Novel ciprofloxacin and norfloxacin-tetrazole hybrids as potential antibacterial and antiviral agents: targeting *S. aureus* topoisomerase and SARS-CoV-2-MPro

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***In silico* calculations**

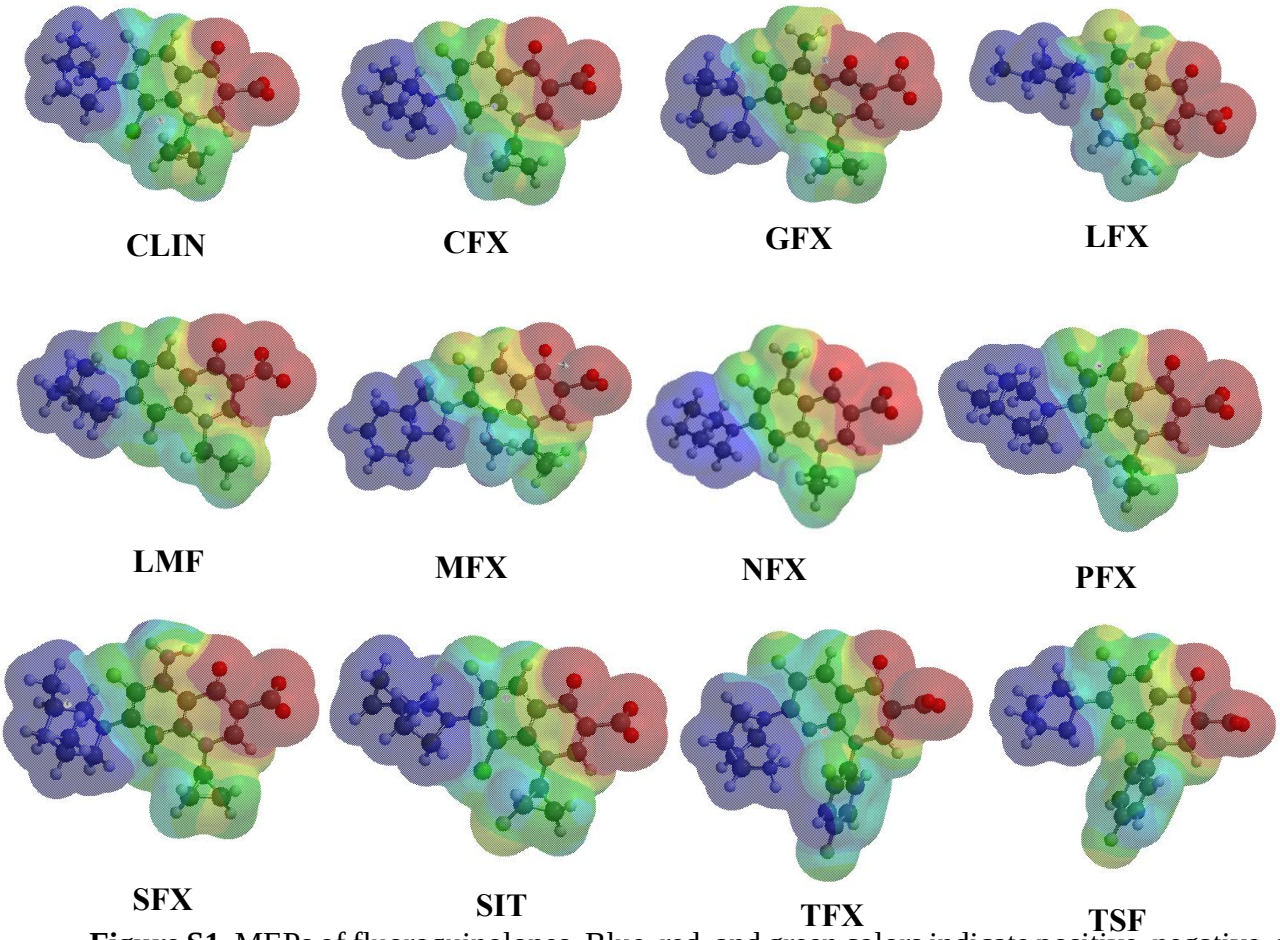

Figure S1. MEPs of fluoroquinolones. Blue, red, and green colors indicate positive, negative, and neutral MEP values zones, respectively.

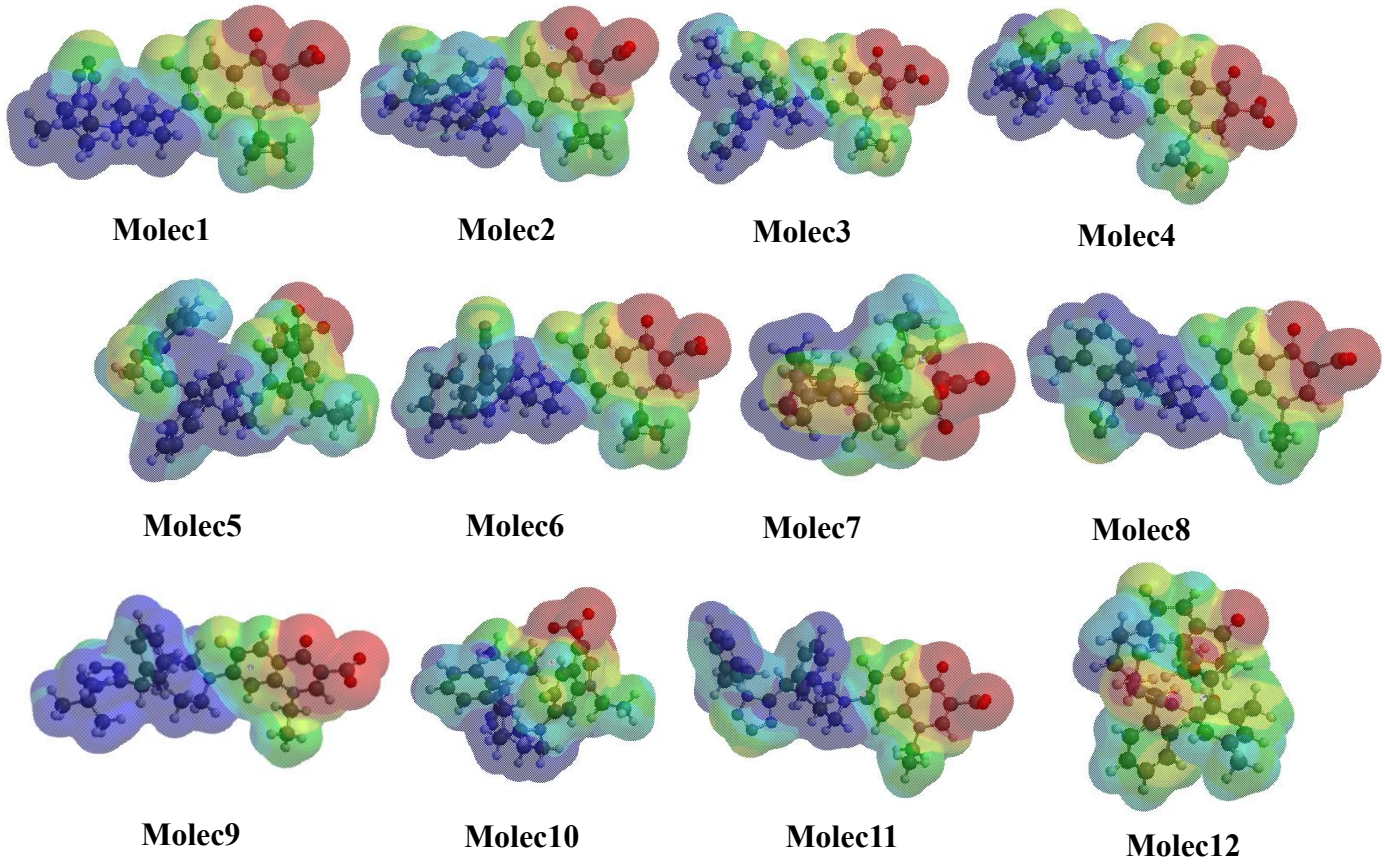

Figure S2. MEPs of synthesized fluoroquinolones. Blue, red, and green colors indicate positive, negative, and neutral MEP values zones, respectively.

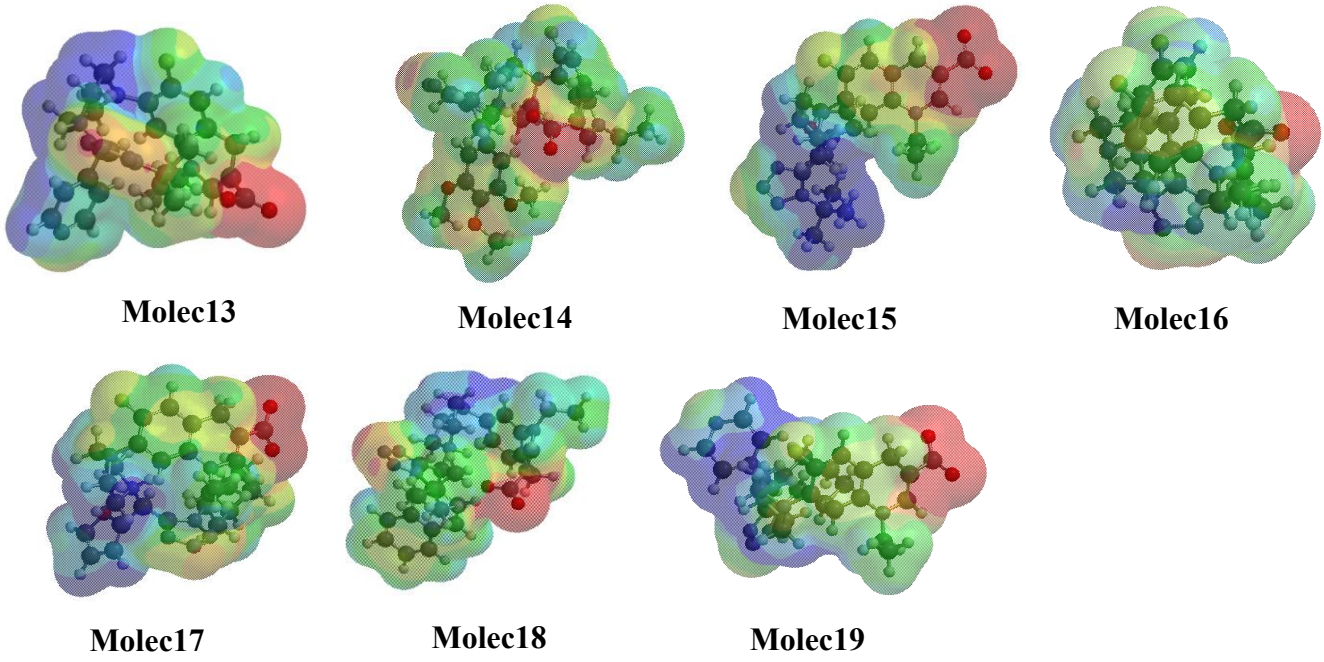

Figure S3. MEPs of fluoroquinolones synthesized by Chauhan et al. blue, red, and green colors indicate positive, negative, and neutral MEP values zones, respectively.

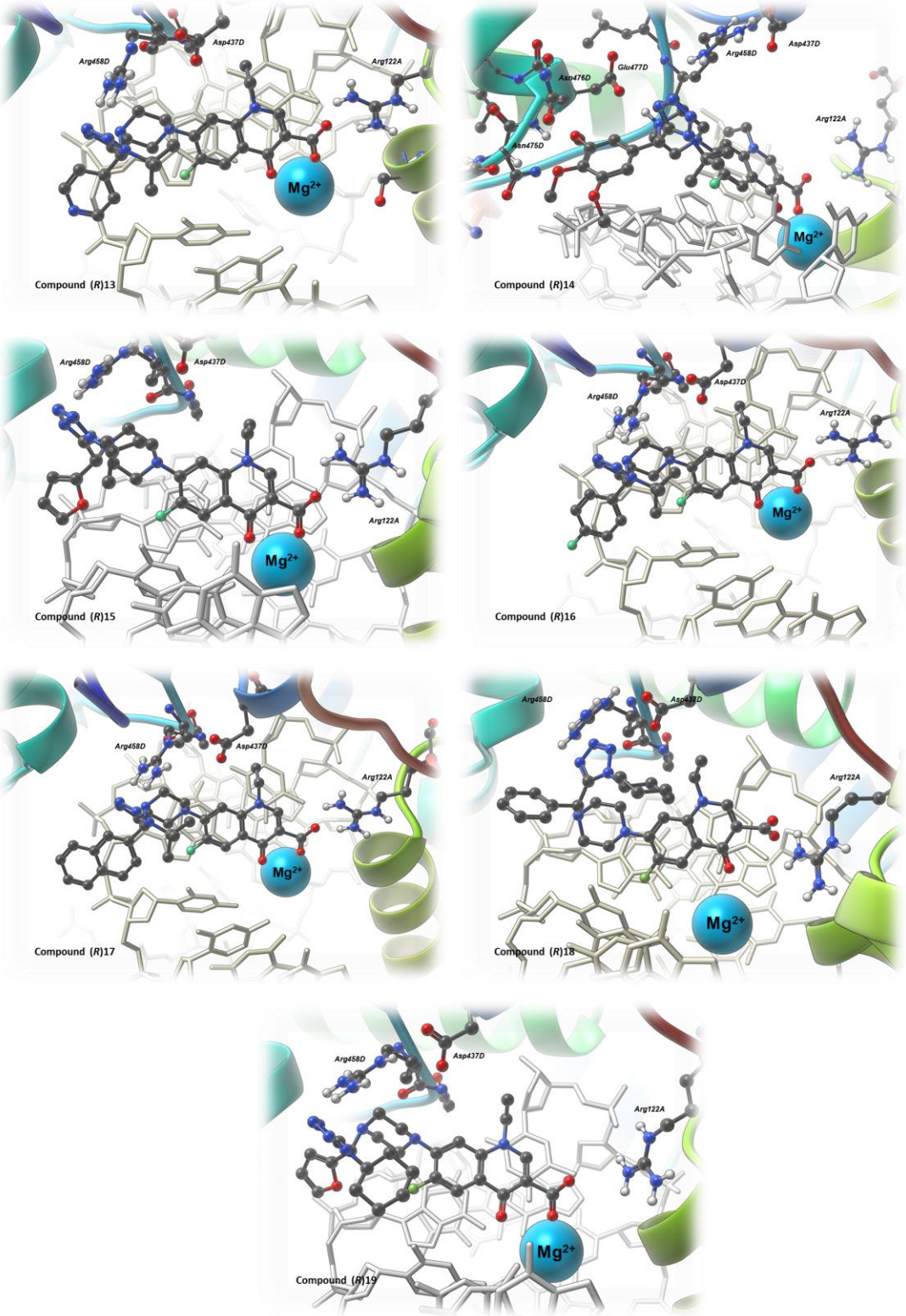

Figure S4. 3D structure representation of the complex formed by the fluoroquinolone-DNA-gyrase for compounds **13** to **19**, only for the (R) isomers.

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Table S1. MolDock Score, LE, torsions and HBond energy values (kcal/mol) of the docking experiments of molecules **1-12** and several known fluoroquinolones. Experimental MIC value is also displayed.

Compounds	Moldock Score	LE	HBond	Torsions	MIC (μg/mL)
1	-255.09	-7.50	-16.11	6	--
2	-182.03	-4.79	-6.89	6	--
3	-202.12	-5.05	-8.69	7	--
4	-253.94	-6.35	-16.39	7	--
5	-255.56	-5.81	-7.58	7	--
6	-245.68	-5.58	-9.03	7	--
7	-244.44	-7.41	-16.17	6	--
8	-229.45	-6.20	-14.65	6	--
9	-212.93	-5.46	-5.42	7	--
10	-251.86	-6.46	-15.32	7	--
11	-182.36	-4.24	-2.83	7	--
12	-258.04	-6.00	-10.66	7	--
CFX	-151.16	-6.30	-4.14	3	0.5
MFX	-198.77	-6.85	-4.20	4	0.6
CLIN	-222.39	-8.90	-4.53	3	0.125
GFX	-205.29	-7.90	-4.35	3	0.25
LFX	-189.19	-7.28	-4.73	2	0.125
LMF	-199.73	-7.99	0.00	3	0.2
NFX	-192.34	-8.36	-4.54	3	0.39
PFX	-177.99	-7.42	-4.26	3	0.5
SIT	-228.22	-8.15	-4.17	3	0.5
SFX	-221.08	-7.62	-4.29	3	0.125
TSF	-245.38	-8.46	0.00	3	0.1
TFX	-200.56	-6.69	0.00	3	0.6

Table S2. Calculated total (E_{Total}) and electrostatic energy (E_{Elec}) for the most contributing oxygen atom to the interaction energy of the complex in each compound. Energies in kcal/mol.

Compound	E_{Total} (O1)	E_{Elec} (O1)	E_{Elec} (Mg^{2+})
1	-20.98	-25.79	-33.49
2	-9.85	-6.13	-5.90
3	-14.68	-19.91	-18.84
4	-21.2	-25.70	-30.74
5	-9.62	2.01	-5.02
6	-21.62	-25.96	-28.93
7	-21.26	-25.97	-33.36
8	-16.33	-19.99	-18.23
9	-7.70	2.48	-1.44
10	-20.89	-25.69	-32.52
11	-19.72	-25.53	-37.24
12	-20.89	-25.72	-32.50

Table S3. MolDock Score, LE, Total HBond energy values (kcal/mol) and number of torsions for the docking experiments for both enantiomers of molecules **13-19**.

Compounds	Moldock Score	LE	Total HBond	Torsions
13R	-288.46	-7.40	-15.92	7
13S	-291.40	-7.47	-1.53	7
14R	-295.77	-6.57	-7.31	10
14S	-273.46	-6.08	-7.38	10
15R	-268.76	-7.07	-15.99	7
15S	-259.21	-6.65	-4.24	7
16R	-255.32	-6.38	-16.47	7
16S	-224.71	-5.62	-3.10	7
17R	-260.05	-6.05	-16.53	7
17S	-283.56	-6.59	-1.28	7
18R	-256.60	-6.26	-6.90	7
18S	-214.71	-5.24	-4.31	7
19R	-220.73	-5.52	-8.12	7
19S	-222.73	-5.43	-0.83	7

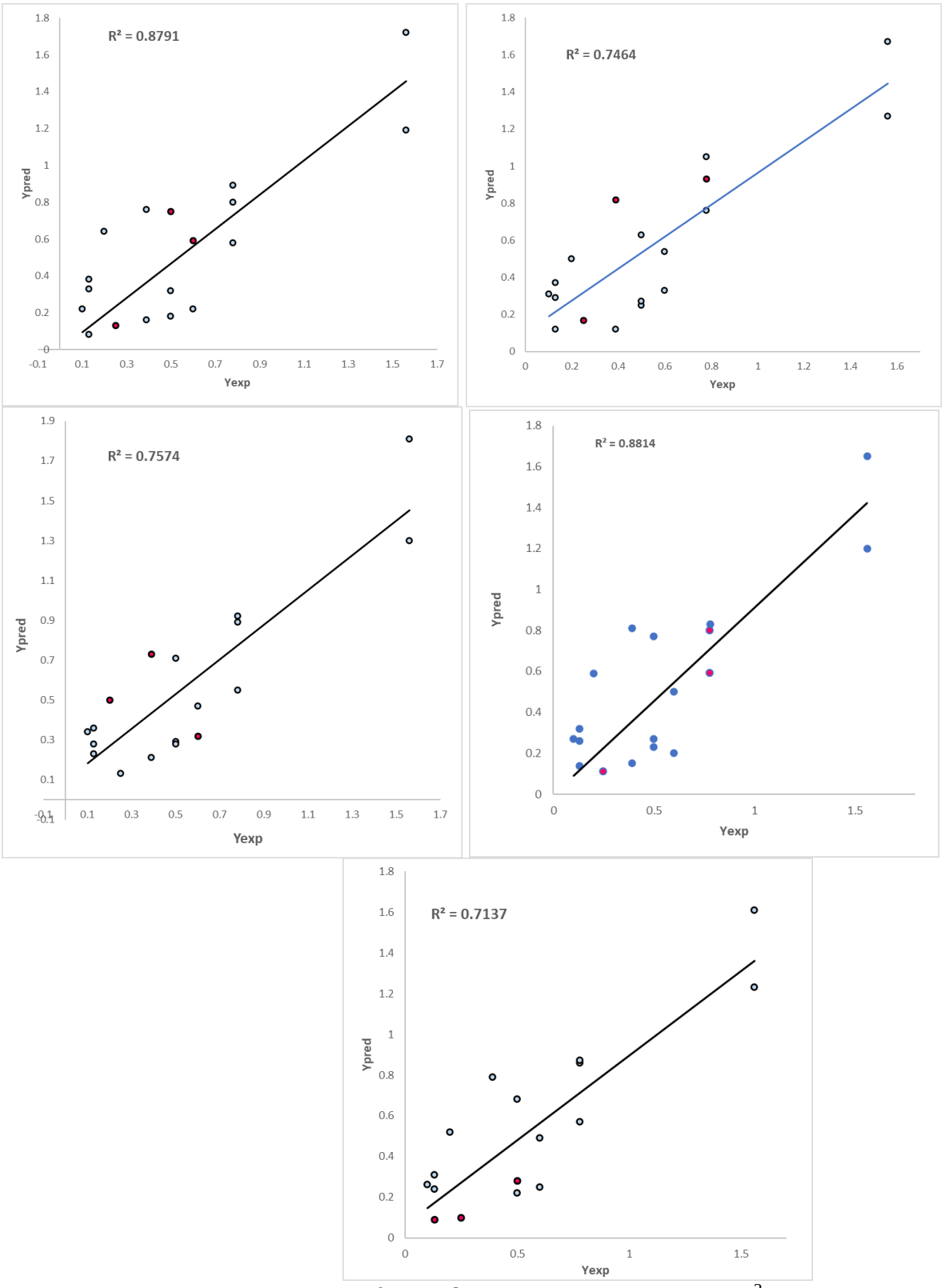

Figure S5. The lineal correlation of *Ypred vs Yexp* is displayed. The R^2 value is also indicated. Blue colored points represent the molecules of the training set and red colored points represent the external set.

Table S4. PSA and Volume values of known fluoroquinolones and new derivatives

Compounds	**PSA (Å²)**	**Volume (Å³)**	**MIC (μg/mL)**
TSF	80.39	362.09	0.1
CLIN	73.64	333.57	0.125
CFX	62.95	323.22	0.5
GFX	60.77	357.65	0.25
LFX	59.42	345.20	0.125
MFX	66.72	391.09	0.6
LMF	62.74	334.40	0.2
NFX	60.68	329.12	0.39
PFX	52.64	331.71	0.5
SFX	80.64	371.82	0.125
SIT	72.75	368.11	0.5
TFX	70.86	372.96	0.6
1	88.73	461.16	--
2	90.21	508.09	--
Molec 3	87.48	543.81	--
Molec 4	89.08	543.40	--
Molec 5	92.32	590.12	--
Molec 6	88.37	556.59	--
Molec 7	81.82	445.68	--
Molec 8	90.00	498.83	--
Molec 9	88.48	532.24	--
Molec 10	83.26	527.31	--
Molec 11	89.03	580.70	--
Molec 12	78.64	576.26	--

Table S5. Interaction energy values (kcal/mol) of the co-crystallized inhibitors with specific aa of CoV-2-Mpro of crystal **6lu7**.

aa	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Leu27	-3.24	-4.57	-1.54	-4.75	-1.59	-1.99	-4.02	-9.76	-3.47	-4.81	--	-5.75
His41	-5.44	-14.45	-9.37	-13.88	-13.60	-11.99	-5.41	-8.27	-14.41	-13.47	-12.49	-17.89
Met49	-4.39	-2.66	-4.66	-9.831	8.13	-11.62	-3.70	-2.97	-6.87	-8.04	-4.71	4.95
Phe140	--	-1.76	--	--	--	-2.24	--	--	--	--	-2.65	--
Leu141	-2.36	-8.23	-2.06	--	--	-8.17	-2.66	-1.80	-1.66	-0.50	-4.72	-1.95

Asn142	-11.79	-11.86	-16.83	-2.48	-11.16	-7.03	-11.11	-14.31	-8.71	-14.51	-8.02	-16.66
Gly143	-11.95	-9.87	-7.86	-3.58	-5.94	-7.57	-11.28	-10.44	-9.35	-8.19	-2.61	-9.11
Ser144	-7.84	-10.00	-9.44	-1.26	-0.63	-10.35	-4.90	-7.99	-5.06	-3.05	-4.58	-3.90
Cys145	-17	-7.63	-22.90	-7.02	-7.18	-14.73	-14.75	-15.99	-20.87	-5.75	-5.71	-13.83
His164	-3.69	-8.47	-6.36	-4.33	-4.49	-5.59	-3.76	-4.65	-6.87	-4.53	-8.96	-6.11
Met165	-20.13	-20.87	-20.59	-21.20	-14.10	-28.20	-20.75	-19.31	-20.19	-19.40	-21.23	-17.11
Glu166	-12.89	-11.66	-11.13	-8.10	-10.12	-15.52	-8.73	-10.55	-9.10	-9.89	-11.99	-8.10
Leu167	-10.97	-7.98	-8.75	-8.66	-6.03	-8.35	-10.76	-10.68	-7.50	-6.49	-3.30	-8.74
Pro168	-8.63	-6.60	-6.16	-6.51	-2.24	-5.69	-9.06	-8.91	-5.33	-2.25	-8.74	-4.47
Arg188	-3.85	-1.66	-1.19	-4.28	2.76	-1.40	-1.35	-1.10	-1.98	-0.98	-6.94	-3.68
Gln189	-29.14	-26.18	-27.94	-29.12	-26.239	-31.838	-29.55	-27.40	-26.92	-25.93	-41.86	3.84872
Gln192	-11.02	-10.47	-12.06	-15.27	-6.70	-13.83	-10.93	-12.43	-15.52	-10.09	-2.47	-2.10
MDSG	-157.84	-167.83	-153.89	-147.62	-112.29	-194.52	-151.07	-159.54	-161.40	-147.79	-158.87	-114.58
Hbtot	-29.03	-19.44	-29.31	-3.51	-3.86	-26	-24.84	-25.65	-17.77	-7.55	-3.16	-17.52
LE	-4.64	-4.42	-3.84	-3.69	-2.552	-4.42	-4.58	-4.31	-4.14	-3.79	-3.50	-2.67

Table S6. Interaction energy values (kcal/mol) of the co-crystallized inhibitors with specific aa of CoV-2-Mpro of crystal **7l0d**.

aa	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Leu27	-1.61	-0.83	-4.53	2.13	-1.00	-5.91	-8.93	-2.40	0.56	2.04	-0.45	-10.76
His41	-10.43	-6.04	-18.56	-18.18	-15.63	-13.92	-13.36	-15.46	-15.71	-12.69	-12.84	-10.82
Met49	--	-3.92	-6.17	-0.31	-2.78	-0.72	-6.00	-1.62	-5.02	--	-1.47	-3.45
Phe140	-3.77	-1.99	-3.69	-2.04	-2.35	-0.30	--	--	--	-4.34	2.26	--
Leu141	-8.70	-6.16	-12.19	-13.43	-6.45	-2.59	--	-1.45	--	-12.53	-14.05	-2.66
Asn142	-16.81	-17.98	-19.26	-25.50	-15.12	-15.86	-2.96	-19.35	-7.29	-17.65	-12.49	-25.31
Gly143	-8.26	-1.08	-4.82	-4.74	-10.12	-11.17	-3.72	-12.27	-4.33	-6.66	-7.25	-9.02
Ser144	-5.50	-6.97	-4.32	-4.72	-3.35	-3.88	-1.09	-0.57	-0.44	-4.92	-4.28	-5.17
Cys145	-6.85	-15.16	-6.02	-9.90	-0.73	-9.04	-3.70	-7.07	-16.04	-6.22	-7.20	-16.17
His164	-2.25	-5.15	-3.33	-2.80	-7.21	-4.60	-0.40	-2.05	-4.66	-2.96	-2.42	-4.03
Met165	-7.76	-11.21	-6.64	-1.58	-16.66	-11.66	--	-11.37	-14.85	-3.52	-2.80	-10.11
Glu166	-12.34	-19.30	-21.94	-13.56	-30.24	-25.42	--	-21.25	-8.77	-14.11	-14.32	-27.25
Leu167	-0.33	--	--	--	-9.18	-11.51	--	-9.21	-4.06	--	--	-8.80
Pro168	--	--	--	--	-20.95	-19.03	--	-19.02	-0.63	--	--	-21.08
Arg188	--	--	--	--	-2.26	--	--	-0.51	-5.91	--	--	-0.42
Gln189	-0.39	--	--	--	-14.96	-3.75	-20.06	-4.14	-15.42	--	-1.08	-8.28
Gln192	--	--	--	--	-2.11	--	--	--	-11.41	--	--	--
MDSG	-101.21	-153.73	-152.49	-134.10	-164.55	-142.63	-91.01	-128.33	-131.10	-140.29	-153.36	-171.20
HBtot	-3.65	-15.81	-2.95	-2.38	-11.05	-10.65	-1.30	-10.13	-13.07	-4.59	-12.13	-30.29
LE	-2.98	-4.05	-3.81	-3.35	-3.74	-3.24	-2.76	-3.47	-3.36	-3.60	-3.57	-3.98

Table S7. Interaction energy values (kcal/mol) of the co-crystallized inhibitors with specific aa of CoV-2-Mpro of crystal **6m2n**.

aa	1	2	3	4	5	6	7	8	9	10	11	12
Leu27	-4.53	-0.30	--	-0.56	-1.79	--	-4.78	-4.91	-1.19	-6.74	-0.72	--
His41	-8.17	-2.21	-20.56	-26.45	-6.13	-23.59	-6.99	-5.41	-6.04	-11.51	2.81	-19.50
Met49	-4.60	-1.37	-6.85	-15.36	-4.08	-19.85	-1.36	-0.58	-1.83	-8.76	-0.80	-8.55
Phe140	--	-7.52	--	--	-5.72	--	--	--	-6.15	--	-4.65	--
Leu141	-2.01	-9.72	--	--	-5.53	--	-1.67	-2.23	-5.26	--	-4.89	--
Asn142	-14.60	-17.10	-12.85	-2.93	-25.52	-0.40	-11.49	-15.98	-16.38	-15.13	-13.94	-8.69
Gly143	-7.21	-10.21	-4.33	--	-6.28	--	-8.84	-12.45	-4.29	-7.51	-1.77	--
Ser144	-6.10	-8.18	-0.38	--	-5.17	--	-4.38	-6.88	-6.25	-0.70	-2.93	--
Cys145	-20.28	-9.37	-7.75	-6.13	-15.54	-4.53	-20.78	-15.00	-16.20	-8.49	-4.79	-7.76
His164	-5.97	-5.98	-4.33	2.53	4.79	-3.32	-8.40	-5.18	-3.55	-4.00	-4.35	-7.20
Met165	-12.77	-20.20	-18.26	-6.81	-22.50	-6.59	-4.66	-16.90	-24.72	-17.99	-17.68	-14.10
Glu166	-7.45	-23.63	-8.49	-3.79	-22.53	-8.12	-12.70	-14.84	-27.09	-9.08	-22.67	-16.63
Leu167	-1.05	-10.20	-6.75	-6.35	-4.25	-5.87	-2.97	-7.84	-3.97	-6.73	-6.53	-5.81
Pro168	-6.45	-17.74	-4.95	-14.34	-6.13	-15.43	-11.09	-12.54	-7.58	-5.09	-18.41	-15.92
Arg188	-6.02	-2.31	--	-7.96	-1.13	-13.06	-4.67	-2.33	-1.06	-2.20	-4.18	-7.65
Gln189	-30.08	-16.68	-24.90	-23.74	-20.73	-21.41	-24.44	-16.31	-24.93	-20.10	-11.34	-23.98
Gln192	-15.14	-12.33	-16.31	-16.71	-7.63	-16.71	-13.69	-14.08	-10.45	-14.78	-9.81	-12.63
MDSG	-139.07	-185.44	-158.75	-136.26	-167.24	-165.05	-134.34	-155.64	-116.50	-159.44	-133.13	-156.30
HBtot	-26.87	-20.03	-7.05	-10.05	-16.46	-9.59	-22.16	-15.10	-16.01	-12.36	-2.74	-8.26
LE	-4.09	-4.88	-3.97	-3.41	-3.80	-3.75	-4.07	-4.21	-2.99	-4.09	-3.10	-3.63

Table S8. Interaction energy values (kcal/mol) of the co-crystallized inhibitors with specific aa of CoV-2-Mpro of crystal **6w63**.

aa	1	2	3	4	5	6	7	8	9	10	11	12
Leu27	--	--	--	--	-0.78	-5.15	-1.02	--	-4.05	-0.35	-0.52	--
His41	-4.20	-36.50	-8.10	-0.50	-20.29	-11.16	-7.25	-3.96	-20.40	--	-1.82	-4.85
Met49	--	-10.40	-7.67	--	-12.42	-10.82	-0.63	--	-7.14	--	-1.52	-3.79
Phe140	-3.68	-7.62	-3.43	-6.79	-1.64	--	--	-7.46	--	-4.97	-1.45	-3.00
Leu141	-5.04	-11.76	-6.75	-5.51	-4.76	-1.46	-1.00	-9.89	-0.64	-5.83	-11.97	-9.61
Asn142	-19.79	-21.15	-28.46	-25.06	-14.93	-14.94	-8.80	-19.45	-10.25	-22.04	-28.37	-21.70
Gly143	-9.44	-2.22	-10.11	-12.64	-5.71	-13.25	-3.31	-10.63	-6.21	-12.50	-13.94	-8.88
Ser144	-13.37	-3.85	-7.97	-7.62	-4.04	-0.94	-0.31	-6.14	-1.25	-12.35	-10.57	-4.05
Cys145	-15.39	-5.20	-17.76	-14.86	-7.02	-12.28	-10.64	-11.45	-13.31	-15.64	-14.05	-9.30
His164	-5.23	-5.66	-5.33	-3.97	-7.04	-2.20	-4.61	-2.27	-3.90	-3.80	-4.09	-2.58
Met165	-23.03	-2.64	-10.39	-15.39	-15.24	-10.49	-17.07	-18.82	-18.98	-12.75	-13.24	-14.22
Glu166	-16.70	-26.82	-9.67	-22.55	-18.77	-9.38	-4.06	-24.23	-7.68	-18.50	-28.73	-21.77
Leu167	-6.13	--	--	-5.92	-6.50	-9.23	-8.96	-2.95	-3.57	-2.93	-2.91	-3.56
Pro168	5.14	--	--	-13.84	-13.99	-3.77	-14.16	-14.29	-4.82	-12.98	-13.02	-12.24
Arg188	7.96	-8.25	--	-2.48	-2.32	--	-5.92	-3.21	-3.01	-2.09	-3.00	-2.31
Gln189	-21.85	-10.15	--	-27.23	-22.35	-30.65	-25.30	-23.53	-20.72	-27.13	-17.70	-28.79
Gln192	77.18	--	--	-10.62	-7.51	-9.12	-13.29	-1.17	-7.27	-12.04	-1.32	-2.74
MDSG	-40.06	-149.30	-148.05	-170.70	-167.30	-168.12	-124.70	-156.18	-146.09	-154.50	-173.24	-163.64
HBtot	-30.01	-9.17	-36.02	-23.26	-10.97	-16.72	16.95	-13.09	-9.69	-29.56	-27.38	-15.39
LE	-1.18	-3.93	-3.70	-4.27	-3.80	-3.82	-3.78	-4.22	-3.75	-3.96	-4.03	-3.81

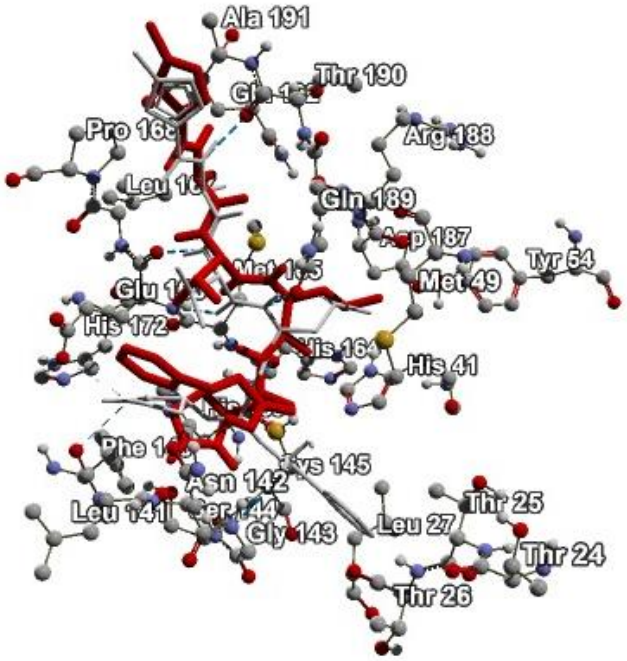

Figure S6. Crystal structure of CoV-2-Mpro (PDB:**6lu7**). Crystal conformation of the ligand is colored according to each atom and conformation obtained from the docking calculations is colored in red, RMSD (2.4 Å).

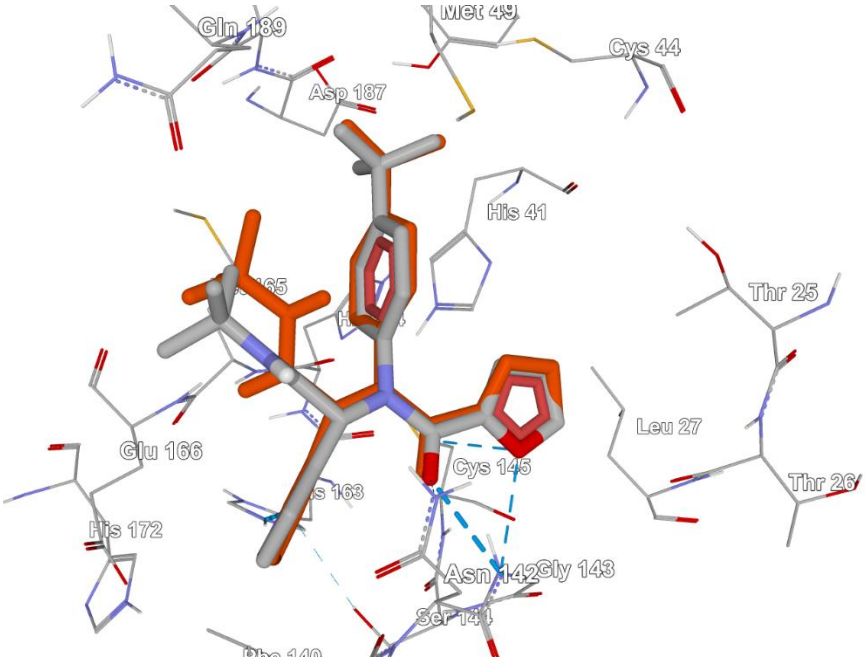

Figure S7. Crystal structure of CoV-2-Mpro (PDB:**7l0d**). Crystal conformation of the ligand is colored according to each atom and conformation obtained from the docking calculations is colored in orange, RMSD (0.4 Å).

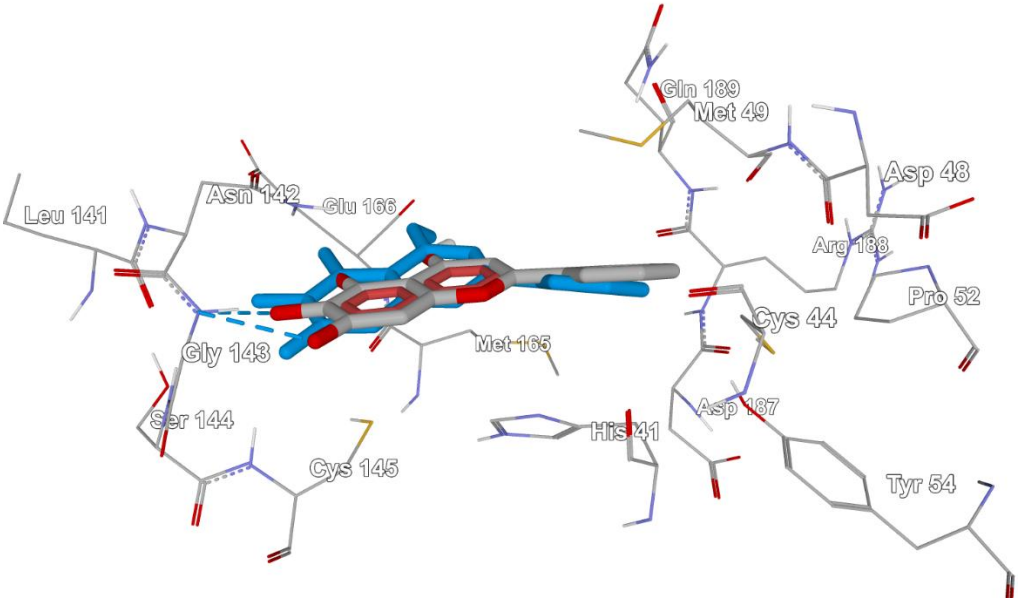

Figure S8. Crystal structure of CoV-2-Mpro (PDB:**6m2n**). Crystal conformation of the ligand is colored according to each atom and conformation obtained from the docking calculations is colored in blue, RMSD (1.2 Å).

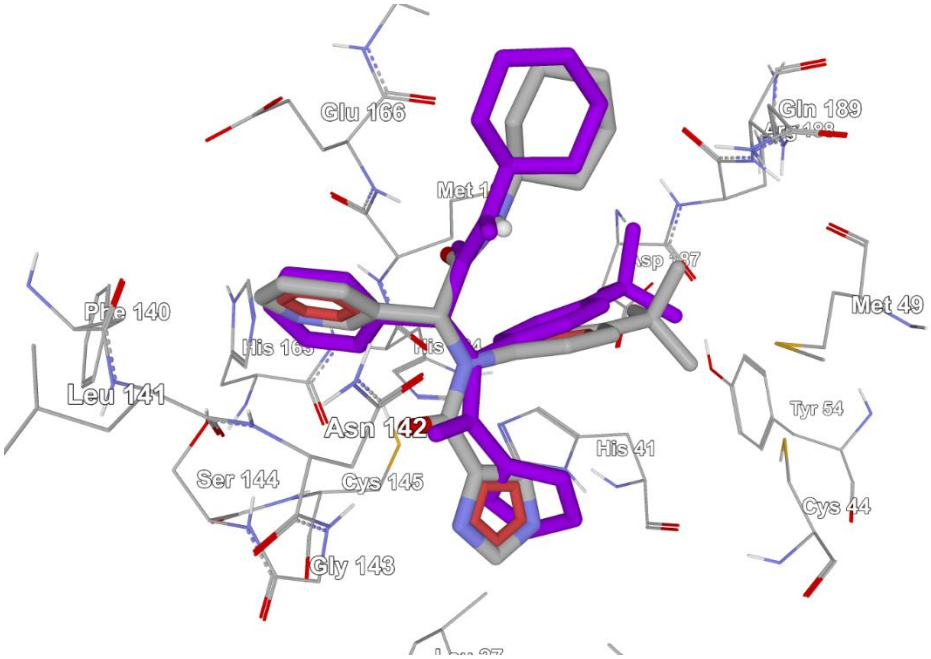

Figure S9. Crystal structure of CoV-2-Mpro (PDB:**6w63**). Crystal conformation of the ligand is colored according to each atom and conformation obtained from the docking calculations is colored in purple, RMSD (0.8 Å).

Table S5. Pharmacokinetics properties of FQ compounds by means of the SwissADME server.

Molecule	MLOGP	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4	Lipinski	Ghose	Veber	Egan	Bioavailability Score
MFX	1.39	No	No	No	Yes	No	0	0	0	0	0.55
CLIN	1.52	No	No	No	No	No	0	0	0	0	0.55
GFX	1.75	No	No	No	Yes	No	0	0	0	0	0.55
TFX	2.78	No	No	No	No	No	0	0	0	0	0.55
LFX	0.72	No	No	No	No	No	0	0	0	0	0.55
CFX	1.28	No	No	No	No	No	0	0	0	0	0.55
SFX	1.33	No	No	No	Yes	No	0	0	0	0	0.55
PFX	1.28	No	No	No	No	No	0	0	0	0	0.55
NFX	1.04	No	No	No	No	No	0	0	0	0	0.55
SIT	2.08	No	No	No	Yes	No	0	0	0	0	0.55
TSF	2.56	No	No	No	No	No	0	0	0	0	0.55
LMF	1.67	No	No	No	No	No	0	0	0	0	0.55
13	1.98	No	No	Yes	No	Yes	2	2	0	0	0.17
14	2.05	No	No	Yes	Yes	Yes	2	3	0	1	0.17
15	1.82	No	No	Yes	No	Yes	2	2	0	0	0.17
16	3.31	No	No	Yes	Yes	Yes	1	3	0	0	0.55
17	3.53	No	Yes	Yes	Yes	Yes	1	3	0	0	0.55
18	3.33	No	Yes	Yes	Yes	Yes	1	3	0	0	0.55
19	2.21	No	No	Yes	Yes	Yes	2	3	0	0	0.17
1	2.14	No	No	No	No	No	0	1	0	0	0.55
2	2.74	No	Yes	Yes	Yes	No	1	2	0	0	0.55
3	3.14	No	No	Yes	Yes	Yes	1	3	0	0	0.55
4	3.14	No	No	Yes	Yes	Yes	1	3	0	0	0.55
5	3.86	No	Yes	Yes	Yes	Yes	1	3	0	0	0.55
6	3.86	No	Yes	Yes	Yes	Yes	1	3	0	0	0.55
7	1.93	No	No	No	No	No	0	0	0	0	0.55
8	2.81	No	Yes	Yes	No	Yes	1	2	0	0	0.55
9	2.94	No	No	Yes	Yes	Yes	1	3	0	0	0.55
10	2.94	No	No	Yes	Yes	Yes	1	3	0	0	4.36
11	3.77	No	Yes	Yes	Yes	Yes	1	3	0	0	4.69
12	3.77	No	Yes	Yes	Yes	Yes	1	3	0	0	4.69

Infrared (FTIR-ATR) Spectroscopy Spectrum

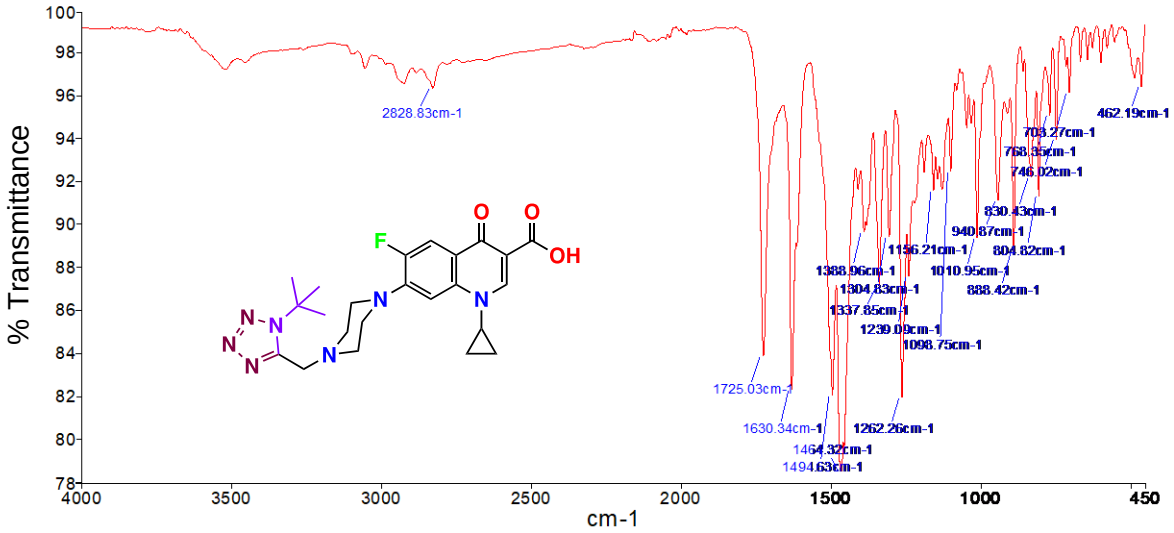

Figure S10. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **1**.

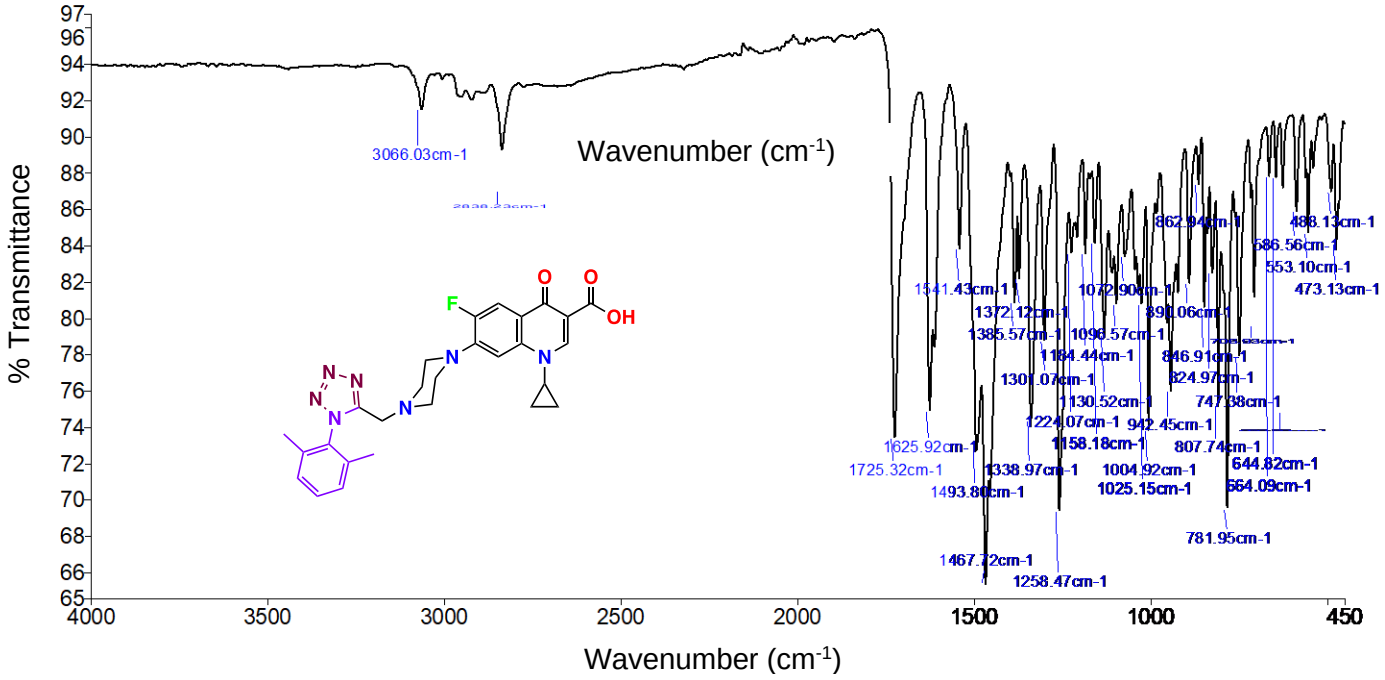

Figure S11. 1-cyclopropyl-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **2**.

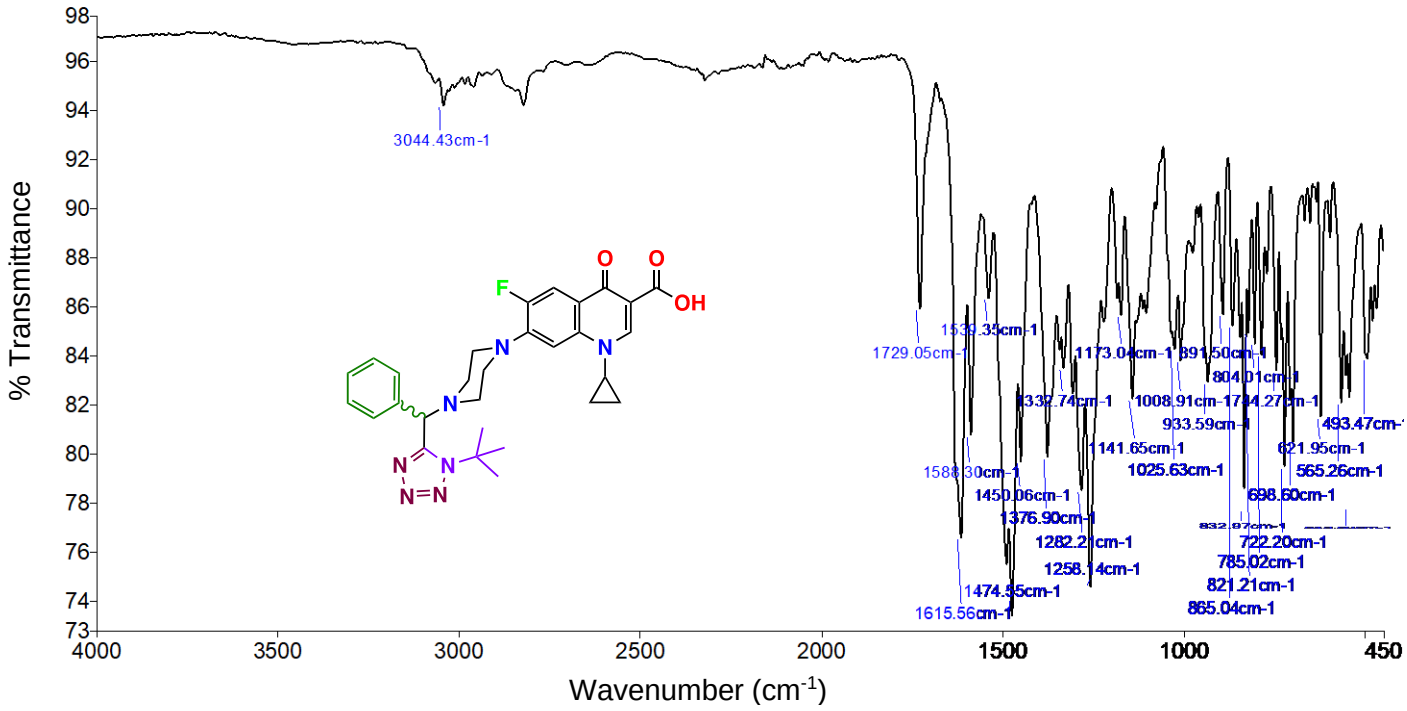

Figure S12. (*R*/*S*)-7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **3,4**.

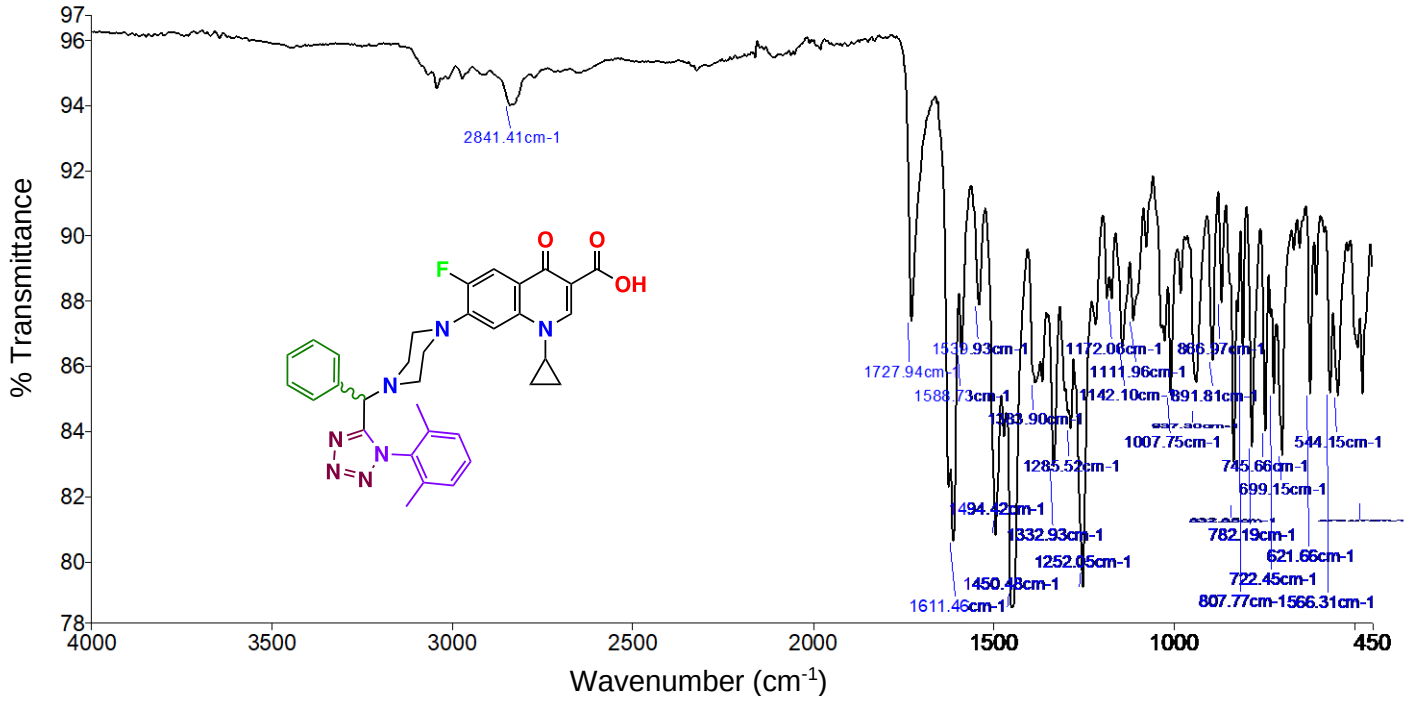

Figure S13. (*R*/*S*)-1-cyclopropyl-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **5, 6**.

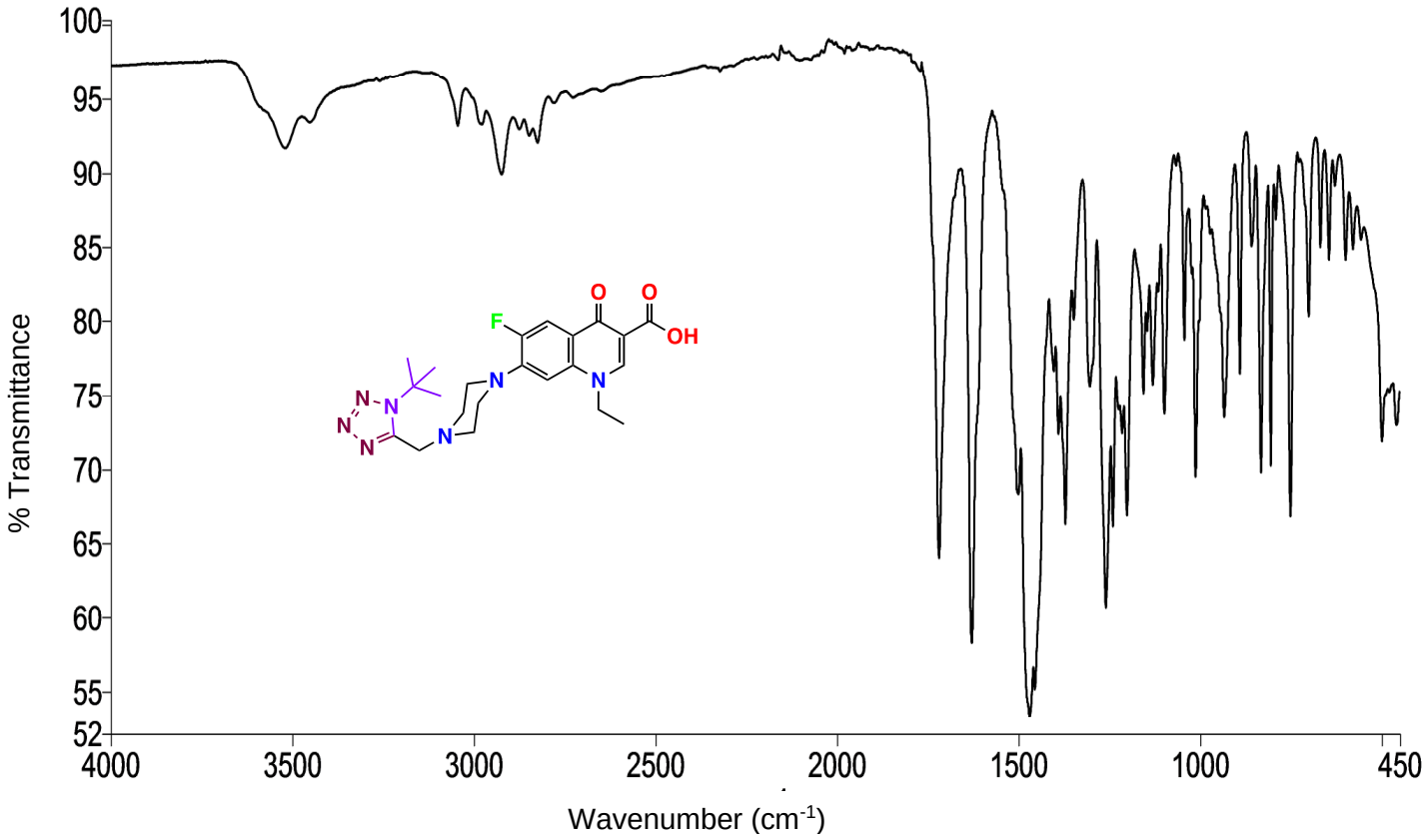

Figure S14. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **7**.

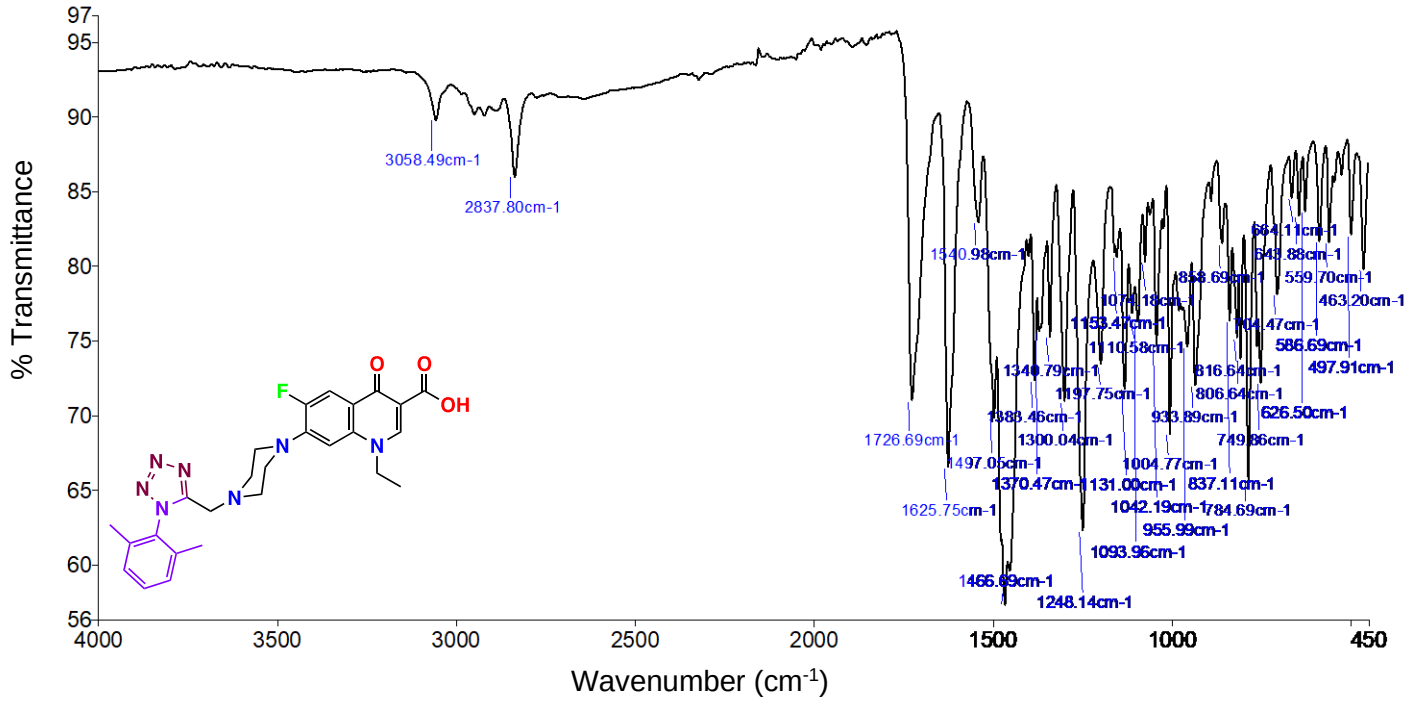

Figure S15. 7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **8**.

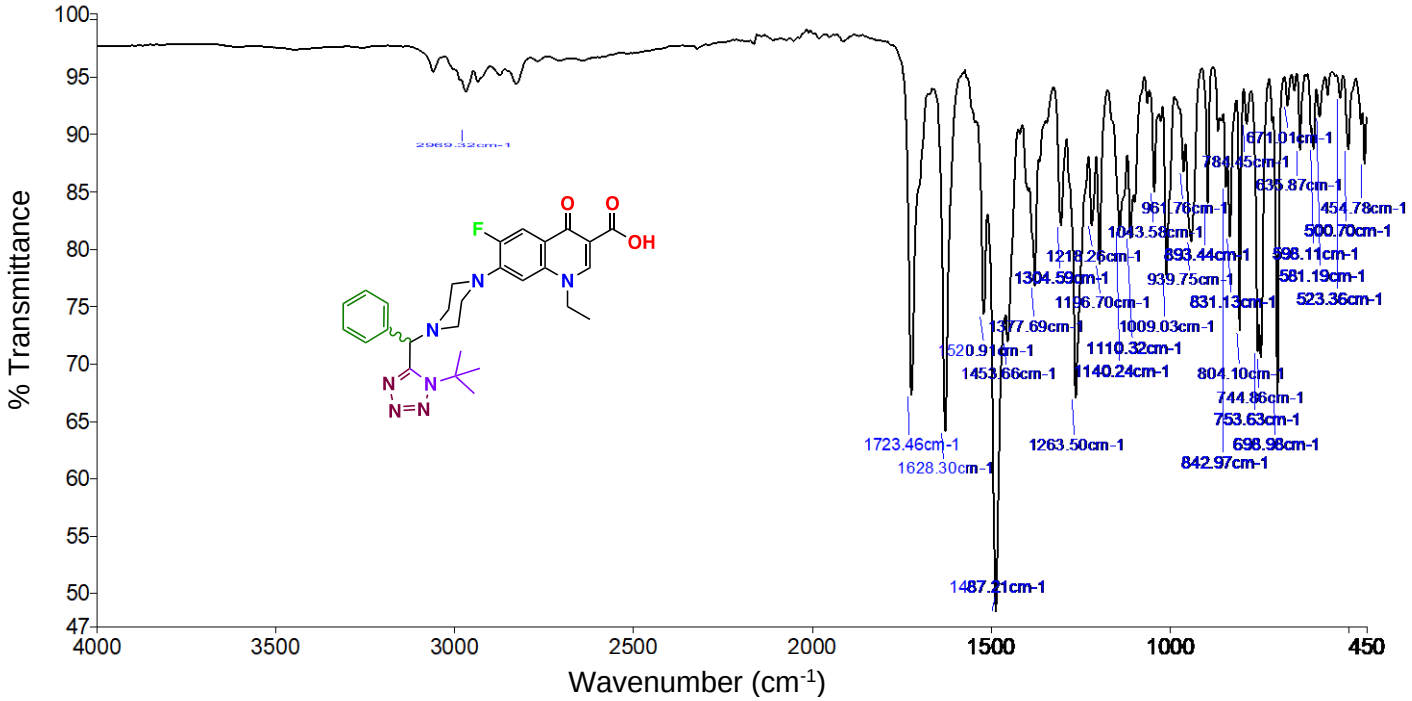

Figure S16. (*R*/*S*)-7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **9**, **10**.

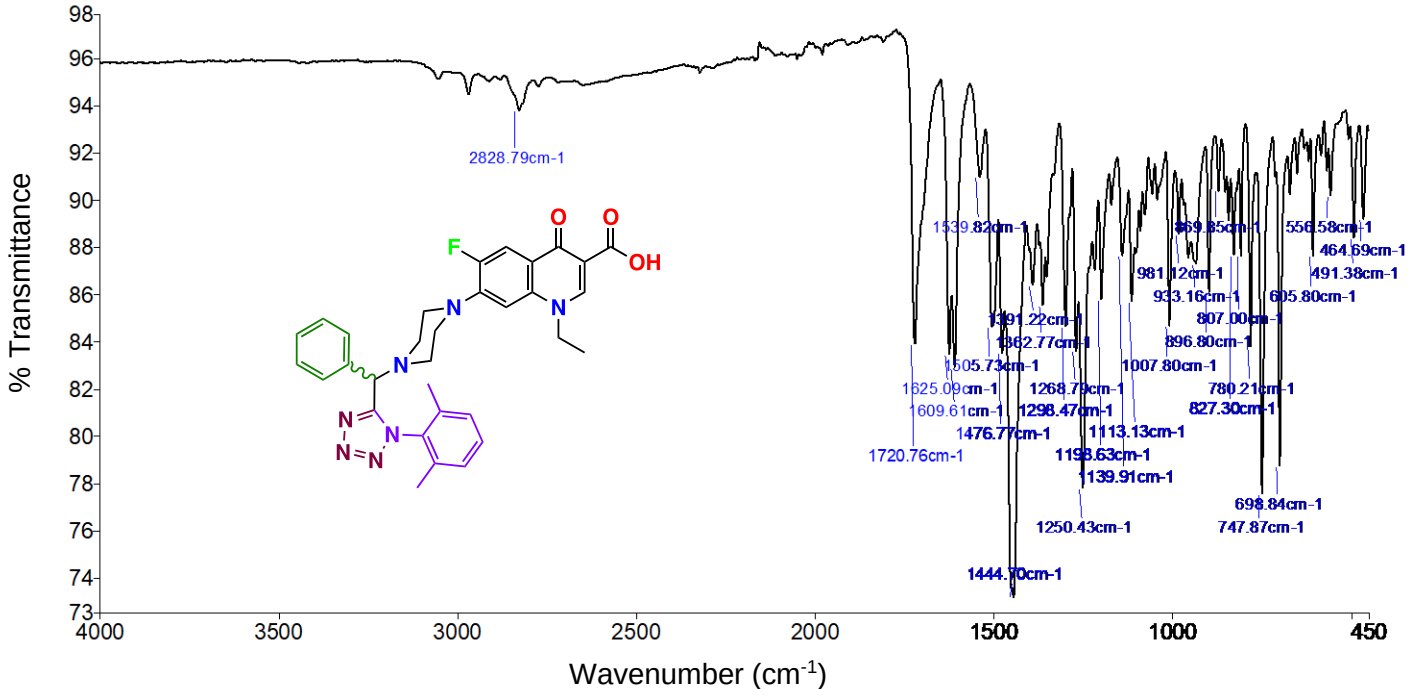

Figure S17. (*R*/*S*)-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **11**, **12**.

^{1}H Resonance Magnetic Nuclear Spectroscopy Spectrum

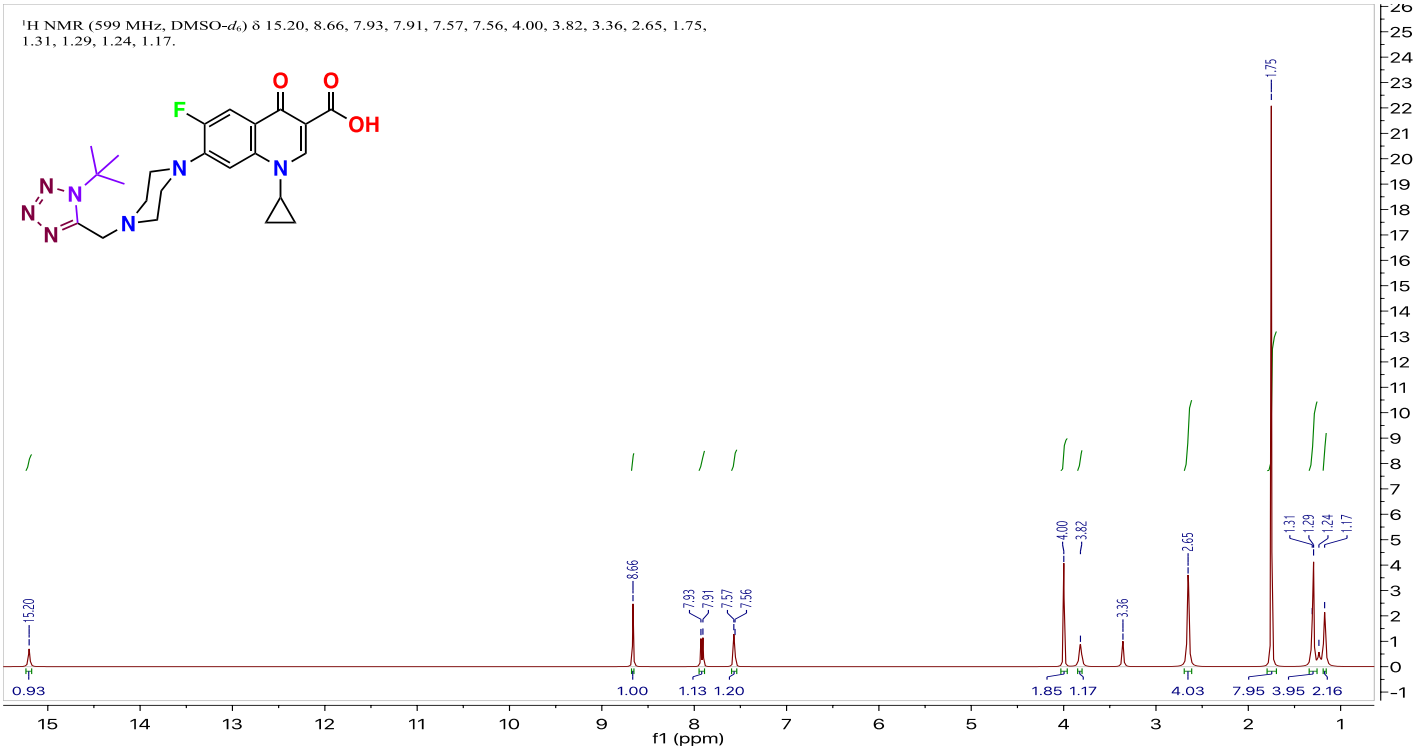

Figure S18. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **1**.

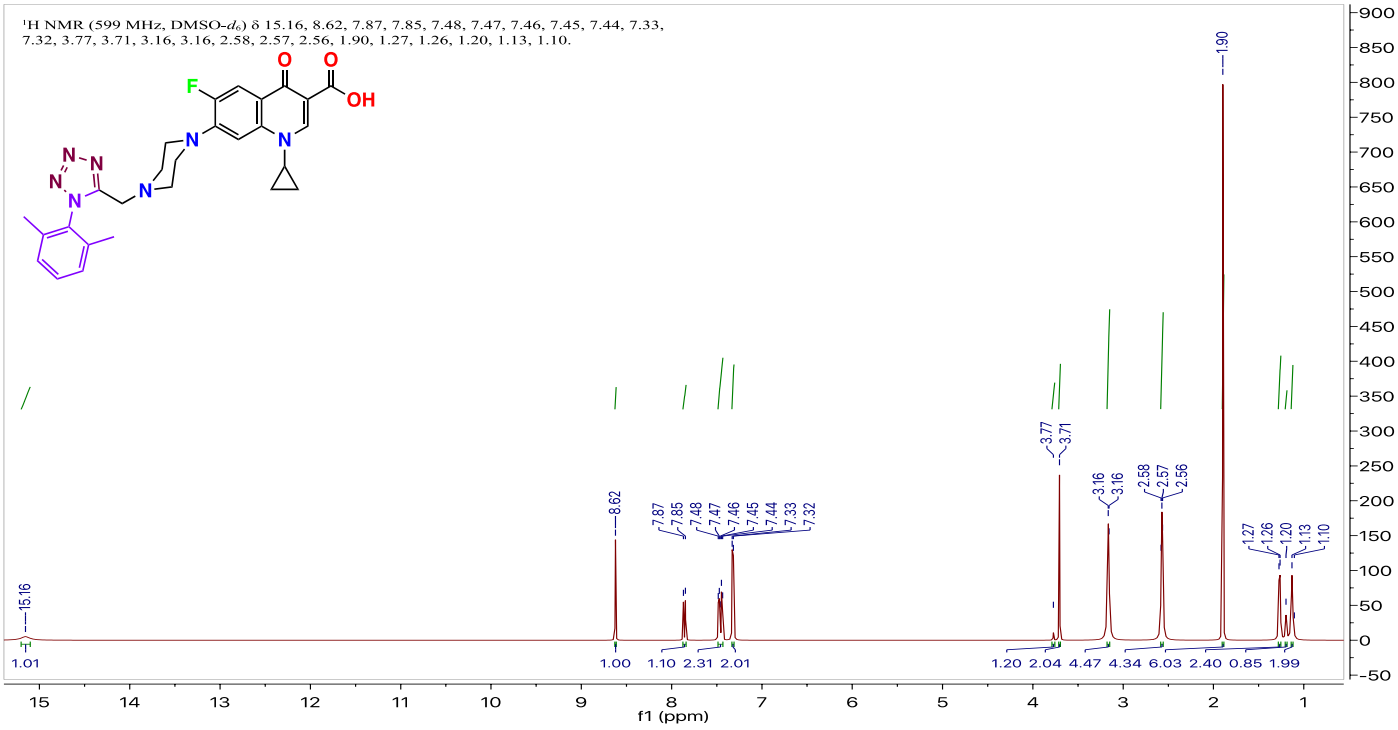

Figure S19. 1-cyclopropyl-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **2**.

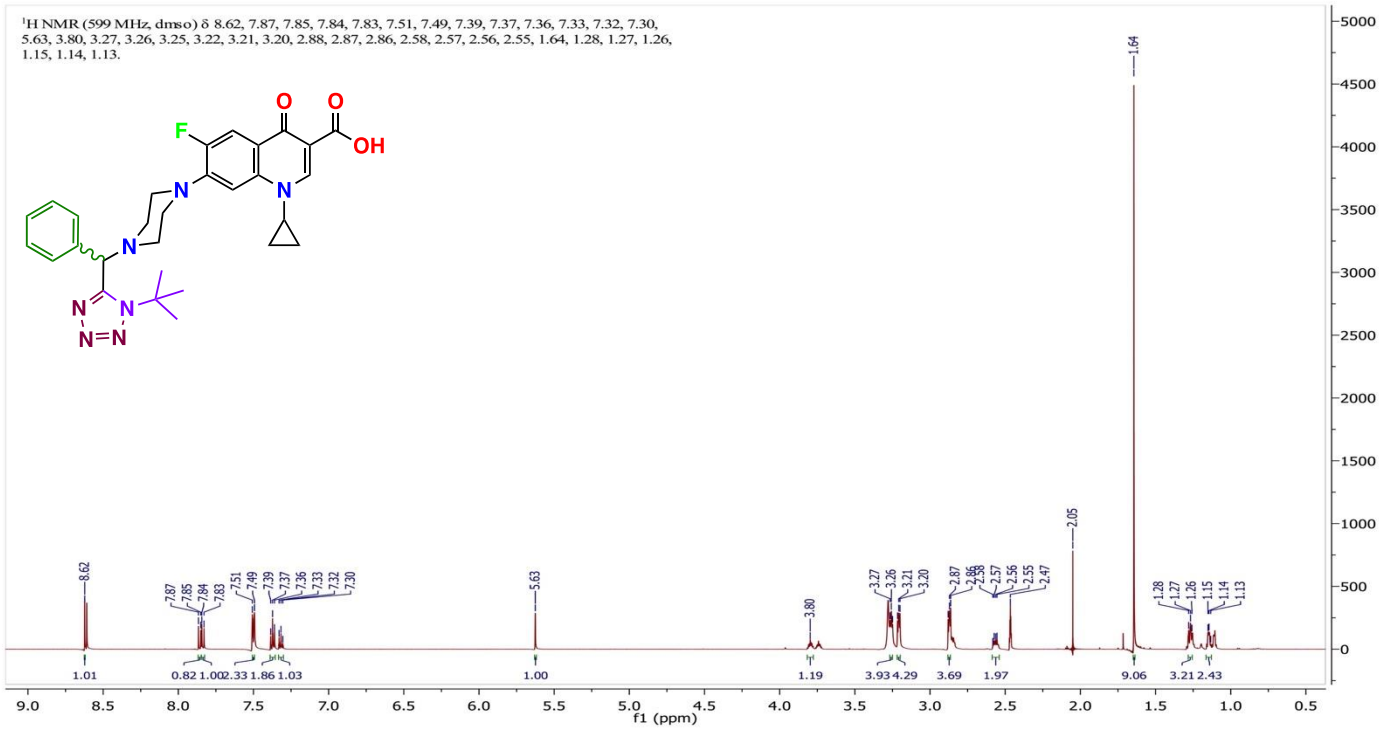

Figure S20. (*R*/*S*)-7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **3**, **4**.

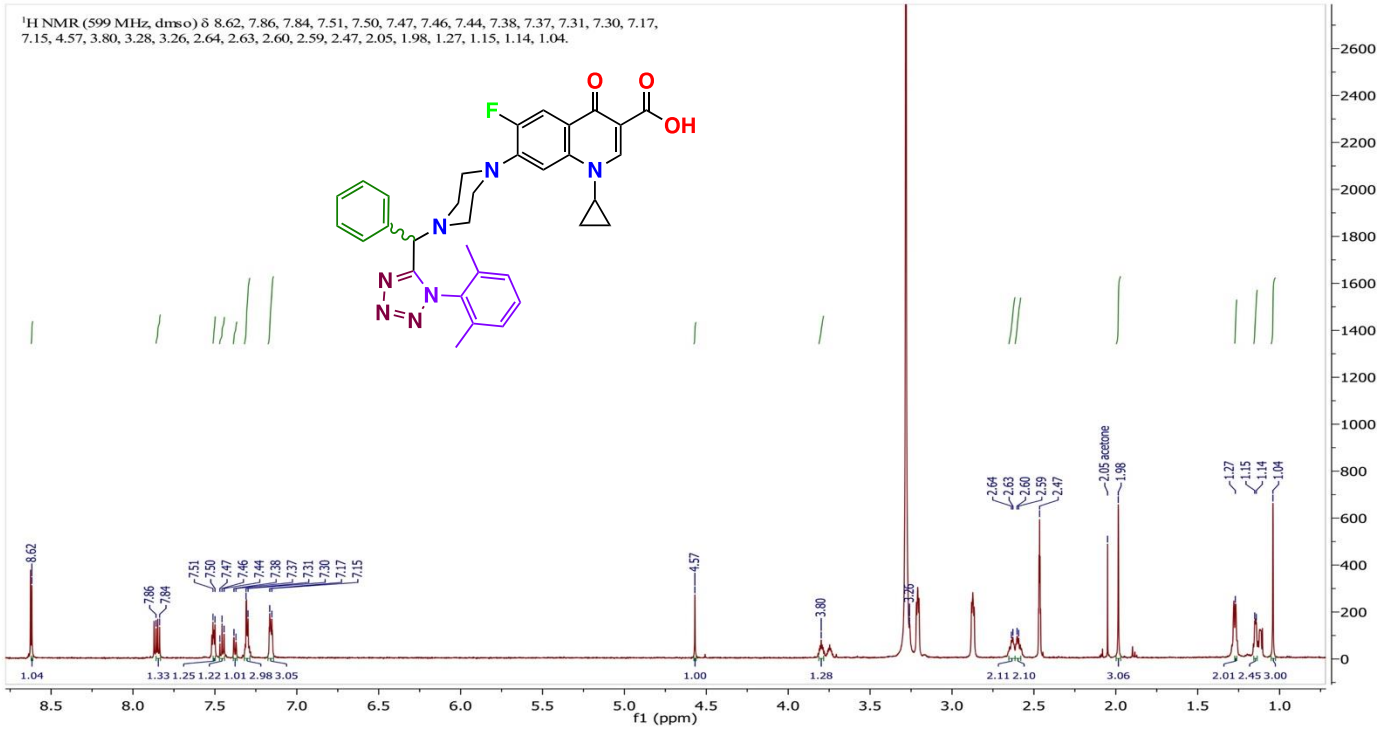

Figure S21. (*R*/*S*)-1-cyclopropyl-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **5**, **6**.

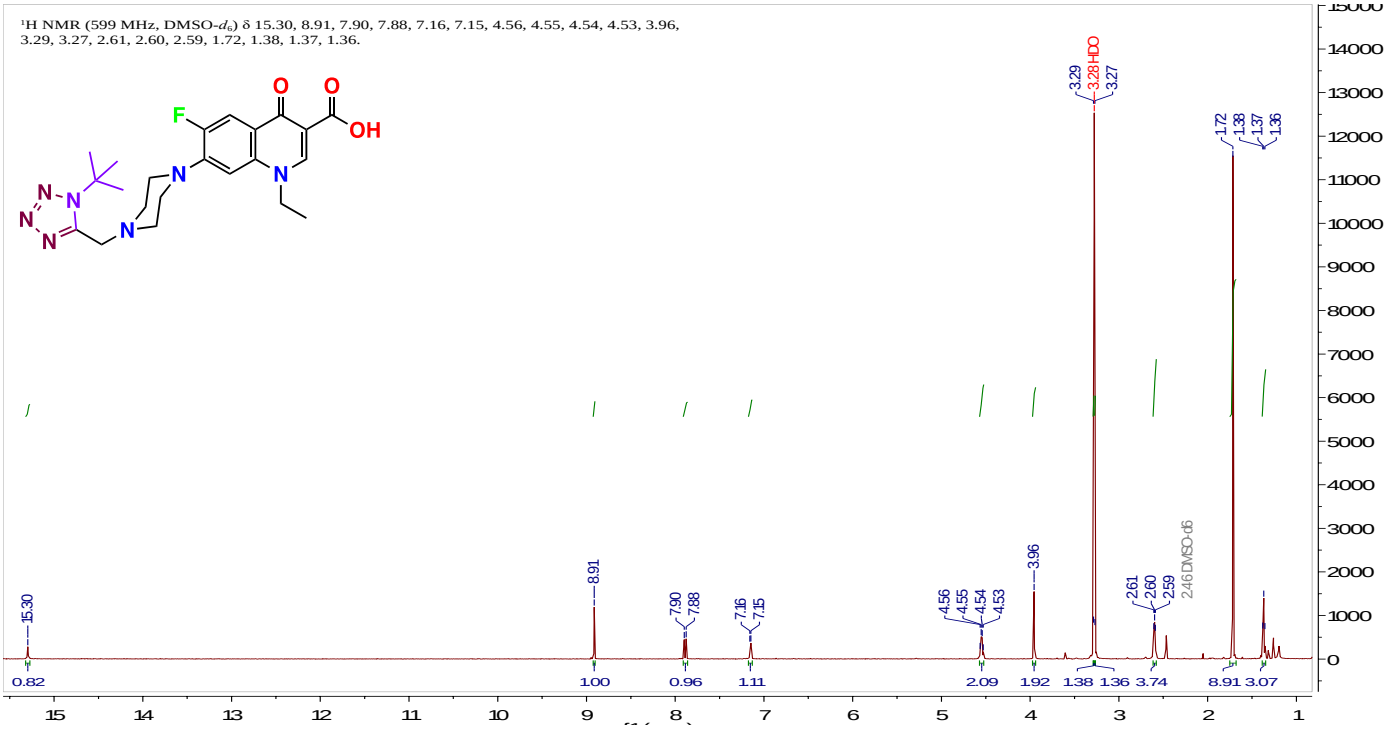

Figure S22. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **7**.

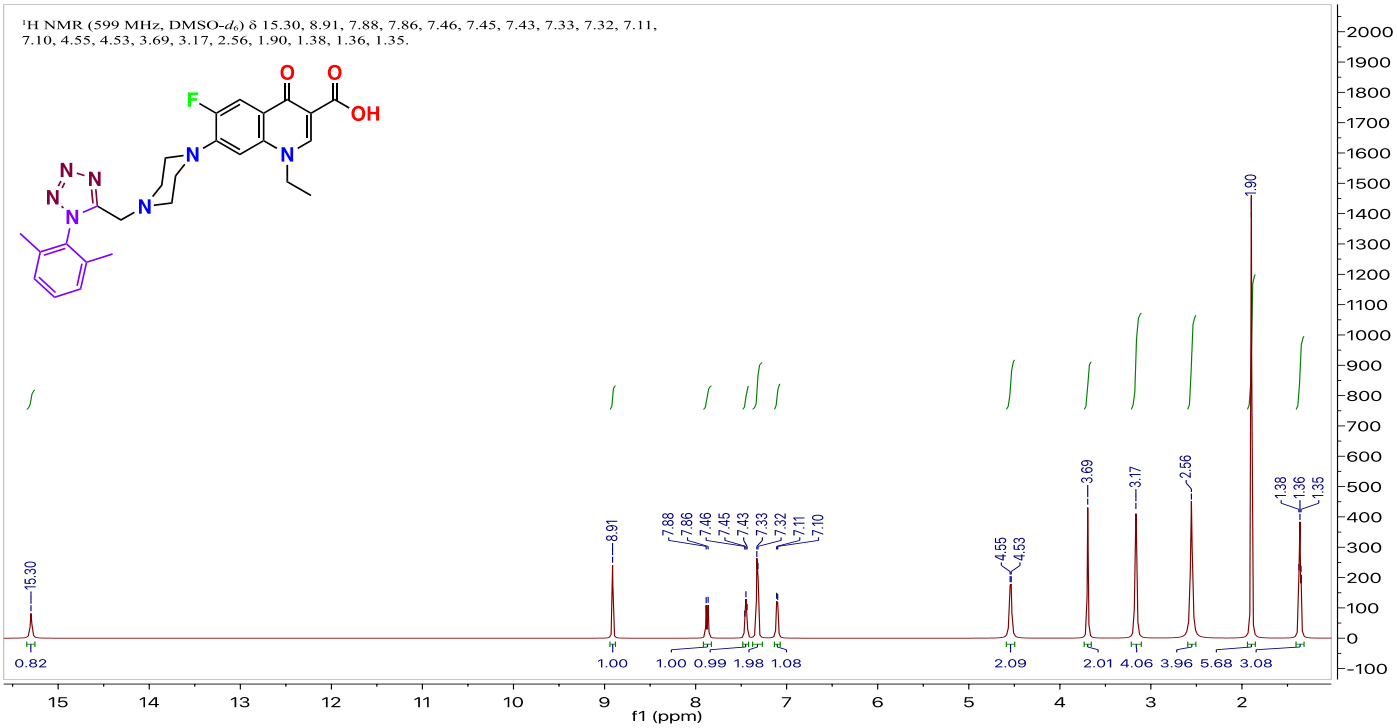

Figure S23. 7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **8**.

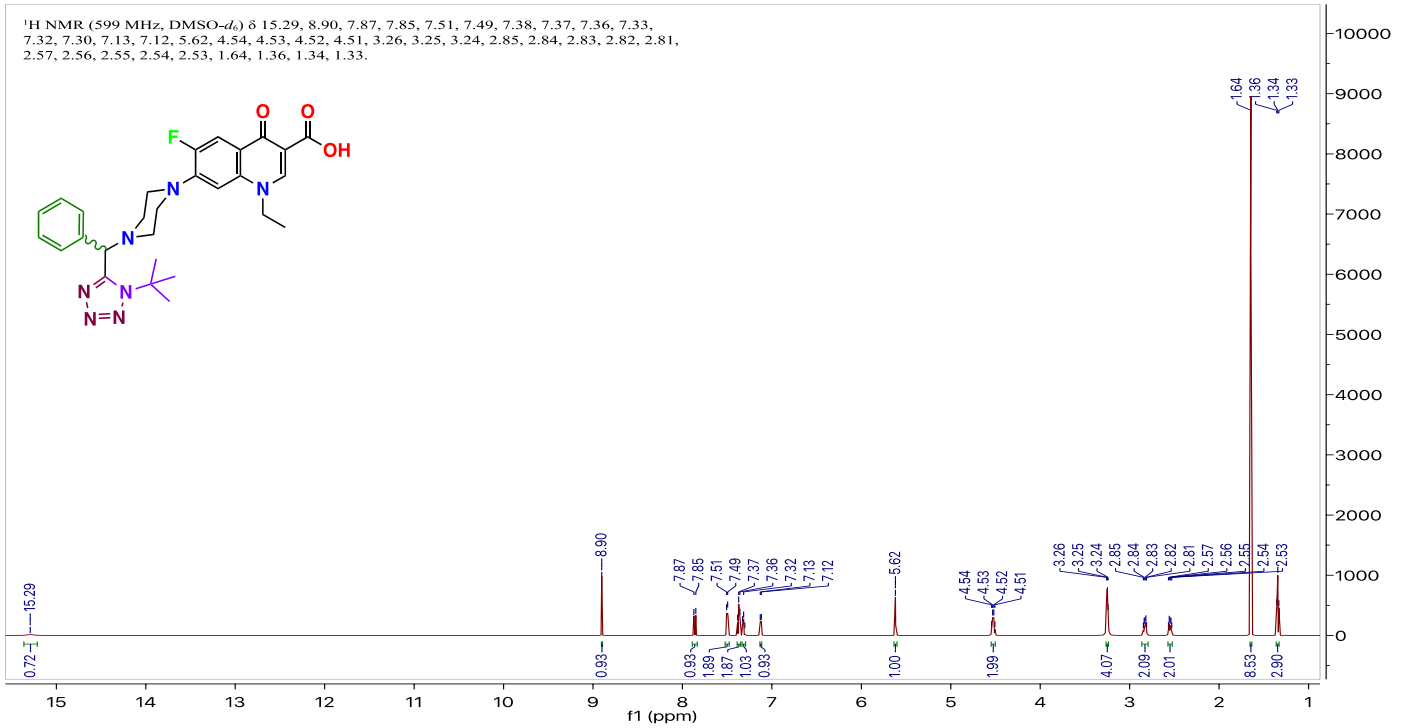

Figure S24. (*R*/*S*)-7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **9**, **10**.

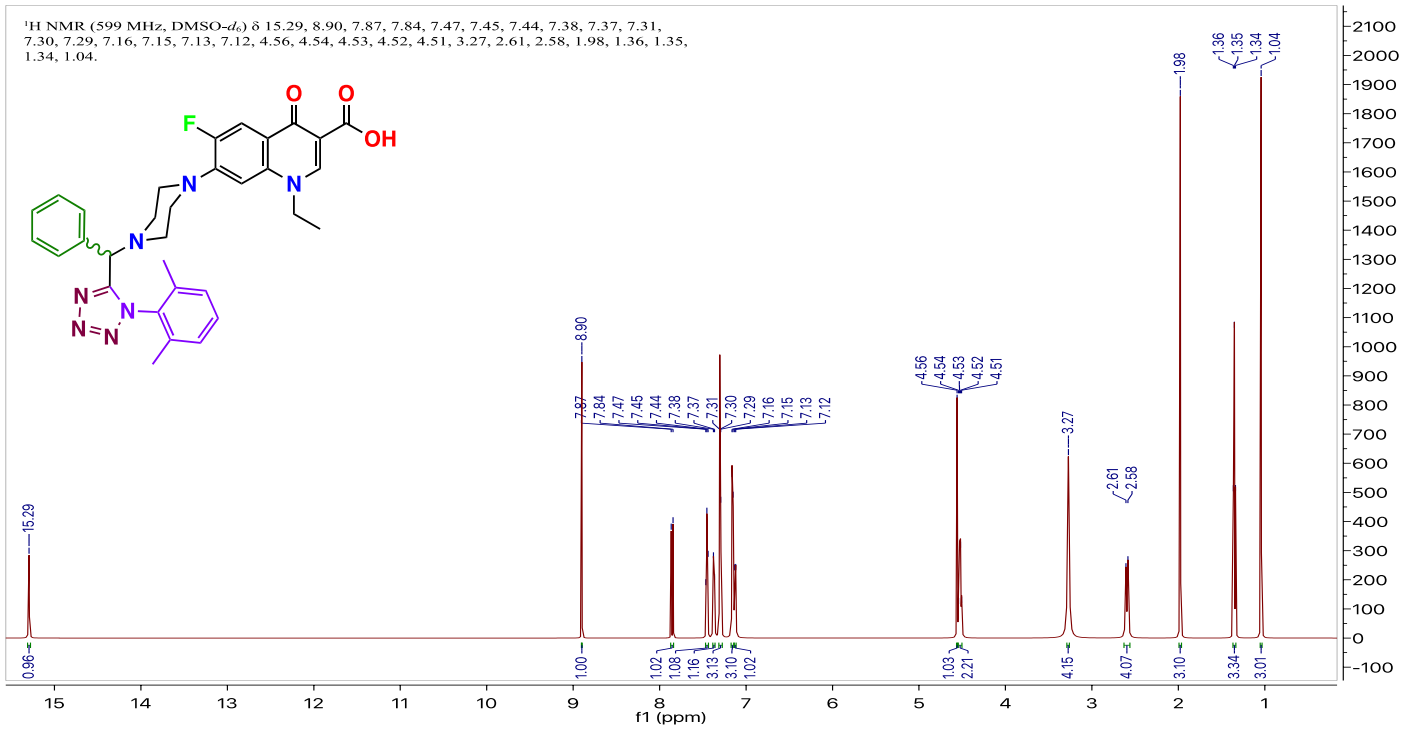

Figure S25. (*R*/*S*)-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **11**, **12**.

^{13}C Resonance Magnetic Nuclear Spectroscopy Spectrum

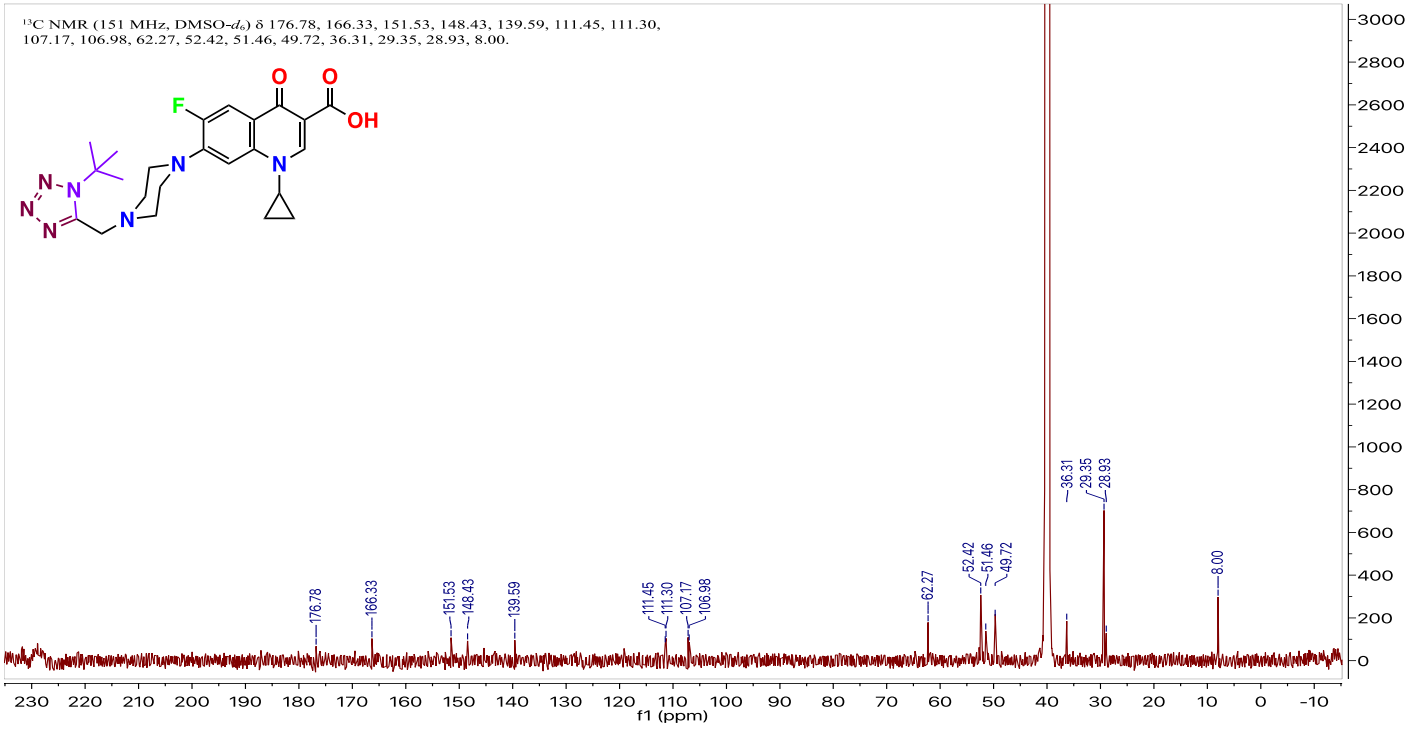

Figure S26. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **1**.

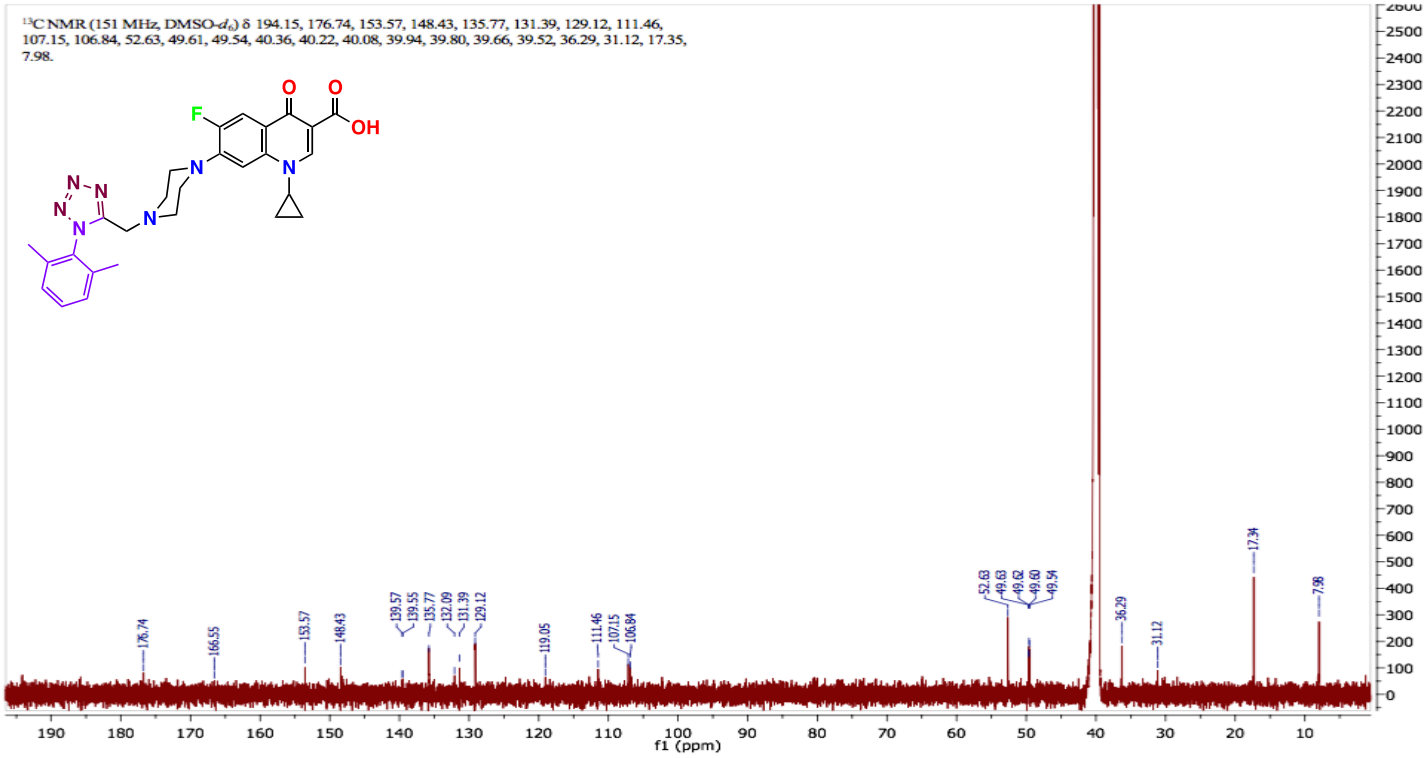

Figure S27. 1-cyclopropyl-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **2**.

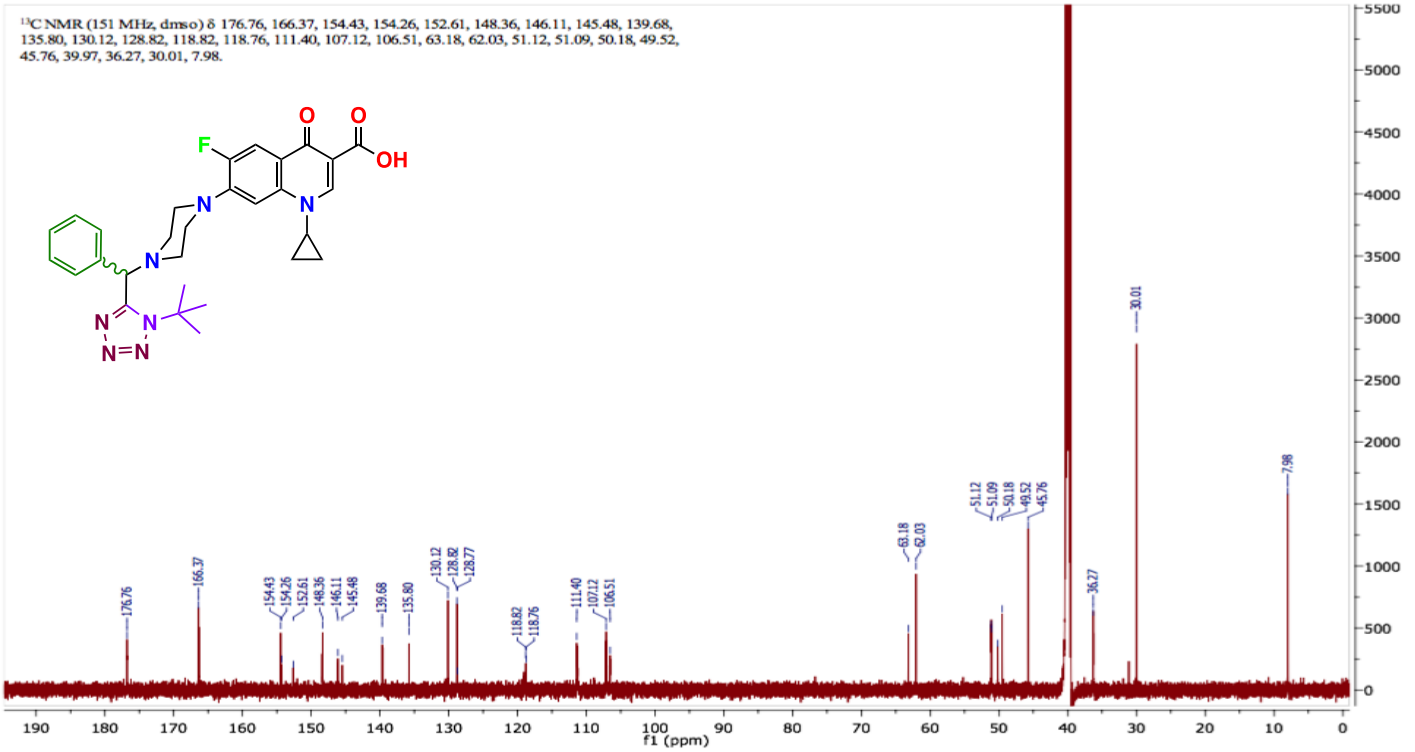

Figure S28. (*R*/*S*)-7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **3**, **4**.

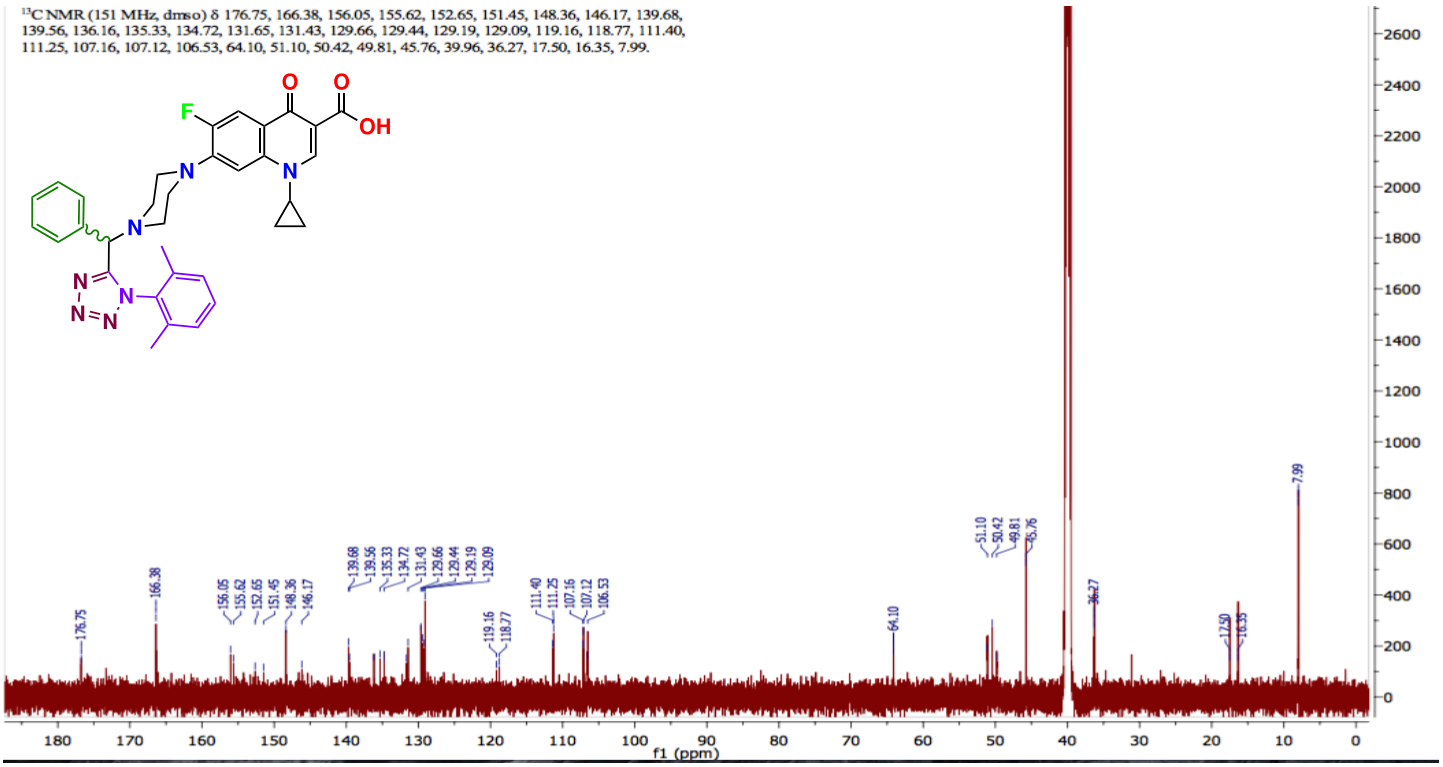

Figure S29. (*R*/*S*)-1-cyclopropyl-7-(4-((1-(2, 6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **5**, **6**.

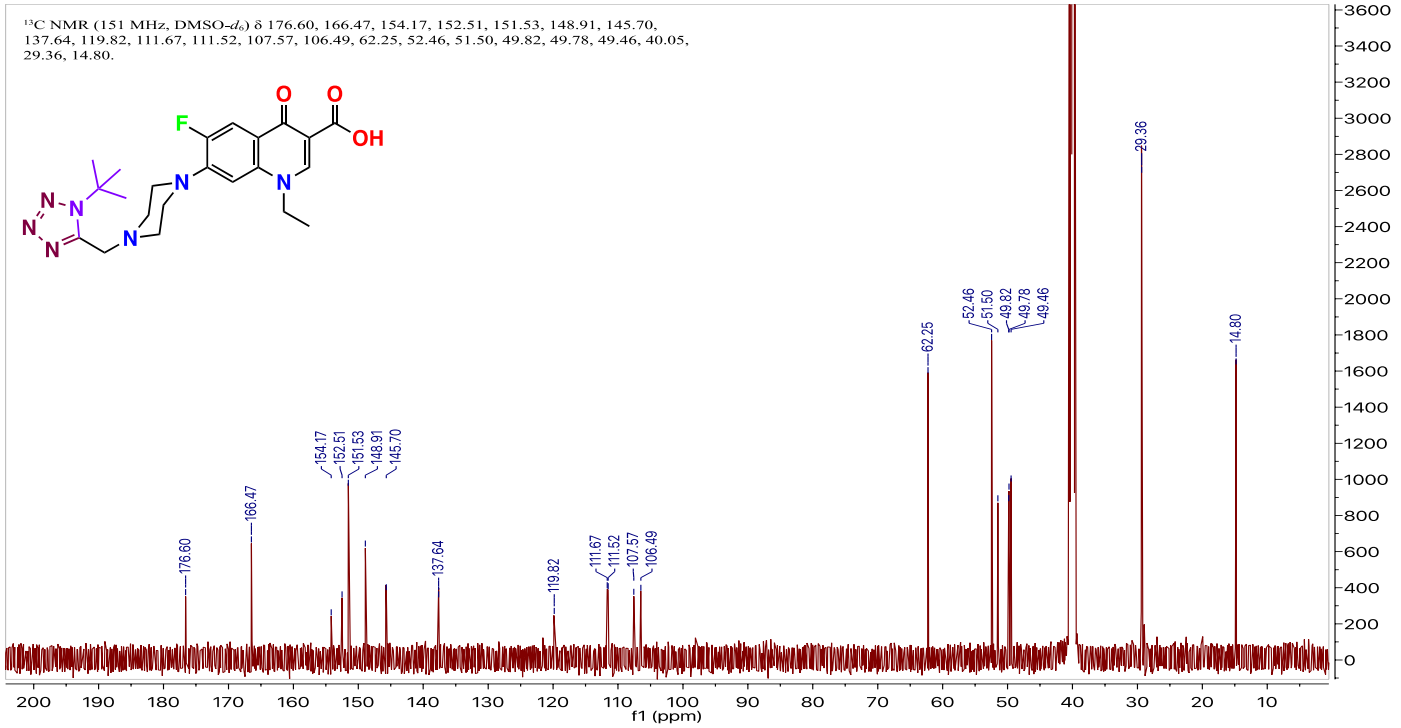

Figure S30. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **7**.

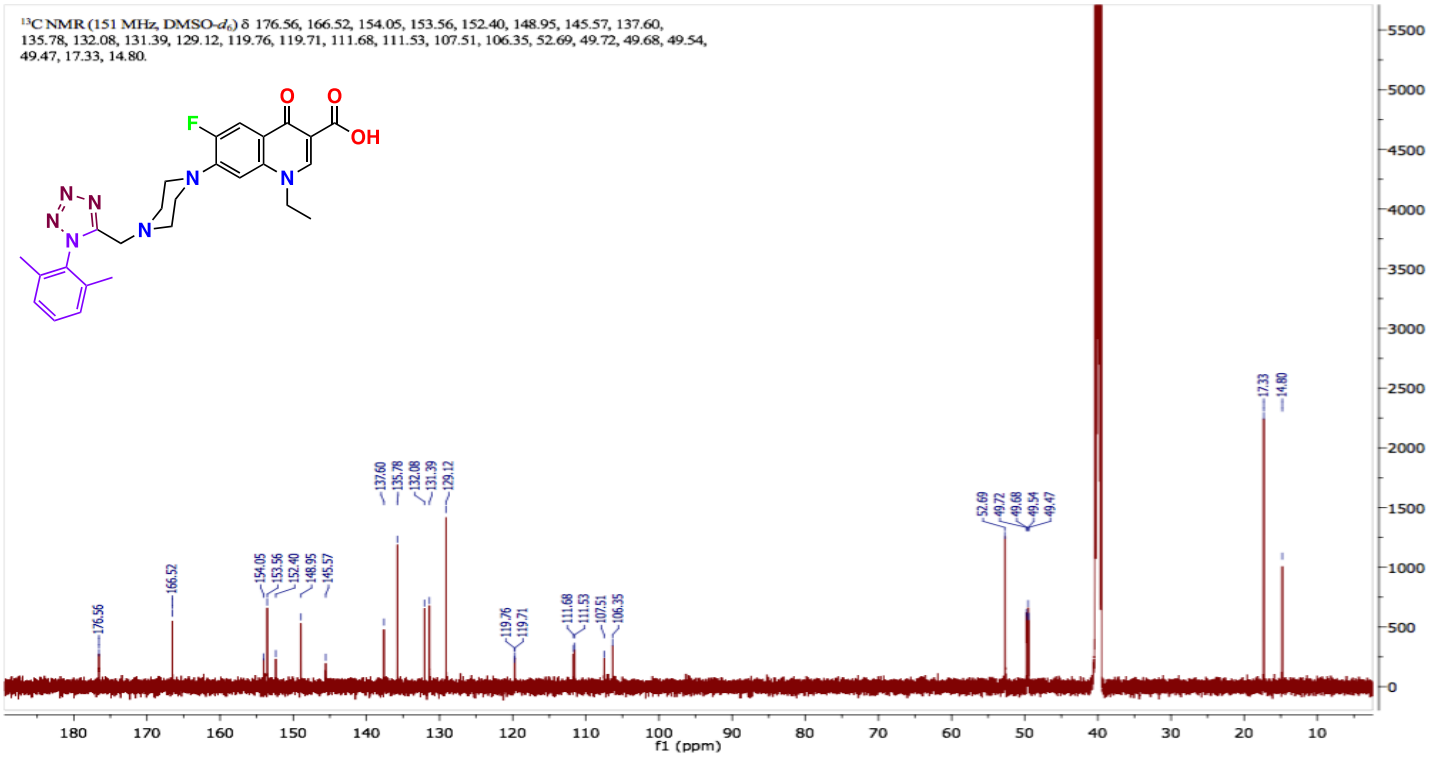

Figure S31. 7-(4-((1-(2, 6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **8**.

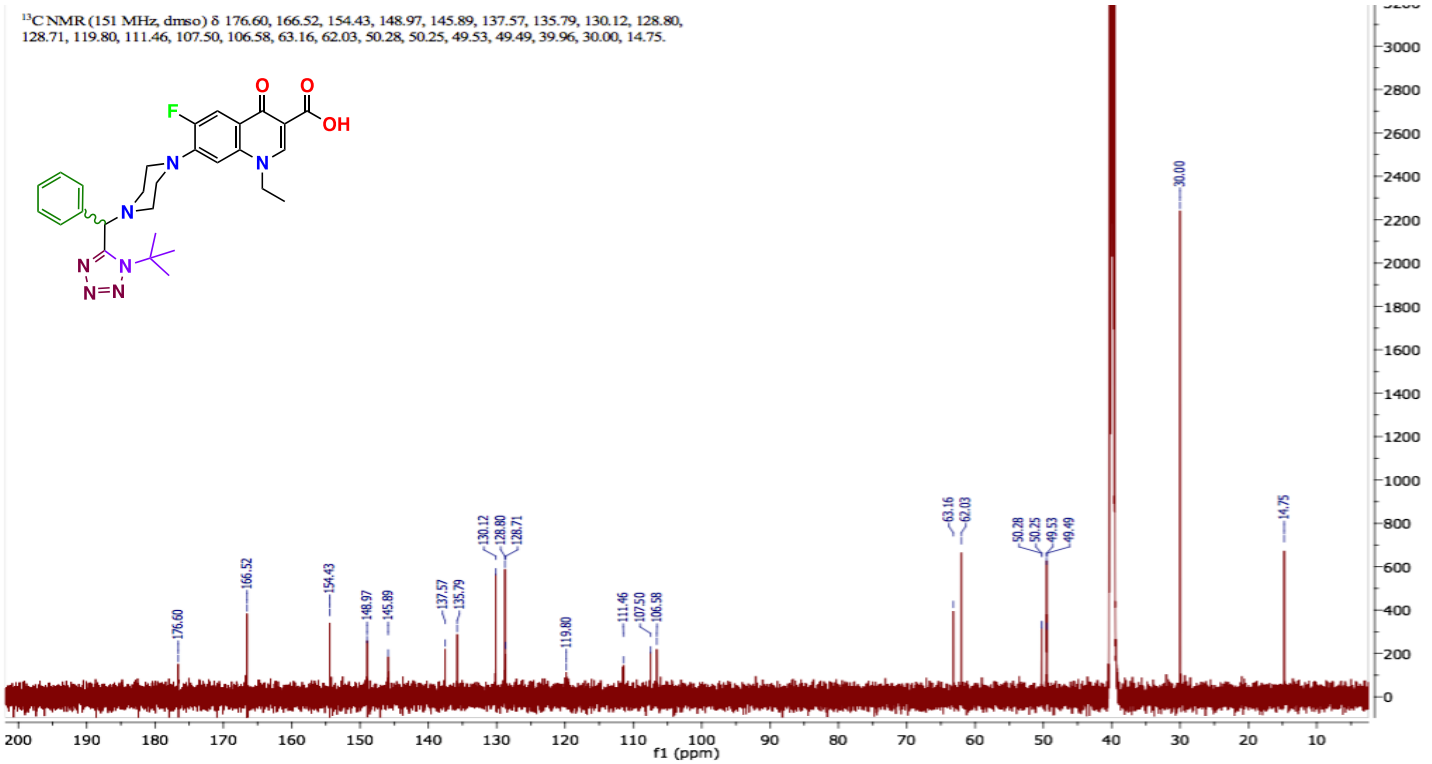

Figure S32. (*R*/*S*)-7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **9**, **10**.

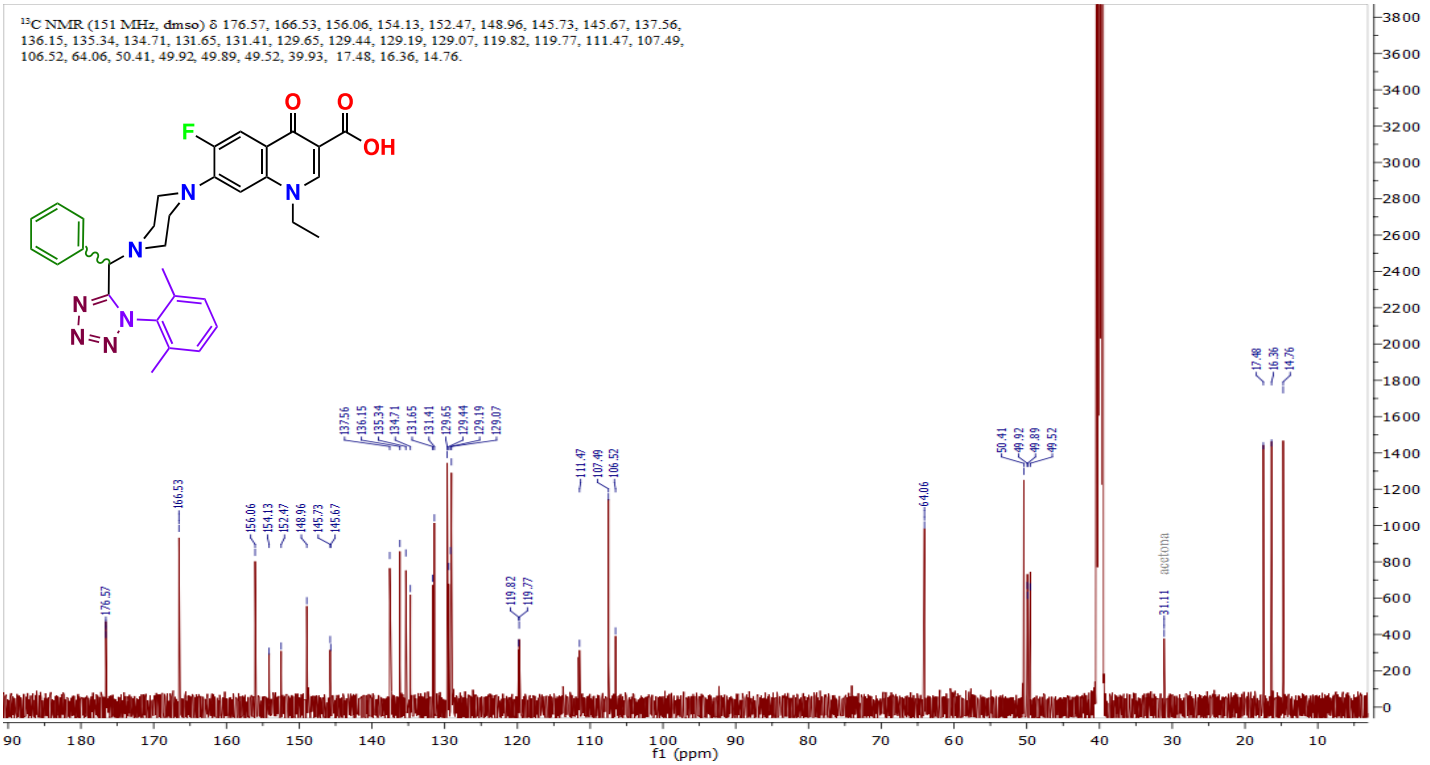

Figure S33. (*R*/*S*)-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **11**, **12**.

^{19}F Resonance Magnetic Nuclear Spectroscopy Spectrum

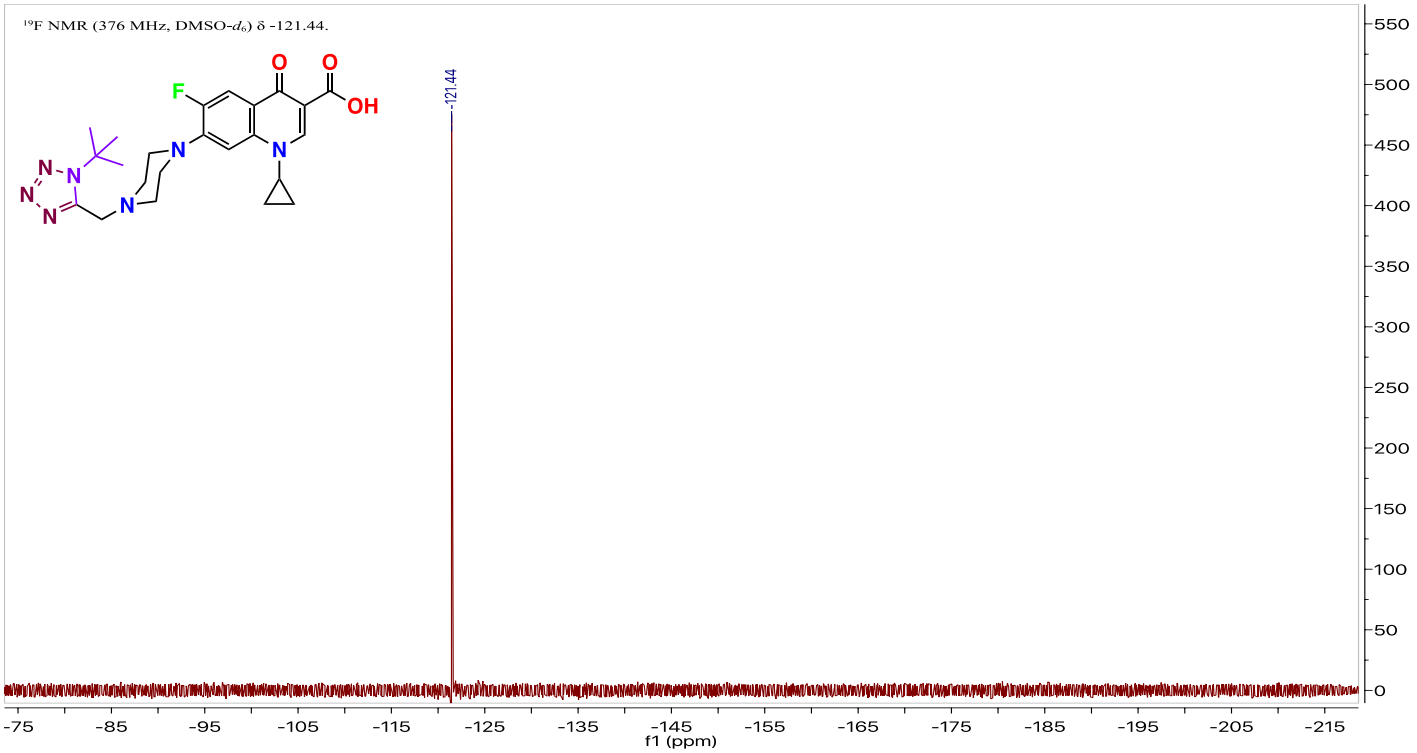

Figure S34. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **1**.

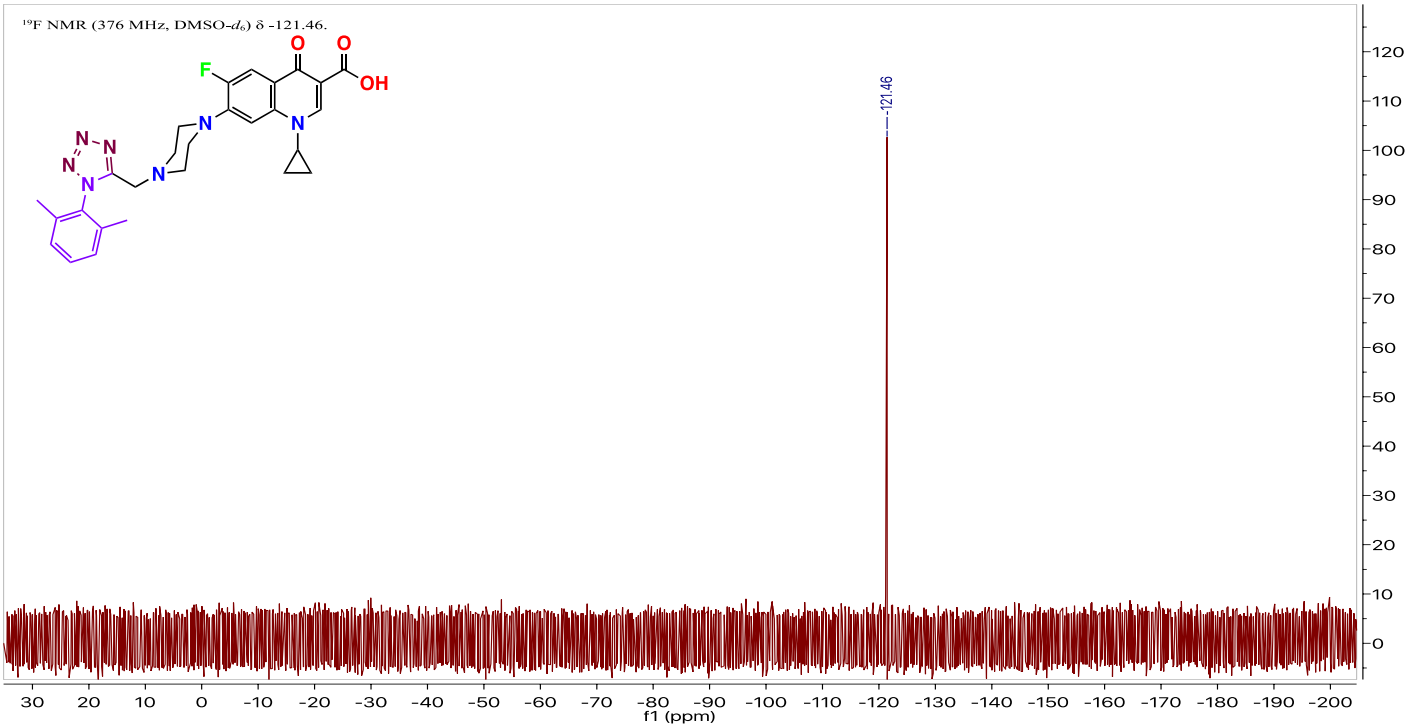

Figure S35. 1-cyclopropyl-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **2**.

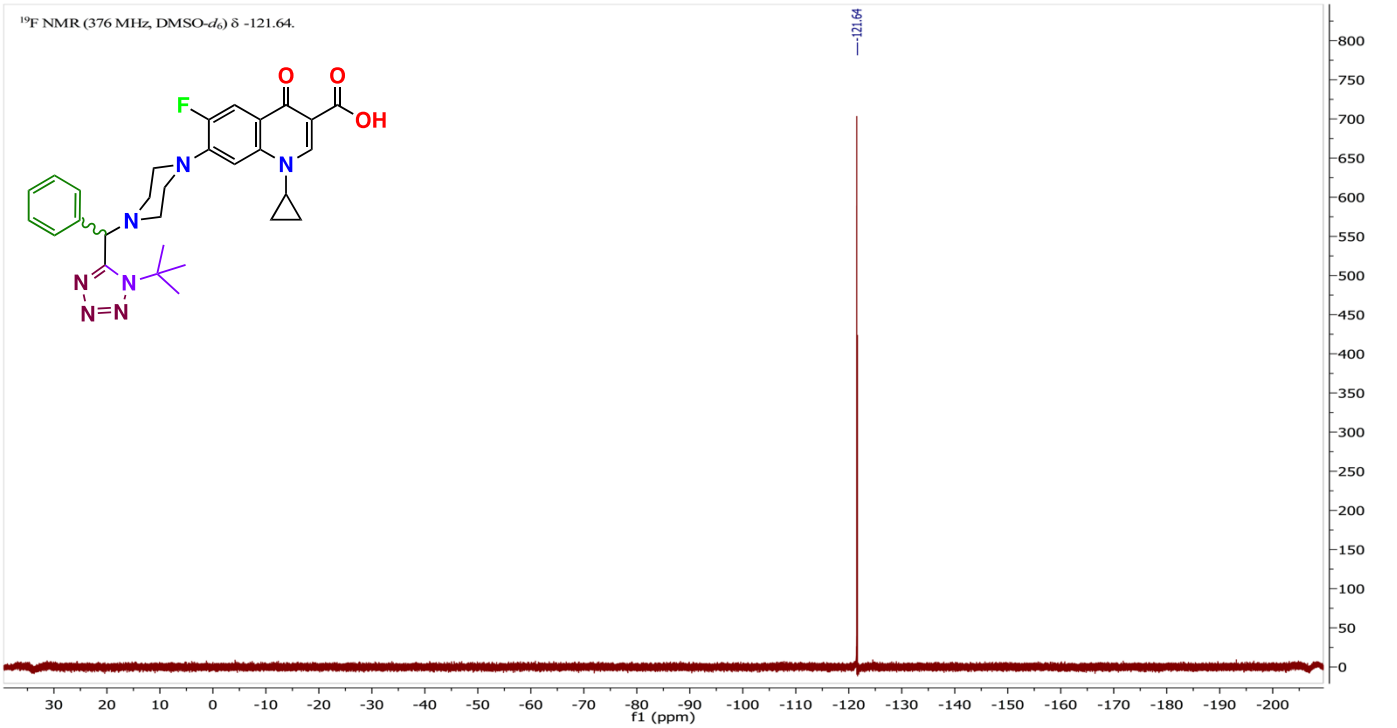

Figure S36. (*R*/*S*)-7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **3, 4**.

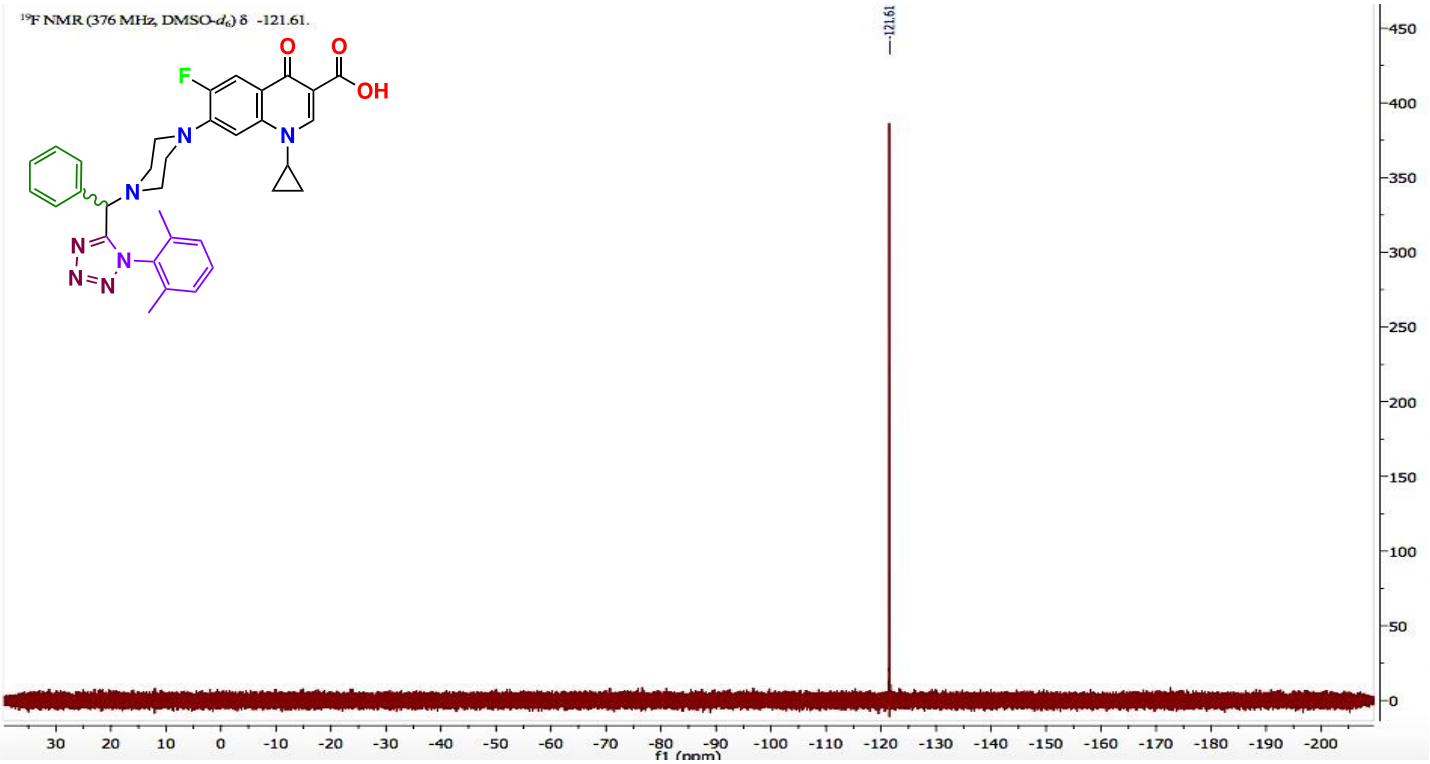

Figure S37. (*R*/*S*)-1-cyclopropyl-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **5**, **6**.

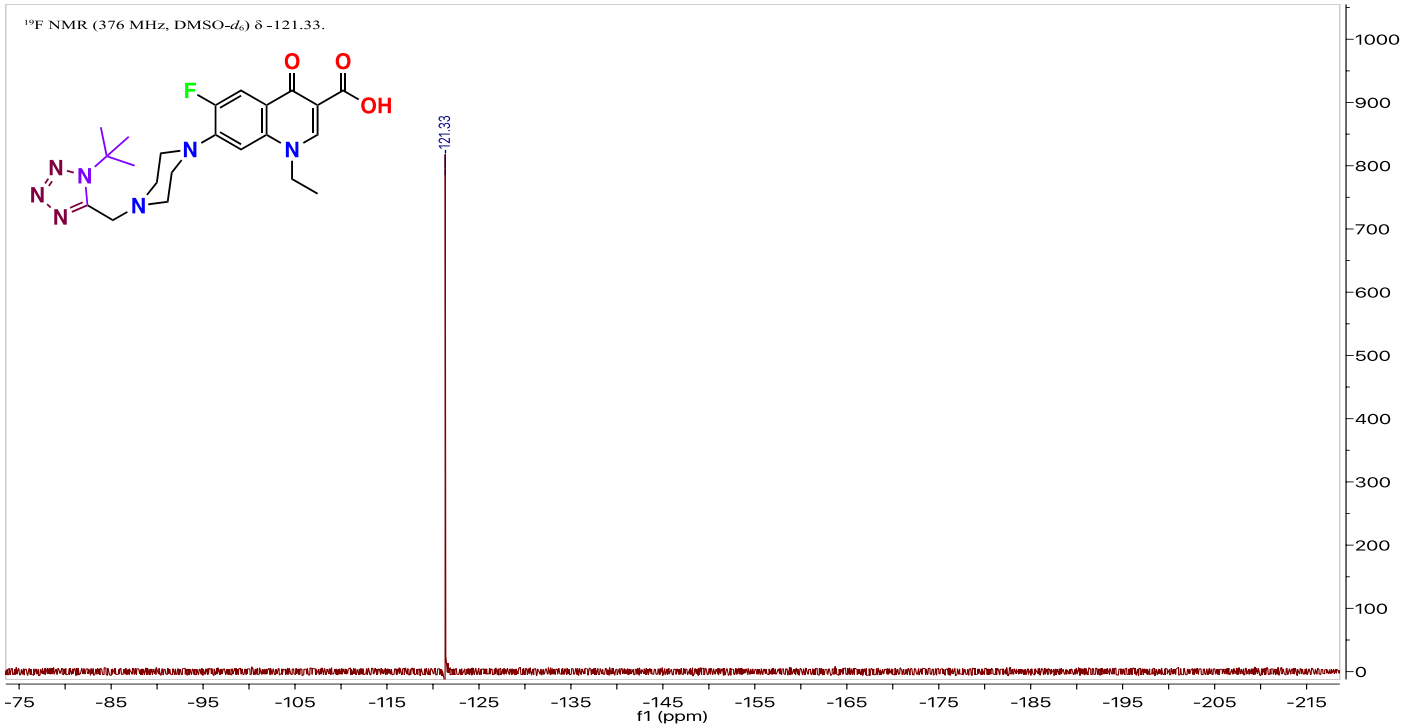

Figure S38. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **7**.

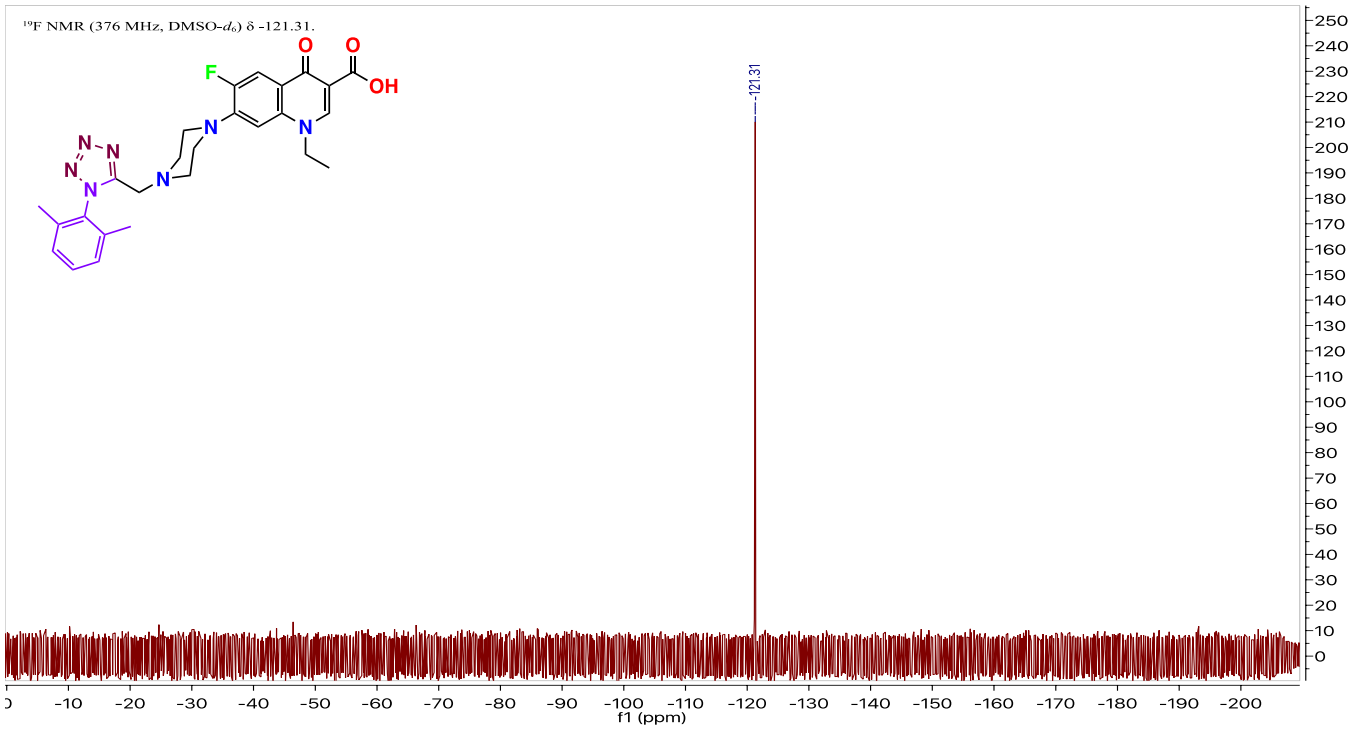

Figure S39. 7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **8**.

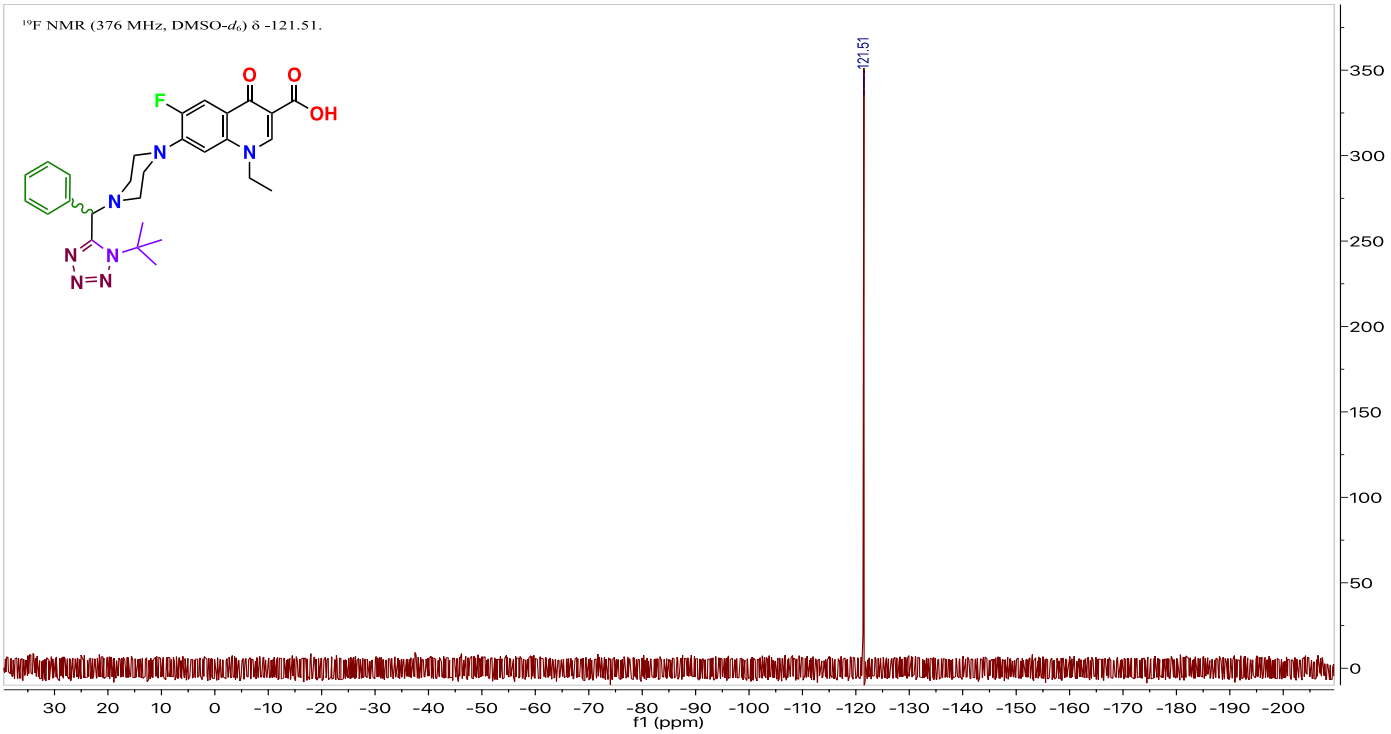

Figure S40. (*R*/*S*)-7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **9**, **10**.

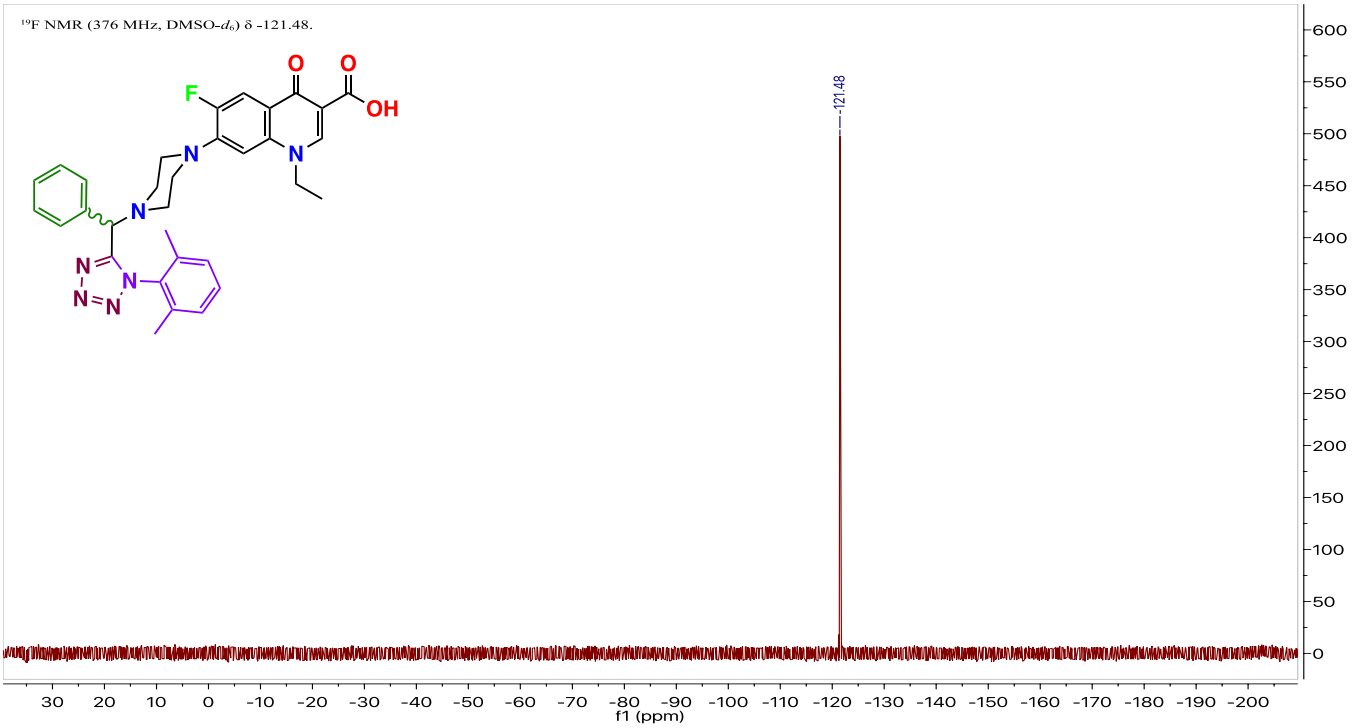

Figure S41. (*R*/*S*)-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **11**, **12**.

Homonuclear Correlation Spectroscopy ^{1}H RMN (COSY) Spectrum

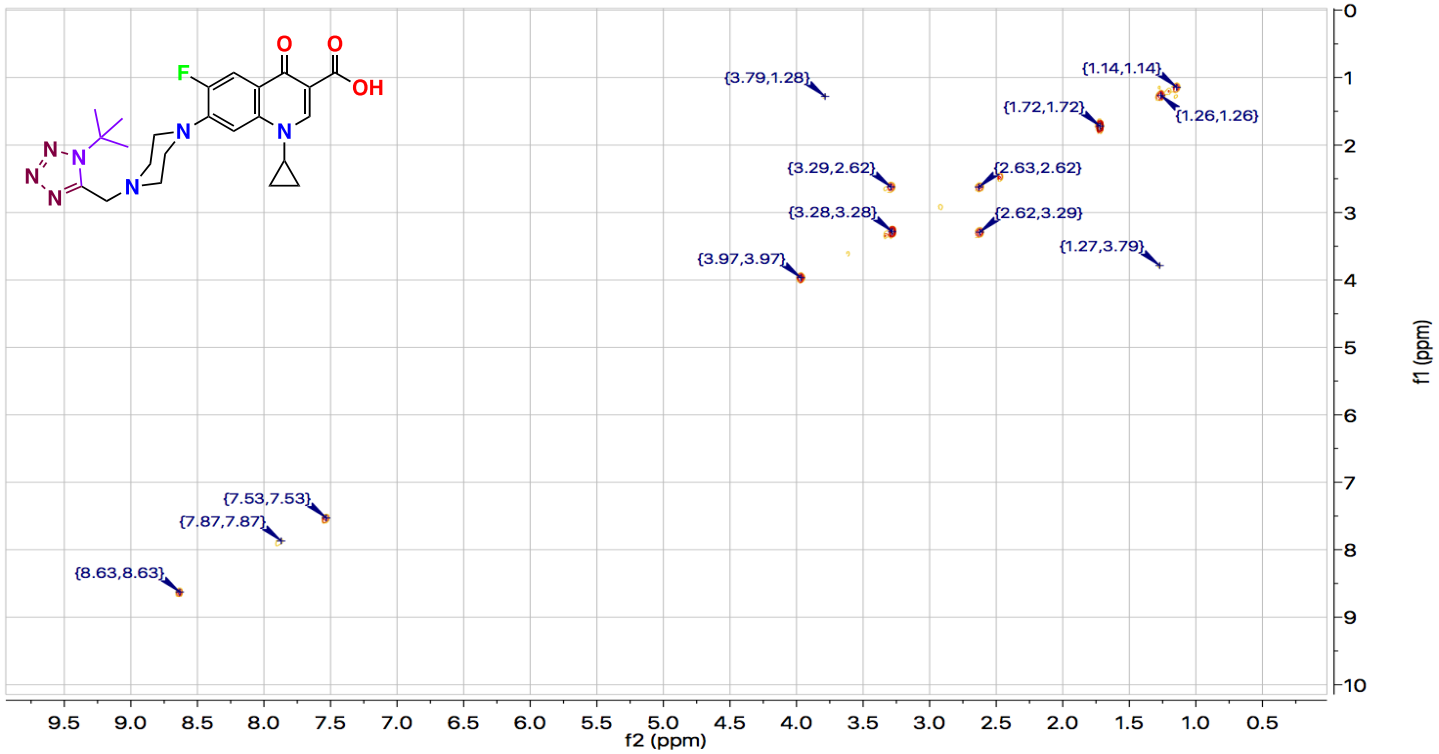

Figure S42. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **1**.

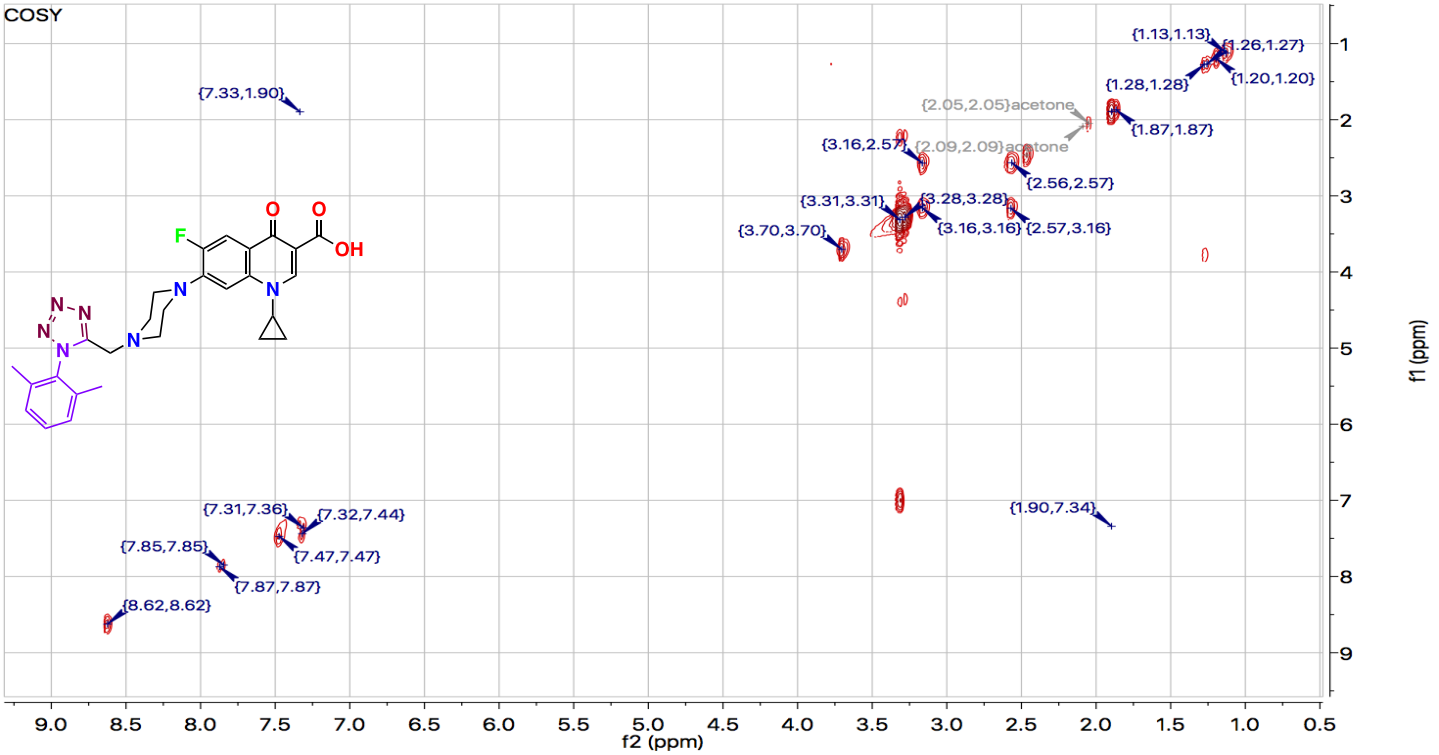

Figure S43. 1-cyclopropyl-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **2**.

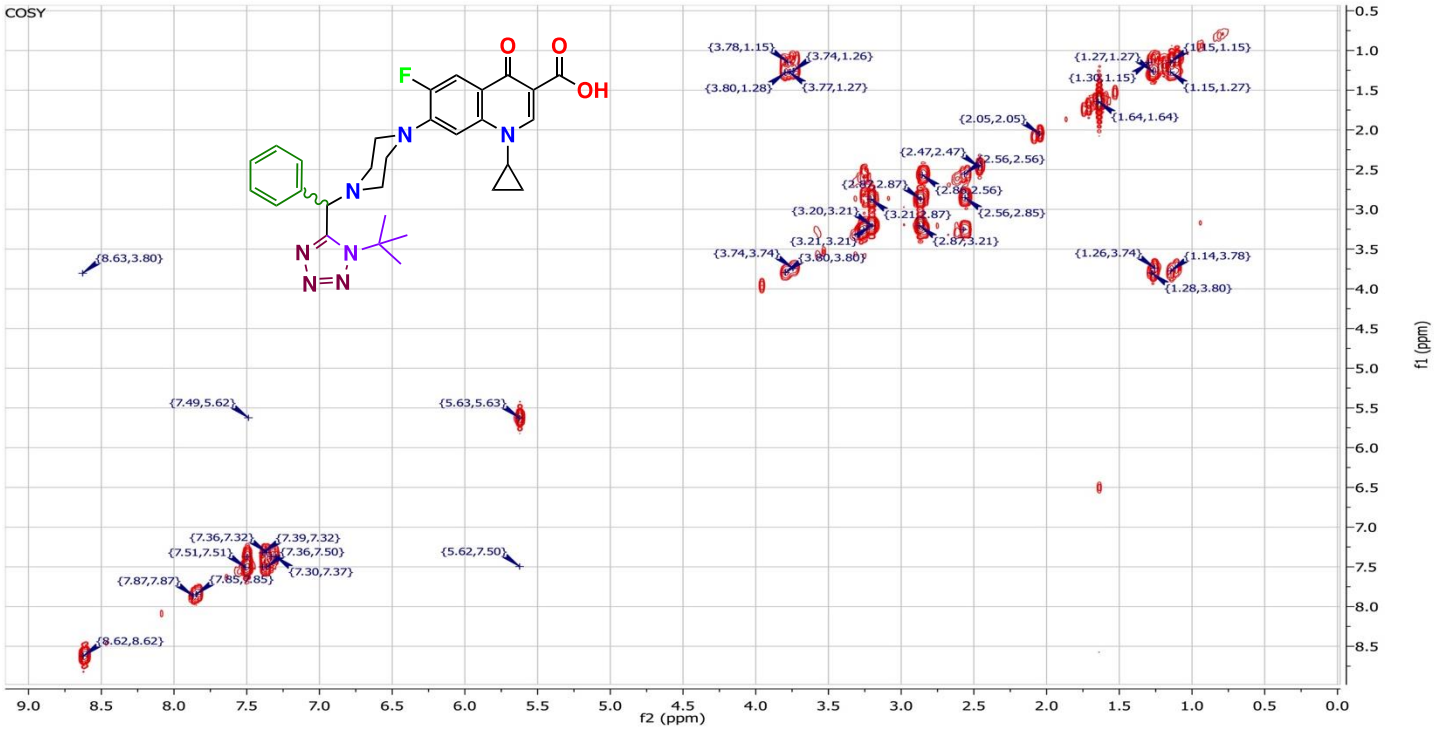

Figure S44. (*R*/*S*)-7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **3**, **4**.

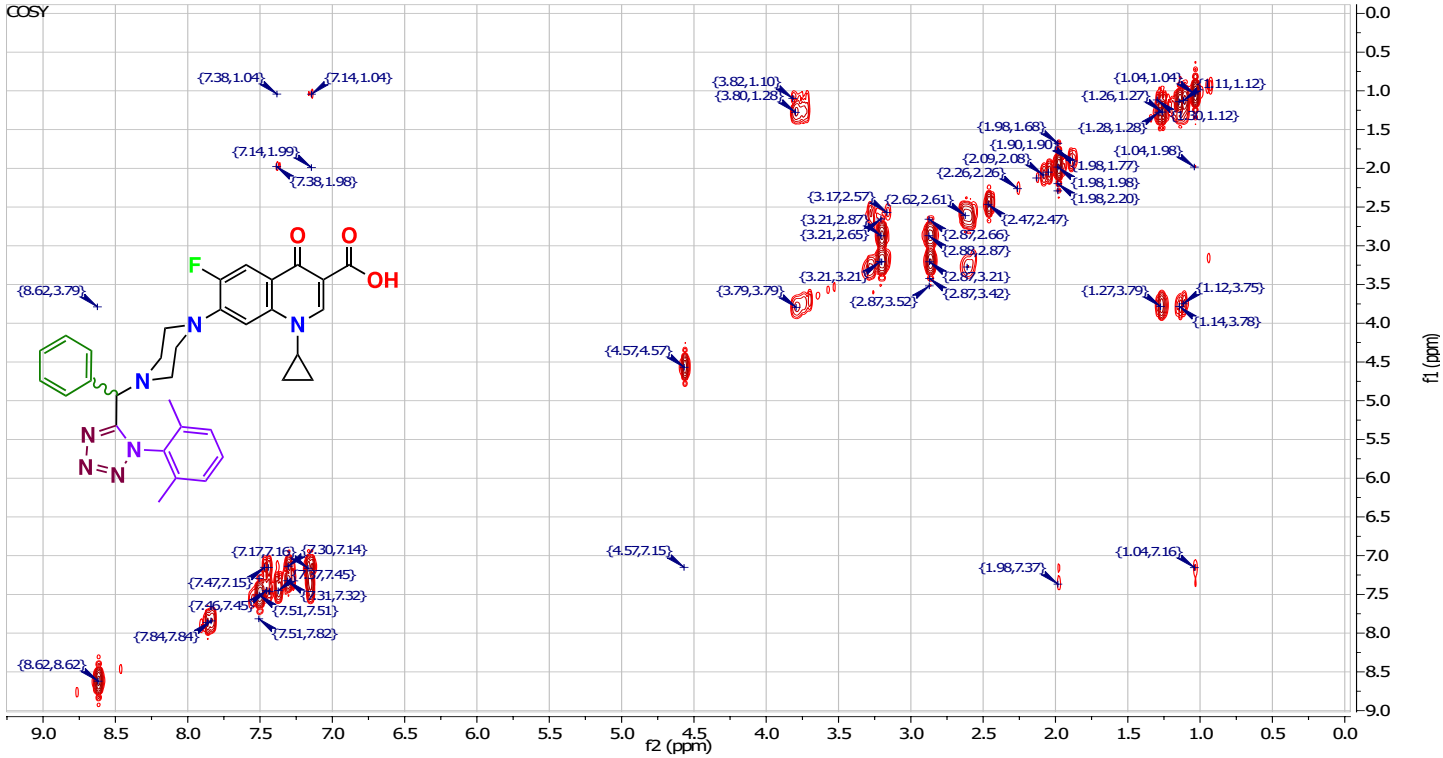

Figure S45. (*R*/*S*)-1-cyclopropyl-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **5**, **6**.

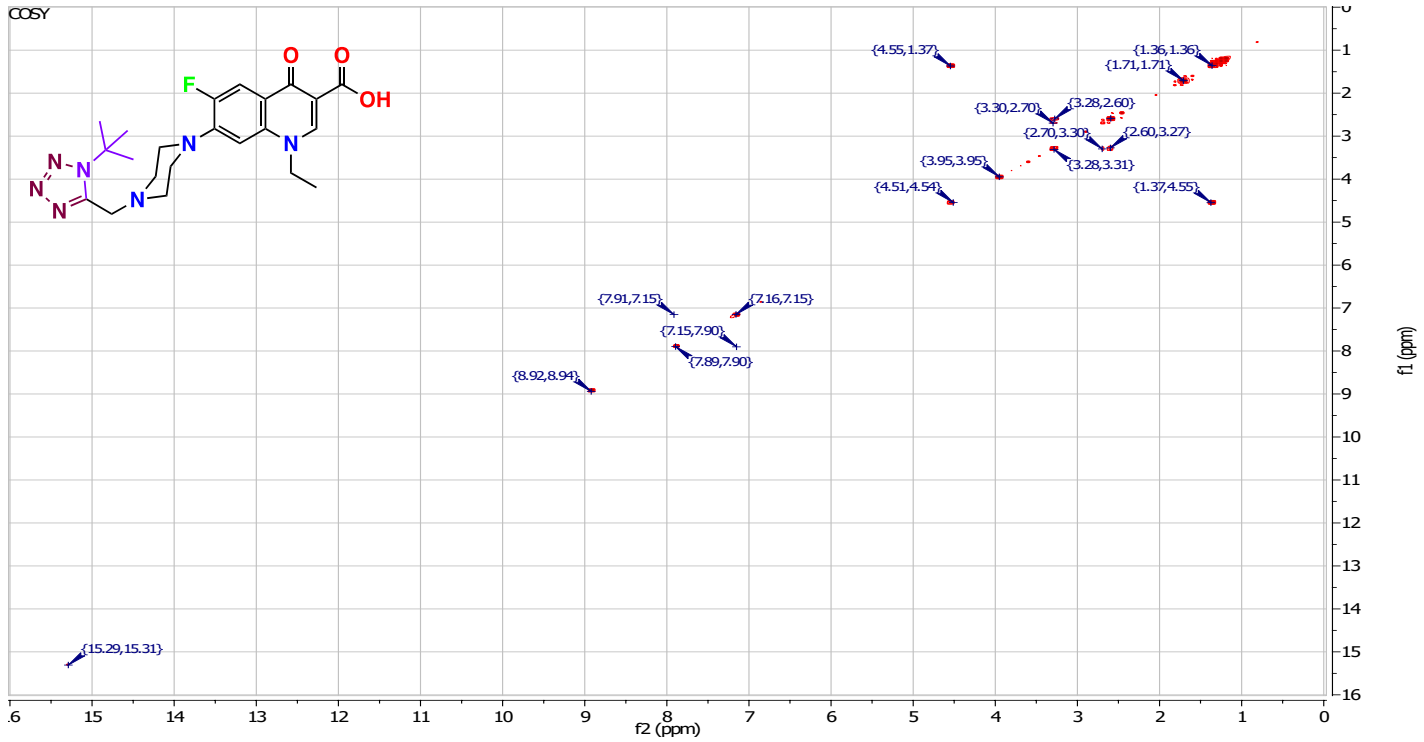

Figure S46. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **7**.

Figure S47. 7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **8**.

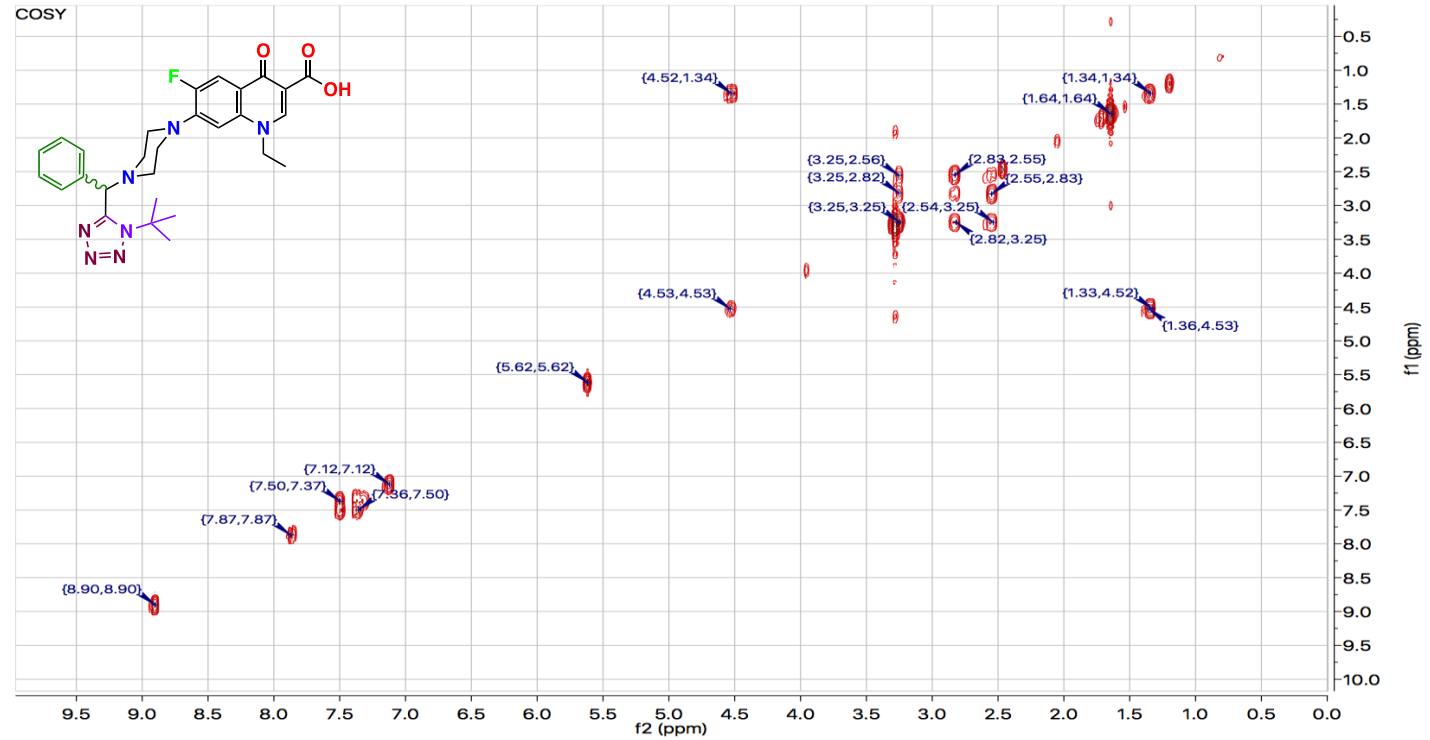

Figure S48. (*R*/*S*)-7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **9**, **10**.

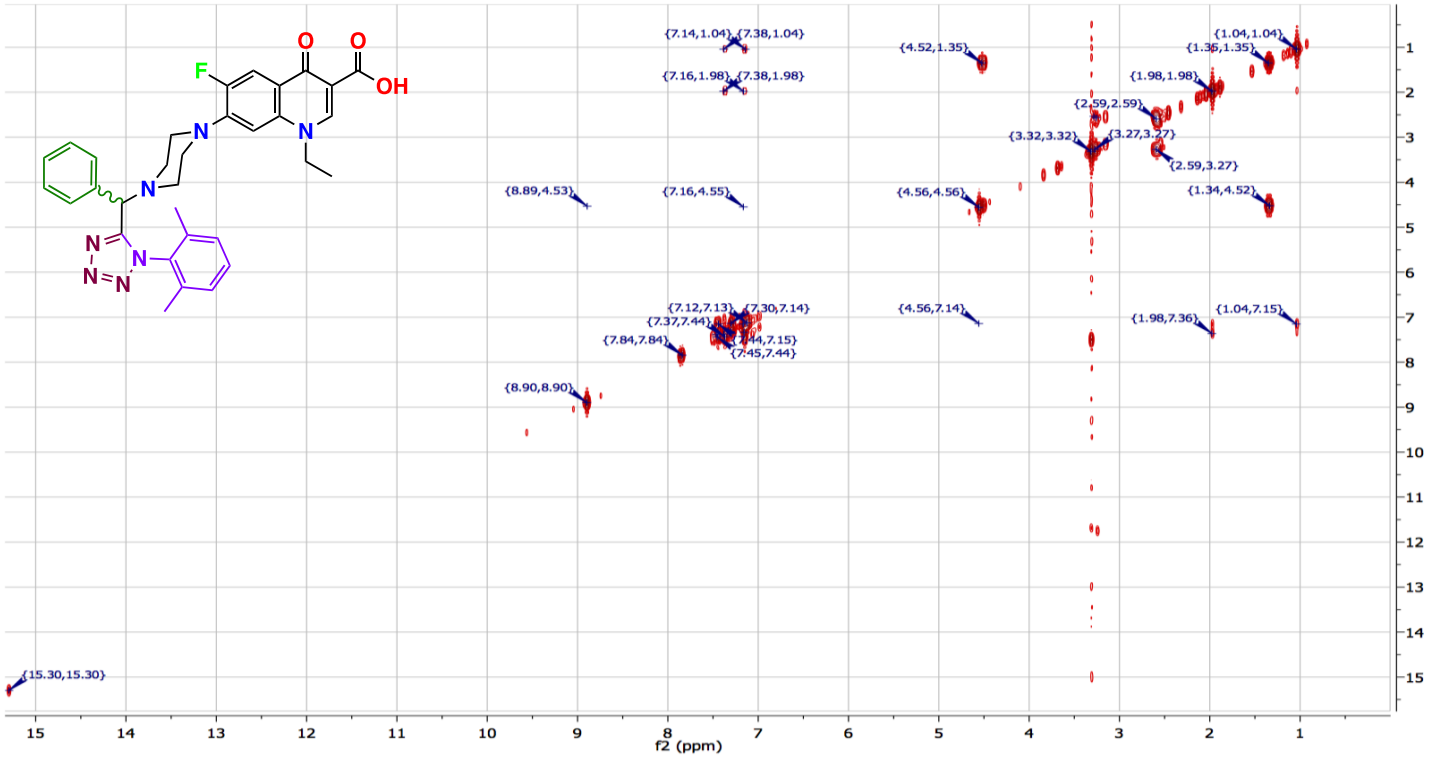

Figure S49. (*R*/*S*)-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **11**, **12**.

Heteronuclear Single-Quantum Correlation (HSQC) Spectroscopy Spectrum

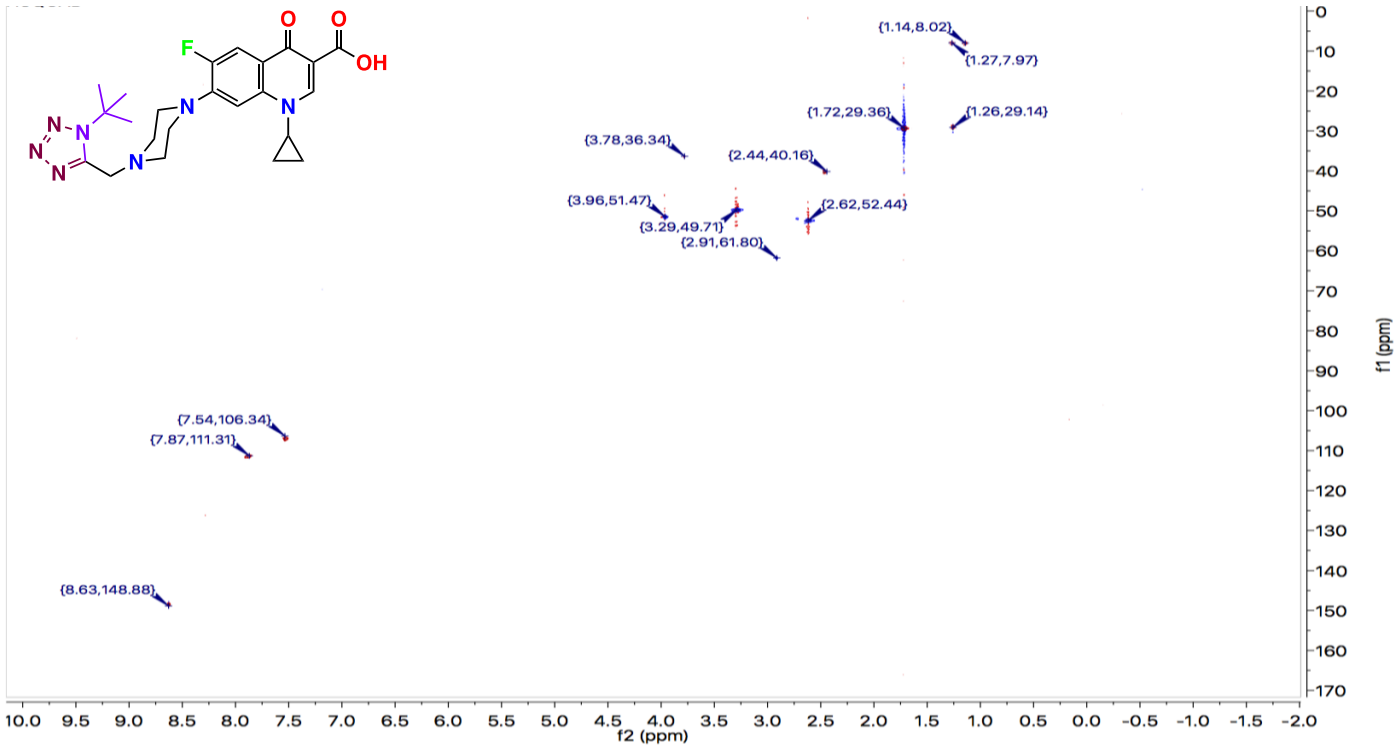

Figure S50. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **1**.

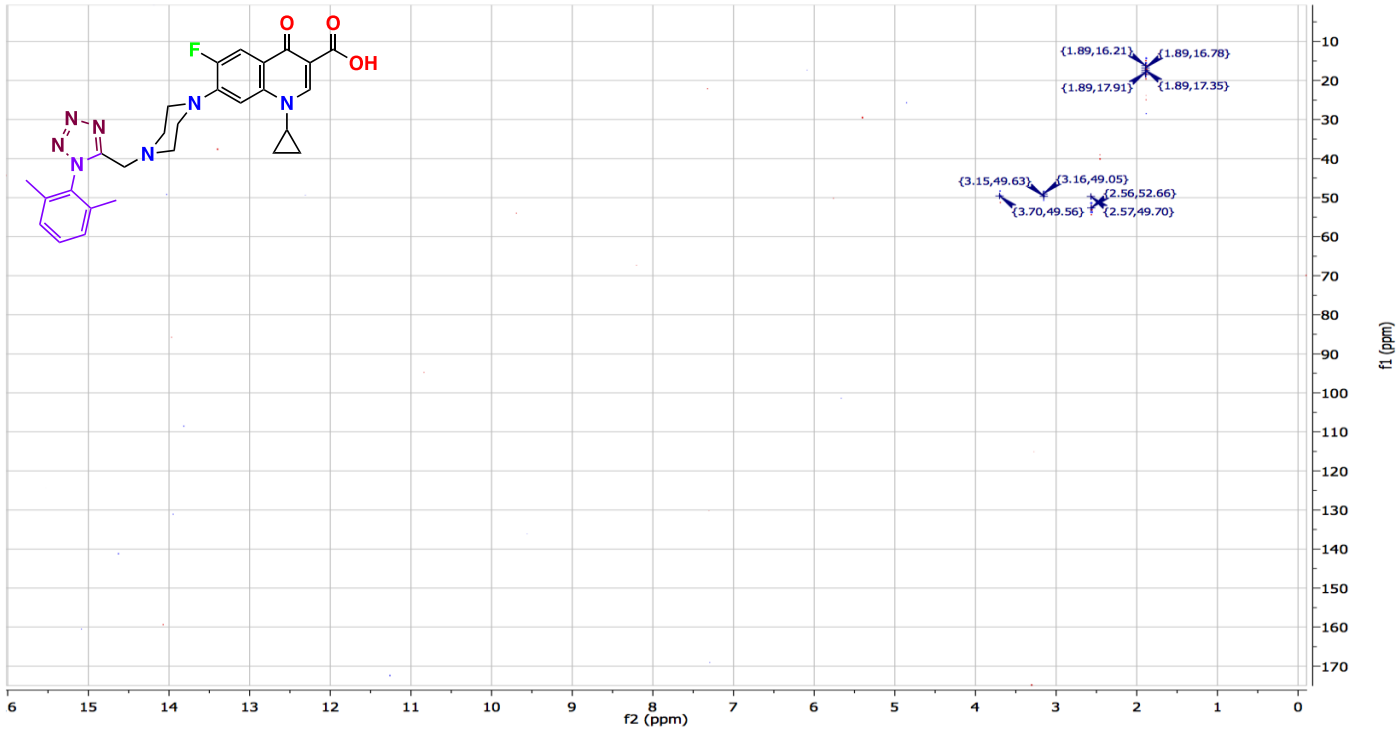

Figure S51. 1-cyclopropyl-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **2**.

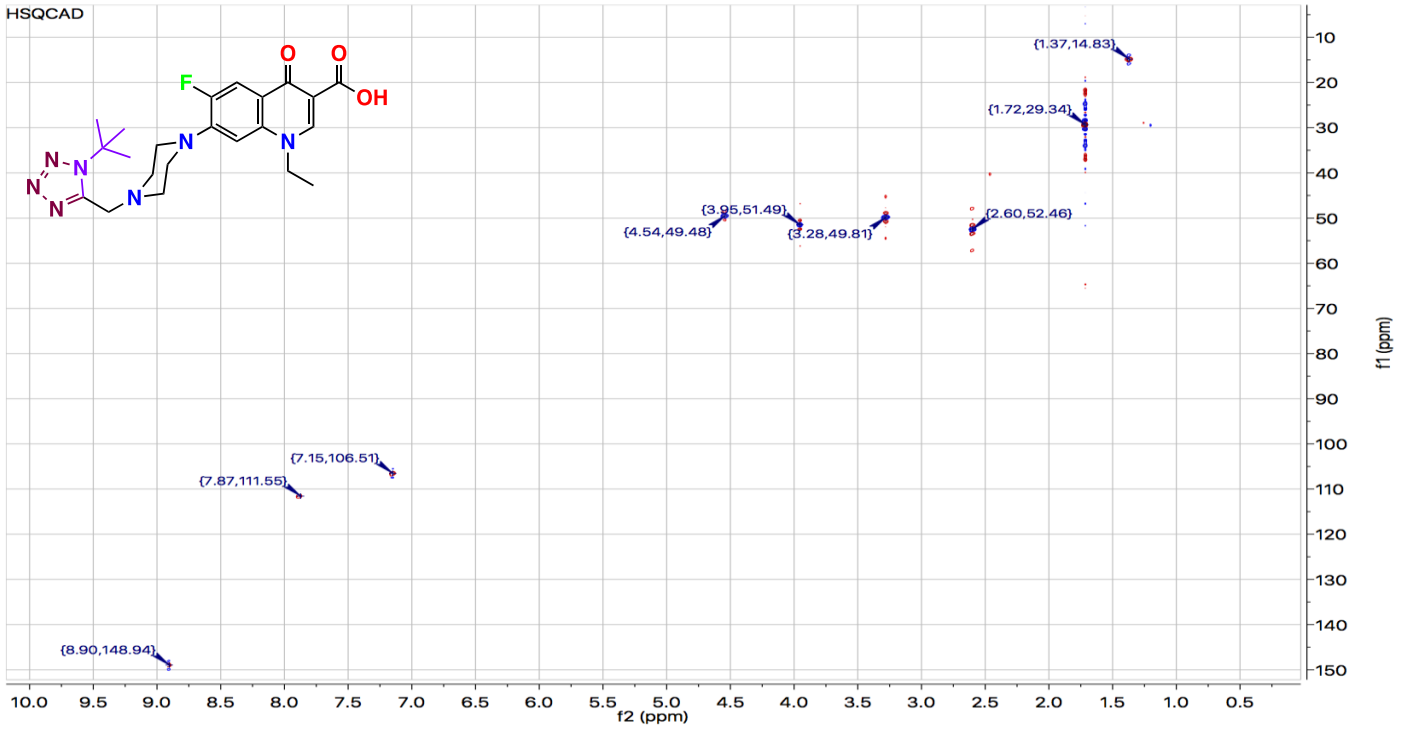

Figure S52. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **7**.

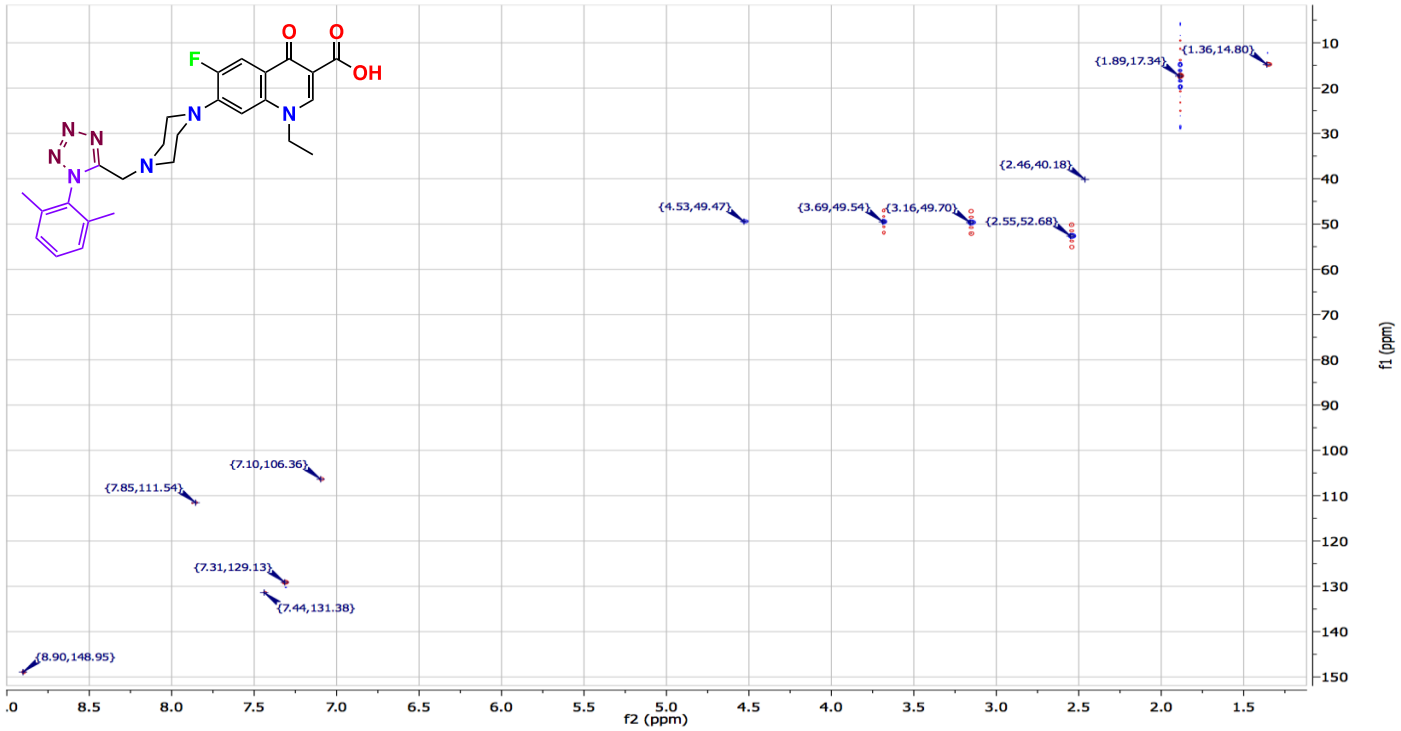

Figure S53. 7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **8**.

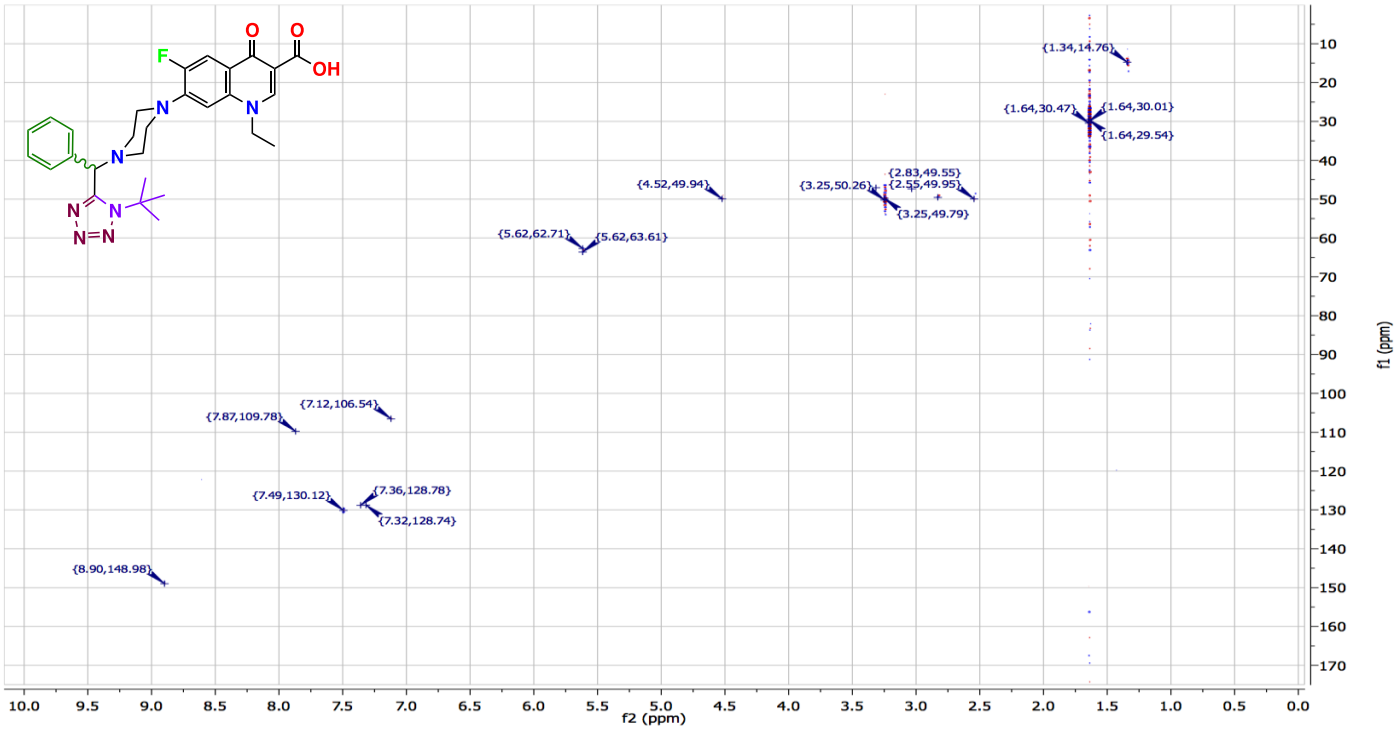

Figure S54. (*R*/*S*)-7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **9**, **10**.

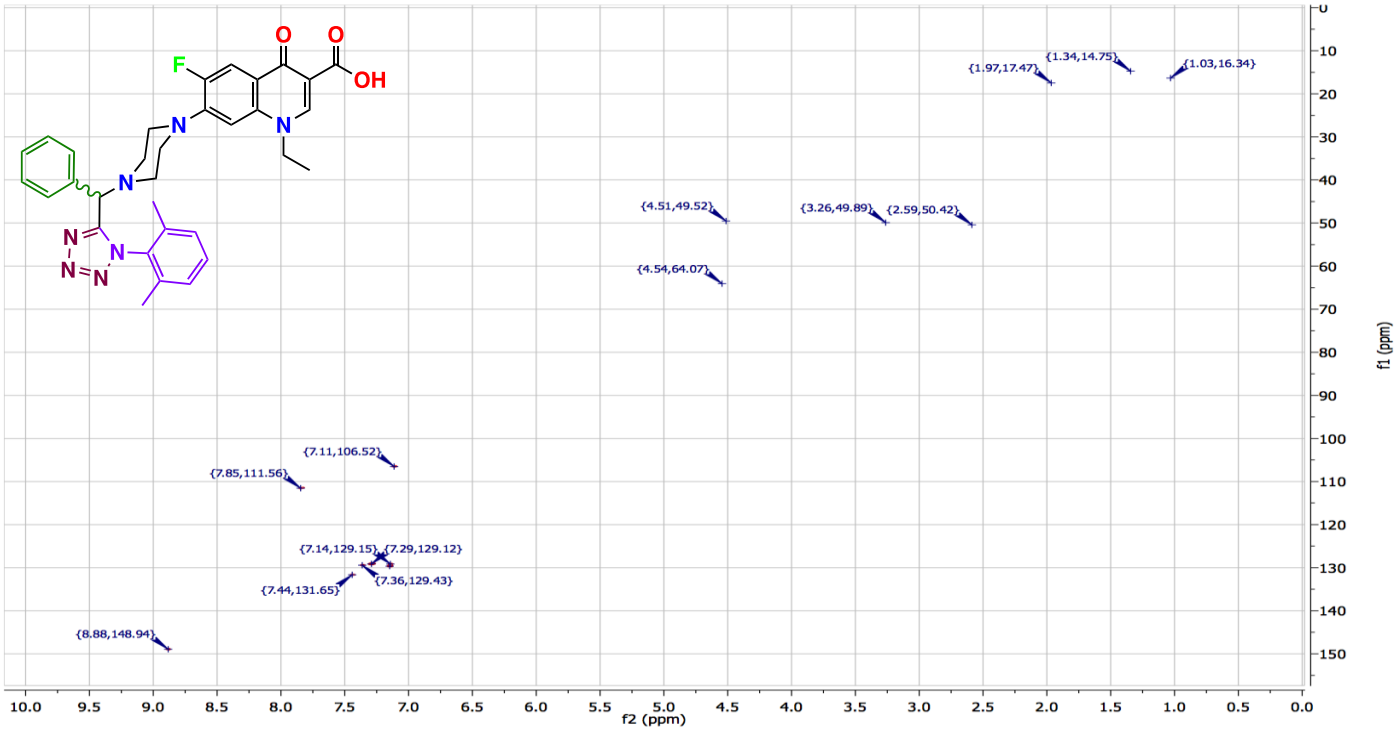

Figure S55. (*R*/*S*)-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **11**, **12**.

Heteronuclear Multiple-Bond Correlation (HMBC) Spectroscopy Spectrum

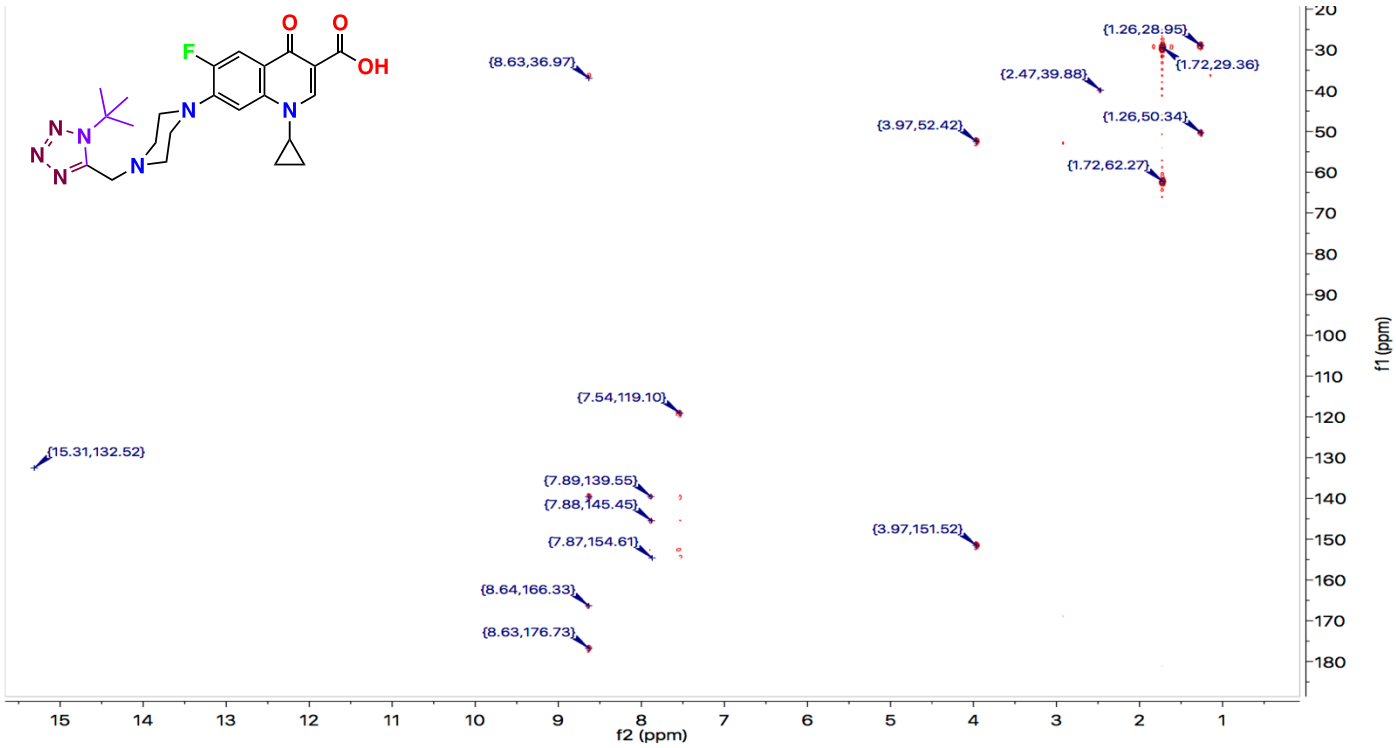

Figure S56. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **1**.

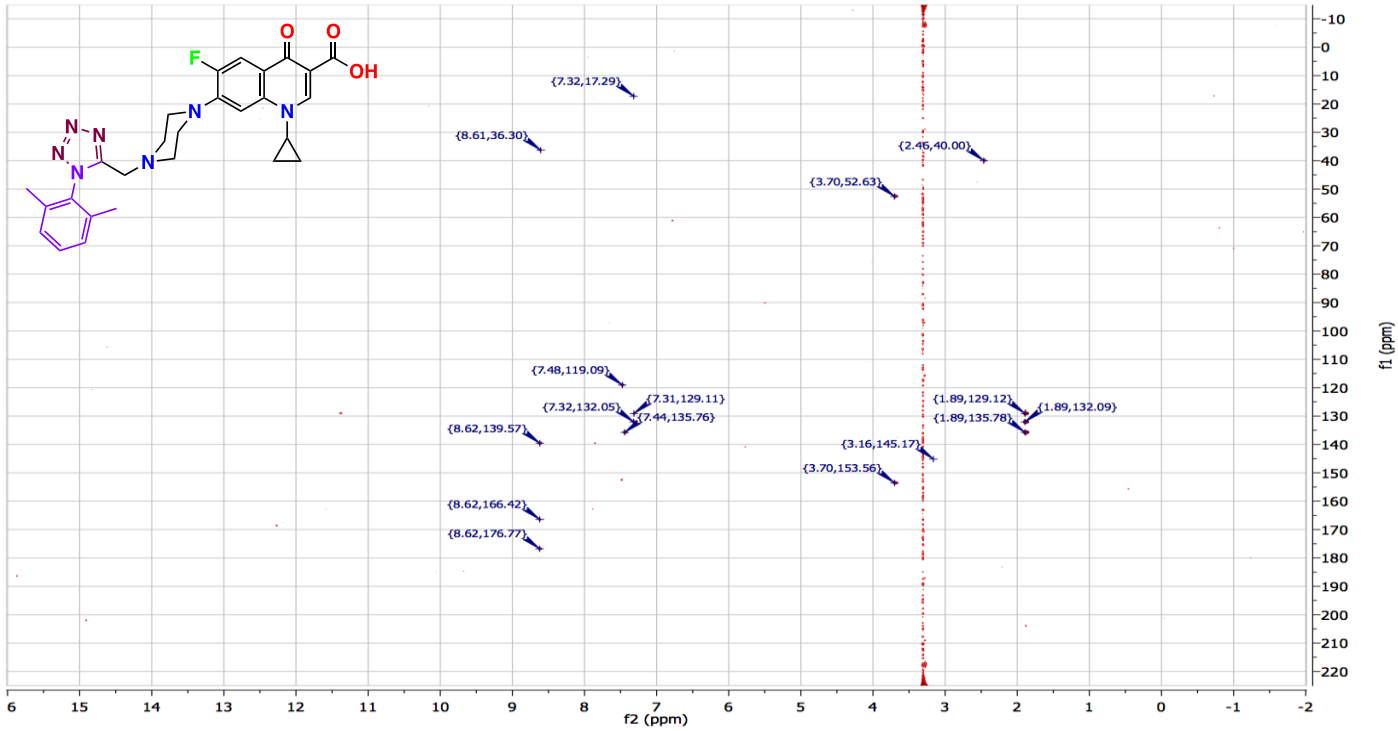

Figure S57. 1-cyclopropyl-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **2**.

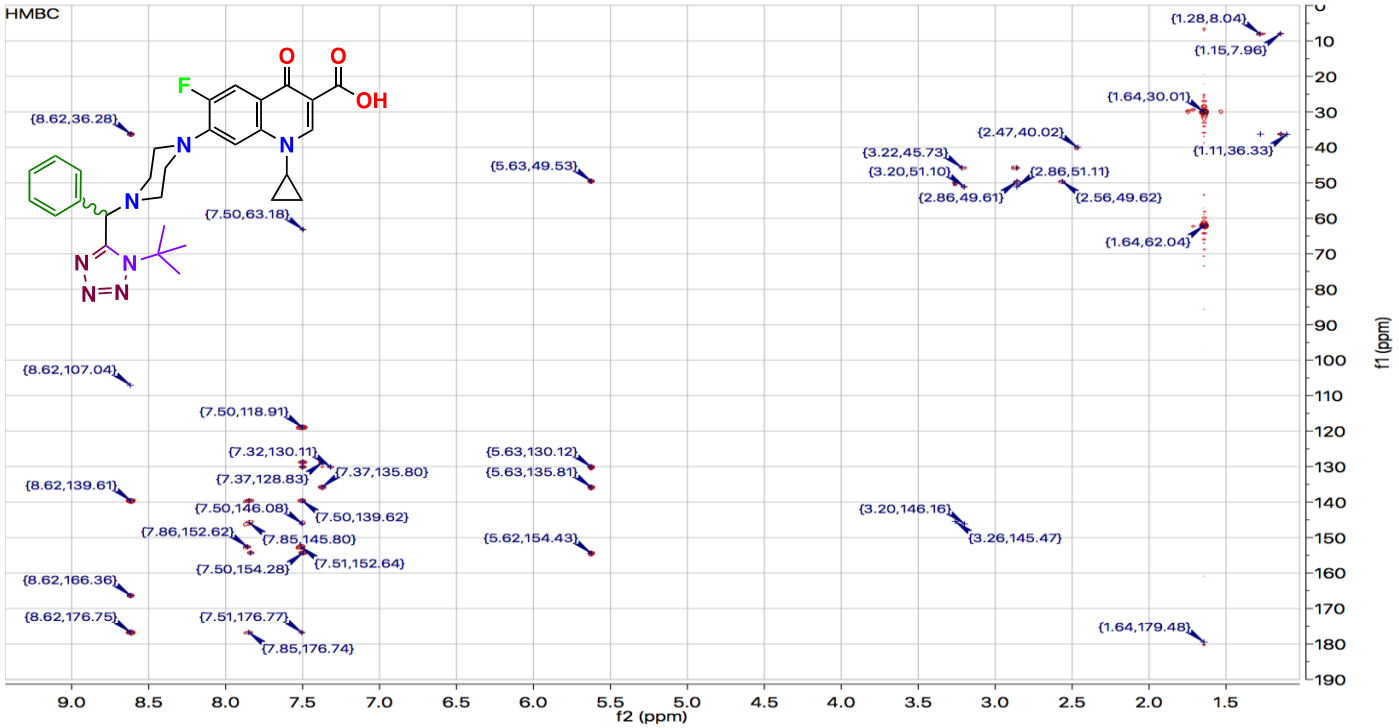

Figure S58. (*R*/*S*)-7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **3**, **4**.

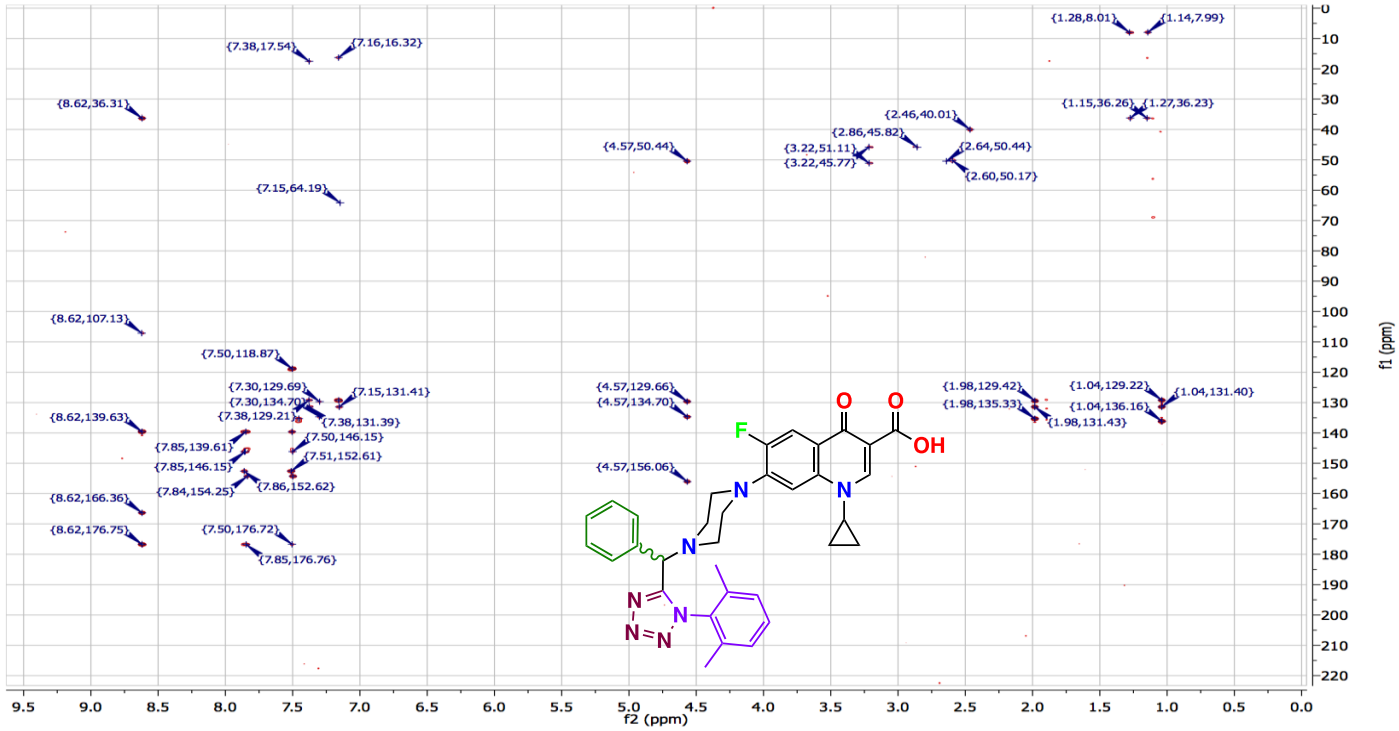

Figure S59. (*R*/*S*)-1-cyclopropyl-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **5**, **6**.

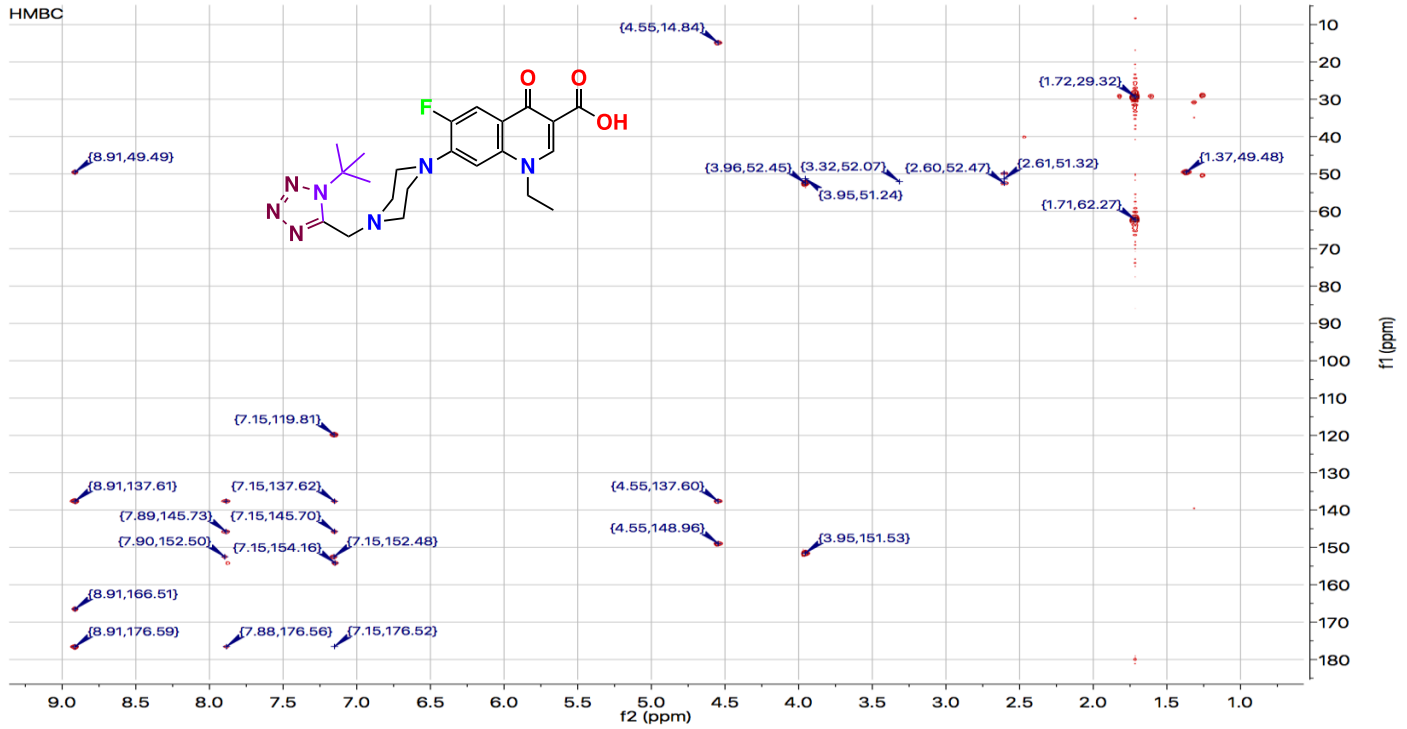

Figure S60. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **7**.

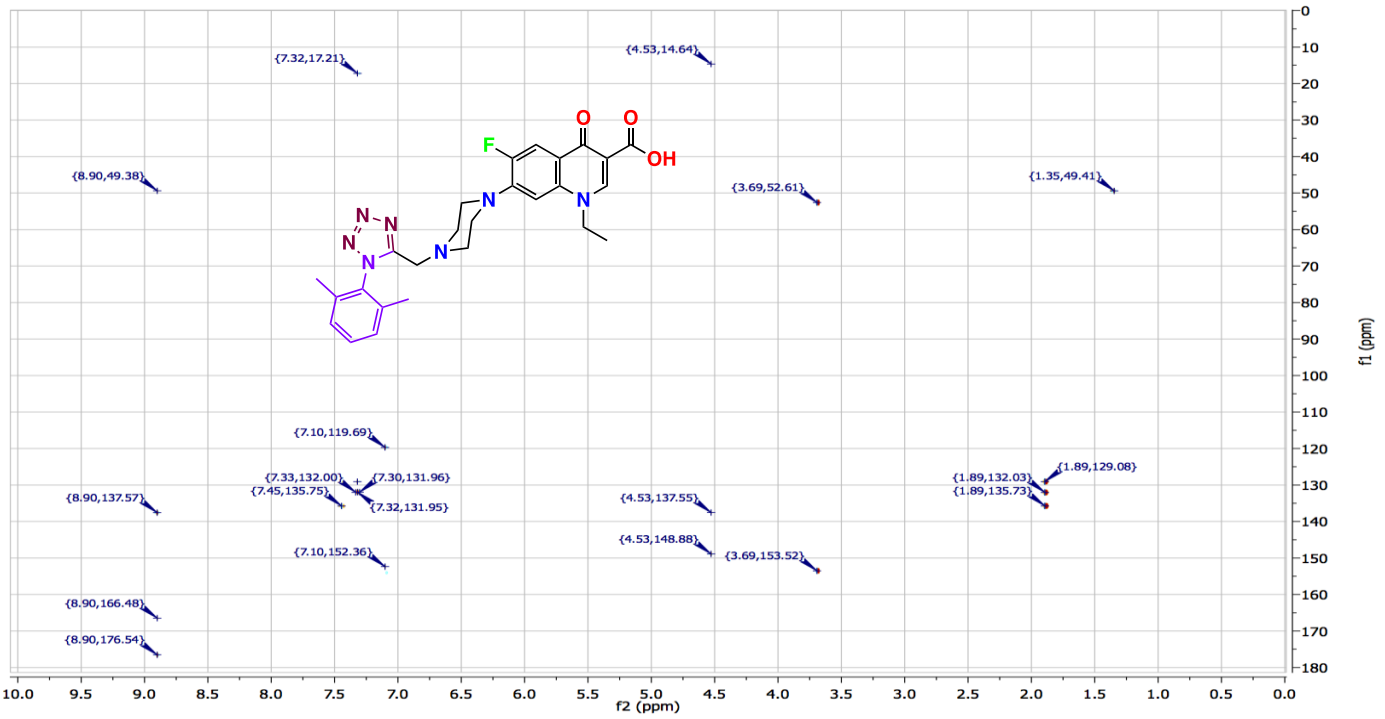

Figure S61. 7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **8**.

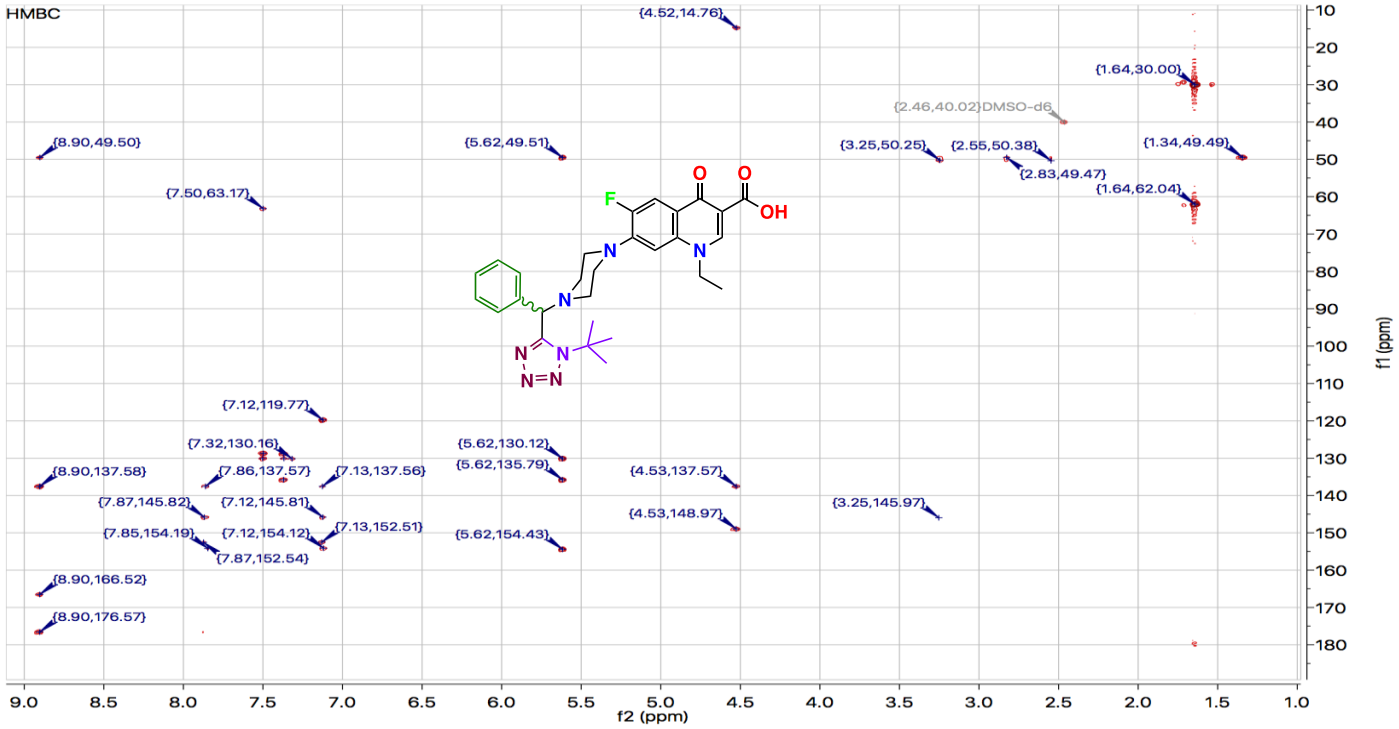

Figure S62. (*R*/*S*)-7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **9**, **10**.

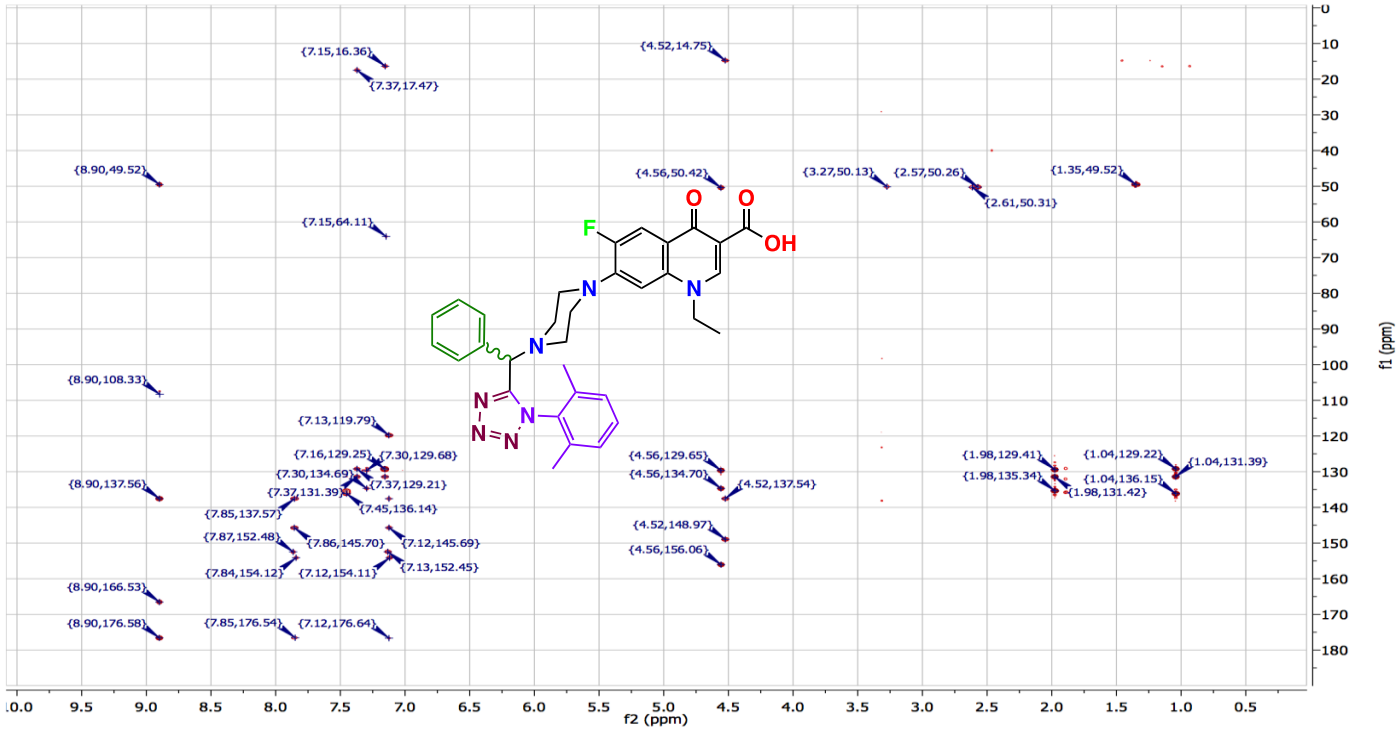

Figure S63. (*R*/*S*)-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **11**, **12**.

Electron-Ionization (EI-MS) and High-Resolution Mass Spectroscopy (HR-MS) Spectrum

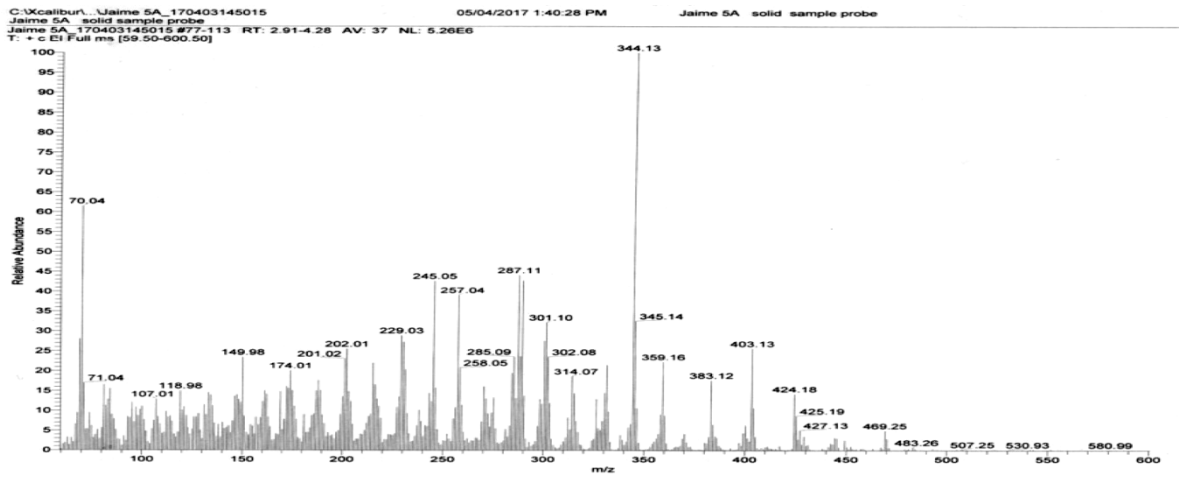

Figure S64. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **1**, EI-MS.

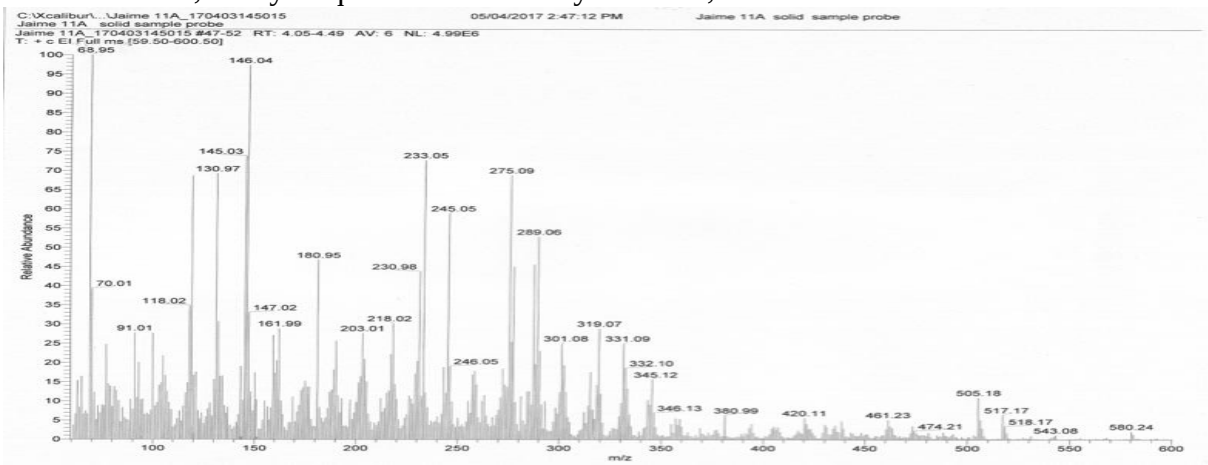

Figure S65. 1-cyclopropyl-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **2**, EI-MS.

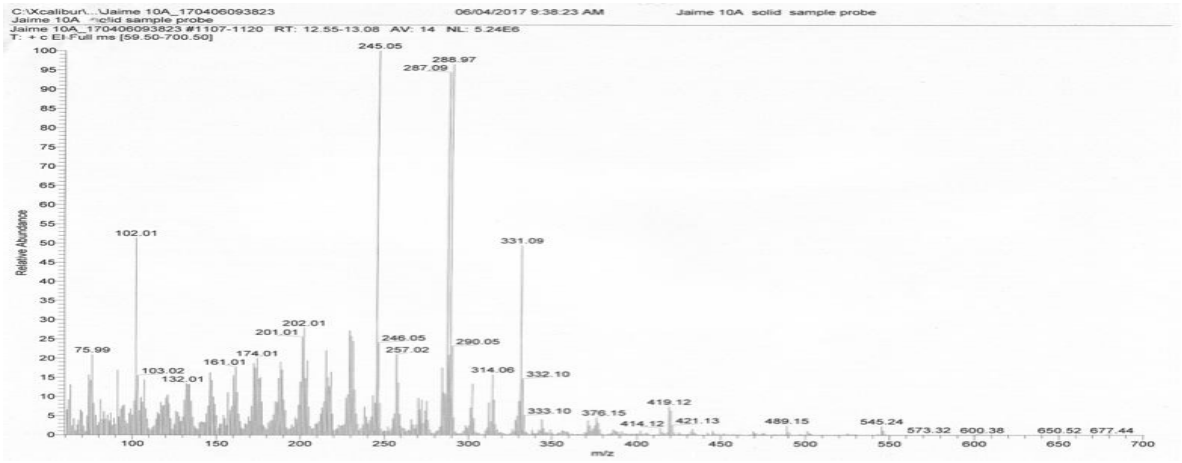

Figure S66. (*R*/*S*)-7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **3**, **4**, EI-MS.

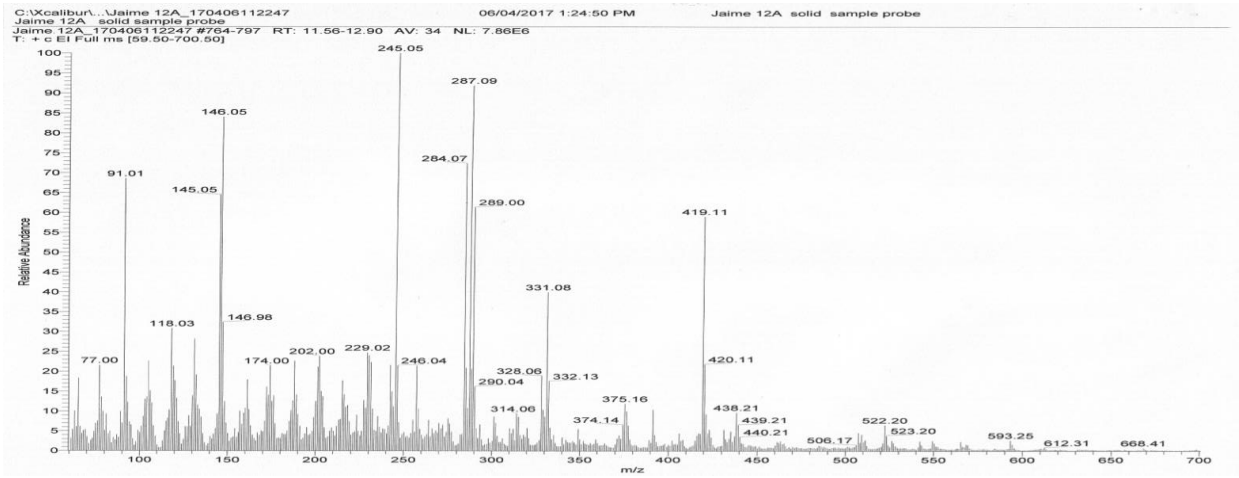

Figure S67. (*R*/*S*)-1-cyclopropyl-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **5**, **6**, EI-MS.

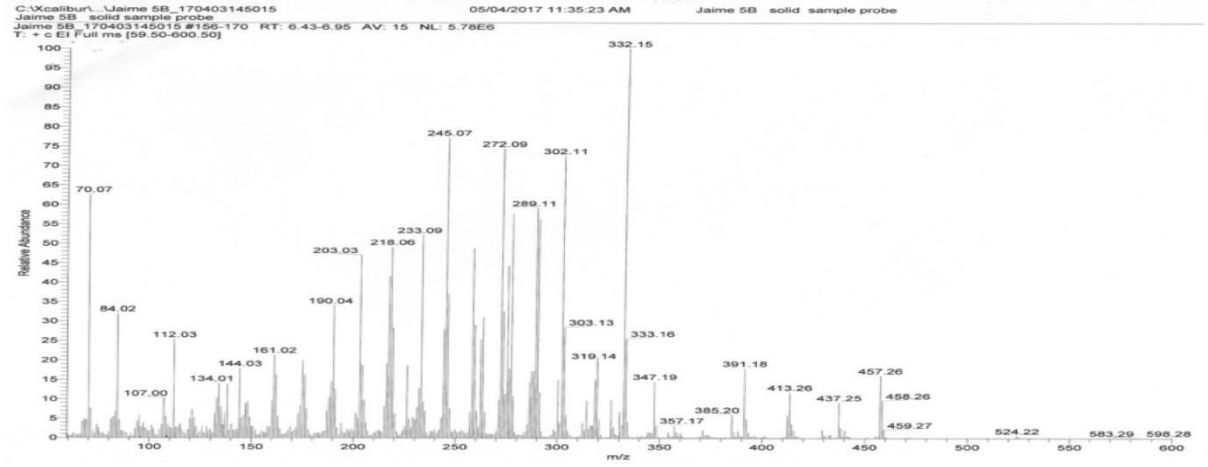

Figure S68. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **7**, EI-MS.

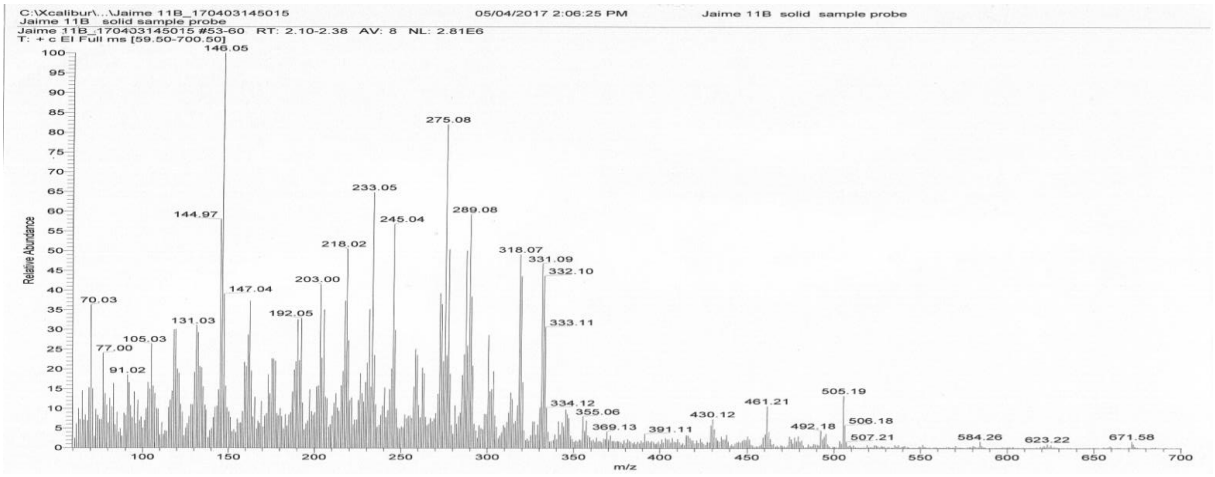

Figure S69. 7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **8**, EI-MS.

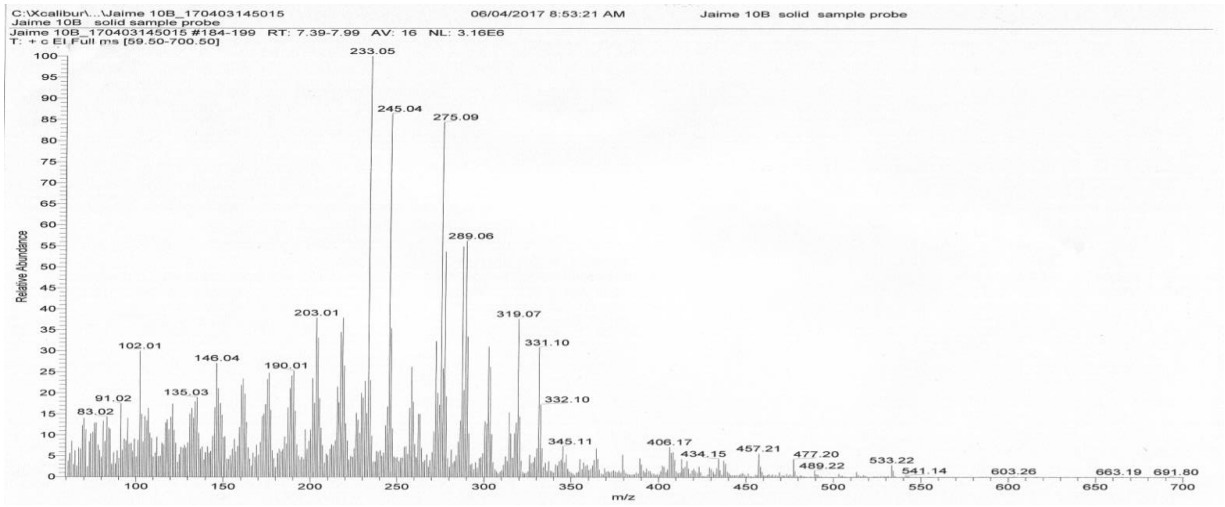

Figure S70. (*R*/*S*)-7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **9**, **10**, EI-MS.

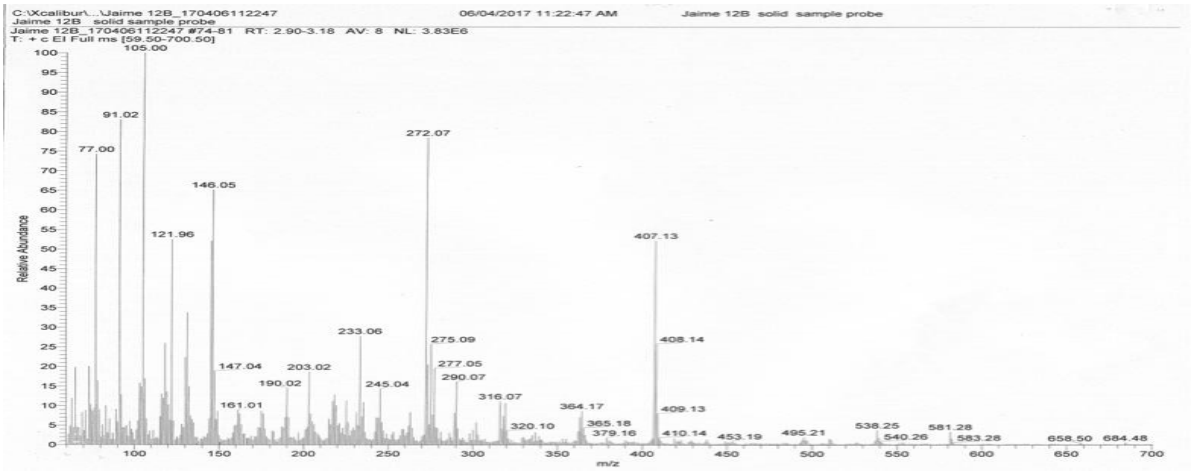

Figure S71. (*R*/*S*)-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **11**, **12**, EI-MS.

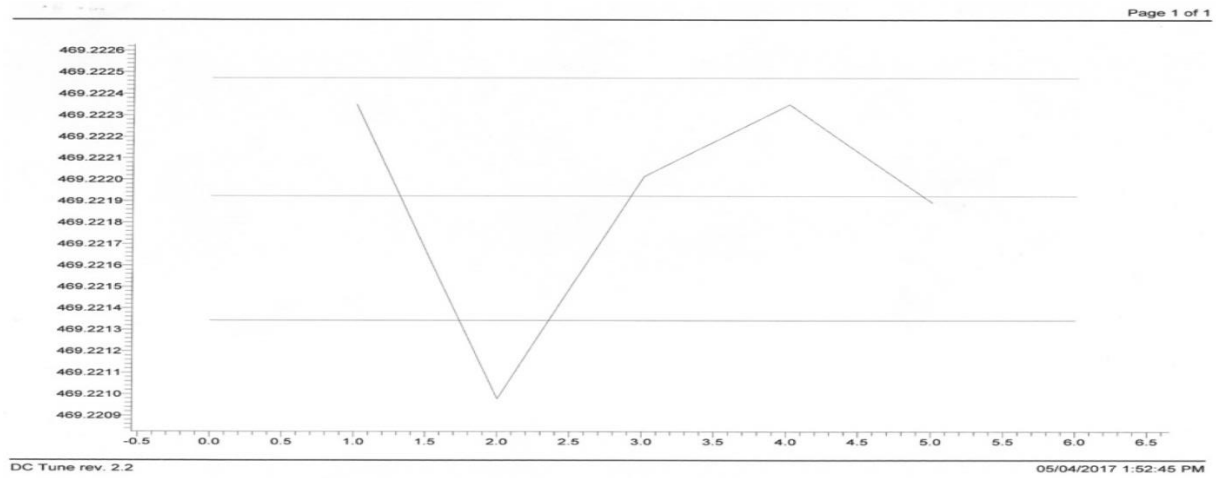

Figure S72. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **1**, HR-MS.

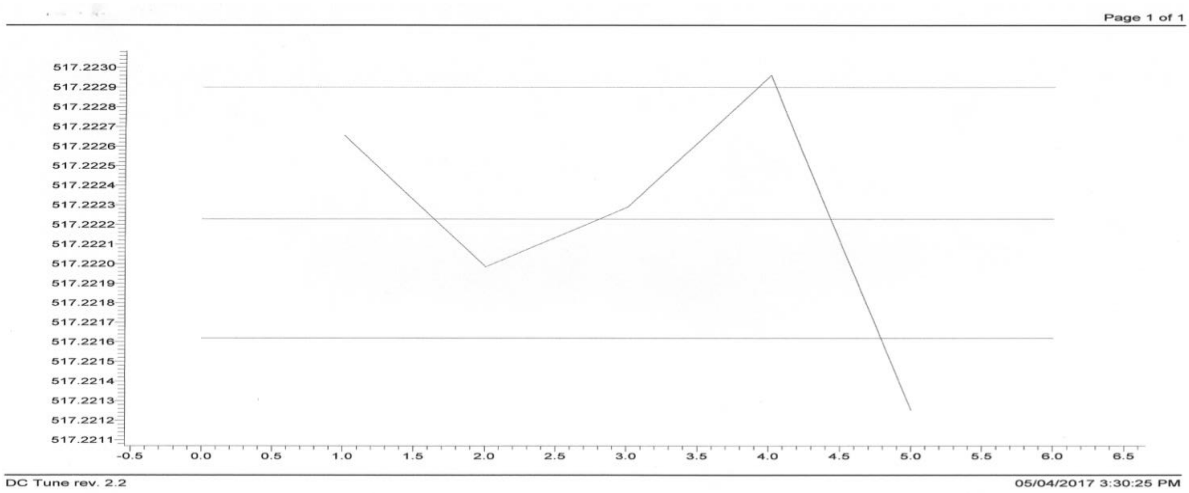

Figure S73. 1-cyclopropyl-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **2**, HR-MS.

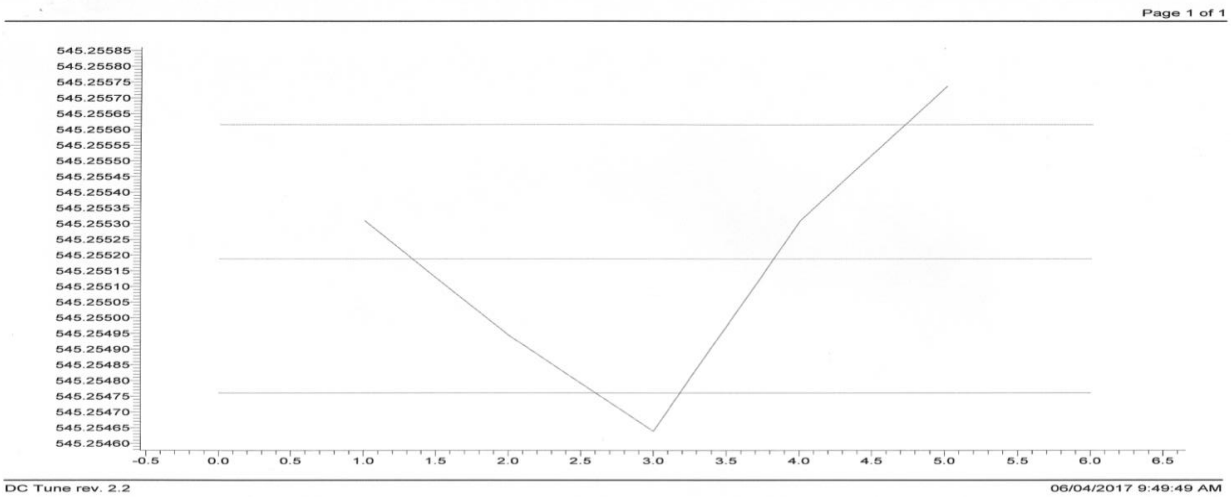

Figure S74. (*R*/*S*)-7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **3**, **4**, HR-MS.

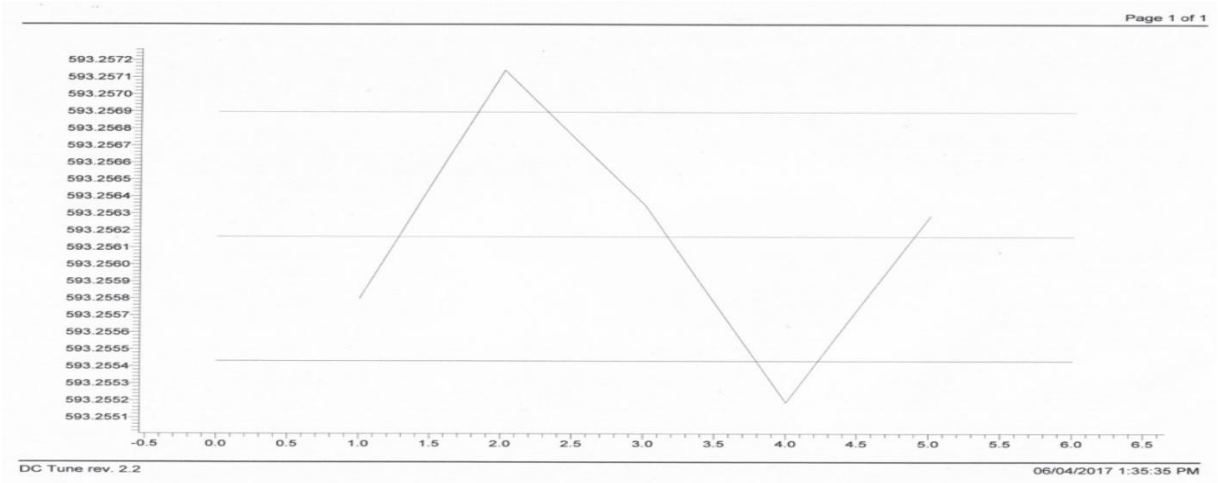

Figure S75. (*R*/*S*)-1-cyclopropyl-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **5**, **6**, HR-MS.

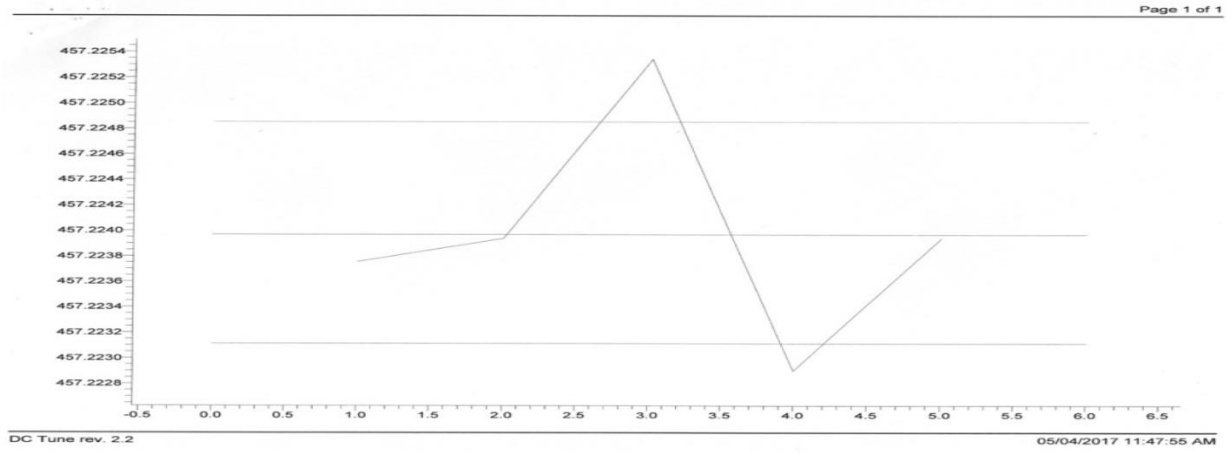

Figure S76. 7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **7**, HR-MS.

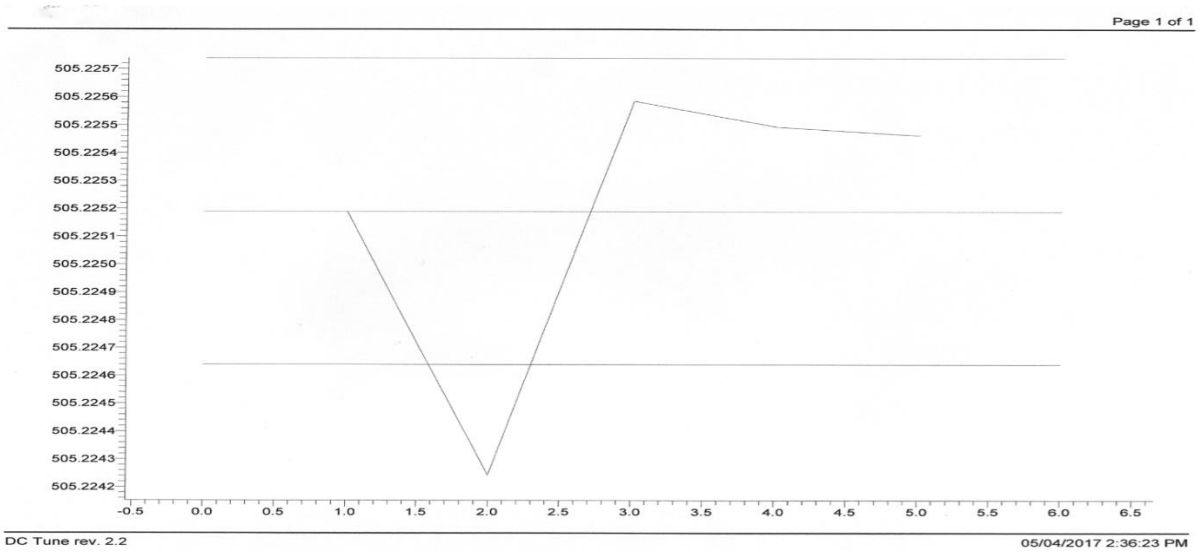

Figure S77. 7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **8**, HR-MS.

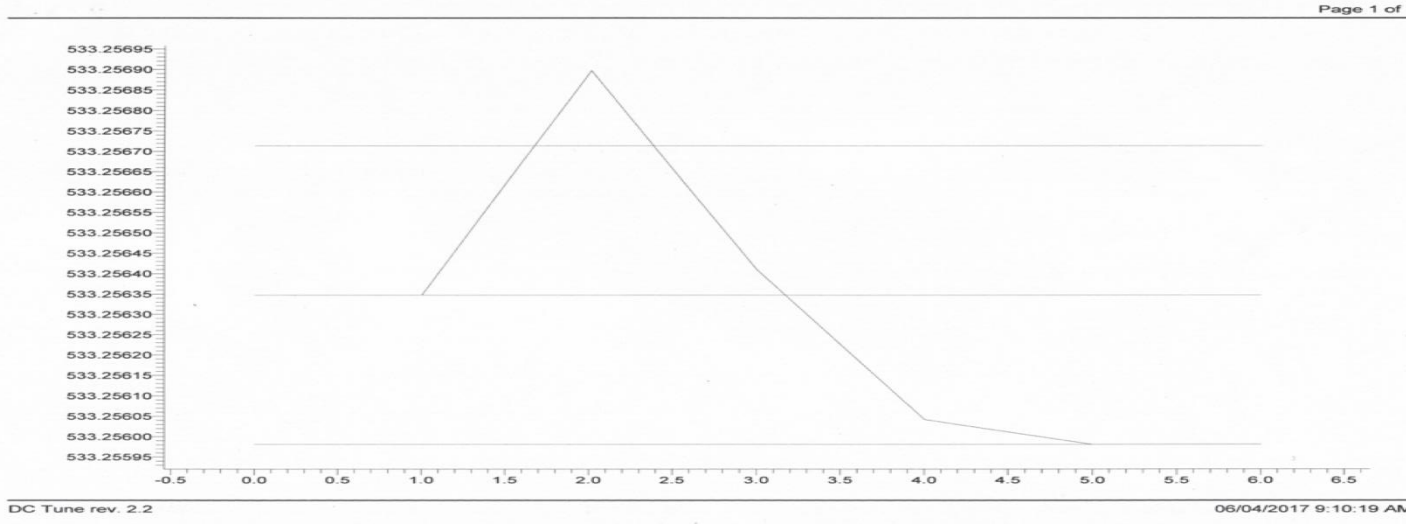

Figure S78. (*R*/*S*)-7-(4-((1-(*ter*-buthyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **9**, **10**, HR-MS.

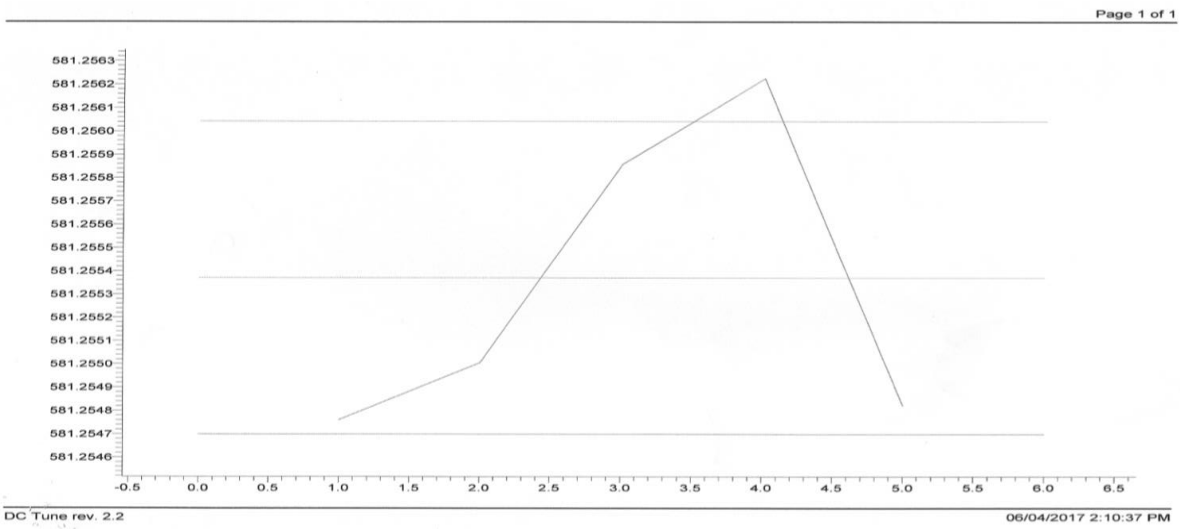

Figure S79. (*R*/*S*)-7-(4-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **11**, **12**, HR-MS.