Electronic Supplementary Information

Synthesis and biological evaluation of virtually designed fluoroquinolone analogs against fluoroquinolone-resistant Escherichia coli intended for UTI

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Synthesis of ethyl 6-fluoro-7-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (1a) (Gould–Jacobs reaction).

Spectral data :^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 13.21 (1H), 8.51 (1H, s.), 7.94 (1H, d, J = 0.5 Hz), 6.56 (1H, s,), 6.49 (1H, s,), 4.86 (2H, q,), 1.11 (3H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz DMSO-d6): 175.2, 164.9 ,154.9, 149.8, 141.1, 133.3, 121.8, 114.0, 111.0, 106.6, 106.3, 103.6, 60.1, 16.3. MS (ESI) m/z (% of relative abundance) calculated for $[C_{12}H_9FN_2O_5]^+$ 280.211, Found 281.65 (M+1). Elemental analysis calculated C (51.44%), H (3.24%), N (10.2%), Found C (50.45%), H (3.56%), N (9.68%).

Synthesis of ethyl 7-amino-6-fluoro-4-oxo-1,4-dihydro quinoline-3-carboxylate (1b) (Reduction process).

Spectral data: ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 13.21 (1H, s), 8.52 (1H, s), 7.98 (1H, d, J = 0.5 Hz,), 6.58 (1H, s,), 6.41 (1H, s,), 4.85 (2H, q,), 3.31 (2H,s),1.15 (3H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz DMSO-d6):175.2, 164.9, 154.8, 149.8, 141.1, 133.3, 121.8, 114.1, 106.6, 106.3, 103.6, 60.1, 16.3. MS (ESI) m/z (% of relative abundance) calculated for $[C_{12}H_{11}FN_2O_3]^+$250.22, Found 251.40 (M+1). Elemental analysis calculated C (57.60%), H (4.43%), N (11.2%), Found C (56.47%), H (3.97%), N (10.81%).

Synthesis of 7-amino-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (1c) (Hydrolysis).

Spectral data: 1H NMR (400 MHz, DMSO-d6, ppm): δ 15.25(1H, s), 13.22 (1H, s), 8.58 (1H, s), 7.93 (1H, d, J = 0.5 Hz), 6.52 (1H, d, J = 0.5 Hz), 3.33 (2H, s). 13C NMR (100 MHz DMSO-d6):175.2, 164.9,154.9,149.8, 141.1, 121.8, 114.2, 111.1, 106.6, 106.3, 103.6. MS (ESI) m/z (% of relative abundance) calculated for $[C_{10}H_7FN_2O_3]^+$ 222.17. Found 223.69. Elemental analysis calculated C (54.06%), H (3.18%), N (12.61%), Found C (53.10%), H (2.91%), N (11.23%).

General procedure of synthesis of 7-(3-chloro-2-oxoazetidin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid derivatives (2a and 2b) (substitution reaction).

Spectral data (FQ-49): ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 14.63 (1H, s), 13.16 (1H, s,), 8.69 (1H, s,), 7.94 (1H, s), 7.34 (2H, ddd, J = 8.8), 7.22 (2H, ddd, J = 8.8), 6.89 (1H, s), 5.64 (1H, d, J = 5.5 Hz), 5.35 (1H, d, J = 5.5 Hz), 3.91-4.01 (2H, t, J = 7.4 Hz), 1.23-1.84 (6H, m), 0.86 (3H, t). ^{13}C NMR (100 MHz DMSO-d6): 173.1,167.8, 166.6, 160.5,152.6, 149.2, 141.3, 139.6, 137.6,125.6, 122.2,114.2, 111.8, 106.3, 103.6, 69.0, 59.7, 58.1, 31.0, 29.2, 25.4, 22.1, 13.8: MS (ESI) m/z (% of relative abundance) calculated for $[C_{25}H_{24}ClFN_2O_5]^+$ 486.92: found 487.84 (M+1). Elemental analysis: C (61.67%), H (4.97%), N (5.75%). Found C (61.66%), H (4.96%), N (5.72%).

Spectral (FQ-70): ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 15.33 (1H, s), 13.26 (1H, s), 8.66 (1H, s), 7.94 (1H, s), 7.36 (2H, ddd, J = 8.8), 7.12 (2H, ddd, J = 8.8), 6.89 (1H, s), 5.62 (1H, d, J = 5.5), 5.33 (1H, d, J = 5.7), 4.03-4.06 (2H, t, J = 7.2), 1.83 (2H, q), 1.25-1.39 (4H,m,), 0.88 (3H, t, J = 7.0). ^{13}C NMR (100 MHz DMSO-d6): 173.9, 167.2, 166.0, 160.5, 152.6, 148.3, 141.1, 139.7, 137.0, 125.6, 122.2, 114.2, 111.0, 106.3, 103.8, 68.2, 59.6, 58.1, 28.7, 28.3, 22.7, 14.0. MS (ESI) m/z (% of relative abundance) calculated for $[C_{24}H_{22}ClFN_2O_5]^+$ 472.12: Found 473.05 (M+1), Elemental analysis :C (60.96%), H (4.69%), N (5.92%). Found C (60.95%), H (4.66%), N (5.82%).

General procedure of synthesis of 6-fluoro-4-oxo-7-(4-oxo-1,3-thiazolidin-3-yl)-1,4-dihydroquinoline-3-carboxylic acid derivatives (2c-j) (substitution reaction)

Spectral data of (FQ-131): ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 15.49 (1H, s), 13.29 (1H, s), 8.69 (1H, s), 7.85 (1H, s), 7.30-7.48 (7H, m), 6.94 (2H, ddd, J = 8.8), 6.36 (1H, s), 3.89-4.08 (2H, d, J = 15). ^{13}C NMR (100 MHz DMSO-d6): 173.8, 170.6, 166.0, 160.4, 152.4, 148.3, 141.0, 139.3, 136.7, 128.7, 127.8, 127.8, 122.2, 114.2, 111.0, 106.3, 103.8, 69.7, 68.2, 34.6. ESI m/z (% of relative abundance) calculated for $[C_{26}H_{19}FN_2O_5S]^+$ 490.21: Found 491.35 (M+1) Elemental analysis :C(63.67%), H (3.90%), N (5.71%). Found C (63.56%), H (3.91%), N (5.72%).

Spectral data (FQ-132): ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 15.43 (1H, s), 13.33 (1H, s), 8.51 (1H, s), 7.88 (1H, s), 7.33 (2H, d, J = 8.4 Hz), 7.08 (2H, d, J = 8.8), 6.80 (1H, d, J = 0.5 Hz), 6.35 (1H, s,), 3.97 (2H, q,), 3.89 (2H, d, J = 15.4 Hz), 1.78 (4H, m,) 0.86 (3H, t, J = 7.1 Hz). ^{13}C NMR (DMSO): 173.9, 170.0, 166.1, 160.3, 152.6, 148.3, 141.1, 139.1, 137.0, 127.1, 111.0, 106.1, 103.1, 68.9, 68.5, 34.1, 32.7, 19.1, 13.0. ESI m/z (% of relative abundance) calculated for $[C_{23}H_{21}FN_2O_5S]^+$ 456.11: Found 457.21 (M+1). Elemental analysis: C (60.52%), H (4.64%), N (6.14%), Found C (60.50%), H (4.54%), N (6.12%).

Spectral data of (FQ-137). ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 15.49 (1H, s), 13.86 (1H, s), 9.36 (2H, s), 8.76 (1H, s), 7.89 (1H, d, J = 0.5 Hz), 7.32 (1H, d, J = 2.6 Hz), 6.90 (1H, d, J = 0.5 Hz), 6.88 (1H, d, J = 8.4), 6.65 (1H, d, J = 8.4Hz), 6.64 (1H, s,), 3.9-4.05 (2H, m,). ^{13}C NMR (100 MHz DMSO-d6): 173.9, 170.1, 166.0 152.5, 148.9 146.6, 145.1, 141.0, 137.2, 136.9, 136.9, 127.0, 122.2, 113.9, 111.0, 106.0, 103.6, 68.0, 34.0. ESI m/z (% of relative abundance) calculated for $[C_{19}H_{13}FN_2O_6S]^+$ 416.38. Found 417.42 (M+1) Elemental analysis: C (54.81%), H (3.15%), N (6.73%), Found C (54.71%), H (3.10%), N (6.70%).

Spectral data of (FQ-147): ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ15.48 (1H, s), 13.22 (1H, s), 9.84 (1H, s), 8.63 (1H, s), 6.74-7.89 (5H, m), 6.39 (1H, s,), 3.9 (2H, q,), 1.26 (3H, t), 3.6 (2H, d, J = 8.3). ^{13}C NMR (100 MHz DMSO-d6): 174.0, 171.1, 166.0 152.9, 148.2, 145.7, 141.3, 137.1, 136.1, 127.1, 122.0, 115.3, 111.1, 106.1, 103.3, 68.8, 64.3, 34.5, 14.3. ESI m/z (% of relative abundance) calculated for $[C_{21}H_{17}FN_2O_6S]^+$ 444.07. Found 445.35 (M+1). Elemental analysis calculated: C (56.75%), H (3.86%), N (6.30%). Found C (56.65%), H (3.56%), N (6.22%).

Spectral data of (FQ-151): ^{1}H NMR : δ 14.64 (1H, s), 13.19 (1H, s), 8.54 (1H, s,), 6.89 (5H, m), 6.34 (1H, s), 4.01 (2H, t, J = 7.4 Hz), 3.67(2H, t, J = 15.9 Hz), 1.23 (6H, m), 0.86 (3H, t, J = 7.0 Hz). ^{13}C NMR (100 MHz DMSO-d6): 173.1, 170.12, 166.5, 160.2, 152.6, 149.2, 141.3, 139.6, 137.6, 127.4, 122.2, 114.2, 111.8, 106.3, 103.6, 68.5, 34.9, 31.9, 29.2, 25.4, 22.1, 22.1, 14.0. MS (ESI) m/z (% of relative abundance) calculated for $[C_{25}H_{25}FN_2O_5S]^+$ 484.14. Found 485.38 (M+1). Elemental analysis calculated C (61.97%), H (5.20%), N (5.78%). Found C (61.92%), H (5.22%), N (5.68%).

Spectral data (FQ-172): ^{1}H NMR (400 MHz, DMSO-d6, ppm),δ 15.39 (1H, s), 13.26 (1H, s), 8.70 (1H, s), 6.88-7.82 (5H, m), 6.33 (1H, s), 4.03 (3H, t, J = 7.4 Hz), 3.70-3.99 (2H, t, J = 15.6 Hz), 1.28-1.89 (6H, m), 1.29 (1H, s,), 0.89 (3H, t, J = 7.0 Hz). ^{13}C NMR (100 MHz DMSO-d6): 172.9, 168.9, 166.0, 160.5, 152.5, 148.3, 141.1, 139.7, 137.3, 127.3, 122.2, 114.2, 111.1, 106.3, 103.8, 68.5, 68.2, 34.3, 28.7, 22.6, 14.0. MS (ESI) m/z (% of relative abundance) calculated for $[C_{24}H_{23}FN_2O_5S]^+$ 470.21. Found: 471.32 (M+1). Elemental analysis calculated C (61.27%), H (4.93%), N (5.95%). Found C (61.25%), H (4.82%), N (5.91%).

Spectral data of (FQ-177): ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 15.39 (1H, s), 13.26 (1H, s), 8.70 (1H, s), 6.88-7.82 (5H, m), 6.34 (1H, s), 4.01(3H, t, J = 15.9 Hz), 3.64 (2H, t, J = 15.9 Hz), 1.80 (2H, d, J = 7.5 Hz), 0.91 (3H, t, J = 7.5 Hz). ^{13}C NMR (100 MHz DMSO-d6): 173.9, 170, 166.1, 160.3, 152.6, 148.3, 141.1, 139.1, 137.0, 127.1, 122.1, 114.2, 111, 106.12, 103.10, 70.02, 68.53, 34.17, 22.78, 10.55. MS (ESI) m/z (% of relative abundance) calculated for $[C_{22}H_{19}FN_2O_5S]^+$ 442.25 Found 443.28. Elemental analysis calculated C (59.72%), H (4.33%), N (6.33%). Found C (59.62%), H (4.31%), N (6.30%).

Spectral data of (FQ-182): ^{1}H NMR (400 MHz, DMSO-d6, ppm): δ15.45 (1H, s), 13.22 (1H, s), 8.69 (1H, s), 7.98-6.90- (5H, m), 6.48 (1H, s), 3.65 (2H, dd, J = 15.9 Hz). ^{13}C NMR (100 MHz DMSO-d6): 174, 171.1, 166, 153.1, 152.9, 148.2, 141.3, 137.1, 136.1, 128.7, 122, 116.3, 111.1, 106.1, 103.3, 68.8, 34.5. MS (ESI) m/z (% of relative abundance) calculated for $[C_{19}H_{13}FN_2O_5S]^+$ 400.42. Found: 401.33. Elemental analysis calculated C (57.00%), H (3.27%), N (7.00%). Found C (57.10%), H (3.13%), N (7.02%).

Table S1

Multiple Linear Regression Model

MLR algorithm developed an activity predicting equation using structural properties of 45 training set compounds. It contains the following equation:

[FQ-MLR] = -109.2 + 160.5 * [ALogP] + 21.78 * [Molecular Weight] + 79.55 * [No. of HBD] + 67.48 * [No. of HBA] - 356.1 * [No. of RB] - 1035 * [No. of Rings] - 841.9 * [No of AR] + 9.641 * [MFSA] - 109.4 * [Count<ECFP_6:781519895>] - 109.4 * [Count<ECFP_6:-1100000244>] - 109.3 * [Count <EC FP_6:-1074141656>] - 109.3 * [Count<ECFP_6:6428100 91 >] - 109.3 * [Count<ECFP_6:-182236392>] - 109.3 * [Count <ECFP_6:670515721>] + 261.6 * [Count<ECFP_6:-1674600 56>] - 109.3 * [Count<ECFP_6:-992506 539>] - 109.3 * [Count <ECFP_6:-1046436026>] - 25.29 * [Count<ECFP_6:-1059365 32 0>] + 82.69 * [Count <ECFP_6:7346 03939>] - 643.3 * [Count <ECFP_6:-1087070950>] - 35.92 * [Count <ECFP_6:-141 6572622>] - 109.3 * [Count<ECFP_6:-6553440 35>] - 109.2 * [Count<ECFP_6:978469901>] - 109.2 * [Count <ECFP _6:209 9 970318>] - 109.2 * [Count<ECFP_6:2132762635>] - 14.19 * [Count <ECFP_6:471356069>] - 249.6 * [Count <EC FP_6:-1811 420270>] - 769.3 * [Coun t<ECFP_6:-58633 1102 >] + 493.5 * [Count<ECFP_6:-1531301414>] - 197.3 * [Count <ECFP_6: 195189 4094>] - 525.5 * [Count<ECFP_6:-75767 9000>] - 365.9 * [Count<ECFP_6:-756348342>] + 290 * [Count<ECFP_6:-1 31128538 9>] - 109.2 * [Count <ECF P_6:220735655>] + 534.1 * [Count<E CFP_6:-786013480>] - 109.2 * [Count <EC FP_ 6:1717462980>] - 109.2 * [Count <EC FP_6:2106656448>] + 66.62 * [Count< ECFP_6:8 64909220>] - 551.8 * [Count<ECFP _6:-408704017>] - 109.2 * [Count<ECFP_6:-662690992>] + 121.1 * [Count<ECFP_6:-8505 65340>] + 149.5 * [Count <ECFP_6:-273513279>] - 283.4 * [Count<ECFP_6:15596504 22>] - 103.9 * [Count<EC FP_6:1629170274>] + 154 * [Count <ECFP_6:-1236953626>] + 65.93 * [Count<ECFP_6:-1475015 494>] - 140.8 * [Count<ECFP_6:-805779993>] + 129.1 * [Count<ECFP_6:1134083857>] + 411.6 * [Count<ECFP_6:157 2579716>] - 1.622 * [Count<ECFP_6:-4109624 35>] - 91.3 * [Count<ECFP_6:-1249514790>] - 162.5 * [Count<E CFP_6:-949 601813>] - 532.8 * [Count<ECFP_6:863188371>] + 128.8 * [Count<ECFP_6:-922113275>] + 71.22 * [Count <ECFP_ 6:770 547857>] + 192.3 * [Count<ECFP_6:-580726395>] + 158.3 * [Count<ECFP_6:655739385>] - 113.1 * [Count<ECFP_6:-124 2983843>] + 6.33 * [Count<ECFP_6:-249785178>] + 78.98 * [Count <ECFP_6:1530134975>] + 78.89 * [Count<ECFP_6:-526062157>] - 637.2 * [Count<ECFP_6:1043790491>] + 207.7 * [Count<ECFP_6:-1869628272>] - 249.2 * [Count<ECFP_6:-1331450522>] + 38.45 * [Count<ECFP_6:779801757>] - 153.7 * [Count<ECFP_6:-100084568>] - 333.8 * [Count<ECFP_6:34 2267039>] + 192.2 * [Count<ECFP_6:-1757441599>] - 742.8 * [Count<ECFP_6:-676041646>] - 186.1 * [Count<ECFP_6:1 151284196>] - 112.9 * [Count<ECFP_ 6:655871555>] + 90.3 * [Count<ECFP_6:344562737>].

Molecular properties of the input 58 molecules

Name	AlogP	Mol. Weight	No of AR	No of HBA	No of HBD	No of Rings	No of RB	MFSA
9a1	-1.703	436.409	1	9	2	4	5	0.281
9a3	-1.951	422.383	1	9	2	4	6	0.293
9b1	-1.687	406.383	1	8	2	4	4	0.282
9b2	-1.562	420.41	1	8	2	4	6	0.27
9b3	-1.935	392.357	1	8	2	4	5	0.296
9b4	-0.328	482.479	2	8	2	5	7	0.239
9b5	-1.935	392.357	1	8	2	4	5	0.296
9b6	-1.586	406.383	1	8	2	4	6	0.283
9b7	-0.352	468.453	2	8	2	5	7	0.249
9b8	-1.935	392.357	1	8	2	4	5	0.296
9b9	-1.586	406.383	1	8	2	4	6	0.283
9b10	-0.352	468.453	2	8	2	5	7	0.249
9c1	-1.022	440.828	1	8	2	4	4	0.268
9c2	-0.898	454.855	1	8	2	4	6	0.257
9c3	-1.271	426.802	1	8	2	4	5	0.28
9c4	0.337	516.924	2	8	2	5	7	0.229
9d1	-1.759	407.371	1	9	2	4	4	0.316
9d2	-1.635	421.398	1	9	2	4	6	0.302

9d3	-2.008	393.345	1	9	2	4	5	0.331
9d4	-0.4	483.467	2	9	2	5	7	0.267
9d5	-2.008	393.345	1	9	2	4	5	0.331
9d6	-1.659	407.371	1	9	2	4	6	0.316
9d7	-0.424	469.441	2	9	2	5	7	0.278
9d8	-2.008	393.345	1	9	2	4	5	0.331
9d9	-1.659	407.371	1	9	2	4	6	0.316
9d10	-0.424	469.441	2	9	2	5	7	0.278
Bay	0.175	370.417	1	5	2	5	3	0.205
Bay-DNP	4.876	536.508	2	9	1	6	6	0.311
Cip-2NP	3.537	452.435	2	8	1	5	5	0.258
Cip-4NP	3.537	452.435	2	8	1	5	5	0.258
Cip-DAP	2.15	437.467	2	8	3	5	4	0.276
Cip-DFP	4.054	443.418	2	6	1	5	4	0.156
Cip-DMP	4.615	435.491	2	6	1	5	4	0.149
Cip-DNP	3.432	497.433	2	10	1	5	6	0.336
Cip-DOMe	3.61	467.489	2	8	1	5	6	0.18
CipEt	-1.648	305.304	1	6	3	3	5	0.327
CipEt-DNP	2.906	471.395	2	10	3	4	9	0.396
CipOMe	-1.286	361.368	1	7	2	4	4	0.237
CipOMe-DNP	3.415	527.459	2	11	1	5	7	0.331
Cip-P	3.643	407.437	2	6	1	5	4	0.165
Ciprofloxacin	-1.27	331.342	1	6	2	4	3	0.234
Enoxacin	-1.483	320.319	1	7	2	3	3	0.268
Gemifloxacin	-1.833	389.381	1	9	2	4	5	0.323
Lev-DNP	3.847	512.444	2	10	1	5	5	0.338
Levofloxacin	-1.374	361.368	1	7	1	4	2	0.206
Moxi-DNP	4.86	566.534	2	10	1	6	7	0.307
Moxifloxacin	-0.702	401.431	1	7	2	5	4	0.218
Nap-DNP	3.898	497.433	2	10	1	5	6	0.358
NApthyridone	-0.803	331.342	1	6	2	4	3	0.266
Nor-DNP	3.291	485.422	2	10	1	4	6	0.331
Norfloxacin	-1.411	319.331	1	6	2	3	3	0.228
Ofloxacin	-1.374	361.368	1	7	1	4	2	0.206
Sparfloxacin	-1.056	392.4	1	7	3	4	3	0.263
Trovafloxacin	-0.266	416.353	2	7	2	5	3	0.271
Zabofloxacin	-1.943	401.392	1	9	2	5	4	0.283
Gatifloxacin	-0.909	375.394	1	7	2	4	4	0.224
Grepafloxacin	-0.406	359.395	1	6	2	4	3	0.207
Clinafloxacin	-0.72	365.787	1	6	2	4	3	0.262

Table S2

Experimental and Predicted activity of training set compounds

Name	Experimental activity	Predicted activity	Name	Experimental activity (mg)	Predicted activity
9a1	0.06	0.148155	Cip-4NP	0.017	0.017
9a3	0.25	0.161845	Cip-DFP	1.24	1.24
9b1	0.25	0.299436	Cip-DMP	1.24	1.24
9b2	0.03	0.004986	Cip-DNP	0.035	0.035
9b3	0.06	0.031483	Cip-DOMe	1.18	1.18
9b4	0.06	0.035579	CipOMe	0.011	0.027055
9b6	0.03	0.129673	CipOMe-DNP	0.059	0.042945
9b7	0.125	0.131344	Ciprofloxacin	0.015	0.015
9b8	0.06	0.031483	Enoxacin	0.01	0.01
9b9	0.06	0.129673	gemifloxacin	0.01	0.01
9b10	0.25	0.131344	Lev-DNP	0.029	0.029
9c1	1	0.74109	Levofloxacin	0.022	0.022
9c2	0.125	0.295755	Moxi-DNP	0.028	0.028
9c3	0.5	0.588155	Moxifloxacin	0.025	0.025
9d1	0.25	0.371319	Nap-DNP	0.0125	0.028555
9d2	0.06	-0.10294	NApthyridone	0.048	0.031945
9d3	0.008	0.157517	Norfloxacin	0.094	0.094
9d4	0.008	0.049618	Sparfloxacin	0.0125	0.0125
9d6	0.125	0.236425	Trovafloxacin	0.025	0.025
9d7	0.125	0.360058	Gatifloxacin	0.05	0.05
9d8	0.25	0.157517	Grepafloxacin	0.008	0.008
9d9	0.5	0.236425	Clinafloxacin	0.015	0.015
9d10	0.5	0.360058			

Table S3

Experimental and Predicted activity of test set compounds

Name	MIC (µg/ml)	
	Experimental activity	Predicted activity
9c4	0.5	0.508
Bay	0.022	0.032
Bay-DNP	0.58	0.752
Cip-2NP	0.035	0.017
Cip-DAP	0.08	0.06
CipEt	1.31	1.631
CipEt-DNP	1.33	1.603
Cip-P	0.077	0.07
Nor-DNP	0.41	0.123
Ofloxacin	0.062	0.022
Zabofloxacin	0.015	0.016

Table S4

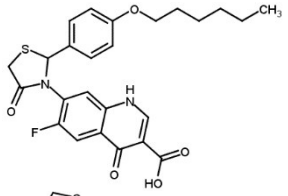
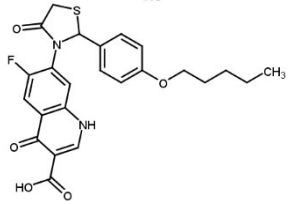
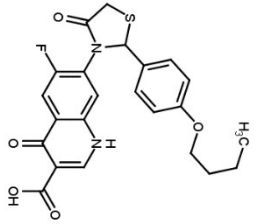
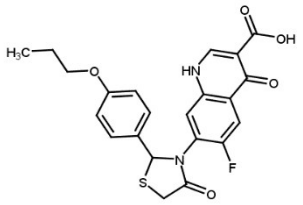
Physicochemical properties of synthesized compounds

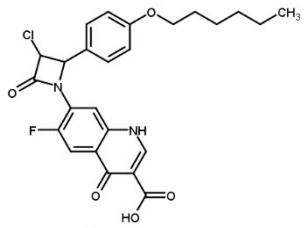
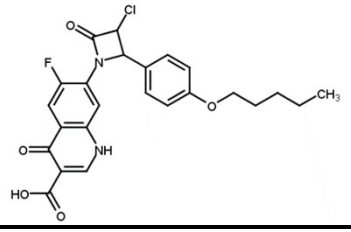
Compound	Rf Value	Yield %	M.P (°C)	Solubility	Appearance
1a	0.56	90	65-67	DMF	Yellow
1b	0.61	75	102-103	Ethanol	Brown
1c	0.49	72	96-97	Methanol	Light brown
FQ-49	0.51	72	118-119	n-Hexane	Red
FQ-70	0.61	69	115-116	n-Hexane	Yellow
FQ-131	0.52	77	154-146	1,4 Dioxane	Orange yellow
FQ-132	0.57	74	133-134	1,4 Dioxane	Yellow

FQ-137	0.42	76	139-140	1,4 Dioxane	Light yellow
FQ-147	0.61	71	184-185	1,4 Dioxane	Brown
FQ-151	0.51	70	177-178	1,4 Dioxane	Light brown
FQ-172	0.60	72	144-145	1,4 Dioxane	Light brown
FQ-177	0.62	71	140-141	1,4 Dioxane	Black
FQ-182	0.48	77	128-129	1,4 Dioxane	Brown

Table S5

Activity comparison of FQ-151, FQ-172, FQ-132, FQ-177, FQ-49, and FQ-70 compounds

Mol. No	Structure	No. of Carbon (Alkyl chain)	MIC (µM)
FQ-151		6-Chains	1.03
FQ-172		5-Chain	1.12
FQ-132		4-Chain	1.48
FQ-177		3-Chain	1.85

FQ-49		6-Chain	1.78
FQ-70		5-Chain	1.93

Figures

Fig. S1

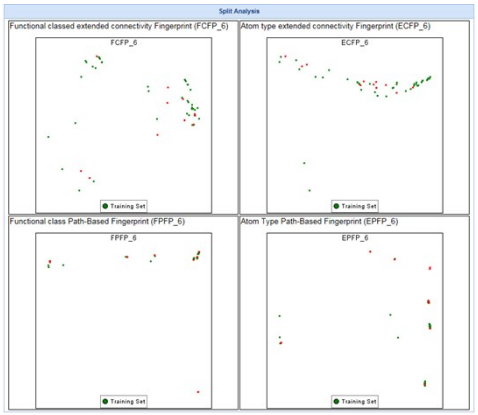


Fig. S1. Separation of 45 molecules as training set compounds based on functional, atom type extended connectivity and path-based fingerprint analysis.

Fig. S2

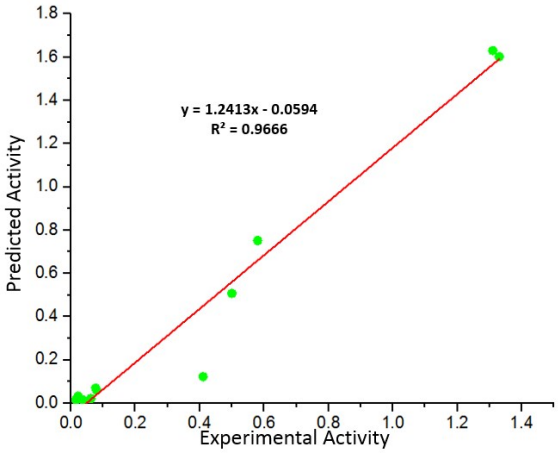


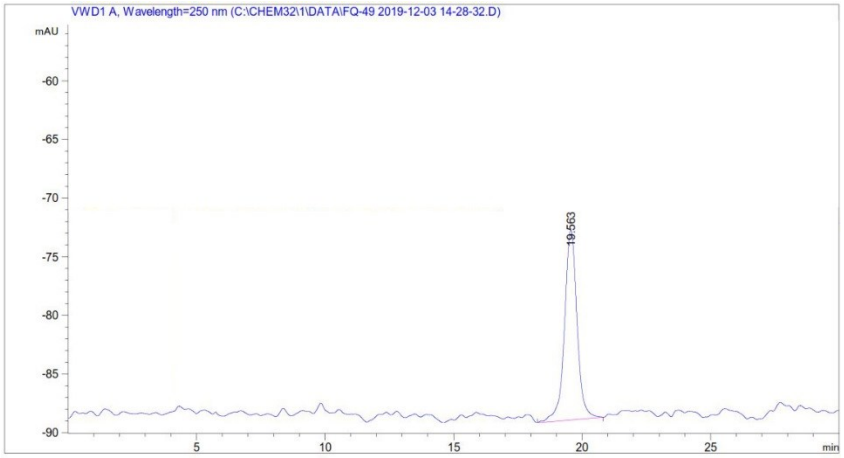
Fig.S2 Experimental and predicted activity of the 11 test set FQ molecules

Fig. S3

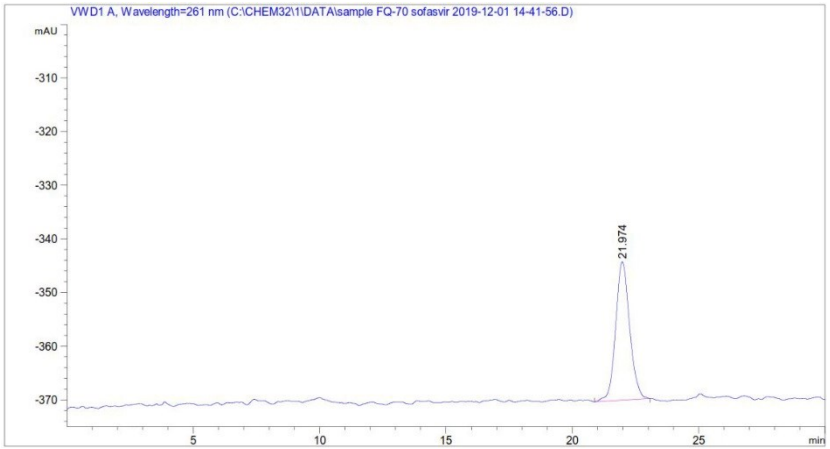
The spectra of HPLC of synthesized compounds

HPLC conditions were set as follows: instrument model: Shimadzu LPGE 30A w/o mixer; detector: 5 μm C_{18}: 4.6 mm× 20 mm. The mobile phase A and B was water and acetonitrile (0.05% TFA) respectively. The gradient program was as follows: 0–20 min, 20% to 95% B; 30 min, 95% B (V/V).

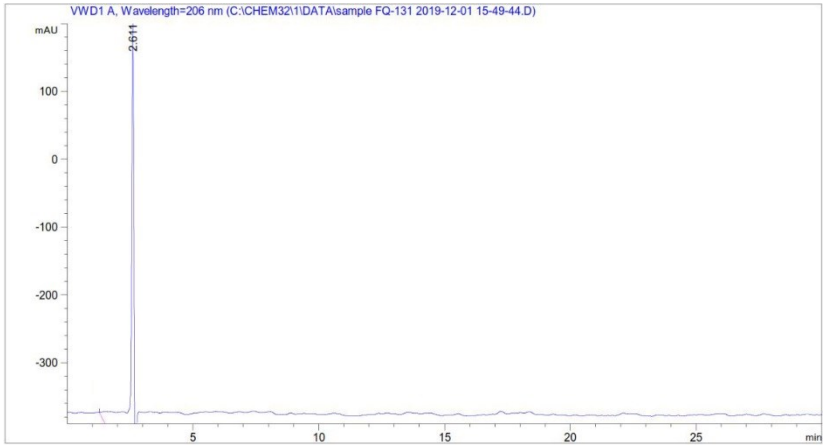
FQ-49



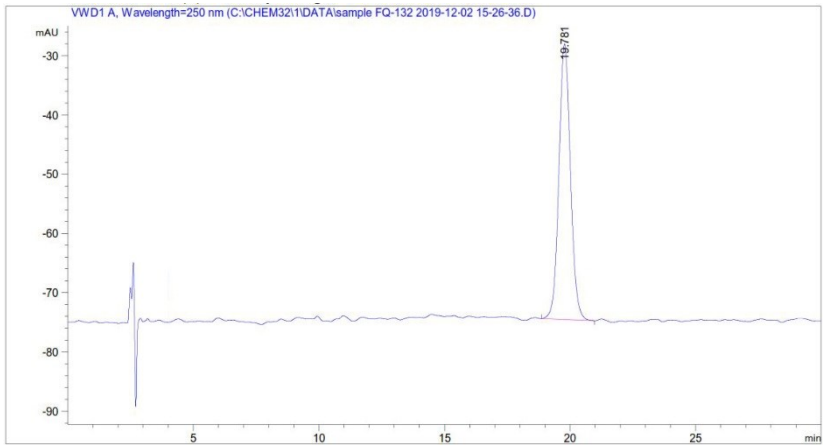
FQ-70



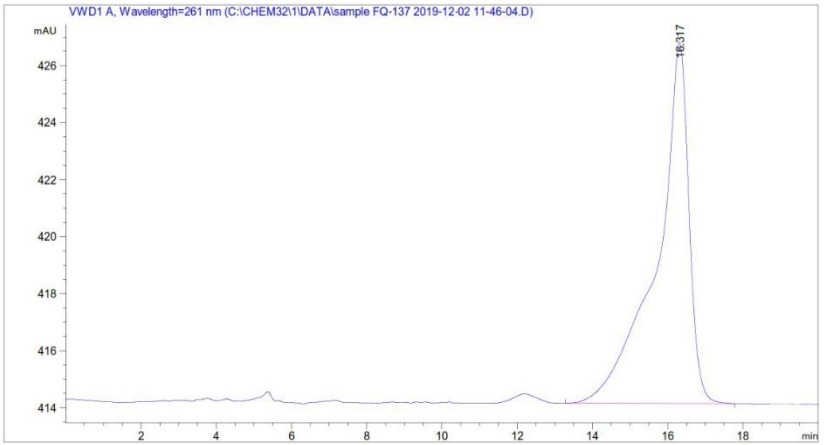
FQ-131


VWD1 A, Wavelength=206 nm (C:\CHEM32\1\DATA\sample FQ-131 2019-12-01 15-49-44.D)
mAU
2.611
100
0
-100
-200
-300
5
10
15
20
25
min

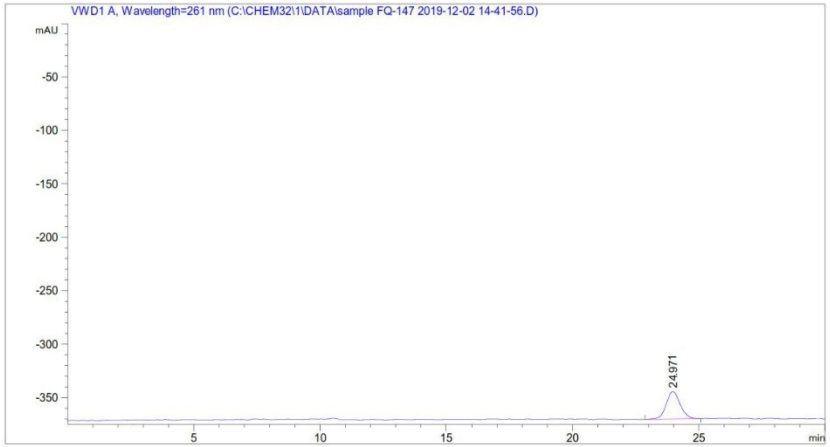
FQ-132


VWD1 A, Wavelength=250 nm (C:\CHEM32\1\DATA\sample FQ-132 2019-12-02 15-26-36.D)
mAU
19.781
-30
-40
-50
-60
-70
-80
-90
5
10
15
20
25
min

FQ-137


VWD1 A, Wavelength=261 nm (C:\CHEM32\1\DATA\sample FQ-137 2019-12-02 11-46-04.D)
mAU
426
424
422
420
418
416
414
16.317
2
4
6
8
10
12
14
16
18
min

FQ-147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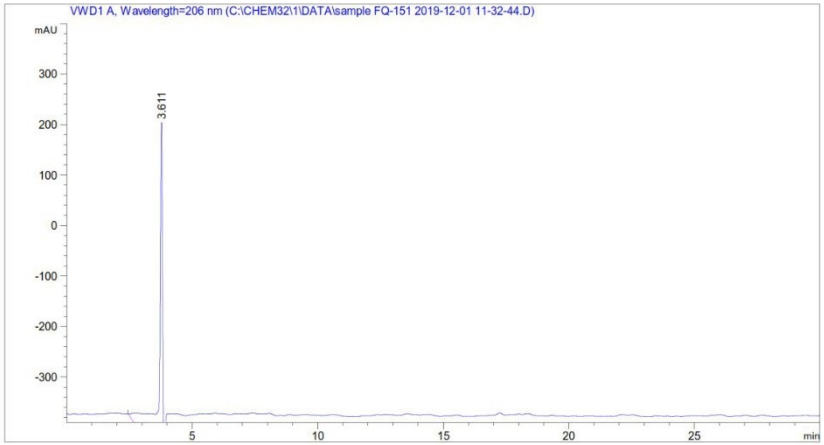
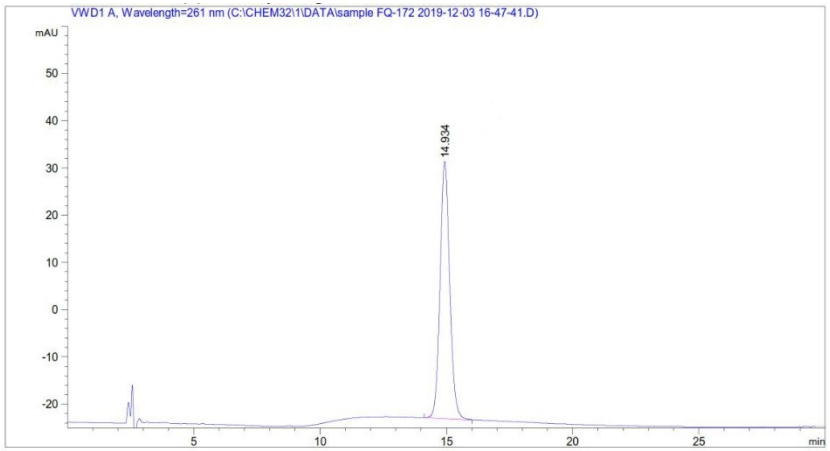
mAU
-50
-100
-150
-200
-250
-300
-350
24.971
5
10
15
20
25
min

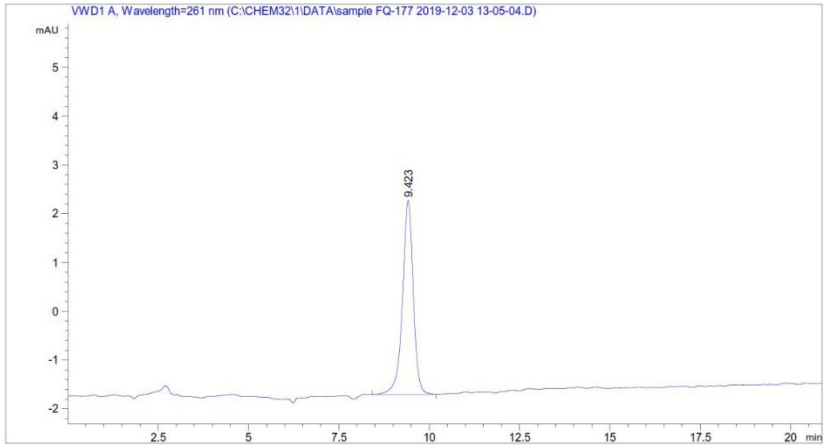
FQ-151


VWD1 A, Wavelength=206 nm (C:\CHEM32\1\DATA\sample FQ-151 2019-12-01 11-32-44.D)
mAU
300
200
100
0
-100
-200
-300
3.611
5
10
15
20
25
min

FQ-172


VWD1 A, Wavelength=261 nm (C:\CHEM32\1\DATA\sample FQ-172 2019-12-03 16-47-41.D)
mAU
50
40
30
20
10
0
-10
-20
14.934
5
10
15
20
25
min

FQ-177


VWD1 A, Wavelength=261 nm (C:\CHEM32\1\DATA\sample FQ-177 2019-12-03 13-05-04.D)
mAU
5
4
3
2
1
0
-1
-2
9.423
2.5
5
7.5
10
12.5
15
17.5
20 min

FQ-182

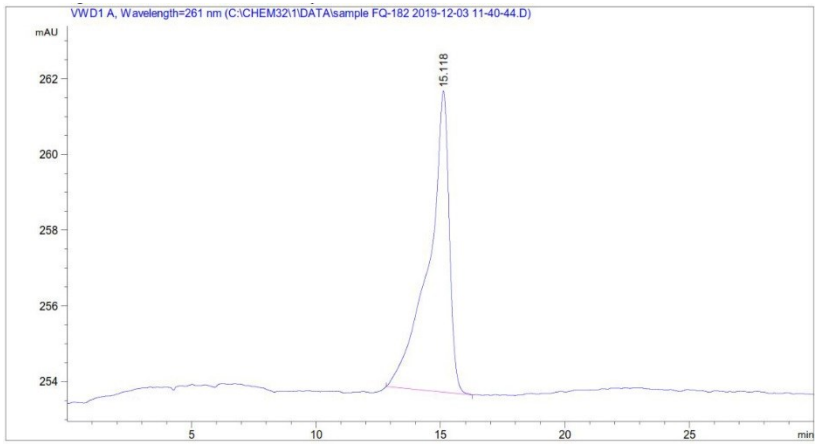

VWD1 A, Wavelength=261 nm (C:\CHEM32\1\DATA\sample FQ-182 2019-12-03 11-40-44.D)
mAU
262
260
258
256
254
15.118
5
10
15
20
25
min

Fig. S4

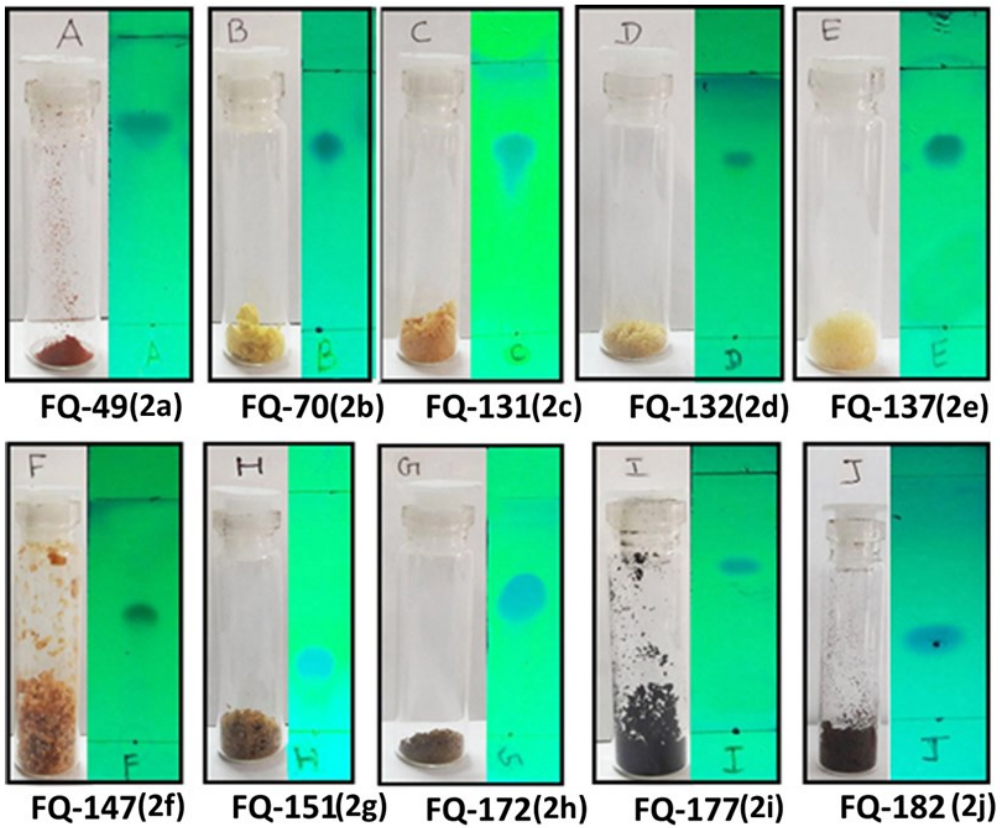
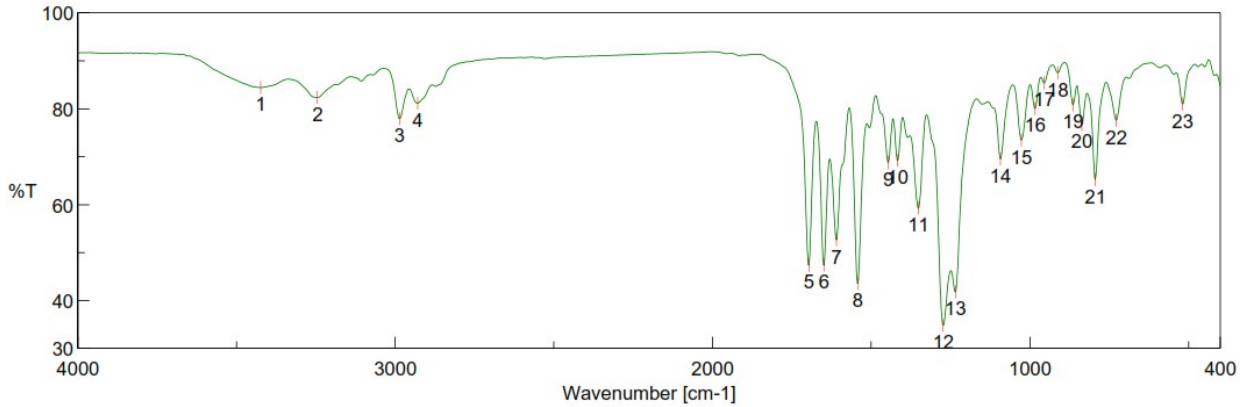


Fig S4 Synthesized compounds with TLC Results

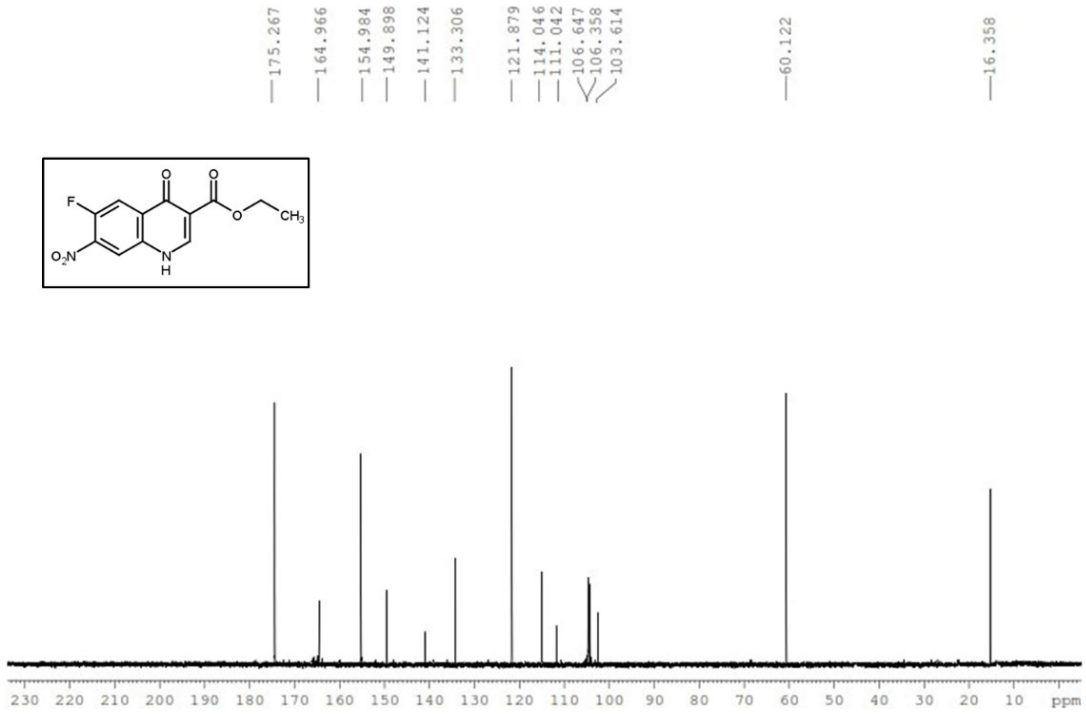
Fig. S5



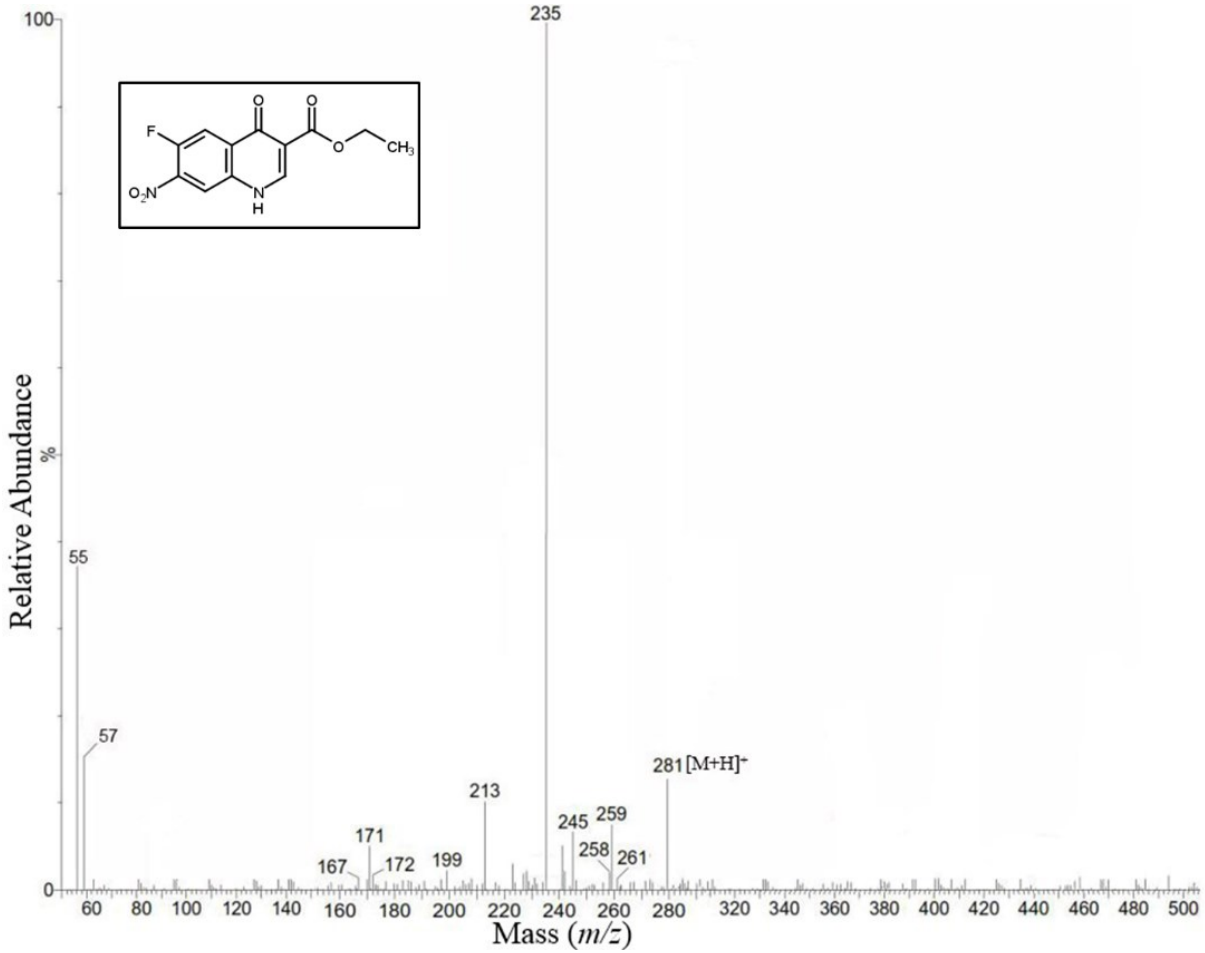
FT-IR spectrum of Ethyl 6-fluoro-7-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (1a)

Fig S5 Characterization analysis

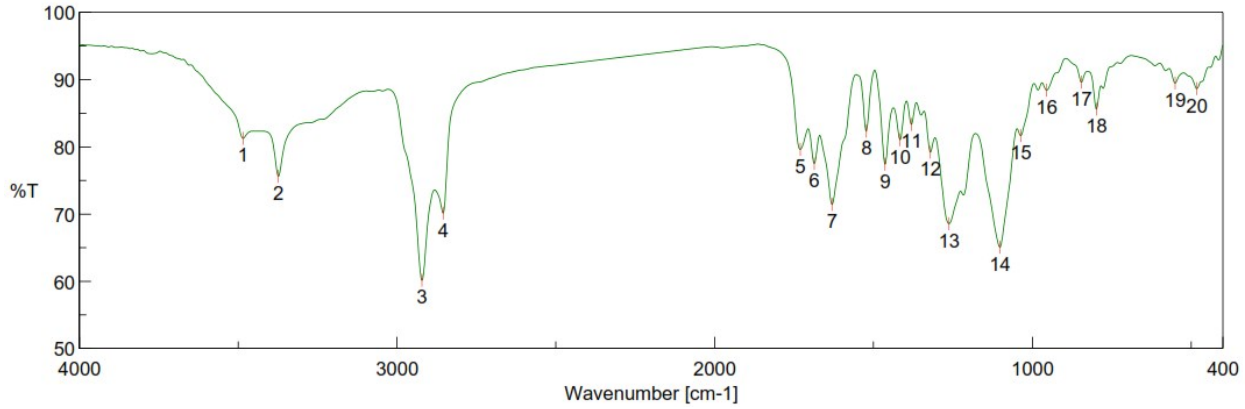
^{1}H NMR spectrum of Ethyl 6-fluoro-7-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (1a)



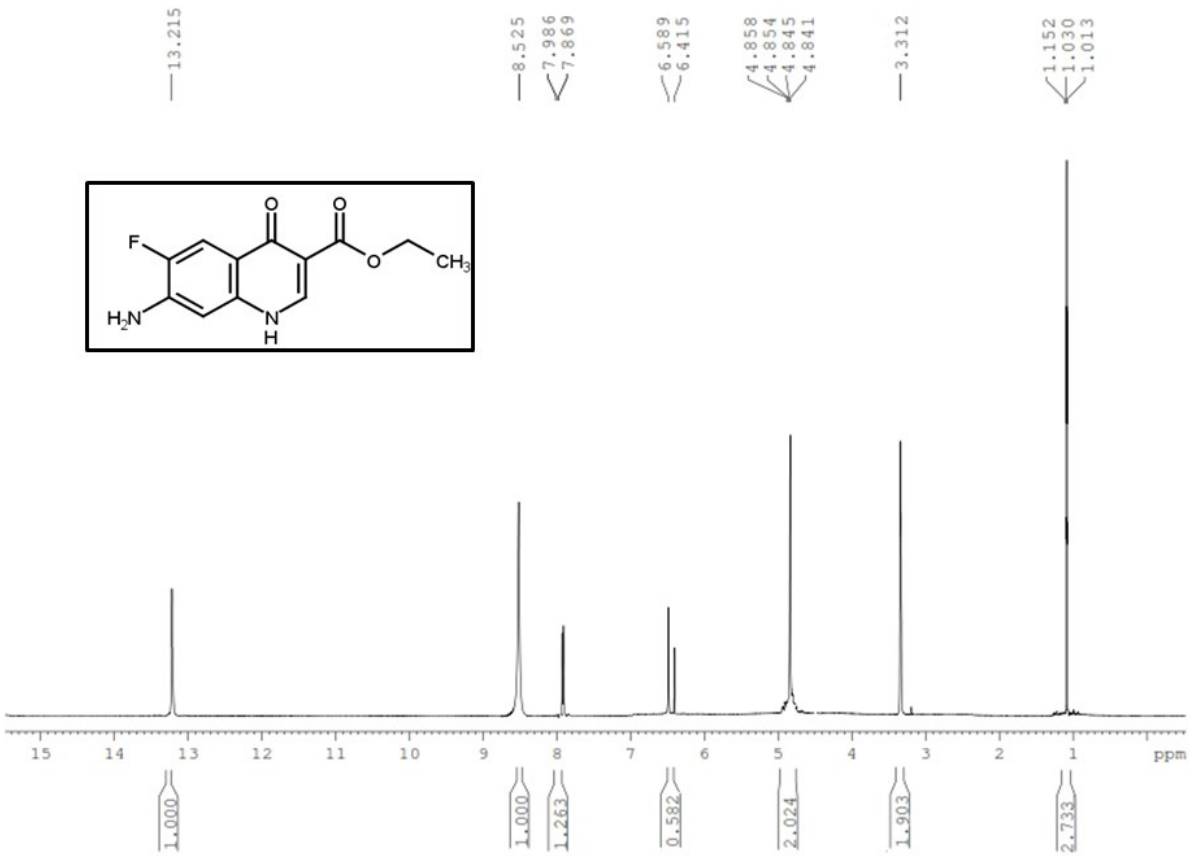
^{13}C NMR spectrum of Ethyl 6-fluoro-7-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (1a)



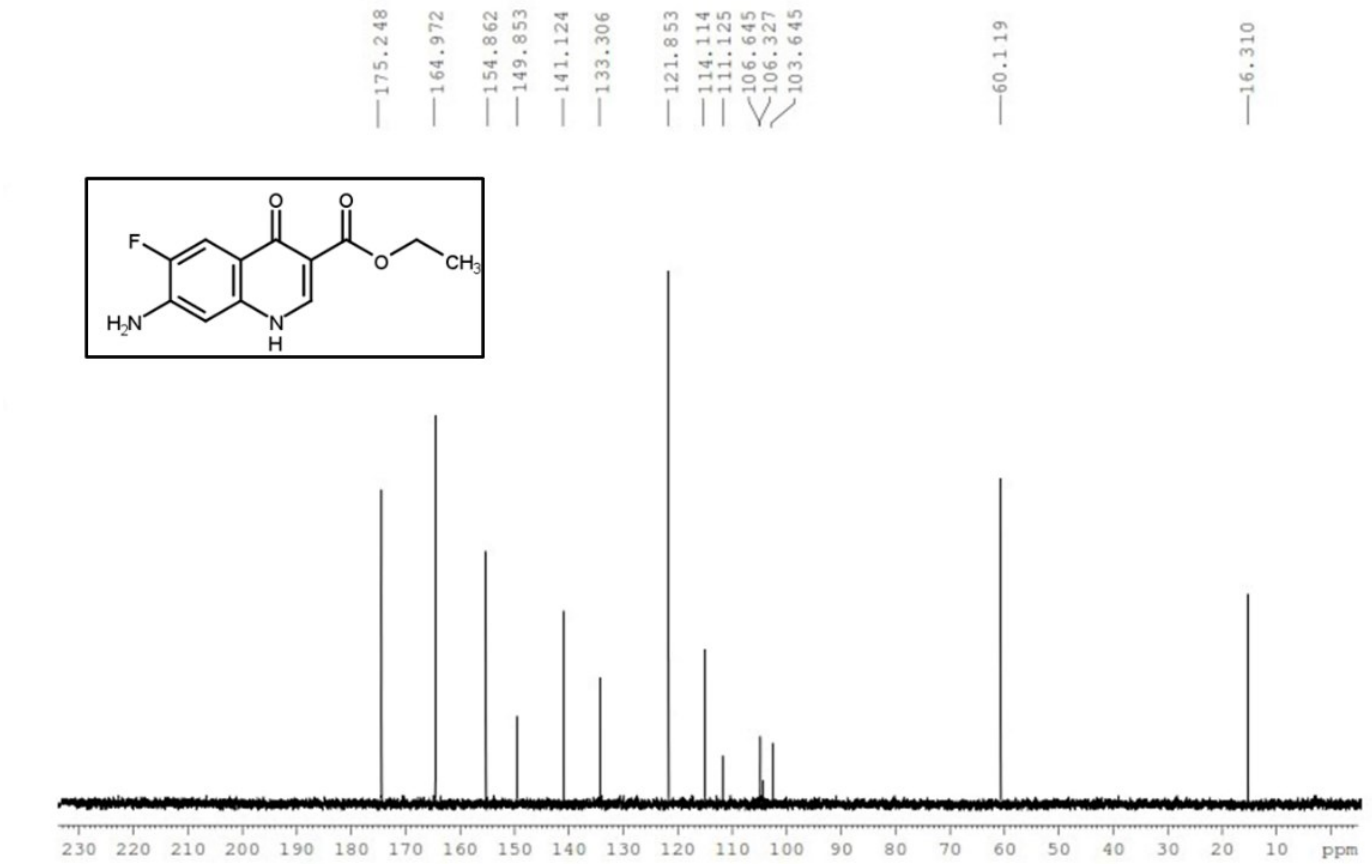
Mass spectroscopy of Ethyl 6-fluoro-7-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (1a)



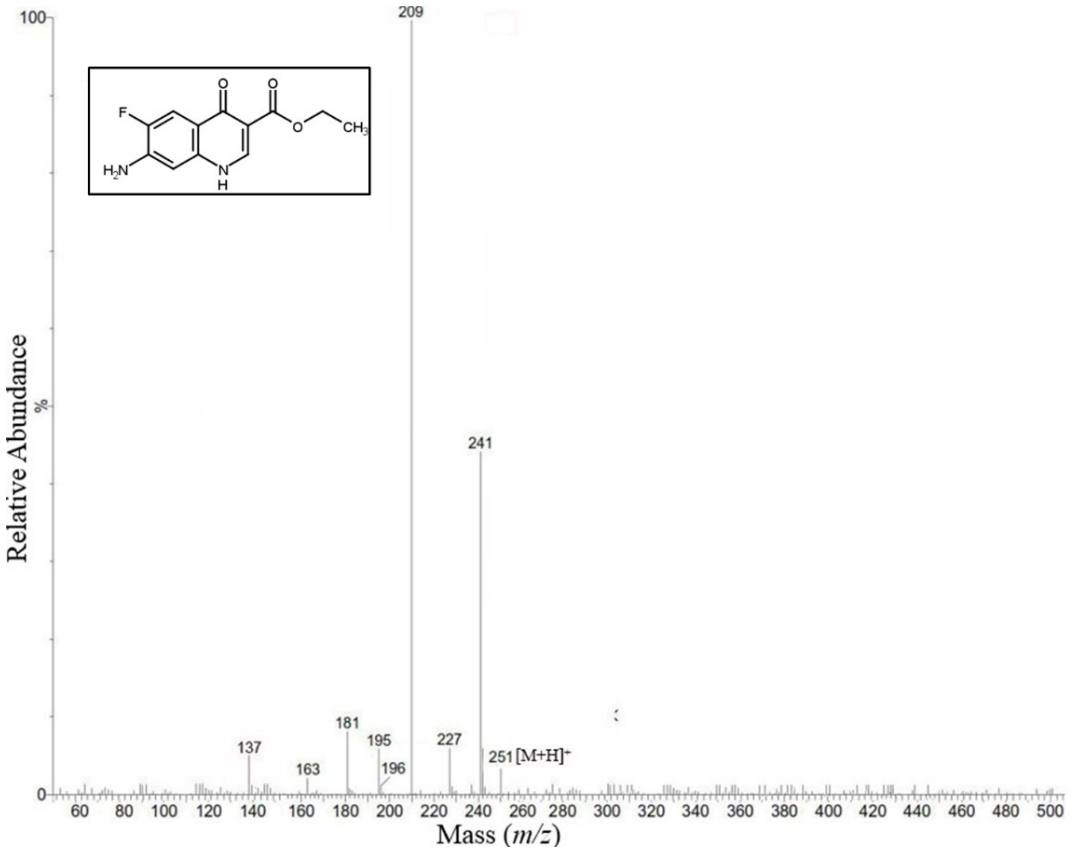
FT-IR spectrum of Ethyl7-amino-6-fluoro-4-oxo-1,4- dihydroquinoline-3-carboxylate (1b)



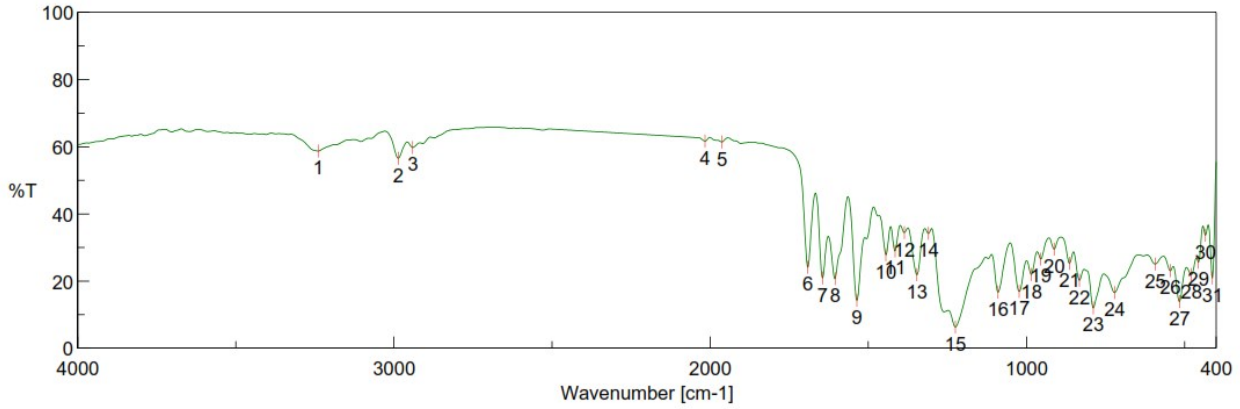
^{1}H NMR spectrum of Ethyl7-amino-6-fluoro-4-oxo-1,4- dihydroquinoline-3-carboxylate (1b)



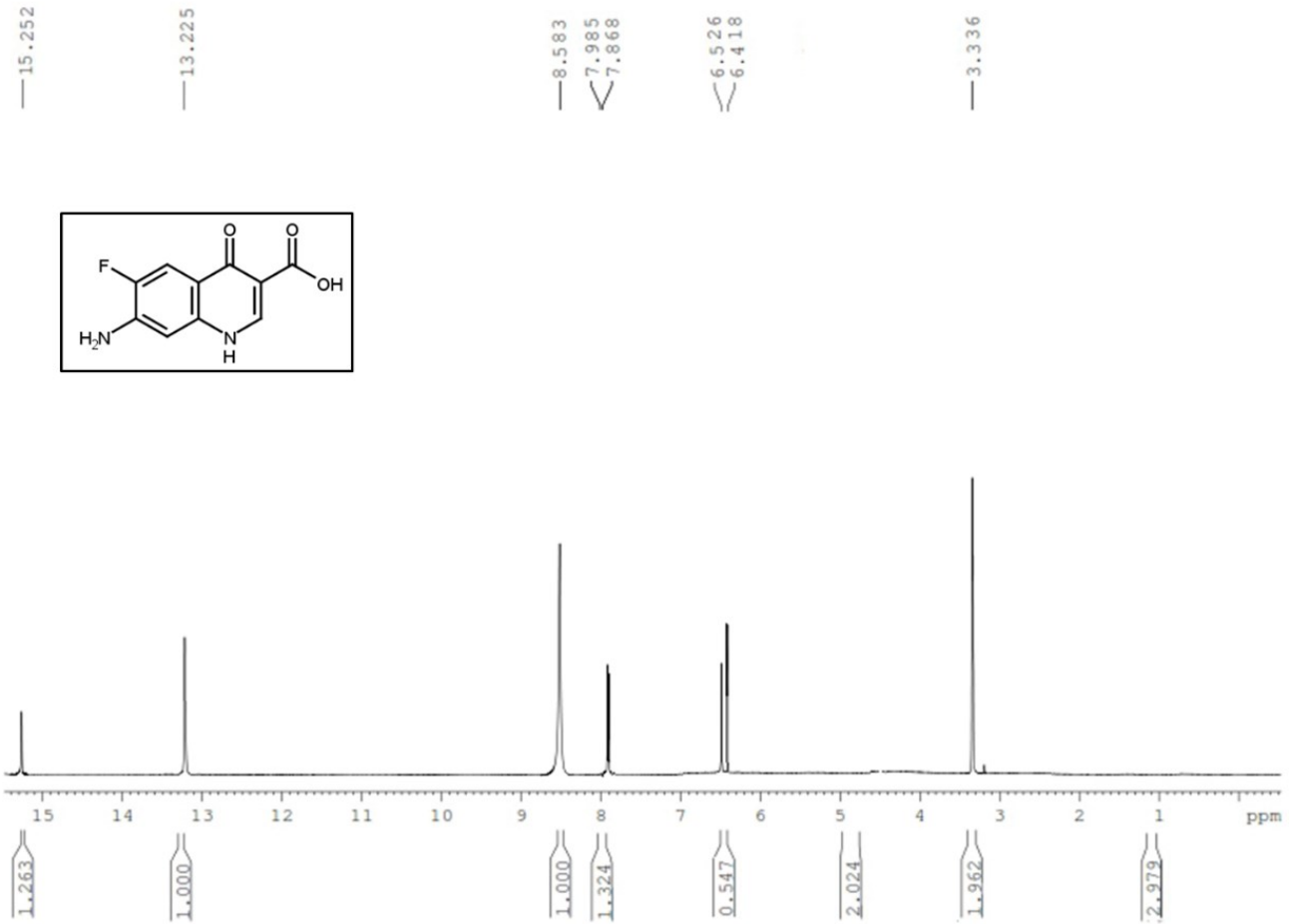
^{13}C NMR spectrum of Ethyl7-amino-6-fluoro-4-oxo-1,4- dihydroquinoline-3-carboxylate (1b)



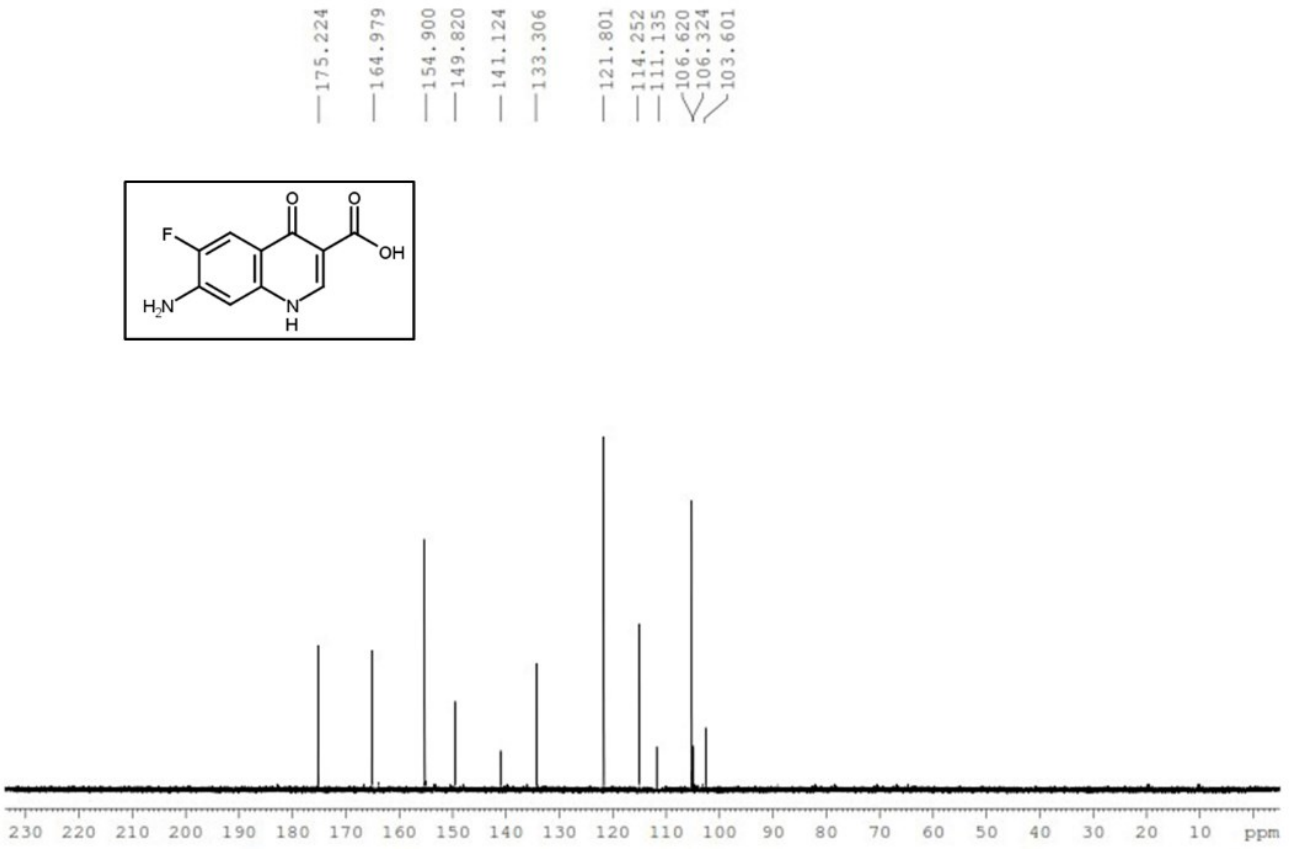
Mass spectrum of Ethyl7-amino-6-fluoro-4-oxo-1,4- dihydroquinoline-3-carboxylate (1b)



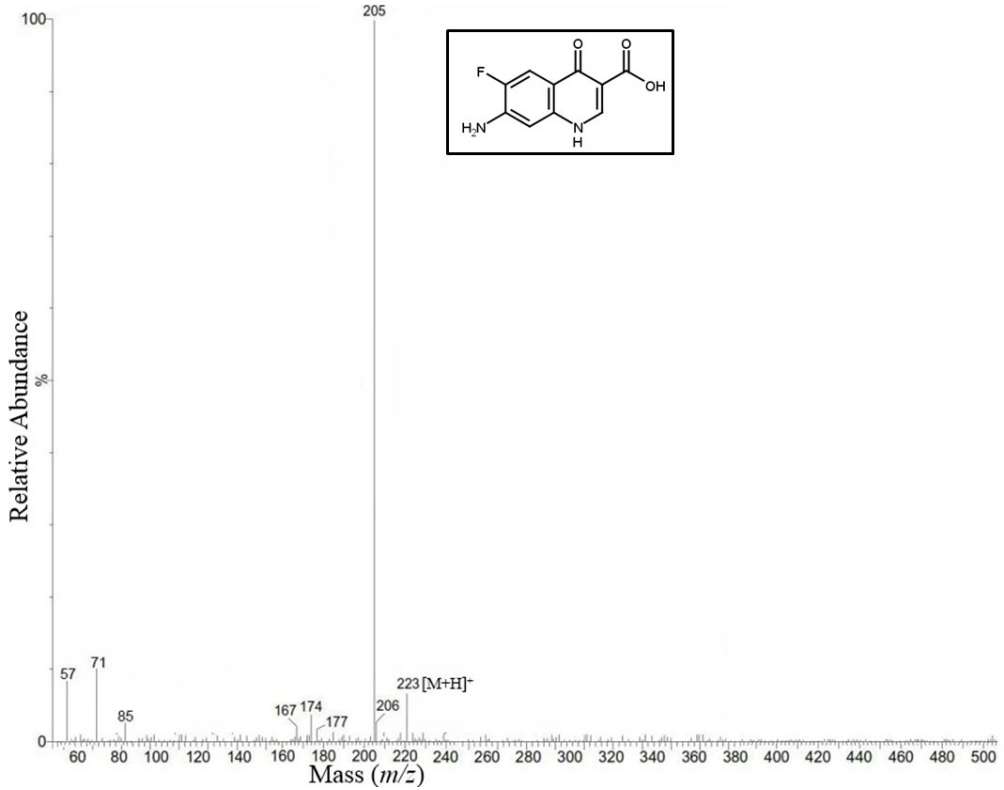
FT-IR Spectrum of 7-amino-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (1c)



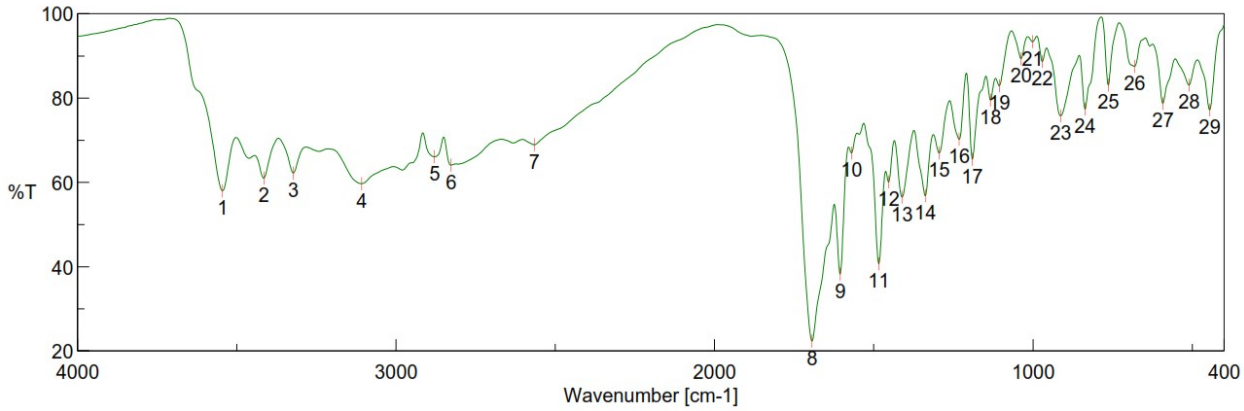
^{1}H Spectrum of IR 7-amino-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (1c)



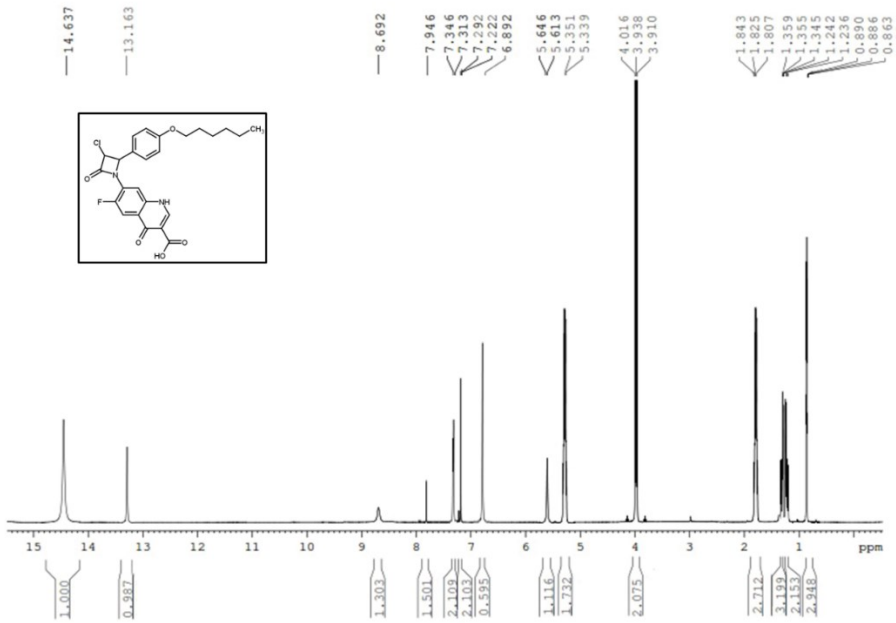
^{13}C Spectrum of IR 7-amino-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (1c)



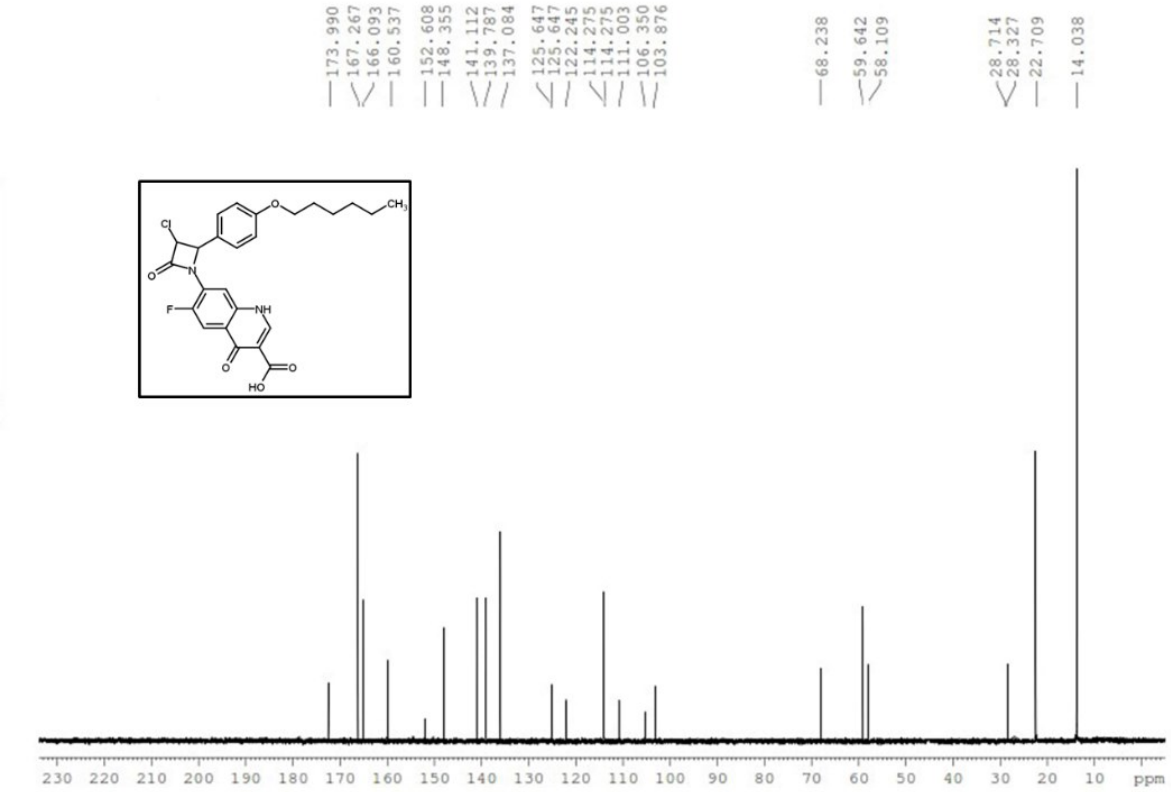
Mass Spectrum of IR 7-amino-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (1c)



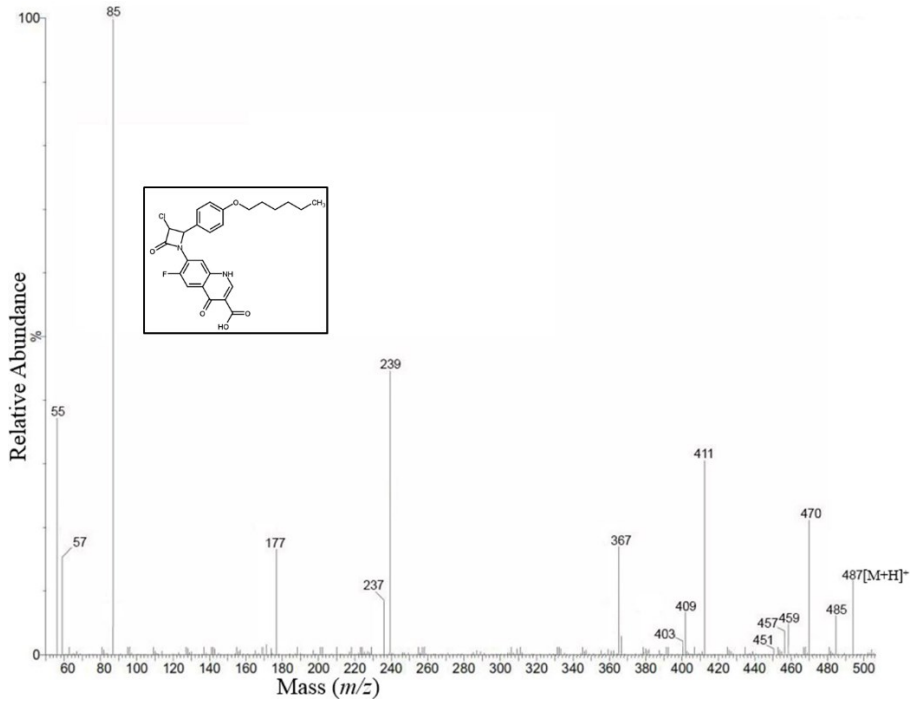
FT-IR spectrum of 7-{3-chloro-2-[4-(hexyloxy)phenyl]-4-oxoazetidin-1- yl}-6-fluoro-4-oxo-1,4 -dihydroquinoline- 3- carboxylic acid (FQ-49).



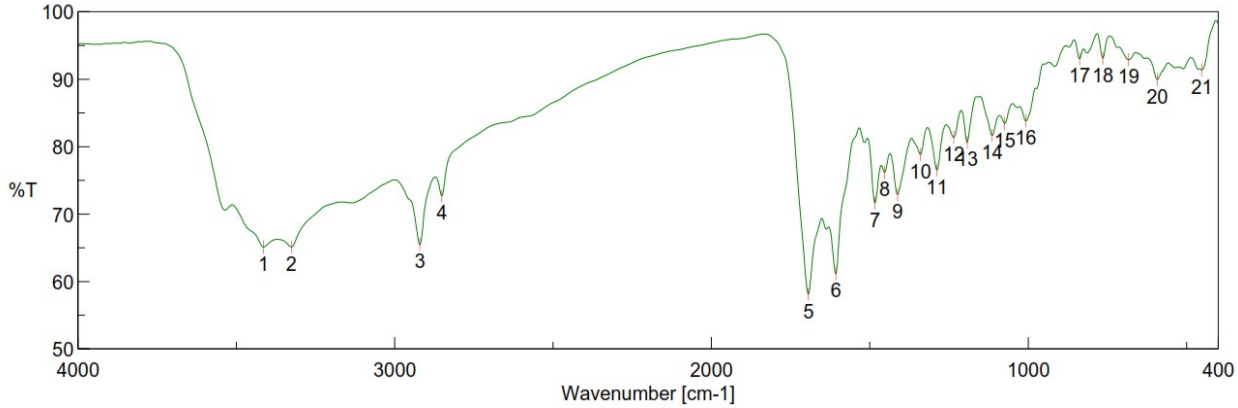
^{1}H NMR spectrum of 7-{3-chloro-2-[4-(hexyloxy)phenyl]-4-oxoazetidin-1- yl}-6-fluoro-4-oxo-1,4-dihydroquinoline-3- carboxylic acid (FQ-49).



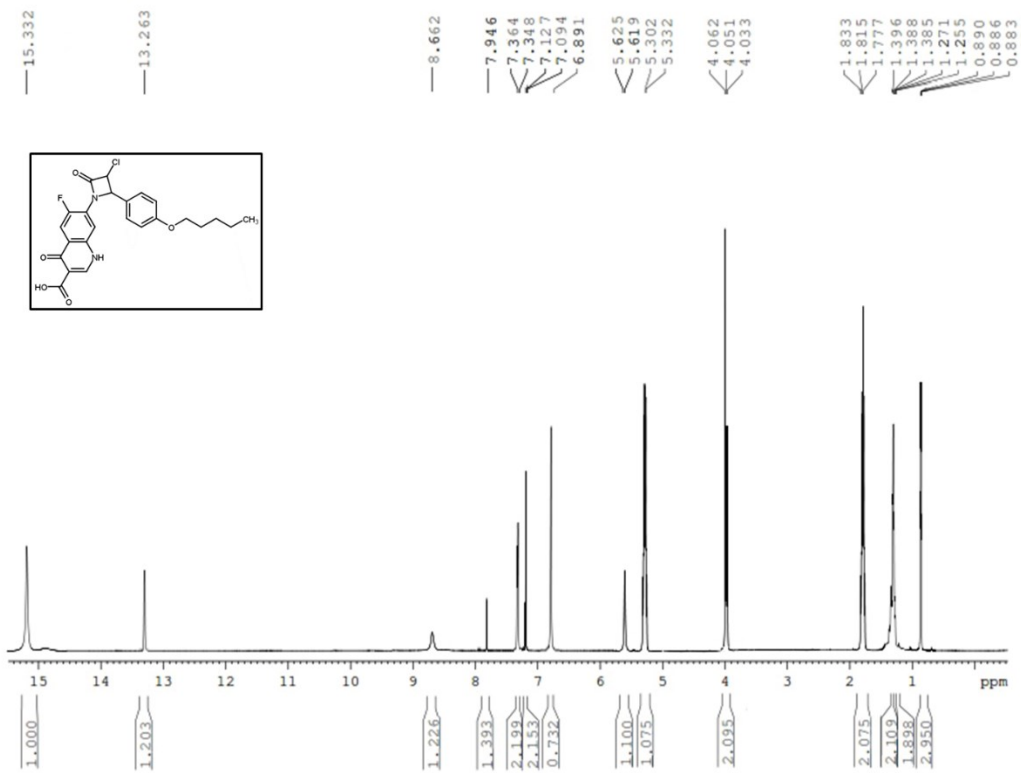
^{13}C NMR spectrum of 7-{3-chloro-2-[4-(hexyloxy)phenyl]-4-oxoazetidin-1- yl}-6-fluoro-4-oxo-1,4-dihydroquinoline-3- carboxylic acid (FQ-49).



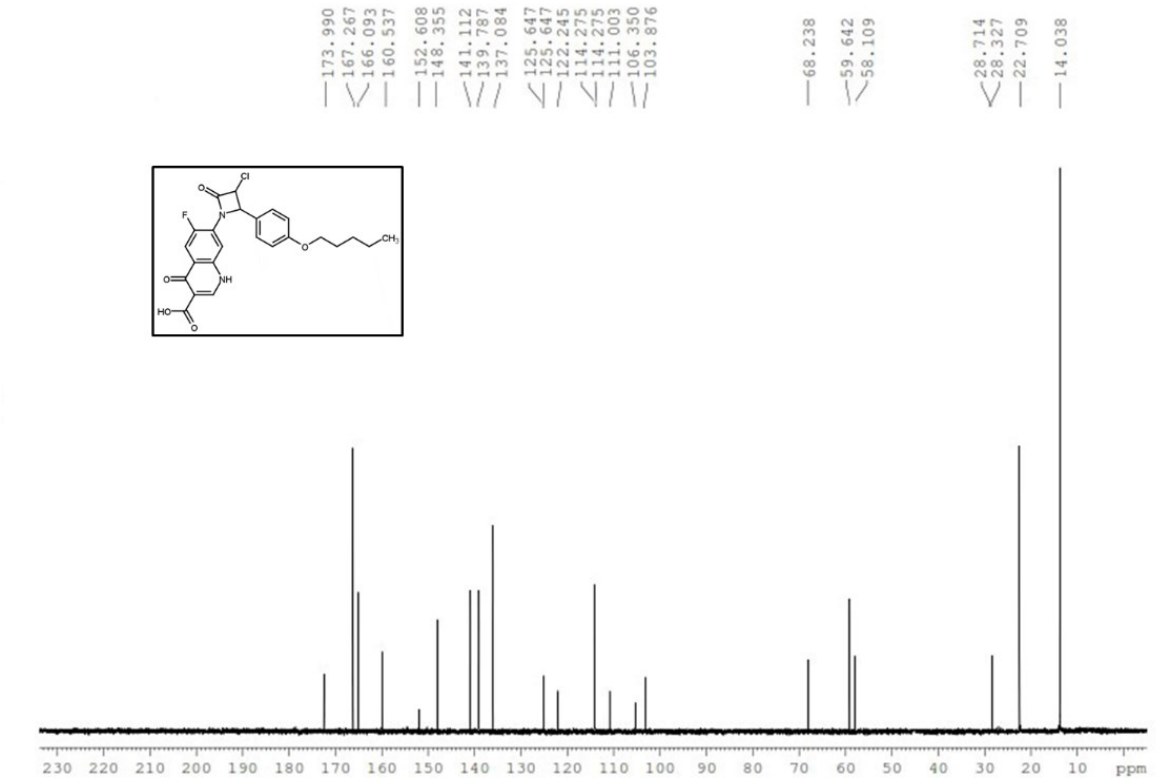
Mass spectrum of 7-{3-chloro-2-[4-(hexyloxy)phenyl]-4-oxoazetidin-1- yl}-6-fluoro-4-oxo-1,4-dihydroquinoline-3- carboxylic acid (FQ-49).



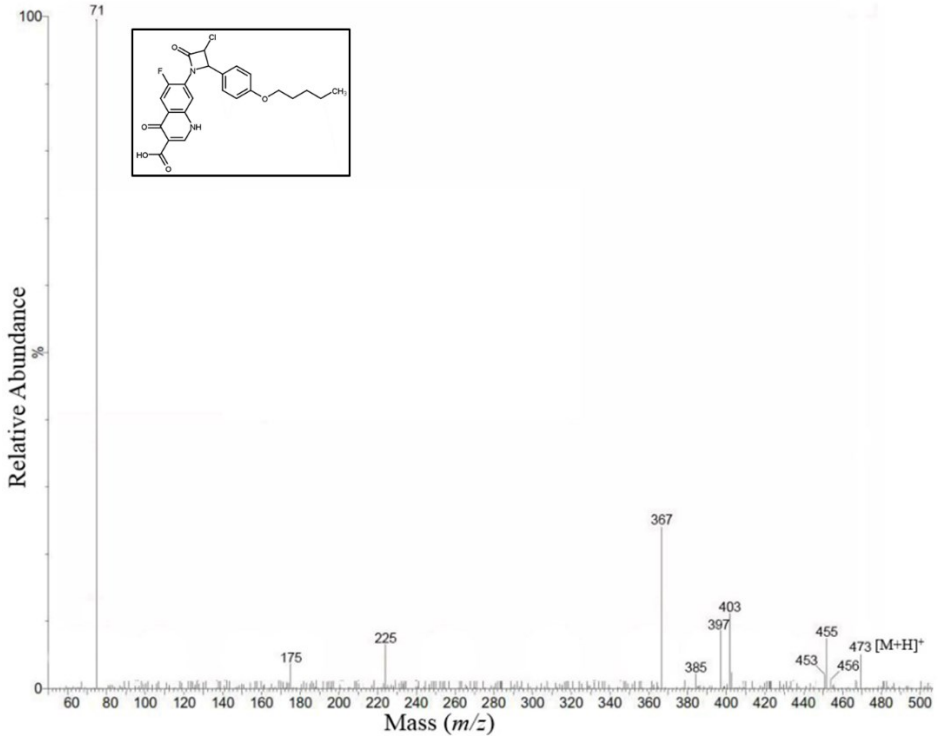
FT-IR spectrum of 7-{3-chloro-2-oxo-4-[4-(pentyloxy)phenyl]azetidin-1- yl}-6-fluoro-4-oxo -1,4-dihydroquinoline-3- carboxylic acid (FQ-70).



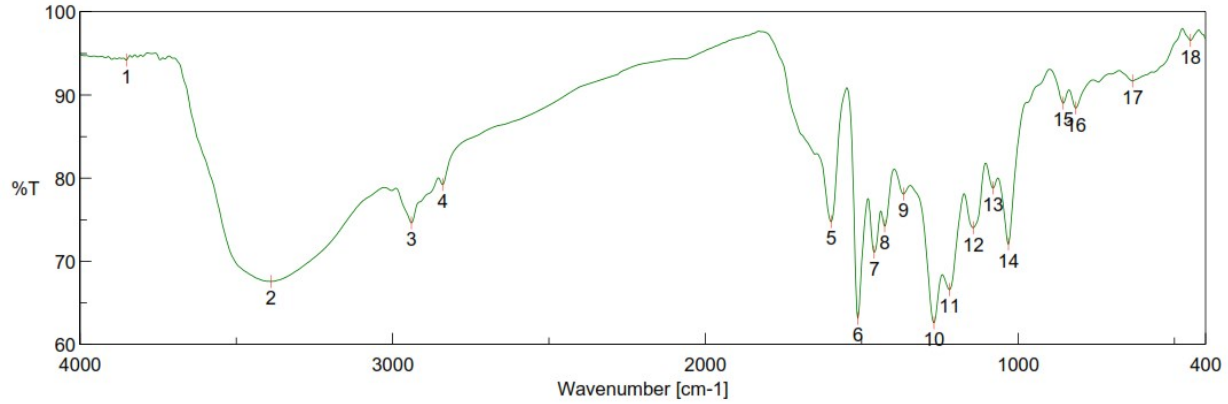
^{1}H spectrum of 7-{3-chloro-2-oxo-4-[4-(pentyloxy)phenyl]azetidin-1- yl}-6-fluoro-4-oxo-1,4-dihydroquinoline-3- carboxylic acid (FQ-70).



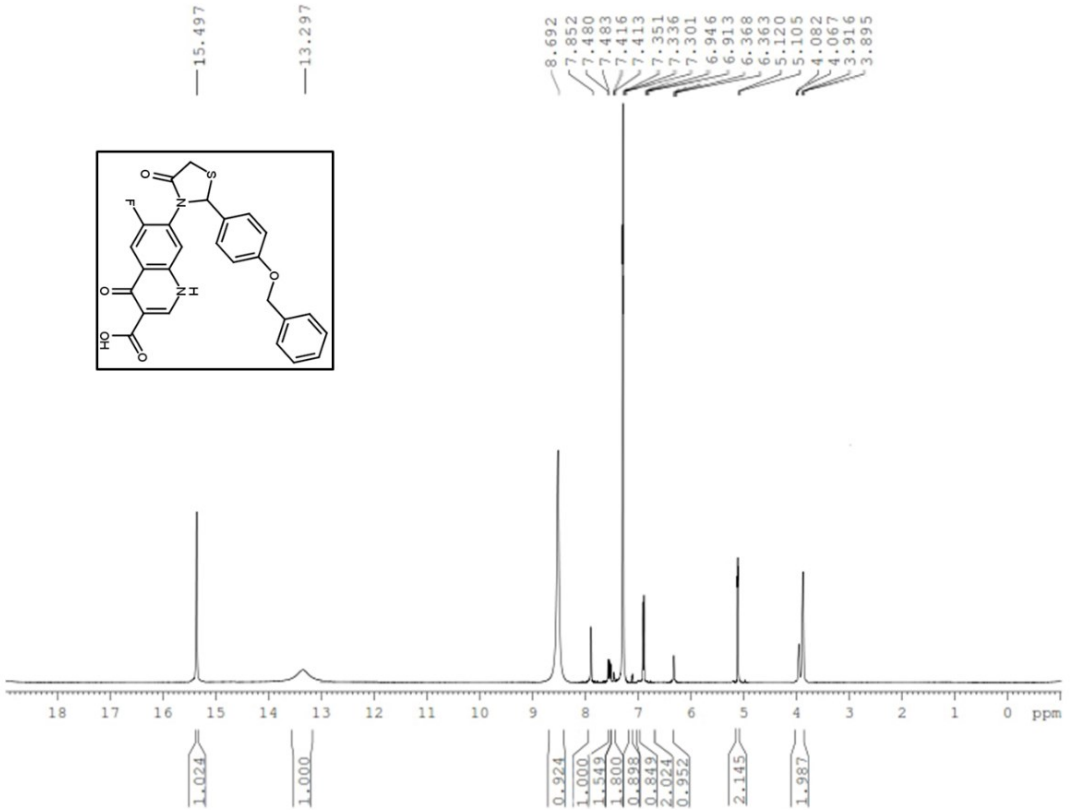
^{13}C NMR spectrum of ^{1}H spectrum of 7-{3-chloro-2-oxo-4-[4-(pentyloxy)phenyl]azetidin-1- yl}-6-fluoro-4-oxo -1,4-dihydroquinoline-3-carboxylic acid (FQ-70).



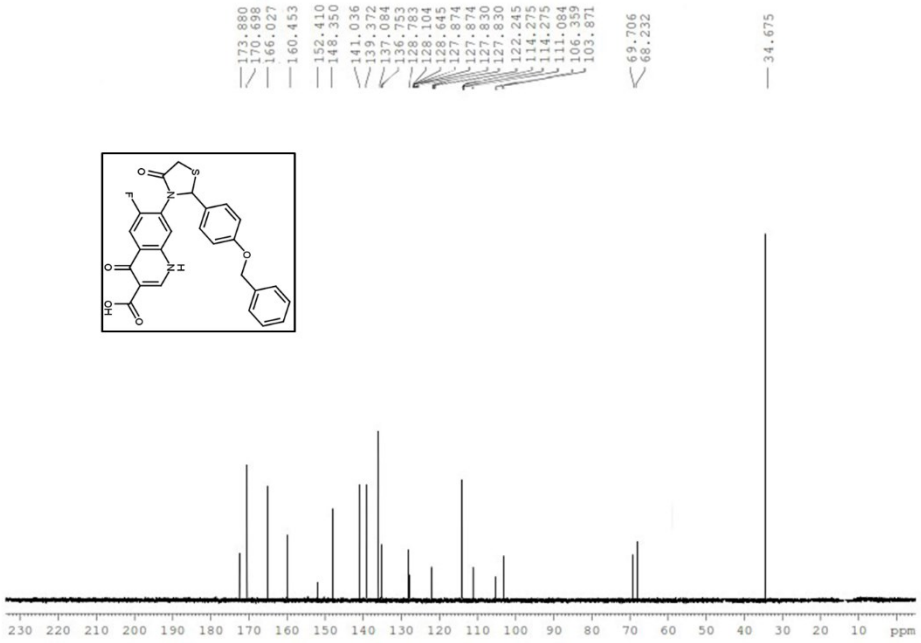
Mass spectrum of ^{1}H spectrum of 7-{3-chloro-2-oxo-4-[4-(pentyloxy)phenyl]azetidin-1- yl}-6-fluoro-4-oxo -1,4-dihydroquinoline-3- carboxylic acid (FQ-70).



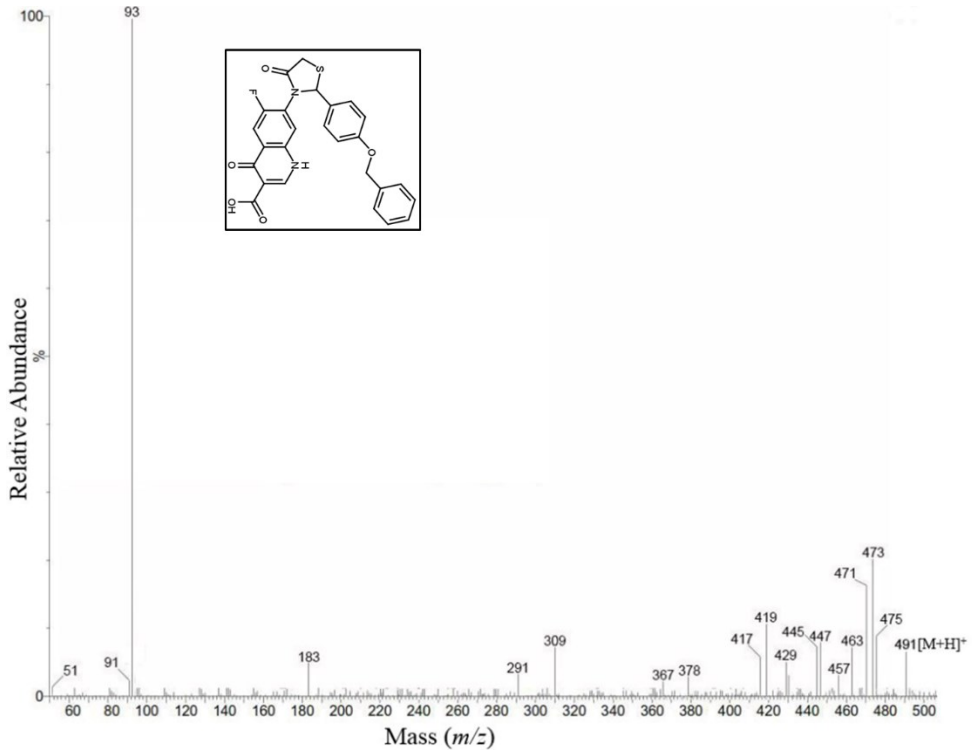
FT-IR spectrum of 7-{2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-3- yl}-6-fluoro-4-oxo- 1,4-dihydroquinoline-3- carboxylic acid (FQ-131).



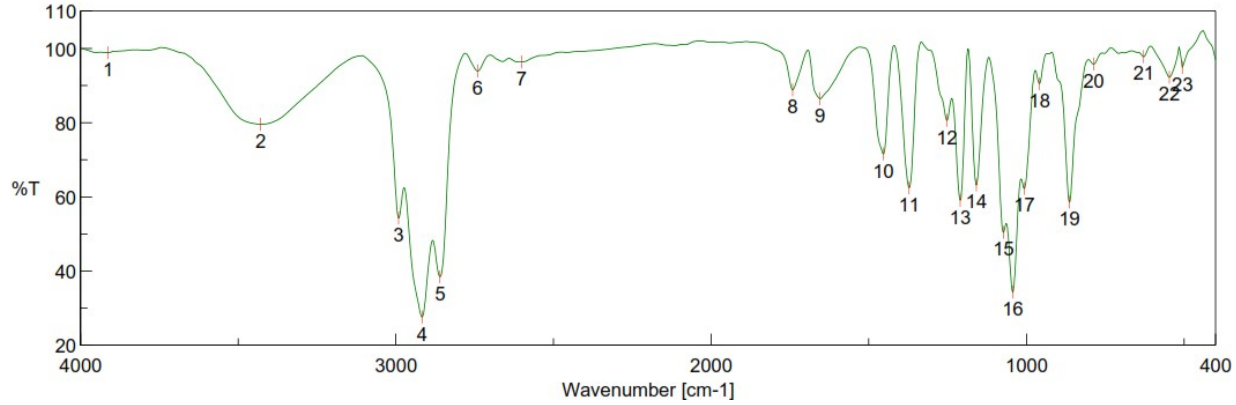
^{1}H NMR spectrum of 7-{2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-3- yl}-6- fluoro-4-oxo-1,4-dihydroquinoline-3- carboxylic acid (FQ-131).



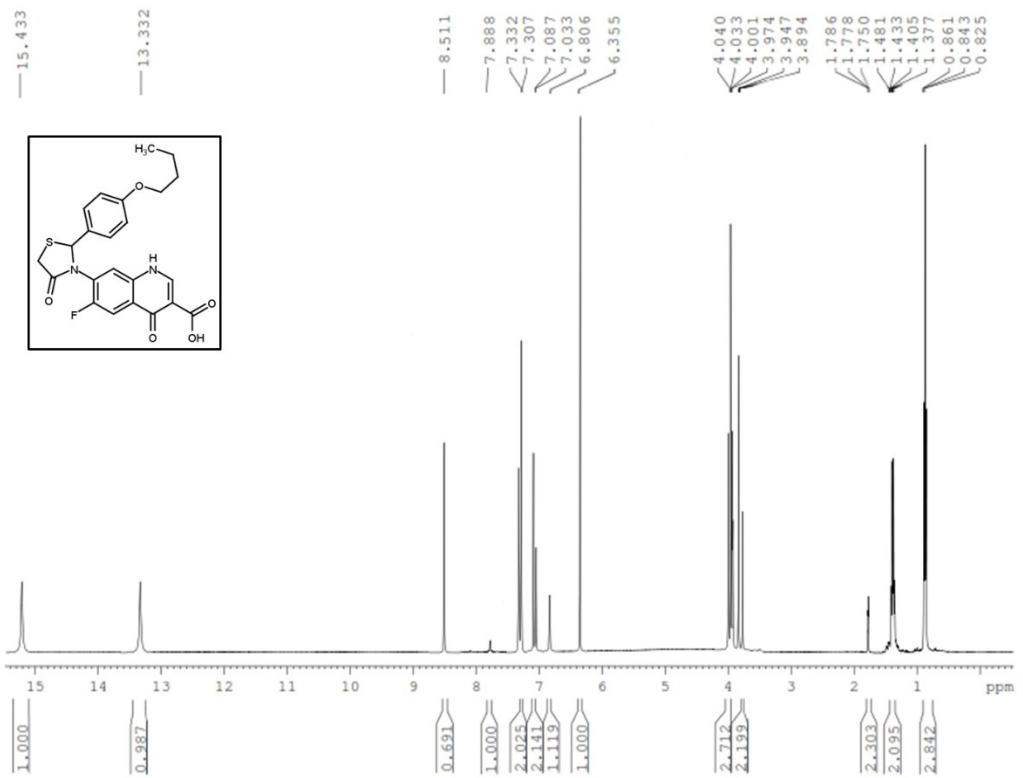
^{13}C NMR spectrum of 7-{2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-3- yl}-6-fluoro-4-oxo-1,4-dihydroquinoline-3- carboxylic acid (FQ-131).



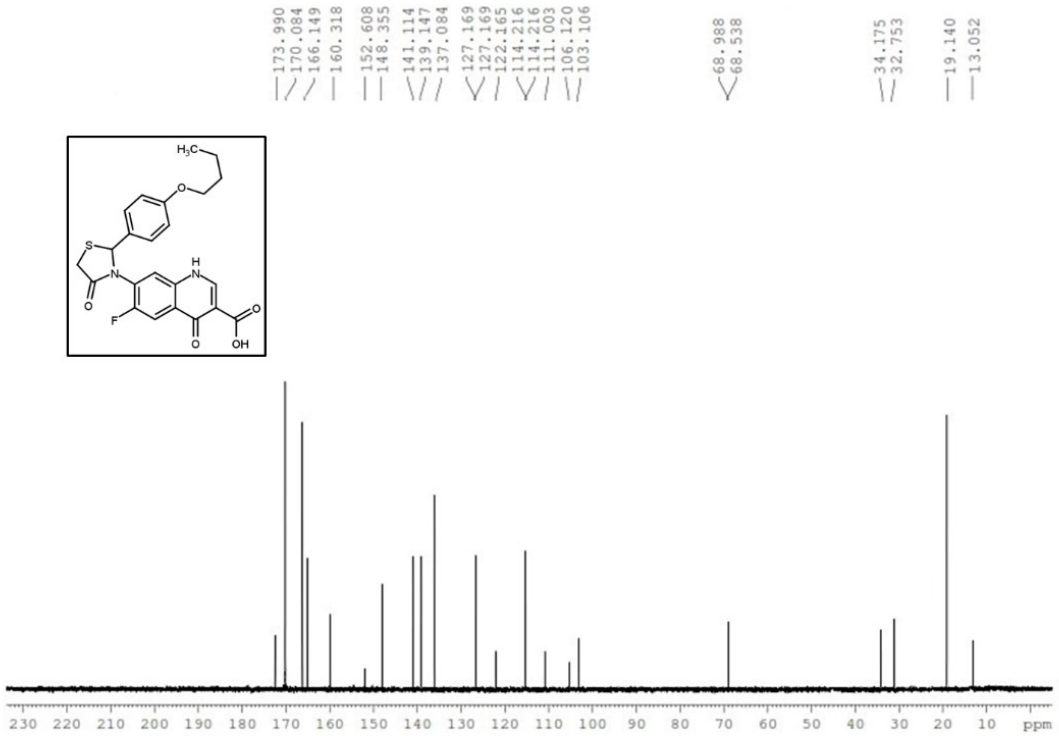
Mass spectrum of 7-{2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-3- yl}-6-fluoro-4-oxo-1,4-dihydroquinoline-3- carboxylic acid (FQ-131).



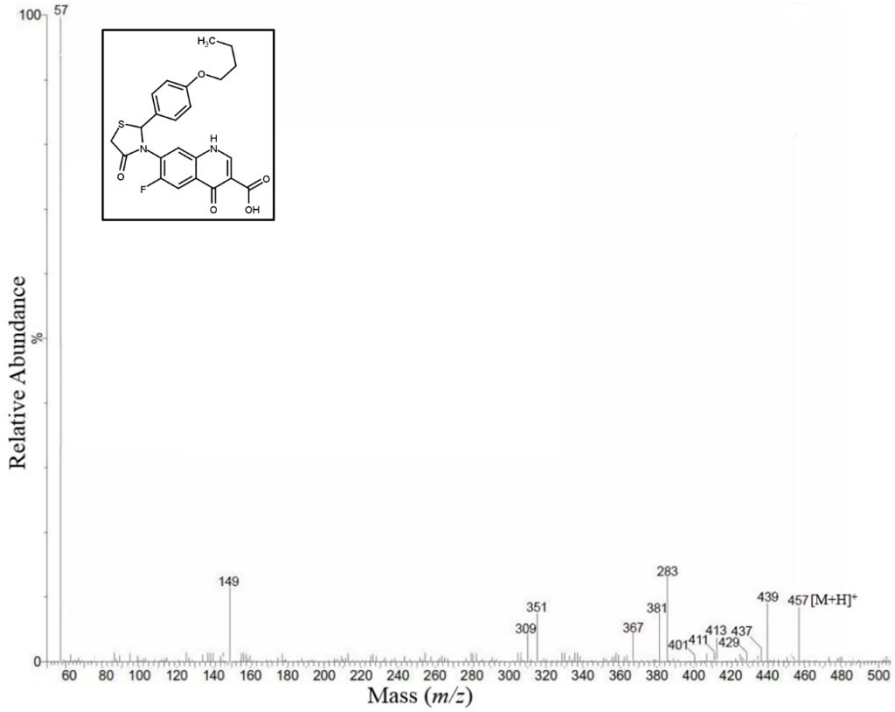
FT-IR spectrum of 7-[2-(4-butoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (FQ-132).



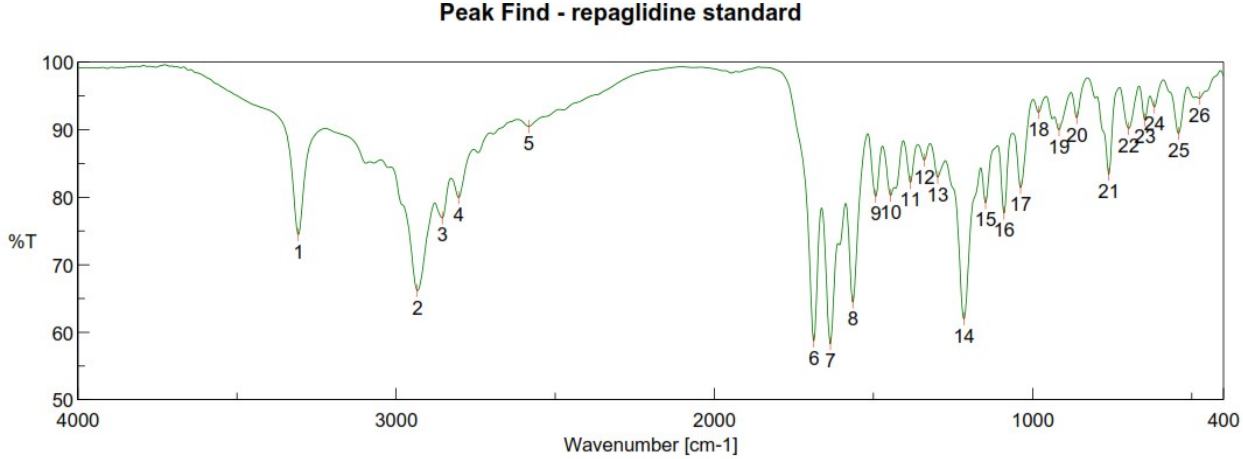
[1]H NMR spectrum of 7-[2-(4-butoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-6-fluoro-4-oxo-1,4- dihydroquinoline-3-carboxylic acid (FQ-132).



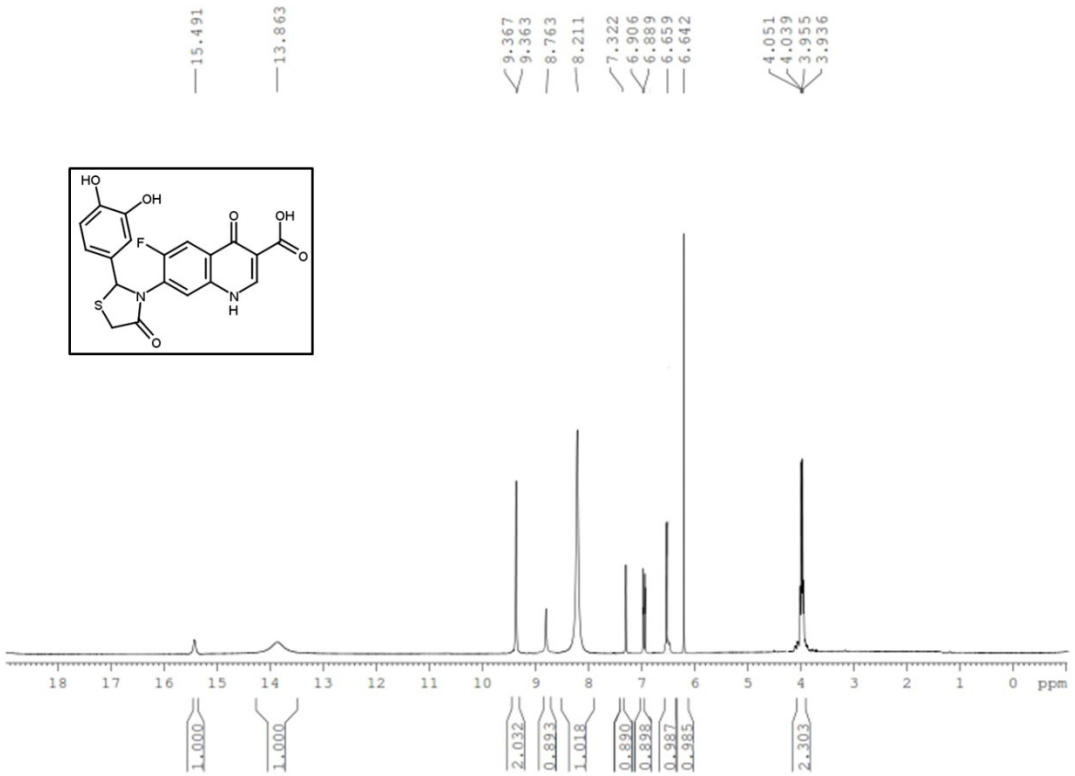
^{13}C spectrum of 7-[2-(4-butoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (FQ-132).



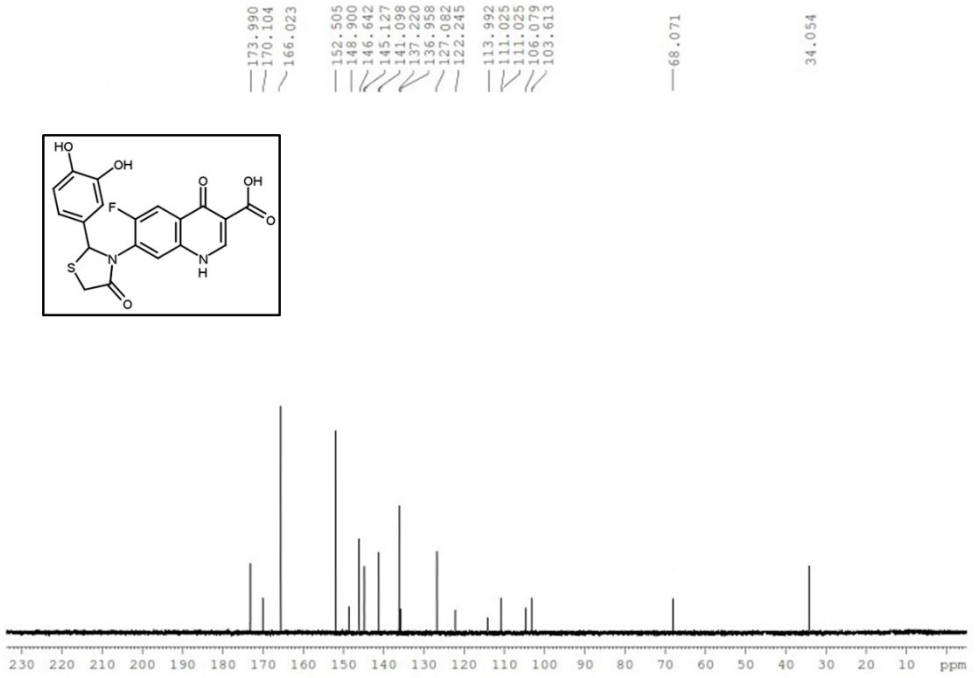
Mass spectrum of 7-[2-(4-butoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (FQ-132).



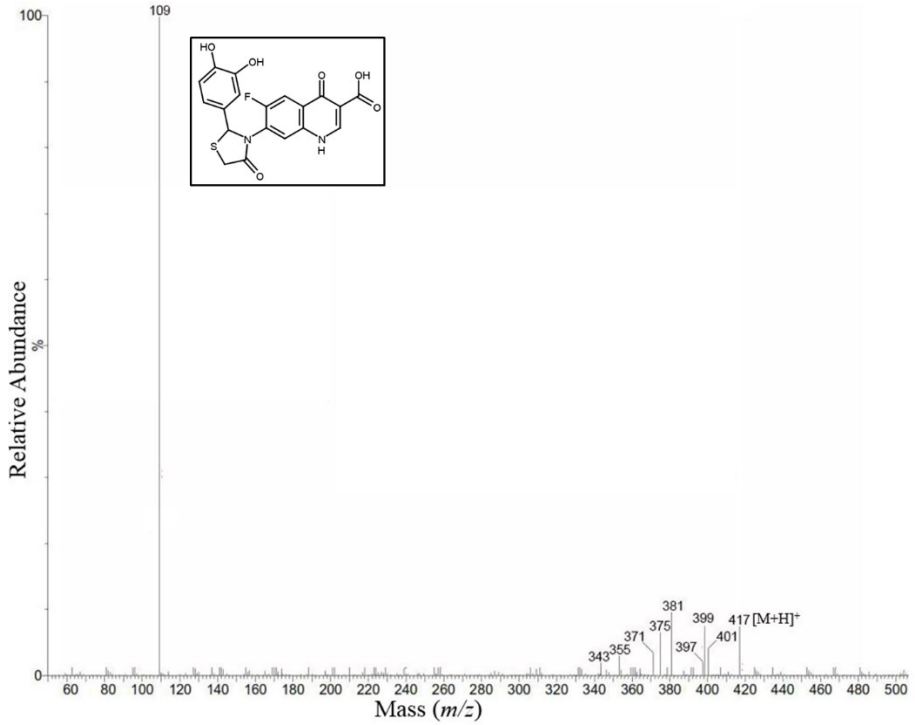
FT-IR spectrum of 7-[2-(3,4-dihydroxyphenyl)-4-oxo-1,3-thiazolidin-3- yl]-6-fluoro-4-oxo- 1,4-dihydroquinoline-3- carboxylic acid (FQ-137).



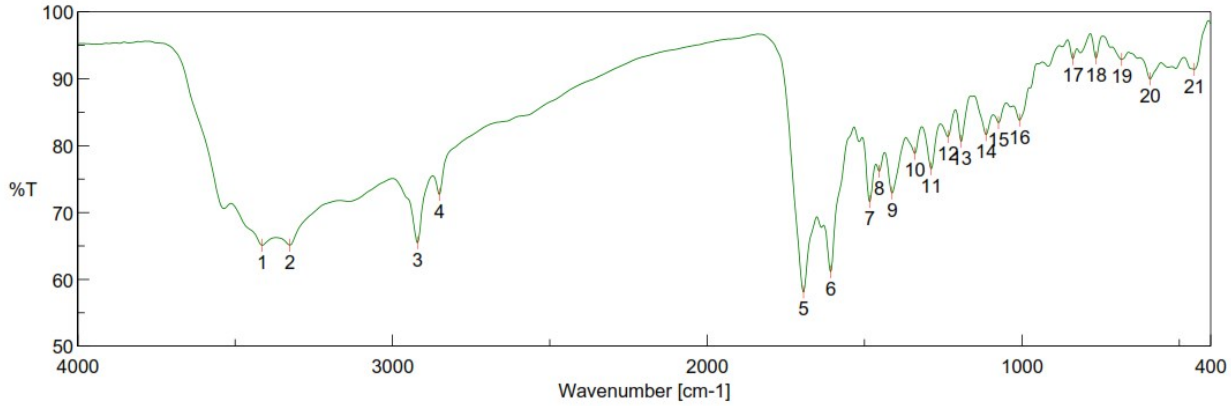
^{1}H NMR spectrum of 7-[2-(3,4-dihydroxyphenyl)-4-oxo-1,3-thiazolidin-3- yl]-6-fluoro-4-oxo-1,4-dihydroquinoline-3- carboxylic acid (FQ-137).



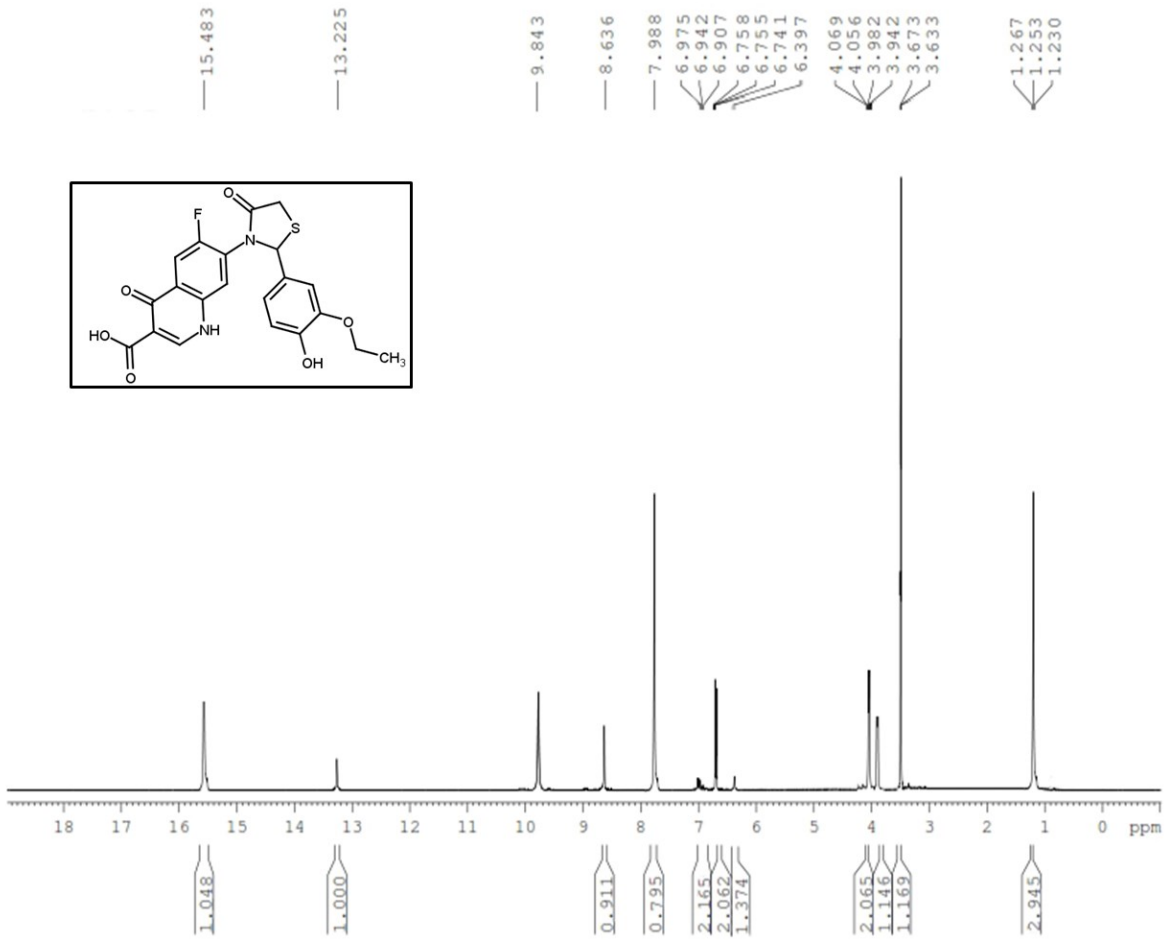
^{13}C spectrum of 7-[2-(3,4-dihydroxyphenyl)-4-oxo-1,3-thiazolidin-3- yl]-6-fluoro-4-oxo-1,4-dihydroquinoline-3- carboxylic acid (FQ-137).



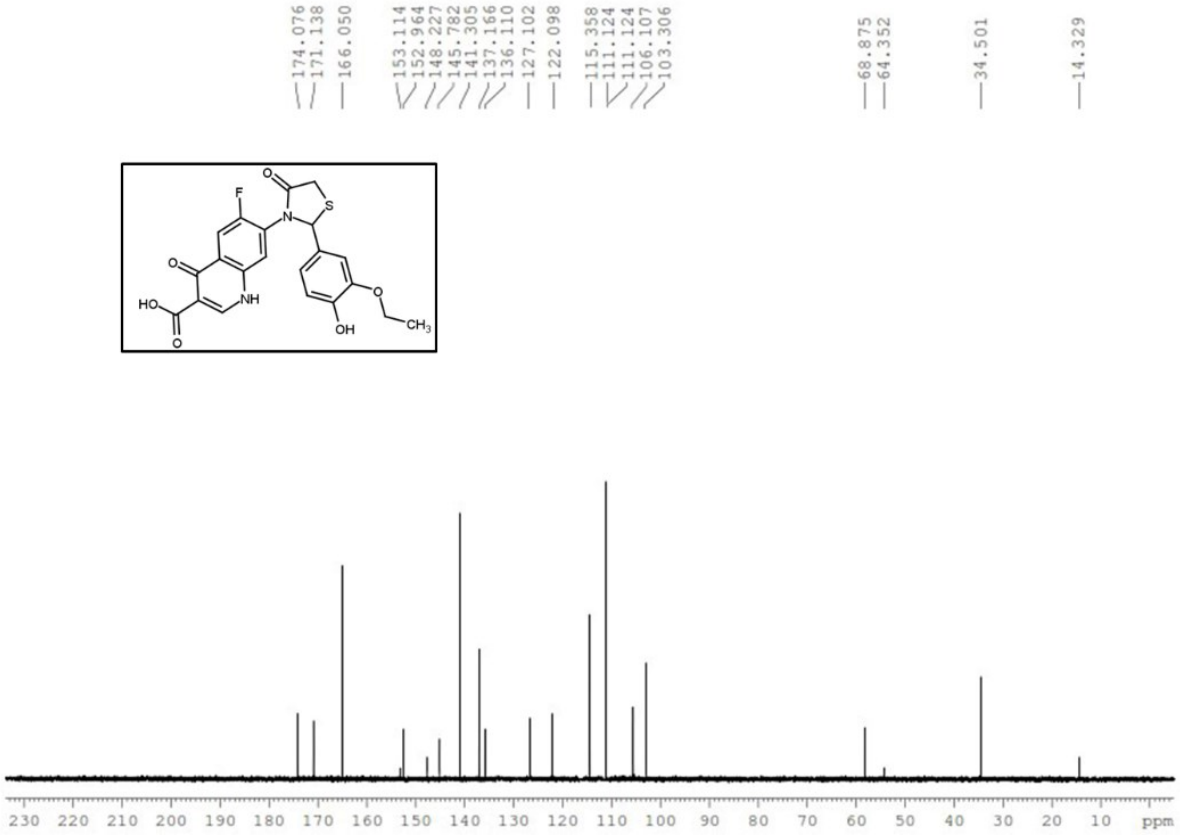
Mass spectrum of 7-[2-(3,4-dihydroxyphenyl)-4-oxo-1,3-thiazolidin-3- yl]-6-fluoro-4-oxo-1,4-dihydroquinoline-3- carboxylic acid (FQ-137).



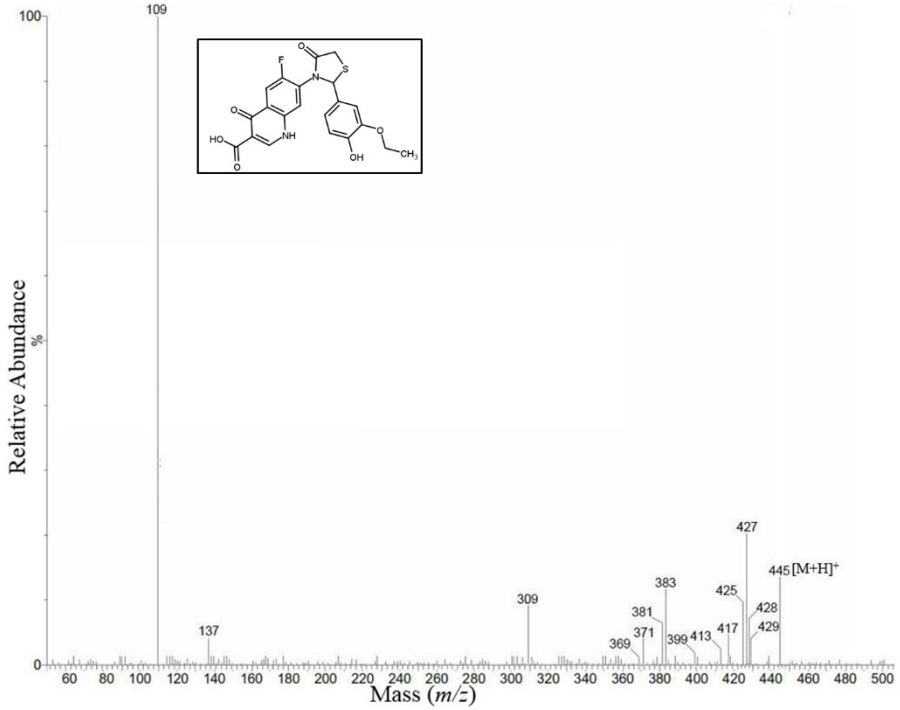
FT-IR spectrum of 7-[2-(3-ethoxy-4-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-6 -fluoro-4-oxo-1,4- dihydroquinoline-3-carboxylic acid (FQ-147).



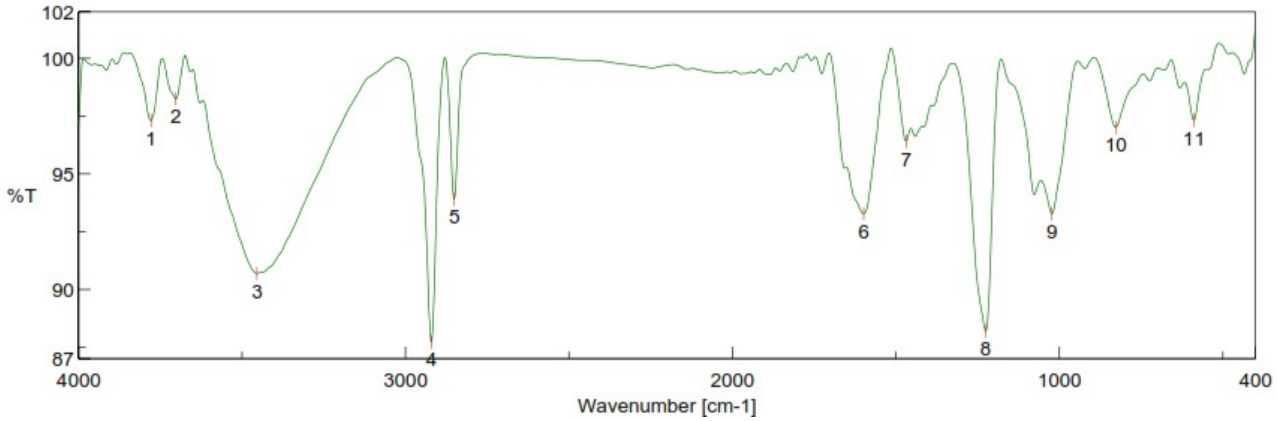
^{1}H NMR spectrum of 7-[2-(3-ethoxy-4-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-6-fluoro-4- oxo- 1,4- dihydroquinoline-3-carboxylic acid (FQ-147).



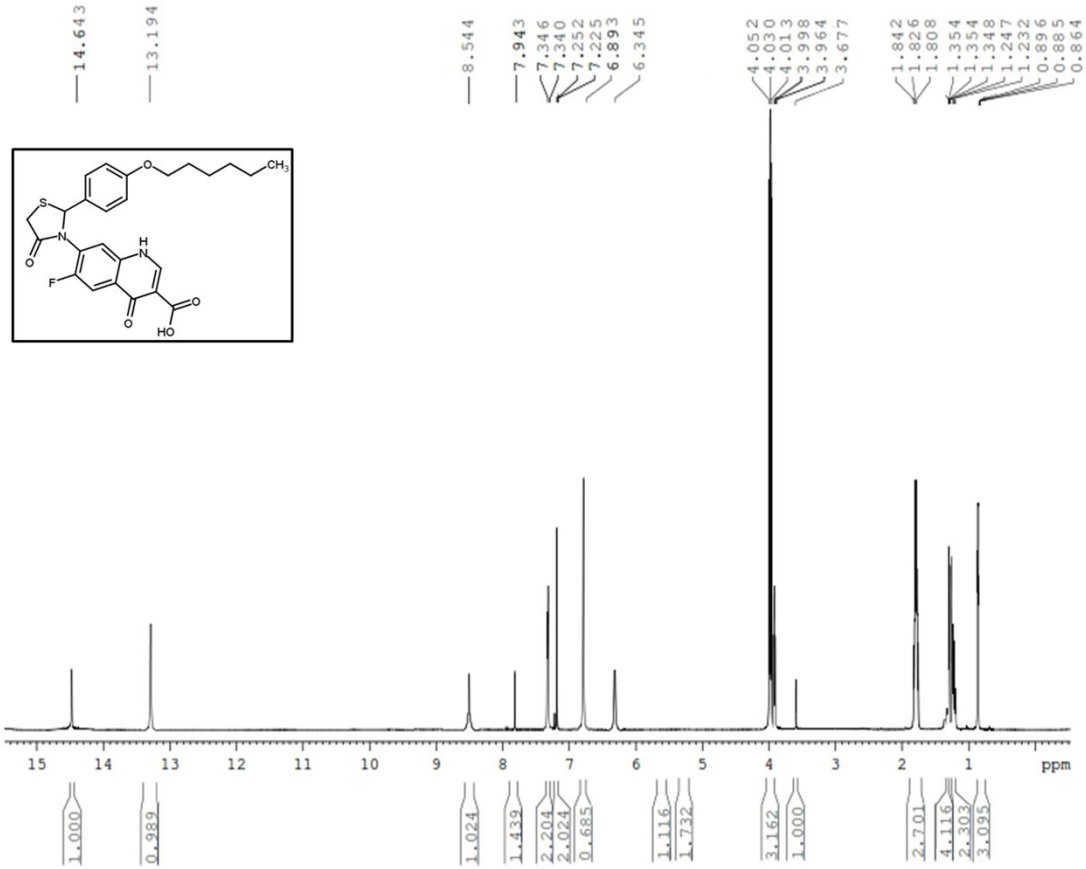
^{13}C NMR spectrum of 7-[2-(3-ethoxy-4-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-6-luoro-4- oxo- 1,4- dihydroquinoline-3-carboxylic acid (FQ-147).



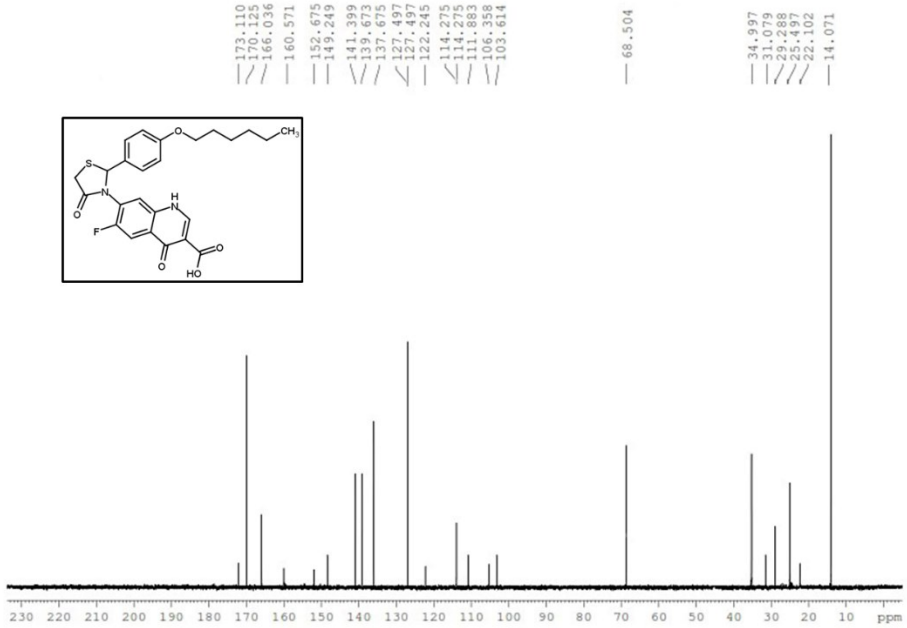
Mass spectrum of 7-[2-(3-ethoxy-4-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-6-fluoro-4- oxo- 1,4- dihydroquinoline-3-carboxylic acid (FQ-147).



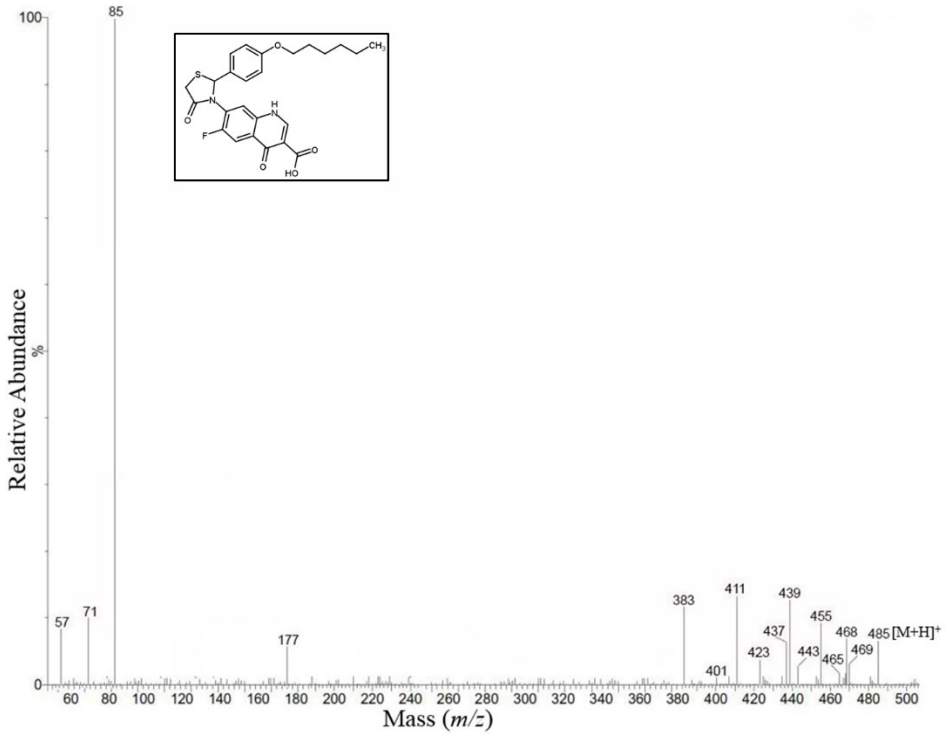
FT-IR spectrum of 6-fluoro-7-{2-[4-(hexyloxy)phenyl]-4-oxo-1,3- thiazolidin-3-yl}-4-oxo-1,4- dihydroquinoline-3- carboxylic acid (FQ-151).



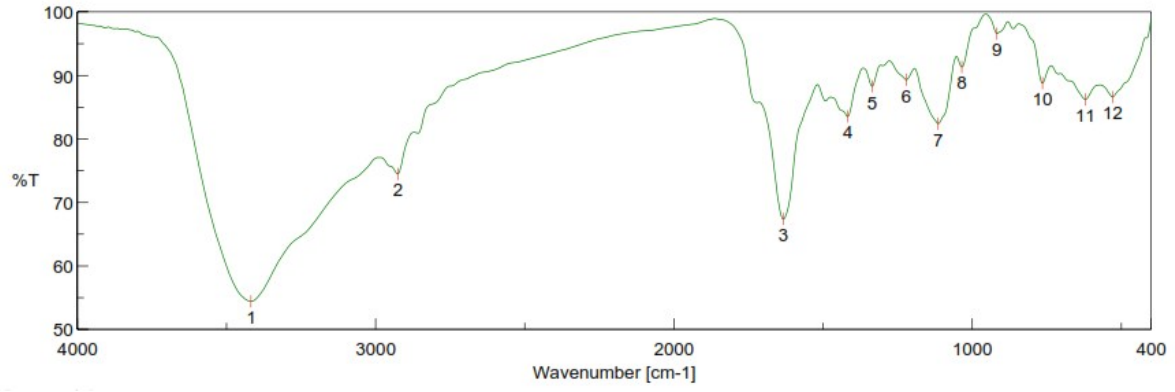
^{1}H NMR spectrum of 6-fluoro-7-{2-[4-(hexyloxy)phenyl]-4-oxo-1,3- thiazolidin-3-yl}-4-oxo- 1,4- dihydroquinoline-3- carboxylic acid (FQ-151).



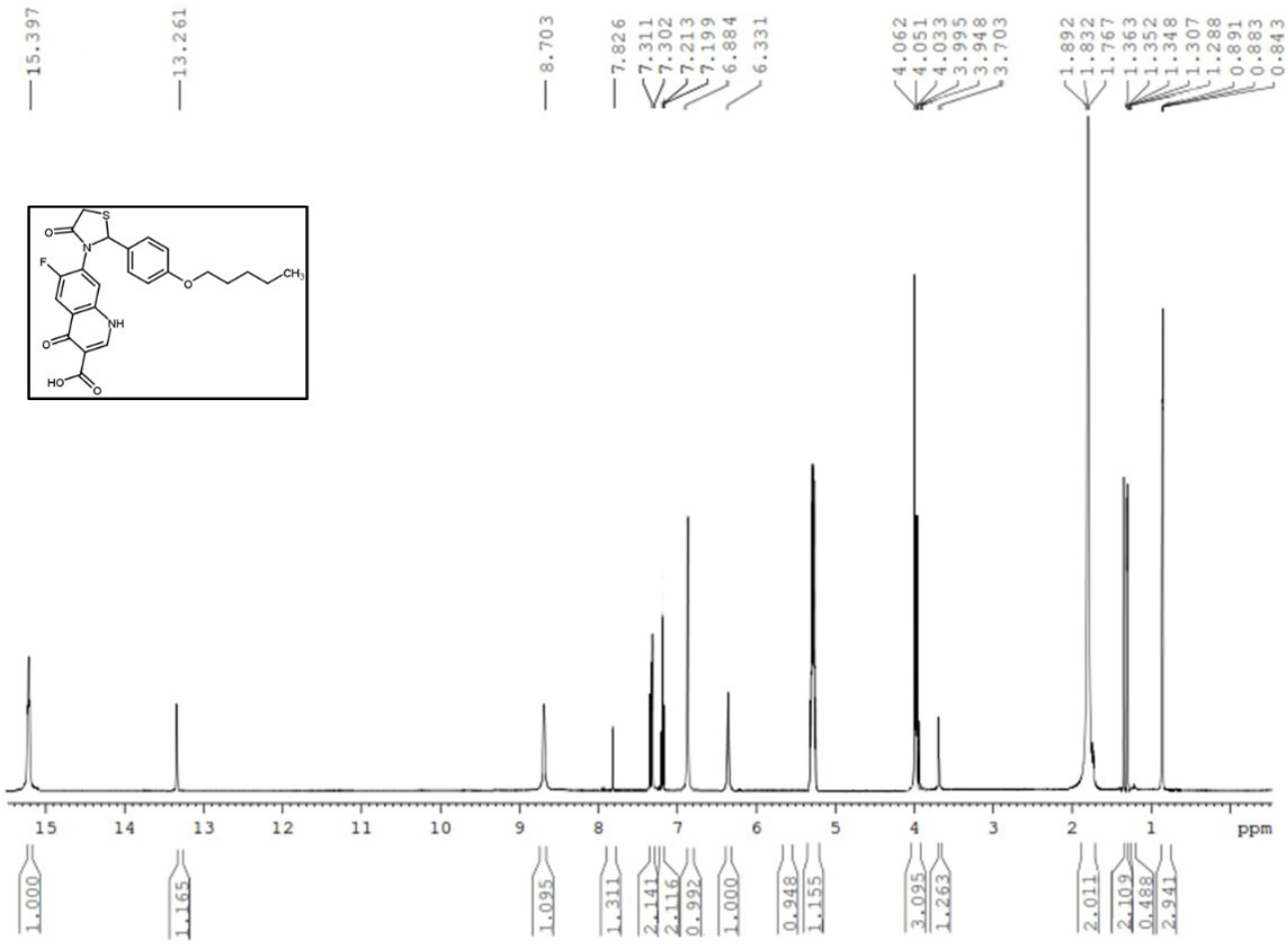
^{13}C NMR spectrum of 6-fluoro-7-{2-[4-(hexyloxy)phenyl]-4-oxo-1,3- thiazolidin-3-yl}-4-oxo- 1,4- dihydroquinoline-3- carboxylic acid (FQ-151).



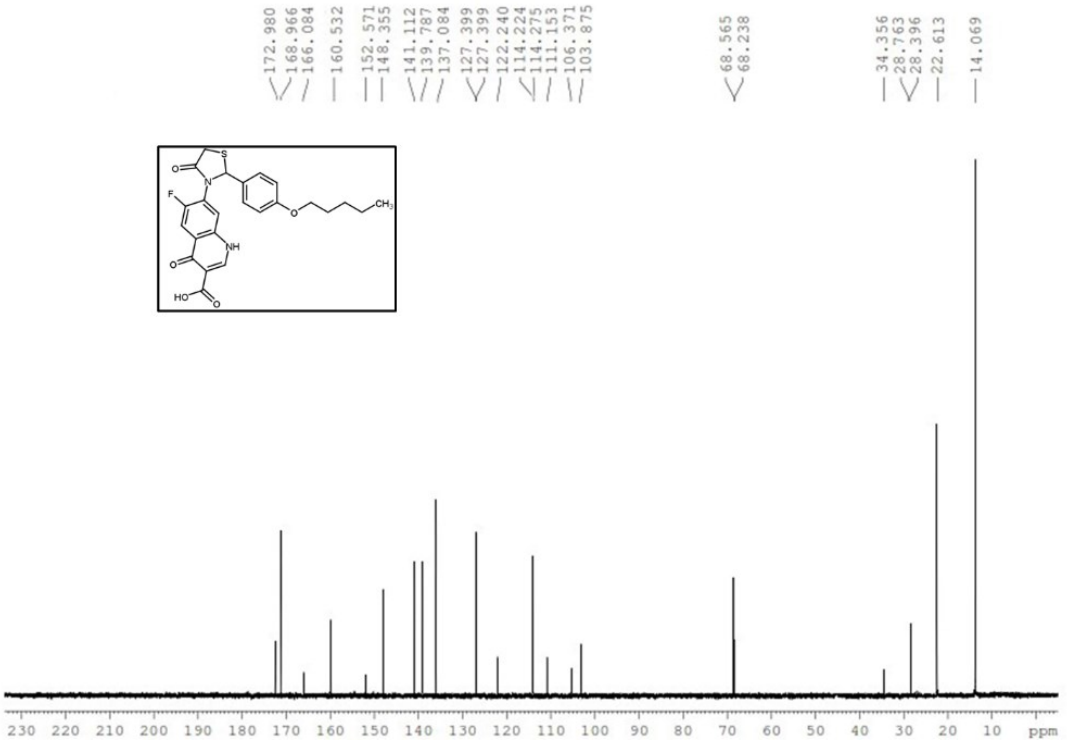
Mass spectrum of 6-fluoro-7-{2-[4-(hexyloxy)phenyl]-4-oxo-1,3- thiazolidin-3-yl}-4-oxo-1,4- dihydroquinoline-3- carboxylic acid (FQ-151).



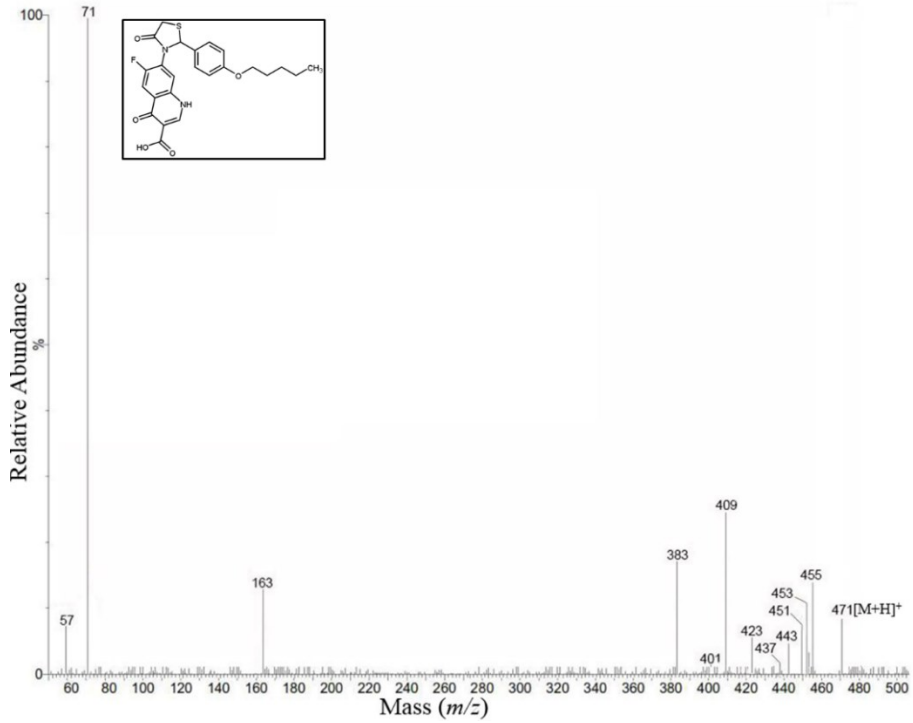
6-fluoro-4-oxo-7-{4-oxo-2-[4-(pentyloxy)phenyl]- 1,3-thiazolidin-3-yl}-1,4-dihydroquinoline -3- carboxylic acid (FQ-172).



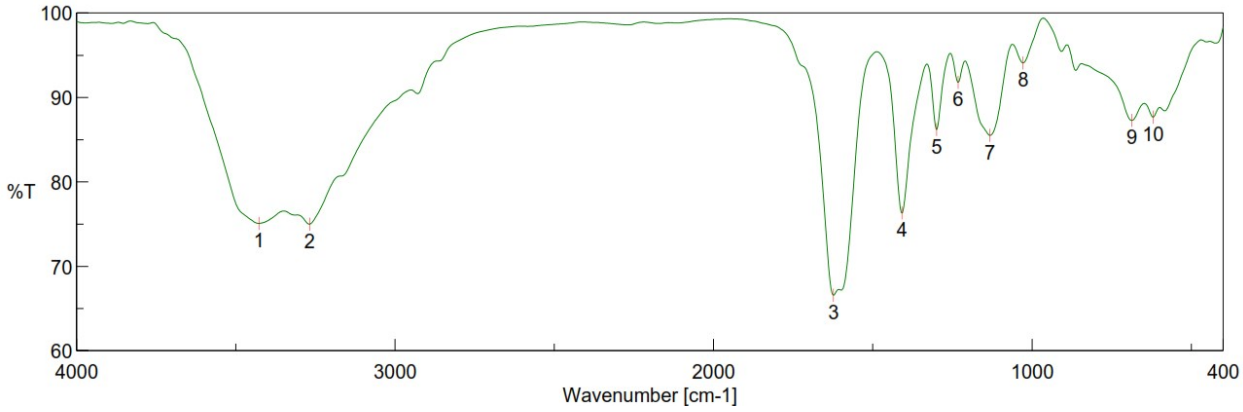
^{1}H NMR spectrum of 6-fluoro-4-oxo-7-{4-oxo-2-[4-(pentyloxy)phenyl]- 1,3-thiazolidin-3-yl}- 1,4-dihydroquinoline -3- carboxylic acid (FQ-172).



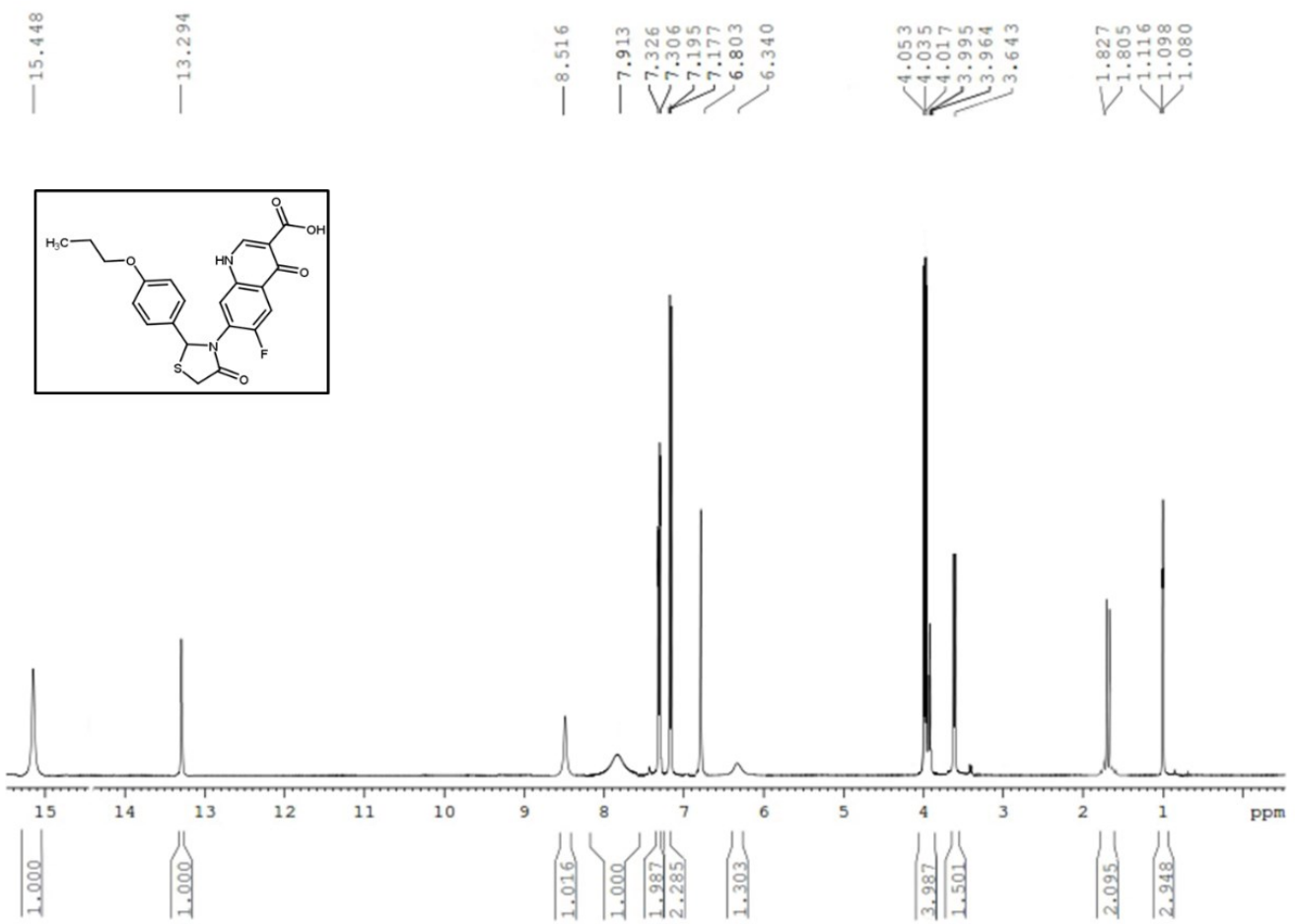
^{13}C NMR spectrum of 6-fluoro-4-oxo-7-{4-oxo-2-[4-(pentyloxy)phenyl]- 1,3-thiazolidin-3-yl}- 1,4-dihydroquinoline -3- carboxylic acid (FQ-172).



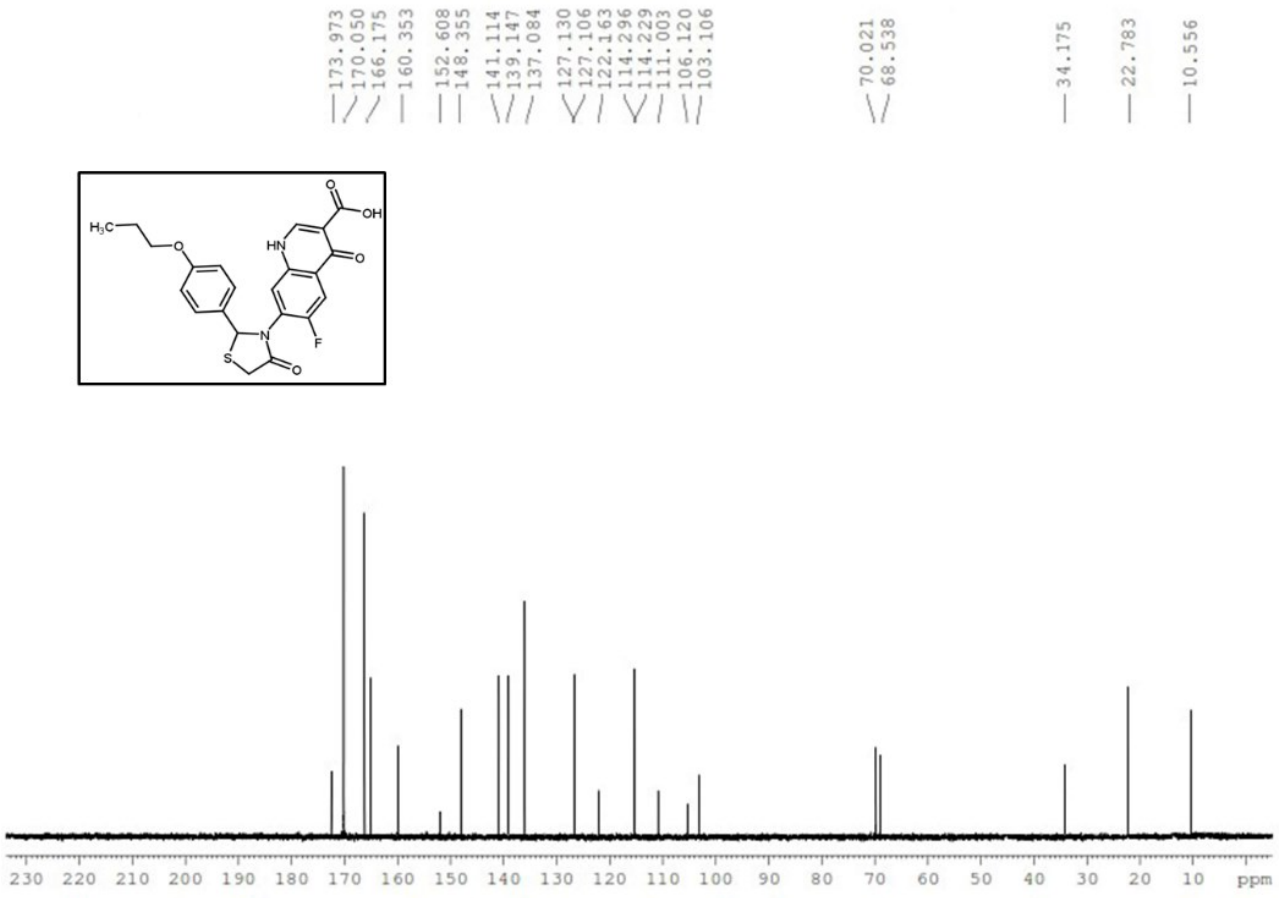
Mass spectrum of 6-fluoro-4-oxo-7-{4-oxo-2-[4-(pentyloxy)phenyl]- 1,3-thiazolidin-3-yl}- 1,4-dihydroquinoline -3- carboxylic acid (FQ-172).



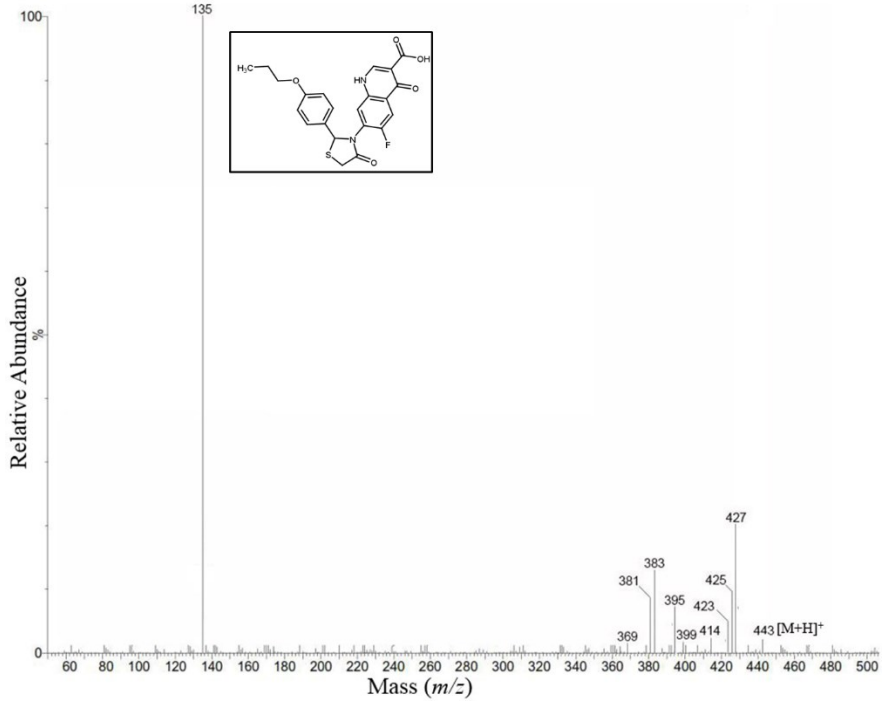
FT-IR spectrum of 6-fluoro-4-oxo-7-[4-oxo-2- (4-propoxyphenyl)-1,3-thiazolidin -3-yl]-1,4-dihydroquinoline-3- carboxylic acid (FQ-177).



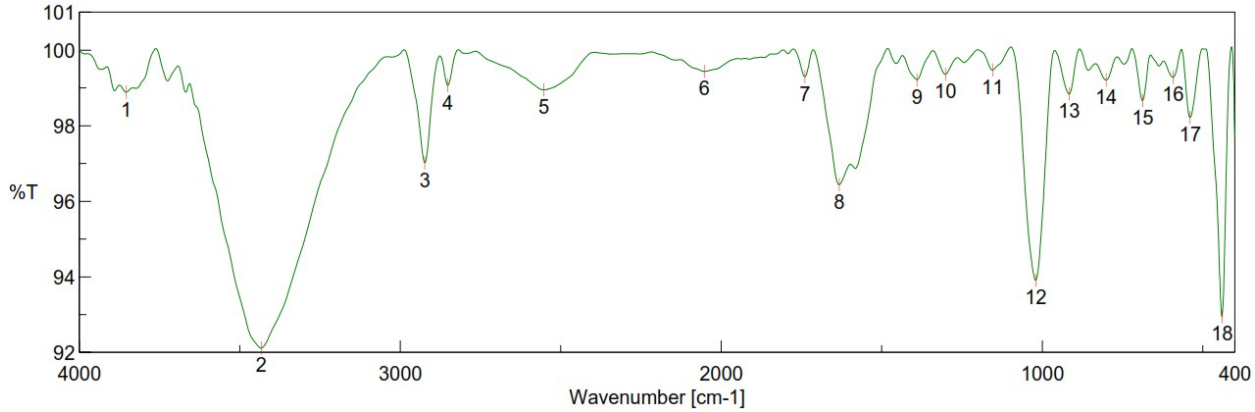
[1]H NMR spectrum of 6-fluoro-4-oxo-7-[4-oxo-2-(4-propoxyphenyl) -1,3-thiazolidine -3-yl]-1,4- dihydroquinoline-3- carboxylic acid (FQ-177).



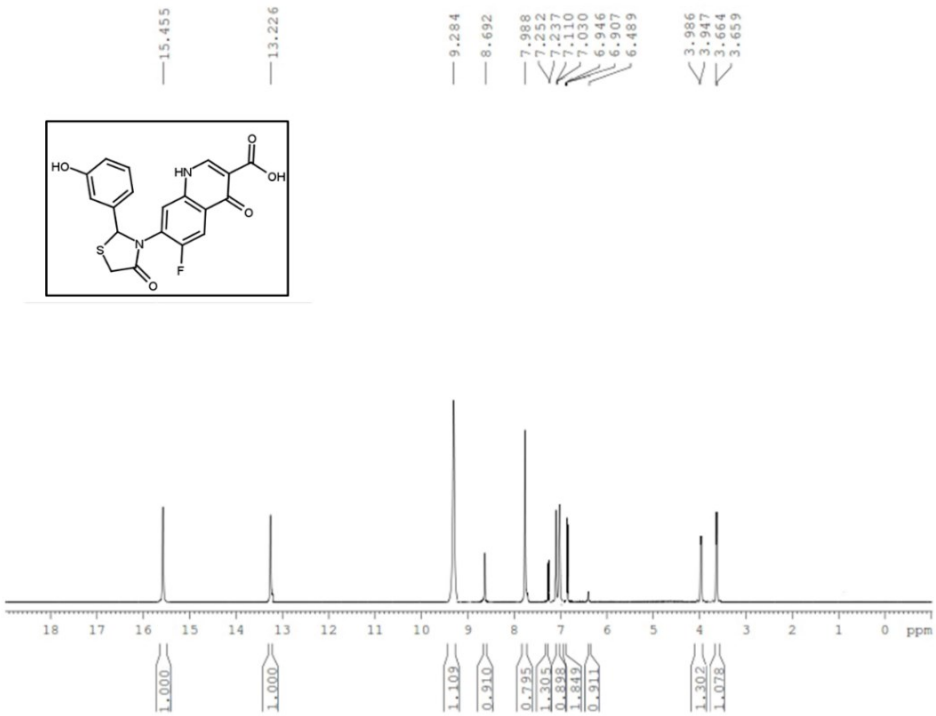
^{13}C spectrum of 6-fluoro-4-oxo-7-[4-oxo-2-(4-propoxyphenyl)-1,3-thiazolidine -3-yl]-1,4- dihydroquinoline-3- carboxylic acid (FQ-177).



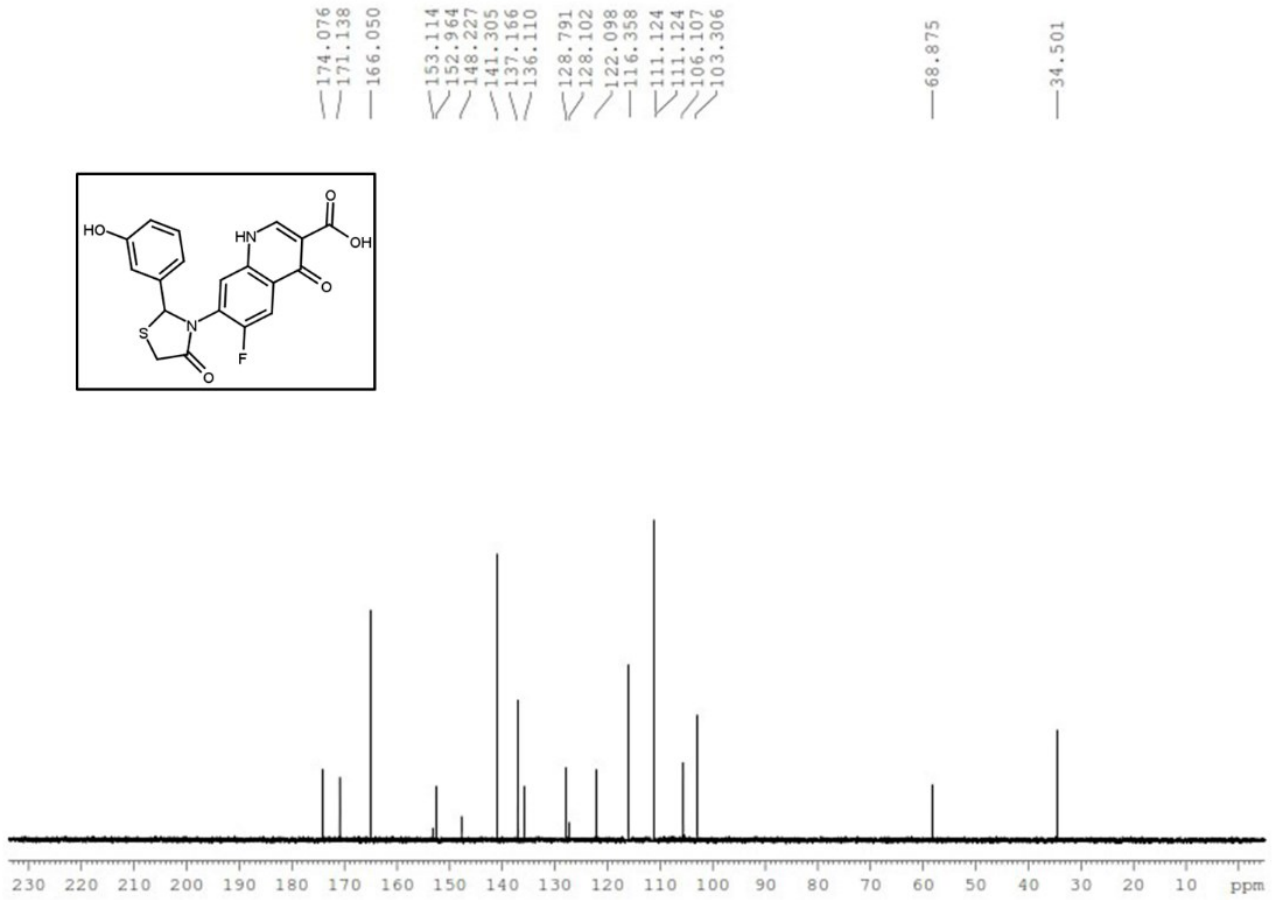
Mass spectrum of 6-fluoro-4-oxo-7-[4-oxo-2-(4-propoxyphenyl)-1,3-thiazolidine -3-yl]-1,4- dihydroquinoline-3- carboxylic acid (FQ-177).



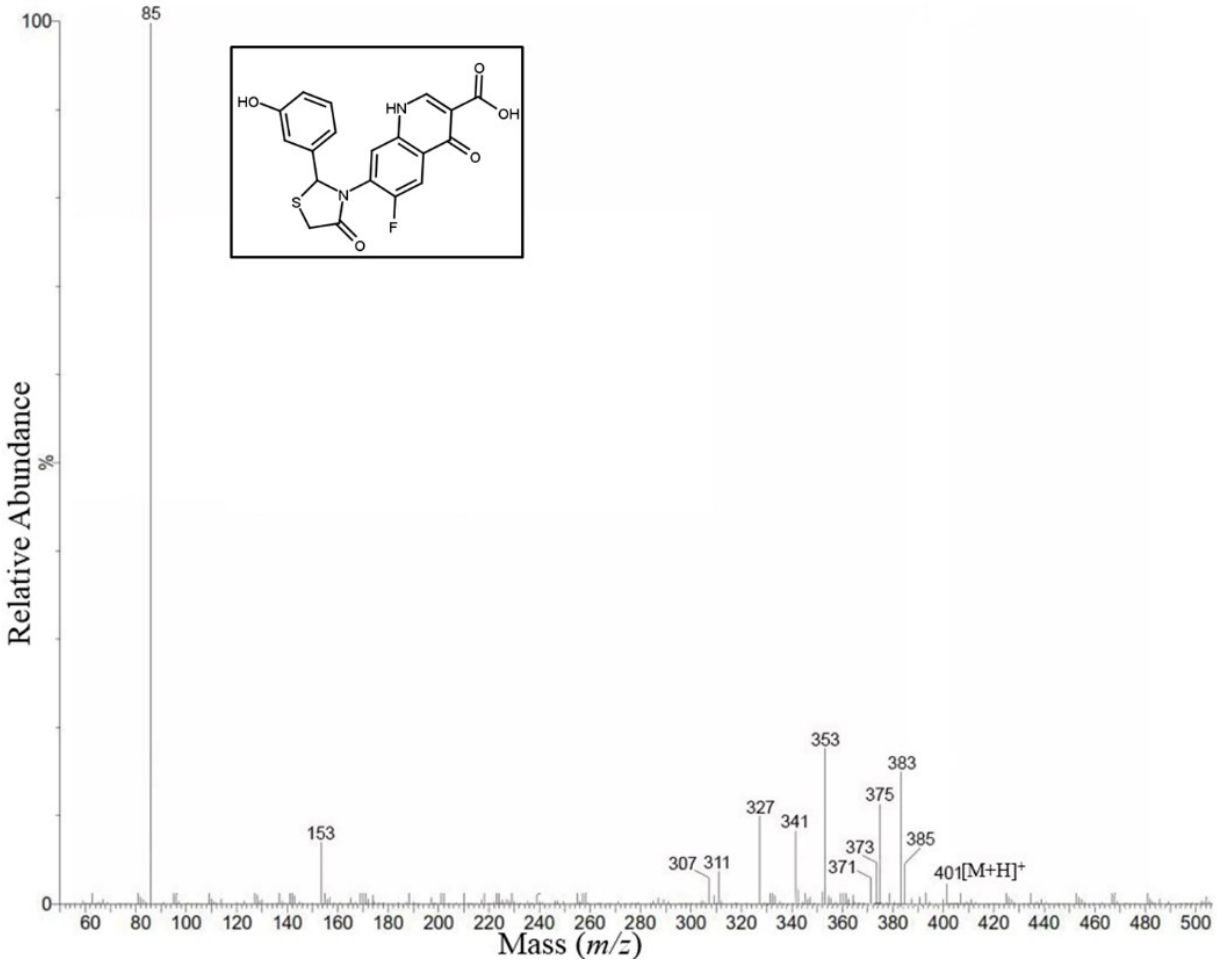
FT-IR 6-fluoro-7-[2-(3-hydroxyphenyl)-4-oxo-1,3- thiazolidin-3-yl]-4-oxo-1,4- dihydroquinoline-3- carboxylic acid (FQ-182).



^{1}H NMR spectrum of 6-fluoro-7-[2-(3-hydroxyphenyl) -4-oxo-1,3- thiazolidin-3-yl] -4- oxo-1,4- dihydroquinoline-3- carboxylic acid (FQ-182).



^{13}C NMR spectrum of 6-fluoro-7-[2-(3-hydroxyphenyl) -4-oxo-1,3- thiazolidin-3-yl] -4- oxo-1,4- dihydroquinoline-3- carboxylic acid (FQ-182).



Mass spectrum of 6-fluoro-7-[2-(3-hydroxyphenyl) -4-oxo-1,3- thiazolidin-3-yl] -4-oxo-1,4- dihydroquinoline-3- carboxylic acid (FQ-182).

Fig. S6

/translation="MSDLAREITPVNIEEELKSSYLDYAMSVIVGRALPDVRDGLKPV
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TKIPNLLVNGSSGIAVGMATNIPPHNLTEVINGCLAYIDDEDISIEGLMEHIPGPDFP
TAAIINGRRGIEEAYRTGRGKVYIRARAEVEVDAKTGRETIIVHEIPYQVNKARLIEK
IAELVKEKRVEGISALRDESDKDGMRIVIEVKRDAVGEVVLNNLYSQTQLQVSFGINM
VALHHGQPKIMNLKDIIAAFVRHRREVVTRRTIFELRKARDRAHILEALAVALANIDP
IIELIRHAPTPAEAKTALVANPWQLGNVAAMLERAGDDAARPEWLEPEFGVRDGLYYL
TEQQAQAILDLRLQKLTGLEHEKLLDEYKELLDQIAELLRILGSADRLMEVIREELEL
VREQFGDKRRTEITANSADINLEDLITQEDVVVTLSHQGYVKYQPLSEYEAQRRGGKG
KSAARIKEEDFIDRLLVANTHDHILCFSSRGRVYSMKVYQLPEATRGARGRPIVNLLP
LEQDERITAILPVTEFEEGVKVFMATANGTVKKTVLTEFNRLRTAGKVAIKLVDGDEL
IGVDLTSGEDEVMLFSAEGKVVRFKESSVRAMGCNTTGVRGIRLGEGDKVVSLIVPRG
DGAILTATQNGYGKRTAVAEYPTKSRATKGVISIKVTERNGLVVGAVQVDDCDQIMMI
TDAGTLVRTRVSEISIVGRNTQGVILIRTAEDENVVGLQRVAEPVDEEDLDTIDGSAA
EGDDEIAPEVDVDDEPEEE"

Fig. S6. The full-length sequence of mtDNA GyrA