave. The reaction was run at 100 °C for 5 minutes. The power of the entire experiment was set at 100 W. The completion of reaction was monitored by TLC. The reaction mixture was cooled to room temperature and purified by SiO_2 gel column chromatography with 9:1 methanol and Methylene dichloride to get pure compounds **3a-i**. The structures of compounds **3a-i** have been established based on IR, Mass and NMR spectra (Scheme 1).

2.2.2. Conventional method

Ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-di hydroquinoline-3-carboxylate (**1**) (100 g, 309.31 mmol) was added into a 1.0 L round bottom flask followed by acetic anhydride (200 mL) under stirring and the contents are heated to 90-95 °C for 2 hrs and cooled to 50-55 °C. At this temperature, boric acid (27.2 g, 439.91 mmol) was added in three lots with 1 hr interval for each lot and again heated to 110-115 °C for 5 hrs. The completion of reaction was monitored by TLC, and then the mass was cooled to 0-5 °C, on adding 100 mL of distilled water the material was precipitated. The reaction mass was maintained for 2 hrs, filtered, washed with 100 mL of chilled water and dried under vacuum for 10-15 hrs until constant weight attained. The resulted borate complex **I** (5 g, 11.08 mmol) immediately dissolved in acetonitrile (50 mL, 10 Volumes) and treated with different substituted morpholine, piperidine, thiomorpholine, 2,6-dimethylmorpholine, 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride, 5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4*H*)-one hydrochloride, 2,3-dichlorophenylpiperazine hydro chloride, 3-(piperidin-4-yl)benzo[d]isoxazole hydrochloride, 5,6,7,8-tetrahydro-[1,2,4] triazolo[4,3-a]pyrazine (**2a-i**) (11.08 mmol) in presence of triethylamine (2.242 g, 22.16 mmol) and the whole mixture stirred at room temperature, heated to 60-65 °C maintained for 3.0 hrs. The completion of reaction was monitored by TLC, the reaction mixture was poured into crushed ice and pH was adjusted to below 2.0 with dil. hydrochloric acid, stirred for 1-2 hrs at 20-30 °C. The precipitated product was filtered, washed with water and dried to obtain crude. The latter on re crystallization from methanol gave pure compounds **3a-i** (Scheme 1).

1-Cyclopropyl-6-fluoro-8-methoxy-7-morpholino-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid hydrochloride (**3a**): Color:

Light yellow. Yield: 64.7% [c] and 89.1% [m]. M.p.: 222-224 °C. FT-IR (KBr, ν, cm^{-1}): 3415 (OH, Acid), 2917 (CH), 2847 (CH), 2128 (CH), 1732 (C=O), 1554 (C=O), 1416 (C=C), 1298 (C-H), 1238 (C-N), 1176 (C-O), 1118 (C-F), 1058 (C-O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.037 (m, 2H, cyclopropane), 1.10 (m, 2H, cyclopropane), 3.329 (m, 4H, 2×CH_2), 3.769 (m, 4H, 2×CH_2), 3.805 (s, 3H, OCH_3), 4.173 (m, 1H, cyclopropane), 7.784-7.743 (d, *J* = 12.3 Hz, 1H, Ar-H), 8.707 (s, 1H, Olefinic proton), 14.931 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 177.5 (1C, COOH), 166.3 (1C, C=O), 148.1 (1C, CH), 146.3 (1C, C), 145.6 (1C, C), 132.5(1C, C), 129.7 (1C, C), 119.2 (1C, C), 109.3 (1C, C), 108.8 (1C, CH), 66.4 (2C, 2×CH_2), 55.9 (1C, OCH_3), 46.6 (2C, 2×CH_2), 36.3 (1C, CH, Cyclopropane), 5.6 (2C, 2×CH_2, Cyclopropane). MS (EI, *m/z* (%)): 363.4 $[M+H]^+$. Anal. calcd. for $C_{18}H_{20}$ $ClFN_2O_5$: C, 54.21; H, 5.05; N, 7.02; Found: C, 54.02; H, 4.02; N, 6.82%.

1-Cyclopropyl-6-fluoro-8-methoxy-4-oxo-7- (piperidin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride (**3b**): Color: Yellow. Yield: 75.7% [c] and 82.3% [m]. M.p.: 222-224 °C. FT-IR (KBr, ν, cm^{-1}): 3449 (OH), 2973 (CH), 2941 (CH) , 2123 (CH), 1732 (C=O), 1556 (C=O), 1466 (C=C), 1415 (C=C), 1370 (C-N), 1336 (-C=C), 1298 (C-O), 1237 (C-N), 1187 (Ar-C=C), 1103 (C-F). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.045-1.027 (m, 2H, cyclopropane), 1.150-1.101 (m, 2H, cyclopropane), 1.659 (m, 6H, 3×CH_2, piperidine), 3.32 (m, 4H, 2×CH_2, piperidine), 3.761 (s, 3H, OCH_3), 4.189-4.154 (m, 1H, cyclo propane), 7.750-7.720 (s, *J* = 9 Hz, 1H, Ar-H), 8.696 (s, 1H, Olefinic proton), 15.001 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 177.5 (1C, C=O), 166.3 (1C, C=O), 148.1 (1C, CH), 146.3 (1C, C), 145.6 (1C, C), 132.5 (1C, C), 129.7 (1C, C), 119.2 (1C, C), 109.3 (1C, C), 108.8 (1C, CH), 55.9 (1C, OCH_3), 52.7 (2C, 2×CH_2), 36.3 (1C, CH), 25.9 (1C, CH_2), 25.5 (2C, 2×CH_2), 5.6 (2C, 2×CH_2). Anal. calcd. For $C_{19}H_{22}ClFN_2O_4$: C, 57.51; H, 5.59; N, 7.06. Found: C, 57.49; H, 5.42; N, 6.86%. MS (EI, *m/z* (%)): 361.38 $[M+H]^+$.

1-Cyclopropyl-6-fluoro-8-methoxy-4-oxo-7- thiomorpholino-1,4-dihydroquinoline-3-carboxylic acid hydrochloride (**3c**): Color: Yellow. Yield: 78.7% [c] and 82.3% [m]. M.p.: 230-232 °C. FT-IR (KBr, ν, cm^{-1}): 3452 (OH), 2980 (CH), 2111 (-C-H), 1709 (C=O), 1628 (C=O), 1551 (C=C), 1473 (C=C), 1445 (-C-H), 1415 (C=C), 1368 (C=C), 1335 (C-N), 1297 (C-O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.037 (m, 2H, cyclopropane), 1.10 (m, 2H, cyclopropane), 3.329 (m, 4H, 2×CH_2), 3.62 (m, 4H, 2×CH_2), 3.81 (s, 3H, OCH_3), 4.45-4.44 (m, 1H, cyclopropane), 7.789-7.792 (d, *J* = 9.3 Hz, 1H, Ar-H), 9.08 (s, 1H, Olefinic proton), 14.931 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 177.5 (1C, COOH), 166.3 (1C, C=O), 148.1 (1C, CH), 146.3 (1C, C), 145.6 (1C, CH), 132.5 (1C, CH), 129.7 (1C, CH), 119.2 (1C, CH), 109.3 (1C, C), 108.8 (1C, CH), 66.4 (2C, 2×CH_2), 55.9 (1C, OCH_3), 46.6 (2C, 2×CH_2), 36.3 (1C, CH), 5.6 (2C, 2×CH_2). Anal. calcd. for $C_{18}H_{20}ClFN_2O_4S$: C, 52.11; H, 4.86; N, 6.75. Found: C, 52.11; H, 4.69; N, 7.62%. MS (EI, *m/z* (%)): 378.38 $[M+H]^+$.

1-Cyclopropyl-7-(2, 6-dimethylmorpholino)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride (**3d**): Color: Off white. Yield: 63.2% [c] and 92.1% [m]. M.p.: 202-213 °C. FT-IR (KBr, ν, cm^{-1}): 3345 (OH), 2725 (CH), 2562 (-C-H), 1745 (C=O), 1715 (C=O), 1492 (C=C), 1362 (C-F), 792 (=C-H). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.14-0.86 (m, 4H, cyclopropane), 1.21 (m, 6H, 2×CH_3), 1.36 (m, 1H, cyclopropane), 2.7 (m, 2H, CH_2), 3.10 (m, 2H, CH_2), 3.702-3.60 (s, 3H, OCH_3), 3.84 (m, 2H, CH), 7.95-7.953 (d, *J* = 9.3 Hz, 1H, Ar-H), 8.70 (s, 1H, Olefinic proton), 14.99 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 177.5 (1C, C=O), 166.3 (1C, C=O), 148.1 (1C, CH), 146.3 (1C, C), 145.6 (1C, C), 132.5 (1C, C), 129.7 (1C, C), 119.2 (1C, C), 109.3 (1C, C), 108.7 (1C, CH), 69.2 (2C, 2×CH), 66.4 (2C, 2×CH_2), 55.9 (1C, OCH_3), 36.3 (1C, CH), 20.5 (2C, 2×CH_3), 5.6 (2C, 2×CH_2). Anal. calcd. for $C_{20}H_{24}ClFN_2O_5$: C, 56.27; H, 5.67; N, 6.56. Found: C, 56.19; H, 5.59; N, 6.51%. MS (EI, *m/z* (%)): 391.42 $[M+H]^+$.

1-Cyclopropyl-7-(6, 7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride (**3e**): Color: Off white. Yield: 75.4% [c] and 90.1% [m]. M.p.: 202-204 °C. FT-IR (KBr, ν, cm^{-1}): 3395 (OH), 2974 (CH), 2940 (CH), 1731 (C=O), 1464 (C=O), 1415 (C=C), 1331 (C=C), 1251 (Ar-C=C), 1215 (C-F). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.074 (m, 4H, cyclopropane), 3.075-3.007 (m, 2H, CH_2), 3.705 (s, 2H, CH_2), 3.724-3.670 (s, 3H, OCH_3), 4.192 (m, 1H, cyclopropane), 4.442 (m, 2H, CH_2), 6.934 (s, 1H, Ar-H), 7.361 (s, 1H, Ar-H), 7.844-7.814 (d, *J* = 9.1 Hz, 1H, Ar-H), 8.719 (s, 1H, Olefinic proton), 14.973 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 177.5 (1C, C=O), 166.3 (1C, C=O), 148.1 (1C, CH), 146.3 (1C, C), 145.6 (1C, CH), 141.6 (1C, C), 135.2 (1C, C), 132.5 (1C, CH), 129.7 (1C, CH), 119.2 (1C, CH), 109.3 (1C, C), 108.8 (1C, CH), 62.3 (1C, CH_2), 55.9 (1C, OCH_3), 55.6 (1C, CH_2), 55.1 (1C, CH), 53.3 (1C, CH_2), 36.3 (1C, CH), 24.5 (1C, CH_2), 5.6 (2C, 2×CH_2). Anal. calcd. for $C_{21}H_{20}ClFN_2O_4S$: C, 55.94; H, 4.47; N, 6.21. Found: C, 55.82; H, 4.95; N, 6.02%. MS (EI, *m/z* (%)): 415.12 $[M+H]^+$.

1-Cyclopropyl-6-fluoro-8-methoxy-4-oxo-7-(2-oxo-7, 7a-dihydrothieno[3, 2-c]pyridin-5-(2H,4H,6H)-yl)-1, 4-dihydroquinoline-3-carboxylic acid hydrochloride (**3f**): Color: Light brown. Yield: 65.4% [c] and 93.1% [m]. M.p.: 208-210 °C. FT-IR (KBr, ν, cm^{-1}): 3383 (OH), 2950 (CH), 2920 (CH), 1780 (C=O), 1730 (C=O), 1420 (C=C), 1405 (C=C), 1235 (C-O), 1220 (Ar-C=C), 1150 (C-F). ^{1}H NMR (300 MHz, DMSO-d_6,δ, ppm): 1.074 (m, 4H, cyclopropane), 3.075-3.007 (m, 4H, CH_2), 3.715 (s, 2H, CH_2), 3.724-3.670 (s, 3H, OCH_3), 4.192 (m, 1H, cyclopropane), 4.442 (m, 1H, CH), 6.934 (s, 1H, CH), 7.844-7.814 (s, *J* = 9.1 Hz, 1H, Ar-H), 8.719 (s, 1H, Olefinic proton), 14.99 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 187.0 (1C, C=O), 177.5 (1C, C=O), 166.3 (1C, C=O), 148.1 (1C, CH), 146.3 (1C, C), 145.6 (1C, CH), 141.6 (1C, C), 132.5 (1C, CH), 129.7 (1C, CH), 119.2 (1C, CH), 109.3 (1C, C), 108.8 (1C, CH), 62.3 (1C, CH_2), 55.9 (1C, OCH_3), 55.6 (1C, CH_2), 55.1 (1C, CH), 36.3 (1C, CH), 24.5 (1C, CH_2), 35.4 (1C, CH_2), 5.6 (2C, 2×CH_2). Anal. calcd. for $C_{21}H_{20}ClFN_2O_5S$: C, 54.02; H, 4.32; N, 6.00. Found: C, 54.20; H, 4.35; N, 6.42%. MS (EI, *m/z* (%)): 431.35 $[M+H]^+$.

1-Cyclopropyl-7-(4-(2, 3-dichlorophenyl)piperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1, 4-dihydro quinoline-3-carboxylic acid hydrochloride (**3g**): Color: Yellow. Yield: 74.7% [c] and 95.2% [m]. M.p.: 238-240 °C. FT-IR (KBr, ν, cm^{-1}): 3438 (OH), 2974 (CH), 2133 (CH), 1730 (C=O), 1551 (C=O), 1465 (C=C), 1370 (C=C), 1336 (-C=C), 1298 (C-O), 1137 (C-F), 1077 (C-O), 1053 (C-Cl). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.045 (m, 2H, cyclopropane), 1.141-1.129 (m, 2H, cyclopropane), 3.081-3.053 (m, 4H, CH_2), 3.172 (m, 5H, cyclopropane + CH_2), 3.828 (s, 3H, OCH_3), 7.250 (m, 1H, Ar-H), 7.345 (m, 2H, Ar-H), 7.795-7.764 (d, *J* = 9.3 Hz, 1H, Ar-H), 9.204 (m, 1H, Olefinic proton), 14.99 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 177.5 (1C, C=O), 166.3 (1C, C=O), 152.1 (1C, CH), 148.1 (1C, CH), 146.3 (1C, C), 145.6 (1C, CH), 134.3 (1C, CH), 132.5 (1C, CH), 129.7 (1C, C), 129.2 (1C, CH), 123.8 (1C, CH), 119.8 (1C, CH), 119.2 (1C, CH), 113.8 (1C, CH), 109.3 (1C, C), 108.8 (1C, CH), 55.9 (1C, OCH_3), 49.9 (2C, 2×CH_2), 49.1 (2C, 2×CH_2), 36.3 (1C, CH), 5.6 (2C, 2×CH_2). Anal. calcd. for $C_{24}H_{23}Cl_3FN_3O_4$: C, 53.10; H, 4.27; N, 7.74. Found: C, 52.93; H, 4.31; N, 7.70%. MS (EI, *m/z* (%)): 507.12 $[M+H]^+$.

7-(4-(Benzo[d]isoxazol-3yl) piperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid hydrochloride (**3h**): Color: Pale yellow. Yield: 80.7% [c] and 83.9% [m]. M.p.**:** 226-228 °C. FT-IR (KBr, ν, cm^{-1}): 3386 (OH), 2980 (CH), 2129 (CH), 1547 (C=O), 1466 (C=O), 1415 (C=C), 1372 (C=C), 1299 (Ar-C=C), 1123 (C-F), 1078 (C-O), 1009 (=C-H). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.15-1.05 (m, 4H, cyclopropane), 1.23 (m, 2H, CH_2), 2.04-2.01 (m, 2H, CH_2), 2.18 (m, 2H, CH_2), 2.78 (m, 1H, CH), 3.61 (m, 2H, CH_2), 3.82 (s, 3H, OCH_3), 4.20 (m, 1H, cyclopropane), 7.36-7.33 (m, 2H, Ar-H), 7.80-7.72 (m, 2H, Ar-H), 8.08 (m, 1H, Ar-H), 8.72 (s, 1H, Olefinic proton), 14.99 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 177.5 (1C, C=O), 166.5 (1C, CH), 166.3 (1C, C=O), 164.2 (1C, CH), 148.1 (1C, CH), 147.1 (1C, CH), 146.3 (1C, C), 145.6 (1C, CH), 132.5 (1C, CH), 129.7 (1C, C), 123.8 (1C,

Table 1. Minimum inhibitory concentration (MIC) values of synthesized compounds.

Test compounds	Microorganisms and minimum inhibitory concentration (µg/mL)						
	Gram positive (Kirby Bauer)			Gram negative (Muller Hinton)			Fungus
	Staphylococcus aureus	*Streptococcus pyogenes*	*Bacillus megaterium*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*	*Cladosporium sps.*
3a	48.57	33.33	28.00	26	30	29	14.66
3b	29.52	26.66	20.33	18	28	21	-
3c	31.66	17.33	23.57	19	30	20	-
3d	32.66	22.52	18.66	19	28	22	20.33
3e	34.57	23.52	20.33	20	23	20	10.66
3f	18.57	18.33	16.57	17	24	15	9.33
3g	32.66	20.66	14.66	29	20	15	-
3h	33.57	19.33	18.57	13	20	15	21.33
3i	43.57	32.33	26.66	29	36	26	29.57
Standard	24.11	28.66	31.57	21.2	21	22	40

CH), 119.2 (1C, C), 117.8 (1C, C), 110.0 (1C, CH), 109.3 (1C, CH), 108.8 (1C, CH), 96.9 (1C, CH), 55.9 (1C, OCH_3), 50.1 (2C, 2xCH_2), 36.3 (1C, CH), 35.4 (1C, CH), 29.8 (2C, 2xCH_2), 5.6 (2C, 2×CH_2). Anal. calcd. for $C_{26}H_{25}ClFN_3O_5$: C, 60.76; H, 4.90; N, 8.18. Found: C, 60.76; H, 5.10; N, 8.26%. MS (EI, *m/z* (%)): 478.38 $[M+H]^+$.

1-Cyclosspropyl-7-(5, 6-dihydro-[1, 2, 4]triazolo[4, 3-a]pyrazin-7-(8H)-yl)-6-fluoro-8-methoxy-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid (**3i**): Color: Off white. Yield: 55.4% [c] and 83.1% [m]. M.p.: 195-226 °C. FT-IR (KBr, ν, cm^{-1}): 3375 (OH), 2853 (CH), 2621 (CH), 1765 (C=O), 1725 (C=O), 1520 (C=C), 1456 (C=C), 1025 (C-F), 1011 (=C-H), 887 (C-N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 0.53 (m, 4H, cyclopropane), 1.35 (m, 1H, cyclopropane), 3.73-3.60 (s, 3H, OCH_3), 3.83 (m, 2H, CH_2), 3.96 (m, 2H, CH_2), 4.61 (s, 2H, CH_2), 6.68 (s, 1H, Ar-H), 7.63 (s, 1H, Ar-H), 7.96 (s, 1H, Ar-H), 14.99 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 177.8 (1C, C=O), 166.3 (1C, C=O), 163.7 (1C, C), 148.3 (1C, CH), 146.6 (1C, C), 145.6 (1C, C), 141.6 (1C, CH), 132.5 (1C, C), 129.7 (1C, C), 119.7 (1C, CH), 109.3 (1C, C), 108.8 (1C, CH), 58.4 (1C, CH_2), 55.9 (1C, OCH_3), 52.3 (1C, CH_2), 36.2 (1C, CH), 27.3 (1C, CH_2), 5.6 (2C, 2×CH_2). Anal. calcd. for $C_{19}H_{19}ClFN_5O_4$: C, 52.36; H, 4.39; N, 16.07. Found: C, 52.25; H, 4.49; N, 17.50%. MS (EI, *m/z* (%)): 400.38 $[M+H]^+$.

2.3. Biological data evaluation

All newly synthesized compounds **3a-i** were screened for their anti-bacterial activity against three Gram positive organisms namely *Bacillus megaterium* (MTCC 1936), *Staphylococcus aureus* (MTCC 1936) and *Streptococcus pyogenes* (MTCC 1936) procured from Microbial Type Culture Collection Institute of Microbial Technology, Chandigarh (MTCC). The lyophilised culture was activated by inoculating into TSA + 5% defibrinated sheep blood and incubated at 37 °C for 48 hrs. This culture was taken further to follow the procedure of MIC and antimicrobial sensitivity. Growth medium for testing sensitivity used nutrient agar media, peptone: 5 g, beef extract: 3 g, sodium chloride (NaCl): 5 g, agar: 20 g (pH = 7) and distilled water: 1000 mL used for testing sensitivity of the compounds.

The in-vitro antibacterial assays were carried out by adopting the Kirby Bauer method according to the National Committee for Clinical Laboratory Standards procedures for aerobic testing [14]. The microbe tested was sub-cultured twice on Mueller-Hinton agar, and the colonies (5-7) were then transferred aseptically into individual tubes containing sterile nutrient broth (10 mL). The tubes were incubated for a period of 8-12 hrs at 37 °C to attain growth at log phase. Subsequently, these inoculates were diluted with sterile distilled water to obtain a density corresponding approximately to 0.5 McFarland standard turbidity scale (1×10^6 CFU/mL). 100 µL of the test organism is aseptically transferred to the sterile nutrient agar plates (each plate containing 20-25 mL of the sterile agar medium) and spread plate technique was followed using a sterile L-shaped glass rod. The organisms were allowed to settle on the medium for 5 mins. Using a sterile cork borer 6mm bore was done. 100 µL of the test sample was transferred aseptically into the bore. In the same plate standard (Cefixime 1 mg/mL) as positive control and blank dimethylsulphoxide as negative control were maintained. The plates were incubated for 24 hrs at 37 °C. The tests were done in triplicates.

All the newly synthesized compounds **3a-i** were screened for their three Gram negative organisms including the cultures *Pseudomonas aeruginosa* (MTCC 779), *Escherichia coli* (MTCC 443) and *Klebsiella pneumoniae* (MTCC 530) were inoculated into 25 mL Luria Bertini (LB) broth and incubated in a shaker at 37 °C and 150 rpm overnight (Table 1). The synthesized compounds **3a-i** considered for the study was dissolved DMSO in aliquots 400 µg concentrations. These concentrations were checked for their antimicrobial activity (MIC) against the above mentioned organisms. The biological activities of these compounds were tested in the agar well diffusion method [15], 1000 mL of Muller-Hinton agar was sterilized and poured 30 mL agar into sterile petri plates in the laminar chamber and allow to solidify. 100 µL of the cultures were spread onto each plate using a spreader. 5 wells were punched on each plate using 8mm mega bore for five different sample concentrations. 100 µL of each sample were loaded into the wells and the plates were incubated at 37 °C for 17 hrs. The zone of inhibition was observed and antifungal activity to determine the sensitivity of the given newly synthesized samples against the selected fungal species *Cladosporium sps* (MTCC), by using the CLSI has proposed a diffusion method for mold susceptibility testing, inoculum preparation from 7-days cultures grown on potato dextrose agar, spore suspension is prepared where inoculum size is maintained 0.4×10^4 to 5×10^4 CFU/mL by adjusting spectrophotometrically at 530 nm to OD ranging from 0.9 to 0.30. Using this broth agar plates should be inoculated within 15 min after adjusting the suspension.

The entire dried agar surface is evenly streaked in the three directions by following spread plate technique using a sterile L-shaped glass rod. Allow the plates to dry for not more than 15 mins. Using a sterile cork borer 6 mm bore is done on the agar plates. The test sample of concentration 400 µg/mL is selected. In the same plate positive control Ketoconazole 1 mg/mL and negative control DMSO is maintained. The plates are incubated at 35 °C for 24-48 hrs. The tests were done in triplicates. The zone of inhibition was measured in mm using standard Hi-media scale and readings were recorded.

3. Results and discussion

Two synthetic methods for the preparation of 5-((2-(4-(1*H*-benzoimidazol-2-yl)piperidino)quinolin-3-yl)methylene) thiazolidine-2,4-dione derivatives (**3a-i**) are shown in Scheme 1. Ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (**1**) was reacted with boric acid, acetic anhydride in presence of catalytic amount of zinc chloride yielded the corresponding borate complex which was

unstable. Hence, immediately dissolved in acetonitrile and treated with 5-substituted-2-(piperidin-4-yl)-1*H*-benzo[d] imidazoles (**2a-i**) [16] in presence of triethylamine gives 7-(4-(5-substituted-benzo[d]imidazol-2-yl)piperidin-1-yl)-1-cyclo propyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**3a-i**) with acceptable yield and quality (Scheme 1).

To avoid usage of acetic anhydride and skip to synthesize unstable borate complex, same compounds were alternatively synthesized under microwave irradiation technique in presence of catalytic amount of triethylamine adsorbed on alumina solid support under microwave irradiation and surprisingly excellent yields (72-90%) were observed. The melting point, FT-IR, ^{1}H NMR, ^{13}C NMR, Mass spectral data was similar to the compounds **3a-i** synthesized under microwave irradiation.

4. Conclusion

In conclusion, we have synthesized a series of new chemical entities of 7-(4-(5-sustituted-benzo[d]imidazol-2-yl)piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro quinoline-3-carboxylic acids (**3a-i**). Alternatively, the same compounds were synthesized by green and environmentally benign methodology with the help of microwave irradiation technique. All the compounds are potentially active against microorganisms. It is evident from the microbial screening results, that most of the compounds exhibited moderate to good activity against each strain of bacteria and a strain of fungi. Among all these compounds **3a**, **3b** and **3i** exhibited excellent antibacterial activity and **3a** and **3i** shown very good activity against all the strains in comparison with others.

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