Supporting information

Discovery of Orally Bioavailable, Quinoline-based Aldehyde Dehydrogenase 1A1 (ALDH1A1) Inhibitors with Potent Cellular Activity

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Table S1. Selectivity Against Other ALDH Isozymes and Dehydrogenases

Cpd.	ALDH1A1 IC_{50} (μM)[a]	hALDH1A2 IC_{50} (μM)[b]	hALDH1A3 IC_{50} (μM)[b]	hALDH2 IC_{50} (μM)[b]	hALDH3A1 IC_{50} (μM)[b]	HPGD IC_{50} (μM)[b]	HSD17β4 IC_{50} (μM)[b]
1[c]	0.010	0.46 ± 0.11	10.8 ± 1.74	13.4 ± 8.18	2.59 ± 0.62	23.1 ± 5.55	>57
2[c]	6.89	>57	32.7 ± 7.95	18.1 ± 8.48	24.3 ± 3.89	>57	>57
3[c]	0.119	20.6 ± 5.0	31.2 ± 10.0	27.3 ± 4.46	>57	35.0 ± 11.3	>57
4[c]	0.041	17.1 ± 0.03	17.5 ± 5.64	17.1[d]	>57	>57	>57
5[c]	0.017	22.8 ± 1.82	22.8 ± 1.82	16.4 ± 3.99	>57	27.1[d]	>57
78	0.008	20.3 ± 1.62	7.39 ± 6.62	8.42 ± 3.35	25.6 ± 2.04	19.2[d]	>57
80	0.013	27.1[d]	13.8 ± 14.6	13.7 ± 2.19	21.5[d]	34.1[d]	>57
81	0.014	38.3[d]	11.4 ± 5.35	17.0[d]	19.2[d]	24.1 ± 0.04	>57
83	0.006	>57	24.8 ± 7.88	22.8 ± 1.82	>57	>57	>57
86	0.007	>57	22.8 ± 1.90	20.1[d]	>57	>57	>57
88	0.021	10.2 ± 0.85	5.63 ± 4.13	5.18 ± 1.26	22.8 ± 1.82	10.8[d]	>57
89	0.012	>57	27.0[d]	19.1[d]	19.2[d]	>57	>57
91	0.007	>57	16.4 ± 3.99	21.5[d]	>57	>57	>57
99	0.038	24.2[d]	17.1[d]	34.8 ± 18.9	31.2 ± 10.0	24.2[d]	>57
105	0.007	29.9 ± 11.9	21.6 ± 3.55	>57	>57	>57	>57
106	0.014	>57	>57	>57	>57	>57	>57
107	0.014	>57	34.8 ± 18.9	24.1[d]	17.1[d]	>57	>57
108	0.006	>57	16.2 ± 1.34	15.7 ± 5.03	>57	>57	>57
109	0.015	>57	24.1[d]	19.1[d]	>57	>57	>57
110	0.014	>57	26.6 ± 10.5	22.1 ± 7.02	>57	>57	>57
111	0.010	>57	32.2 ± 15.1	>57	>57	>57	>57
112	0.012	>57	21.5[d]	>57	>57	>57	>57
113	0.012	>57	10.4 ± 9.35	24.1[d]	>57	>57	>57
114	0.014	>57	25.6 ± 2.04	15.9 ± 11.6	27.1[d]	34.1[d]	>57
115	0.012	>57	21.5 ± 0.04	24.1 ± 0.04	>57	>57	>57
116	0.011	>57	24.7 ± 13.4	21.5[d]	>57	>57	>57
117	0.006	>57	>57	42.8[d]	>57	>57	>57
118	0.008	20.6 ± 5.01	19.7 ± 6.33	24.1[d]	>57	>57	>57

119	0.007	>57	17.5 ± 5.64	24.0[d]	>57	>57	>57
120	0.013	>57	24.1[d]	32.6 ± 21.9	>57	>57	>57
121	0.020	>57	42.9[d]	31.0 ± 16.8	>57	>57	>57
122	0.017	>57	>57	>57	>57	>57	>57
123	0.007	25.9 ± 6.32	29.9 ± 11.9	12.1[d]	>57	23.1 ± 5.63	>57
124	0.005	>57	22.8 ± 1.82	27.0[d]	>57	22.8 ± 1.90	>57
125	0.008	21.5 ± 0.04	10.0 ± 7.34	12.8 ± 1.02	28.1[d]	24.2[d]	>57
126	0.009	>57	27.5[d]	24.0[d]	>57	>57	>57

[a]Values represent the average from at least three experiments. [b]Values represent the average from two experiments unless otherwise specified. Compounds noted as >57 μM represent a very weak or no inhibition [efficacy of ≤ 50% of full inhibition at highest tested concentration (57 μM)]. [c]In internal re-screened data. [d]Single experiment.

Table S2. Inhibitory Activities in ALDH1A1 Enzymatic Assay and Aldefluor Cell-Based Assays

Cpd.	hALDH1A1 IC_{50} (μM)[a]	MIA PaCa-2 IC_{50} (μM)[a]	OV-90 IC_{50} (μM)[a]	HT-29 IC_{50} (μM)[a]
1[b]	0.010 ± 0.002	12.9 ± 4.52	21.5 ± 2.33	6.53 ±3.51
2[b]	6.89 ± 3.17	> 57	> 57	> 57
3[b]	0.119 ± 0.045	1.13 ± 0.07	1.19 ± 0.27	0.65 ± 0.40
4[b]	0.041 ± 0.005	6.79 ± 2.00	4.04 ± 2.19	3.65 ± 1.28
5[b]	0.017 ± 0.003	3.43 ± 0.23	2.14 ± 2.18	1.91 ± 1.00
25	0.028 ± 0.002	12.4 ± 4.62	16.3 ± 6.44	8.42 ± 6.67
26	26.41 ± 3.94	> 57	NA[c]	NA[c]
27	0.068 ± 0.008	9.76 ± 1.76	6.19 ± 2.32	6.59 ± 7.24
28	0.019 ± 0.003	4.09 ± 0.99	3.07 ± 0.39	4.94 ± 2.32
29	0.021 ± 0.004	2.43 ± 0.83	1.66 ± 0.6	2.15 ± 1.52
30	0.035 ± 0.011	2.22 ± 0.63	1.80 ± 0.71	2.27 ± 0.9
31	0.035 ± 0.007	2.27 ± 0.90	2.00 ± 0.59	0.97 ± 0.5
32	0.019 ± 0.001	2.42 ± 1.15	2.26 ± 0.31	2.43 ± 0.17
33	0.013 ± 0.001	1.97 ± 0.16	0.335 ± 0.129	0.397 ± 0.178
34	0.022 ± 0.002	3.93 ± 0.32	2.27 ± 1.07	2.78 ± 1.21
35	0.050 ± 0.015	2.46 ± 0.93	3.03 ± 1.42	1.54 ± 0.20
36	0.023 ± 0.002	2.88 ± 1.17	2.06 ± 0.57	1.78 ± 0.53
37	0.043 ± 0.008	3.55 ± 2.21	3.73 ± 0.60	2.17 ± 0.74
38	0.028 ± 0.004	1.11 ± 0.09	1.44 ± 0.85	1.66 ± 0.27
39	0.019 ± 0.002	3.12 ± 1.46	0.565 ± 0.185	0.312 ± 0.025
40	0.067 ± 0.025	4.04 ± 0.69	4.36 ± 0.78	3.18 ± 0.21
41	0.035 ± 0.006	5.61 ± 1.66	4.93 ± 1.11	2.62 ± 0.01
42	0.113 ± 0.020	11.8 ± 1.91	16.9 ± 9.14	16.5 ± 0.01
43	0.211 ± 0.053	11.7 ± 0.01	15.6 ± 7.34	10.3 ± 4.07
44	0.045 ± 0.003	9.22 ± 3.95	6.91 ± 2.39	5.40 ± 2.26
45	0.194 ± 0.036	11.6 ± 4.98	16.6 ± 2.70	13.5 ± 4.32
46	0.046 ± 0.003	2.57 ± 0.97	1.51 ± 0.81	1.03 ± 0.60
47	0.086 ± 0.010	4.57 ± 1.14	4.17 ± 1.37	2.17 ± 1.72
48	0.033 ± 0.008	2.89 ± 0.70	2.50 ± 1.27	1.75 ± 0.82
49	1.90 ± 0.82	> 57	> 57	> 57
50	2.33 ± 0.76	> 57	> 57	> 57

51	> 57	> 57	> 57	> 57
52	1.40 ± 0.76	> 57	> 57	23.4
53	0.024 ± 0.001	1.45 ± 0.35	1.71 ± 0.55	1.51 ± 0.81
54	0.027 ± 0.003	1.48 ± 0.17	2.51 ± 0.74	2.21 ± 0.18
55	0.122 ± 0.020	3.89 ± 0.70	4.68 ± 1.54	4.17 ± 2.12
56	0.343 ± 0.039	11.4 ± 5.82	6.19 ± 2.32	3.76 ± 4.00
57	0.025 ± 0.008	0.477 ± 0.165	0.292 ± 0.161	0.530 ± 0.204
58	0.371 ± 0.051	6.34 ± 2.08	6.98 ± 0.57	8.64 ± 6.35
59	0.122 ± 0.047	1.41 ± 0.66	1.66 ± 0.60	1.73 ± 1.27
60	0.094 ± 0.063	5.08 ± 0.87	3.02 ± 0.97	2.02 ± 0.35
61	0.127 ± 0.047	2.80 ± 0.85	2.75 ± 0.50	2.79 ± 0.79
62	0.089 ± 0.032	1.57 ± 0.48	2.04 ± 0.51	1.04 ± 0.78
63	0.388 ± 0.081	5.38 ± 2.84	7.84 ± 0.64	4.72 ± 3.09
64	0.086 ± 0.036	1.98 ± 0.56	1.86 ± 0.01	1.48 ± 0.24
65	4.49 ± 1.53	> 57	> 57	> 57
66	0.060 ± 0.017	2.95 ± 0.34	2.48 ± 0.20	1.57 ± 1.93
67	0.064 ± 0.011	2.45± 0.44	3.09 ± 0.56	2.10 ± 0.34
68	0.032 ± 0.002	1.21 ± 0.34	1.45 ± 0.35	1.80 ± 0.25
69	0.017 ± 0.002	1.05 ± 0.12	1.68 ± 0.86	1.76 ± 0.50
70	0.251 ± 0.017	15.6 ± 7.34	23.4 ± 0.01	20.8 ± 0.01
71	0.087 ± 0.020	5.23 ± 2.65	5.30 ± 0.99	2.48 ± 1.89
72	0.193 ± 0.022	5.44 ± 0.37	13.8 ± 2.48	2.34 ± 0.01
73	0.597 ± 0.145	13.6 ± 5.68	20.8 ± 0.01	17.3 ± 12.67
74	2.51 ± 0.17	17.3 ± 3.12	> 57	> 57
75	23.38 ± 1.90	> 57	> 57	> 57
76	0.015 ± 0.004	0.153 ± 0.052	0.196 ± 0.044	0.099 ± 0.096
77	0.013 ± 0.001	0.572 ± 0.311	0.582 ± 0.249	0.265 ± 0.050
78	0.008 ± 0.002	0.063 ± 0.041	0.095 ± 0.035	0.018 ± 0.007
79	0.767 ± 0.279	22.6 ± 3.11	22.1 ± 1.80	8.28[d]
80	0.013 ± 0.001	0.112 ± 0.057	0.140 ± 0.041	0.035 ± 0.034
81	0.014 ± 0.002	0.039 ± 0.019	0.077 ± 0.038	0.010 ± 0.003
82	0.006 ± 0.003	0.032 ± 0.010	0.041 ± 0.008	0.006 ± 0.004
83	0.006 ± 0.003	0.047 ± 0.009	0.059 ± 0.026	0.022 ± 0.014
84	4.83 ± 1.59	> 57	> 57	> 57

85	0.012 ± 0.001	0.206 ± 0.142	0.188 ± 0.073	0.123 ± 0.042
86	0.007 ± 0.003	0.030 ± 0.010	0.033 ± 0.004	0.012 ± 0.007
87	0.574 ± 0.047	4.51 ± 0.62	5.49 ± 0.99	2.06 ± 1.25
88	0.021 ± 0.010	0.873 ± 0.234	1.05 ± 0.31	0.279 ± 0.151
89	0.012 ± 0.007	0.062 ± 0.041	0.086 ± 0.027	0.019 ± 0.014
90	0.009 ± 0.002	0.024 ± 0.013	0.044 ± 0.020	0.009 ± 0.006
91	0.007 ± 0.001	0.077 ± 0.040	0.161 ± 0.038	0.048 ± 0.022
92	0.199 ± 0.037	7.42 ± 1.20	6.97 ± 1.57	8.61 ± 5.87
93	0.080 ± 0.017	4.11 ± 1.23	5.75 ± 1.40	2.01 ± 1.63
94	0.010 ± 0.003	0.094 ± 0.037	0.604 ± 0.204	0.091 ± 0.082
95	0.011 ± 0.005	0.106 ± 0.050	0.104 ± 0.021	0.035 ± 0.016
96	0.047 ± 0.008	2.20 ± 0.50	1.58 ± 0.71	0.77 ± 0.50
97	0.018 ± 0.001	0.472 ± 0.088	0.538 ± 0.150	0.131 ± .078
98	0.061 ± 0.007	4.68 ± 0.54	4.68 ± 0.54	1.42 ± 0.81
99	0.038 ± 0.009	1.59 ± 0.52	1.48 ± 0.49	1.01 ± 0.48
100	0.011 ± 0.004	0.087 ± 0.029	0.112 ± 0.030	0.056 ± 0.023
101	0.023 ± 0.013	0.346 ± 0.088	0.376 ± 0.186	0.260 ± 0.084
102	0.007 ± 0.001	0.032 ± 0.009	0.047 ± 0.010	0.007 ± 0.003
103	0.009 ± 0.001	0.096 ± 0.053	0.117 ± 0.036	0.056 ± 0.022
104	0.016 ± 0.003	0.486 ± 0.178	0.407 ± 0.130	0.216 ± 0.103
105	0.007 ± 0.003	0.033 ± 0.008	0.038 ± 0.010	0.011 ± 0.005
106	0.014 ± 0.002	0.028 ± 0.006	0.042 ± 0.016	0.015 ± 0.010
107	0.014 ± 0.002	0.040 ± 0.013	0.047 ± 0.005	0.011 ± 0.003
108	0.006 ± 0.002	0.040 ± 0.008	0.059 ± 0.023	0.012 ± 0.002
109	0.015 ± 0.003	0.048 ± 0.015	0.047 ± 0.007	0.016 ± 0.007
110	0.014 ± 0.002	0.065 ± 0.023	0.082 ± 0.019	0.009 ± 0.004
111	0.010 ± 0.002	0.022 ± 0.007	0.044 ± 0.009	0.010 ± 0.005
112	0.012 ± 0.002	0.071 ± 0.027	0.055 ± 0.021	0.028 ± 0.016
113	0.012 ± 0.001	0.032 ± 0.002	0.040 ± 0.007	0.008 ± 0.005
114	0.014 ± 0.001	0.045 ± 0.044	0.044 ± 0.013	0.008 ± 0.001
115	0.012 ± 0.002	0.022 ± 0.017	0.057 ± 0.004	0.008 ± 0.002
116	0.011 ± 0.001	0.047 ± 0.009	0.061 ± 0.008	0.009 ± 0.008
117	0.006 ± 0.002	0.031 ± 0.014	0.053 ± 0.027	0.012 ± 0.005
118	0.008 ± 0.003	0.054 ± 0.020	0.086 ± 0.014	0.029 ± 0.037

119	0.007 ± 0.001	0.053 ± 0.023	0.056 ± 0.017	0.009 ± 0.003
120	0.013 ± 0.004	0.053 ± 0.017	0.064 ± 0.023	0.022 ± 0.008
121	0.020 ± 0.004	0.507 ± 0.258	0. 471± 0.081	0.397 ± 0.292
122	0.017± 0.002	0.319 ± 0.054	0.475 ± 0.109	0.150 ± 0.094
123	0.007 ± 0.001	0.042 ± 0.035	0.076 ± 0.021	0.021 ± 0.018
124	0.005 ± 0.001	0.074 ± 0.024	0.121 ± 0.058	0.011 ± 0.006
125	0.008 ± 0.001	0.055 ± 0.024	0.084 ± 0.016	0.013 ± 0.002
126	0.009 ± 0.002	0.111 ± 0.064	0.119 ± 0.022	0.019 ± 0.004

[a]Values with standard deviation (SD) represent the average from at least three experiments unless otherwise specified. Compounds noted as >57 μM represent a very weak or no inhibition [efficacy of ≤ 50% of full inhibition at highest tested concentration (57 μM)]. [b]Internal re-screened data. [c]Data not available. [d]Single experiment.

Table S3. Pharmacokinetics (PK) of 78, 108, 109, 118 and 119 in CD-1 mouse.

Cpd.	Route[a]	C_{max} (ng/mL)[b]	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (h•ng/mL)	Vss (L/kg)	CL_p (mL/min/kg)	F (%)
78[c]	iv	1500	0.49	505	1.2	66	–
78[c]	po	215	4.6	227	–	–	9
108[d]	iv	1803	0.23	661	0.72	53	–
108[d]	po	1111	1.26	844	–	–	30
109[e]	iv	1100	0.29	459	1.39	73	–
109[e]	po	471	1.03	720	–	–	31
118[c]	iv	1960	1.6	1410	2.2	24	–
118[c]	po	1170	5.0	2140	–	–	30
119[c]	iv	1570	0.81	1127	1.14	30	–
119[c]	po	1470	1.15	2764	–	–	49

[a]n= 3; Dosage: 2 mg/kg for intravenous (iv) and 10 mg/kg for oral (po) administration. Plasma sample was measured for drug exposure by LC-MS/MS. [b]The maximum drug concentration (Cmax) was observed at t = 5 min, the first sampling time point after iv administration. [c]The compound was formulated as solution in 20% HP-β-CD in saline. [d]The compound was formulated as solution in 20% HP-β-CD in water. [e]The compound was formulated as solution in 30% solutol in water.

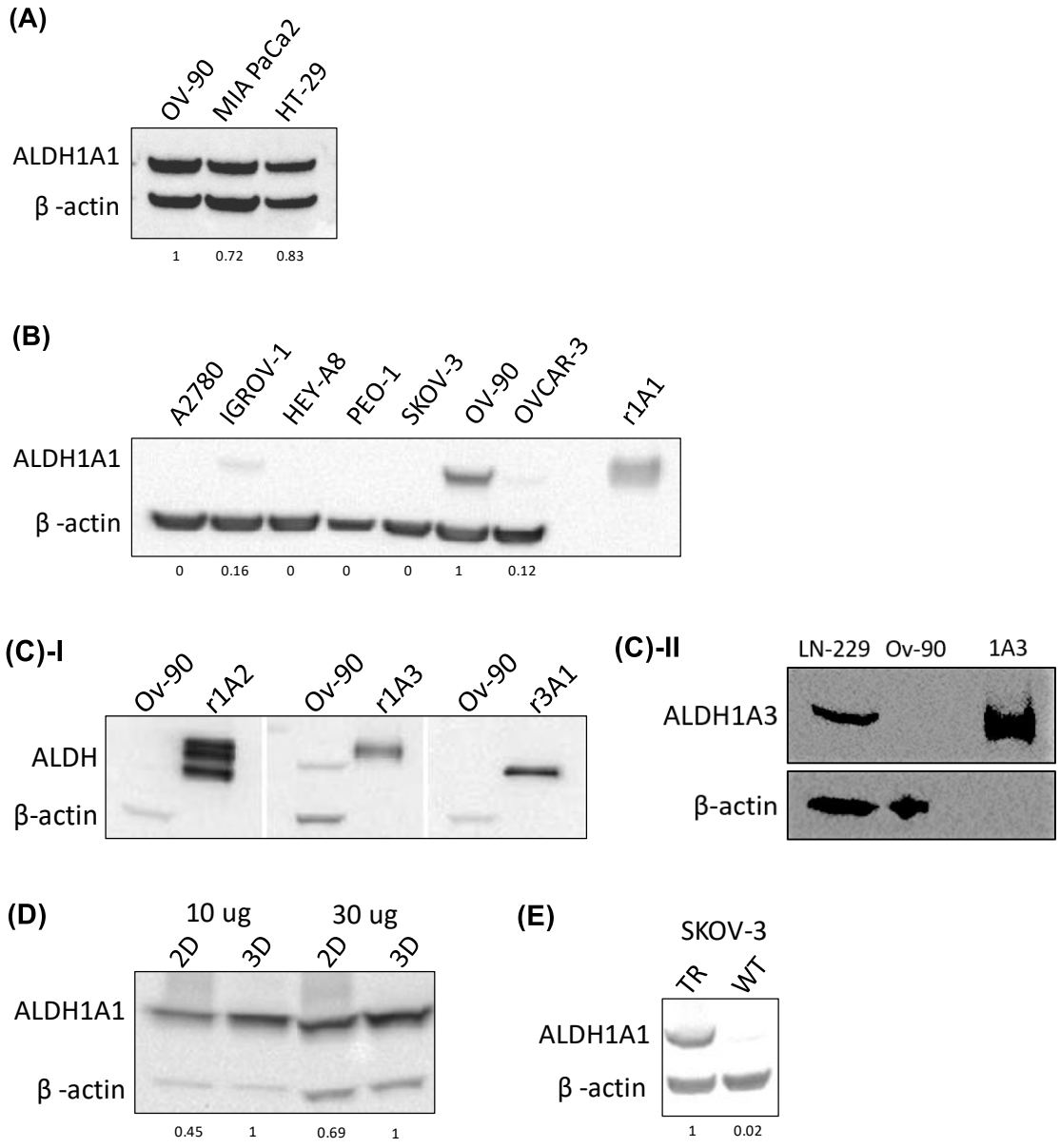
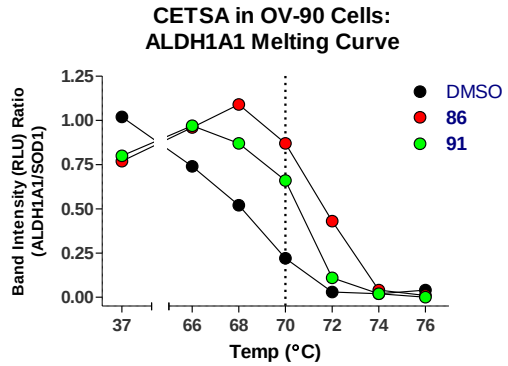


Figure S1. Western blotting for (A) ALDH1A1 expression in cell lines used for Aldefluor assay. (B) ALDH1A1 expression level in ovarian cancer cell lines. (C)-I. No expression of other ALDHs 1A2, 1A3, and 3A1 in OV-90 cells. (C)-II. No expression of ALDH1A3 in OV-90 cells was further confirmed by using LN-229 cells as a positive control that expresses ALDH1A3.[1] (D) ALDH1A1 expression in 2D vs. 3D cultures of OV-90 cells. (E) ALDH1A1 expression in SKOV-3-WT (wild-type) and -TR (paclitaxel-resistant). The number under the band indicates the relative intensity of ALDH1A1 expression.

[1] Yasgar, A.; Titus, S. A.; Wang, Y.; Danchik, C.; Yang, S.-M.; Vasiliou, V.; Jadhav, A.; Maloney, D. J.; Simeonov, A.; Martinez, N. J. A high-content assay enables the automated screening and identification of small molecules with specific ALDH1A1-inhibitory activity. *PLoS ONE* **2017**, *12*, e0170937.



Band Intensities (ALDH1A1 / SOD1)			
°C	DMSO	Cpd. 86	Cpd. 91
37	1.02	0.77	0.80
66	0.74	0.96	0.97
68	0.52	1.09	0.87
70	0.22	0.87	0.66
72	0.03	0.43	0.11
74	0.02	0.04	0.02
76	0.04	0.01	0.00

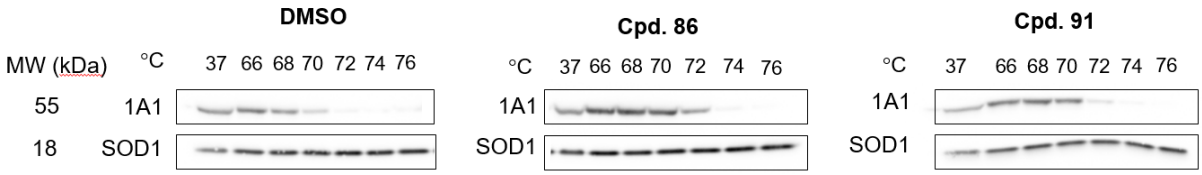


Figure S2. CETSA assay: ALDH1A1 melting curve in OV-90 cells.

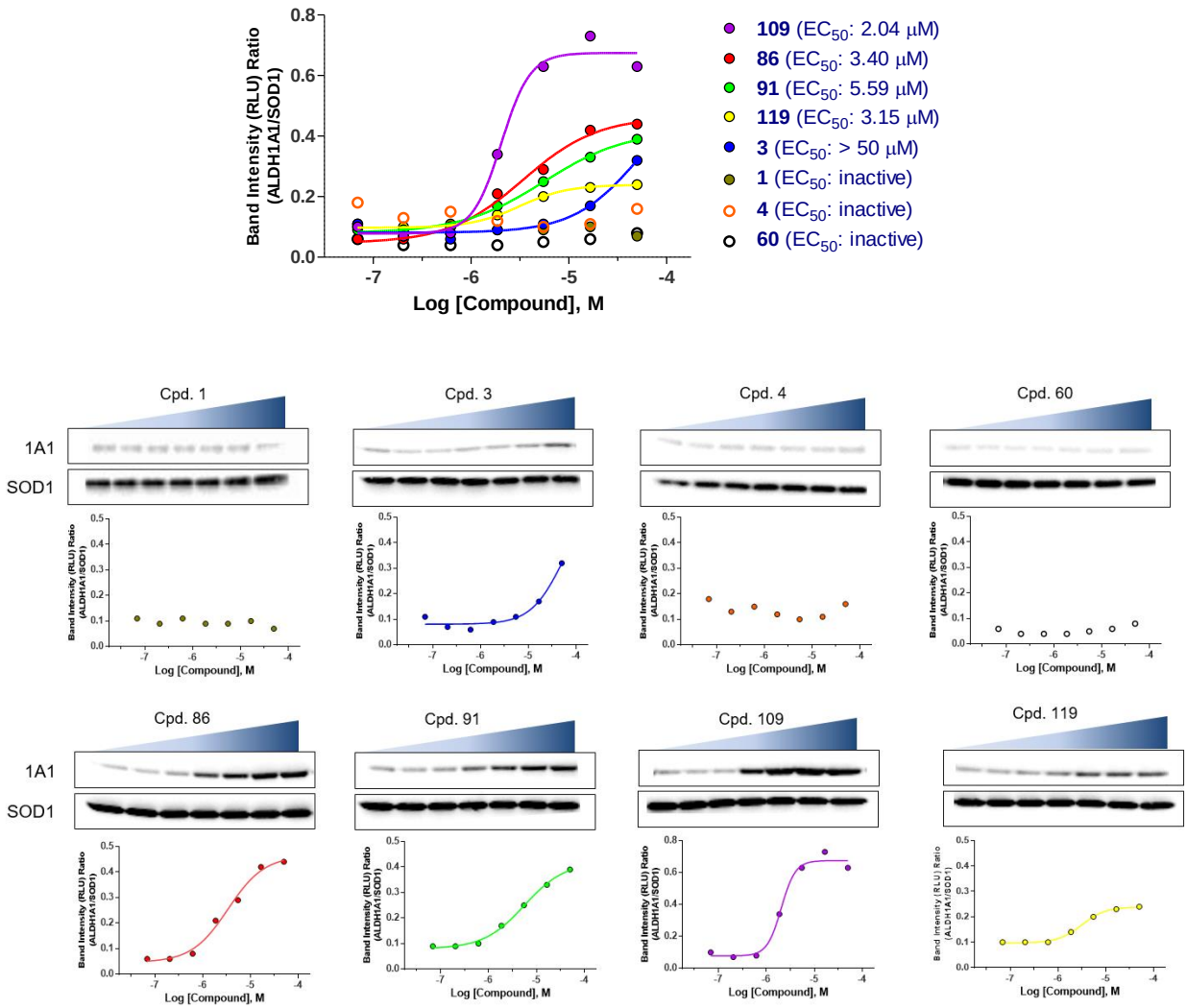


Figure S3. CETSA assay: Compound titration and EC_{50} determination in OV-90 cells at 70 °C.

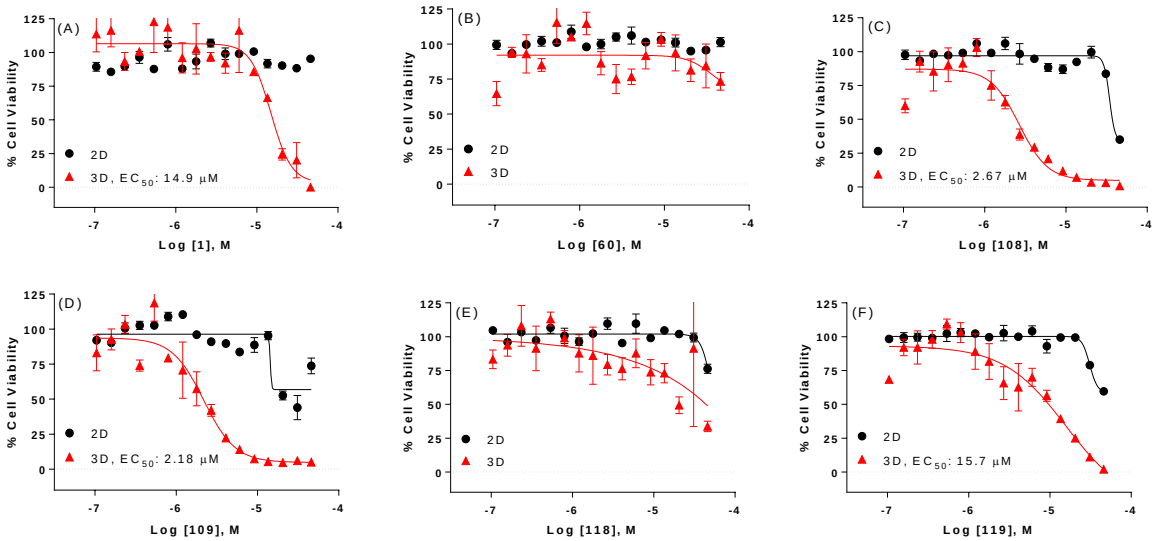
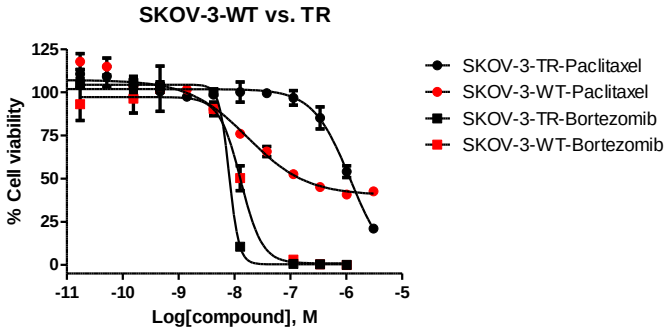


Figure S4. Viability of OV-90 cells in 2D and 3D cultures treated with representative ALDH1A1 inhibitors. For (A): compound **1**; (B): compound **60**; (C): compound **108**; (D): compound **109**; (E): compound **118**; (F): compound **119**. (●) 2D; (▲) 3D.



Compound	WT; IC_{50}	TR; IC_{50}
bortezomib	12.9 nM	8.0 nM
paclitaxel	17.4 nM	1175 nM

Figure S5. Cell viability in SKOV-3-WT vs SKOV-3-TR with treatment of paclitaxel or bortezomib.

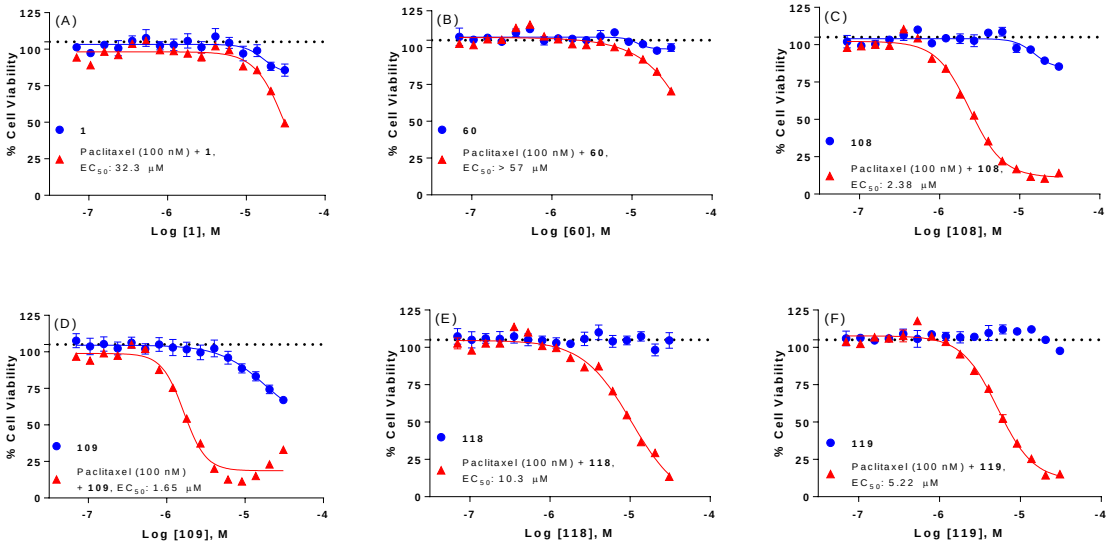
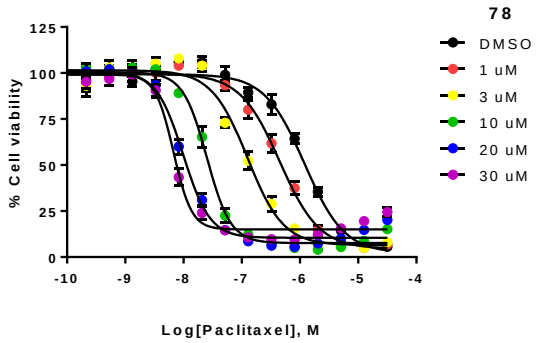
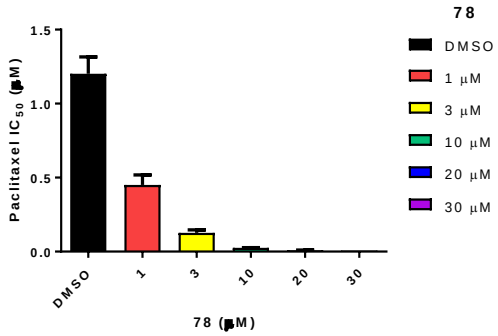
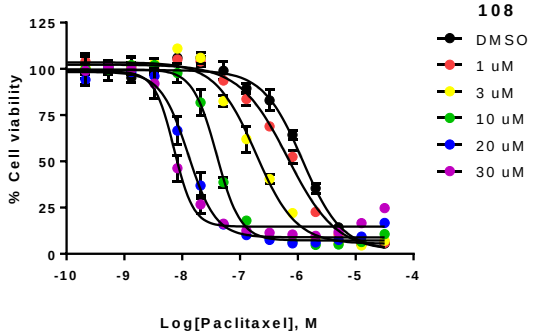
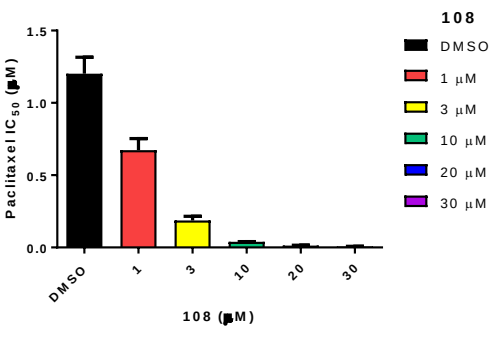


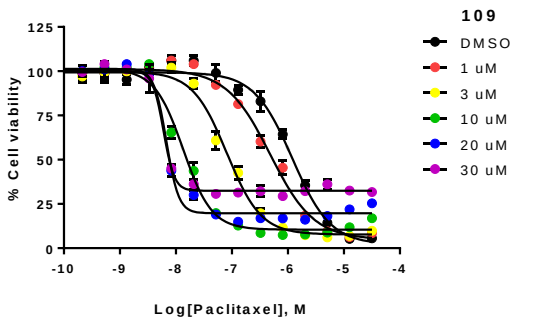
Figure S6. Cell viability of SKOV-3-TR (paclitaxel-resistant) cells in combined treatments of paclitaxel (Taxol, 100 nM) and ALDH1A1 inhibitor (dose-dependent). For (A): compound **1**; (B): compound **60**; (C): compound **108**; (D): compound **109**; (E): compound **118**; (F): compound **119**. (●) ALDH1A1 inhibitor (dose dependent). (▲) paclitaxel (100 nM) + ALDH1A1 inhibitor (dose dependent). Black dotted line represents paclitaxel only at 100 nM.

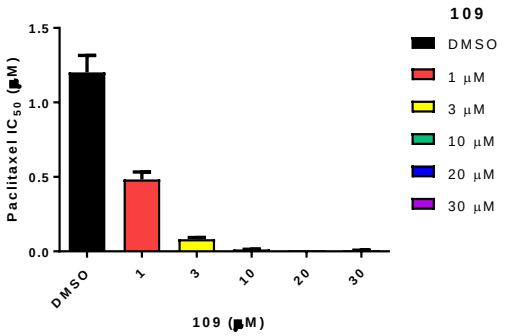

78
DMSO
1 uM
3 uM
10 uM
20 uM
30 uM
% Cell viability
Log[Paclitaxel], M

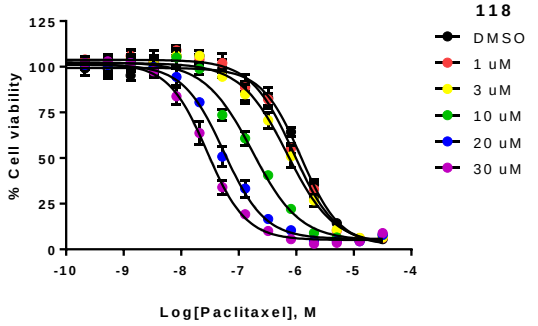

78
DMSO
1 μM
3 μM
10 μM
20 μM
30 μM
Paclitaxel IC50 (μM)
78 (μM)

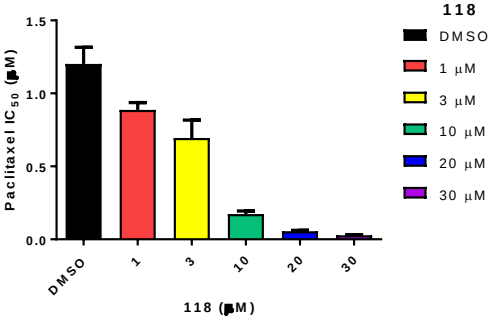

108
DMSO
1 uM
3 uM
10 uM
20 uM
30 uM
% Cell viability
Log[Paclitaxel], M

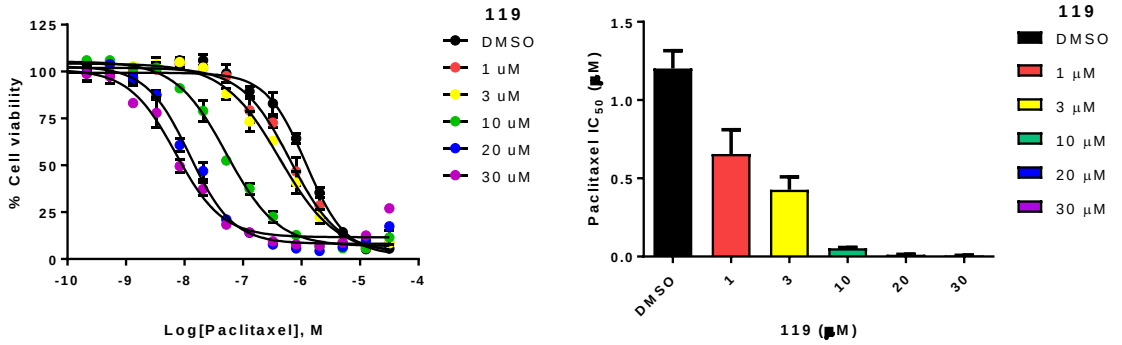

108
DMSO
1 μM
3 μM
10 μM
20 μM
30 μM
Paclitaxel IC50 (μM)
108 (μM)


109
DMSO
1 uM
3 uM
10 uM
20 uM
30 uM
% Cell viability
Log[Paclitaxel], M


109
DMSO
1 μM
3 μM
10 μM
20 μM
30 μM
Paclitaxel IC50 (μM)
109 (μM)


118
DMSO
1 uM
3 uM
10 uM
20 uM
30 uM
% Cell viability
Log[Paclitaxel], M


118
DMSO
1 μM
3 μM
10 μM
20 μM
30 μM
Paclitaxel IC50 (μM)
118 (μM)



ALDH1A1 inhibitor concentration	IC_{50} (nM)[a] of paclitaxel with **78**	IC_{50} (nM)[a] of paclitaxel with **108**	IC_{50} (nM)[a] of paclitaxel with **109**	IC_{50} (nM)[a] of paclitaxel with **118**	IC_{50} (nM)[a] of paclitaxel with **119**
0 (DMSO)	1202	1202	1202	1202	1202
1 μM	447	678	482	889	640
3 μM	125	187	81.2	692	422
10 μM	25.3	39.7	13.5	172	52.4
20 μM	9.9	12.8	6.8	55.4	12.3
30 μM	6.7	7.3	6.0	28.4	7.1

[a]IC_{50} values represent the average of three experiments.

Figure S7. Cell viability of SKOV-3-TR (paclitaxel-resistant) cells in combination treatments of paclitaxel (dose dependent) and ALDH1A1 inhibitor (fixed concentration at 0 (DMSO), 1, 3, 10, 20, 30 μM, respectively).

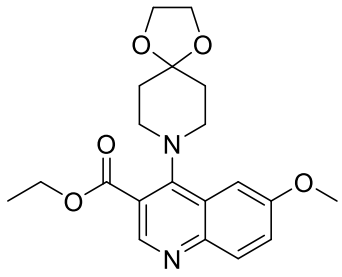
	paclitaxel IC_{50} (nM)	**vincristine** IC_{50} (nM)
KB-3-1 (WT) + DMSO	4.5	1.9
KB-8-5-11 (P-gp) + tariquidar (1 μM final)	1.8	2.1
KB-8-5-11 (P-gp) + DMSO	660	1130
KB-8-5-11 (P-gp) + **60** (3 μM final)	634	1329
KB-8-5-11 (P-gp) + **86** (3 μM final)	460	795
KB-8-5-11 (P-gp) + **91** (3 μM final)	661	944

Figure S8. P-gp assays. Sensitive KB-3-1 (WT–blue line) cells were killed by paclitaxel or vincristine with a single digit nanomolar IC_{50}. In contrast, the KB-8-5-11 cell line with overexpressed P-gp exhibited a 660-1130 nM of IC_{50} (a roughly 370-540 fold right shift from KB-3-1). In the presence of the P-gp inhibitor tariquidar (TQR–red line), KB-8-5-11 exhibited a single digit nanomolar IC_{50} as well, similar to WT cells. However, in the presence of all three studied compounds (**60**, **86**, and **91**), the IC_{50} values for paclitaxel and vincristine clustered along the KB-8-5-11 + DMSO control with around 460–1329 nM.

Experimental Procedures.

General Methods for Chemistry. All air or moisture sensitive reactions were performed under positive pressure of nitrogen with oven-dried glassware. Chemical reagents and anhydrous solvents were obtained from commercial sources and used as-is. Preparative purification was performed on a Waters semi-preparative HPLC. The column used was a Phenomenex Luna C18 (5 micron, 30 x 75 mm) at a flow rate of 45 mL/min. The mobile phase consisted of acetonitrile and water (each containing 0.1% trifluoroacetic acid). A gradient of 10% to 50% acetonitrile over 8 minutes was used during the purification. Fraction collection was triggered by UV detection (220 nm). Analytical analysis for purity was determined by two different methods denoted as Final QC Methods 1 and 2. Method 1: Analysis was performed on an Agilent 1290 Infinity Series HPLC. UHPLC Long Gradient Equivalent 4% to 100% acetonitrile (0.05% trifluoroacetic acid) in water over 3 minutes run time of 4.5 minutes with a flow rate of 0.8 mL/min. A Phenomenex Luna C18 column (3 micron, 3 x 75 mm) was used at a temperature of 50 °C. Method 2: analysis was performed on an Agilent 1260 with a 7 minute gradient of 4% to 100% acetonitrile (containing 0.025% trifluoroacetic acid) in water (containing 0.05% trifluoroacetic acid) over 8 minute run time at a flow rate of 1 mL/min. A Phenomenex Luna C18 column (3 micron, 3 x 75 mm) was used at a temperature of 50 °C. Purity determination was performed using an Agilent Diode Array Detector for both Method 1 and Method 2. Mass determination was performed using an Agilent 6130 mass spectrometer with electrospray ionization in the positive mode. All of the analogs for assay have purity greater than 95% based on both analytical methods. ^{1}H NMR spectra were recorded on Varian 400 MHz spectrometers. High resolution mass spectrometry was recorded on Agilent 6210 Time-of-Flight LC/MS system.

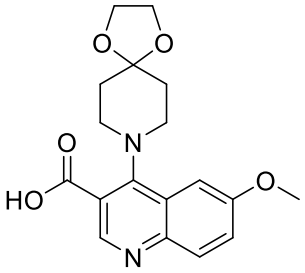
Synthesis of Ethyl 6-methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carboxylate (8a)



8a

In a microwave vial was placed ethyl 4-chloro-6-methoxyquinoline-3-carboxylate (266 mg, 1 mmol) and 1,4-dioxa-8-azaspiro[4.5]decane (215 mg, 1.50 mmol). Then EtOH (2 ml) and Hunig's base (0.26 ml, 1.50 mmol) were added sequentially. The tube was sealed and heated at 80 °C for 3 h. After cooling to rt, the mixture was concentrated and purified by silica gel chromatography using 40-70% EtOAc/hexane as the eluent to give ethyl 6-methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carboxylate (360 mg, 0.967 mmol, 97 % yield) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.76 (s, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.40 (d, *J* = 2.8 Hz, 1H), 7.37 (dd, *J* = 9.0, 2.8 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 4.04 (s, 4H), 3.94 (s, 3H), 3.45 – 3.32 (m, 4H), 2.03 – 1.89 (m, 4H), 1.45 (t, *J* = 7.1 Hz, 3H); LC-MS (Method 1): t_R = 2.86 min, m/z $(M+H)^+$ = 373.

Synthesis of 6-Methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carboxylic acid (11a)

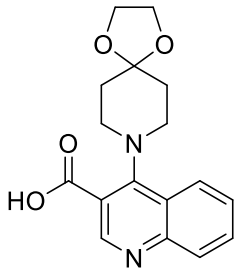


11a

To a solution of ethyl 6-methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carboxylate (360 mg, 0.97 mmol) in THF (4 ml)/MeOH (1 ml) was added $NaOH_{(aq)}$ (1N in H_2O, 3 mL, 3 mmol). The mixture was heated to 50-60 °C and stirred for overnight. After cooling to rt, 1N $HCl_{(aq)}$ was added until the pH of aqueous layer is ca. 4-5. The mixture was concentrated to removal most of solvent. The solid was filtered and triturated with small amount of ice-water and then dried to give 6-methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carboxylic acid (two crops, 335 mg, 0.97 mmol, > 99 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.06 (dd, *J* = 9.3, 1.2 Hz, 1H), 7.67 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.40 (d, *J* = 2.7 Hz, 1H), 3.98 (d, *J* = 1.1 Hz, 7H), 3.62 – 3.54 (m, 4H), 1.98 (dd, *J* = 6.9, 4.5 Hz, 4H) (The proton of carboxylic acid did not show.); LC-MS (Method 1): t_R = 2.58 min, m/z $(M+H)^+$ = 345.

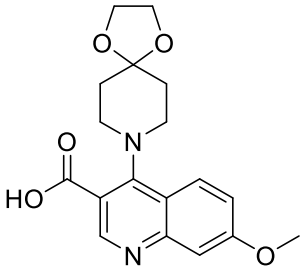
Synthesis of compounds 8b–**8j**, **9**, **10a**, **10c**, **10f**, **10g**, **10i**, **10j**, and **11b**–**11j**, **12**, **13a**, **13c**, **13f**, **13g**, **13i**, and **13j**

Compounds **8b**–**8j**, **9**, **10a**, **10c**, **10f**, **10g**, **10i**, and **10j** were prepared from compound **7** and corresponding amines, such as 1,4-dioxa-8-azaspiro[4.5]decane, 4-cyano-4-methylpiperidine, or 4-cyano-4-phenylpiperidine, according to the similar procedure described in compound **8a**. These ester intermediates were hydrolyzed directly to give compounds **11b**–**11j**, **12**, **13a**, **13c**, **13f**, **13g**, **13i**, and **13j**, respectively, according to the similar procedure described in compound **11a**.



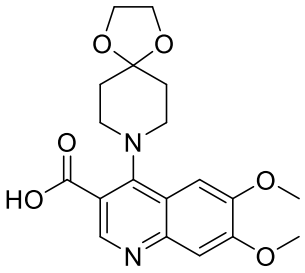
11b

4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.36 (s, 1H), 8.74 (s, 1H), 8.11 (dd, J = 8.5, 1.4 Hz, 1H), 7.94 (dd, J = 8.4, 1.2 Hz, 1H), 7.74 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 7.60 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 3.93 (s, 4H), 3.37 – 3.29 (m, 4H), 1.92 – 1.82 (m, 4H); LC-MS (Method 1): t_R = 2.39 min, m/z $(M+H)^+$ = 315.



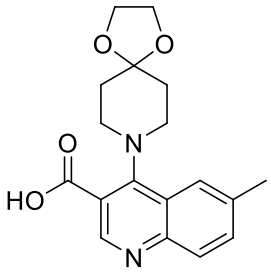
11c

7-methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.21 (s, 1H), 8.70 (s, 1H), 8.01 (d, J = 9.3 Hz, 1H), 7.32 (d, J = 2.6 Hz, 1H), 7.23 (dd, J = 9.2, 2.7 Hz, 1H), 3.92 (s, 4H), 3.89 (s, 3H), 3.29 (dd, J = 7.3, 3.7 Hz, 4H), 1.86-1.83 (m, 4H); LC-MS (Method 1): t_R = 2.60 min, m/z $(M+H)^+$ = 345.



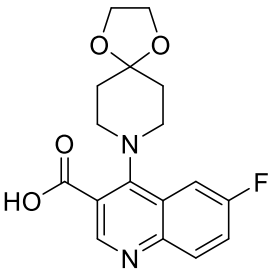
11d

6,7-dimethoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (s, 1H), 8.59 (s, 1H), 7.32 (s, 1H), 7.28 (s, 1H), 3.92 (s, 4H), 3.91 (s, 3H), 3.90 (s, 3H), 3.29-3.27 (m, 4H), 1.85 (t, J = 5.6 Hz, 4H); LC-MS (Method 1): t_R = 2.60 min, m/z $(M+H)^+$ = 375.



11e

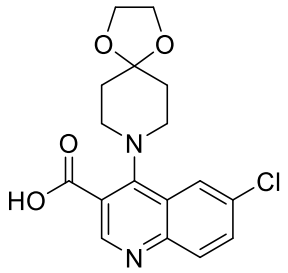
6-methyl-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.31 (s, 1H), 8.67 (d, J = 1.3 Hz, 1H), 7.88 – 7.81 (m, 2H), 7.58 (dd, J = 8.6, 1.8 Hz, 1H), 3.93 (s, 4H), 3.35 – 3.21 (m, 4H), 2.51 (s, 3H), 1.89–1.86 (m, 4H); LC-MS (Method 1): t_R = 2.55 min, m/z $(M+H)^+$ = 329.



11f

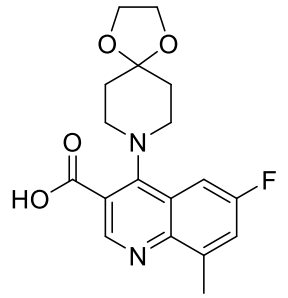
6-fluoro-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.44 (s, 1H), 8.73 (s, 1H), 8.03 (dd, J = 9.0, 5.6 Hz, 1H), 7.74 –

7.61 (m, 2H), 3.93 (s, 4H), 3.33 – 3.23 (m, 4H), 1.90 – 1.81 (m, 4H); LC-MS (Method 1): t_R = 2.49 min, m/z $(M+H)^+$ = 333.



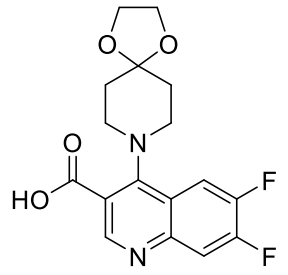
11g

6-chloro-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.47 (s, 1H), 8.75 (s, 1H), 8.02 (d, J = 2.4 Hz, 1H), 7.97 (d, J = 8.9 Hz, 1H), 7.77 (dd, J = 9.0, 2.3 Hz, 1H), 3.93 (s, 4H), 3.30–3.28 (m, 4H), 1.91 – 1.81 (m, 4H); LC-MS (Method 1): t_R = 2.66 min, m/z $(M+H)^+$ = 349.



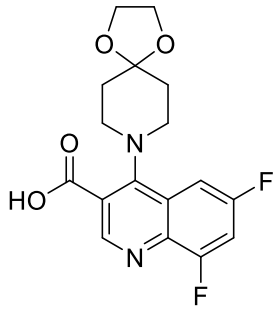
11h

6-fluoro-8-methyl-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.43 (s, 1H), 8.74 (s, 1H), 7.58-7.53 (m, 2H), 3.92 (s, 4H), 3.28-3.25 (m, 4H), 2.68 (s, 3H), 1.84 (t, J = 5.6 Hz, 4H); LC-MS (Method 1): t_R = 2.64 min, m/z $(M+H)^+$ = 347.



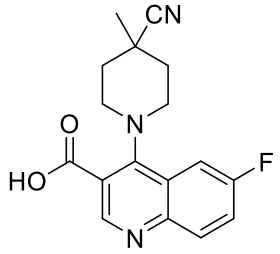
11i

6,7-difluoro-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.46 (s, 1H), 8.75 (s, 1H), 8.01 – 7.87 (m, 2H), 3.92 (s, 4H), 3.29–3.25 (m, 4H), 1.87 (dd, J = 6.9, 4.4 Hz, 4H); LC-MS (Method 1): t_R = 2.61 min, m/z $(M+H)^+$ = 351.



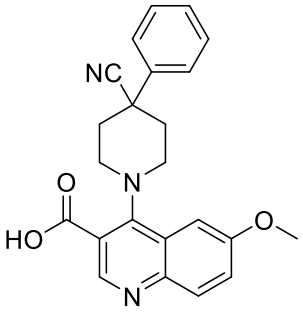
11j

6,8-difluoro-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.58 (s, 1H), 8.75 (s, 1H), 7.74 (ddd, J = 11.1, 8.9, 2.7 Hz, 1H), 7.55 (ddd, J = 10.2, 2.8, 1.4 Hz, 1H), 3.92 (s, 4H), 3.30-3.27 (m, 4H), 1.86 (t, J = 5.6 Hz, 4H); LC-MS (Method 1): t_R = 2.72 min, m/z $(M+H)^+$ = 351.



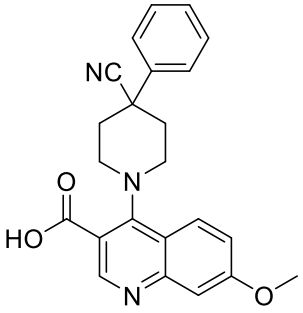
12

4-(4-cyano-4-methylpiperidin-1-yl)-6-fluoroquinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.56 (s, 1H), 8.77 (s, 1H), 8.05 (dd, J = 9.1, 5.6 Hz, 1H), 7.74–7.66 (m, 2H), 3.40 – 3.20 (m, 4H), 2.00–1.88 (m, 4H), 1.45 (s, 3H); LC-MS (Method 1): t_R = 2.56 min, m/z $(M+H)^+$ = 314.



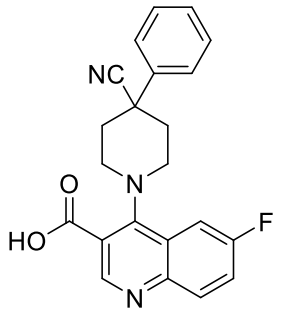
13a

4-(4-cyano-4-phenylpiperidin-1-yl)-6-methoxyquinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.51 (s, 1H), 8.68 (s, 1H), 7.91 (d, J = 9.1 Hz, 1H), 7.69 – 7.60 (m, 2H), 7.53 – 7.34 (m, 5H), 3.91 (s, 3H), 3.60 (td, J = 12.4, 11.7, 2.6 Hz, 2H), 3.49 – 3.38 (m, 2H), 2.42 – 2.25 (m, 4H); LC-MS (Method 1): t_R = 2.95 min, m/z $(M+H)^+$ = 388.



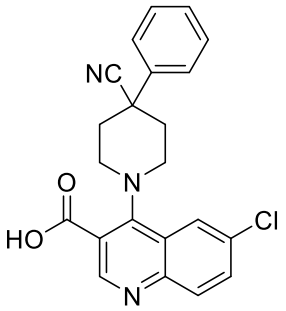
13c

4-(4-cyano-4-phenylpiperidin-1-yl)-7-methoxyquinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.38 (s, 1H), 8.78 (s, 1H), 8.13 (d, J = 9.3 Hz, 1H), 7.68 – 7.61 (m, 2H), 7.47 (dd, J = 8.4, 6.9 Hz, 2H), 7.42 – 7.37 (m, 1H), 7.36 (d, J = 2.6 Hz, 1H), 7.24 (dd, J = 9.3, 2.7 Hz, 1H), 3.90 (s, 3H), 3.66 – 3.54 (m, 2H), 3.42 (d, J = 12.9 Hz, 2H), 2.40 (td, J = 12.8, 3.9 Hz, 2H), 2.25 (d, J = 13.1 Hz, 2H); LC-MS (Method 1): t_R = 2.97 min, m/z $(M+H)^+$ = 388.



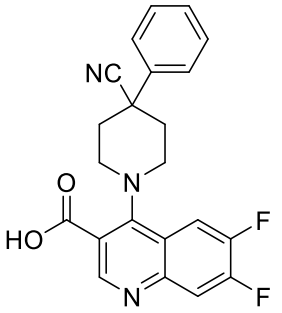
13f

4-(4-cyano-4-phenylpiperidin-1-yl)-6-fluoroquinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.64 (s, 1H), 8.80 (s, 1H), 8.06 (dd, J = 9.2, 5.6 Hz, 1H), 7.87 (dd, J = 10.3, 2.9 Hz, 1H), 7.74 – 7.62 (m, 3H), 7.51 – 7.43 (m, 2H), 7.42 – 7.36 (m, 1H), 3.59 (ddd, J = 13.5, 9.0, 2.2 Hz, 2H), 3.41 (d, J = 13.0 Hz, 2H), 2.48– 2.40 (m, 2H), 2.27 – 2.19 (m, 2H); LC-MS (Method 1): t_R = 2.85 min, m/z $(M+H)^+$ = 376.



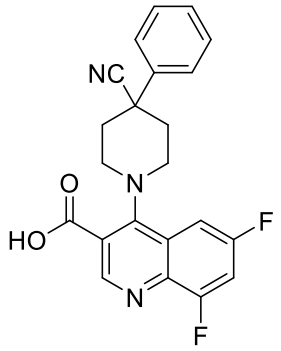
13g

6-chloro-4-(4-cyano-4-phenylpiperidin-1-yl)quinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.66 (s, 1H), 8.83 (s, 1H), 8.13 (d, J = 2.4 Hz, 1H), 8.01 (d, J = 8.9 Hz, 1H), 7.79 (dd, J = 8.9, 2.3 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.48 (t, J = 7.7 Hz, 2H), 7.43 – 7.35 (m, 1H), 3.65 – 3.54 (m, 2H), 3.48 – 3.39 (m, 2H), 2.40 (dt, J = 12.5, 6.4 Hz, 2H), 2.32 – 2.24 (m, 2H); LC-MS (Method 1): t_R = 2.56 min, m/z $(M+H)^+$ = 314.



13i

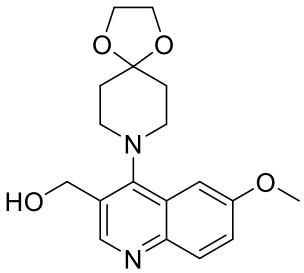
4-(4-cyano-4-phenylpiperidin-1-yl)-6,7-difluoroquinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.67 (s, 1H), 8.82 (s, 1H), 8.12 (dd, J = 11.9, 8.8 Hz, 1H), 8.00 (dd, J = 11.4, 7.8 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.47 (dd, J = 8.5, 6.8 Hz, 2H), 7.38 (t, J = 7.3 Hz, 1H), 3.58 (td, J = 12.6, 2.0 Hz, 2H), 3.39 (d, J = 13.5 Hz, 2H), 2.51–2.43 (m, 2H), 2.27 – 2.16 (m, 2H); LC-MS (Method 1): t_R = 3.14 min, m/z $(M+H)^+$ = 394.



13j

4-(4-cyano-4-phenylpiperidin-1-yl)-6,8-difluoroquinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.81 (s, 1H), 8.81 (s, 1H), 7.80 – 7.74 (m, 1H), 7.72 (dd, *J* = 9.2, 2.1 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.41 – 7.33 (m, 1H), 3.57 (td, *J* = 12.6, 2.1 Hz, 2H), 3.42 (dt, *J* = 13.2, 3.0 Hz, 2H), 2.50 – 2.37 (m, 2H), 2.27 – 2.19 (m, 2H); LC-MS (Method 1): t_R = 3.29 min, m/z $(M+H)^+$ = 394.

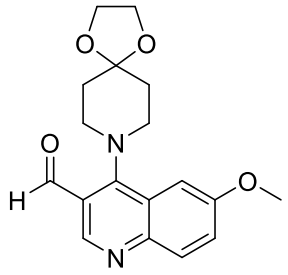
Synthesis of (6-Methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methanol (14)



14

In a microwave tube was placed ethyl 6-methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carboxylate (149 mg, 0.4 mmol). The tube was sealed and the air was removed and refilled with N_2. Then, $LiBH_4$ (87 mg, 4.0 mmol) (2M in THF, 2 mL, 4 mmol) was added. The mixture was heated at 60 °C for 3 h. After cooling to rt, the mixture was poured into EtOAc/H_2O (5 mL/5 mL). The aqueous layer was extracted with EtOAc (5 mL x 2). The combined organic layer was dried (Na_2SO_4) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 0-10% MeOH/EtOAc as the eluent to give (6-methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methanol (54 mg, 0.163 mmol, 40.9 % yield). LC-MS (Method 1): t_R = 2.61 min, m/z $(M+H)^+$= 331.

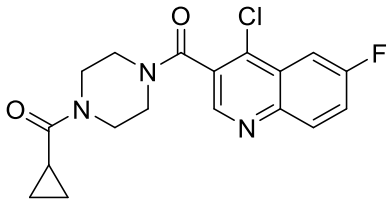
Synthesis of 6-Methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carbaldehyde (15)



15

To a solution of (6-methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methanol (54 mg, 0.16 mmol) in CH_2Cl_2 (2 ml) was added Dess-Martin periodinane (139 mg, 0.33 mmol). The mixture was stirred at rt for 2 h. The mixture was concentrated and the residue was purified by silica gel chromatography using 50-80% EtOAc/hexane as the eluent to give 6-methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carbaldehyde (23 mg, 0.07 mmol, 42.9 % yield). LC-MS (Method 1): t_R = 2.55 min, m/z $(M+H)^+$= 329.

Synthesis of (4-chloro-6-fluoroquinolin-3-yl)(4-(cyclopropanecarbonyl)piperazin-1-yl)methanone (17)

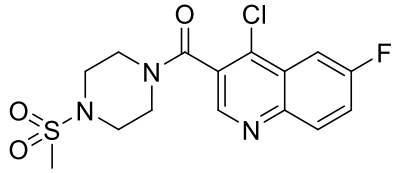


17

To a mixture of 4-chloro-6-fluoroquinoline-3-carboxylic acid (451 mg, 2 mmol), cyclopropyl(piperazin-1-yl)methanone, HCl (477 mg, 2.50 mmol), and HATU (951 mg, 2.50 mmol) was added DMF (5 ml) and then Hunig's base (1.397 ml, 8.0 mmol). The mixture was stirred at rt for 1.5 h. The mixture was poured into EtOAc/H_2O (50 mL/50 mL). The organic layer was washed with H_2O (50 mL), dried (Na_2SO_4), and filtered. After removal of solvent, the product was purified by silica gel chromatography using 0-10% MeOH/EtOAc as the eluent to give (4-chloro-6-fluoroquinolin-3-yl)(4-(cyclopropanecarbonyl)piperazin-1-yl)methanone (625 mg, 1.727 mmol, 86 % yield). LC-MS (Method 1): t_R = 2.99 min, m/z $(M+H)^+$= 362.

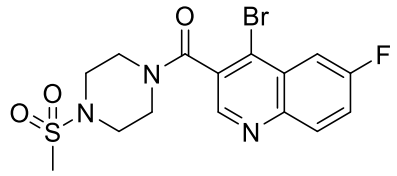
Synthesis of compounds 18a–b

Compounds **18a**–**b** were prepared from compounds **16a**–**b**, respectively, according to the similar procedure described in compound **17**.



18a

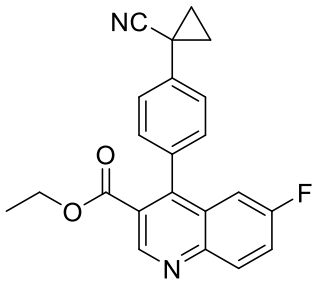
(4-chloro-6-fluoroquinolin-3-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.21 (dd, J = 9.3, 5.4 Hz, 1H), 7.97 (dd, J = 9.6, 2.8 Hz, 1H), 7.85 (td, J = 8.8, 2.8 Hz, 1H), 3.85 (dt, J = 13.4, 5.0 Hz, 1H), 3.76 (dt, J = 13.2, 5.3 Hz, 1H), 3.36 – 3.18 (m, 4H), 3.08 (q, J = 4.6 Hz, 2H), 2.90 (s, 3H); LC-MS (Method 1): t_R = 2.88 min, m/z $(M+H)^+$= 372.



18b

(4-bromo-6-fluoroquinolin-3-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.20 (dd, J = 9.3, 5.4 Hz, 1H), 7.91 (dd, J = 9.8, 2.8 Hz, 1H), 7.84 (td, J = 8.7, 2.8 Hz, 1H), 3.89–3.70 (m, 2H), 3.35 – 3.22 (m, 4H), 3.09 (t, J = 5.1 Hz, 2H), 2.90 (s, 3H); LC-MS (Method 1): t_R = 2.84 min, m/z $(M+H)^+$= 418.

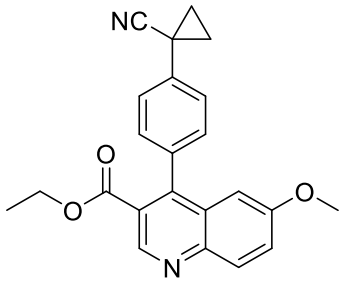
Synthesis of Ethyl 4-(4-(1-cyanocyclopropyl)phenyl)-6-fluoroquinoline-3-carboxylate (20a)



20a

In a 2-neck flask was placed ethyl 4-bromo-6-fluoroquinoline-3-carboxylate (852 mg, 2 mmol), (4-(1-cyanocyclopropyl)phenyl)boronic acid (468 mg, 2.50 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (163 mg, 0.20 mmol) , and K_2CO_3 (829 mg, 6.0 mmol). The air was removed and re-filled with N_2 (2-3 times). Then, a mixture of 1,4-dioxane (6 ml)/water (3 ml) was added and stirred at 95 °C (pre-heated) for 2 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (5 mL x 2). The combined organic layer was dried (Na_2SO_4) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 20-50% EtOAc/hexane as the eluent to give ethyl 4-(4-(1-cyanocyclopropyl)phenyl)-6-fluoroquinoline-3-carboxylate (526 mg, 1.46 mmol, 73.0 % yield). LC-MS (Method 1): t_R = 3.61 min, m/z $(M+H)^+$= 361.

Synthesis of Ethyl 4-(4-(1-cyanocyclopropyl)phenyl)-6-methoxyquinoline-3-carboxylate (20b)

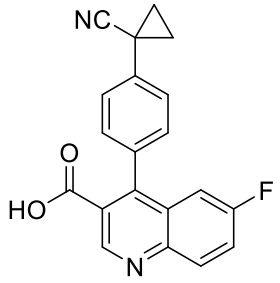


20b

In a 2-neck flask was placed ethyl 4-chloro-6-methoxyquinoline-3-carboxylate (797 mg, 3 mmol), 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropanecarbonitrile (1050 mg, 3.90 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (245 mg, 0.30 mmol), and K_2CO_3 (1368 mg, 9.90 mmol). The air was removed and re-filled with N_2 (2-3 times). Then DMF (6 ml) was added and stirred at 110 °C (pre-heated) for 1.5 h. The mixture was poured into EtOAc/H_2O (40 mL/40 mL). The organic layer was washed with H_2O (40 mL), dried (Na_2SO_4) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 20-70% EtOAc/hexane as the eluent to give ethyl 4-(4-(1-cyanocyclopropyl)phenyl)-6-methoxyquinoline-3-carboxylate (850 mg, 2.28 mmol, 76 % yield). LC-MS (Method 1): t_R = 3.43 min, m/z $(M+H)^+$= 373.

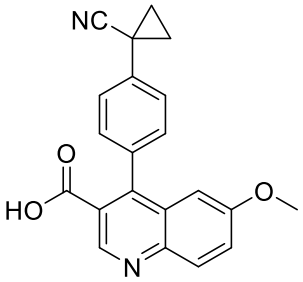
Synthesis of compounds 20c–f and **21a-f**

Compounds **20c**–**f** were prepared from compounds **7g**, **7c**, **7i**, **7j**, respectively, according to the similar procedure described in compound **20b**. These ester intermediates were hydrolyzed directly to give compounds corresponding carboxylic acid intermediates. Compounds **21a**–**f** were prepared from compounds **20a**–**f**, respectively, according to the similar procedure described in compound **11a**.



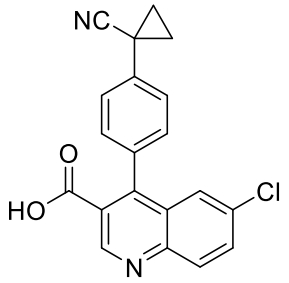
21a

4-(4-(1-cyanocyclopropyl)phenyl)-6-fluoroquinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.19 (s, 1H), 9.18 (s, 1H), 8.20 (dd, *J* = 9.3, 5.6 Hz, 1H), 7.78 (td, *J* = 8.7, 2.9 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.39 – 7.31 (m, 2H), 7.04 (dd, *J* = 10.2, 2.9 Hz, 1H), 1.82 (q, *J* = 4.9 Hz, 2H), 1.65 – 1.58 (m, 2H); LC-MS (Method 1): t_R = 3.21 min, m/z $(M+H)^+$= 333.



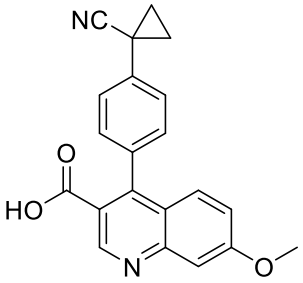
21b

4-(4-(1-cyanocyclopropyl)phenyl)-6-methoxyquinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (s, 1H), 9.02 (s, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.52 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.38 – 7.32 (m, 2H), 6.73 (d, *J* = 2.8 Hz, 1H), 3.66 (s, 3H), 1.83 (q, *J* = 5.0 Hz, 2H), 1.64 – 1.56 (m, 2H); LC-MS (Method 1): t_R = 2.99 min, m/z $(M+H)^+$= 345.



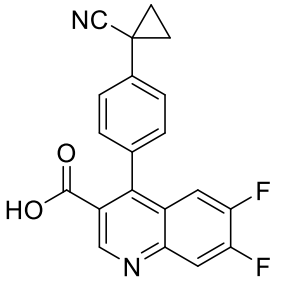
21c

6-chloro-4-(4-(1-cyanocyclopropyl)phenyl)quinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.21 (s, 1H), 9.21 (s, 1H), 8.15 (d, J = 9.0 Hz, 1H), 7.87 (dd, J = 9.0, 2.4 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.39 – 7.32 (m, 3H), 1.82 (q, J = 4.9 Hz, 2H), 1.63 (q, J = 5.1 Hz, 2H); LC-MS (Method 1): t_R = 3.33 min, m/z $(M+H)^+$= 349.



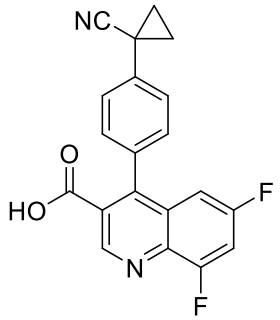
21d

4-(4-(1-cyanocyclopropyl)phenyl)-7-methoxyquinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 9.15 (s, 1H), 7.48 (d, J = 2.6 Hz, 1H), 7.45 – 7.39 (m, 2H), 7.34 – 7.26 (m, 3H), 7.21 (dd, J = 9.3, 2.6 Hz, 1H), 3.92 (s, 3H), 1.81 (q, J = 4.9 Hz, 2H), 1.62 – 1.56 (m, 2H); LC-MS (Method 1): t_R = 2.94 min, m/z $(M+H)^+$= 345.



21e

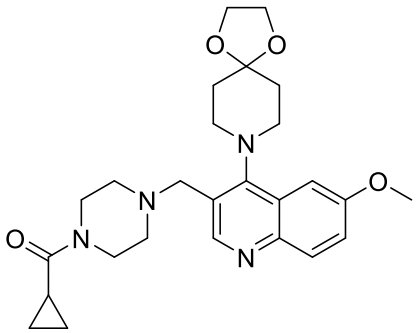
4-(4-(1-cyanocyclopropyl)phenyl)-6,7-difluoroquinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.23 (s, 1H), 9.21 (s, 1H), 8.17 (dd, *J* = 11.3, 7.9 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.38 – 7.32 (m, 2H), 7.26 (dd, *J* = 11.7, 8.6 Hz, 1H), 1.82 (q, *J* = 4.9 Hz, 2H), 1.61 (q, *J* = 5.1 Hz, 2H); LC-MS (Method 1): t_R = 3.32 min, m/z $(M+H)^+$= 351.



21f

4-(4-(1-cyanocyclopropyl)phenyl)-6,8-difluoroquinoline-3-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.44 (s, 1H), 9.16 (s, 1H), 7.84 (ddd, *J* = 11.1, 9.0, 2.7 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 6.90 (dt, *J* = 9.9, 2.0 Hz, 1H), 1.82 (dd, *J* = 8.0, 4.0 Hz, 2H), 1.61 (dd, *J* = 8.0, 4.1 Hz, 2H); LC-MS (Method 1): t_R = 3.27 min, m/z $(M+H)^+$= 351.

Synthesis of Cyclopropyl(4-((6-methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methyl)piperazin-1-yl)methanone, TFA (25)

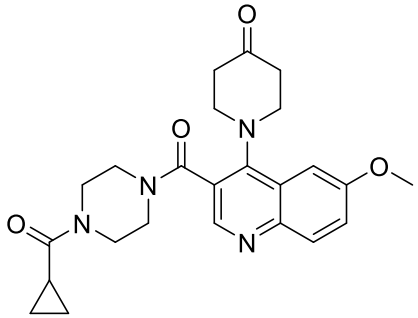


25

To 6-methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carbaldehyde (23 mg, 0.07 mmol) and cyclopropyl(piperazin-1-yl)methanone, HCl (26.7 mg, 0.14 mmol) was added CH_2Cl_2 (1 ml) and then Et_3N (0.06 ml, 0.42 mmol). The mixture was stirred for 3-5 min and sodium triacetoxyborohydride (29.7 mg, 0.14 mmol) was added. The mixture was stirred at rt for 4 h. The mixture was concentrated, re-dissolved in MeOH, filtered, and then submitted for

purification by semi-preparative HPLC to give cyclopropyl(4-((6-methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methyl)piperazin-1-yl)methanone, TFA (11.4 mg, 0.02 mmol, 28.0 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (br s, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.61 (br s, 1H), 7.38 (d, J = 2.7 Hz, 1H), 4.50 (br s, 2H), 3.97 (s, 4H), 3.95 (s, 3H), 3.90-3.15 (m, 12H), 1.93 (s, 5H), 0.71 (br s, 4H); LC-MS (Method 2): t_R = 3.63 min, m/z $(M+H)^+$= 467; HRMS calculated for $C_{26}H_{35}N_4O_4$ $(M+H)^+$: 467.2653, found: 467.2671.

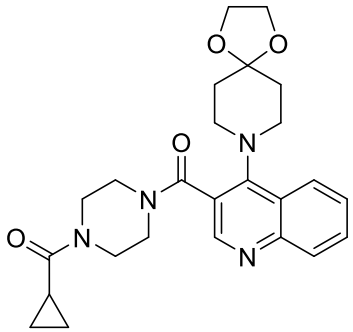
Synthesis of 1-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-6-methoxyquinolin-4-yl)piperidin-4-one (26)



26

To a microwave tube was placed (4-(cyclopropanecarbonyl)piperazin-1-yl)(6-methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methanone (**28**, 90 mg, 0.187 mmol) and *p*-toluenesulfonic acid-mono hydrate (35.6 mg, 0.187 mmol). Then, acetone (5 ml) and water (0.5 ml) were added. The tube was sealed and heated at 55 °C for 48 h. K_2CO_3 (276 mg, 2 mmol) was added and stirred for 15 min. The mixture was filtered through a filter and the filtrate was concentrated. After removal of solvent, the product was dissolved in CH_2Cl_2, dried (Na_2SO_4), and filtered. After removal of solvent, the product was dissolved in DMF (2 mL), filtered and then submitted for purification by semi-preparative HPLC under basic condition to give 1-(3-(4-(cyclopropanecarbonyl)piperazine-1-carbonyl)-6-methoxyquinolin-4-yl)piperidin-4-one (11 mg, 0.025 mmol, 13.5 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.92 (d, J = 9.0 Hz, 1H), 7.51 – 7.39 (m, 2H), 3.94 (s, 3H), 3.90 – 3.21 (m, 12H), 2.65-2.50 (m, 4H), 1.95 (m, 1H), 0.80 – 0.58 (m, 4H); LC-MS (Method 2): t_R = 3.14 min, m/z $(M+H)^+$= 437, HRMS calculated for $C_{24}H_{29}N_4O_4$ $(M+H)^+$: 437.2183, found: 437.2185.

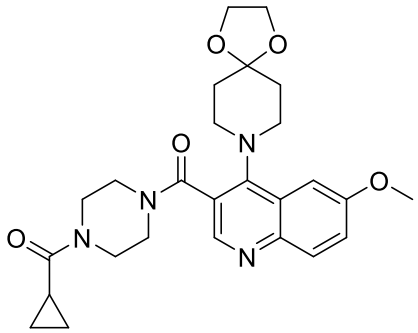
Synthesis of (4-(1,4-Dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)(4-(cyclopropanecarbonyl)piperazin-1-yl)methanone, TFA (27)



27

To a mixture of 4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carboxylic acid (31.4 mg, 0.1 mmol), cyclopropyl(piperazin-1-yl)methanone, HCl (25.4 mg, 0.13 mmol), and HATU (76 mg, 0.20 mmol) was added DMF (1 ml) and then Hunig's base (0.11 ml, 0.60 mmol). The mixture was stirred at rt for 1 h. The mixture was filtered and submitted for purification by semi-preparative HPLC to give (4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)(4-(cyclopropanecarbonyl)piperazin-1-yl)methanone, TFA (8 mg, 0.014 mmol, 14.2 % yield) ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.18 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.93 (t, J = 7.7 Hz, 1H), 7.72 (t, J = 7.7 Hz, 1H), 3.95 (d, J = 1.6 Hz, 4H), 3.56 (q, J = 69.1, 57.6 Hz, 12H), 2.13 – 1.74 (m, 5H), 0.85 – 0.64 (m, 4H); LC-MS (Method 2): t_R = 3.34 min, m/z $(M+H)^+$= 451; HRMS calculated for $C_{25}H_{31}N_4O_4$ $(M+H)^+$: 451.2340, found: 451.2324.

Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(6-methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methanone, TFA (28)

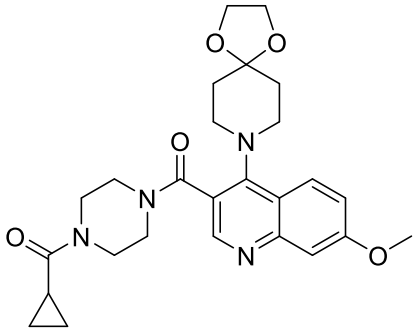


28

To a mixture of 6-methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinoline-3-carboxylic acid (34.4 mg, 0.1 mmol), cyclopropyl(piperazin-1-yl)methanone, HCl (28.6 mg, 0.15 mmol), and HATU (95 mg, 0.25 mmol) was added DMF (1 ml) and then Hunig's base (0.11 ml, 0.60 mmol). The mixture was stirred at rt for 1 h. The mixture was filtered and submitted for

purification by semi-preparative HPLC to give (4-(cyclopropanecarbonyl)piperazin-1-yl)(6-methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methanone, TFA (30.9 mg, 0.052 mmol, 52.0 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 7.95 (d, J = 9.2 Hz, 1H), 7.68 – 7.52 (m, 1H), 7.33 (d, J = 2.8 Hz, 1H), 3.94 (d, J = 3.9 Hz, 7H), 3.87 – 3.13 (m, 12H), 2.10 – 1.75 (m, 5H), 0.73 (d, J = 6.3 Hz, 4H); LC-MS (Method 2): t_R = 3.56 min, m/z $(M+H)^+$= 481; HRMS calculated for $C_{26}H_{33}N_4O_5$ $(M+H)^+$: 481.2445, found: 481.2423.

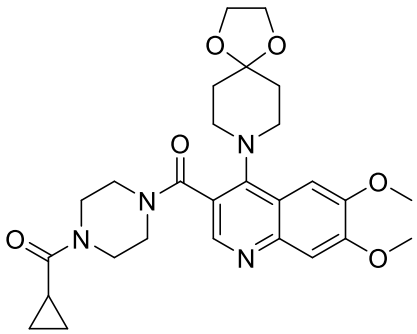
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(7-methoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methanone, TFA (29)



29

The title compound was prepared from **11c** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.10 (d, J = 9.3 Hz, 1H), 7.41 – 7.28 (m, 2H), 3.99 – 3.90 (m, 7H), 3.89 – 3.24 (m, 12H), 1.91 (dddd, J = 76.2, 12.4, 7.3, 3.6 Hz, 5H), 0.84 – 0.60 (m, 4H); LC-MS (Method 2): t_R = 3.54 min, m/z $(M+H)^+$= 481; HRMS calculated for $C_{26}H_{33}N_4O_5$ $(M+H)^+$: 481.2445, found: 481.2459.

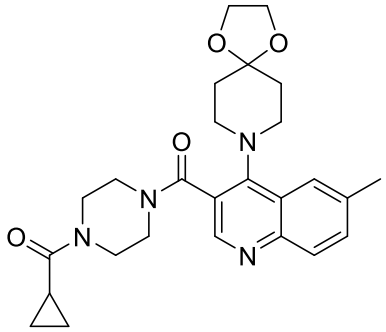
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(6,7-dimethoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methanone, TFA (30)



30

The title compound was prepared from **11d** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 7.35 (s, 1H), 7.27 (s, 1H), 3.97 (s, 7H), 3.94 (s, 3H), 3.53 (m, 12H), 2.09 – 1.80 (m, 5H), 0.74 (d, J = 4.6 Hz, 4H); LC-MS (Method 2): t_R = 3.56 min, m/z $(M+H)^+$= 511; HRMS calculated for $C_{27}H_{35}N_4O_6$ $(M+H)^+$: 511.2551, found: 511.2537.

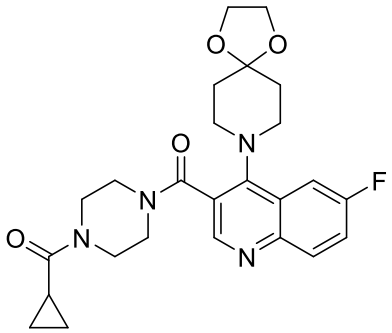
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(6-methyl-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methanone, TFA (31)



31

The title compound was prepared from **11e** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1H), 7.92 (d, J = 8.5 Hz, 2H), 7.82 (dd, J = 8.5, 1.7 Hz, 1H), 3.96 (s, 4H), 3.87 – 3.25 (m, 12H), 2.56 (s, 3H), 2.18 – 1.68 (m, 5H), 0.91 – 0.59 (m, 4H); LC-MS (Method 2): t_R = 3.51 min, m/z $(M+H)^+$= 465; HRMS calculated for $C_{26}H_{33}N_4O_4$ $(M+H)^+$: 465.2496, found: 465.2490.

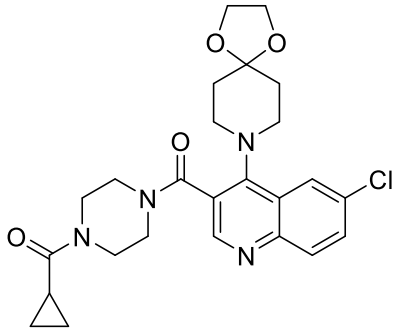
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(6-fluoro-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methanone, TFA (32)



32

The title compound was prepared from **11f** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (d, J = 4.0 Hz, 1H), 8.07 (dd, J = 8.9, 5.3 Hz, 1H), 7.80 (t, J = 9.9 Hz, 2H), 3.97 – 3.91 (m, 4H), 3.90 – 3.08 (m, 12H), 2.12 – 1.65 (m, 5H), 0.90 – 0.54 (m, 4H); LC-MS (Method 2): t_R = 3.49 min, m/z $(M+H)^+$= 469; HRMS calculated for $C_{25}H_{30}FN_4O_4$ $(M+H)^+$: 469.2246, found: 469.2260.

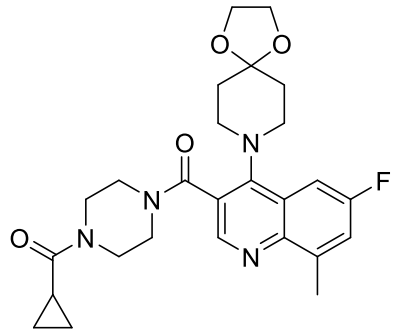
Synthesis of (6-Chloro-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)(4-(cyclopropanecarbonyl)piperazin-1-yl)methanone, TFA (33)



33

The title compound was prepared from **11g** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.04 (d, J = 2.3 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.83 (dd, J = 8.9, 2.2 Hz, 1H), 3.98 – 3.89 (m, 4H), 3.88 – 3.07 (m, 12H), 2.07 – 1.74 (m, 5H), 0.74 (dd, J = 4.7, 2.8 Hz, 4H); LC-MS (Method 2): t_R = 3.78 min, m/z $(M+H)^+$= 485; HRMS calculated for $C_{25}H_{30}ClN_4O_4$ $(M+H)^+$: 485.1950, found: 485.1938.

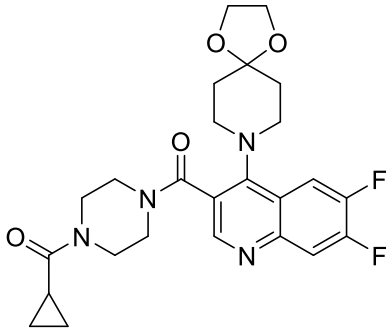
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(6-fluoro-8-methyl-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methanone, TFA (34)



34

The title compound was prepared from **11h** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 7.58 (m, 2H), 3.92 (s, 4H), 3.87 – 3.25 (m, 10H), 3.13 – 3.01 (m, 2H), 2.70 (s, 3H), 2.08 – 1.70 (m, 5H), 0.74 (dd, J = 4.7, 2.8 Hz, 4H); LC-MS (Method 2): t_R = 3.81 min, m/z $(M+H)^+$= 483; HRMS calculated for $C_{26}H_{32}FN_4O_4$ $(M+H)^+$: 483.2402, found: 483.2408.

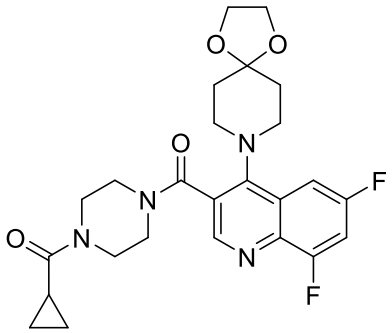
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(6,7-difluoro-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methanone, TFA (35)



35

The title compound was prepared from **11i** following the similar procedure as described in the synthesis of **27**. . ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.03 – 7.86 (m, 2H), 3.96 – 3.88 (m, 4H), 3.85 – 2.99 (m, 12H), 2.07 – 1.70 (m, 5H), 0.72 (d, J = 4.6 Hz, 4H); LC-MS (Method 2): t_R = 3.79 min, m/z $(M+H)^+$= 487; HRMS calculated for $C_{25}H_{29}F_2N_4O_4$ $(M+H)^+$: 487.2151, found: 487.2152.

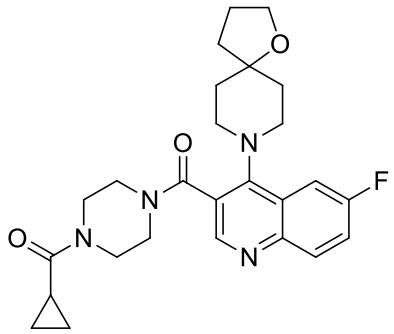
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(6,8-difluoro-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methanone, TFA (36)



36

The title compound was prepared from **11j** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 7.74 (ddd, J = 11.1, 8.9, 2.7 Hz, 1H), 7.55 (dt, J = 10.0, 2.0 Hz, 1H), 3.92 (t, J = 2.2 Hz, 4H), 3.88 – 3.21 (m, 10H), 3.04 (ddd, J = 11.7, 7.2, 3.5 Hz, 2H), 2.07 – 1.62 (m, 5H), 0.74 (d, J = 4.4 Hz, 4H); LC-MS (Method 2): t_R = 4.11 min, m/z $(M+H)^+$= 487; HRMS calculated for $C_{25}H_{29}F_2N_4O_4$ $(M+H)^+$: 487.2151, found: 487.2146.

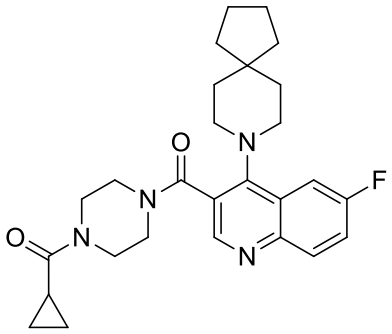
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(6-fluoro-4-(1-oxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methanone, TFA (37)



37

In a microwave tube was placed (4-chloro-6-fluoroquinolin-3-yl)(4-(cyclopropanecarbonyl)piperazin-1-yl)methanone (18.1 mg, 0.05 mmol) and 1-oxa-8-azaspiro[4.5]decane, HCl (53.3 mg, 0.30 mmol). Then, DMF (1 ml) and Hunig's base (0.085 mL, 0.5 mmol) were added. The tube was sealed and heated at 160 °C for 1 h under microwave irradiation. After cooling to rt, the mixture was filtered and submitted for purification by semi-preparative HPLC to give (4-(cyclopropanecarbonyl)piperazin-1-yl)(6-fluoro-4-(1-oxa-8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methanone, TFA (26.3 mg, 0.045 mmol, 91 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.05 (dd, J = 9.1, 5.4 Hz, 1H), 7.83 – 7.69 (m, 2H), 4.34 – 2.96 (m, 14H), 2.09 – 1.57 (m, 9H), 0.74 (d, J = 4.5 Hz, 4H); LC-MS (Method 2): t_R = 3.82 min, m/z $(M+H)^+$= 467; HRMS calculated for $C_{26}H_{32}FN_4O_3$ $(M+H)^+$: 467.2453, found: 467.2447.

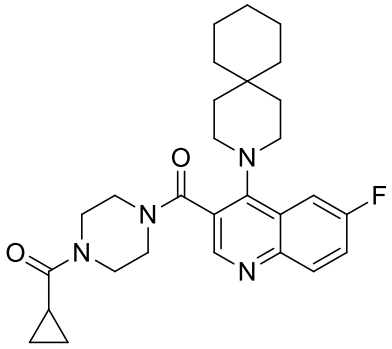
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(6-fluoro-4-(8-azaspiro[4.5]decan-8-yl)quinolin-3-yl)methanone, TFA (38)



38

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.05 (dd, J = 9.1, 5.4 Hz, 1H), 7.77 (t, J = 8.8 Hz, 2H), 4.02 – 2.81 (m, 12H), 2.11 – 0.97 (m, 13H), 0.74 (d, J = 4.6 Hz, 4H); LC-MS (Method 2): t_R = 4.65 min, m/z $(M+H)^+$= 465; HRMS calculated for $C_{27}H_{34}FN_4O_2$ $(M+H)^+$: 465.2660, found: 465.2645.

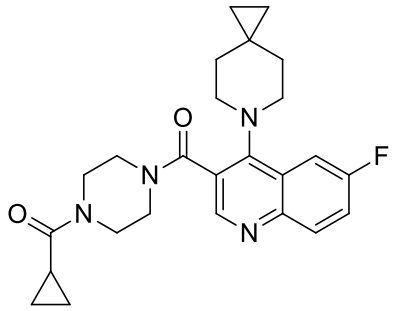
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(6-fluoro-4-(3-azaspiro[5.5]undecan-3-yl)quinolin-3-yl)methanone, TFA (39)



39

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.05 (dd, J = 9.5, 5.4 Hz, 1H), 7.76 (d, J = 9.6 Hz, 2H), 4.21 – 3.01 (m, 12H), 1.96 (m, 2H), 1.77 – 1.50 (m, 5H), 1.42 (s, 8H), 0.74 (d, J = 4.7 Hz, 4H); LC-MS (Method 2): t_R = 4.87 min, m/z $(M+H)^+$= 479; HRMS calculated for $C_{28}H_{36}FN_4O_2$ $(M+H)^+$: 479.2817, found: 479.2832.

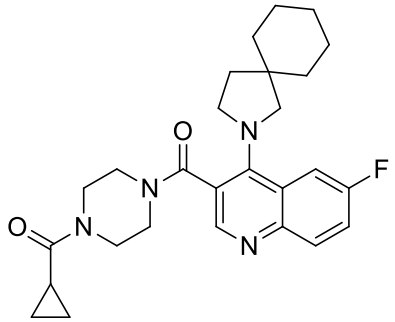
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(6-fluoro-4-(6-azaspiro[2.5]octan-6-yl)quinolin-3-yl)methanone, TFA (40)



40

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.06 (dd, J = 10.0, 5.5 Hz, 1H), 7.78 (d, J = 9.5 Hz, 2H), 4.40 – 3.01 (m, 12H), 1.97 (m, 1H), 1.59 (m, 4H), 0.73 (d, J = 4.6 Hz, 4H), 0.38 (br s, 4H); LC-MS (Method 2): t_R = 4.16 min, m/z $(M+H)^+$= 437; HRMS calculated for $C_{25}H_{29}FN_4O_2Na$ $(M+Na)^+$: 459.2167, found: 459.2182.

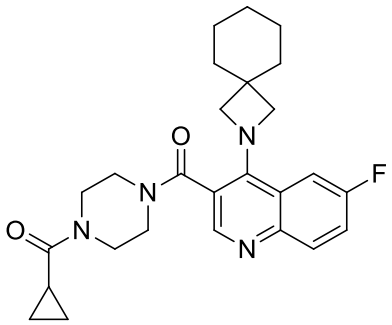
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(6-fluoro-4-(2-azaspiro[4.5]decan-2-yl)quinolin-3-yl)methanone, TFA (41)



41

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.28 (dd, J = 11.1, 2.6 Hz, 1H), 7.93 (dd, J = 9.3, 5.4 Hz, 1H), 7.86 (td, J = 9.4, 8.5, 2.5 Hz, 1H), 3.96-3.30 (m, 12H), 2.00 (s, 1H), 1.85 (s, 2H), 1.57 – 1.29 (m, 10H), 0.75 (q, J = 7.9, 5.5 Hz, 4H); LC-MS (Method 2): t_R = 4.36 min, m/z $(M+H)^+$= 465; HRMS calculated for $C_{27}H_{34}FN_4O_2$ $(M+H)^+$: 465.2660, found: 465.2663.

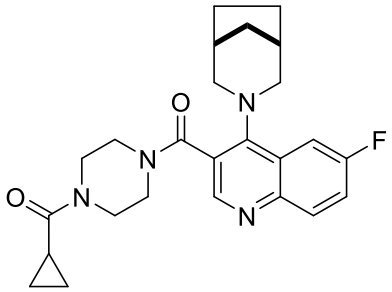
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(6-fluoro-4-(2-azaspiro[3.5]nonan-2-yl)quinolin-3-yl)methanone, TFA (42)



42

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.01 (dd, J = 10.7, 2.6 Hz, 1H), 7.97 – 7.81 (m, 2H), 3.96 – 3.41 (m, 12H), 2.06 – 1.22 (m, 11H), 0.75 (d, J = 4.9 Hz, 4H); LC-MS (Method 2): t_R = 4.27 min, m/z $(M+H)^+$= 451; HRMS calculated for $C_{26}H_{31}FN_4O_2Na$ $(M+Na)^+$: 473.2323, found: 473.2325.

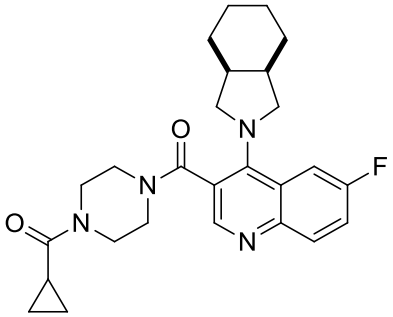
Synthesis of (4-(3-Azabicyclo[3.2.1]octan-3-yl)-6-fluoroquinolin-3-yl)(4-(cyclopropanecarbonyl)piperazin-1-yl)methanone, TFA (43)



43

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.08 (dd, J = 9.2, 5.5 Hz, 1H), 7.99 (dd, J = 10.6, 2.9 Hz, 1H), 7.73 (td, J = 8.6, 2.8 Hz, 1H), 4.19 – 3.16 (m, 10H), 3.08 (d, J = 11.4 Hz, 1H), 2.88 (d, J = 9.9 Hz, 1H), 2.37 – 1.42 (m, 9H), 0.73 (d, J = 4.7 Hz, 4H); LC-MS (Method 2): t_R = 4.18 min, m/z $(M+H)^+$= 437; HRMS calculated for $C_{25}H_{29}FN_4O_2Na$ $(M+Na)^+$: 459.2167, found: 459.2162.

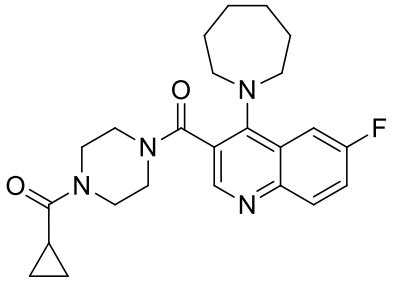
Synthesis of (4-(cyclopropanecarbonyl)piperazin-1-yl)(6-fluoro-4-((cis)-hexahydro-1H-isoindol-2(3H)-yl)quinolin-3-yl)methanone (44)



44

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 1H), 8.08 – 8.00 (m, 1H), 7.88 (dd, J = 9.2, 5.9 Hz, 1H), 7.61 (t, J = 8.2 Hz, 1H), 3.94 – 3.36 (m, 12H), 2.31 – 1.08 (m, 11H), 0.73 (d, J = 4.7 Hz, 4H); LC-MS (Method 2): t_R = 4.03 min, m/z $(M+H)^+$= 451; HRMS calculated for $C_{26}H_{32}FN_4O_2$ $(M+H)^+$: 451.2504, found: 451.2520.

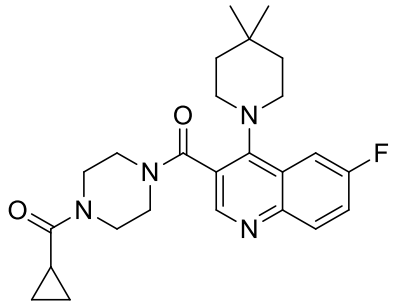
Synthesis of (4-(Azepan-1-yl)-6-fluoroquinolin-3-yl)(4-(cyclopropanecarbonyl)piperazin-1-yl)methanone, TFA (45)



45

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.04 (dd, J = 9.2, 5.4 Hz, 1H), 7.96 (d, J = 10.5 Hz, 1H), 7.80 (d, J = 9.3 Hz, 1H), 3.92 – 3.23 (m, 12H), 2.07 – 1.49 (m, 9H), 0.74 (d, J = 4.6 Hz, 4H); LC-MS (Method 2): t_R = 3.93 min, m/z $(M+H)^+$= 425; HRMS calculated for $C_{24}H_{30}FN_4O_2$ $(M+H)^+$: 425.2347, found: 425.2340.

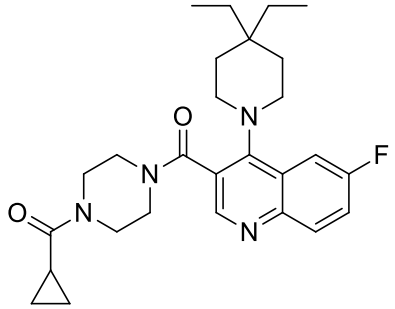
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(4-(4,4-dimethylpiperidin-1-yl)-6-fluoroquinolin-3-yl)methanone, TFA (46)



46

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.05 (dd, J = 9.2, 5.4 Hz, 1H), 7.76 (t, J = 8.7 Hz, 2H), 4.35 – 3.03 (m,12H), 2.13 – 1.17 (m, 5H), 1.01 (s, 6H), 0.74 (d, J = 4.6 Hz, 4H); LC-MS (Method 2): t_R = 4.29 min, m/z $(M+H)^+$= 439; HRMS calculated for $C_{25}H_{32}FN_4O_2$ $(M+H)^+$: 439.2504, found: 439.2516.

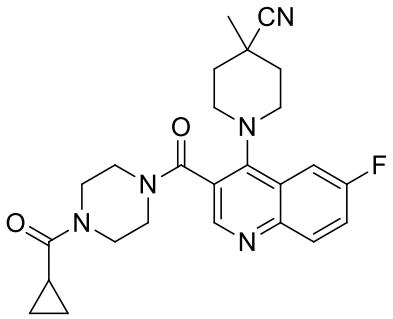
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(4-(4,4-diethylpiperidin-1-yl)-6-fluoroquinolin-3-yl)methanone, TFA (47)



47

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.05 (dd, J = 10.1, 5.4 Hz, 1H), 7.87 – 7.67 (m, 2H), 4.22 – 2.96 (m, 12H), 2.13 – 1.31 (m, 9H), 0.88 – 0.56 (m, 10H); LC-MS (Method 2): t_R = 4.74 min, m/z $(M+H)^+$= 467; HRMS calculated for $C_{27}H_{36}FN_4O_2$ $(M+H)^+$: 467.2817, found: 467.2836.

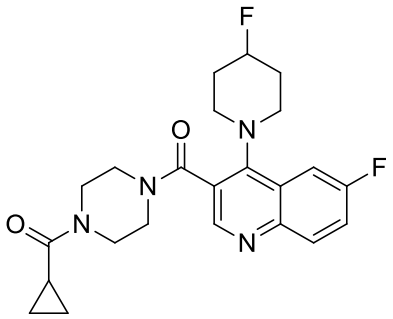
Synthesis of 1-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-6-fluoroquinolin-4-yl)-4-methylpiperidine-4-carbonitrile, TFA (48)



48

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 – 8.58 (m, 1H), 8.07 (dd, J = 10.3, 5.5 Hz, 1H), 7.81 – 7.66 (m, 2H), 4.14 – 2.97 (m, 12H), 2.15 – 1.71 (m, 5H), 1.45 (s, 3H), 0.74 (d, J = 4.7 Hz, 4H); LC-MS (Method 2): t_R = 3.74 min, m/z $(M+H)^+$= 450; HRMS calculated for $C_{25}H_{29}FN_5O_2$ $(M+H)^+$: 450.2300, found: 450.2313.

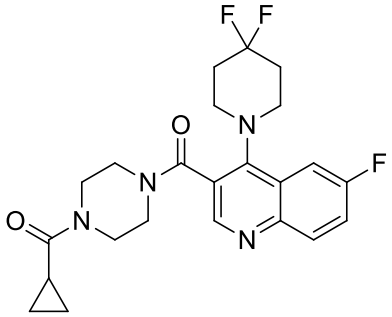
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(6-fluoro-4-(4-fluoropiperidin-1-yl)quinolin-3-yl)methanone, TFA (49)



49

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.07 (dd, J = 10.1, 5.4 Hz, 1H), 7.80 – 7.68 (m, 2H), 4.93 (d, J = 48.4 Hz, 1H), 4.40 – 2.92 (m, 12H), 2.29 – 1.79 (m, 5H), 0.74 (dd, J = 4.8, 2.9 Hz, 4H); LC-MS (Method 2): t_R = 3.61 min, m/z $(M+H)^+$= 429; HRMS calculated for $C_{23}H_{27}F_2N_4O_2$ $(M+H)^+$: 429.2097, found: 429.2114.

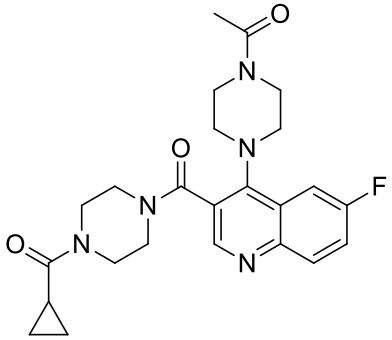
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(4-(4,4-difluoropiperidin-1-yl)-6-fluoroquinolin-3-yl)methanone, TFA (50)



50

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.08 (dd, J = 9.2, 5.5 Hz, 1H), 7.83 (dd, J = 10.4, 2.8 Hz, 1H), 7.73 (t, J = 8.8 Hz, 1H), 4.36 – 2.98 (m, 12H), 2.42 – 1.71 (m, 5H), 0.74 (d, J = 4.6 Hz, 4H); LC-MS (Method 2): t_R = 3.96 min, m/z $(M+H)^+$= 447; HRMS calculated for $C_{23}H_{26}F_3N_4O_2$ $(M+H)^+$: 447.2002, found: 447.2024.

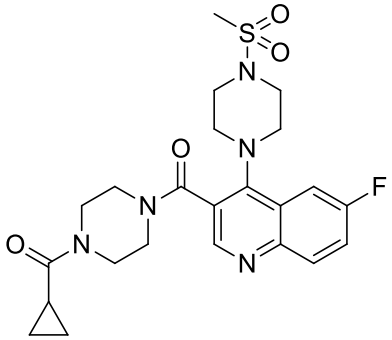
Synthesis of 1-(4-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-6-fluoroquinolin-4-yl)piperazin-1-yl)ethanone, TFA (51)



51

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.07 (dd, J = 9.2, 5.5 Hz, 1H), 7.82 (dd, J = 10.3, 2.8 Hz, 1H), 7.73 (ddd, J = 9.2, 8.2, 2.8 Hz, 1H), 3.91 – 2.88 (m, 16H), 2.03 (s, 3H), 2.02 – 1.83 (m, 1H), 0.72 (d, J = 4.2 Hz, 4H); LC-MS (Method 2): t_R = 2.96 min, m/z $(M+H)^+$= 454; HRMS calculated for $C_{24}H_{29}FN_5O_3$ $(M+H)^+$: 454.2249, found: 454.2227.

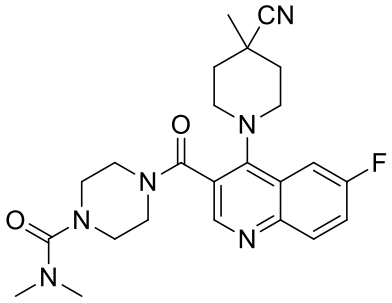
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(6-fluoro-4-(4-(methylsulfonyl)piperazin-1-yl)quinolin-3-yl)methanone, TFA (52)



52

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.08 (dd, J = 9.2, 5.6 Hz, 1H), 7.82 (dd, J = 10.3, 2.9 Hz, 1H), 7.71 (ddd, J = 9.2, 8.2, 2.9 Hz, 1H), 4.21 – 3.00 (m, 16H), 2.96 (s, 3H), 2.10 – 1.84 (m, 1H), 0.72 (d, J = 4.4 Hz, 4H); LC-MS (Method 2): t_R = 3.23 min, m/z $(M+H)^+$= 490; HRMS calculated for $C_{23}H_{29}FN_5O_4S$ $(M+H)^+$: 490.1919, found: 490.1908.

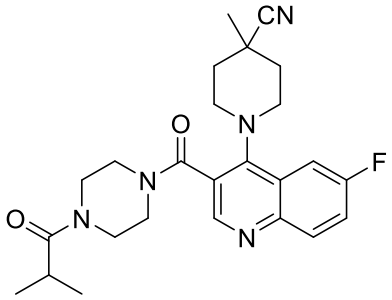
Synthesis of 4-(4-(4-Cyano-4-methylpiperidin-1-yl)-6-fluoroquinoline-3-carbonyl)-*N*,*N*-dimethylpiperazine-1-carboxamide, TFA (53)



53

The title compound was prepared from **12** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.10 – 8.00 (m, 1H), 7.80 – 7.68 (m, 2H), 3.79 – 3.00 (m, 12H), 2.73 (s, 6H), 2.13 – 1.69 (m, 4H), 1.44 (s, 3H); LC-MS (Method 2): t_R = 3.66 min, m/z $(M+H)^+$= 453; HRMS calculated for $C_{24}H_{30}FN_6O_2$ $(M+H)^+$: 453.2409, found: 453.2403.

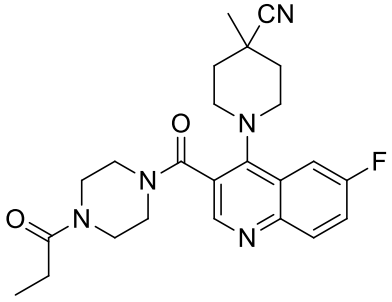
Synthesis of 1-(6-Fluoro-3-(4-isobutyrylpiperazine-1-carbonyl)quinolin-4-yl)-4-methylpiperidine-4-carbonitrile, TFA (54)



54

The title compound was prepared from **12** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.07 (dd, J = 10.2, 5.4 Hz, 1H), 7.85 – 7.57 (m, 2H), 3.90 – 2.71 (m, 13H), 2.18 – 1.69 (m, 4H), 1.45 (s, 3H), 0.98 (q, J = 6.7 Hz, 6H); LC-MS (Method 2): t_R = 3.88 min, m/z $(M+H)^+$= 452; HRMS calculated for $C_{25}H_{30}FN_5O_2Na$ $(M+Na)^+$: 474.2276, found: 474.2292.

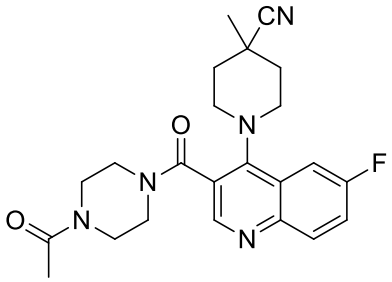
Synthesis of 1-(6-Fluoro-3-(4-propionylpiperazine-1-carbonyl)quinolin-4-yl)-4-methylpiperidine-4-carbonitrile, TFA (55)



55

The title compound was prepared from **12** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, J = 3.0 Hz, 1H), 8.07 (dd, J = 10.2, 5.3 Hz, 1H), 7.74 (d, J = 10.4 Hz, 2H), 3.92 – 2.81 (m, 12H), 2.41 – 2.22 (m, 2H), 2.09 – 1.69 (m, 4H), 1.45 (s, 3H), 0.99 (dd, J = 12.1, 5.6 Hz, 3H); LC-MS (Method 2): t_R = 3.66 min, m/z $(M+H)^+$= 438; HRMS calculated for $C_{24}H_{28}FN_5O_2Na$ $(M+Na)^+$: 460.2119, found: 460.2130.

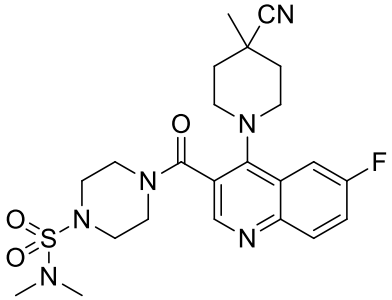
Synthesis of 1-(3-(4-Acetylpiperazine-1-carbonyl)-6-fluoroquinolin-4-yl)-4-methylpiperidine-4-carbonitrile, TFA (56)



56

The title compound was prepared from **12** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 1.6 Hz, 1H), 8.15 – 7.98 (m, 1H), 7.84 – 7.66 (m, 2H), 3.83 – 3.08 (m, 12H), 2.12 – 1.70 (m, 7H), 1.43 (s, 3H); LC-MS (Method 2): t_R = 3.45 min, m/z $(M+H)^+$= 424; HRMS calculated for $C_{23}H_{27}FN_5O_2$ $(M+H)^+$: 424.2143, found: 424.2144.

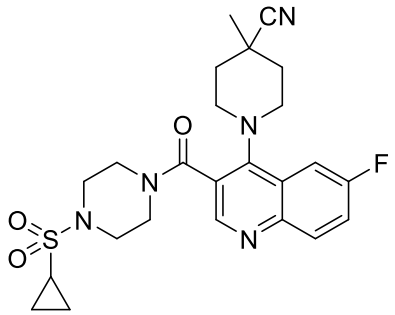
Synthesis of 4-(4-(4-Cyano-4-methylpiperidin-1-yl)-6-fluoroquinoline-3-carbonyl)-*N*,*N*-dimethylpiperazine-1-sulfonamide, TFA (57)



57

The title compound was prepared from **12** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.22 – 7.96 (m, 1H), 7.74 (m, 2H), 3.91 – 3.00 (m, 12H), 2.76 (s, 6H), 2.10 – 1.74 (m, 4H), 1.44 (s, 3H); LC-MS (Method 2): t_R = 4.03 min, m/z $(M+H)^+$= 489; HRMS calculated for $C_{23}H_{30}FN_6O_3S$ $(M+H)^+$: 489.2079, found: 489.2063.

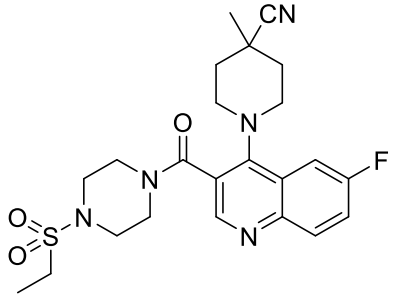
Synthesis of 1-(3-(4-(Cyclopropylsulfonyl)piperazine-1-carbonyl)-6-fluoroquinolin-4-yl)-4-methylpiperidine-4-carbonitrile, TFA (58)



58

The title compound was prepared from **12** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 3.5 Hz, 1H), 8.07 (dd, J = 10.0, 5.6 Hz, 1H), 7.74 (dt, J = 7.8, 2.5 Hz, 2H), 3.95 – 3.03 (m, 12H), 2.62 (ddt, J = 12.5, 8.0, 3.9 Hz, 1H), 2.10 – 1.92 (m, 3H), 1.92 – 1.74 (m, 1H), 1.45 (s, 3H), 1.07 – 0.84 (m, 4H); LC-MS (Method 2): t_R = 4.01 min, m/z $(M+H)^+$= 486; HRMS calculated for $C_{24}H_{29}FN_5O_3S$ $(M+H)^+$: 486.1970, found: 486.1970.

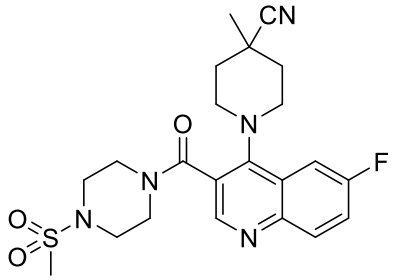
Synthesis of 1-(3-(4-(Ethylsulfonyl)piperazine-1-carbonyl)-6-fluoroquinolin-4-yl)-4-methylpiperidine-4-carbonitrile, TFA (59)



59

The title compound was prepared from **12** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (t, J = 1.5 Hz, 1H), 8.06 (ddd, J = 9.7, 4.4, 2.0 Hz, 1H), 7.74 (t, J = 8.5 Hz, 2H), 3.90 – 3.03 (m, 14H), 2.09 – 1.74 (m, 4H), 1.44 (s, 3H), 1.20 (t, J = 7.4 Hz, 3H); LC-MS (Method 2): t_R = 3.89 min, m/z $(M+H)^+$= 474; HRMS calculated for $C_{23}H_{29}FN_5O_3S$ $(M+H)^+$: 474.1970, found: 474.1957.

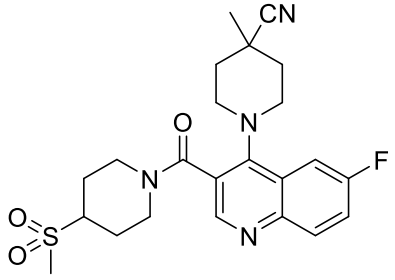
Synthesis of 1-(6-Fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-methylpiperidine-4-carbonitrile, TFA (60)



60

The title compound was prepared from **12** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.07 (dd, J = 10.1, 5.5 Hz, 1H), 7.74 (m, 2H), 3.97 – 3.03 (m, 12H), 2.91 (s, 3H), 2.14 – 1.70 (m, 4H), 1.45 (s, 3H).; LC-MS (Method 2): t_R = 3.72 min, m/z $(M+H)^+$= 460; HRMS calculated for $C_{22}H_{27}FN_5O_3S$ $(M+H)^+$: 460.1813, found: 460.1804.

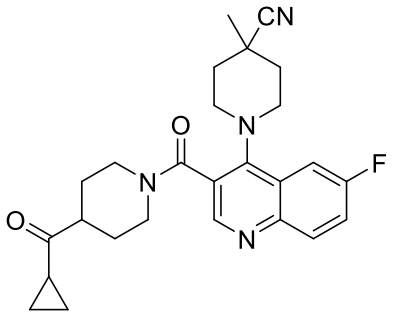
Synthesis of 1-(6-Fluoro-3-(4-(methylsulfonyl)piperidine-1-carbonyl)quinolin-4-yl)-4-methylpiperidine-4-carbonitrile, TFA (61)



61

The title compound was prepared from **12** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (two singlet, rotamers, 1H), 8.12 – 8.00 (m, 1H), 7.75 (t, *J* = 8.9 Hz, 2H), 4.68 (d, *J* = 12.8 Hz, 1H), 3.87 – 2.77 (m, 11H), 2.25 – 1.46 (m, 8H), 1.44 (s, 3H); LC-MS (Method 2): t_R = 3.45 min, m/z $(M+H)^+$= 459; HRMS calculated for $C_{23}H_{28}FN_4O_3S$ $(M+H)^+$: 459.1861, found: 459.1868.

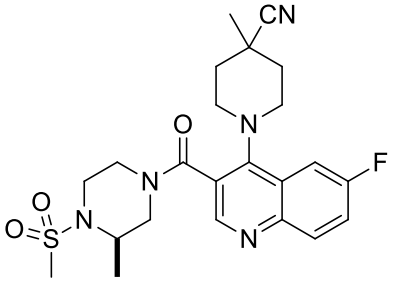
Synthesis of 1-(3-(4-(Cyclopropanecarbonyl)piperidine-1-carbonyl)-6-fluoroquinolin-4-yl)-4-methylpiperidine-4-carbonitrile, TFA (62)



62

The title compound was prepared from **12** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (two singlet due to rotamer, 1H), 8.06 (m, 1H), 7.74 (m, 2H), 4.54 – 4.41 (m, 1H), 3.68 – 2.77 (m, 8H), 2.24 – 2.10 (m, 1H), 2.10 – 1.48 (m, 8H), 1.43 (two singlet due to rotamer, 3H), 0.93 – 0.71 (m, 4H); LC-MS (Method 2): t_R = 4.08 min, m/z $(M+H)^+$= 449; HRMS calculated for $C_{26}H_{30}FN_4O_2$ $(M+H)^+$: 449.2347, found: 449.2341.

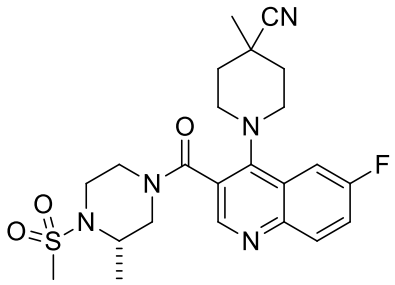
Synthesis of (*R*)-1-(6-Fluoro-3-(3-methyl-4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-methylpiperidine-4-carbonitrile, TFA (63)



63

The title compound was prepared from **12** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 – 8.44 (m, 1H), 8.16 – 7.93 (m, 1H), 7.89 – 7.50 (m, 2H), 4.52 – 2.84 (m, 14H), 2.13 – 1.71 (m, 4H), 1.44 (2 set of s, 3H), 1.32 – 1.03 (m, 3H) (rotamers observed); LC-MS (Method 2): t_R = 3.92 min, m/z $(M+H)^+$= 474; HRMS calculated for $C_{23}H_{29}FN_5O_3S$ $(M+H)^+$: 474.1970, found: 474.1983.

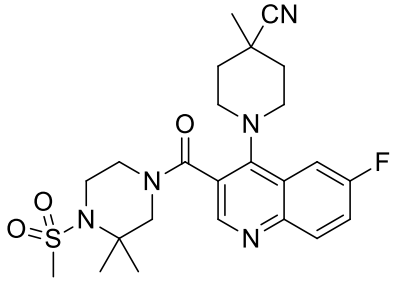
Synthesis of (*S*)-1-(6-Fluoro-3-(3-methyl-4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-methylpiperidine-4-carbonitrile, TFA (64)



64

The title compound was prepared from **12** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 – 8.46 (m, 1H), 8.15 – 7.93 (m, 1H), 7.80 – 7.59 (m, 2H), 4.53 – 3.01 (m, 11H), 3.00 – 2.95 (m, 3H), 2.12 – 1.72 (m, 4H), 1.44 (2 set of s, 3H), 1.33 – 1.02 (m, 3H). (rotamers were observed); LC-MS (Method 2): t_R = 3.89 min, m/z $(M+H)^+$= 474; HRMS calculated for $C_{23}H_{29}FN_5O_3S$ $(M+H)^+$: 474.1970, found: 474.1979.

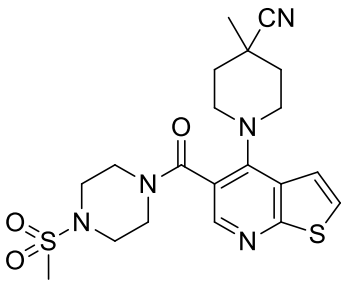
Synthesis of 1-(3-(3,3-Dimethyl-4-(methylsulfonyl)piperazine-1-carbonyl)-6-fluoroquinolin-4-yl)-4-methylpiperidine-4-carbonitrile, TFA (65)



65

The title compound was prepared from **12** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (2 set of s, 1H), 8.06 (m, 1H), 7.73 (m, 2H), 4.04 – 3.02 (m, 10H), 2.99 (s, 3H), 2.08 – 1.69 (m, 4H), 1.53 – 1.39 (m, 6H), 1.32 (2 set of s, 3H). (rotamers were observed); LC-MS (Method 2): t_R = 3.92 min, m/z $(M+H)^+$= 488; HRMS calculated for $C_{24}H_{31}FN_5O_3S$ $(M+H)^+$: 488.2126, found: 488.2139.

Synthesis of 4-Methyl-1-(5-(4-(methylsulfonyl)piperazine-1-carbonyl)thieno[2,3-*b*]pyridin-4-yl)piperidine-4-carbonitrile, TFA (66)



66

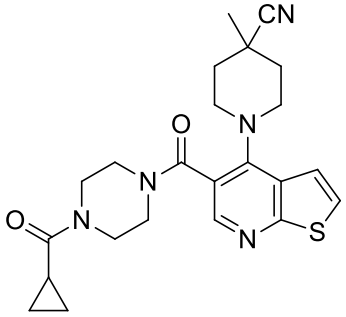
Step 1. Synthesis of ethyl 4-(4-cyano-4-methylpiperidin-1-yl)thieno[2,3-*b*]pyridine-5-carboxylate. In a microwave vial was placed ethyl 4-chlorothieno[2,3-*b*]pyridine-5-carboxylate (**22a**, 242 mg, 1) and 4-methylpiperidine-4-carbonitrile, HCl (241 mg, 1.50 mmol). Then EtOH (3 ml) and Hunig's base (0.53 ml, 3.0 mmol) were added sequentially. The tube was sealed and heated at 80 °C for overnight. After cooling to rt, the mixture was concentrated and purified by silica gel chromatography using 10-40% EtOAc/hexane as the eluent to give ethyl 4-(4-cyano-4-methylpiperidin-1-yl)thieno[2,3-*b*]pyridine-5-carboxylate (325 mg, 0.99 mmol, 99 % yield). LC-MS (Method 1): t_R = 3.15 min, m/z $(M+H)^+$= 330.

Step 2. Synthesis of 4-(4-cyano-4-methylpiperidin-1-yl)thieno[2,3-*b*]pyridine-5-carboxylic acid. To a suspension of ethyl 4-(4-cyano-4-methylpiperidin-1-yl)thieno[2,3-*b*]pyridine-5-carboxylate (325 mg, 0.99 mmol) in THF (5 ml)/MeOH (1 ml) was added $NaOH_{(aq)}$ (1 N, 4 mL) and stirred at 50 °C for overnight. The mixture was added with 1N $HCl_{(aq)}$ until the pH of aqueous layer is about 4. The mixture was concentrated to remove most of the solvent. The resulting solid was triturated with small amount of H_2O (1 mL x 3), hexane (5 mL x 2), and then dried to give 4-(4-cyano-4-methylpiperidin-1-yl)thieno[2,3-*b*]pyridine-5-carboxylic acid (270 mg, 0.896 mmol, 91 % yield). This material was used for next step without further purification.

Step 3. Synthesis of 4-methyl-1-(5-(4-(methylsulfonyl)piperazine-1-carbonyl)thieno[2,3-*b*]pyridin-4-yl)piperidine-4-carbonitrile, TFA (**66**). To a mixture of 4-(4-cyano-4-methylpiperidin-1-yl)thieno[2,3-*b*]pyridine-5-carboxylic acid (15.1 mg, 0.05 mmol), 1-(methylsulfonyl)piperazine (24.63 mg, 0.15 mmol), and HATU (76 mg, 0.20 mmol) was added DMF (1 ml) and then Hunig's base (0.052 ml, 0.30 mmol). The mixture was stirred at rt for 2 h. The mixture was filtered and submitted for purification by semi-preparative HPLC to give 4-methyl-1-(5-(4-(methylsulfonyl)piperazine-1-carbonyl)thieno[2,3-*b*]pyridin-4-yl)piperidine-4-carbonitrile, TFA (8 mg, 0.014 mmol, 28.5 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.79 (d, *J* = 6.1 Hz, 1H), 7.41 (d, *J* = 6.1 Hz, 1H), 4.03 – 2.99 (m, 12H), 2.88 (s, 3H), 2.02 –

1.59 (m, 4H), 1.40 (s, 3H); LC-MS (Method 2): t_R = 3.86 min, m/z $(M+H)^+$= 448; HRMS calculated for $C_{20}H_{26}N_5O_3S_2$ $(M+H)^+$: 448.1472, found: 448.1483.

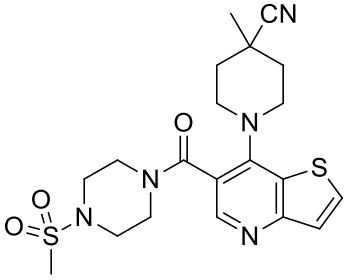
Synthesis of 1-(5-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)thieno[2,3-b]pyridin-4-yl)-4-methylpiperidine-4-carbonitrile, TFA (67)



67

The title compound was prepared from **22a** following the similar procedure as described in the synthesis of **66**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.79 (d, J = 6.1 Hz, 1H), 7.41 (d, J = 6.1 Hz, 1H), 4.23 – 3.08 (m, 12H), 2.05 – 1.54 (m, 5H), 1.40 (s, 3H), 0.71 (dd, J = 5.6, 2.8 Hz, 4H); LC-MS (Method 2): t_R = 3.85 min, m/z $(M+H)^+$= 438; HRMS calculated for $C_{23}H_{27}N_5O_2SNa$ $(M+Na)^+$: 460.1778, found: 460.1788.

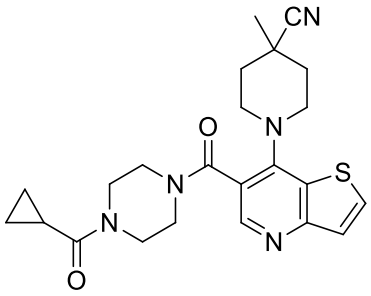
Synthesis of 4-Methyl-1-(6-(4-(methylsulfonyl)piperazine-1-carbonyl)thieno[3,2-b]pyridin-7-yl)piperidine-4-carbonitrile, TFA (68)



68

The title compound was prepared from **22b** following the similar procedure as described in the synthesis of **66**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.28 (d, J = 5.6 Hz, 1H), 7.54 (d, J = 5.6 Hz, 1H), 3.99 – 3.12 (m, 10H), 3.07 (t, J = 5.1 Hz, 2H), 2.89 (s, 3H), 2.07 –2.04 (m, 2H), 1.77 –1.59 (m, 2H), 1.41 (s, 3H); LC-MS (Method 2): t_R = 3.26 min, m/z $(M+H)^+$= 448; HRMS calculated for $C_{20}H_{26}N_5O_3S_2$ $(M+H)^+$: 448.1472, found: 448.1480.

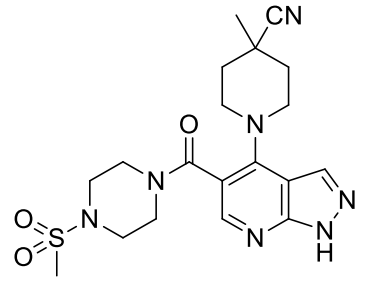
Synthesis of 1-(6-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)thieno[3,2-b]pyridin-7-yl)-4-methylpiperidine-4-carbonitrile, TFA (69)



69

The title compound was prepared from **22b** following the similar procedure as described in the synthesis of **66**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.27 (d, J = 5.6 Hz, 1H), 7.53 (d, J = 5.6 Hz, 1H), 3.95 – 3.15 (m, 12H), 2.11 – 1.82 (m, 3H), 1.77-1.59 (m, 2H), 1.41 (s, 3H), 0.72 (dd, J = 4.6, 1.8 Hz, 4H).; LC-MS (Method 2): t_R = 3.49 min, m/z $(M+H)^+$= 438; HRMS calculated for $C_{23}H_{28}N_5O_2S$ $(M+H)^+$: 438.1958, found: 438.1972.

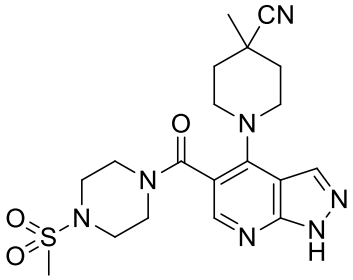
Synthesis of 4-Methyl-1-(5-(4-(methylsulfonyl)piperazine-1-carbonyl)-1H-pyrazolo[3,4-b]pyridin-4-yl)piperidine-4-carbonitrile, TFA (70)



70

The title compound was prepared from **22c** following the similar procedure as described in the synthesis of **66**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.71 – 13.49 (m, 1H), 8.22 (d, J = 1.5 Hz, 1H), 8.04 (s, 1H), 4.02 (d, J = 13.5 Hz, 1H), 3.81 (d, J = 13.4 Hz, 1H), 3.71 (d, J = 13.9 Hz, 1H), 3.47 (t, J = 10.6 Hz, 1H), 3.38-3.20 (m, 4H), 3.17 – 2.90 (m, 4H), 2.87 (s, 3H), 1.99 (d, J = 13.5 Hz, 2H), 1.83 – 1.55 (m, 2H), 1.40 (s, 3H).; LC-MS (Method 2): t_R = 2.95 min, m/z $(M+H)^+$= 432; HRMS calculated for $C_{19}H_{26}N_7O_3S$ $(M+H)^+$: 432.1812, found: 432.1824.

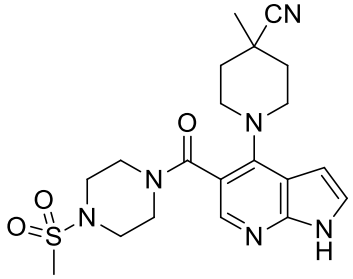
Synthesis of 4-Methyl-1-(5-(4-(methylsulfonyl)piperazine-1-carbonyl)-1H-pyrazolo[3,4-b]pyridin-4-yl)piperidine-4-carbonitrile, TFA (71)



71

The title compound was prepared from **22d** following the similar procedure as described in the synthesis of **66**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 8.08 (s, 1H), 4.04-4.01 (m, 2H), 3.94 (s, 3H), 3.86 – 2.88 (m, 10H), 2.87 (s, 3H), 2.01-1.97 (m, 2H), 1.72-1.57 (m, 2H), 1.40 (s, 3H); LC-MS (Method 2): t_R = 3.48 min, m/z $(M+H)^+$= 446; HRMS calculated for $C_{20}H_{28}N_7O_3S$ $(M+H)^+$: 446.1969, found: 446.1982.

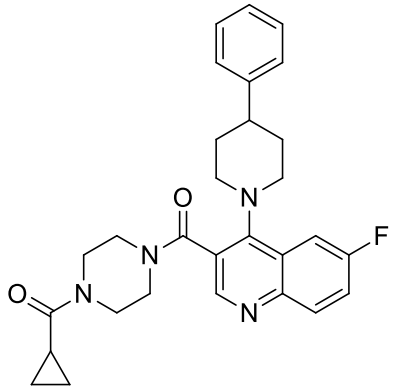
Synthesis of 4-Methyl-1-(5-(4-(methylsulfonyl)piperazine-1-carbonyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)piperidine-4-carbonitrile (72)



72

The title compound was prepared from **23** following the similar procedure as described in the synthesis of **66**. The crude product was purified by silica gel chromatography using 0-10% MeOH/EtOAc as the eluent to give compound **72**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.64 (t, J = 2.3 Hz, 1H), 7.86 (s, 1H), 7.33 (dd, J = 3.6, 2.5 Hz, 1H), 6.52 (dd, J = 3.6, 1.9 Hz, 1H), 4.13 – 2.88 (m, 12H), 2.86 (s, 3H), 2.02 – 1.50 (m, 4H), 1.39 (s, 3H); LC-MS (Method 2): t_R = 3.22 min, m/z $(M+H)^+$= 431; HRMS calculated for $C_{20}H_{27}N_6O_3S$ $(M+H)^+$: 431.1860, found: 431.1866.

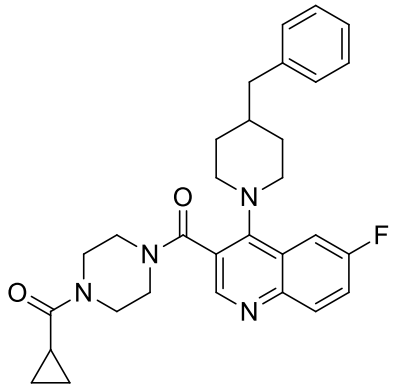
Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(6-fluoro-4-(4-phenylpiperidin-1-yl)quinolin-3-yl)methanone, TFA (73)



73

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.07 (dd, J = 9.2, 5.4 Hz, 1H), 7.84 (d, J = 10.2 Hz, 1H), 7.78 (s, 1H), 7.41 – 7.26 (m, 4H), 7.25 – 7.16 (m, 1H), 3.98 – 3.24 (m, 11H), 3.16 (m, 1H), 2.81 (s, 1H), 2.17 – 1.78 (m, 5H), 0.74 (dd, J = 4.7, 2.9 Hz, 4H); LC-MS (Method 2): t_R = 4.58 min, m/z $(M+H)^+$= 487; HRMS calculated for $C_{29}H_{32}FN_4O_2$ $(M+H)^+$: 487.2504, found: 487.2508.

Synthesis of (4-(4-Benzylpiperidin-1-yl)-6-fluoroquinolin-3-yl)(4-(cyclopropanecarbonyl)piperazin-1-yl)methanone, TFA (74)

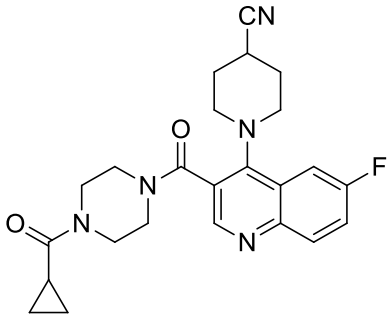


74

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.03 (dd, J = 9.2, 5.5 Hz, 1H), 7.80 – 7.63 (m, 2H), 7.33 – 7.11 (m, 5H), 3.92 – 2.84 (m, 12H), 2.60 (t, J = 7.8 Hz, 2H),

2.07 – 1.30 (m, 6H), 0.71 (d, J = 4.9 Hz, 4H); LC-MS (Method 2): t_R = 4.86 min, m/z $(M+H)^+$= 501; HRMS calculated for $C_{30}H_{34}FN_4O_2$ $(M+H)^+$: 501.2660, found: 501.2683.

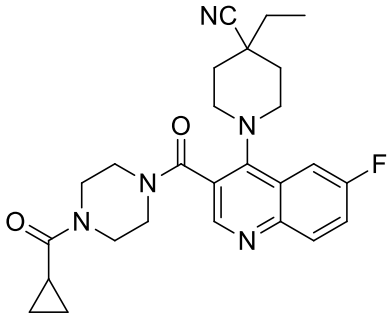
Synthesis of 1-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-6-fluoroquinolin-4-yl)piperidine-4-carbonitrile, TFA (75)



75

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.13 – 7.97 (m, 1H), 7.80 – 7.61 (m, 2H), 3.89 – 2.92 (m, 13H), 2.21 – 1.79 (m, 5H), 0.79 – 0.60 (m, 4H); LC-MS (Method 2): t_R = 3.32 min, m/z $(M+H)^+$= 436; HRMS calculated for $C_{24}H_{26}FN_5O_2Na$ $(M+Na)^+$: 458.1963, found: 458.1962.

Synthesis of 1-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-6-fluoroquinolin-4-yl)-4-ethylpiperidine-4-carbonitrile, TFA (76)

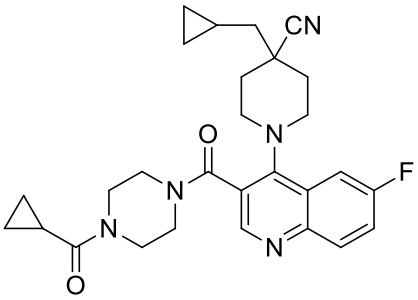


76

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.05 (dd, J = 10.1, 5.5 Hz, 1H), 7.82 – 7.59 (m, 2H), 3.97 – 2.97 (m, 12H), 2.13 – 1.59 (m, 7H), 1.02 (t, J = 7.4 Hz, 3H),

0.73 – 0.71 (m, 4H); LC-MS (Method 2): t_R = 4.08 min, m/z $(M+H)^+$= 464; HRMS calculated for $C_{26}H_{31}FN_5O_2$ $(M+H)^+$: 464.2456, found: 464.2477.

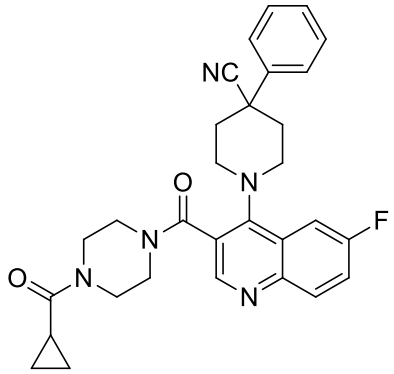
Synthesis of 1-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-6-fluoroquinolin-4-yl)-4-(cyclopropylmethyl)piperidine-4-carbonitrile, TFA (77)



77

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.06 (dd, J = 10.1, 5.5 Hz, 1H), 7.77 – 7.59 (m, 2H), 3.89 – 2.99 (m, 12H), 2.19 – 1.74 (m, 5H), 1.62 (d, J = 6.9 Hz, 2H), 0.87 – 0.84 (m, 1H), 0.77 – 0.60 (m, 4H), 0.58 – 0.43 (m, 2H), 0.21 – 0.18 (m, 2H); LC-MS (Method 2): t_R = 4.31 min, m/z $(M+H)^+$= 490; HRMS calculated for $C_{28}H_{33}FN_5O_2$ $(M+H)^+$: 490.2613, found: 490.2626.

Synthesis of 1-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-6-fluoroquinolin-4-yl)-4-phenylpiperidine-4-carbonitrile, TFA (78)

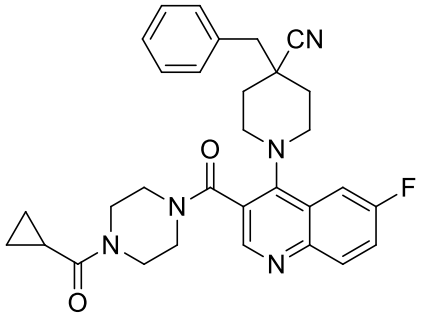


78

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.07 (dd, J = 9.2, 5.5 Hz,

1H), 7.89 (d, *J* = 10.1 Hz, 1H), 7.73 (t, *J* = 8.9 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.51 – 7.43 (m, 2H), 7.42 – 7.35 (m, 1H), 3.95 – 3.24 (m, 12H), 2.60 – 1.81 (m, 5H), 0.72 (d, *J* = 4.9 Hz, 4H); LC-MS (Method 2): t_R = 4.45 min, m/z $(M+H)^+$= 512; HRMS calculated for $C_{30}H_{31}FN_5O_2$ $(M+H)^+$: 512.2456, found: 512.2470.

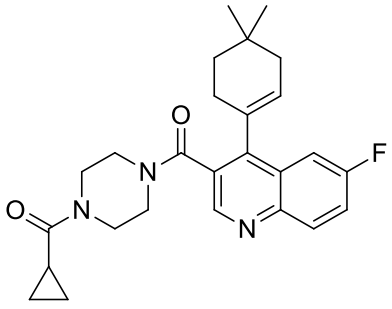
Synthesis of 4-Benzyl-1-(3-(4-(cyclopropanecarbonyl)piperazine-1-carbonyl)-6-fluoroquinolin-4-yl)piperidine-4-carbonitrile, TFA (79)



79

The title compound was prepared from **17** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.05 (dd, *J* = 9.1, 5.6 Hz, 1H), 7.75 – 7.62 (m, 2H), 7.39 – 7.22 (m, 5H), 3.78-3.00 (m, 14H), 2.21 – 1.78 (m, 5H), 0.70 (s, 4H); LC-MS (Method 2): t_R = 4.61 min, m/z $(M+H)^+$= 526; HRMS calculated for $C_{31}H_{33}FN_5O_2$ $(M+H)^+$: 526.2613, found: 526.2627.

Synthesis of (4-(Cyclopropanecarbonyl)piperazin-1-yl)(4-(4,4-dimethylcyclohex-1-en-1-yl)-6-fluoroquinolin-3-yl)methanone (80)



80

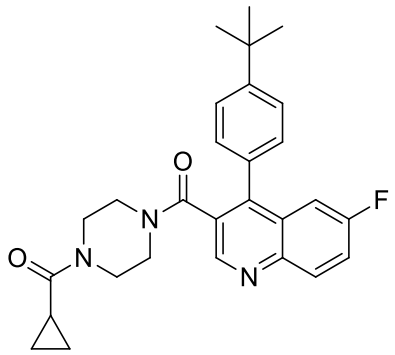
Step 1. Synthesis of ethyl 4-(4,4-dimethylcyclohex-1-en-1-yl)-6-fluoroquinoline-3-carboxylate. In a microwave tube was placed ethyl 4-bromo-6-fluoroquinoline-3-carboxylate

(426 mg, 1 mmol), 2-(4,4-dimethylcyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (236 mg, 1.0 mmol), $PdCl_2$(dppf) (73.2 mg, 0.10 mmol), and K_2CO_3 (415 mg, 3.0 mmol). The tube was then sealed. The air was removed and re-filled with N_2 (3 times). Then, a mixture of 1,4-dioxane (3 ml)/water (1.5 ml) was added and the mixture was heated (pre-heated oil bath) at 95 °C for 3 h. The mixture was poured into EtOAc/H_2O (15 mL/15 mL). The aqueous layer was extracted with EtOAc (10 mL x 2). The combined organic layer was dried (Na_2SO_4), and filtered. After removal of solvent, the product was purified by silica gel chromatography using 15-30% EtOAc/hexane as the eluent to give ethyl 4-(4,4-dimethylcyclohex-1-en-1-yl)-6-fluoroquinoline-3-carboxylate (253 mg, 0.77 mmol, 77 % yield) as a white solid. LC-MS (Method 1): t_R = 3.98 min, m/z $(M+H)^+$= 328.

Step 2. Synthesis of 4-(4,4-dimethylcyclohex-1-en-1-yl)-6-fluoroquinoline-3-carboxylic acid. To a solution of ethyl 4-(4,4-dimethylcyclohex-1-en-1-yl)-6-fluoroquinoline-3-carboxylate (253 mg, 0.77 mmol) in THF (2 ml)/MeOH (0.5 ml) was added $NaOH_{(aq)}$ (1 N in H_2O, 1 mL, 1 mmol). The mixture was heated to 50 °C and stirred for 3 h. After cooling to rt, 1N $HCl_{(aq)}$ (ca.1 mL) was added . Then, hexane (10 mL) was added. The white solid was filtered, triturated with hexane (3 mL) and dried to give product 4-(4,4-dimethylcyclohex-1-en-1-yl)-6-fluoroquinoline-3-carboxylic acid (215 mg, 0.718 mmol, 93 % yield), which was used without further purification. LC-MS (Method 1): t_R = 3.46 min, m/z $(M+H)^+$= 300.

Step 3. Synthesis of (4-(cyclopropanecarbonyl)piperazin-1-yl)(4-(4,4-dimethylcyclohex-1-en-1-yl)-6-fluoroquinolin-3-yl)methanone (**80**). To a mixture of 4-(4,4-dimethylcyclohex-1-en-1-yl)-6-fluoroquinoline-3-carboxylic acid (90 mg, 0.3 mmol), cyclopropyl(piperazin-1-yl)methanone, HCl (86 mg, 0.45 mmol), and HATU (228 mg, 0.60 mmol) was added DMF (1 ml) and then Hunig's base (0.21 ml, 1.20 mmol). The mixture was stirred at rt for 1.5 h. The mixture was poured into EtOAc/H_2O (20 mL/20 mL). The organic layer was washed with H_2O (20 mL), dried (Na_2SO_4), and filtered. After removal of solvent, the product was purified by silica gel chromatography using 80-100 EtOAc/hexane as the eluent to give (4-(cyclopropanecarbonyl)piperazin-1-yl)(4-(4,4-dimethylcyclohex-1-en-1-yl)-6-fluoroquinolin-3-yl)methanone (113 mg, 0.259 mmol, 86 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 8.12 (dd, *J* = 10.1, 5.4 Hz, 1H), 7.57 – 7.44 (m, 2H), 5.60 (s, 1H), 4.06 – 2.99 (m, 8H), 2.61 – 1.81 (m, 4H), 1.17 – 0.65 (m, 13H); LC-MS (Method 2): t_R = 5.50 min, m/z $(M+H)^+$= 436; HRMS calculated for $C_{26}H_{31}FN_3O_2$ $(M+H)^+$: 436.2395, found: 436.2391.

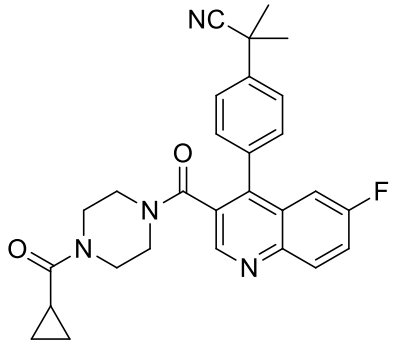
Synthesis of (4-(4-(tert-Butyl)phenyl)-6-fluoroquinolin-3-yl)(4-(cyclopropanecarbonyl)piperazin-1-yl)methanone, TFA (81)



81

The title compound was prepared from **19** following the similar procedure as described in the synthesis of **80**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.21 (dd, *J* = 9.2, 5.6 Hz, 1H), 7.77 (td, *J* = 8.7, 2.9 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.41 (dd, *J* = 10.3, 2.8 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 4.00-1.75 (m, 9H), 1.31 (s, 9H), 0.64 (s, 4H); LC-MS (Method 2): t_R = 5.71 min, m/z $(M+H)^+$= 460; HRMS calculated for $C_{28}H_{31}FN_3O_2$ $(M+H)^+$: 460.2395, found: 460.2415.

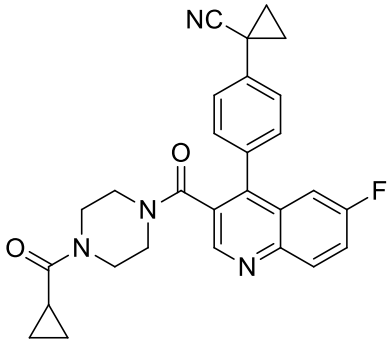
Synthesis of 2-(4-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-6-fluoroquinolin-4-yl)phenyl)-2-methylpropanenitrile, TFA (82)



82

The title compound was prepared from **19** following the similar procedure as described in the synthesis of **80**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.21 (dd, *J* = 9.3, 5.6 Hz, 1H), 7.77 (ddd, *J* = 9.3, 8.2, 2.9 Hz, 1H), 7.71 (d, *J* = 7.2 Hz, 2H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.32 (dd, *J* = 10.2, 2.8 Hz, 1H), 3.88 – 2.31 (m, 8H), 1.94 – 1.74 (m, 1H), 1.71 (s, 6H), 0.64 (d, *J* = 7.9 Hz, 4H); LC-MS (Method 2): t_R = 4.82 min, m/z $(M+H)^+$= 471; HRMS calculated for $C_{28}H_{28}FN_4O_2$ $(M+H)^+$: 471.2191, found: 471.2198.

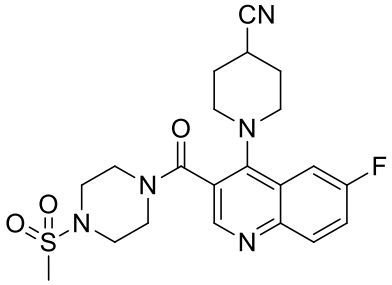
Synthesis of 1-(4-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-6-fluoroquinolin-4-yl)phenyl)cyclopropanecarbonitrile, TFA (83)



83

The title compound was prepared from **19** following the similar procedure as described in the synthesis of **80**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.20 (dd, J = 9.3, 5.6 Hz, 1H), 7.76 (ddd, J = 9.2, 8.2, 2.9 Hz, 1H), 7.50 – 7.40 (d, J = 42.8 Hz, 4H), 7.26 (dd, J = 10.2, 2.9 Hz, 1H), 3.72 – 2.65 (m, 8H), 1.96 – 1.85 (m, 1H), 1.85 – 1.79 (m, 2H), 1.62 – 1.54 (m, 2H), 0.67 – 0.65 (m, 4H); LC-MS (Method 2): t_R = 4.67 min, m/z $(M+H)^+$= 469; HRMS calculated for $C_{28}H_{26}FN_4O_2$ $(M+H)^+$: 469.2034, found: 469.2049.

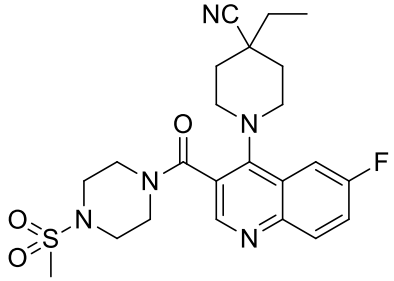
Synthesis of 1-(6-Fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)piperidine-4-carbonitrile, TFA (84)



84

The title compound was prepared from **18a** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.13 – 7.93 (m, 1H), 7.80 – 7.62 (m, 2H), 3.92 (dt, J = 13.3, 4.7 Hz, 1H), 3.63 (ddd, J = 12.5, 7.3, 3.9 Hz, 1H), 3.54 – 3.34 (m, 2H), 3.32 – 2.94 (m, 9H), 2.91 (s, 3H), 2.20 – 1.83 (m, 4H); LC-MS (Method 2): t_R = 3.26 min, m/z $(M+H)^+$= 446; HRMS calculated for $C_{21}H_{25}FN_5O_3S$ $(M+H)^+$: 446.1657, found: 446.1669.

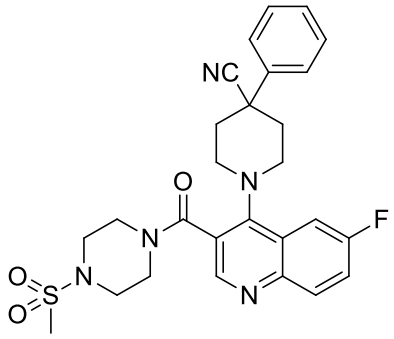
Synthesis of 4-Ethyl-1-(6-fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)piperidine-4-carbonitrile, TFA (85)



85

The title compound was prepared from **18a** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, J = 3.7 Hz, 1H), 8.05 (dd, J = 10.0, 5.5 Hz, 1H), 7.77 – 7.63 (m, 2H), 3.97 – 3.01 (m, 12H), 2.90 (s, 3H), 2.10 – 1.75 (m, 4H), 1.71 (q, J = 7.4 Hz, 2H), 1.03 (t, J = 7.4 Hz, 3H); LC-MS (Method 2): t_R = 4.11 min, m/z $(M+H)^+$= 474; HRMS calculated for $C_{27}H_{32}FN_4O_3S$ $(M+H)^+$: 511.2174, found: 511.2182.

Synthesis of 1-(6-Fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-phenylpiperidine-4-carbonitrile, TFA (86)



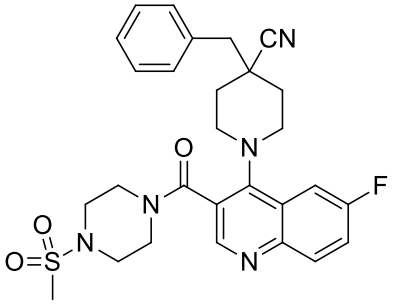
86

The title compound was prepared from **18a** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (d, J = 3.4 Hz, 1H), 8.07 (dd, J = 9.2, 5.5 Hz, 1H), 7.89 (dd, J = 10.2, 2.8 Hz, 1H), 7.73 (td, J = 8.8, 2.8 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.52 – 7.43 (m, 2H), 7.43 – 7.35 (m, 1H), 3.96 – 2.97 (m, 12H), 2.90 (s, 3H), 2.57-2.21 (m, 4H); LC-MS (Method 2): t_R = 4.44 min, m/z $(M+H)^+$= 522; HRMS calculated for $C_{27}H_{29}FN_5O_3S$ $(M+H)^+$: 522.1970, found: 522.1971.

Alternatively, compound **86** can be prepared from **13f** following the similar procedure as described in the synthesis of **27**. The product was purified by silica gel chromatography using 0-10% MeOH/EtOAc as the eluent to give 1-(6-fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-phenylpiperidine-4-carbonitrile (free base). ^{1}H NMR (400 MHz, DMSO-d_6) (free base) δ 8.58 (s, 1H), 8.06 (dd, J = 9.2, 5.6 Hz, 1H), 7.86 (dd, J = 10.3, 2.9 Hz, 1H), 7.73 – 7.63 (m, 3H), 7.52 – 7.43 (m, 2H), 7.42 – 7.34 (m, 1H), 3.99 – 3.85 (m, 1H), 3.71 (ddd, J = 13.1, 6.3, 4.4 Hz, 1H), 3.63 – 3.05 (m, 10H), 2.90 (s, 3H), 2.56 – 2.14 (m, 4H).

To a solution of 1-(6-fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-phenylpiperidine-4-carbonitrile (1.93 g, 3.70 mmol) in CH_2Cl_2 (10 ml) was added HCl (4M in dioxane, 1.85 mL, 7.4 mmol, 2 equiv). The mixture was stirred at rt for 30 min. Then hexane (2 mL) was added dropwise. Once the solid was formed, hexane (30 mL) was added and stirred for another 15 min. The solid was filtered and washed with hexane (3 mL x 2). The solid was transfer into a vial and dried in vacuo to give 1-(6-fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-phenylpiperidine-4-carbonitrile, HCl (2.0 g, 3.6 mmol, 97 % yield) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) (HCl salt) δ 8.83 (s, 1H), 8.21 (dd, J = 9.3, 5.2 Hz, 1H), 7.98 (dd, J = 10.1, 2.8 Hz, 1H), 7.92 – 7.83 (m, 1H), 7.69 – 7.58 (m, 2H), 7.53 – 7.44 (m, 2H), 7.43 – 7.34 (m, 1H), 3.91 – 3.01 (m, 12H), 2.91 (s, 3H), 2.61 (td, J = 13.0, 4.0 Hz, 1H), 2.37 – 2.20 (m, 3H).

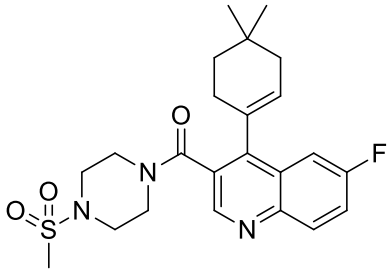
Synthesis of 4-Benzyl-1-(6-fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)piperidine-4-carbonitrile, TFA (87)



87

The title compound was prepared from **18a** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.05 (dd, J = 9.1, 5.5 Hz, 1H), 7.75 – 7.63 (m, 2H), 7.40 – 7.20 (m, 5H), 3.83-3.01 (m, 14H), 2.87 (s, 3H), 2.19 – 1.79 (m, 4H); LC-MS (Method 2): t_R = 4.75 min, m/z $(M+H)^+$= 536; HRMS calculated for $C_{28}H_{31}FN_5O_3S$ $(M+H)^+$: 536.2126, found: 536.2148.

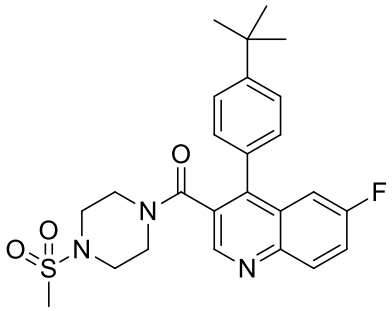
Synthesis of (4-(4,4-Dimethylcyclohex-1-en-1-yl)-6-fluoroquinolin-3-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone, TFA (88)



88

In a 2-neck flask was placed (4-bromo-6-fluoroquinolin-3-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone (**18b**, 20.81 mg, 0.05 mmol), 2-(4,4-dimethylcyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (23.62 mg, 0.10 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (8.17 mg, 10.0 µmol), and K_2CO_3 (69.1 mg, 0.50 mmol). The air was removed and re-filled with N_2 (2-3 times). Then a mixture of 1,4-dioxane (1 ml)/water (0.5 ml) was added and stirred at 90 °C (pre-heated) for 1 h. The organic layer was separated and filtered through a PL-Thiol MP-resin with Na_2SO_4, and then eluted with EtOAc. After removal of solvent, the crude product dissolved in DMF, filtered, and submitted for purification by semi-preparative HPLC to give (4-(4,4-dimethylcyclohex-1-en-1-yl)-6-fluoroquinolin-3-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone, TFA (2.3 mg, 4.11 µmol, 8.2 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.13 (dd, J = 9.2, 5.6 Hz, 1H), 7.72 (ddd, J = 9.3, 8.3, 2.9 Hz, 1H), 7.57 – 7.41 (m, 1H), 5.66 (t, J = 3.7 Hz, 1H), 4.00 – 2.92 (m, 8H), 2.89 (s, 3H), 2.37 – 1.28 (m, 6H), 1.01 (s, 3H), 0.93 (s, 3H); LC-MS (Method 2): t_R = 5.44 min, m/z $(M+H)^+$= 446; HRMS calculated for $C_{23}H_{28}FN_3O_3SNa$ $(M+Na)^+$: 468.1728, found: 468.1731.

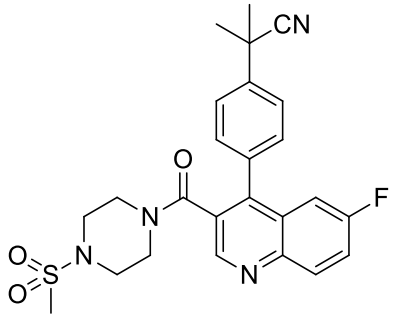
Synthesis of (4-(4-(tert-Butyl)phenyl)-6-fluoroquinolin-3-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone, TFA (89)



89

The title compound was prepared from **18b** following the similar procedure as described in the synthesis of **88**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.20 (dd, J = 9.2, 5.6 Hz, 1H), 7.76 (ddd, J = 9.2, 8.2, 2.9 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.36 – 7.23 (m, 2H), 3.65 – 2.89 (m, 7H), 2.74 (s, 3H), 2.13 (t, J = 8.4 Hz, 1H), 1.32 (s, 9H); LC-MS (Method 2): t_R = 5.69 min, m/z $(M+H)^+$= 470; HRMS calculated for $C_{25}H_{29}FN_3O_3S$ $(M+H)^+$: 470.1908, found: 470.1922.

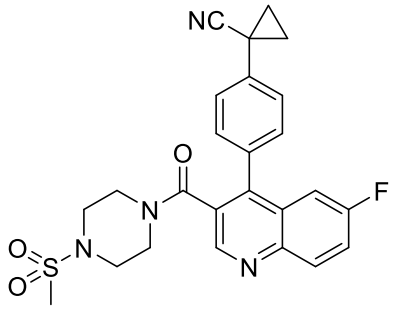
Synthesis of 2-(4-(6-Fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)phenyl)-2-methylpropanenitrile, TFA (90)



90

The title compound was prepared from **18b** following the similar procedure as described in the synthesis of **88**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.21 (dd, J = 9.2, 5.6 Hz, 1H), 7.84 – 7.72 (m, 2H), 7.70 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.27 (dd, J = 10.2, 2.8 Hz, 1H), 3.79 – 2.91 (m, 6H), 2.76 (s, 3H), 2.55 – 2.47 (m, 1H), 2.25 – 2.11 (m, 1H), 1.74 (s, 6H); LC-MS (Method 2): t_R = 4.85 min, m/z $(M+H)^+$= 481; HRMS calculated for $C_{25}H_{25}FN_4O_3SNa$ $(M+Na)^+$: 503.1524, found: 503.1541.

Synthesis of 1-(4-(6-Fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)phenyl)cyclopropanecarbonitrile, TFA (91)

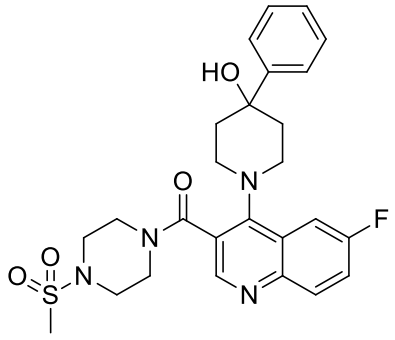


91

The title compound was prepared from **18b** following the similar procedure as described in the synthesis of **88**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.21 (dd, *J* = 9.2, 5.6 Hz, 1H), 7.77 (ddd, *J* = 9.3, 8.2, 2.9 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.28 (dd, *J* = 10.2, 2.8 Hz, 1H), 3.67 – 2.86 (m, 6H), 2.75 (s, 3H), 2.53 (d, *J* = 9.0 Hz, 1H), 2.09 (d, *J* = 9.4 Hz, 1H), 1.82 (q, *J* = 4.1 Hz, 2H), 1.67 – 1.58 (m, 2H); LC-MS (Method 2): t_R = 4.71 min, m/z $(M+H)^+$= 479; HRMS calculated for $C_{25}H_{24}FN_4O_3S$ $(M+H)^+$: 479.1548, found: 479.1562.

Alternatively, compound **91** can be prepared from **21a** following the similar procedure as described in the synthesis of **117**. The product was purified by silica gel chromatography using 0-10% MeOH/EtOAc as the eluent to give 1-(4-(6-Fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)phenyl)cyclopropanecarbonitrile.

Synthesis of (6-Fluoro-4-(4-hydroxy-4-phenylpiperidin-1-yl)quinolin-3-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone, TFA (92)

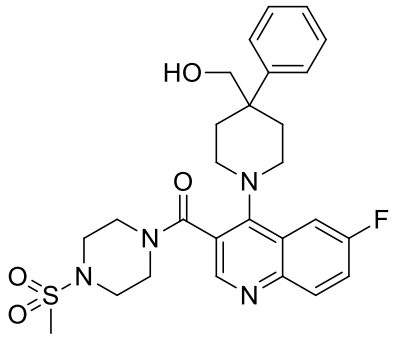


92

The title compound was prepared from **18a** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.05 (dd, *J* = 9.2, 5.5 Hz, 1H), 7.87 (dd, *J* = 10.3, 2.8 Hz, 1H), 7.81 – 7.72 (m, 1H), 7.63 – 7.56 (m, 2H), 7.35 (dd, *J* = 8.4,

7.0 Hz, 2H), 7.27 – 7.20 (m, 1H), 3.98 – 3.84 (m, 1H), 3.68 – 3.63 (m, 3H), 3.57 – 3.42 (m, 3H), 3.25 (t, J = 5.3 Hz, 2H), 3.19 – 3.08 (m, 4H), 2.91 (s, 3H), 2.44 – 2.32 (m, 1H), 2.25 – 2.12 (m, 1H), 1.83 – 1.64 (m, 2H).; LC-MS (Method 2): t_R = 3.82 min, m/z $(M+H)^+$= 513; HRMS calculated for $C_{26}H_{30}FN_4O_4S$ $(M+H)^+$: 513.1966, found: 513.1990.

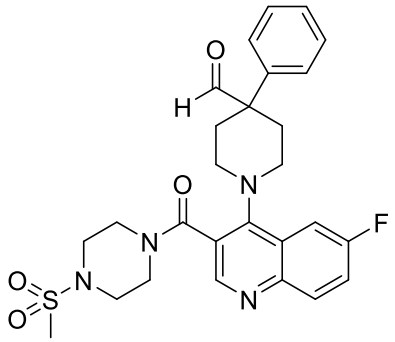
Synthesis of (6-Fluoro-4-(4-(hydroxymethyl)-4-phenylpiperidin-1-yl)quinolin-3-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone, TFA (93)



93

The title compound was prepared from **18a** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.02 (dd, J = 10.1, 5.5 Hz, 1H), 7.79 – 7.67 (m, 2H), 7.45 – 7.29 (m, 4H), 7.25 – 7.17 (m, 1H), 3.89 – 3.81 (m, 1H), 3.43 (s, 2H), 3.54 – 2.93 (m, 14H), 2.88 (s, 3H), 2.33 – 2.04 (m, 2H).; LC-MS (Method 2): t_R = 3.86 min, m/z $(M+H)^+$= 527; HRMS calculated for $C_{27}H_{32}FN_4O_4S$ $(M+H)^+$: 527.2123, found: 527.2128.

Synthesis of 1-(6-Fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-phenylpiperidine-4-carbaldehyde (94)

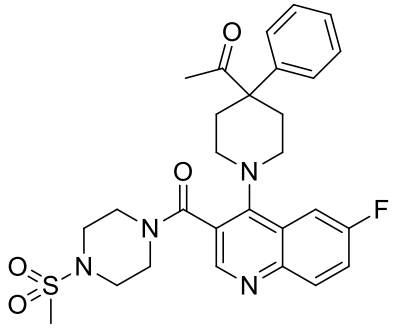


94

To a suspension of (6-fluoro-4-(4-(hydroxymethyl)-4-phenylpiperidin-1-yl)quinolin-3-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone (30 mg, 0.06 mmol) in CH_2Cl_2 (2 ml) was

added Dess-Martin periodinane (48.3 mg, 0.12 mmol). The mixture was stirred at rt for 1 h. Then 2 N $Na_2CO_{3(aq)}$ (5 mL) was added. The mixture was extracted with EtOAc (5 mL x 3). The combined organic layer was dried (Na_2SO_4) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 0-10% MeOH/EtOAc as the eluent to give 1-(6-fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-phenylpiperidine-4-carbaldehyde (22.6 mg, 0.043 mmol, 76 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.46 (s, 1H), 8.44 (s, 1H), 8.05 (dd, *J* = 9.2, 5.5 Hz, 1H), 7.64 (dd, *J* = 10.0, 2.8 Hz, 1H), 7.51 – 7.40 (m, 3H), 7.39 – 7.31 (m, 3H), 4.08 (ddd, *J* = 13.4, 6.2, 3.4 Hz, 1H), 3.81 (d, *J* = 11.4 Hz, 1H), 3.63 – 3.07 (m, 10H), 2.86 (s, 3H), 2.64 (d, *J* = 13.5 Hz, 2H), 2.33-2.29 (m, 2H); LC-MS (Method 2): t_R = 4.50 min, m/z $(M+H)^+$= 525; HRMS calculated for $C_{27}H_{30}FN_4O_4S$ $(M+H)^+$: 525.1966, found: 525.1979.

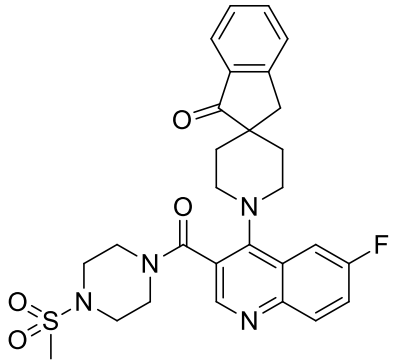
Synthesis of 1-(1-(6-Fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-phenylpiperidin-4-yl)ethanone, TFA (95)



95

The title compound was prepared from **18a** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.03 (dd, *J* = 9.1, 5.5 Hz, 1H), 7.75 (t, *J* = 9.1 Hz, 2H), 7.46 – 7.23 (m, 5H), 3.90 – 2.96 (m, 12H), 2.92 (s, 3H), 2.61-2.23 (m, 4H), 1.93 (s, 3H); LC-MS (Method 2): t_R = 4.36 min, m/z $(M+H)^+$= 539; HRMS calculated for $C_{28}H_{32}FN_4O_4S$ $(M+H)^+$: 539.2123, found: 539.2135.

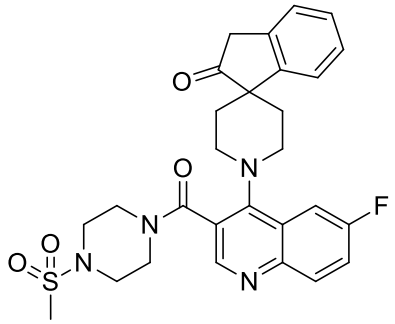
Synthesis of 1'-(6-Fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)spiro[indene-2,4'-piperidin]-1(3H)-one, TFA (96)



96

The title compound was prepared from **18a** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.07 (dd, J = 9.6, 5.5 Hz, 1H), 7.81 – 7.66 (m, 4H), 7.63 (d, J = 7.6 Hz, 1H), 7.45 (t, J = 7.3 Hz, 1H), 3.99 – 3.01 (m, 14H), 2.92 (s, 3H), 2.15 – 1.84 (m, 2H), 1.56 (t, J = 14.8 Hz, 2H); LC-MS (Method 2): t_R = 4.36 min, m/z $(M+H)^+$= 537; HRMS calculated for $C_{28}H_{30}FN_4O_4S$ $(M+H)^+$: 537.1966, found: 537.1974.

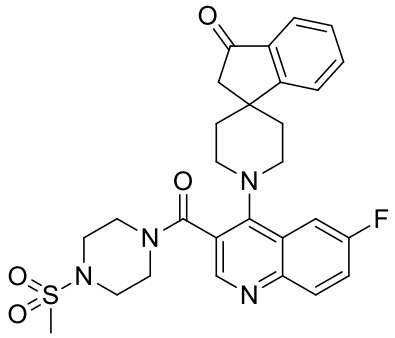
Synthesis of 1'-(6-Fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)spiro[indene-1,4'-piperidin]-2(3H)-one, TFA (97)



97

The title compound was prepared from **18a** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.06 (dd, J = 9.1, 5.5 Hz, 1H), 7.87 (d, J = 10.4 Hz, 1H), 7.79 – 7.70 (m, 1H), 7.67 – 7.59 (m, 1H), 7.39 – 7.23 (m, 3H), 4.04 – 3.03 (m, 14H), 2.92 (s, 3H), 2.20 – 1.83 (m, 4H); LC-MS (Method 2): t_R = 4.33 min, m/z $(M+H)^+$= 537; HRMS calculated for $C_{28}H_{30}FN_4O_4S$ $(M+H)^+$: 537.1966, found: 537.1978.

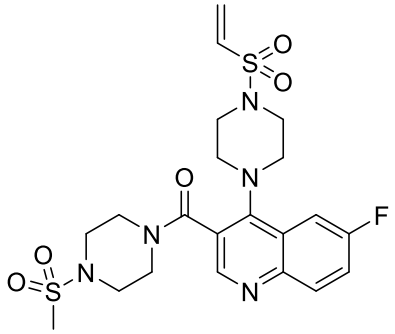
Synthesis of 1'-(6-Fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)spiro[indene-1,4'-piperidin]-3(2H)-one, TFA (98)



98

The title compound was prepared from **18a** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.07 (dd, J = 9.2, 5.5 Hz, 1H), 7.95 (t, J = 8.9 Hz, 2H), 7.80 – 7.69 (m, 2H), 7.63 (d, J = 7.5 Hz, 1H), 7.47 (t, J = 7.4 Hz, 1H), 4.03 – 3.01 (m, 12H), 2.90 (s, 3H), 2.72 (s, 2H), 2.46 (m, 2H), 1.69 – 1.53 (m, 2H); LC-MS (Method 2): t_R = 4.20 min, m/z $(M+H)^+$= 537; HRMS calculated for $C_{28}H_{30}FN_4O_4S$ $(M+H)^+$: 537.1966, found: 537.1984.

Synthesis of (6-Fluoro-4-(4-(vinylsulfonyl)piperazin-1-yl)quinolin-3-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone (99)



99

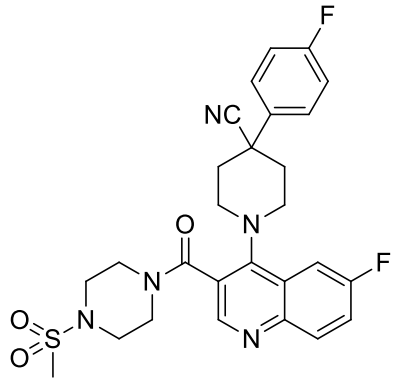
The compound **24** was prepared from **7f** following the similar procedure as described in the synthesis of **27**. LC-MS (Method 1): t_R = 2.87 min, m/z $(M+H)^+$= 522.

Step 1. Synthesis of (6-fluoro-4-(piperazin-1-yl)quinolin-3-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone, 2HCl. To a solution of tert-butyl 4-(6-fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)piperazine-1-carboxylate (510 mg, 0.99

mmol) in 1,4-dioxane/CH_2Cl_2 (5 ml/8 ml) was added HCl (4 N in dioxane, 4 mL, 16 mmol). Salt formed right after HCl solution was added. The deprotection proceeded slowly with stirring suspension. The suspension was stirred at rt for overnight and the reaction went completion by HPLC analysis. The mixture was concentrated to remove most of solvent. Then hexane (30 mL) was added and the solid was filtered, washed with hexane (2 mL x 3), and dried to give (6-fluoro-4-(piperazin-1-yl)quinolin-3-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone, 2HCl as a pale yellow solid. LC-MS (Method 1): t_R = 2.27 min, m/z $(M+H)^+$= 422.

Step 2. Synthesis of (6-fluoro-4-(4-(vinylsulfonyl)piperazin-1-yl)quinolin-3-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone (**99**). To a solution of (6-fluoro-4-(piperazin-1-yl)quinolin-3-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone, 2HCl (49.4 mg, 0.1 mmol) in CH_2Cl_2 (1 ml) was added Et_3N (0.14 ml, 1.0 mmol) and then ethenesulfonyl chloride (63.3 mg, 0.50 mmol). The mixture was stirred at rt for 30 min. The mixture was poured into EtOAc/H_2O (10 mL/10 mL). The organic layer was dried (Na_2SO_4) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 0-5% MeOH/EtOAc as the eluent to give (6-fluoro-4-(4-(vinylsulfonyl)piperazin-1-yl)quinolin-3-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone (24 mg, 0.047 mmol, 46.9 % yield). The material can be converted to its HCL salt. ^{1}H NMR (HCl salt, 400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.22 – 8.01 (m, 1H), 7.85 – 7.68 (m, 2H), 6.90 (dd, J = 16.5, 10.0 Hz, 1H), 6.24 (d, J = 10.1 Hz, 1H), 6.17 (d, J = 16.5 Hz, 1H), 3.93 – 2.98 (m, 16H), 2.92 (s, 3H).LC-MS (Method 2): t_R = 3.74 min, m/z $(M+H)^+$= 512; HRMS calculated for $C_{21}H_{27}FN_5O_5S_2$ $(M+H)^+$: 512.1432, found: 512.1440.

Synthesis of 1-(6-Fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-(4-fluorophenyl)piperidine-4-carbonitrile, TFA (100)

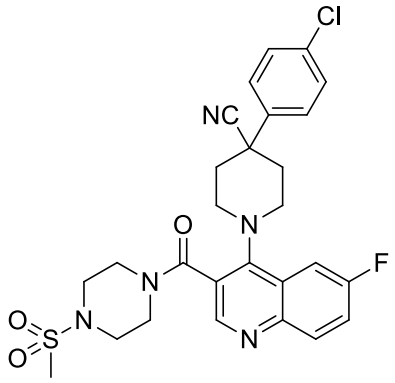


100

The title compound was prepared from **18a** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (d, J = 1.2 Hz, 1H), 8.06 (dd, J =

9.2, 5.6 Hz, 1H), 7.88 (dd, *J* = 10.3, 2.9 Hz, 1H), 7.77 – 7.64 (m, 3H), 7.36 – 7.26 (m, 2H), 3.96 – 3.84 (m, 1H), 3.77 – 3.67 (m, 1H), 3.60 (d, *J* = 13.2 Hz, 1H), 3.55 – 3.05 (m, 9H), 2.90 (s, 3H), 2.56 – 2.49 (m, 1H), 2.39 – 2.17 (m, 3H); LC-MS (Method 2): t_R = 4.61 min, m/z $(M+H)^+$= 540; HRMS calculated for $C_{27}H_{28}F_2N_5O_3S$ $(M+H)^+$: 540.1875, found: 540.1894.

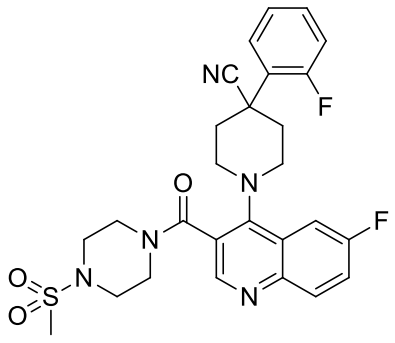
Synthesis of 4-(4-Chlorophenyl)-1-(6-fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)piperidine-4-carbonitrile, TFA (101)



101

The title compound was prepared from **18a** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (d, *J* = 2.5 Hz, 1H), 8.06 (dd, *J* = 9.2, 5.5 Hz, 1H), 7.88 (dd, *J* = 10.3, 2.7 Hz, 1H), 7.72 – 7.65 (m, 3H), 7.51 – 7.46 (m, 2H), 3.95 – 3.06 (m, 12H), 2.89 (s, 3H), 2.39 – 2.06 (m, 4H); LC-MS (Method 2): t_R = 4.80 min, m/z $(M+H)^+$= 557; HRMS calculated for $C_{27}H_{28}ClFN_5O_3S$ $(M+H)^+$: 556.1580, found: 556.1589.

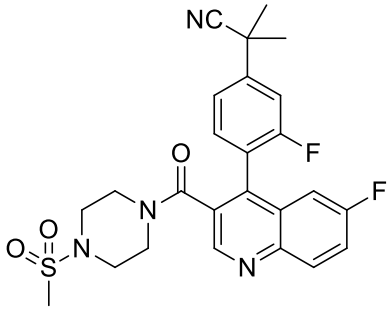
Synthesis of 1-(6-Fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-(2-fluorophenyl)piperidine-4-carbonitrile, TFA (102)



102

The title compound was prepared from **18a** following the similar procedure as described in the synthesis of **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.07 (dd, *J* = 9.2, 5.6 Hz, 1H), 7.80 (dd, *J* = 10.3, 2.9 Hz, 1H), 7.71 (ddd, *J* = 9.2, 8.1, 2.9 Hz, 1H), 7.60 (td, *J* = 8.0, 1.6 Hz, 1H), 7.49 (dddd, *J* = 8.3, 7.0, 5.2, 1.6 Hz, 1H), 7.39 – 7.29 (m, 2H), 3.98 – 3.03 (m, 12H), 2.90 (s, 3H), 2.57 – 2.31 (m, 4H); LC-MS (Method 2): t_R = 4.40 min, m/z $(M+H)^+$= 540; HRMS calculated for $C_{27}H_{28}F_2N_5O_3S$ $(M+H)^+$: 540.1875, found: 540.1890.

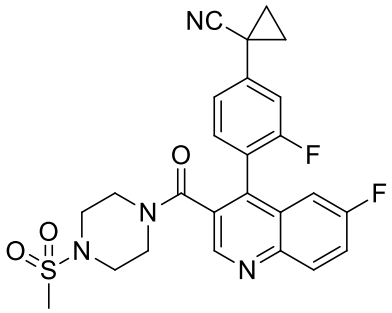
Synthesis of 2-(3-Fluoro-4-(6-fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)phenyl)-2-methylpropanenitrile, TFA (103)



103

The title compound was prepared from **18b** following the similar procedure as described in the synthesis of **88**. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.96 (s, 1H), 8.24 (dd, J = 9.3, 5.6 Hz, 1H), 7.80 (ddd, J = 9.3, 8.3, 2.9 Hz, 1H), 7.63 (s, 1H), 7.56 (dd, J = 8.0, 1.8 Hz, 1H), 7.46 (s, 1H), 7.14 (s, 1H), 3.69 – 2.54 (m, 11H), 1.76 (s, 3H), 1.75 (s, 3H); LC-MS (Method 2): t_R = 4.92 min, m/z $(M+H)^+$= 499; HRMS calculated for $C_{25}H_{25}F_2N_4O_3S$ $(M+H)^+$: 499.1610, found: 499.1626.

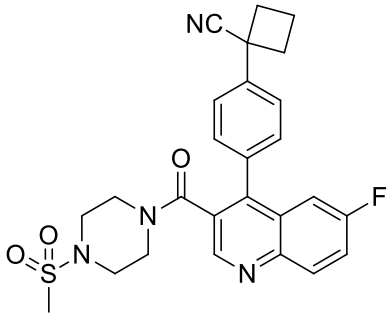
Synthesis of 1-(3-Fluoro-4-(6-fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)phenyl)cyclopropanecarbonitrile, TFA (104)



104

In a 2-neck flask was placed (4-chloro-6-fluoroquinolin-3-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone (**18a**, 37.2 mg, 0.1 mmol), 1-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropanecarbonitrile (57.4 mg, 0.20 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (16.3 mg, 0.02 mmol), and K_2CO_3 (83 mg, 0.60 mmol). The air was removed and re-filled with N_2 (2-3 times). Then DMF (1 ml) was added and stirred at 110 °C (pre-heated) for 1.5 h. The mixture was filtered and submitted for purification by semi-preparative HPLC to give 1-(3-fluoro-4-(6-fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)phenyl)cyclopropanecarbonitrile, TFA (15.1 mg, 0.025 mmol, 24.7 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (s, 1H), 8.23 (dd, *J* = 9.3, 5.5 Hz, 1H), 7.79 (ddd, *J* = 9.3, 8.2, 2.8 Hz, 1H), 7.27 (d, *J* = 107.2 Hz, 4H), 3.07 (d, *J* = 184.5 Hz, 11H), 1.85 (td, *J* = 4.1, 3.6, 2.2 Hz, 2H), 1.72 – 1.65 (m, 2H); LC-MS (Method 2): t_R = 4.79 min, m/z $(M+H)^+$= 497; HRMS calculated for $C_{25}H_{23}F_2N_4O_3S$ $(M+H)^+$: 497.1453, found: 497.1453.

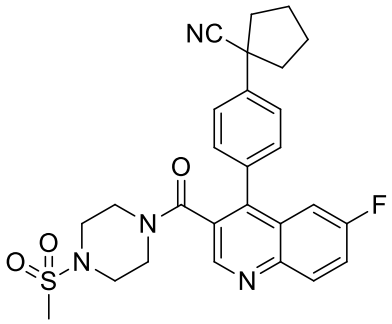
Synthesis of 1-(4-(6-Fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)phenyl)cyclobutanecarbonitrile, TFA (105)



105

The title compound was prepared from **18b** following the similar procedure as described in the synthesis of **88**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.21 (dd, *J* = 9.2, 5.6 Hz, 1H), 7.77 (ddd, *J* = 9.2, 8.2, 2.9 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.29 (dd, *J* = 10.2, 2.8 Hz, 1H), 3.64 – 2.92 (m, 6H), 2.75 (s, 3H), 2.81 – 2.59 (m, 4H), 2.56 – 2.49 (m, 1H), 2.37 – 2.24 (m, 1H), 2.20 (t, *J* = 9.2 Hz, 1H), 2.04 (dtt, *J* = 11.3, 8.9, 4.5 Hz, 1H); LC-MS (Method 2): t_R = 5.08 min, m/z $(M+H)^+$= 493; HRMS calculated for $C_{26}H_{26}FN_4O_3S$ $(M+H)^+$: 493.1704, found: 493.1709.

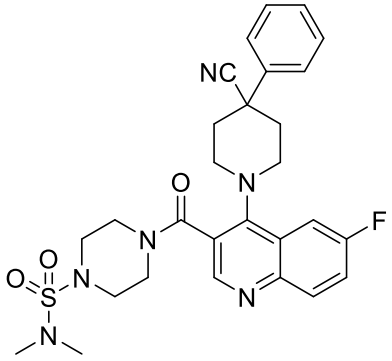
Synthesis of 1-(4-(6-Fluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)phenyl)cyclopentanecarbonitrile, TFA (106)



106

The title compound was prepared from **18b** following the similar procedure as described in the synthesis of **88**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.21 (dd, J = 9.3, 5.6 Hz, 1H), 7.81 – 7.64 (m, 3H), 7.59 – 7.53 (m, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.28 (dd, J = 10.2, 2.8 Hz, 1H), 4.11 – 2.88 (m, 8H), 2.76 (s, 3H), 2.45 – 2.02 (m, 4H), 1.91 – 1.88 (m, 4H); LC-MS (Method 2): t_R = 5.29 min, m/z $(M+H)^+$= 507; HRMS calculated for $C_{27}H_{28}FN_4O_3S$ $(M+H)^+$: 507.1861, found: 507.1851.

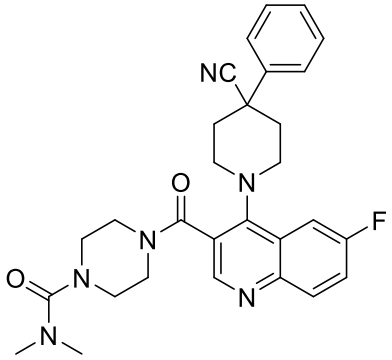
Synthesis of 4-(4-(4-Cyano-4-phenylpiperidin-1-yl)-6-fluoroquinoline-3-carbonyl)-*N*,*N*-dimethylpiperazine-1-sulfonamide, TFA (107)



107

The title compound was prepared from **13f** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.07 (dd, J = 9.2, 5.5 Hz, 1H), 7.89 (dd, J = 10.3, 2.8 Hz, 1H), 7.73 (td, J = 8.7, 2.8 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.52 – 7.44 (m, 2H), 7.44 – 7.35 (m, 1H), 3.94 – 3.10 (m, 12H), 2.76 (s, 6H), 2.57-2.15 (m, 4H); LC-MS (Method 2): t_R = 4.67 min, m/z $(M+H)^+$= 551; HRMS calculated for $C_{28}H_{32}FN_6O_3S$ $(M+H)^+$: 551.2235, found: 551.2249.

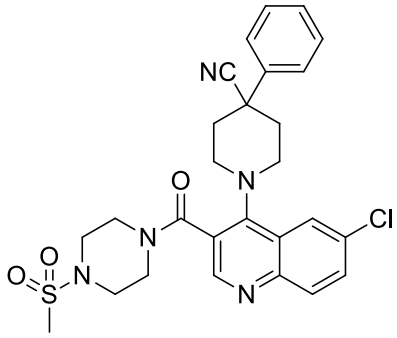
Synthesis of 4-(4-(4-Cyano-4-phenylpiperidin-1-yl)-6-fluoroquinoline-3-carbonyl)-*N*,*N*-dimethylpiperazine-1-carboxamide, TFA (108)



108

The title compound was prepared from **13f** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.07 (dd, J = 9.2, 5.5 Hz, 1H), 7.89 (dd, J = 10.2, 2.8 Hz, 1H), 7.73 (td, J = 8.7, 2.8 Hz, 1H), 7.69 – 7.61 (m, 2H), 7.52 – 7.42 (m, 2H), 7.42 – 7.35 (m, 1H), 3.79 – 3.01 (m, 12H), 2.73 (s, 6H), 2.59 – 2.49 (m, 1H), 2.38 – 2.18 (m, 3H); LC-MS (Method 2): t_R = 4.28 min, m/z $(M+H)^+$= 515; HRMS calculated for $C_{29}H_{32}FN_6O_2$ $(M+H)^+$: 515.2565, found: 515.2570.

Synthesis of 1-(6-Chloro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-phenylpiperidine-4-carbonitrile, TFA (109)

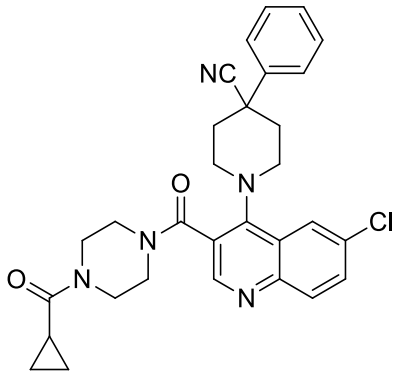


109

The title compound was prepared from **13g** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.15 (d, J = 2.3 Hz, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.83 (dd, J = 8.9, 2.3 Hz, 1H), 7.68 – 7.62 (m, 2H), 7.53 – 7.44 (m, 2H), 7.43 – 7.35 (m, 1H), 3.95 – 3.00 (m, 12H), 2.91 (s, 3H), 2.45 – 2.22 (m, 4H); LC-MS (Method

2): t_R = 4.66 min, m/z $(M+H)^+$= 538; HRMS calculated for $C_{27}H_{28}ClN_5O_3SNa$ $(M+Na)^+$: 560.1494, found: 560.1512.

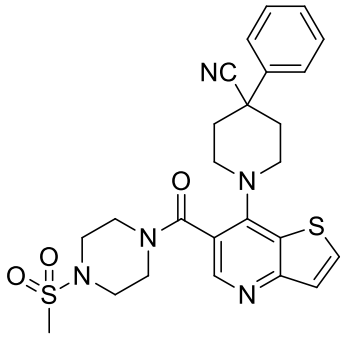
Synthesis of 1-(6-Chloro-3-(4-(cyclopropanecarbonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-phenylpiperidine-4-carbonitrile, TFA (110)



110

The title compound was prepared from **13g** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.16 (d, J = 2.3 Hz, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.84 (dd, J = 9.0, 2.3 Hz, 1H), 7.68 – 7.61 (m, 2H), 7.53 – 7.44 (m, 2H), 7.43 – 7.36 (m, 1H), 3.93 – 3.26 (m, 12H), 2.46 – 2.22 (m, 4H), 2.02-1.92 (m, 1H), 0.73 (d, J = 4.8 Hz, 4H); LC-MS (Method 2): t_R = 4.61 min, m/z $(M+H)^+$= 528; HRMS calculated for $C_{30}H_{31}ClN_5O_2$ $(M+H)^+$: 528.2161, found: 528.2178.

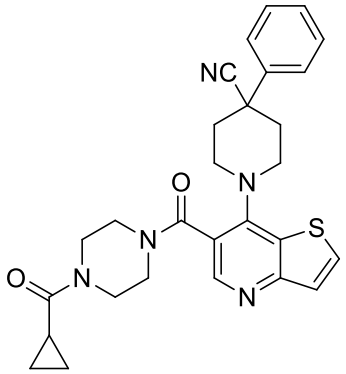
Synthesis of 1-(6-(4-(Methylsulfonyl)piperazine-1-carbonyl)thieno[3,2-b]pyridin-7-yl)-4-phenylpiperidine-4-carbonitrile, TFA (111)



111

The title compound was prepared from **22b** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.27 (d, *J* = 5.6 Hz, 1H), 7.59 – 7.53 (m, 3H), 7.47 (ddd, *J* = 7.9, 6.9, 1.3 Hz, 2H), 7.42 – 7.35 (m, 1H), 4.05 – 3.63 (m, 4H), 3.50 (t, *J* = 12.3 Hz, 4H), 3.23 (t, *J* = 5.2 Hz, 2H), 3.15 – 3.05 (m, 2H), 2.89 (s, 3H), 2.38 – 2.34 (m, 2H), 2.22 (td, *J* = 12.7, 3.8 Hz, 1H), 2.12 (td, *J* = 12.9, 4.0 Hz, 1H); LC-MS (Method 2): t_R = 4.13 min, m/z $(M+H)^+$= 510; HRMS calculated for $C_{25}H_{28}N_5O_3S_2$ $(M+H)^+$: 510.1628, found: 510.1633.

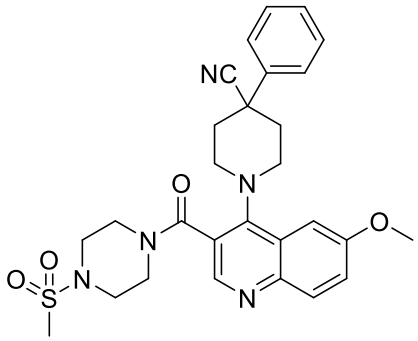
Synthesis of 1-(6-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)thieno[3,2-b]pyridin-7-yl)-4-phenylpiperidine-4-carbonitrile, TFA (112)



112

The title compound was prepared from **22b** following the similar procedure as described in the synthesis of **27**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.27 (d, *J* = 5.6 Hz, 1H), 7.58 – 7.52 (m, 3H), 7.51 – 7.42 (m, 2H), 7.42 – 7.35 (m, 1H), 4.00 (d, *J* = 13.9 Hz, 1H), 3.88 – 3.31 (m, 11H), 2.41 – 1.82 (m, 5H), 0.72 (d, *J* = 4.2 Hz, 4H); LC-MS (Method 2): t_R = 4.10 min, m/z $(M+H)^+$= 500; HRMS calculated for $C_{28}H_{30}N_5O_2S$ $(M+H)^+$: 500.2115, found: 500.2123.

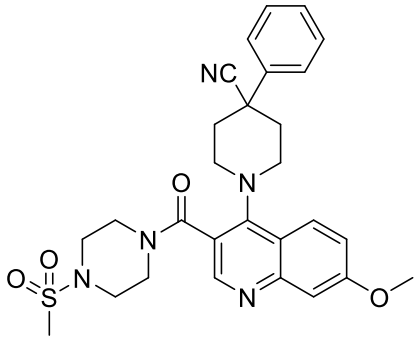
Synthesis of 1-(6-methoxy-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-phenylpiperidine-4-carbonitrile, HCl (113)



113

The title compound was prepared from **13a** following the similar procedure as described in the synthesis of **27**. The product was purified by silica gel chromatography using 0-10% MeOH/EtOAc as the eluent and then converted to its HCl salt according to the similar procedure as described in the synthesis of **86**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.09 (d, J = 9.2 Hz, 1H), 7.70 – 7.60 (m, 3H), 7.54 – 7.45 (m, 2H), 7.43 – 7.36 (m, 2H), 3.97 (s, 3H), 3.94 – 3.02 (m, 12H), 2.92 (s, 3H), 2.43 – 2.26 (m, 4H); LC-MS (Method 2): t_R = 4.28 min, m/z $(M+H)^+$= 534; HRMS calculated for $C_{28}H_{32}N_5O_4S$ $(M+H)^+$: 534.2170, found: 534.2169.

Synthesis of 1-(7-methoxy-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-phenylpiperidine-4-carbonitrile, HCl (114)

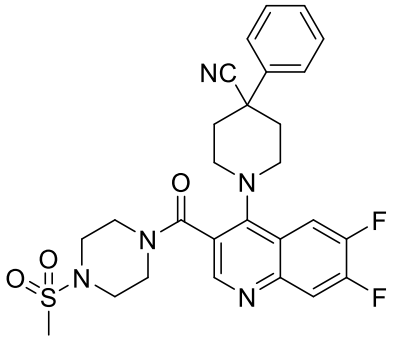


114

The title compound was prepared from **13c** following the similar procedure as described in the synthesis of **27**. The product was purified by silica gel chromatography using 0-10% MeOH/EtOAc as the eluent and then converted to its HCl salt according to the similar procedure as described in the synthesis of **86**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, J = 4.2 Hz, 1H), 8.20 (d, J = 9.4 Hz, 1H), 7.67 – 7.58 (m, 2H), 7.49 (dd, J = 8.5, 6.9 Hz, 2H), 7.46 – 7.37 (m, 2H), 7.34 (dd, J = 9.4, 2.5 Hz, 1H), 3.95 (s, 3H), 3.92 – 2.99 (m, 12H), 2.91 (s, 3H), 2.63 – 2.15 (m,

4H); LC-MS (Method 2): t_R = 4.23 min, m/z $(M+H)^+$= 534; HRMS calculated for $C_{28}H_{31}N_5O_4SNa$ $(M+Na)^+$: 556.1989, found: 556.1994.

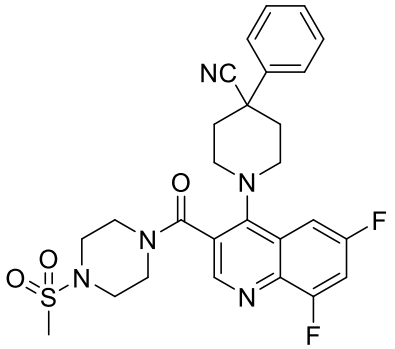
Synthesis of 1-(6,7-difluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-phenylpiperidine-4-carbonitrile, HCl (115)



115

The title compound was prepared from **13i** following the similar procedure as described in the synthesis of **27**. The product was purified by silica gel chromatography using 0-10% MeOH/EtOAc as the eluent and then converted to its HCl salt according to the similar procedure as described in the synthesis of **86**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (d, J = 3.0 Hz, 1H), 8.16 (dd, J = 11.6, 8.6 Hz, 1H), 8.04 (dd, J = 11.1, 7.8 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.54 – 7.43 (m, 2H), 7.43 – 7.33 (m, 1H), 3.94 – 3.84 (m, 1H), 3.79 – 3.69 (m, 1H), 3.65 (d, J = 13.3 Hz, 1H), 3.57 – 3.03 (m, 9H), 2.90 (s, 3H), 2.58 (td, J = 12.7, 3.9 Hz, 1H), 2.36 (td, J = 12.5, 11.8, 3.8 Hz, 1H), 2.31 – 2.16 (m, 2H); LC-MS (Method 2): t_R = 4.89 min, m/z $(M+H)^+$= 540; HRMS calculated for $C_{27}H_{28}F_2N_5O_3S$ $(M+H)^+$: 540.1875, found: 540.1869.

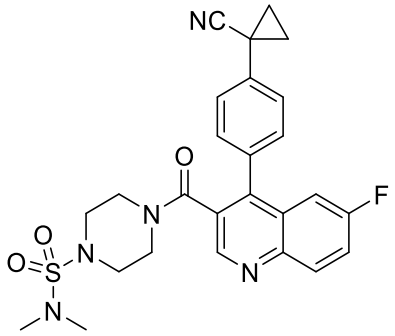
Synthesis of 1-(6,8-difluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)-4-phenylpiperidine-4-carbonitrile, HCl (116)



116

The title compound was prepared from **13j** following the similar procedure as described in the synthesis of **27**. The product was purified by silica gel chromatography using 0-10% MeOH/EtOAc as the eluent and then converted to its HCl salt according to the similar procedure as described in the synthesis of **86**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 7.81 – 7.69 (m, 2H), 7.69 – 7.63 (m, 2H), 7.52 – 7.44 (m, 2H), 7.42 – 7.33 (m, 1H), 3.93 (dt, *J* = 13.3, 4.8 Hz, 1H), 3.71 (dt, *J* = 13.1, 5.1 Hz, 1H), 3.64 – 3.05 (m, 10H), 2.91 (s, 3H), 2.57 – 2.13 (m, 4H); LC-MS (Method 2): t_R = 5.19 min, m/z $(M+H)^+$= 540; HRMS calculated for $C_{27}H_{28}F_2N_5O_3S$ $(M+H)^+$: 540.1875, found: 540.1887.

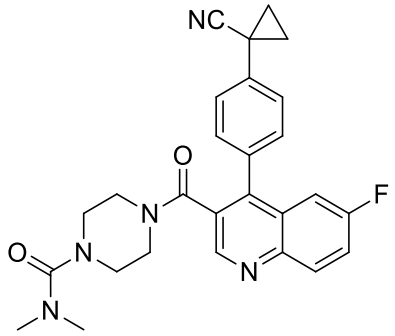
Synthesis of 4-(4-(4-(1-Cyanocyclopropyl)phenyl)-6-fluoroquinoline-3-carbonyl)-*N*,*N*-dimethylpiperazine-1-sulfonamide, TFA (117)



117

To a mixture of 4-(4-(1-cyanocyclopropyl)phenyl)-6-fluoroquinoline-3-carboxylic acid (16.62 mg, 0.05 mmol), *N*,*N*-dimethylpiperazine-1-sulfonamide (29.0 mg, 0.15 mmol), and HATU (76 mg, 0.20 mmol) was added DMF (2 ml) and then Hunig's base (0.087 ml, 0.50 mmol). The mixture was stirred at rt for 1.5 h. The mixture was filtered and submitted for purification to give 4-(4-(4-(1-cyanocyclopropyl)phenyl)-6-fluoroquinoline-3-carbonyl)-*N*,*N*-dimethylpiperazine-1-sulfonamide, TFA (12.3 mg, 0.02 mmol, 39.6 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.20 (dd, *J* = 9.3, 5.6 Hz, 1H), 7.77 (ddd, *J* = 9.3, 8.2, 2.9 Hz, 1H), 7.57–7.52 (m, 2H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.29 (dd, *J* = 10.2, 2.8 Hz, 1H), 3.66 (d, *J* = 12.6 Hz, 1H), 3.33 – 2.93 (m, 5H), 2.68 (s, 6H), 2.52 (t, *J* = 9.0 Hz, 1H), 2.08 (t, *J* = 8.7 Hz, 1H), 1.85–1.82 (m, 2H), 1.66 – 1.52 (m, 2H); LC-MS (Method 2): t_R = 5.00 min, m/z $(M+H)^+$= 508; HRMS calculated for $C_{26}H_{27}FN_5O_3S$ $(M+H)^+$: 508.1813, found: 508.1838.

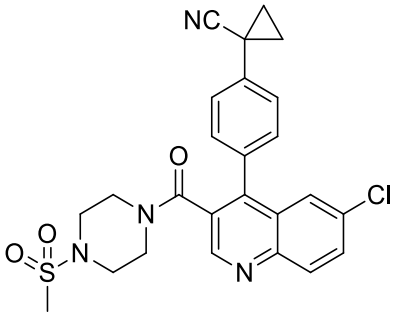
Synthesis of 4-(4-(4-(1-Cyanocyclopropyl)phenyl)-6-fluoroquinoline-3-carbonyl)-*N*,*N*-dimethylpiperazine-1-carboxamide, TFA (118)



118

The title compound was prepared from **21a** following the similar procedure as described in the synthesis of **117**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (s, 1H), 8.20 (dd, *J* = 9.2, 5.6 Hz, 1H), 7.76 (ddd, *J* = 9.2, 8.2, 2.9 Hz, 1H), 7.53-7.47 (m, 3H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.27 (dd, *J* = 10.2, 2.8 Hz, 1H), 3.37 – 3.33 (m, 2H), 3.14 – 3.09 (m, 2H), 2.93 – 2.91 (m, 2H), 2.66 (s, 6H), 2.65 – 2.55 (m, 1H), 2.28 – 2.16 (m, 1H), 1.85 – 1.77 (m, 2H), 1.62 – 1.52 (m, 2H)' LC-MS (Method 2): t_R = 4.56 min, m/z $(M+H)^+$= 472; HRMS calculated for $C_{27}H_{27}FN_5O_2$ $(M+H)^+$: 472.2143, found: 472.2155.

Synthesis of 1-(4-(6-Chloro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)phenyl)cyclopropanecarbonitrile, TFA (119)

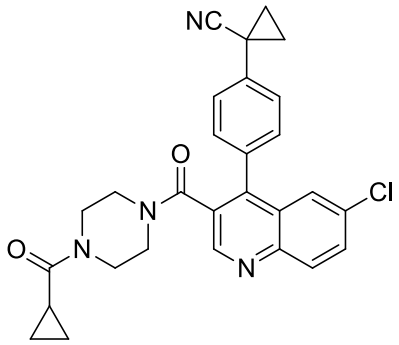


119

The title compound was prepared from **21c** following the similar procedure as described in the synthesis of **117**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 (d, *J* = 1.9 Hz, 1H), 8.15 (dd, *J* = 9.2, 1.8 Hz, 1H), 7.86 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.62 – 7.50 (m, 3H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 3.70 – 2.86 (m, 6H), 2.76 (s, 3H), 2.54 (d, *J* = 9.5 Hz, 1H), 2.11 (t, *J* =

9.6 Hz, 1H), 1.82 (q, J = 2.7 Hz, 2H), 1.71 – 1.57 (m, 2H); LC-MS (Method 2): t_R = 5.02 min, m/z $(M+H)^+$= 495; HRMS calculated for $C_{25}H_{24}ClN_4O_3S$ $(M+H)^+$: 495.1252, found: 495.1249.

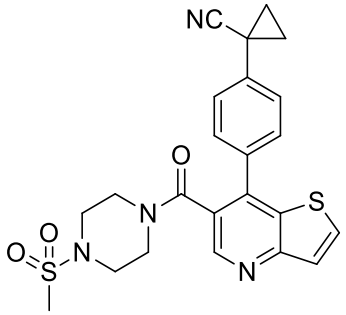
Synthesis of 1-(4-(6-Chloro-3-(4-(cyclopropanecarbonyl)piperazine-1-carbonyl)quinolin-4-yl)phenyl)cyclopropanecarbonitrile, TFA (120)



120

The title compound was prepared from **21c** following the similar procedure as described in the synthesis of **117**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 8.15 (d, J = 9.0 Hz, 1H), 7.86 (dd, J = 9.0, 2.4 Hz, 1H), 7.61 – 7.33 (m, 5H), 3.72 – 2.69 (m, 8H), 1.88 (br s, 1H), 1.85 – 1.79 (m, 2H), 1.60 (d, J = 2.8 Hz, 2H), 0.66 (d, J = 7.9 Hz, 4H); LC-MS (Method 2): t_R = 4.99 min, m/z $(M+H)^+$= 485; HRMS calculated for $C_{28}H_{26}ClN_4O_2$ $(M+H)^+$: 485.1739, found: 485.1743.

Synthesis of 1-(4-(6-(4-(Methylsulfonyl)piperazine-1-carbonyl)thieno[3,2-b]pyridin-7-yl)phenyl)cyclopropanecarbonitrile, TFA (121)

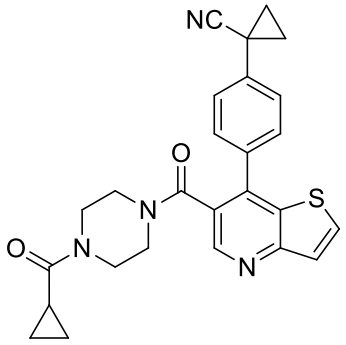


121

The title compound was prepared from **22b** following the similar procedure as described in the synthesis of **117**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.26 (d, J = 5.6 Hz, 1H),

7.67 (d, *J* = 5.6 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.55 – 7.48 (m, 2H), 3.68 (s, 1H), 3.41 (s, 1H), 3.15 (br s, 2H), 3.04 (s, 1H), 2.91 (br s, 2H), 2.72 (s, 4H), 2.61 – 2.49 (m, 1H), 1.90 (br s, 1H), 1.81 (q, *J* = 3.0 Hz, 2H), 1.67 – 1.58 (m, 2H); LC-MS (Method 2): t_R = 4.44 min, m/z $(M+H)^+$= 467; HRMS calculated for $C_{23}H_{23}N_4O_3S_2$ $(M+H)^+$: 467.1206, found: 467.1225.

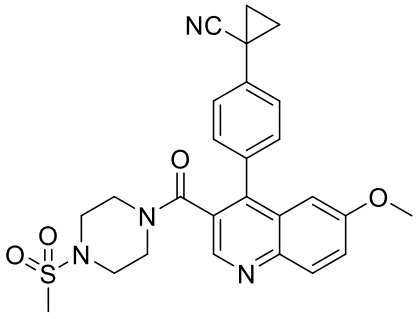
Synthesis of 1-(4-(6-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)thieno[3,2-b]pyridin-7-yl)phenyl)cyclopropanecarbonitrile, TFA (122)



122

The title compound was prepared from **22b** following the similar procedure as described in the synthesis of **117**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.26 (d, *J* = 5.6 Hz, 1H), 7.67 (d, *J* = 5.6 Hz, 1H), 7.63 – 7.56 (m, 2H), 7.55 – 7.48 (m, 2H), 3.84 – 2.68 (m, 7H), 1.89 (d, *J* = 8.0 Hz, 1H), 1.81 (m, 3H), 1.58 (q, *J* = 4.7 Hz, 2H), 0.66 (d, *J* = 6.3 Hz, 4H); LC-MS (Method 2): t_R = 4.40 min, m/z $(M+H)^+$= 457; HRMS calculated for $C_{26}H_{24}N_4O_2SNa$ $(M+Na)^+$: 479.1512, found: 479.1528.

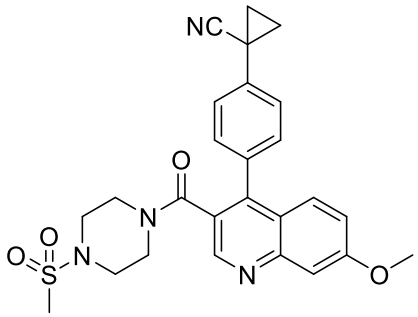
Synthesis of 1-(4-(6-methoxy-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)phenyl)cyclopropane-1-carbonitrile, HCl (123)



123

The title compound was prepared from **21b** following the similar procedure as described in the synthesis of **117**. The product was purified by silica gel chromatography using 0-10% MeOH/EtOAc as the eluent and then converted to its HCl salt according to the similar procedure as described in the synthesis of **86**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (d, J = 0.8 Hz, 1H), 8.06 (d, J = 9.2 Hz, 1H), 7.62 – 7.50 (m, 3H), 7.45 (d, J = 8.2 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 6.97 (d, J = 2.8 Hz, 1H), 3.73 (s, 3H), 3.57 (s, 1H), 3.41 (t, J = 9.0 Hz, 1H), 3.17 (d, J = 8.3 Hz, 2H), 2.98 (t, J = 12.7 Hz, 2H), 2.76 (s, 3H), 2.58 – 2.50 (m, 1H), 2.10 (t, J = 8.7 Hz, 1H), 1.83 (dd, J = 6.0, 2.7 Hz, 2H), 1.67 – 1.55 (m, 2H); LC-MS (Method 2): t_R = 4.27 min, m/z $(M+H)^+$= 491; HRMS calculated for $C_{26}H_{27}N_4O_4S$ $(M+H)^+$: 491.1748, found: 491.1750.

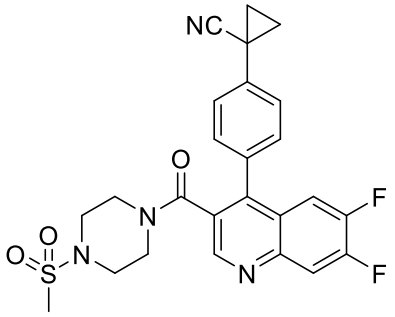
Synthesis of 1-(4-(7-methoxy-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)phenyl)cyclopropane-1-carbonitrile, HCl (124)



124

The title compound was prepared from **21d** following the similar procedure as described in the synthesis of **117**. The product was purified by silica gel chromatography using 0-10% MeOH/EtOAc as the eluent and then converted to its HCl salt according to the similar procedure as described in the synthesis of **86**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (s, 1H), 7.64 – 7.35 (m, 6H), 7.32 (dt, J = 6.4, 2.3 Hz, 1H), 3.95 (s, 3H), 3.57 (s, 1H), 3.43 (d, J = 8.6 Hz, 1H), 3.29 – 2.90 (m, 4H), 2.76 (s, 3H), 2.56 (d, J = 10.4 Hz, 1H), 2.12 (s, 1H), 1.82 (q, J = 4.6, 4.2 Hz, 2H), 1.66 – 1.58 (m, 2H); LC-MS (Method 2): t_R = 4.14 min, m/z $(M+H)^+$= 491; HRMS calculated for $C_{26}H_{27}N_4O_4S$ $(M+H)^+$: 491.1748, found: 491.1751.

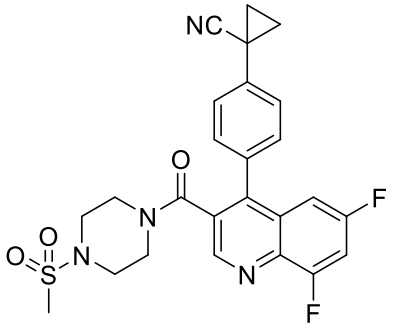
Synthesis of 1-(4-(6,7-difluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)phenyl)cyclopropane-1-carbonitrile, HCl (125)



125

The title compound was prepared from **21e** following the similar procedure as described in the synthesis of **117**. The product was purified by silica gel chromatography using 0-10% MeOH/EtOAc as the eluent and then converted to its HCl salt according to the similar procedure as described in the synthesis of **86**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 (s, 1H), 8.18 (dd, J = 11.4, 7.9 Hz, 1H), 7.63 – 7.43 (m, 4H), 7.38 (d, J = 8.1 Hz, 1H), 3.60 (d, J = 13.0 Hz, 1H), 3.48 – 3.35 (m, 1H), 3.18 (d, J = 9.3 Hz, 2H), 3.03 – 2.96 (m, 2H), 2.76 (s, 3H), 2.60 – 2.50 (m, 1H), 2.17 – 2.03 (m, 1H), 1.86 – 1.79 (m, 2H), 1.63 (td, J = 5.5, 4.9, 3.1 Hz, 2H); LC-MS (Method 2): t_R = 4.90 min, m/z $(M+H)^+$= 497; HRMS calculated for $C_{25}H_{23}F_2N_4O_3S$ $(M+H)^+$: 497.1453, found: 497.1465.

Synthesis of 1-(4-(6,8-difluoro-3-(4-(methylsulfonyl)piperazine-1-carbonyl)quinolin-4-yl)phenyl)cyclopropane-1-carbonitrile, HCl (126)



126

The title compound was prepared from **21f** following the similar procedure as described in the synthesis of **117**. The product was purified by silica gel chromatography using 0-10% MeOH/EtOAc as the eluent and then converted to its HCl salt according to the similar procedure as described in the synthesis of **86**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 7.86 (ddd, J = 11.0, 9.0, 2.6 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.13 (dt, J = 9.9, 1.9 Hz, 1H), 3.65 – 3.35 (m, 2H), 3.20 (q, J =

12.3, 10.6 Hz, 2H), 3.10 – 2.90 (m, 2H), 2.76 (s, 3H), 2.55 (ddd, *J* = 11.5, 8.1, 3.3 Hz, 1H), 2.13 (t, *J* = 9.1 Hz, 1H), 1.82 (q, *J* = 4.1, 3.6 Hz, 2H), 1.63 (q, *J* = 3.9 Hz, 2H); LC-MS (Method 2): t_R = 4.80 min, m/z $(M+H)^+$= 497; HRMS calculated for $C_{25}H_{23}F_2N_4O_3S$ $(M+H)^+$: 497.1453, found: 497.1444.