

Supporting Information

Development of a Potent Brain-Penetrant EGFR Tyrosine Kinase Inhibitor Against Malignant Brain Tumors

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S1. Supplementary Figures and Tables

As an illustration of the characteristic protein interactions of the type I scaffold, Figure S1 shows the binding mode of erlotinib to the ATP-binding pocket of EGFR and, for comparison, the binding mode of its natural substrate ATP.¹⁻³ The “classical” binding interactions comprise two hydrogen bonds formed between N1 and N3 of the quinazoline with hinge residue Met769 and “gatekeeper” residue Thr766 (mediated through a water molecule (O10)) (Figure S1C), which mimic those of the adenine ring of ATP³ (Figure S1D), and the filling of the apolar hole at the back of the binding site by the aniline ring with the 3'-alkyne substituent pointing into the hydrophobic “chimney” (as termed by Bridges⁴) at the end of the apolar hole. The substituents at C6 and C7 of the quinazoline protrude from the binding cleft into the solvent channel (Figure S1B), making minimal interactions with the protein environment, but are important for pharmacological properties.^{5,6} These positions (C6 and C7) are known to be tolerant of substitution as opposed to C2, C5, and C8, and substituents are preferably attached via electron donating groups to the quinazoline.^{5,7}

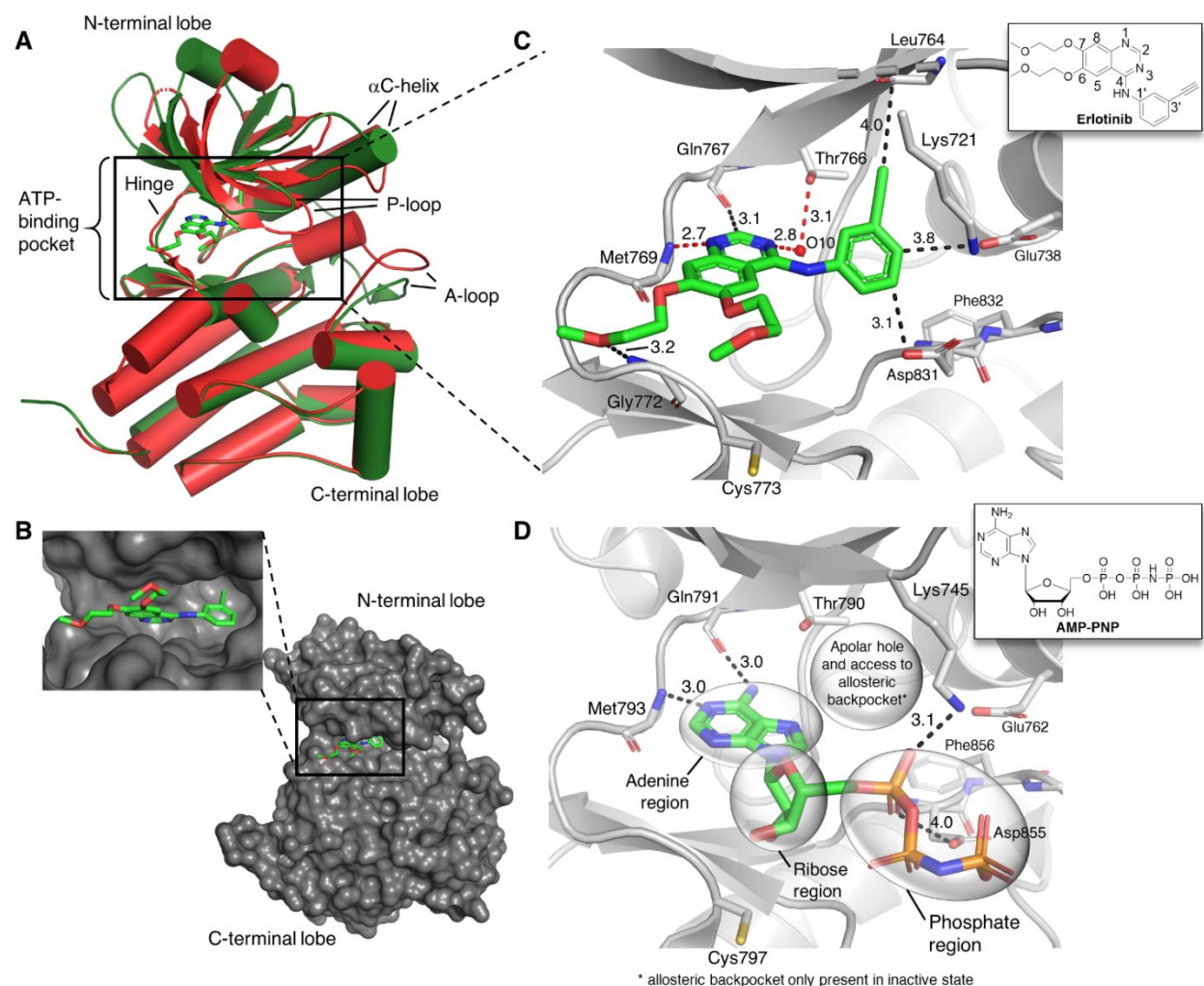
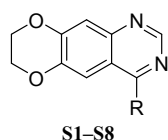


Figure S1. Structure of the EGFR kinase domain and binding mode at the ATP-binding pocket. (A) Active (green, PDB 1M17)¹ and inactive (red, PDB 4HJO)² EGFR kinase domains superimposed on their C-terminal lobes. The ATP-binding site is occupied by erlotinib (sticks).

The main structural elements are labelled, but more detailed descriptions can be found in the relevant biophysical publications. (B) Surface representation of the active EGFR kinase domain in complex with erlotinib (PDB 1M17). The expanded view shows erlotinib in the narrow binding cleft with the apolar hole at the back filled by the aniline ring. (C) Binding mode of erlotinib at the ATP-binding pocket (PDB 1M17). “Classical” hydrogen bonds are indicated as dashed, red lines, and additional close contact interactions are shown as dashed, black lines. (D) Binding mode of the non-hydrolyzable ATP-analogue AMP-PNP at the ATP-binding pocket (PDB 3VJO).³ The apolar hole is not occupied by ATP. The P-loops have been removed for clarity in (C) and (D). Color code: C_{enzyme} gray, O red, N blue, P orange, C_{ligand} green. Distances are in Å.

Table S1. SAR of placing fluorine(s) on the aniline ring of the 4-anilinoquinazolines.



Compound	R	EGFR IC ₅₀ (nM)	p-wtEGFR IC ₅₀ (nM)	p-EGFRvIII IC ₅₀ (nM)	HK301 GI ₅₀ (nM)	GBM39 GI ₅₀ (nM)
S1		57.3 ±22.6	64.1 ±4.8	169.4 ±10.4	4040 ±553	9998 ±1529
S2		107.3 ±18.6	86.5 ±4.0	379.0 ±54.3	3238 ±124	10221 ±1320
S3		18.9 ±3.6	28.9 ±1.4	109.6 ±4.4	1688 ±188	5572 ±371
S4		363.0 ±49.7	435.1 ±50.9	851.9 ±68.4	10659 ±1487	27706 ±5589
S5		115.0 ±15.9	92.7 ±0.8	304.4 ±17.0	6124 ±1041	16525 ±1817
S6		50.0 ±10.5	40.0 ±3.9	211.1 ±54.4	5807 ±675	11837 ±2197
S7		427.9 ±41.1	362.4 ±106.5	1319.6 ±136.4	24395 ±1333	33970 ±5345
S8		1243.0 ±142.0	4785.5 ±385.7	10935 ±641.4	>100000	>100000

All EGFR inhibition data are represented as mean ± SEM from *n*=2 or more independent replicates. All growth inhibition data are represented as mean ± SEM from *n*=3 or more independent replicates.

The compounds of Table S1, **S1-S8**, were prepared according to all other anilinoquinazoline compounds as outlined in Scheme 1.

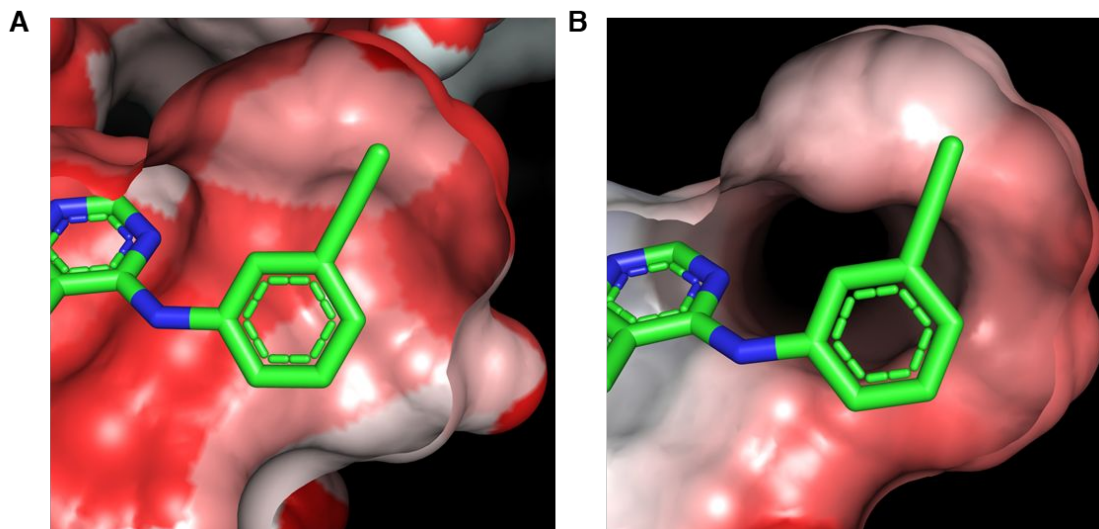


Figure S2. Surface representations of the apolar hole of the wtEGFR kinase domain (PDB 1M17) with bound erlotinib. A) Lipophilic surface according to the Eisenberg hydrophobicity scale, generated with the PyMOL color_h script; color code: red = lipophilic, white = hydrophilic surface area. B) Electrostatic surface, generated with the PyMOL APBS plugin; color code: red = increasing negative potential, blue = increasing positive surface potential.

Table S2. Calculated physicochemical properties of compound **5** and related 3'-halide substituted compounds.

Compound	clogD at pH 7.4 ^a	IC ₅₀ (nM)
S3	3.26	18.9
4	3.72	3.91
5	3.88	2.49
6	4.04	10.4

^a Calculated with Chemicalize, ChemAxon.

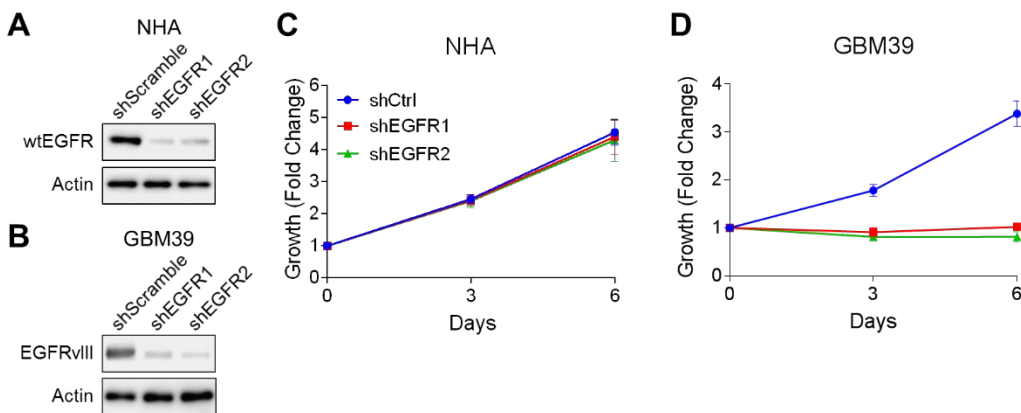
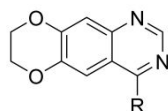


Figure S3. NHAs are not dependent on EGFR for growth. (A) Immunoblot of EGFR and actin in NHA cells transduced with shRNA against a scramble control and EGFR. (B) Same as (A) but with EGFRvIII and actin in GBM39. (C) Proliferation of NHA cells from (A).

Table S3. GI50 of NHAs and primary GBM lines of potent compounds.



Compound	R	HK301 GI ₅₀ ^a (nM)	GBM39 GI ₅₀ ^b (nM)	NHA GI ₅₀ ^c (nM)	Ratio of NHA/HK301 GI ₅₀	Ratio of NHA/GBM39 GI ₅₀
Erlotinib		700.2 ±76.8	2788 ±179	43312 ±3837	62.1	15.6
Lapatinib		1290 ±144	2101 ±370	16186 ±2321	12.5	7.7
1		8824 ±1109	20536 ±1212	>100000	11.3	4.9
2		791.1 ±108.1	2946 ±353	6647 ±597	7.7	2.1
S3		1688 ±188	5572 ±371	23905 ±2063	14.6	4.4
4		780.5 ±148.3	2594 ±299	7616 ±328	9.8	2.9
5		329.3 ±31.0	1116 ±114.9	8168 ±346	24.7	7.3
6		2042 ±341	4521 ±574	9336 ±609	4.6	2.1
15		3681 ±738	4226 ±371	670 ±185	0.6	0.4
18		290.1 ±32.7	966.4 ±163.4	1430 ±259	4.9	1.5
19		418.7 ±62.7	1356 ±196.3	1167 ±175	2.8	0.9

^a3 day growth inhibition in patient-derived GBM line, HK301. ^b3 day growth inhibition in patient-derived GBM line, GBM39. ^c3 day growth inhibition in NHA. All growth inhibition data are represented as mean ± SEM from *n*=3 or more independent replicates.

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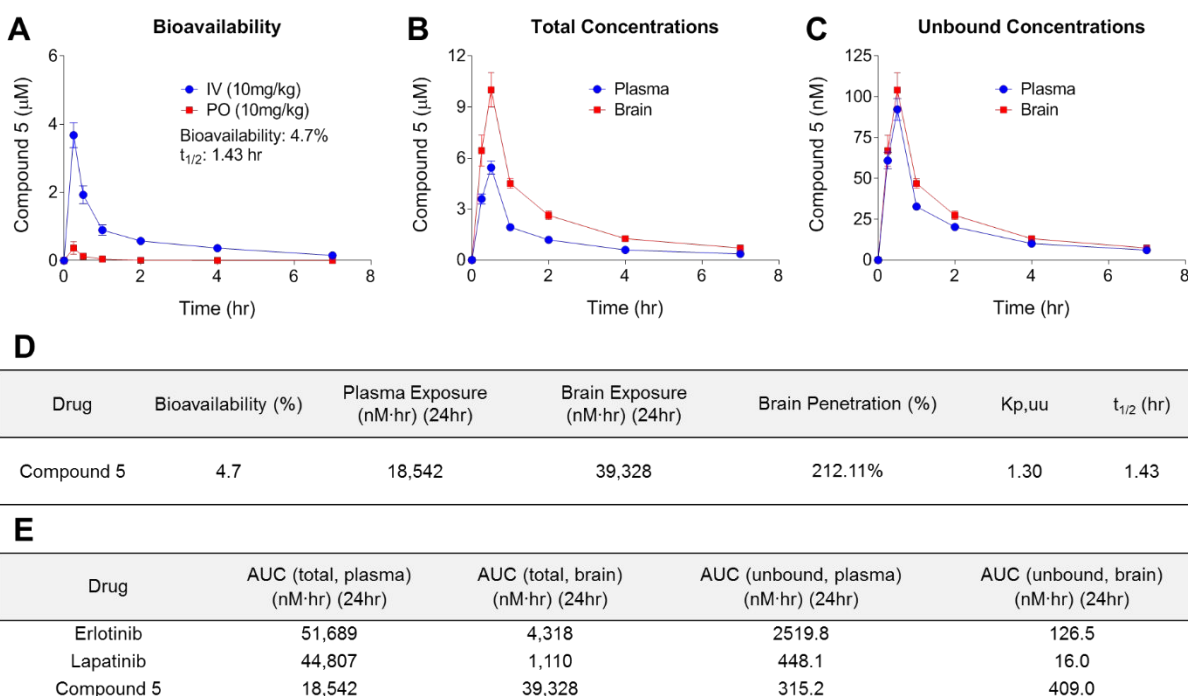
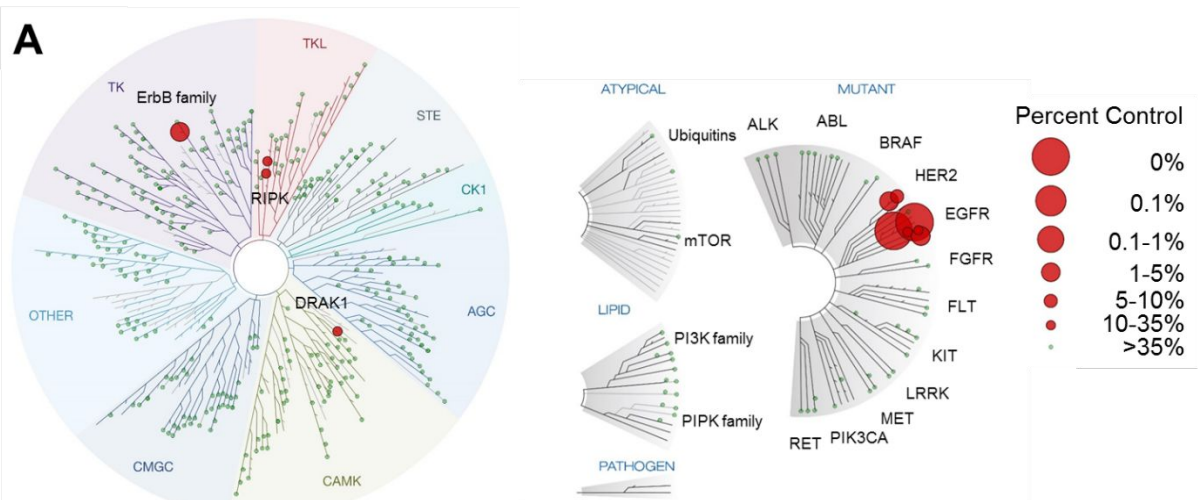


Figure S4. Pharmacokinetics of compound **5**. (A) Oral bioavailability of compound **5**. (B) Total plasma and brain concentrations of compound **5** in healthy CD-1 mice. (C) Unbound plasma and brain concentrations of compound **5** in healthy CD-1 mice. (D) Pharmacokinetics parameters of compound **5**. (E) Exposures of erlotinib (10mg/kg), lapatinib (80mg/kg), and compound **5** (300mg/kg) in plasma and brain for total and unbound.

Table S4. Permeability of **5** in MDCK-BCRP transwell cells.

Compound	Concentration (µM)	P _{app} (10 ⁻⁶ cm/s)	Efflux Ratio ^c
5	10	18.59	0.303



#	Kinase	Compound 5 % Kinase Inhibition (1μM)
1	AAK1	1
2	ABL1	4
3	ABL2 (Arg)	2
4	ACVR1 (ALK2)	6
5	ACVR1B (ALK4)	-1
6	ACVR2A	-7
7	ACVR2B	-8
8	ACVRL1 (ALK1)	-2
9	ADCK3	9
10	ADRBK1 (GRK2)	-3
11	ADRBK2 (GRK3)	-1
12	AKT1 (PKB alpha)	3
13	AKT2 (PKB beta)	4
14	AKT3 (PKB gamma)	6
15	ALK	9
16	AMPK (A1/B1/G2)	-6
17	AMPK (A1/B1/G3)	-6
18	AMPK (A1/B2/G1)	1
19	AMPK (A1/B2/G2)	0
20	AMPK (A1/B2/G3)	0
21	AMPK (A2/B1/G2)	1
22	AMPK (A2/B1/G3)	-2
23	AMPK (A2/B2/G1)	-4
24	AMPK (A2/B2/G2)	-1
25	AMPK (A2/B2/G3)	-1
26	AMPK A1/B1/G1	-5
27	AMPK A2/B1/G1	5
28	ANKK1	-5
29	AURKA (Aurora A)	0
30	AURKB (Aurora B)	6
31	AURKC (Aurora C)	11
32	AXL	-1
33	BLK	6
34	BMPR1A (ALK3)	-6
35	BMPR1B (ALK6)	-2
36	BMPR2	1
37	BMX	0
38	BRAF	3
39	BRAF	-3
40	BRSK1 (SAD1)	1
41	BRSK2	-5
42	BTK	0
43	CAMK1 (CaMKI)	-2
44	CAMK1D (CaMKI delta)	-1
45	CAMK1G (CaMKI gamma)	-4
46	CAMK2A (CaMKII alpha)	6
47	CAMK2B (CaMKII beta)	5
48	CAMK2D (CaMKII delta)	3
49	CAMK2G (CaMKII gamma)	-5
50	CAMK4 (CaMKIV)	12
51	CAMKK1 (CaMKKA)	-5
52	CAMKK2 (CaMKK beta)	-3
53	CASK	-8
54	CDC42 BPA (MRCKA)	1
55	CDC42 BPB (MRCKB)	-1
56	CDC42 BPG (MRCKG)	-3
57	CDC7/DBF4	3
58	CDK1/cyclin B	2
59	CDK11 (Inactive)	-13

#	Kinase	Compound 5 % Kinase Inhibition (1μM)
60	CDK11/cyclin C	6
61	CDK13/cyclin K	-4
62	CDK14 (PFTK1)/cyclin Y	-3
63	CDK16 (PCTK1)/cyclin Y	-4
64	CDK17/cyclin Y	4
65	CDK18/cyclin Y	3
66	CDK2/cyclin A	2
67	CDK2/cyclin A1	-1
68	CDK2/cyclin E1	-5
69	CDK2/cyclin O	-4
70	CDK3/cyclin E1	-7
71	CDK4/cyclin D1	22
72	CDK4/cyclin D3	-10
73	CDK5 (Inactive)	-4
74	CDK5/p25	2
75	CDK5/p35	1
76	CDK6/cyclin D1	3
77	CDK7/cyclin H/MNAT1	3
78	CDK8/cyclin C	0
79	CDK9 (Inactive)	-4
80	CDK9/cyclin K	2
81	CDK9/cyclin T1	-1
82	CDKL5	-1
83	CHEK1 (CHK1)	-2
84	CHEK2 (CHK2)	0
85	CHUK (IKK alpha)	-3
86	CLK1	2
87	CLK2	5
88	CLK3	1
89	CLK4	20
90	CSF1R (FMS)	6
91	CSK	-1
92	CSNK1A1 (CK1 alpha 1)	2
93	CSNK1A1L	2
94	CSNK1D (CK1 delta)	3
95	CSNK1E (CK1 epsilon)	2
96	CSNK1G1 (CK1 gamma 1)	-1
97	CSNK1G2 (CK1 gamma 2)	2
98	CSNK1G3 (CK1 gamma 3)	1
99	CSNK2A1 (CK2 alpha 1)	2
100	CSNK2A2 (CK2 alpha 2)	1
101	DAPK1	-1
102	DAPK2	4
103	DAPK3 (ZIPK)	1
104	DCAMKL1 (DCLK1)	-3
105	DCAMKL2 (DCK2)	-2
106	DDR1	37
107	DDR2	7
108	DMPK	0
109	DNA-PK	4
110	DYRK1A	2
111	DYRK1B	2
112	DYRK2	3
113	DYRK3	3
114	DYRK4	-3
115	EEF2K	1
116	EGFR (ErbB1)	96
117	EIF2AK2 (PKR)	20
118	EPHA1	14

#	Kinase	Compound 5 % Kinase Inhibition (1μM)
119	EPHA2	4
120	EPHA3	1
121	EPHA4	5
122	EPHA5	4
123	EPHA6	54
124	EPHA7	20
125	EPHA8	8
126	EPHB1	5
127	EPHB2	29
128	EPHB3	0
129	EPHB4	26
130	ERBB2 (HER2)	40
131	ERBB4 (HER4)	27
132	ERN1	-1
133	ERN2	-7
134	FER	2
135	FES (FPS)	4
136	FGFR1	2
137	FGFR2	4
138	FGFR3	-4
139	FGFR4	6
140	FGFR	15
141	FLT1 (VEGFR1)	22
142	FLT3	24
143	FLT3 ITD	-2
144	FLT4 (VEGFR3)	-1
145	FRAP1 (mTOR)	1
146	FRK (PTK5)	2
147	FYN	1
148	FYN A	-2
149	GAK	50
150	GRK1	-2
151	GRK4	0
152	GRK5	-7
153	GRK6	0
154	GRK7	3
155	GSG2 (Haspin)	6
156	GSK3A (GSK3 alpha)	1
157	GSK3B (GSK3 beta)	0
158	HCK	5
159	HIPK1 (Myak)	2
160	HIPK2	6
161	HIPK3 (YAK1)	3
162	HIPK4	-2
163	HUNK	-3
164	ICK	2
165	IGF1R	2
166	IKBKB (IKK beta)	2
167	IKBKE (IKK epsilon)	1
168	INSR	-7
169	INSRR (IRR)	4
170	IRAK1	-4
171	IRAK3	11
172	IRAK4	-1
173	ITK	10
174	JAK1	-2
175	JAK2	0
176	JAK2 JH1 JH2	-4
177	JAK3	1

#	Kinase	Compound 5 % Kinase Inhibition (1 μM)
178	KDR (VEGFR2)	9
179	KIT	3
180	KSR2	1
181	LATS2	-7
182	LCK	9
183	LIMK1	0
184	LIMK2	-2
185	LRRK2	-3
186	LRRK2 FL	-4
187	LTk (TYK1)	1
188	LYN A	29
189	LYN B	45
190	MAP2K1 (MEK1)	3
191	MAP2K1 (MEK1)	3
192	MAP2K2 (MEK2)	7
193	MAP2K2 (MEK2)	-1
194	MAP2K4 (MEK4)	-2
195	MAP2K5 (MEK5)	0
196	MAP2K6 (MKK6)	-4
197	MAP2K6 (MKK6)	-5
198	MAP3K10 (MLK2)	-1
199	MAP3K11 (MLK3)	-3
200	MAP3K14 (NIK)	-2
201	MAP3K19 (YSK4)	1
202	MAP3K2 (MEKK2)	-5
203	MAP3K3 (MEKK3)	-2
204	MAP3K5 (ASK1)	-4
205	MAP3K7/MAP3K7IP1 (TAK1-TAB1)	-5
206	MAP3K8 (COT)	6
207	MAP3K9 (MLK1)	-3
208	MAP4K1 (HPK1)	3
209	MAP4K2 (GCK)	3
210	MAP4K3 (GLK)	-5
211	MAP4K4 (HGK)	9
212	MAP4K5 (KHS1)	7
213	MAPK1 (ERK2)	2
214	MAPK10 (JNK3)	6
215	MAPK10 (JNK3)	5
216	MAPK11 (p38 beta)	5
217	MAPK12 (p38 gamma)	3
218	MAPK13 (p38 delta)	1
219	MAPK14 (p38 alpha)	6
220	MAPK14 (p38 alpha) Direct	5
221	MAPK15 (ERK7)	0
222	MAPK3 (ERK1)	-1
223	MAPK7 (ERK5)	1
224	MAPK8 (JNK1)	13
225	MAPK8 (JNK1)	2
226	MAPK9 (JNK2)	8
227	MAPK9 (JNK2)	2
228	MAPKAPK2	2
229	MAPKAPK3	-2
230	MAPKAPK5 (PRAK)	0
231	MARK1 (MARK)	1
232	MARK2	0
233	MARK3	3
234	MARK4	-2
235	MASTL	-1
236	MATK (HYL)	1
237	MELK	2
238	MERTK (cMER)	-4
239	MET (cMet)	1
240	MINK1	9
241	MKNK1 (MNK1)	-4
242	MKNK2 (MNK2)	10
243	MLCK (MLCK2)	1
244	MLK4	-1
245	MST1R (RON)	-4
246	MST4	2
247	MUSK	-10
248	MYLK (MLCK)	-1
249	MYLK2 (skMLCK)	-2
250	MYLK4	4
251	MYO3A (MYO3 alpha)	-2
252	MYO3B (MYO3 beta)	-2
253	NEK1	-1
254	NEK2	2
255	NEK4	0
256	NEK6	1
257	NEK8	-6
258	NEK9	-2
#	Kinase	Compound 5 % Kinase Inhibition (1 μM)
259	NIM1K	2
260	NLK	0
261	NTRK1 (TRKA)	14
262	NTRK2 (TRKB)	7
263	NTRK3 (TRKC)	11
264	NUAK1 (ARK5)	-7
265	NUAK2	-9
266	PAK1	-2
267	PAK2 (PAK65)	2
268	PAK3	-3
269	PAK4	0
270	PAK6	8
271	PAK7 (K1AA1264)	3
272	PASK	-1
273	PDGFRA (PDGFR alpha)	0
274	PDGFRB (PDGFR beta)	-2
275	PKD1	3
276	PKD1 Direct	-2
277	PEAK1	7
278	PHKG1	8
279	PHKG2	3
280	PI4K2A (PI4K2 alpha)	5
281	PI4K2B (PI4K2 beta)	2
282	PI4KA (PI4K alpha)	1
283	PI4KB (PI4K beta)	8
284	PIK3C2A (PI3K-C2 alpha)	7
285	PIK3C2B (PI3K-C2 beta)	5
286	PIK3C2G (PI3K-C2 gamma)	22
287	PIK3C3 (hVPS34)	-3
288	PIK3CA/PIK3R1 (p110 alpha/p85 alpha)	34
289	PIK3CA/PIK3R3 (p110 alpha/p55 gamma)	10
290	PIK3CB/PIK3R1 (p110 beta/p85 alpha)	-3
291	PIK3CB/PIK3R2 (p110 beta/p85 beta)	-2
292	PIK3CD/PIK3R1 (p110 delta/p85 alpha)	4
293	PIK3CG (p110 gamma)	40
294	PIM1	2
295	PIM2	2
296	PIM3	-1
297	PIP4K2A	-18
298	PIP5K1A	-2
299	PIP5K1B	-6
300	PIP5K1C	-1
301	PKMYT1	2
302	PKN1 (PRK1)	1
303	PKN2 (PRK2)	2
304	PLK1	0
305	PLK2	2
306	PLK3	-7
307	PLK4	-3
308	PRKACA (PKA)	-1
309	PRKACB (PRKAC beta)	-8
310	PRKACG (PRKAC gamma)	-1
311	PRKCA (PKC alpha)	-8
312	PRKCB1 (PKC beta I)	5
313	PRKCB2 (PKC beta II)	21
314	PRKCD (PKC delta)	-3
315	PRKCE (PKC epsilon)	11
316	PRKCG (PKC gamma)	12
317	PRKCH (PKC eta)	-2
318	PRKCI (PKC iota)	15
319	PRKCN (PKD3)	6
320	PRKCQ (PKC theta)	14
321	PRKCZ (PKC zeta)	8
322	PRKD1 (PKC mu)	5
323	PRKD2 (PKD2)	0
324	PRKG1	0
325	PRKG2 (PKG2)	-3
326	PRKX	9
327	PTK2 (FAK)	0
328	PTK2B (FAK2)	3
329	PTK6 (Brk)	9
330	RET	8
331	RIPK2	67
332	RIPK3	75
333	ROCK1	1
334	ROCK2	0
335	ROSI	7
#	Kinase	Compound 5 % Kinase Inhibition (1 μM)
336	RPS6KA1 (RSK1)	3
337	RPS6KA2 (RSK3)	1
338	RPS6KA3 (RSK2)	1
339	RPS6KA4 (MSK2)	-2
340	RPS6KA5 (MSK1)	-3
341	RPS6KA6 (RSK4)	-2
342	RPS6KB1 (p70S6K)	6
343	RPS6KB2 (p70S6Kb)	3
344	SBK1	12
345	SGK (SGK1)	2
346	SGK2	3
347	SGKL (SGK3)	4
348	SIK1	0
349	SIK3	2
350	SLK	4
351	SNF1LK2	5
352	SPHK1	-3
353	SPHK2	-8
354	SRC	6
355	SRC N1	4
356	SRMS (Srm)	6
357	SRPK1	-2
358	SRPK2	3
359	STK16 (PKL12)	-2
360	STK17A (DRAK1)	65
361	STK17B (DRAK2)	12
362	STK22B (TSSK2)	3
363	STK22D (TSSK1)	0
364	STK23 (MSSK1)	-2
365	STK24 (MST3)	2
366	STK25 (YSK1)	-1
367	STK3 (MST2)	-1
368	STK32B (YANK2)	0
369	STK32C (YANK3)	-2
370	STK33	1
371	STK38 (NDR)	-2
372	STK38L (NDR2)	12
373	STK39 (STLK3)	5
374	STK4 (MST1)	-1
375	SYK	-2
376	TAOK1	-3
377	TAOK2 (TAO1)	-3
378	TAOK3 (JIK)	-1
379	TBK1	0
380	TEC	-3
381	TEK (Tie2)	-8
382	TESK1	3
383	TESK2	-3
384	TGFBR1 (ALK5)	-3
385	TGFBR2	28
386	TLK1	-11
387	TLK2	-6
388	TNIK	6
389	TNK1	4
390	TNK2 (ACK)	0
391	TTK	-4
392	TXK	5
393	TYK2	5
394	TYRO3 (RSE)	1
395	ULK1	0
396	ULK2	-3
397	ULK3	0
398	VRK2	5
399	WEE1	3
400	WNK1	-3
401	WNK2	1
402	WNK3	-2
403	YES1	10
404	ZAK	-2
405	ZAP70	1
406	EGFR (ErbB1) C797S	88
407	EGFR (ErbB1) d746-750	100
408	EGFR (ErbB1) d747-749	103
409	EGFR (ErbB1) G719C	88
410	EGFR (ErbB1) G719S	89
411	EGFR (ErbB1) L858R	93
412	EGFR (ErbB1) L861Q	96
413	EGFR (ErbB1) T790M	11
414	EGFR (ErbB1) T790M C797S L858R	8
415	EGFR (ErbB1) T790M L858R	8

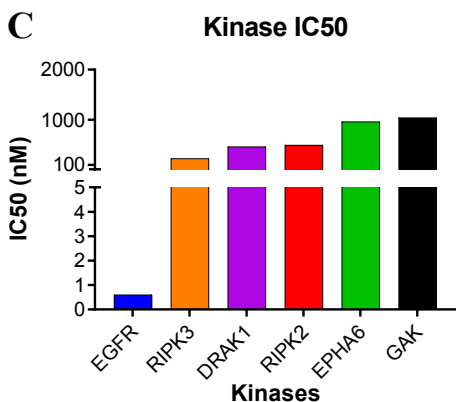


Figure S5. Kinome profiling of compound **5**. (A) TREEspot™ kinome profile of wild-type kinases (left) and mutant kinases (right) of compound **5**. The size of the circle refers to the percent of control of kinase activity remaining at a drug concentration of 1 μ M. Image generated using TREEspot™ Software Tool and reprinted with permission from KINOMEScan®, a division of DiscoverX Corporation, © DISCOVERX CORPORATION 2010. (B) Tabular list of kinases tested and their percent kinase inhibition (Thermofisher). (C) IC₅₀ determinations of the top wild-type kinase hits from the primary screen.

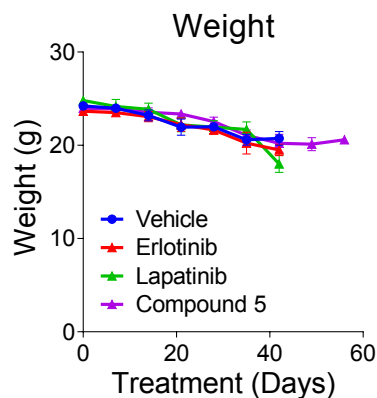


Figure S6. Mouse weights in orthotopic GBM39 xenograft mice treated with indicated EGFR inhibitors from survival study in Figure 2.

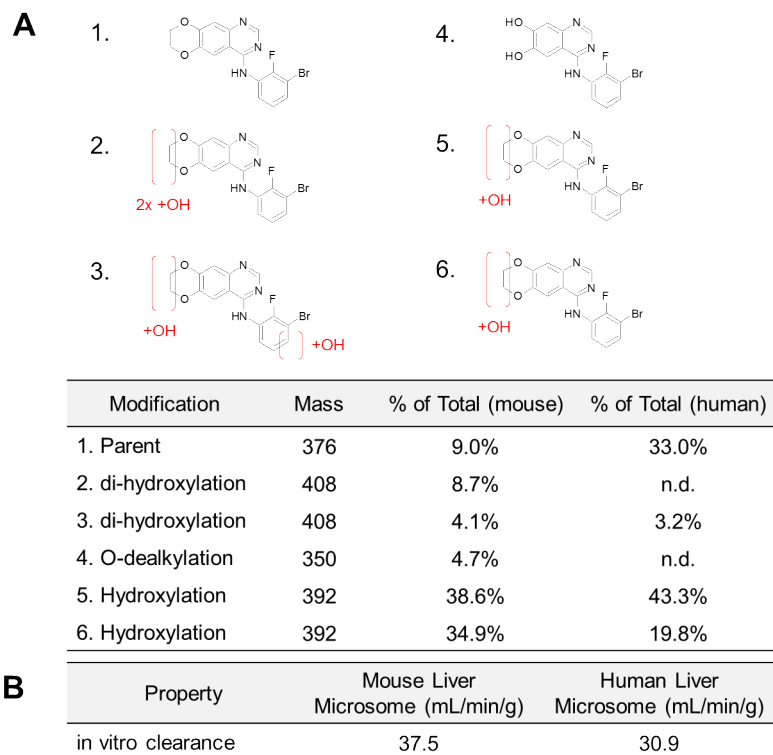


Figure S7. Metabolism of compound **5** in mouse and human liver microsomes. (A) Compound **5** was incubated for 30 minutes with liver microsomes and profiled by LC-MS to determine metabolites. n.d., not detected. (B) in vitro clearance from mouse and human liver microsomes.

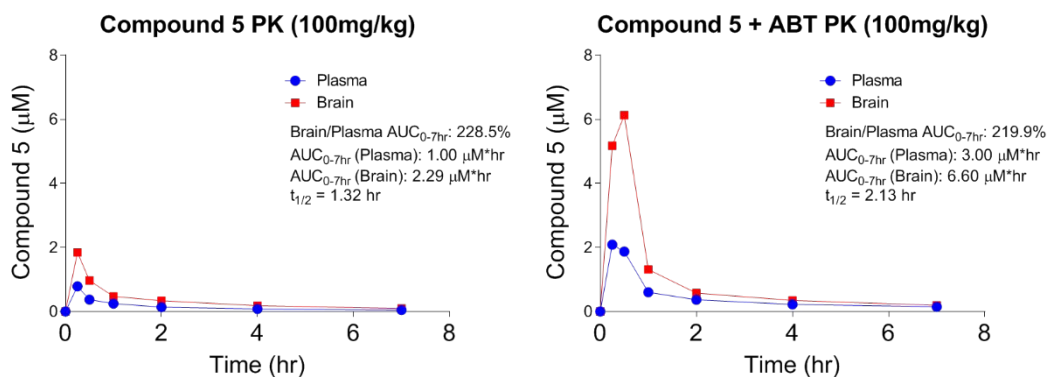


Figure S8. Oral pharmacokinetics of plasma and brain tissue from healthy CD-1 mice of compound **5** alone (A) and compound **5** combined with 1-aminobenzotriazole (ABT) (B).

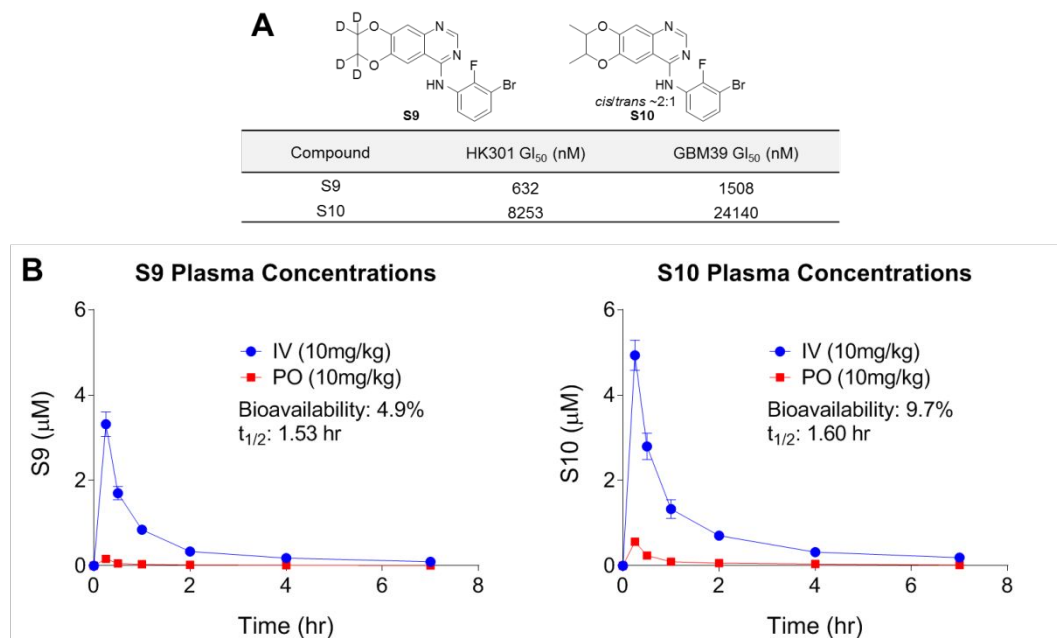


Figure S9. Analogues with modified fused 1,4-dioxane ring for mitigating metabolic labile sites. (A) Structures and *in vitro* potency of **S9** and **S10**. (B) Bioavailability of **S9** and **S10**.

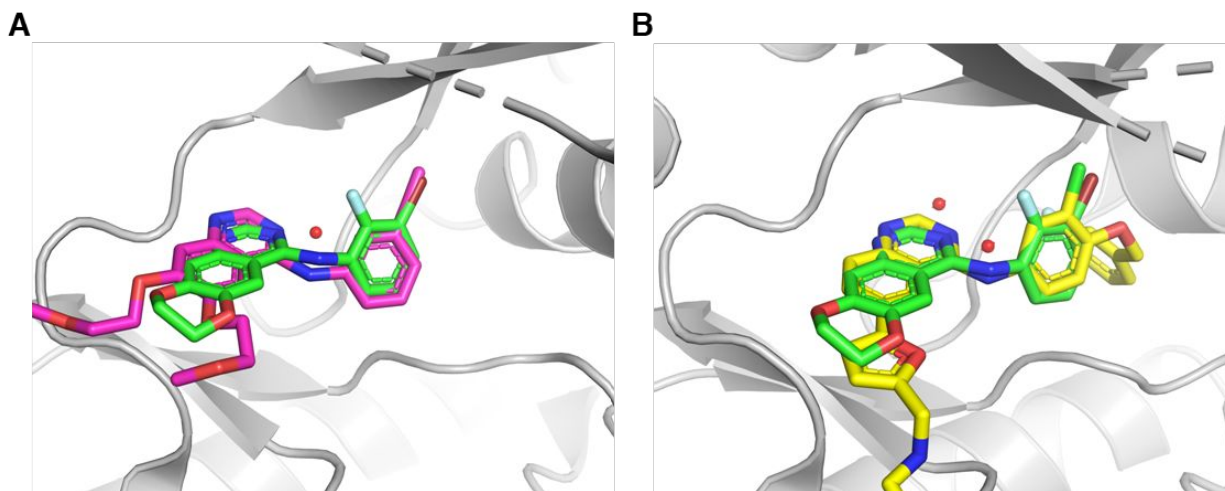


Figure S10. Overlays of compound **5** docked into the active site of wtEGFR together with the original ligand of the crystal structure: (A) erlotinib (PDB 1M17), (B) lapatinib (PDB 1XKK).⁸ For both docking results, the quinazoline ring system is slightly tilted, and the aniline ring is slightly displaced compared to the ligand in the crystal structure. However, the observed close contact interactions with the protein are in line with the binding mode of the type I TKI scaffold. The P-loops have been removed for clarity. Color code: C_{enzyme} gray, C₅ green, C_{erlotinib} purple, C_{lapatinib} yellow, O red, N blue, F light blue, Cl green, Br dark red.

Table S5. Efflux ratios and K_{puu} of AZD3759, osimertinib, and compound **5**.

Compound	Concentration (μ M)	Efflux Ratio (P-gp)	Efflux Ratio (BCRP)	$K_{p,uu,brain}$ (Mouse)
AZD3759	1	0.41 ⁹	0.64 ⁹	1.30 ⁹
AZD9291	1	13.4 ¹⁰	5.4 ¹⁰	0.39 ¹⁰
Compound 5	10	0.58	0.30	1.30

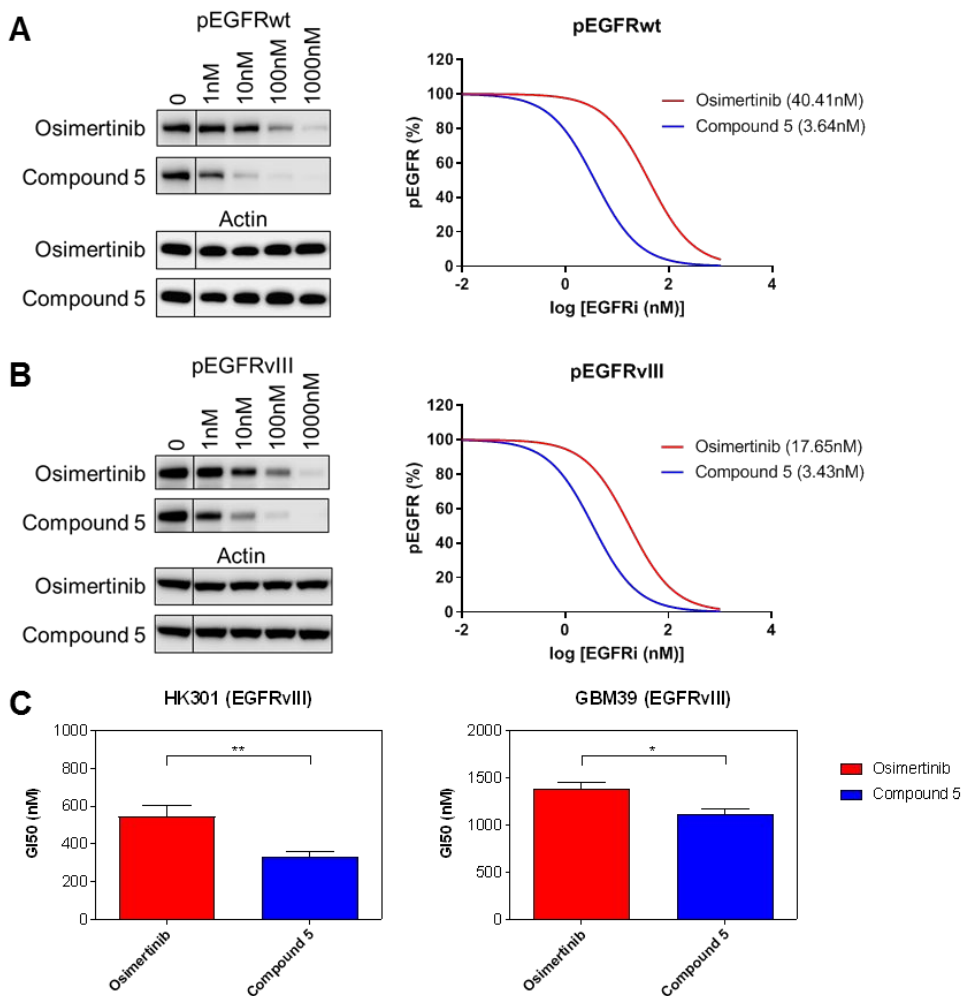


Figure S11. Potency comparisons of osimertinib and compound **5**. Compound **5** is more potent at inhibiting (A) EGF-stimulated wtEGFR and (B) EGFRvIII than osimertinib (C) Osimertinib and compound **5** GI_{50} show compound **5** more potently inhibits growth of EGFRvIII mutant HK301 and GBM39 patient-derived lines. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

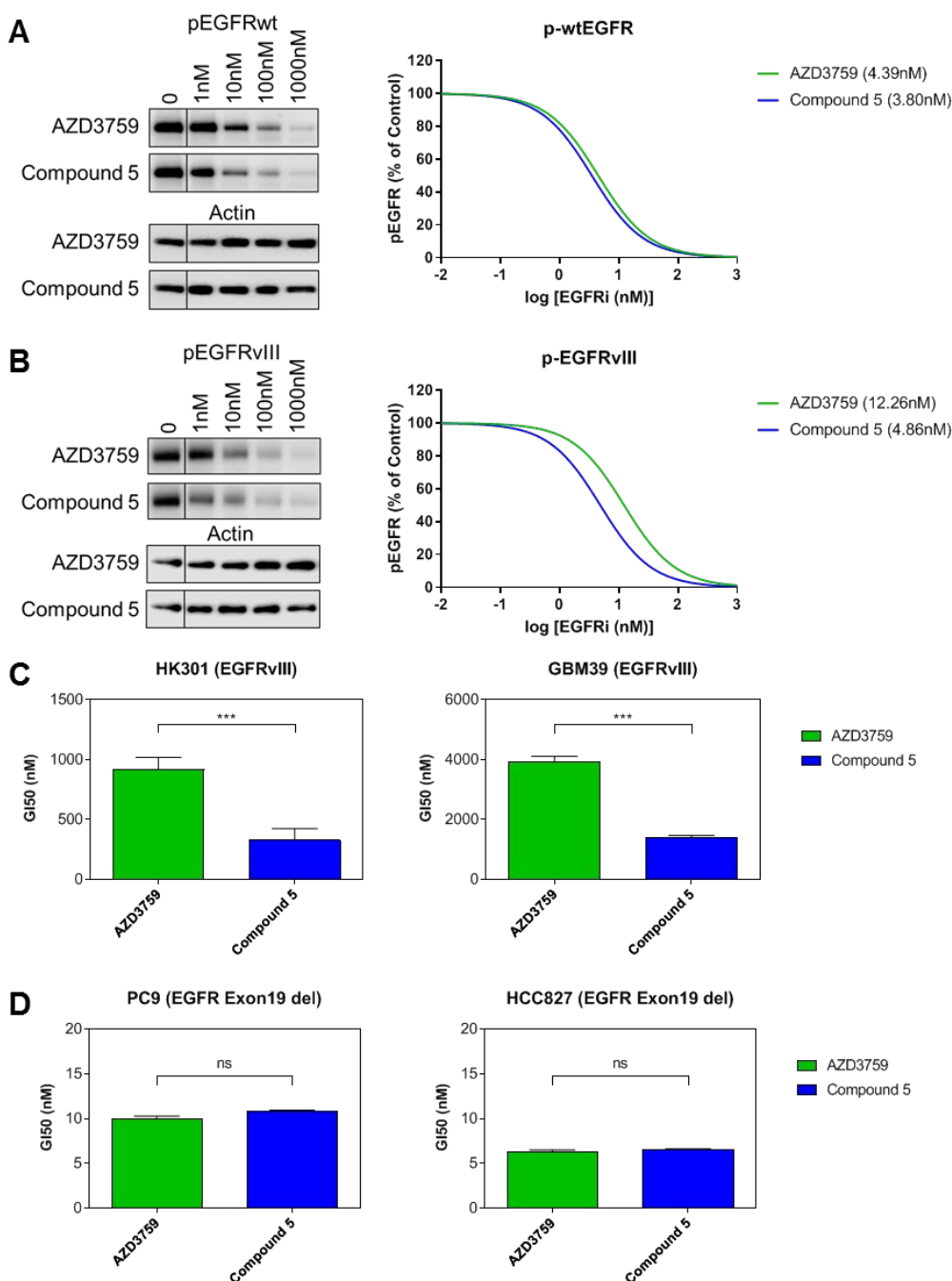


Figure S12. Potency comparisons of AZD3759 and compound **5**. Compound **5** is equally potent at inhibiting EGF-stimulated wtEGFR (A) but is more potent at inhibiting EGFRvIII (B) compared with AZD3759. (C) AZD3759 and compound **5** GI₅₀ show compound **5** more potently inhibits growth of EGFRvIII mutant HK301 and GBM39 patient-derived cell lines. (D) AZD3759 and compound **5** equally inhibit growth of Exon 19 EGFR-mutant PC9 and HCC827 lung cancer lines. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

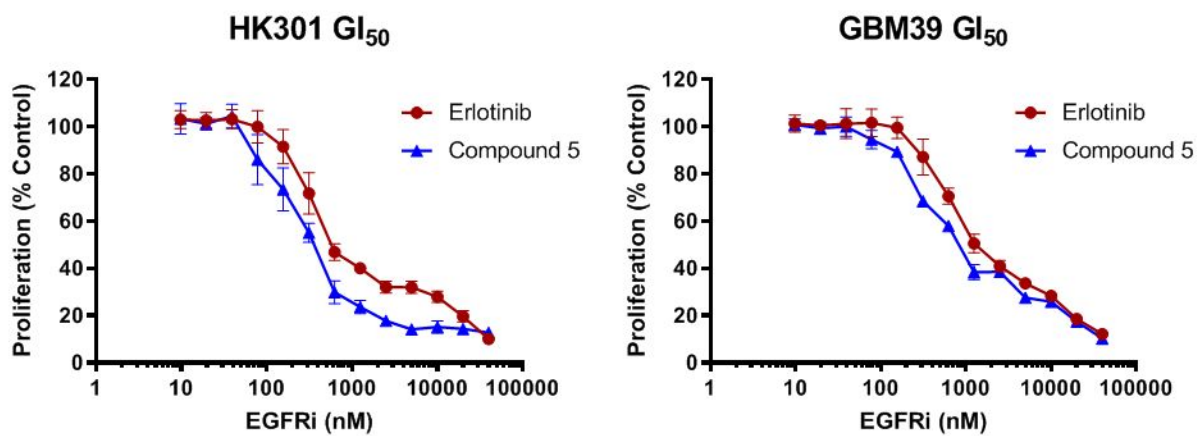
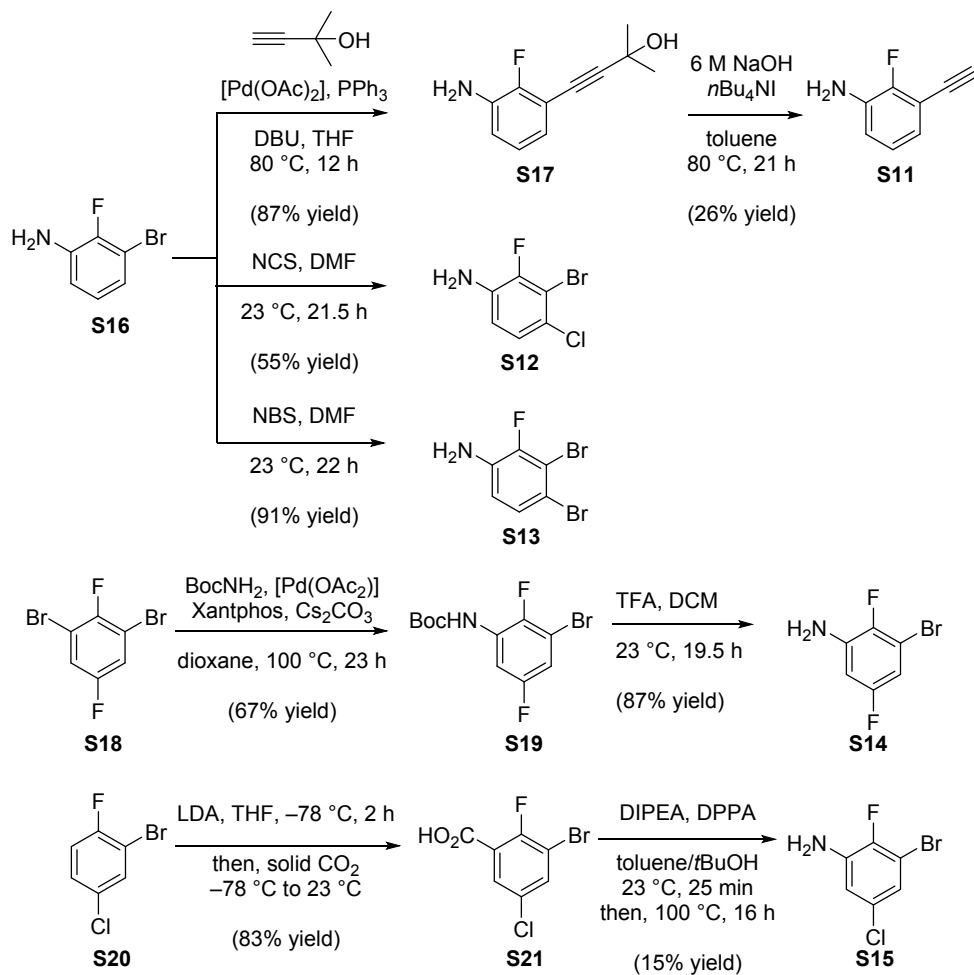


Figure S13. GI₅₀s of erlotinib and Compound 5 against patient-derived EGFRvIII mutant GBM cell lines indicate no paradoxical increase in growth was observed at any concentration of the tested EGFR TKI.

S2. Synthesis Schemes

Synthesis of halogenated anilines:

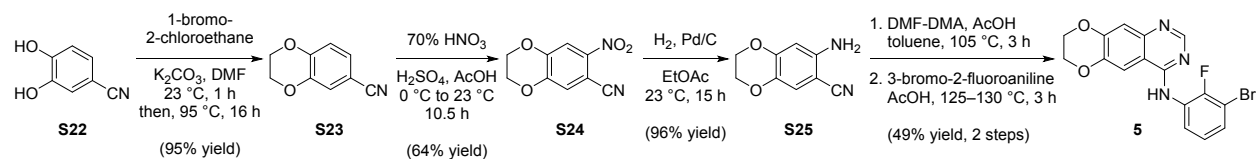
Scheme S1 shows the preparation of the halogenated anilines **S11**–**S15**, which were used in the reaction with the chloroquinazoline **24** for the synthesis of the final compounds **2**, and **13**–**16**. 2-Amino-6-bromophenol was prepared as described in ¹¹.



Scheme S1. Synthesis of the halogenated anilines **S11**–**S15**.

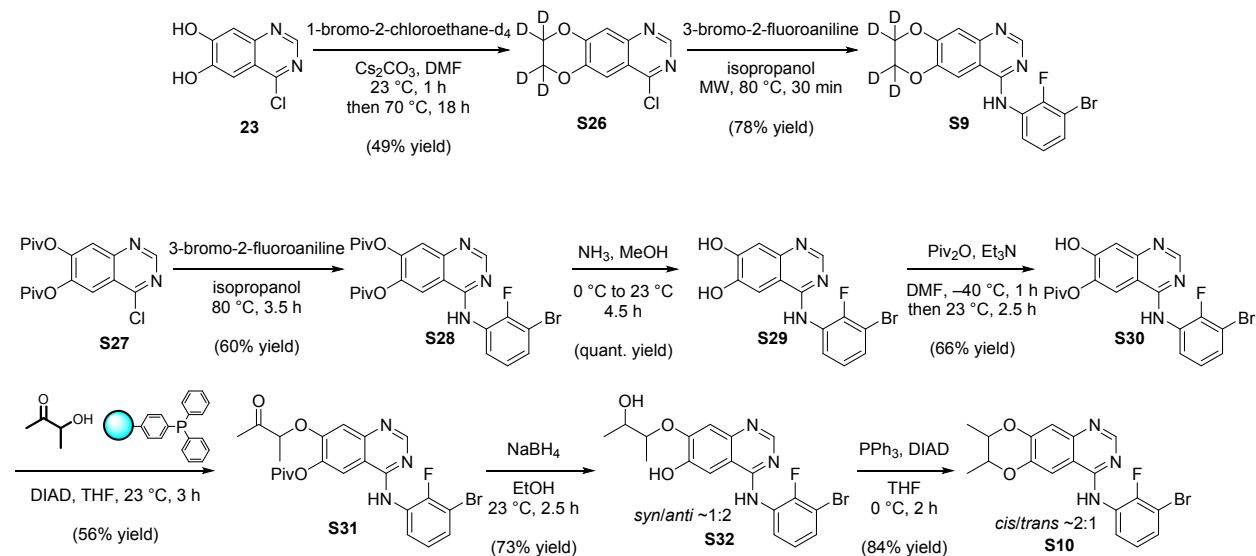
Short route to compound **5**:

Alkylation of 3,4-dihydroxybenzonitrile (**S22**) with 1-bromo-2-chloroethane gave benzodioxanecarbonitrile **S23** in good yield and sufficient purity to directly continue with its nitration to **S24**, which was purified by recrystallization. Hydrogenation of **S24** afforded the anthranilonitrile **S25**, which was subjected to the usual conditions for the quinazoline synthesis by the Dimroth rearrangement to obtain **5**.



Scheme S2. Short synthetic route to compound **5**.

Synthesis of perdeuterated (**S9**) and vic-dimethyl (**S10**) substituted analogues of compound **5**:



Scheme S3. Synthesis of analogues **S9** and **S10** with a modified fused-1,4-dioxane ring for improved metabolic stability.

S3. Experimental Procedures

Chemistry. *General.* Unless otherwise noted, all chemicals, reagents, and solvents were purchased from commercial sources when available and were used as received. When necessary, reagents and solvents were purified and dried by standard methods. Air- and moisture-sensitive reactions were carried out under an inert atmosphere of argon in oven-dried glassware. Microwave-irradiated reactions were carried out in a single mode reactor CEM Discover microwave synthesizer or with a Biotage Initiator+ system. Room temperature (RT) reactions were carried out at ambient temperature (approximately 23 °C). All reactions were monitored by thin layer chromatography (TLC) on precoated Merck 60 F₂₅₄ silica gel plates with spots visualized by UV light (λ = 254, 365 nm), or colored by using a KMnO₄ solution. Flash column chromatography was carried out on SiO₂ 60 (particle size 0.040–0.063 mm, 230–400 mesh). Preparative thin-layer chromatography (PTLC) was carried out with Merck 60 F₂₅₄ silica gel plates (20 x 20 cm, 210–270 μ m) or Analtech Silica Gel GF TLC plates (20 x 20 cm, 1000 μ m). Concentration under reduced pressure (in vacuo) was performed by rotary evaporation typically at 25–35 °C. Purified compounds were further dried under high vacuum (HV) or in a desiccator. Yields correspond to purified compounds unless otherwise indicated, and were generally not further optimized. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on Bruker spectrometers (operating at 300, 400, or 500 MHz). Carbon NMR (¹³C NMR) spectra were recorded on Bruker spectrometers (either at 400 or 500 MHz). NMR chemical shifts (δ ppm) were referenced to the residual solvent signals. ¹H NMR data are reported as follows: chemical shift in ppm; multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet/complex pattern, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, ddd = doublet of doublet of doublets, tdd = triplet of doublet of doublets, br = broad signal); coupling constants (*J*) in Hz, integration. Data

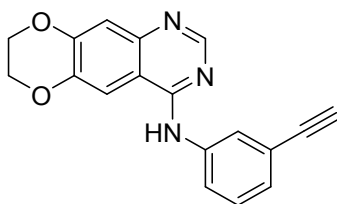
for ^{13}C NMR spectra are reported in terms of chemical shift, and if applicable coupling constants. High resolution mass (HRMS) spectra were recorded on a Thermo Fisher Scientific Exactive Plus with IonSense ID-CUBE DART source mass spectrometer, or on a Waters LCT Premier mass spectrometer with ACQUITY UPLC with autosampler. All final compounds were purified to >95% purity as determined by HPLC (11 min). HPLC (11 min) methods used the following: Agilent 1260 Infinity LC system, Agilent Polaris C18-A 4.6 x 150 mm, 5 μm at 40 $^{\circ}\text{C}$ with a 0.8 mL/min flow rate; solvent A of 0.1% (v/v) formic acid in water, solvent B of 0.1% (v/v) in acetonitrile; 0.0–2.0 min, 5% B; 2.1–10.0 min, 5–95% B; 10.1–11 min, 95% B. Compounds were named according to the IUPAC nomenclature and numbering system following suggestions of ACD/ChemSketch from Advanced Chemistry Development, Inc.

General Procedures (GP). *GP-1: Nucleophilic Aromatic Substitution of 4-Chloroquinazoline with Anilines (Method A).* A mixture of the 4-chloroquinazoline **24** (1 equiv) in isopropanol (0.1–0.3 M) was treated with the aniline (1 equiv), and the mixture was heated at 80 $^{\circ}\text{C}$ under microwave irradiation for 15–20 min. The mixture was cooled to RT, treated with additional equiv of the aniline, and again subjected to microwave irradiation (80 $^{\circ}\text{C}$, 15–20 min). (Alternatively, **24** (1 equiv) was treated with aniline (2 equiv) and heated in the microwave for 30 min under otherwise identical conditions). The mixture was either concentrated under reduced pressure, or the precipitated 4-anilinoquinazoline hydrochloride salt was isolated by filtration (washings with cold isopropanol). The residue was suspended in sat. aq. NaHCO_3 , and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography (elution with a gradient of $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ or hexanes/ EtOAc) afforded the desired products typically as white to off-white, or pale-yellow solids.

GP-2: Nucleophilic Aromatic Substitution of 4-Chloroquinazoline with Anilines (Method B). A mixture of the 4-chloroquinazoline **24** (1 equiv) in acetonitrile (0.1–0.3 M) was treated with the aniline (2 equiv) and a 4 M solution of HCl in dioxane (1 equiv). The mixture was heated at 80 °C under microwave irradiation for 30 min. The mixture was either concentrated under reduced pressure, or the precipitated 4-anilinoquinazoline hydrochloride salt was isolated by filtration (washings with Et₂O). The residue was suspended in sat. aq. NaHCO₃, and extracted with CH₂Cl₂ (3x). The combined organic extracts were washed with water, brine, dried (Na₂SO₄), filtered, and concentrated. Purification by flash chromatography (elution with a gradient of CH₂Cl₂/EtOAc or hexanes/EtOAc) afforded the desired products typically as white to off-white, or pale-yellow solids.

GP-3: Nucleophilic Aromatic Substitution of 4-Chloroquinazoline with Anilines (Method C). A mixture of the 4-chloroquinazoline **24** (1 equiv) in anhydrous DMF (0.1 – 0.2 M) was treated with the aniline (2–3.5 equiv), and the mixture was stirred at 60 °C for 24 h. The mixture was cooled to RT, and diluted with water (30 mL) and EtOAc (30 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed successively with water and brine, dried (MgSO₄), filtered, and evaporated. Purification by flash chromatography (elution with a gradient of hexanes/EtOAc) afforded the desired products.

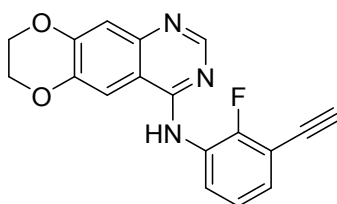
***N*-(3-Ethynylphenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (1)**



Following general procedure **GP-1**, compound **1** was prepared from the chloroquinazoline **24** (35 mg, 0.16 mmol) and 3-ethynylaniline (36 μ L, 0.32 mmol) in isopropanol (1.5 mL). Flash chromatography (CH₂Cl₂/EtOAc 1:0 \rightarrow 10:4) gave **1** (39 mg, 82%) as an off-white solid.

¹H NMR (500 MHz, DMSO-*d*₆): δ 9.49 (s, 1H), 8.47 (s, 1H), 8.11 – 8.06 (m, 1H), 8.08 (s, 1H), 7.95 – 7.90 (m, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.22 – 7.16 (m, 1H), 7.19 (s, 1H), 4.45 – 4.36 (m, 4H), 4.19 (s, 1H). ¹³C NMR (126 MHz, DMSO-*d*₆): δ 156.39, 152.86, 149.13, 146.06, 143.65, 139.81, 128.87, 126.29, 124.46, 122.26, 121.70, 112.59, 109.99, 108.38, 83.57, 80.52, 64.50, 64.17. HRMS (DART): *m/z* [M + H]⁺ calcd for C₁₈H₁₄N₃O₂⁺, 304.1081; found, 304.1078.

***N*-(3-Ethynyl-2-fluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (2)**



Preparation from the chloroquinazoline **24**: following general procedure **GP-1**, compound **2** was prepared from the chloroquinazoline **24** (35 mg, 0.16 mmol) and 3-ethynyl-2-fluoroaniline (**S11**) (42 mg, 0.31 mmol) in isopropanol (1.5 mL). After the reaction, the precipitated hydrochloride salt of **2** was converted into the free base by extraction of a sat. aq. NaHCO₃ solution to obtain pure **2** (34 mg, 67%) as an off-white solid.

Preparation from the quinazoline **4**: a 1 dram vial was charged with **4** (75 mg, 0.23 mmol), XPhos (19.7 mg, 0.041 mmol), Cs₂CO₃ (195 mg, 0.60 mmol), [PdCl₂•(MeCN)₂] (3.6 mg, 0.014 mmol). The vial was evacuated and backfilled with argon (repeated at least twice). Dry acetonitrile (1 mL) was added, and the orange suspension was stirred at RT for 25 min, then ethynyltriethylsilane (150 μ L, 0.84 mmol) was injected. The tube was sealed, and the reaction mixture stirred at 95 °C in a

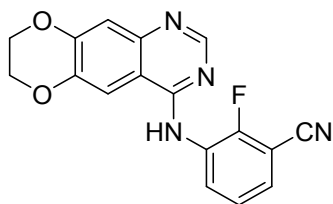
preheated oil bath for 3.5 h. The suspension was allowed to reach 23 °C, diluted with EtOAc, filtered through a plug of SiO₂ (washings with EtOAc), and evaporated. Purification by flash chromatography (hexanes/EtOAc 8:2 → 4:6) afforded the triethylsilyl-protected compound **2** (48 mg, 49%) as a yellow foamy solid.

¹H NMR (500 MHz, CDCl₃): δ 8.681 (td, J = 8.1, 1.9 Hz, 1H), 8.678 (s, 1H), 7.382 (s, 1H), 7.376 (br, 1H), 7.28 (s, 1H), 7.21 – 7.12 (m, 2H), 4.44 – 4.38 (m, 4H), 1.07 (t, J = 7.9 Hz, 9H), 0.71 (q, J = 7.9 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃): δ 155.95, 153.81 (d, J_{CF} = 248.0 Hz), 153.44, 149.62, 146.66, 144.47, 127.68, 127.60, 124.15 (d, J_{CF} = 4.5 Hz), 122.79, 114.49, 111.77 (d, J_{CF} = 14.6 Hz), 110.61, 105.97, 98.65, 98.49 (d, J_{CF} = 3.7 Hz), 64.70, 64.51, 7.63, 4.50. HRMS (DART): m/z [M + H]⁺ calcd for C₂₄H₂₇FN₃O₂Si⁺, 436.1851; found, 436.1831.

A mixture of triethylsilyl-protected compound **2** (40 mg, 0.09 mmol) in wet THF (0.9 mL) was treated dropwise with a 1 M solution of TBAF in THF (450 μ L, 0.45 mmol), and the mixture was stirred at RT for 18 h. Water (10 mL) was added, and the mixture was extracted with EtOAc (3 x 15 mL). The combined organics were washed with brine (20 mL), dried (Na₂SO₄), filtered, and evaporated. Purification by flash chromatography (hexanes/EtOAc 7:3 → 3:7), followed by a second flash chromatography (CH₂Cl₂/EtOAc 1:0 → 6:4) afforded **2** (19 mg, 64%) as an off-white solid.

¹H NMR (500 MHz, CDCl₃): δ 8.69 (td, J = 8.0, 1.9 Hz, 1H), 8.67 (s, 1H), 7.38 (s, 1H), 7.36 (br, 1H), 7.29 (s, 1H), 7.21 (ddd, J = 8.1, 6.3, 1.9 Hz, 1H), 7.17 (td, J = 7.8, 0.9 Hz, 1H), 4.44 – 4.37 (m, 4H), 3.34 (s, 1H). ¹³C NMR (126 MHz, CDCl₃): δ 155.94, 154.04 (d, J_{CF} = 248.6 Hz), 153.39, 149.65, 146.69, 144.47, 127.81, 127.67 (d, J_{CF} = 9.2 Hz), 124.29 (d, J_{CF} = 4.7 Hz), 123.48, 114.48, 110.58, 110.50 (d, J_{CF} = 14.3 Hz), 105.99, 82.95 (d, J_{CF} = 3.6 Hz), 76.70 (d, J_{CF} = 1.7 Hz), 64.69, 64.50. HRMS (DART): m/z [M + H]⁺ calcd for C₁₈H₁₃FN₃O₂⁺, 322.0986; found, 322.0981.

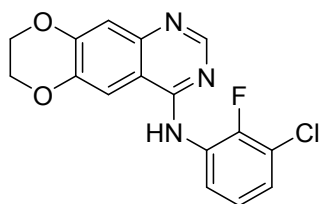
3-[(7,8-Dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-yl)amino]-2-fluorobenzonitrile (**3**)



A 1 dram vial was charged with **4** (75 mg, 0.23 mmol), *t*BuXPhos-Pd-G3 (9 mg, 0.01 mmol), and Zn(CN)₂ (18 mg, 0.15 mmol). The vial was evacuated and backfilled with Ar (3x). THF (190 μ L) and degassed water (940 μ L) were added. The vial was sealed, and vigorously stirred at 40 °C for 18.5 h. Sat. aq. NaHCO₃ (20 mL) was added, and the mixture was extracted with EtOAc (3 x 13 mL). The combined organics were washed with water (13 mL), brine (13 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo. Flash chromatography (CH₂Cl₂/EtOAc 1:0 \rightarrow 1:1) gave **3** (20 mg, 27%) as a yellow solid together with recovered **4** (46 mg, 61%) as a white solid.

¹H NMR (500 MHz, CDCl₃): δ 9.06 – 8.98 (m, 1H), 8.69 (s, 1H), 7.41 (s, 1H), 7.39 (br, 1H), 7.35 – 7.31 (m, 2H), 7.30 (s, 1H), 4.45 – 4.37 (m, 4H). ¹³C NMR (126 MHz, CDCl₃): δ 155.63, 153.63 (d, *J*_{CF} = 254.6 Hz), 153.04, 149.94, 146.80, 144.76, 128.60 (d, *J*_{CF} = 7.8 Hz), 127.48, 126.58, 125.31 (d, *J*_{CF} = 4.5 Hz), 114.56, 113.80, 110.45, 105.83, 101.30 (d, *J*_{CF} = 13.9 Hz), 64.70, 64.51. HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₇H₁₂FN₄O₂⁺, 323.0939; found, 323.0927.

N-(3-Chloro-2-fluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (**4**)

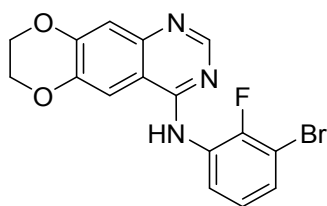


Following general procedure **GP-1**, compound **4** was prepared from the chloroquinazoline **24** (401 mg, 1.80 mmol) and 3-chloro-2-fluoroaniline (396 μ L, 3.60 mmol) in isopropanol (3.6 mL). After

the reaction, the precipitated hydrochloride salt of **4** was converted into the free base by extraction of a sat. aq. NaHCO₃ solution to obtain pure **4** (507 mg, 85%) as a pale-yellow solid.

¹H NMR (500 MHz, CDCl₃): δ 8.69 (s, 1H), 8.60 (td, J = 7.3, 2.3 Hz, 1H), 7.39 (s, 1H), 7.34 (br, 1H), 7.30 (s, 1H), 7.20 – 7.10 (m, 2H), 4.45 – 4.38 (m, 4H). ¹³C NMR (126 MHz, CDCl₃): δ 155.90, 153.37, 149.71, 149.33 (d, J_{CF} = 244.2 Hz), 146.75, 144.53, 128.75 (d, J_{CF} = 9.3 Hz), 124.71 (d, J_{CF} = 5.1 Hz), 124.48, 121.07, 120.86 (d, J_{CF} = 16.1 Hz), 114.54, 110.59, 105.95, 64.70, 64.52. HRMS (DART): m/z [M – H][–] calcd for C₁₆H₁₀ClFN₃O₂[–], 330.0451; found, 330.0457.

N-(3-Bromo-2-fluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (**5**)



Preparation from the chloroquinazoline **24**: following general procedure **GP-1**, compound **5** was prepared from the chloroquinazoline **24** (100 mg, 0.45 mmol) and 3-bromo-2-fluoroaniline (100 μ L, 0.89 mmol) in isopropanol (1.5 mL). Flash chromatography (CH₂Cl₂/EtOAc 10:0 \rightarrow 10:3) gave **5** (150 mg, 89%) as a pale-yellow solid.

Preparation from the anthranilonitrile **S25**: a mixture of anthranilonitrile **S25** (2.388 g, 13.6 mmol) in toluene (35 mL) was treated with AcOH (35 μ L, 0.61 mmol) and DMF-DMA (3.24 mL, 24.4 mmol), and stirred at 105 °C for 3 h. The mixture was cooled to 23 °C and evaporated to afford the corresponding *N,N*-dimethyl formamidine derivative (3.292 g, quant.) as a yellow, amorphous solid, which was used in the next step without any further purification.

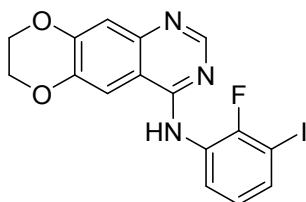
¹H NMR (500 MHz, CDCl₃): δ 7.50 (s, 1H), 7.02 (s, 1H), 6.43 (s, 1H), 4.29 – 4.26 (m, 2H), 4.23 – 4.20 (m, 2H), 3.05 (s, 3H), 3.03 (s, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 153.69, 150.53, 148.11,

139.03, 121.05, 118.72, 108.10, 99.17, 64.91, 64.12, 40.39, 34.69. HRMS (DART): m/z $[M + H]^+$ calcd for $C_{12}H_{14}N_3O_2^+$, 232.1081; found, 232.1087.

A mixture of the crude *N,N*-dimethyl formamidine derivative (3.265 g, 14.1 mmol) in AcOH (36.4 mL) was treated with 3-bromo-2-fluoroaniline (1.98 mL, 17.6 mmol) and stirred at 125–130 °C for 3 h. The mixture was cooled to 23 °C, and poured into ice-water (70 mL). The pH was adjusted to ~9 with 30% aq. NH_4OH (46 mL), and EtOAc (18 mL) was added. The resulting mixture was stirred at 23 °C for 45 min, and filtered. The yellow residue was suspended in MeOH (70 mL), treated dropwise with conc. HCl (3.5 mL), and stirred vigorously until a precipitate formed, which was collected by filtration (washings with cold MeOH, 3 x 4 mL), and dried under HV to obtain the hydrochloride salt of **5** (3159 mg, 54%). The residue was suspended in sat. aq. $NaHCO_3$ (500 mL), and extracted with CH_2Cl_2 (3 x 200 mL). The combined organics were washed with water (150 mL), brine (150 mL), dried (Na_2SO_4), filtered, and evaporated to give **5** (2.622 g, 49%) as a yellow solid.

1H NMR (500 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.65 (ddd, $J = 8.3, 7.4, 1.5$ Hz, 1H), 7.39 (s, 1H), 7.35 (br, 1H), 7.29 (s, 1H), 7.29 – 7.24 (m, 1H), 7.11 (td, $J = 8.2, 1.6$ Hz, 1H), 4.44 – 4.38 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.89, 153.37, 150.15 (d, $J_{CF} = 242.2$ Hz), 149.70, 146.75, 144.53, 128.65 (d, $J_{CF} = 10.5$ Hz), 127.24, 125.31 (d, $J_{CF} = 4.7$ Hz), 121.79, 114.53, 110.59, 108.59 (d, $J_{CF} = 19.4$ Hz), 105.93, 64.70, 64.51. HRMS (DART): m/z $[M - H]^-$ calcd for $C_{16}H_{10}BrFN_3O_2^-$, 373.9946; found, 373.9946.

***N*-(2-Fluoro-3-iodophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (6)**

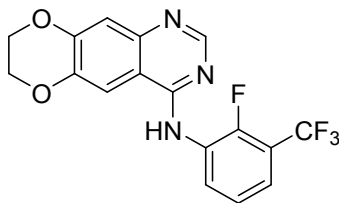


A 1 dram vial was charged with **5** (50 mg, 0.13 mmol), CuI (3.8 mg, 0.02 mmol), and NaI (42 mg, 0.28 mmol), and evacuated and backfilled with Ar (3x). Dioxane (0.9 mL) and (±)-*trans*-*N,N*-dimethylcyclohexane-1,2-diamine (6.3 μ L, 0.04 mmol) were added. The vial was sealed and heated at 110 °C for 24 h. After cooling to 23 °C, sat. aq. NaHCO₃ (3 mL) was added, and the mixture transferred into water (15 mL). The mixture was extracted with CH₂Cl₂ (3 x 13 mL), and the combined organics were dried (Na₂SO₄), filtered, and evaporated. Purification by flash chromatography (CH₂Cl₂/EtOAc 1:0 \rightarrow 3:1) gave **6** (47 mg, 84%) as an off-white solid.

¹H NMR (500 MHz, CDCl₃): δ 8.71 – 8.64 (m, 1H), 8.68 (s, 1H), 7.46 (ddd, *J* = 8.0, 5.9, 1.5 Hz, 1H), 7.39 (s, 1H), 7.34 (br, 1H), 7.28 (s, 1H), 6.99 (td, *J* = 8.1, 1.3 Hz, 1H), 4.45 – 4.38 (m, 4H).
¹³C NMR (126 MHz, CDCl₃): δ 155.88, 153.39, 152.51 (d, *J*_{CF} = 240.3 Hz), 149.69, 146.73, 144.53, 132.95, 127.86 (d, *J*_{CF} = 11.5 Hz), 126.14 (d, *J*_{CF} = 4.3 Hz), 122.82, 114.53, 110.60, 105.93, 80.32 (d, *J*_{CF} = 23.9 Hz), 64.70, 64.51. HRMS (DART): *m/z* [M + H]⁺ calcd for C₁₆H₁₂FIN₃O₂⁺, 423.9953; found, 423.9958.

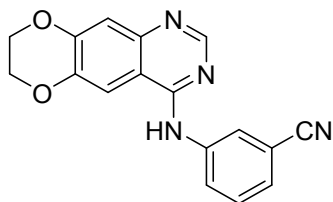
***N*-[2-Fluoro-3-(trifluoromethyl)phenyl]-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine**

(7)



Following general procedure **GP-1**, compound **7** was prepared from the chloroquinazoline **24** (37 mg, 0.17 mmol) and 2-fluoro-3-(trifluoromethyl)aniline (42 μ L, 0.33 mmol) in isopropanol (1.5 mL). Flash chromatography (CH₂Cl₂/EtOAc 1:0 \rightarrow 10:3) gave **7** (35 mg, 58%) as an off-white solid. ¹H NMR (500 MHz, CDCl₃): δ 9.00 – 8.92 (m, 1H), 8.70 (s, 1H), 7.42 (br, 1H), 7.40 (s, 1H), 7.35 – 7.28 (m, 2H), 7.30 (s, 1H), 4.46 – 4.38 (m, 4H). ¹³C NMR (126 MHz, CDCl₃): δ 155.77, 153.24, 150.27 (d, J_{CF} = 252.0 Hz), 149.81, 146.80, 144.66, 128.62 (d, J_{CF} = 8.5 Hz), 126.34, 124.44, 124.40, 122.66 (q, J_{CF} = 272.4 Hz), 120.41 (q, J_{CF} = 4.6 Hz), 114.58, 110.55, 105.86, 64.70, 64.51. HRMS (DART): m/z [M – H][–] calcd for C₁₇H₁₀F₄N₃O₂[–], 364.0715; found, 364.0712.

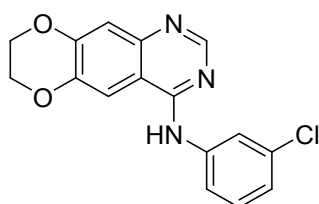
3-[(7,8-Dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-yl)amino]benzonitrile (8)



Following general procedure **GP-1**, compound **8** was prepared from the chloroquinazoline **24** (35 mg, 0.16 mmol) and 3-aminobenzonitrile (42 mg, 0.35 mmol) in isopropanol (1.5 mL). Flash chromatography (CH₂Cl₂/EtOAc 1:0 \rightarrow 6:4) gave **8** (43 mg, 89%) as a white solid.

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 9.68 (s, 1H), 8.52 (s, 1H), 8.46 (t, $J = 1.9$ Hz, 1H), 8.18 (ddd, $J = 8.2, 2.3, 1.2$ Hz, 1H), 8.08 (s, 1H), 7.58 (t, $J = 7.9$ Hz, 1H), 7.53 (dt, $J = 7.6, 1.4$ Hz, 1H), 7.22 (s, 1H), 4.45 – 4.38 (m, 4H). ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$): δ 156.24, 152.69, 149.31, 146.15, 143.80, 140.52, 129.87, 126.35, 125.96, 124.15, 118.93, 112.66, 111.23, 109.96, 108.30, 64.52, 64.19. HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{13}\text{N}_4\text{O}_2^+$, 305.1033; found, 305.1018.

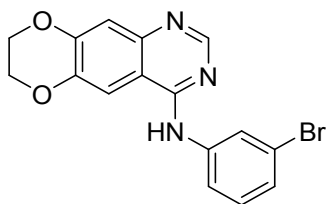
***N*-(3-Chlorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (9)**



Following general procedure **GP-1**, compound **9** was prepared from the chloroquinazoline **24** (40 mg, 0.18 mmol) and 3-chloroaniline (38 μL , 0.36 mmol) in isopropanol (1.5 mL). Flash chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 8:2 \rightarrow 1:1) gave **9** (51 mg, 91%) as a white solid.

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 9.54 (s, 1H), 8.50 (s, 1H), 8.13 (t, $J = 2.1$ Hz, 1H), 8.08 (s, 1H), 7.85 (ddd, $J = 8.2, 2.1, 0.9$ Hz, 1H), 7.39 (t, $J = 8.1$ Hz, 1H), 7.20 (s, 1H), 7.13 (ddd, $J = 8.0, 2.1, 0.9$ Hz, 1H), 4.45 – 4.37 (m, 4H). ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$): δ 156.29, 152.76, 149.19, 146.09, 143.71, 141.15, 132.70, 130.03, 122.62, 120.86, 119.82, 112.62, 110.00, 108.34, 64.50, 64.17. HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{13}\text{ClN}_3\text{O}_2^+$, 314.0691; found, 314.0688.

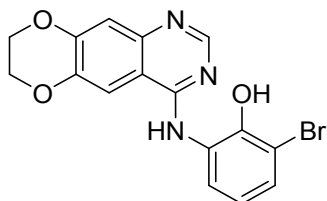
***N*-(3-Bromophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (10)**



Following general procedure **GP-2**, compound **10** was prepared from the chloroquinazoline **24** (35 mg, 0.16 mmol), 3-bromoaniline (34 μ L, 0.32 mmol), and a 4 M solution of HCl in dioxane (39 μ L, 0.16 mmol) in acetonitrile (1.5 mL). Flash chromatography (CH₂Cl₂/EtOAc 9:1 \rightarrow 6:4) gave **10** (54 mg, 96%) as a white solid.

¹H NMR (500 MHz, DMSO-*d*₆): δ 9.53 (s, 1H), 8.49 (s, 1H), 8.25 (t, *J* = 2.0 Hz, 1H), 8.08 (s, 1H), 7.92 (ddd, *J* = 8.1, 2.1, 1.0 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.26 (ddd, *J* = 7.9, 2.0, 1.0 Hz, 1H), 7.20 (s, 1H), 4.45 – 4.37 (m, 4H). ¹³C NMR (126 MHz, DMSO-*d*₆): δ 156.27, 152.77, 149.19, 146.09, 143.71, 141.29, 130.35, 125.52, 123.68, 121.18, 120.22, 112.62, 110.00, 108.34, 64.50, 64.17. HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₆H₁₃BrN₃O₂⁺, 358.0186; found, 358.0182.

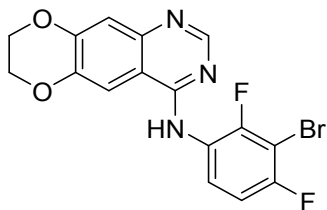
2-Bromo-6-[(7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-yl)amino]phenol (**11**)



Following general procedure **GP-1**, compound **11** was prepared from the chloroquinazoline **24** (150 mg, 0.67 mmol) and 2-amino-6-bromophenol (254 mg, 1.35 mmol) in isopropanol (1.5 mL). Flash chromatography (CH₂Cl₂/EtOAc 9:1 \rightarrow 6:4) afforded **11** (241 mg, 96%) as a rose-colored solid.

¹H NMR (500 MHz, DMSO-*d*₆): δ 10.60 (br, 1H), 9.50 (br, 1H), 8.35 (s, 1H), 8.04 (s, 1H), 7.45 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.34 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.18 (s, 1H), 6.83 (t, *J* = 8.0 Hz, 1H), 4.44 – 4.37 (m, 4H). ¹³C NMR (126 MHz, DMSO-*d*₆): δ 157.19, 152.05, 149.33, 148.65, 145.62, 143.55, 130.14, 128.35, 126.32, 120.29, 112.54, 112.12, 109.82, 109.18, 64.55, 64.14. HRMS (DART): *m/z* [M + H]⁺ calcd for C₁₆H₁₃BrN₃O₃⁺, 374.0135; found, 374.0142.

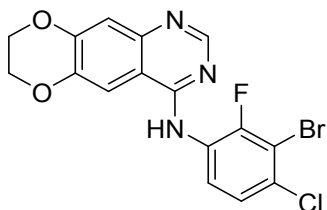
***N*-(3-Bromo-2,4-difluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (12)**



Following general procedure **GP-2**, compound **12** was prepared from the chloroquinazoline **24** (35 mg, 0.16 mmol), 3-bromo-2,4-difluoroaniline (65 mg, 0.31 mmol), and a 4 M solution of HCl in dioxane (39 μ L, 0.16 mmol) in acetonitrile (1.5 mL). Flash chromatography (CH₂Cl₂/EtOAc 1:0 \rightarrow 7:3) gave **12** (54 mg, 87%) as an off-white solid.

¹H NMR (500 MHz, CDCl₃): δ 8.64 (s, 1H), 8.51 (td, J = 9.0, 5.6 Hz, 1H), 7.38 (s, 1H), 7.29 (s, 1H), 7.23 (br, 1H), 7.04 (ddd, J = 9.2, 7.8, 2.1 Hz, 1H), 4.45 – 4.37 (m, 4H). ¹³C NMR (126 MHz, CDCl₃): δ 156.10, 155.80 (dd, J_{CF} = 246.6, 3.5 Hz), 153.28, 151.25 (dd, J_{CF} = 245.1, 4.0 Hz), 149.74, 146.56, 144.53, 124.39 (dd, J_{CF} = 10.8, 3.4 Hz), 122.72 (dd, J_{CF} = 8.3, 1.8 Hz), 114.42, 111.49 (dd, J_{CF} = 22.5, 3.9 Hz), 110.34, 105.98, 97.86 (dd, J_{CF} = 25.7, 22.9 Hz), 64.69, 64.50. HRMS (ESI): m/z [M + H]⁺ calcd for C₁₆H₁₁BrF₂N₃O₂⁺, 393.9997; found, 394.0013.

***N*-(3-Bromo-4-chloro-2-fluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (13)**

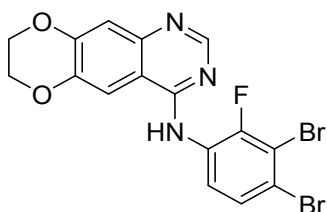


Following general procedure **GP-1**, compound **13** was prepared from the chloroquinazoline **24** (35 mg, 0.16 mmol) and 3-bromo-4-chloro-2-fluoroaniline (**S12**) (70 mg, 0.31 mmol) in isopropanol (1.5 mL). After the reaction, the precipitated hydrochloride salt of **13** was converted into the free

base by extraction of a sat. aq. NaHCO₃ solution to obtain pure **13** (35 mg, 54%) as a fluffy pale-yellow solid.

¹H NMR (500 MHz, DMSO-*d*₆): □ 9.70 (s, 1H), 8.35 (s, 1H), 7.94 (s, 1H), 7.61 (dd, *J* = 8.8, 7.7 Hz, 1H), 7.55 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.20 (s, 1H), 4.47 – 4.35 (m, 4H). ¹³C NMR (126 MHz, DMSO-*d*₆): □ 157.03, 154.14 (d, *J*_{CF} = 249.5 Hz), 153.01, 149.36, 146.08, 143.74, 130.75, 127.77 (d, *J*_{CF} = 2.9 Hz), 126.80 (d, *J*_{CF} = 13.4 Hz), 125.37 (d, *J*_{CF} = 3.8 Hz), 112.50, 110.15 (d, *J*_{CF} = 22.5 Hz), 109.66, 108.39, 64.51, 64.14. HRMS (DART): *m/z* [M + H]⁺ calcd for C₁₆H₁₁BrClFN₃O₂⁺, 409.9702; found, 409.9697.

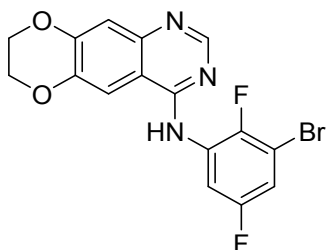
***N*-(3,4-Dibromo-2-fluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (14)**



Following general procedure **GP-2**, compound **14** was prepared from the chloroquinazoline **24** (40 mg, 0.18 mmol), 3,4-dibromo-2-fluoroaniline (**S13**) (96 mg, 0.36 mmol), and a 4 M solution of HCl in dioxane (45 □L, 0.18 mmol) in acetonitrile (1.5 mL). Flash chromatography (CH₂Cl₂/EtOAc 1:0 → 7:3) gave **14** (67 mg, 82%) as a white solid.

¹H NMR (500 MHz, DMSO-*d*₆): □ 9.65 (s, 1H), 8.34 (s, 1H), 7.92 (s, 1H), 7.67 (d, *J* = 8.7 Hz, 1H), 7.55 (t, *J* = 8.2 Hz, 1H), 7.20 (s, 1H), 4.45 – 4.35 (m, 4H). ¹³C NMR (126 MHz, DMSO-*d*₆): □ 156.95, 153.98 (d, *J*_{CF} = 249.1 Hz), 152.99, 149.35, 146.09, 143.74, 128.50 (d, *J*_{CF} = 3.7 Hz), 128.14, 127.21 (d, *J*_{CF} = 13.7 Hz), 120.96, 112.51, 112.33, 109.68, 108.36, 64.51, 64.14. HRMS (DART): *m/z* [M + H]⁺ calcd for C₁₆H₁₁Br₂FN₃O₂⁺, 453.9197; found, 453.9191.

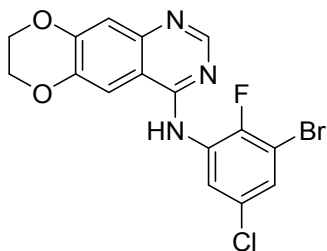
***N*-(3-Bromo-2,5-difluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (15)**



Following general procedure **GP-2**, compound **15** was prepared from the chloroquinazoline **24** (35 mg, 0.16 mmol), 3-bromo-2,5-difluoroaniline (**S14**) (54 mg, 0.26 mmol), and a 4 M solution of HCl in dioxane (39 μ L, 0.16 mmol) in acetonitrile (1.5 mL). Flash chromatography (CH₂Cl₂/EtOAc 1:0 \rightarrow 7:3) gave **15** (57 mg, 92%) as an off-white solid.

¹H NMR (500 MHz, DMSO-*d*₆): δ 9.65 (s, 1H), 8.40 (s, 1H), 7.93 (s, 1H), 7.63 – 7.54 (m, 2H), 7.21 (s, 1H), 4.45 – 4.37 (m, 4H). ¹³C NMR (126 MHz, DMSO-*d*₆): δ 157.29 (d, J_{CF} = 243.5 Hz), 156.84, 152.93, 149.97 (d, J_{CF} = 242.9 Hz), 149.43, 146.16, 143.81, 128.83 (m), 116.30 (d, J_{CF} = 26.7 Hz), 113.99 (d, J_{CF} = 25.7 Hz), 112.53, 109.73, 108.76 (dd, J_{CF} = 22.5, 12.5 Hz), 108.33, 64.52, 64.15. HRMS (DART): m/z [M + H]⁺ calcd for C₁₆H₁₁BrF₂N₃O₂⁺, 393.9997; found, 393.9988.

***N*-(3-Bromo-5-chloro-2-fluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (16)**

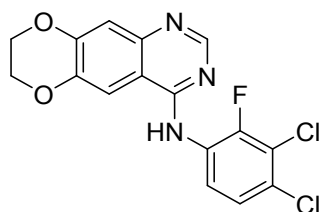


Following general procedure **GP-2**, compound **16** was prepared from the chloroquinazoline **24** (35 mg, 0.16 mmol), 3-bromo-5-chloro-2-fluoroaniline (**S15**) (71 mg, 0.32 mmol), and a 4 M

solution of HCl in dioxane (39 μ L, 0.16 mmol) in acetonitrile (1.5 mL). Flash chromatography (hexanes/ CH₂Cl₂ 1:9 \rightarrow CH₂Cl₂/EtOAc 1:0 \rightarrow 7:3) gave **16** (36 mg, 56%) as a white solid.

¹H NMR (500 MHz, CDCl₃): δ 8.88 (dd, J = 6.6, 2.6 Hz, 1H), 8.73 (s, 1H), 7.41 (s, 1H), 7.37 (br, 1H), 7.26 (s, 1H), 7.28 – 7.23 (m, 1H), 4.44 – 4.39 (m, 4H). ¹³C NMR (126 MHz, CDCl₃): δ 155.45, 153.13, 149.88, 148.60 (d, J_{CF} = 241.7 Hz), 146.76, 144.72, 130.30 (d, J_{CF} = 4.4 Hz), 129.26 (d, J_{CF} = 10.8 Hz), 126.08, 121.21, 114.60, 110.49, 108.68 (d, J_{CF} = 20.9 Hz), 105.71, 64.70, 64.52. HRMS (ESI): m/z [M + H]⁺ calcd for C₁₆H₁₁BrClFN₃O₂⁺, 409.9702; found, 409.9713.

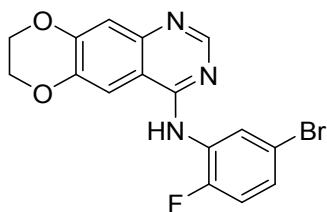
***N*-(3,4-Dichloro-2-fluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (17)**



Following general procedure **GP-2**, compound **17** was prepared from the chloroquinazoline **24** (35 mg, 0.16 mmol), 3,4-dichloro-2-fluoroaniline (57 mg, 0.32 mmol), and a 4 M solution of HCl in dioxane (39 μ L, 0.16 mmol) in acetonitrile (1.5 mL). Flash chromatography (CH₂Cl₂/EtOAc 1:0 \rightarrow 3:1) gave **17** (46 mg, 80%) as a white solid.

¹H NMR (500 MHz, CDCl₃): δ 8.67 (s, 1H), 8.59 (t, J = 8.6 Hz, 1H), 7.40 (s, 1H), 7.38 (br, 1H), 7.33 (dd, J = 9.1, 2.1 Hz, 1H), 7.31 (s, 1H), 4.45 – 4.38 (m, 4H). ¹³C NMR (126 MHz, CDCl₃): δ 155.84, 153.08, 149.98 (d, J_{CF} = 246.3 Hz), 149.88, 146.42, 144.67, 127.55, 127.19 (d, J_{CF} = 10.0 Hz), 125.30 (d, J_{CF} = 4.1 Hz), 121.05, 120.47 (d, J_{CF} = 18.2 Hz), 114.36, 110.43, 105.97, 64.71, 64.51. HRMS (ESI): m/z [M + H]⁺ calcd for C₁₆H₁₁Cl₂FN₃O₂⁺, 366.0207; found, 366.0207.

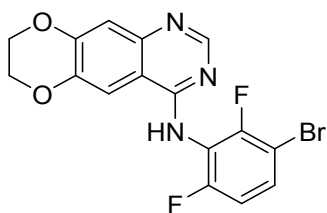
***N*-(5-Bromo-2-fluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (18)**



Following general procedure **GP-2**, compound **18** was prepared from the chloroquinazoline **24** (35 mg, 0.16 mmol), 5-bromo-2-fluoroaniline (60 mg, 0.32 mmol), and a 4 M solution of HCl in dioxane (40 μ L, 0.16 mmol) in acetonitrile (1.5 mL). Flash chromatography (CH₂Cl₂/EtOAc 1:0 \rightarrow 7:3) gave **18** (42 mg, 71%) as a white solid.

¹H NMR (500 MHz, CDCl₃): δ 8.99 (dd, J = 7.3, 2.5 Hz, 1H), 8.72 (s, 1H), 7.38 (s, 1H), 7.36 (br, 1H), 7.27 (s, 1H), 7.16 (ddd, J = 8.7, 4.6, 2.5 Hz, 1H), 7.04 (dd, J = 10.9, 8.7 Hz, 1H), 4.44 – 4.36 (m, 4H). ¹³C NMR (126 MHz, CDCl₃): δ 155.59, 153.35, 152.16 (d, J_{CF} = 243.1 Hz), 149.69, 146.67, 144.52, 128.75 (d, J_{CF} = 10.5 Hz), 126.16 (d, J_{CF} = 7.6 Hz), 125.06, 117.19 (d, J_{CF} = 3.4 Hz), 116.20 (d, J_{CF} = 20.9 Hz), 114.52, 110.48, 105.85, 64.68, 64.50. HRMS (DART): m/z [M + H]⁺ calcd for C₁₆H₁₂BrFN₃O₂⁺, 376.0091; found, 376.0077.

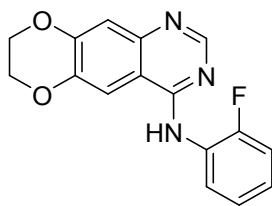
***N*-(3-Bromo-2,6-difluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (19)**



Following general procedure **GP-2**, compound **19** was prepared from chloroquinazoline **24** (35 mg, 0.16 mmol), 3-bromo-2,6-difluoroaniline (65 mg, 0.31 mmol), and a 4 M solution of HCl in dioxane (39 μ L, 0.16 mmol) in acetonitrile (1.5 mL). Flash chromatography (CH₂Cl₂/EtOAc 1:0 \rightarrow 6:4) gave **19** (29 mg, 47%) as a white solid.

^1H NMR (500 MHz, DMSO- d_6): δ 9.60 (s, 1H), 8.32 (s, 1H), 7.94 (s, 1H), 7.74 (td, J = 8.1, 5.5 Hz, 1H), 7.28 (t, J = 9.3 Hz, 1H), 7.21 (s, 1H), 4.44 – 4.38 (m, 4H). ^{13}C NMR (126 MHz, DMSO- d_6): δ 157.78 (dd, J_{CF} = 248.8, 3.3 Hz), 157.37, 155.01 (dd, J_{CF} = 247.9, 4.9 Hz), 153.08, 149.47, 146.04, 143.86, 130.76 (d, J_{CF} = 9.3 Hz), 117.30 (t, J_{CF} = 17.5 Hz), 113.30 (dd, J_{CF} = 21.8, 3.0 Hz), 112.56, 109.45, 108.28, 103.55 (dd, J_{CF} = 20.4, 3.6 Hz), 64.52, 64.14. HRMS (ESI): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{16}\text{H}_{11}\text{BrF}_2\text{N}_3\text{O}_2^+$, 393.9997; found, 394.0008.

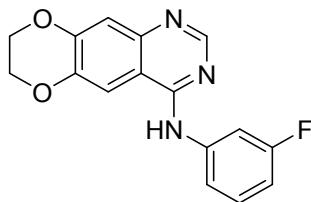
***N*-(2-Fluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (S1)**



Following general procedure **GP-1**, compound **S1** was prepared from the chloroquinazoline **24** (51 mg, 0.23 mmol) and 2-fluoroaniline (40 μL , 0.48 mmol) in isopropanol (1.5 mL). Flash chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 10:1 \rightarrow 10:4) gave **S1** (56 mg, 82%) as a white solid.

^1H NMR (500 MHz, CDCl_3): δ 8.68 (s, 1H), 8.64 (td, J = 8.2, 1.7 Hz, 1H), 7.38 (s, 1H), 7.36 (br, 1H), 7.31 (s, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.17 (ddd, J = 11.2, 8.3, 1.5 Hz, 1H), 7.10 – 7.05 (m, 1H), 4.44 – 4.37 (m, 4H). ^{13}C NMR (126 MHz, CDCl_3): δ 156.08, 153.60, 153.50 (d, J_{CF} = 242.7 Hz), 149.52, 146.65, 144.34, 127.31 (d, J_{CF} = 9.5 Hz), 124.66 (d, J_{CF} = 3.7 Hz), 123.97 (d, J_{CF} = 7.8 Hz), 122.89, 115.06 (d, J_{CF} = 19.3 Hz), 114.46, 110.62, 106.10, 64.69, 64.51. HRMS (DART): m/z [$\text{M} - \text{H}$] $^-$ calcd for $\text{C}_{16}\text{H}_{11}\text{FN}_3\text{O}_2^-$, 296.0841; found, 296.0841.

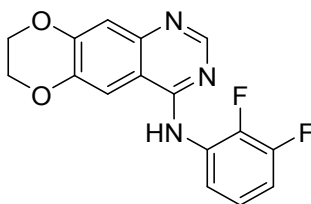
***N*-(3-Fluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (S2)**



Following general procedure **GP-1**, compound **S2** was prepared from the chloroquinazoline **24** (40 mg, 0.18 mmol) and 3-fluoroaniline (35 μ L, 0.36 mmol) in isopropanol (1.5 mL). After the reaction, the precipitated hydrochloride salt of **S2** was converted into the free base by extraction of a sat. aq. NaHCO₃ solution to obtain pure **S2** (30 mg, 56%) as an off-white solid.

¹H NMR (500 MHz, DMSO-*d*₆): δ 9.56 (s, 1H), 8.50 (s, 1H), 8.09 (s, 1H), 7.97 (dt, *J* = 12.1, 2.3 Hz, 1H), 7.69 (ddd, *J* = 8.3, 2.0, 0.9 Hz, 1H), 7.39 (td, *J* = 8.2, 6.9 Hz, 1H), 7.20 (s, 1H), 6.90 (tdd, *J* = 8.4, 2.6, 0.9 Hz, 1H), 4.45 – 4.36 (m, 4H). ¹³C NMR (126 MHz, DMSO-*d*₆): δ 161.98 (d, *J*_{CF} = 240.4 Hz), 156.31, 152.77, 149.17, 146.09, 143.70, 141.44 (d, *J*_{CF} = 11.4 Hz), 129.89 (d, *J*_{CF} = 9.5 Hz), 117.11 (d, *J*_{CF} = 2.4 Hz), 112.62, 110.02, 109.36 (d, *J*_{CF} = 21.1 Hz), 108.35, 108.16 (d, *J*_{CF} = 26.2 Hz), 64.51, 64.18. HRMS (DART): *m/z* [M + H]⁺ calcd for C₁₆H₁₃FN₃O₂⁺, 298.0986; found, 298.0988.

***N*-(2,3-Difluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (S3)**

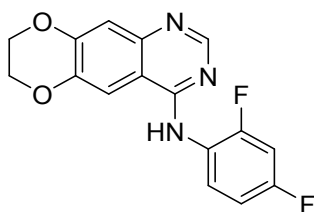


Following general procedure **GP-2**, compound **S3** was prepared from the chloroquinazoline **24** (35 mg, 0.16 mmol), 2,3-difluoroaniline (32 μ L, 0.32 mmol), and a 4 M solution of HCl in dioxane (39 μ L, 0.16 mmol) in acetonitrile (1.5 mL). After the reaction, the precipitated hydrochloride salt

of **S3** was converted into the free base by extraction of a sat. aq. NaHCO₃ solution to obtain pure **S3** (41 mg, 83%) as a white solid.

¹H NMR (500 MHz, DMSO-*d*₆): δ 9.64 (s, 1H), 8.34 (s, 1H), 7.94 (s, 1H), 7.36 – 7.29 (m, 2H), 7.27 – 7.21 (m, 1H), 7.19 (s, 1H), 4.44 – 4.37 (m, 4H). ¹³C NMR (126 MHz, DMSO-*d*₆): δ 157.13, 153.12, 150.33 (dd, *J*_{CF} = 244.5, 11.7 Hz), 149.28, 146.06, 145.07 (dd, *J*_{CF} = 248.6, 13.5 Hz), 143.69, 128.60 (d, *J*_{CF} = 9.1 Hz), 124.01 (dd, *J*_{CF} = 8.3, 4.6 Hz), 123.27 (d, *J*_{CF} = 2.9 Hz), 114.14 (d, *J*_{CF} = 17.1 Hz), 112.49, 109.66, 108.40, 64.51, 64.14. HRMS (DART): *m/z* [M + H]⁺ calcd for C₁₆H₁₂F₂N₃O₂⁺, 316.0892; found 316.0878.

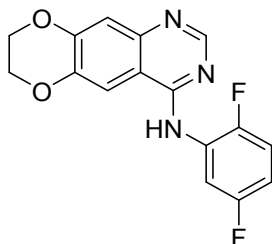
***N*-(2,4-Difluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (S4)**



Following general procedure **GP-3**, compound **S4** was prepared from chloroquinazoline **24** (88 mg, 0.40 mmol) and 2,4-difluoroaniline (140 μL, 1.38 mmol) in DMF (2.2 mL). Flash chromatography afforded **S4** (36 mg, 29%) as a white solid.

¹H NMR (500 MHz, DMSO-*d*₆): δ 9.46 (s, 1H), 8.29 (s, 1H), 7.92 (s, 1H), 7.53 (td, *J* = 8.8, 6.2 Hz, 1H), 7.36 (ddd, *J* = 10.6, 9.1, 2.9 Hz, 1H), 7.17 (s, 1H), 7.14 (tdd, *J* = 8.5, 2.9, 1.3 Hz, 1H), 4.44 – 4.35 (m, 4H). ¹³C NMR (126 MHz, DMSO-*d*₆): δ 159.90 (dd, *J*_{CF} = 244.4, 11.5 Hz), 157.56, 157.07 (dd, *J*_{CF} = 249.6, 12.9 Hz), 153.21, 149.14, 145.93, 143.57, 129.64 (dd, *J*_{CF} = 9.8, 3.1 Hz), 123.02 (dd, *J*_{CF} = 12.6, 3.7 Hz), 112.46, 111.24 (dd, *J*_{CF} = 22.0, 3.6 Hz), 109.56, 108.36, 104.47 (dd, *J*_{CF} = 26.5, 24.7 Hz), 64.49, 64.12. HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₆H₁₂F₂N₃O₂⁺, 316.0892; found, 316.0890.

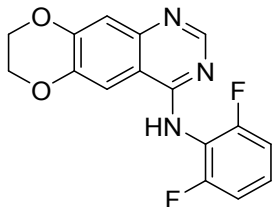
***N*-(2,5-Difluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (S5)**



Following general procedure **GP-3**, compound **S5** was prepared from the chloroquinazoline **24** (44 mg, 0.20 mmol) and 2,5-difluoroaniline (67 μ L, 0.66 mmol) in DMF (1.5 mL). Flash chromatography afforded **S5** (16 mg, 26%) as a white solid.

^1H NMR (500 MHz, DMSO- d_6): δ 9.52 (s, 1H), 8.36 (s, 1H), 7.95 (s, 1H), 7.52 (ddd, J = 9.5, 5.9, 3.2 Hz, 1H), 7.35 (td, J = 9.5, 5.0 Hz, 1H), 7.19 (s, 1H), 7.13 (ddd, J = 11.6, 8.1, 3.1 Hz, 1H), 4.45 – 4.35 (m, 4H). ^{13}C NMR (126 MHz, DMSO- d_6): δ 157.62 (dd, J_{CF} = 239.3, 1.6 Hz), 157.06, 153.04, 152.82 (dd, J_{CF} = 243.5, 2.3 Hz), 149.27, 146.08, 143.68, 127.78 (td, J_{CF} = 11.4, 2.3 Hz), 116.77 (dd, J_{CF} = 22.9, 9.7 Hz), 114.47 (d, J_{CF} = 25.9 Hz), 112.79 (dd, J_{CF} = 24.2, 8.1 Hz), 112.49, 109.72, 108.38, 64.50, 64.13. HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{12}\text{F}_2\text{N}_3\text{O}_2^+$, 316.0892; found, 316.0893.

***N*-(2,6-Difluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (S6)**

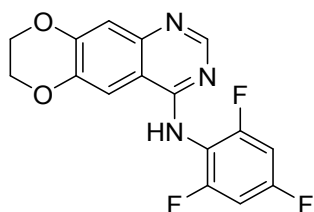


Following general procedure **GP-2**, compound **S6** was prepared from the chloroquinazoline **24** (35 mg, 0.16 mmol), 2,6-difluoroaniline (34 μ L, 0.32 mmol), and a 4 M solution of HCl in dioxane (39 μ L, 0.16 mmol) in acetonitrile (1.5 mL). After the reaction, the precipitated hydrochloride salt

of **S6** was converted into the free base by extraction of a sat. aq. NaHCO_3 solution to obtain crude **S6**, which was purified by PTLC ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 4:6) to obtain pure **S6** (31 mg, 63%) as a white solid.

^1H NMR (500 MHz, CDCl_3): δ 8.59 (s, 1H), 7.38 (s, 1H), 7.35 (s, 1H), 7.29 – 7.21 (m, 1H), 7.06 – 6.99 (m, 2H), 6.69 (br, 1H), 4.44 – 4.34 (m, 4H). ^{13}C NMR (126 MHz, CDCl_3): δ = 158.23 (dd, J_{CF} = 250.0, 4.8 Hz), 157.14, 153.86, 149.66, 146.71, 144.29, 127.37 (t, J_{CF} = 9.7 Hz), 115.44 (t, J_{CF} = 16.1 Hz), 114.20, 112.02 (dd, J_{CF} = 19.2, 4.4 Hz), 110.45, 106.79, 64.70, 64.48. HRMS (DART): m/z $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{16}\text{H}_{10}\text{F}_2\text{N}_3\text{O}_2^-$, 314.0747; found 314.0733.

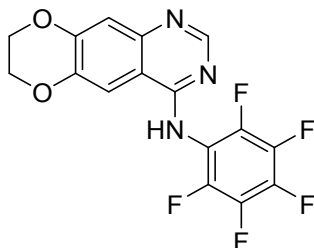
***N*-(2,4,6-Trifluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (**S7**)**



Following general procedure **GP-2**, compound **S7** was prepared from the chloroquinazoline **24** (35 mg, 0.16 mmol), 2,4,6-trifluoroaniline (46 mg, 0.32 mmol), and a 4 M solution of HCl in dioxane (39 μL , 0.16 mmol) in acetonitrile (1.5 mL). After the reaction, the precipitated hydrochloride salt of **S7** was converted into the free base by extraction of a sat. aq. NaHCO_3 solution to obtain pure **S7** (52 mg, 99%) as a white solid.

^1H NMR (500 MHz, CDCl_3): δ 8.56 (s, 1H), 7.38 (s, 1H), 7.34 (s, 1H), 6.85 – 6.78 (m, 2H), 6.56 (br, 1H), 4.43 – 4.36 (m, 4H). ^{13}C NMR (126 MHz, CDCl_3): δ 160.85 (dt, J_{CF} = 249.3, 14.6 Hz), 158.67 (ddd, J_{CF} = 251.2, 15.1, 7.0 Hz), 157.25, 153.77, 149.73, 146.70, 144.35, 114.24, 111.95 (td, J_{CF} = 16.5, 5.0 Hz), 110.23, 106.66, 100.96 (td, J_{CF} = 26.0, 2.9 Hz), 64.70, 64.48. HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{11}\text{F}_3\text{N}_3\text{O}_2^+$, 334.0798; found 334.0789.

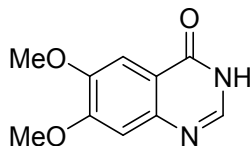
***N*-(Pentafluorophenyl)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (**S8**)**



Following general procedure **GP-2**, compound **S8** was prepared from the chloroquinazoline **24** (35 mg, 0.16 mmol), pentafluoroaniline (58 mg, 0.32 mmol), and a 4 M solution of HCl in dioxane (39 μ L, 0.16 mmol) in acetonitrile (1.5 mL). Flash chromatography (CH₂Cl₂/EtOAc 1:0 \rightarrow 7:3) followed by PTLC (hexanes/EtOAc 4:6) gave **S8** (36 mg, 62%) as a white solid.

¹H NMR (500 MHz, CDCl₃): δ 8.57 (s, 1H), 7.41 (s, 1H), 7.34 (s, 1H), 6.64 (br, 1H), 4.45 – 4.37 (m, 4H). ¹³C NMR (126 MHz, CDCl₃): δ 156.57, 153.40, 150.05, 146.89, 144.67, 114.34, 110.22, 106.52, 64.71, 64.50, carbons of perfluorophenyl ring not observed. HRMS (DART): *m/z* [M + H]⁺ calcd for C₁₆H₉F₅N₃O₂⁺, 370.0609; found, 370.0592.

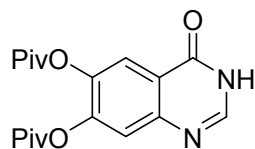
6,7-Dimethoxyquinazolin-4(3*H*)-one (21**)¹²**



A mixture of methyl 2-amino-4,5-dimethoxybenzoate (**21**) (100.45 g, 475.6 mmol), formamide (793 mL), and formic acid (22.6 mL, 599.2 mmol) was stirred at 145 °C for 18 h. The mixture was cooled to 5 °C, water (800 mL) was added, and the suspension was stirred at 0–5 °C for 30 min. The precipitate was filtered off (washings with water), and recrystallized from EtOH (600 mL), and dried in a desiccator to afford the title compound **21** (89.44 g, 91%) as an off-white solid.

^1H NMR (300 MHz, $\text{DMSO-}d_6$): δ 12.07 (s, 1H), 7.98 (d, $J = 3.5$ Hz, 1H), 7.44 (s, 1H), 7.13 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$): δ 160.03, 154.43, 148.53, 144.84, 143.82, 115.58, 108.00, 104.91, 55.91, 55.68. HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{O}_3^+$, 207.0764; found, 207.0755.

4-Oxo-3,4-dihydroquinazoline-6,7-diyl bis(2,2-dimethylpropanoate) (22)^{13,14}



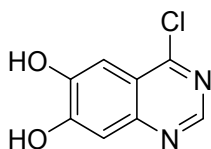
A mixture of quinazolinone **21** (89.39 g, 433.5 mmol) in 48% hydrobromic acid (1250 mL) was stirred at 135 °C for 18.5 h. The mixture was cooled to 10 °C, and filtered off. The residue was suspended in water (800 mL), and stirred at 10 °C for 30 min. The pH was adjusted to ~7 with sat. aq. NH_4OH (70 mL), and the precipitate was filtered off (washings with water (80 mL)), and dried in a desiccator to afford 6,7-dihydroxyquinazolin-4(3*H*)-one (81.36 g, quant.) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 11.82 (br, 1H), 10.15 (s, 1H), 9.77 (s, 1H), 7.84 (s, 1H), 7.36 (s, 1H), 6.94 (s, 1H). ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$): δ 160.02, 152.38, 145.93, 143.65, 142.78, 115.06, 111.22, 109.10. HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_7\text{N}_2\text{O}_3^+$, 179.0451; found, 179.0444.

A mixture of 6,7-dihydroxyquinazolin-4(3*H*)-one (41.62 g, 233.6 mmol) in DMF (467 mL) was treated with Et_3N (98 mL, 700.9 mmol), cooled to 0 °C, and treated dropwise with pivaloyl chloride (86.3 mL, 700.9 mmol) over 45 min at 0–10 °C. The cooling bath was removed, and the mixture was stirred at 23 °C for 18 h. The mixture was treated dropwise with MeOH (20 mL) at 0 °C, stirred at 23 °C for 15 min, and concentrated. The residue was taken up in EtOAc (1250 mL), washed with water (1 x 100 mL, 4 x 20 mL), and concentrated. The residue was triturated with

water (100 mL), and filtered to give a red solid, which was washed several times with water (2 x 50 mL), and MeCN (2 x 40 mL), and dried in a desiccator to afford the title compound **22** (43.18 g, 53%) as an off-white solid.

^1H NMR (400 MHz, DMSO- d_6): δ 12.39 (br, 1H), 8.14 (s, 1H), 7.92 (s, 1H), 7.59 (s, 1H), 1.31 (s, 18H). ^{13}C NMR (101 MHz, DMSO- d_6): δ 175.34, 174.91, 159.75, 147.33, 147.25, 146.20, 141.06, 121.52, 120.81, 120.02, 38.76, 38.70, 26.75, 26.72. HRMS (DART): m/z $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_5^-$, 345.1456; found, 345.1454.

4-Chloroquinazoline-6,7-diol (**23**)^{14,15}



A stirred suspension of quinazolinone **22** (79.28 g, 228.9 mmol) in toluene (320 mL) was cooled to 10 °C, treated with DIPEA (120 mL, 689.0 mmol), and subsequently with POCl₃ (57 mL, 620.9 mmol) over 40 min. Stirring was continued at 23 °C for 1 h, and then at 90 °C for 6 h. The mixture was cooled to 23 °C, and concentrated. The residue was treated carefully with sat. aq. NaHCO₃ (700 mL) at 0 °C, and let stand for 1 h. The mixture was diluted with water (400 mL), and extracted with CH₂Cl₂ (3 x 500 mL). The combined organics were washed with half-sat. NaHCO₃ (400 mL), brine (400 mL), dried (Na₂SO₄), filtered, and evaporated to obtain crude 4-chloroquinazoline-6,7-diyl bis(2,2-dimethylpropanoate) (**S27**) (65.28 g, 78%) as a viscous brown oil, which was used without any further purification in the next step.

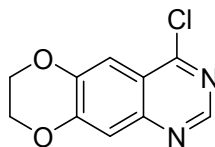
^1H NMR (400 MHz, CDCl₃): δ 9.02 (s, 1H), 8.03 (s, 1H), 7.88 (s, 1H), 1.41 (s, 9H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, CDCl₃): δ 175.74, 175.31, 161.70, 154.16, 149.74, 149.62, 144.22, 122.33,

122.28, 119.11, 39.64, 39.57, 27.38, 27.31. HRMS (DART): m/z $[M + H]^+$ calcd for $C_{18}H_{22}ClN_2O_4^+$, 365.1263; found, 365.1251.

A stirred slurry of 4-chloroquinazoline-6,7-diyl bis(2,2-dimethylpropanoate) (**S27**) (23.39 g, 64.1 mmol) was treated dropwise at 0 °C with a 7 M solution of NH_3 in MeOH (229 mL, 1.603 mol). The mixture was stirred at 0 °C for 15 min, and then at 23 °C for 4 h, and evaporated. The residue was triturated with MeCN (150 mL), filtered, and washed several times with CH_2Cl_2 (4 x 100 mL), Et_2O (2 x 100 mL), and dried in a desiccator to yield the title compound **23** (11.92 g, 95%) as a yellow solid.

1H NMR (500 MHz, $DMSO-d_6$): δ 8.35 (s, 1H), 6.98 (s, 1H), 6.59 (s, 1H), signals of phenolic protons missing (due to peak broadening). ^{13}C NMR (126 MHz, $DMSO-d_6$): δ 165.28, 154.36, 153.44, 150.45, 150.08, 114.74, 105.08, 99.75. HRMS (DART): m/z $[M - H]^-$ calcd for $C_8H_4ClN_2O_2^-$, 194.9967; found, 194.9968.

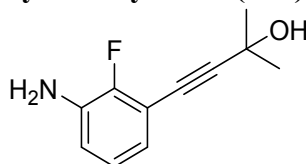
4-Chloro-7,8-dihydro[1,4]dioxino[2,3-g]quinazoline (**24**)^{16,17}



A solution of diol **23** (3.528 g, 17.9 mmol) in DMF (123 mL) was treated with K_2CO_3 (5586 mg, 40.4 mmol), stirred for 5–10 min, and treated dropwise with 1-bromo-2-chloroethane (5.4 mL, 64.6 mmol). The mixture was stirred at 23 °C for 1 h, and then at 70 °C for 15 h. The mixture was cooled to 23 °C, and evaporated. CH_2Cl_2 (400 mL) was added, and the organic phase was washed with water (2 x 60 mL), brine (60 mL), dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexanes/ CH_2Cl_2 1:10 \rightarrow CH_2Cl_2 / $EtOAc$ 1:0 \rightarrow 85:15) afforded the chloroquinazoline **24** (1.631 g, 41%) as a fluffy white solid.

^1H NMR (400 MHz, CDCl_3): δ 8.84 (s, 1H), 7.65 (s, 1H), 7.47 (s, 1H), 4.46 – 4.39 (m, 4H). ^{13}C NMR (101 MHz, CDCl_3): δ 160.19, 152.52, 151.55, 147.93, 146.07, 120.10, 113.73, 110.84, 64.75, 64.38. HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_8\text{ClN}_2\text{O}_2^+$, 223.0269; found, 223.0264.

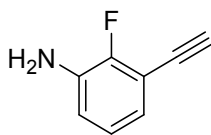
4-(3-Amino-2-fluorophenyl)-2-methylbut-3-yn-2-ol (S17)



A vial was charged with $[\text{Pd}(\text{OAc})_2]$ (18 mg, 0.08 mmol) and PPh_3 (42 mg, 0.16 mmol), and evacuated and backfilled with Ar (3x). THF (8 mL), DBU (1.18 mL, 7.89 mmol), 2-methyl-3-butyne-2-ol (316 μL , 3.26 mmol), and 3-bromo-2-fluoroaniline (**S16**) (546 mg, 2.87 mmol) were added, and the mixture was stirred at 80 $^\circ\text{C}$ for 12 h. The mixture was cooled to 23 $^\circ\text{C}$, diluted with EtOAc (10 mL), and filtered through a plug of Celite (washings with EtOAc), and evaporated. Flash chromatography (hexanes/EtOAc 9:1 \rightarrow 65:35) gave the title compound **S17** (482 mg, 87%) as a yellow oil, which solidified upon standing to give an off-white solid.

^1H NMR (400 MHz, CDCl_3): δ 6.85 (td, $J = 7.8, 0.9$ Hz, 1H), 6.77 (ddd, $J = 7.7, 6.1, 1.7$ Hz, 1H), 6.73 (td, $J = 8.1, 1.8$ Hz, 1H), 3.74 (br, 2H), 2.13 (s, 1H), 1.63 (s, 6H). ^{13}C NMR (101 MHz, CDCl_3): δ 151.74 (d, $J_{\text{CF}} = 244.0$ Hz), 134.67 (d, $J_{\text{CF}} = 12.5$ Hz), 124.08 (d, $J_{\text{CF}} = 4.5$ Hz), 122.58, 117.20 (d, $J_{\text{CF}} = 3.9$ Hz), 111.20 (d, $J_{\text{CF}} = 13.5$ Hz), 98.65 (d, $J_{\text{CF}} = 3.7$ Hz), 75.97 (d, $J_{\text{CF}} = 1.9$ Hz), 65.85, 31.55. HRMS (DART): m/z $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{11}\text{H}_{11}\text{FNO}^-$, 192.0830; found, 192.0826.

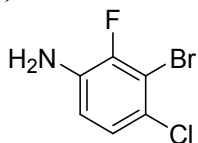
3-Ethynyl-2-fluoroaniline (S11)



A mixture of aniline **S17** (360 mg, 1.86 mmol) and *n*Bu₄NI (69 mg, 0.19 mmol) in toluene (9.3 mL) was treated with 6 M NaOH (9.3 mL, 55.9 mmol), and stirred at 80 °C for 21 h. The mixture was cooled to 5 °C, treated with 1 M HCl (80 mL) and Et₂O (100 mL). The organic layer was separated, and washed with water, brine, dried (MgSO₄), filtered, and evaporated. Flash chromatography (hexanes/EtOAc 40:1 → 8:2) gave the title compound **S11** (66 mg, 26%) as a yellow oil.

¹H NMR (500 MHz, CDCl₃): δ 6.90 – 6.82 (m, 2H), 6.77 (ddd, *J* = 8.5, 7.6, 2.1 Hz, 1H), 3.77 (br, 2H), 3.27 (d, *J* = 0.7 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃): δ 152.27 (d, *J*_{CF} = 244.8 Hz), 134.74 (d, *J*_{CF} = 12.3 Hz), 124.19 (d, *J*_{CF} = 4.3 Hz), 122.98, 117.69 (d, *J*_{CF} = 4.1 Hz), 110.51 (d, *J*_{CF} = 13.4 Hz), 82.00 (d, *J*_{CF} = 3.7 Hz), 77.46 (d, *J*_{CF} = 2.1 Hz). HRMS (DART): *m/z* [M]⁺⁺ calcd for C₈H₆FN⁺⁺, 135.0479; found, 135.0470.

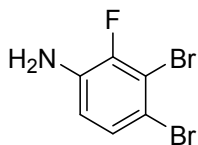
3-Bromo-4-chloro-2-fluoroaniline (S12)¹⁸



A mixture of 3-bromo-2-fluoroaniline (**S16**) (266 μL, 2.37 mmol) in DMF (2.4 mL) was treated with NCS (333 mg, 2.49 mmol), and stirred at 23 °C for 21.5 h. The reaction mixture was diluted with EtOAc (100 mL), and washed with brine (4 x 5 mL), dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (hexanes/EtOAc 40:1 → 85:15) afforded the title compound **S12** (294 mg, 55%) as orange-red crystals which were grinded into a light-brown solid.

^1H NMR (500 MHz, CDCl_3): δ 7.04 (dd, $J = 8.7, 1.9$ Hz, 1H), 6.67 (t, $J = 8.8$ Hz, 1H), 3.81 (br, 2H). ^{13}C NMR (126 MHz, CDCl_3): δ 148.84 (d, $J_{\text{CF}} = 240.9$ Hz), 134.17 (d, $J_{\text{CF}} = 14.2$ Hz), 125.26 (d, $J_{\text{CF}} = 3.7$ Hz), 123.60, 115.76 (d, $J_{\text{CF}} = 4.3$ Hz), 110.61 (d, $J_{\text{CF}} = 20.5$ Hz). HRMS (DART): m/z $[\text{M}]^{++}$ calcd for $\text{C}_6\text{H}_4\text{BrClFN}^{++}$, 222.9194; found, 222.9188.

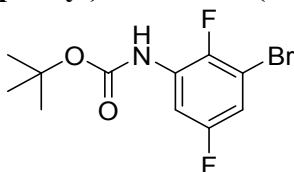
3,4-Dibromo-2-fluoroaniline (**S13**)



A mixture of 3-bromo-2-fluoroaniline (**S16**) (266 μL , 2.37 mmol) in DMF (2.4 mL) was treated with NBS (445 mg, 2.50 mmol), and stirred at 23 $^\circ\text{C}$ for 22 h. The reaction mixture was diluted with EtOAc (100 mL), and washed with brine (4 x 5 mL), dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (hexanes/EtOAc 40:1 \rightarrow 8:2) afforded the title compound **S13** (581 mg, 91%) as a light-brown solid.

^1H NMR (400 MHz, CDCl_3): δ 7.18 (dd, $J = 8.6, 1.8$ Hz, 1H), 6.62 (t, $J = 8.7$ Hz, 1H), 3.83 (br, 2H). ^{13}C NMR (101 MHz, CDCl_3): δ 148.80 (d, $J_{\text{CF}} = 241.6$ Hz), 134.72 (d, $J_{\text{CF}} = 14.2$ Hz), 128.39 (d, $J_{\text{CF}} = 3.8$ Hz), 116.36 (d, $J_{\text{CF}} = 4.3$ Hz), 112.74 (d, $J_{\text{CF}} = 20.3$ Hz), 112.40. HRMS (DART): m/z $[\text{M}]^{++}$ calcd for $\text{C}_6\text{H}_4\text{Br}_2\text{FN}^{++}$, 266.8689; found, 266.8686.

tert-Butyl *N*-(3-bromo-2,5-difluorophenyl)carbamate (**S19**)

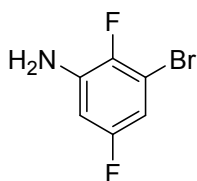


A 1 dram vial was charged with 1,3-dibromo-2,5-difluorobenzene (**S18**) (150 mg, 0.55 mmol), *tert*-butyl carbamate (66 mg, 0.56 mmol), $[\text{Pd}(\text{OAc})_2]$ (12.4 mg, 0.06 mmol), Xantphos (64 mg,

0.11 mmol), and Cs₂CO₃ (270 mg, 0.83 mmol). The vial was evacuated and backfilled with Ar (3x), and dioxane (2.5 mL) was added. The mixture was stirred at 23 °C for 5 min, and then at 100 °C for 23 h. The reaction mixture was cooled to 23 °C, diluted with EtOAc, filtered through a plug of Celite (washings with EtOAc), and evaporated. Flash chromatography (hexanes/EtOAc 40:1 → 15:1) provided the title compound **S19** (113 mg, 67%) as a clear, colorless oil, which turned into a white solid upon standing.

¹H NMR (400 MHz, CDCl₃): δ 7.93 (ddd, *J* = 9.8, 5.8, 3.2 Hz, 1H), 6.90 (ddd, *J* = 7.4, 5.2, 3.1 Hz, 1H), 6.76 (br, 1H), 1.53 (s, 9H). ¹³C NMR (126 MHz, CDCl₃): δ 158.55 (dd, *J*_{CF} = 244.7, 3.1 Hz), 151.86, 145.33 (dd, *J*_{CF} = 237.7, 3.6 Hz), 128.91 (t, *J*_{CF} = 12.7 Hz), 112.68 (d, *J*_{CF} = 27.2 Hz), 108.15 (dd, *J*_{CF} = 21.4, 12.2 Hz), 106.37 (d, *J*_{CF} = 30.2 Hz), 82.15, 28.34. HRMS (DART): *m/z* [M – H][–] calcd for C₁₁H₁₁BrF₂NO₂[–], 305.9947; found, 305.9949.

3-Bromo-2,5-difluoroaniline (**S14**)¹⁹

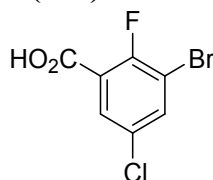


A mixture of compound **S19** (106 mg, 0.34 mmol) in CH₂Cl₂/CF₃CO₂H 2:1 (3.45 mL) was stirred at 23 °C for 19.5 h. The reaction mixture was concentrated, diluted with half-sat. aq. NaHCO₃ (20 mL), and extracted with CH₂Cl₂ (3 x 20 mL). The combined organics were washed with water (20 mL), brine (20 mL), dried (Na₂SO₄), filtered, and evaporated to give the title compound **S14** (62 mg, 87%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 6.61 (ddd, *J* = 7.8, 4.8, 2.9 Hz, 1H), 6.43 (ddd, *J* = 9.5, 6.6, 2.9 Hz, 1H), 3.85 (br, 2H). ¹³C NMR (101 MHz, CDCl₃): δ 158.82 (dd, *J*_{CF} = 243.7, 3.0 Hz), 145.01 (dd, *J*_{CF} = 234.6, 3.3 Hz), 136.42 (dd, *J*_{CF} = 15.5, 12.2 Hz), 108.88 (dd, *J*_{CF} = 20.7, 12.8 Hz), 108.39

(d, $J_{\text{CF}} = 27.0$ Hz), 102.63 (dd, $J_{\text{CF}} = 27.0, 3.0$ Hz). HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_6\text{H}_5\text{BrF}_2\text{N}^+$, 207.9568; found, 207.9563.

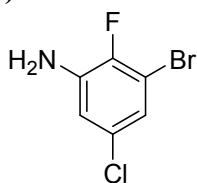
3-Bromo-5-chloro-2-fluorobenzoic acid (**S21**)¹⁸



A mixture of 1.6 M *n*-butyllithium (*n*BuLi) in hexanes (15.4 mL, 24.64 mmol) in THF (32 mL) was treated consecutively with (*i*Pr)₂NH (3.45 mL, 24.63 mmol) and 2-bromo-4-chloro-1-fluorobenzene (**S20**) (4.962 g, 23.69 mmol) at -78 °C. After 2 h at that temperature, the mixture was poured via cannula onto an excess of freshly crushed pieces of solid CO₂ under an Ar atmosphere. The suspension was allowed to warm to 23 °C while stirring. All volatiles were removed in vacuo, water (200 mL) was added, and the mixture was extracted with Et₂O (3 x 70 mL). The aqueous layer was acidified with 6 M HCl (10 mL), and extracted with CH₂Cl₂ (3 x 100 mL). The combined organics were washed with brine (100 mL), dried (MgSO₄), filtered, and evaporated to afford the title compound **S21** (4.953 g, 83%) as a white solid, contaminated with about 10% of the regioisomer.

¹H NMR (400 MHz, DMSO-*d*₆): δ 13.88 (br, 1H), 8.13 (dd, $J = 5.4, 2.7$ Hz, 1H), 7.83 (dd, $J = 5.7, 2.7$ Hz, 1H). ¹³C NMR (101 MHz, DMSO-*d*₆): δ 163.05 (d, $J_{\text{CF}} = 3.6$ Hz), 156.16 (d, $J_{\text{CF}} = 256.9$ Hz), 136.48, 130.55, 128.89 (d, $J_{\text{CF}} = 4.4$ Hz), 122.08 (d, $J_{\text{CF}} = 13.1$ Hz), 111.17 (d, $J_{\text{CF}} = 23.5$ Hz). HRMS (DART): m/z $[\text{M} - \text{H}]^-$ calcd for $\text{C}_7\text{H}_2\text{BrClFO}_2^-$, 250.8916; found, 250.8918.

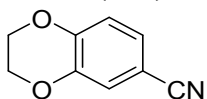
3-Bromo-5-chloro-2-fluoroaniline (**S15**)¹⁶



A mixture of benzoic acid **S21** (2.500 g, 9.86 mmol) in toluene/*t*BuOH 1:1 (50 mL) was treated with diisopropylethylamine (2.1 mL, 12.08 mmol), and with diphenylphosphoryl azide (2.6 mL, 12.08 mmol) at 10 °C. The mixture was stirred at 23 °C for 25 min, and then at 100 °C for 16 h. The reaction mixture was cooled to 23 °C, and evaporated. The residue was dissolved in EtOAc (350 mL), and washed with sat. NaHCO₃ (100 mL), water (100 mL), brine (100 mL), dried (MgSO₄), filtered, and evaporated. Purification by flash chromatography (hexanes/EtOAc 50:1 → 7:3) gave a mixture of compounds which was again purified by flash chromatography (hexanes/CH₂Cl₂ 1:0 → 7:3) to directly afford the deprotected aniline **S15** (328 mg, 15%) as a hard, white solid.

¹H NMR (500 MHz, CDCl₃): δ 6.87 (dd, *J* = 5.3, 2.4 Hz, 1H), 6.69 (dd, *J* = 7.1, 2.5 Hz, 1H), 3.88 (br, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 147.07 (d, *J*_{CF} = 238.8 Hz), 136.40 (d, *J*_{CF} = 14.9 Hz), 129.89 (d, *J*_{CF} = 4.2 Hz), 121.27, 115.52 (d, *J*_{CF} = 3.3 Hz), 109.43 (d, *J*_{CF} = 20.0 Hz). HRMS (DART): *m/z* [M]⁺⁺ calcd for C₆H₄BrClFN⁺⁺, 222.9194; found, 222.9196.

2,3-Dihydro-1,4-benzodioxine-6-carbonitrile (**S23**)

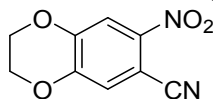


A mixture of 3,4-dihydroxybenzonitrile (**S22**) (3.708 g, 27.4 mmol) in DMF (55 mL) was treated with K₂CO₃ (9.481 g, 68.6 mmol), stirred for 10 min at 23 °C, and treated dropwise with 1-bromo-2-chloroethane (4.57 mL, 54.9 mmol). The mixture was stirred at 23 °C for 1 h, and then at 95 °C for 16 h. The mixture was cooled to 23 °C, diluted with water (200 mL), and extracted with EtOAc

(3 x 125 mL). The combined organics were washed with half-sat. aq. NaHCO₃ (100 mL), water (100 mL), brine (100 mL), dried (Na₂SO₄), filtered, and evaporated to give the title compound **S23** (4.178 g, 95%) as a light-brown solid, which was used in the next step without any further purification.

¹H NMR (500 MHz, CDCl₃): δ 7.16 – 7.12 (m, 2H), 6.91 (dd, J = 8.1, 0.6 Hz, 1H), 4.34 – 4.26 (m, 4H). ¹³C NMR (126 MHz, CDCl₃): δ 147.84, 143.92, 126.07, 121.39, 119.02, 118.38, 104.64, 64.72, 64.25. HRMS (DART): m/z [M + H]⁺ calcd for C₉H₈NO₂⁺, 162.0550; found, 162.0542.

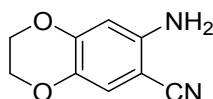
7-Nitro-2,3-dihydro-1,4-benzodioxine-6-carbonitrile (**S24**)



A mixture of carbonitrile **S23** (3.719 g, 23.1 mmol) in AcOH (22.9 mL) was treated at 10 °C with H₂SO₄ (6.4 mL, 120 mmol), cooled to 0 °C, and treated dropwise with 70% HNO₃ (8.2 mL, 120 mmol). The mixture was stirred at 0 °C for 30 min, and then at 23 °C for 10.5 h. The mixture was poured into ice-water (300 mL), and filtered. The residue was washed with water (3 x 30 mL), and dried in a desiccator for 1 h to obtain crude **S24** as a pale-yellow solid. Recrystallization from EtOH gave pure **S24** (3.058 g, 64%) as an off-white powder.

¹H NMR (500 MHz, CDCl₃): δ 7.86 (s, 1H), 7.33 (s, 1H), 4.41 (s, 4H). ¹³C NMR (126 MHz, CDCl₃): δ 148.41, 146.89, 142.67, 123.87, 115.73, 115.16, 101.22, 64.77, 64.72. HRMS (DART): m/z [M + H]⁺ calcd for C₉H₇N₂O₄⁺, 207.0400; found, 207.0399.

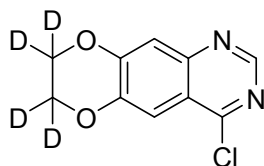
7-Amino-2,3-dihydro-1,4-benzodioxine-6-carbonitrile (**S25**)



A mixture of carbonitrile **S24** (3.011 mg, 14.6 mmol) in EtOAc (146 mL) under argon was treated with 5% Pd/C (782 mg, 0.37 mmol), and the mixture was stirred under 1 atm (balloon) of hydrogen at 23 °C for 15 h. The mixture was filtered through a plug of Celite (washings with EtOAc), and evaporated to afford the anthranilonitrile **S25** (2.461 mg, 96%) as a yellow solid, which was used in the next step without any further purification.

^1H NMR (500 MHz, DMSO- d_6): δ 6.91 (s, 1H), 6.28 (s, 1H), 5.50 (s, 2H), 4.26 – 4.21 (m, 2H), 4.15 – 4.10 (m, 2H). ^{13}C NMR (126 MHz, DMSO- d_6): δ 148.89, 147.37, 134.69, 119.11, 118.03, 102.58, 86.55, 64.82, 63.57. HRMS (DART): m/z $[\text{M}]^+$ calcd for $\text{C}_9\text{H}_8\text{N}_2\text{O}_2^+$, 176.0580; found, 176.0578.

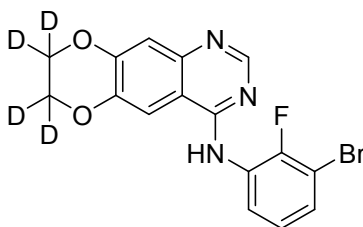
4-Chloro(7,7,8,8- $^2\text{H}_4$)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazoline (**S26**)



A solution of compound **23** (193 mg, 0.98 mmol) in dry DMF (4.8 mL) was treated with Cs_2CO_3 (788 mg, 2.42 mmol), stirred for 5 min, and treated dropwise with 1-bromo-2-chloro($^2\text{H}_4$)ethane (270 μL , 3.16 mmol). The mixture was stirred at RT for 1 h, and then at 70 °C for 18 h. After cooling to RT, all volatiles were removed in vacuo. The residue was dissolved in CH_2Cl_2 (40 mL), washed with water (2 x 13 mL), brine (13 mL), dried (Na_2SO_4), filtered, and evaporated. Purification by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 1:0 \rightarrow 10:1.5) afforded the title compound **S26** (109 mg, 49%) as a white fluffy solid.

^1H NMR (400 MHz, CDCl_3): δ 8.84 (s, 1H), 7.64 (s, 1H), 7.47 (s, 1H). ^{13}C NMR (101 MHz, CDCl_3): δ 160.19, 152.52, 151.54, 147.93, 146.06, 120.10, 113.72, 110.83. HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_4\text{D}_4\text{ClN}_2\text{O}_2^+$, 227.0520; found, 227.0516.

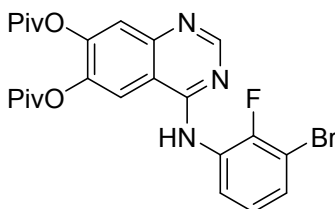
***N*-(3-Bromo-2-fluorophenyl)(7,7,8,8-²H₄)-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine (S9)**



Following general procedure **GP-1**, compound **S9** was prepared from chloroquinazoline **S26** (29 mg, 0.128 mmol) and 3-bromo-2-fluoroaniline (30 μ L, 0.267 mmol) in *i*PrOH (1.26 mL). Flash chromatography (CH₂Cl₂/EtOAc 1:0 \rightarrow 1:1) gave **S9** (38 mg, 78%) as an off-white solid.

¹H NMR (500 MHz, DMSO-*d*₆): δ 9.61 (s, 1H), 8.33 (s, 1H), 7.93 (s, 1H), 7.59 (ddd, *J* = 7.9, 6.3, 1.6 Hz, 1H), 7.54 (ddd, *J* = 8.4, 7.1, 1.6 Hz, 1H), 7.21 (td, *J* = 8.1, 1.2 Hz, 1H), 7.19 (s, 1H). ¹³C NMR (126 MHz, DMSO-*d*₆): δ 157.19, 153.37 (d, *J* = 247.2 Hz), 153.10, 149.27, 146.03, 143.67, 130.12, 128.03 (d, *J* = 13.0 Hz), 127.74, 125.44 (d, *J* = 4.2 Hz), 112.47, 109.63, 108.55 (d, *J* = 19.9 Hz), 108.35. HRMS (DART): *m/z* [M + H]⁺ calcd for C₁₆H₈D₄BrFN₃O₂⁺, 380.0342; found, 380.0327.

4-(3-Bromo-2-fluoroanilino)quinazoline-6,7-diyl bis(2,2-dimethylpropanoate) (S28)

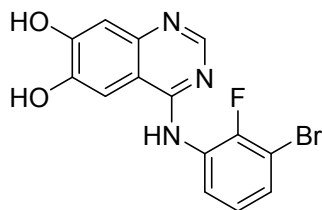


A mixture of 4-chloroquinazoline-6,7-diyl bis(2,2-dimethylpropanoate) (**S27**) (41.08 g, 113 mmol) in *i*PrOH (450 mL) was treated with 3-bromo-2-fluoroaniline (17.05 mL, 152 mmol) and stirred at 80 °C for 3.5 h. The mixture was cooled to 23 °C and evaporated. The residue was several

times resuspended in hexanes (50 mL) and concentrated, and then dried under HV. The residue was recrystallized from EtOH to give a yellow solid, which was suspended in sat. aq. NaHCO₃ (1 L), and extracted with CH₂Cl₂ (3 x 550 mL). The combined organics were washed with water (400 mL), brine (400 mL), dried (MgSO₄), filtered, and evaporated to afford the title compound **S28** (35.057 g, 60%) as a yellow friable foam.

¹H NMR (500 MHz, CDCl₃): δ 8.76 (s, 1H), 8.46 (t, J = 7.5 Hz, 1H), 7.72 (s, 1H), 7.68 (s, 1H), 7.56 (br, 1H), 7.32 (ddd, J = 8.0, 6.4, 1.5 Hz, 1H), 7.11 (td, J = 8.2, 1.5 Hz, 1H), 1.40 (s, 9H), 1.39 (s, 9H). ¹³C NMR (126 MHz, CDCl₃): δ 176.13, 175.55, 156.71, 154.96, 150.69 (d, J_{CF} = 243.7 Hz), 148.75, 147.83, 142.45, 128.27, 127.86 (d, J_{CF} = 10.8 Hz), 125.29 (d, J_{CF} = 4.7 Hz), 122.70, 122.51, 114.43, 113.21, 108.84 (d, J_{CF} = 19.4 Hz), 39.54, 39.51, 27.40, 27.32. HRMS (DART): m/z [M + H]⁺ calcd for C₂₄H₂₆BrFN₃O₄⁺, 518.1085; found, 518.1072.

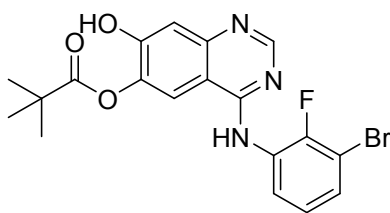
4-(3-Bromo-2-fluoroanilino)quinazoline-6,7-diol (**S29**)



A stirred slurry of **S28** (34.988 g, 67.5 mmol) was treated at 0 °C with 7 M solution of NH₃ in MeOH (241 mL, 1.69 mol). The mixture was stirred at 0 °C for 15 min, and then at 23 °C for 4.5 h. The mixture was evaporated, and the residue suspended in water (400 mL), stirred overnight, and filtered. The residue was washed with water (500 mL), acetonitrile (100 mL), CH₂Cl₂ (4 x 150 mL), Et₂O (2 x 150 mL), and dried in a desiccator to afford the title compound **S29** (23.68 g, quant.) as a pale-yellow powder.

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.38 (br, 1H), 8.26 (s, 1H), 7.61 (s, 1H), 7.59 – 7.48 (m, 2H), 7.18 (t, J = 8.0 Hz, 1H), 7.05 (s, 1H), signals of phenolic protons missing (due to peak broadening). ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$): δ 156.43, 156.12, 153.06 (d, J_{CF} = 246.7 Hz), 151.34, 148.39, 146.80, 129.23, 129.01, 127.12, 125.23 (d, J_{CF} = 4.3 Hz), 108.47, 108.32, 107.09, 103.04. HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{10}\text{BrFN}_3\text{O}_2^+$, 349.9935; found, 349.9923.

4-(3-Bromo-2-fluoroanilino)-7-hydroxyquinazolin-6-yl 2,2-dimethylpropanoate (S30)

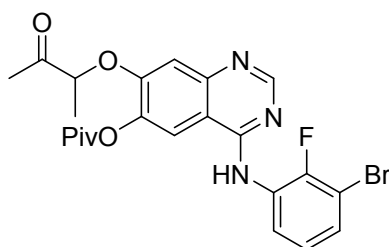


A stirred suspension of **S29** (3500 mg, 10.0 mmol) in DMF (52.6 mL) was treated with Et_3N (5.57 mL, 40.0 mmol), cooled to $-40\text{ }^\circ\text{C}$, and treated dropwise with Piv_2O (3.14 mL, 15.5 mmol). The mixture was stirred at $-40\text{ }^\circ\text{C}$ for 1 h, after which the cooling bath was removed, and stirring was continued for 2.5 h. The reaction mixture was diluted with CH_2Cl_2 (500 mL), washed with 10% citric acid (2 x 50 mL), dried (Na_2SO_4), filtered, and evaporated. Purification by flash chromatography (DCM/EtOAc 1:1 \rightarrow 0:1) afforded a solid, which was redissolved in EtOAc (750 mL), and washed with half-sat. aq. NH_4Cl (4 x 75 mL), dried (Na_2SO_4), filtered, and evaporated to afford the title compound **S30** (2.844 g, 66%) as a beige-yellow solid.

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 11.00 (br, 1H), 9.70 (s, 1H), 8.39 (s, 1H), 8.14 (s, 1H), 7.59 (ddd, J = 8.0, 6.2, 1.6 Hz, 1H), 7.53 (ddd, J = 8.3, 7.1, 1.6 Hz, 1H), 7.21 (td, J = 8.1, 1.2 Hz, 1H), 7.17 (s, 1H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$): δ 175.93, 157.68, 154.61, 154.53, 153.34 (d, J_{CF} = 247.3 Hz), 149.80, 139.65, 130.14, 127.92 (d, J_{CF} = 12.9 Hz), 127.62, 125.47 (d,

$J_{\text{CF}} = 4.4 \text{ Hz}$), 116.36, 111.00, 108.55 (d, $J = 20.0 \text{ Hz}$), 107.77, 38.64, 26.93. HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{18}\text{BrFN}_3\text{O}_3^+$, 434.0510; found, 434.0489.

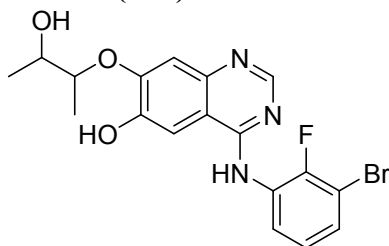
(±)-4-(3-Bromo-2-fluoroanilino)-7-[(3-oxobutan-2-yl)oxy]quinazolin-6-yl 2,2-dimethylpropanoate (S31)



A mixture of **S30** (100 mg, 0.230 mmol) and resin-bound PPh_3 (1% crosslinked with DVB, 100–200 mesh, 1.0–1.5 mmol/g) (480 mg, 0.576 mmol) was swollen in THF (3.4 mL) for 5 min, treated with acetoin (48 μL , 0.553 mmol), cooled to 0 °C, and treated dropwise with DIAD (109 μL , 0.553 mmol). The mixture was stirred at 23 °C for 3 h, diluted with CH_2Cl_2 , filtered, and evaporated. Flash chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 1:0 \rightarrow 6:4) afforded the title compound **S31** (65 mg, 56%) as a white, friable foam.

^1H NMR (500 MHz, CDCl_3): δ 8.73 (s, 1H), 8.52 (t, $J = 7.6 \text{ Hz}$, 1H), 7.58 (s, 1H), 7.49 (br, 1H), 7.32 (ddd, $J = 8.1, 6.4, 1.6 \text{ Hz}$, 1H), 7.19 (s, 1H), 7.12 (td, $J = 8.2, 1.5 \text{ Hz}$, 1H), 4.82 (q, $J = 6.9 \text{ Hz}$, 1H), 2.19 (s, 3H), 1.56 (d, $J = 6.8 \text{ Hz}$, 3H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3): δ 207.51, 176.68, 156.54, 154.88, 154.25, 150.51 (d, $J = 243.3 \text{ Hz}$), 149.95, 141.03, 128.10, 128.01, 125.33 (d, $J = 4.7 \text{ Hz}$), 122.35, 114.41, 109.75, 109.61, 108.78 (d, $J = 19.5 \text{ Hz}$), 79.93, 39.38, 27.43, 24.91, 17.42. HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{24}\text{BrFN}_3\text{O}_4^+$, 504.0929; found, 504.0919.

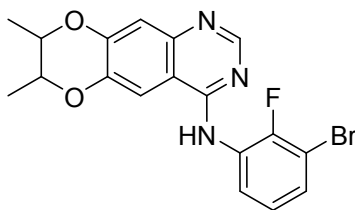
Diastereoisomeric mixture of (±)-*syn*- and (±)-*anti*-4-(3-Bromo-2-fluoroanilino)-7-[(3-hydroxybutan-2-yl)oxy]quinazolin-6-ol (S32)



A mixture of **S31** (49 mg, 0.097 mmol) in EtOH (1 mL) was treated with NaBH₄ (21 mg, 0.554 mmol), and stirred at 23 °C for 2.5 h. Sat. aq. NH₄Cl (1 mL) was added, and EtOH was removed in vacuo. Half-sat. aq. NH₄Cl (14 mL) was added, and the mixture extracted with EtOAc (3 x 13 mL). The combined organics were dried (Na₂SO₄), filtered, and evaporated. Flash chromatography (EtOAc) afforded a diastereoisomeric mixture (*syn/anti* ~1:2) of the title compound **S32** (30 mg, 73%) as a yellow solid.

¹H NMR (500 MHz, CDCl₃; (±)-*syn/anti* 1:2): □ 8.59 (s, 0.33H), 8.56 (s, 0.67H), 8.53 – 8.44 (m, 1H), 7.50 (br, 1H), 7.29 – 7.19 (m, 3H), 7.06 (t, *J* = 8.1 Hz, 1H), 4.56 (qd, *J* = 6.3, 2.6 Hz, 0.33H), 4.37 (p, *J* = 6.2 Hz, 0.67H), 4.22 (qd, *J* = 6.5, 2.7 Hz, 0.33H), 4.02 (p, *J* = 6.3 Hz, 0.37H), 1.39 – 1.28 (m, 6H). ¹³C NMR (126 MHz, CDCl₃; (±)-*syn/anti* 1:2): □ 155.83, 155.81, 152.64, 152.59, 151.92, 151.59, 150.46 (d, *J* = 243.2 Hz), 147.86, 147.82, 145.96, 145.81, 128.46 (d, *J* = 10.5 Hz), 128.42 (d, *J* = 10.5 Hz), 127.63, 127.59, 125.24, 125.20, 122.18, 122.13, 110.28, 109.71, 109.52, 108.72 (d, *J* = 19.4 Hz), 103.64, 103.49, 80.35, 79.09, 70.86, 69.38, 19.41, 18.09, 15.91, 13.00. HRMS (DART): *m/z* [M – H][–] calcd for C₁₈H₁₆BrFN₃O₃[–], 420.0365; found, 420.0352.

Diastereoisomeric mixture of (\pm)-*cis*- and (\pm)-*trans*-N-(3-Bromo-2-fluorophenyl)-7,8-dimethyl-7,8-dihydro[1,4]dioxino[2,3-*g*]quinazolin-4-amine ((\pm)-*cis/trans*-S10)



A mixture of PPh₃ (19 mg, 0.071 mmol) and DIAD (13.5 μ L, 0.069 mmol) in THF (0.5 mL) was stirred at 0 °C for 15 min, and added dropwise to a mixture of **S32** (25 mg, 0.059 mmol) in THF (0.6 mL) at 0 °C during 5 min. The resulting mixture was stirred at 0 °C for 2 h, and evaporated. Purification by PTLC (hexanes/EtOAc 35:65) afforded a diastereoisomeric mixture (*cis/trans* ~2:1) of the title compound **S10** (20 mg, 84%) as a white, friable foam.

¹H NMR (500 MHz, CDCl₃; (\pm)-*cis/trans* 2:1): δ 8.68 (s, 1H), 8.68 – 8.63 (m, 1H), 7.37 (s, 1H), 7.35 (br, 1H), 7.28 (s, 1H), 7.28 – 7.24 (m, 1H), 7.10 (td, *J* = 8.2, 1.6 Hz, 1H), 4.52 – 4.39 (m, 1.3H), 4.09 – 3.98 (m, 0.7H), 1.453 (d, *J* = 6.1 Hz, 1.1H), 1.451 (d, *J* = 6.1 Hz, 1.1H), 1.369 (d, *J* = 6.6 Hz, 1.9H), 1.368 (d, *J* = 6.6 Hz, 1.9H). ¹³C NMR (126 MHz, CDCl₃; (\pm)-*cis/trans* 2:1): δ 155.87, 155.84, 153.19, 150.12 (d, *J* = 242.5 Hz), 150.09 (d, *J* = 242.2 Hz), 149.87, 148.89, 146.77, 144.64, 143.63, 128.73 (d, *J* = 10.0 Hz), 127.15, 127.12, 125.31 (d, *J* = 4.7 Hz), 121.71, 121.70, 114.30, 113.93, 110.54, 110.47, 108.57 (d, *J* = 19.4 Hz), 105.66, 105.28, 75.30, 75.05, 72.85, 72.58, 17.24, 17.20, 14.71, 14.55. HRMS (DART): *m/z* [M + H]⁺ calcd for C₁₈H₁₆BrFN₃O₂⁺, 404.0404; found, 404.0393.

Cell culture conditions. Patient-derived GBM cells were cultured in serum-free gliomasphere conditions consisting of DMEM/F12 (Thermofisher), B27 (Thermofisher), Penicillin-Streptomycin (100U/mL penicillin, 100mg/mL streptomycin, Thermofisher), and Glutamax

(Thermofisher) supplemented with Heparin (5µg/mL, Sigma), Human EGF (50ng/mL, Thermofisher), and Human FGF-β (20ng/mL, Thermofisher). U87 cells were cultured in DMEM (Thermofisher), FBS (10%, Gemini Bio-Products), Penicillin-Streptomycin, and Glutamax. Cells were dissociated to single cell suspensions with TrypLE (Thermofisher) and resuspended in its respective media. Cell lines were regularly tested for mycoplasma infection using Myco Alert™ Mycoplasma Detection Kit according to the manufacturer's protocol (Lonza).

Reagents and antibodies. The following chemical inhibitors were dissolved in DMSO for all in vitro studies: Erlotinib (Chemietek), Lapatinib (MedChemExpress). The following antibodies for immunoblotting were obtained from the listed sources: p-EGFR Y1086 (Thermofisher, 36-9700), t-EGFR (Millipore, 06-847), p-AKT T308 (Cell Signaling, 13038), p-AKT S473 (Cell Signaling, 4060), t-AKT (Cell Signaling, 4685), p-ERK T202/Y204 (Cell Signaling, 4370), t-ERK (Cell Signaling, 4695), p-S6 S235/236 (Cell Signaling, 4858), t-S6 (Cell Signaling, 2217), β-Actin (Cell Signaling, 3700).

Cell-free kinase assays. Cell-free EGFR kinase assays were performed using the EGFR Kinase Enzyme System (Promega, V9261). Briefly, 25 ng of recombinant EGFR kinase domain was incubated at RT with 10 µM ATP, 1 µg/µL poly (4:1 Glu, Tyr) peptide substrate, and an EGFR inhibitor in a 384-well plate for 40 min. Equal volume of ADP-Glo™ Reagent was then added and incubated for 40 min followed by the addition of the Kinase Detection Reagent and a final 30 min incubation. Luminescence (integration time 1 sec) was recorded on a CLARIOstar microplate reader (BMG Labtech). A 10-point titration curve of each EGFR inhibitor was performed in duplicate.

Cell based IC₅₀. U87-wtEGFR and U87-EGFRvIII cells were acclimated overnight in standard cell culture conditions. Cells were washed with PBS and cultured overnight in serum-free DMEM (Thermofisher), Penicillin-Streptomycin, and Glutamax. U87-wtEGFR cells were stimulated with Heparin (5µg/mL, Sigma), Human EGF (50ng/mL, Thermofisher) for 1 hr followed by EGFR TKI treatment for 1 hr before being collected. U87-EGFRvIII cells were treated with EGFR TKI for 1 hr before being collected.

Immunoblotting. Cells were collected and lysed in RIPA buffer (Boston BioProducts) containing Halt™ Protease and Phosphatase Inhibitor (Thermofisher). Lysates were centrifuged at 14,000g for 15min at 4°C. Protein samples were then boiled in NuPAGE LDS Sample Buffer (Thermofisher) and NuPAGE Sample Reducing Agent (Thermofisher), separated using SDS-PAGE on 12% Bis-Tris gels (Thermofisher), and transferred to nitrocellulose membrane (GE Healthcare). Immunoblotting was performed per antibody's manufacturer's specifications. Membranes were developed using the SuperSignal™ system (Thermofisher) and imaged using the Odyssey Fc Imaging System (LI-COR). Signal quantification was performed using the Image Studio™ software (LI-COR).

Growth inhibition assays. Growth inhibition assays were performed by incubating 1500 cells per well in 384-well plates for 72 hours with EGFR inhibitor. A 14-point titration curve of each EGFR inhibitor was performed in quadruplicate. All growth inhibition assays were independently repeated at least 3 times. Cell Titer Glo Luminescent Cell Viability Assay (Promega) was used to measure growth inhibition from control of each EGFR inhibitor. Luminescence (integration time 1 sec) was recorded on a CLARIOstar microplate reader (BMG Labtech).

Proliferation assays. Cells were plated at 50,000 cells/mL with EGFR inhibitors and were dissociated to single cell suspensions every 3 days. Cells were replated and EGFR inhibitors were refreshed. At day 9, cell numbers were recorded and compared to vehicle treated cells. Proliferation assays were independently repeated 3 times.

Permeability assays. Permeability assays were performed by Charles River using a confluent monolayer of Madin Darby Canine Kidney (MDCK) epithelial cells stably transfected with the human *MDR1* gene (gene encoding P-gp). For the apical to basolateral (A→B) permeability, the EGFR inhibitors in the presence or absence of 50 μ M verapamil (a P-gp inhibitor) was added to the apical side and permeation was measured from the basolateral side after a 2 hr incubation; the converse was applied for the basolateral to apical (B→A) permeability. The EGFR inhibitors in the supernatant of the apical and basolateral sides were analyzed by LC-MS/MS to determine permeability and efflux ratios.

Pharmacokinetic studies. Male CD-1 mice were treated by oral gavage with 10 mg/kg of EGFR inhibitor. Mice were euthanized and whole blood and brain tissue were collected at 0, 0.25, 0.5, 1, 2, 4, and 7 hrs post treatment (n=2 mice per time point). Whole blood from mice was centrifuged to isolate plasma. EGFR inhibitors were isolated by liquid-liquid extraction from plasma: 50 μ L plasma was added to 150 μ L acetonitrile and 5 pmol gefitinib internal standard. Mouse brain tissue was washed with 2 mL cold PBS and homogenized using a tissue homogenizer in 2 mL cold water. EGFR inhibitors were then isolated and reconstituted in a similar manner by liquid-liquid extraction: 100 μ L brain homogenate was added to 5 pmol gefitinib internal standard and 300 μ L acetonitrile. After vortex mixing, the samples were centrifuged. The supernatant was removed and

evaporated by a rotary evaporator and reconstituted in 100 μ L 50:50:0.1 water:acetonitrile:formic acid.

EGFR inhibitor detection. Chromatographic separations were performed on a 100 x 2.1 mm Phenomenex Kinetex C18 column (Kinetex) using the 1290 Infinity LC system (Agilent). The mobile phase was composed of solvent A: 0.1% formic acid in Milli-Q water, and B: 0.1% formic acid in acetonitrile. Analytes were eluted with a gradient of 5% B (0-4 min), 5-99% B (4-32 min), 99% B (32-36 min), and then returned to 5% B for 12 min to re-equilibrate between injections. Injections of 20 μ L into the chromatographic system were used with a solvent flow rate of 0.10 mL/min. Mass spectrometry was performed on the 6460 triple quadrupole LC/MS system (Agilent). Ionization was achieved by using electrospray in the positive mode and data acquisition was made in multiple reactions monitoring (MRM) mode. Analyte signal was normalized to the internal standard and concentrations were determined by extrapolating on to the calibration curve (10, 100, 1000, 4000 nM). EGFR inhibitor brain concentrations were adjusted by 1.4% of the mouse brain weight for the residual blood in the brain vasculature as described previously.²⁰

Genetic manipulation. Lentiviruses used for genetic manipulation were produced by transfecting 293-FT cells (ATCC) using lipofectamine 2000 (Thermofisher). Viruses were collected following 48 hr after transfection. Lentiviral vector backbones for the overexpression of wtEGFR and EGFRvIII in U87 cells contained a CMV promoter. U87-wEGFR and U87-EGFRvIII cells were generated by transfection with these overexpression vectors. Short hairpin RNAs (shRNAs) against EGFR were purchased from Sigma (shEGFR1: TRCN0000295969, shEGFR2:

TRCN0000010329). For in vivo tumors, GBM gliomaspheres were infected with a lentiviral vector containing Gaussia luciferase (Gluc) reporter gene.

Intracranial Gaussia luciferase measurements. To measure the levels of Gluc, 6 μ L of blood was collected from the tail vein of the mice and immediately mixed with 50mM EDTA to prevent coagulation. Gluc activity was obtained by measuring chemiluminescence following injection of 100 μ L of 100uM coelenterazine (Nanolight) in a 96 well plate as described previously.²¹

Ex vivo immunoblot studies. GBM39 cells were injected (3×10^5 cells per injection) into the right basal ganglia of the brain (2mm lateral and 1mm anterior to bregma) of NSG mice (Radiation Oncology, UCLA). When the tumors were engrafted and began an exponential growth phase by gaussia luciferase measurement as described above, mice were randomized into treatments arms and were treated with either vehicle (5% DMSO, 10% Transcutol, 30% PEG400), erlotinib (10 mg/kg), lapatinib (80 mg/kg), or **13** (300 mg/kg, BID) for 3 consecutive days. Mice were then euthanized, and tumors were isolated by macro dissection with GFP fluorescence. Tumors were lysed by sonication in RIPA buffer (Boston BioProducts) containing Halt™ Protease and Phosphatase Inhibitor (Thermofisher). The immunoblotting protocol above was then performed on lysates.

Intracranial mouse treatment studies. GBM39 cells were intracranially injected as described above NSG mice. When the tumors were engrafted and began an exponential growth phase by gaussia luciferase measurement as described above, mice were randomized into treatments arms and initiated treatment by oral gavage with either vehicle, erlotinib (10 mg/kg), lapatinib (80

mg/kg), or **13** (300 mg/kg, BID). Mice were treated for 5 days followed by 2 days of no treatment each week until endpoints were reached. Mice were euthanized when moribund or reached a 25% loss in body weight. All studies were in accordance with UCLA Animal Research Committee protocol guidelines.

Statistical Analyses. Unless otherwise specified, student's t-tests were performed for statistical analyses and p-values <0.05 were considered significant. All statistical analyses were calculated using GraphPad Prism.

Molecular Docking of Compound 5 into the EGFR Kinase Domain. The active and inactive wtEGFR protein structures used for the docking studies were retrieved from the RCSB Protein Data Bank (rcsb.org)²² (PDB IDs: 1M17¹ (active) and 1XKK⁸ (inactive)). The receptor protein structures were prepared as follows: 1) all crystallographic water molecules were removed, except for one water molecule making a direct hydrogen bonding interaction with N3 of the quinazoline; 2) hydrogen atoms were manually added to this water molecule with Schrödinger Maestro 2018-1; 3) in case of the protein structure derived from 1M17, Cys751 and Asp831 were manually corrected with PyMOL 2.0.7 due to crystallographic disordering; 4) addition of polar hydrogen atoms, merging of non-polar hydrogen atoms and charges, and assignment of aromatic carbons were then carried out with AutoDockTools 4.2 (The Scripps Research Institute, La Jolla, California, USA).²³ The ligand coordinates were generated as follows: 1) for control docking experiments, the coordinates of erlotinib or lapatinib were retrieved from the protein crystal structure (PDB IDs 1M17 and 1XKK); 2) the coordinates of compound **5** were generated using a conformational search starting with the geometry of the X-ray crystal structure of **5**, performed

with Schrödinger Maestro 2014-2 using MacroModel with the OPLS_2005 force field in water; these conformers were docked separately, and the results manually inspected; 3) all ligands were prepared for docking with AutoDockTools, which assigned Gasteiger charges and torsional angles to the ligand conformers. Docking was performed by AutoDock Vina 1.1.2 (The Scripps Research Institute)²⁴ with exhaustiveness set to 16; docking results were manually inspected, and the binding poses with the most favorable binding affinity and meaningful geometry were visualized with PyMOL.

S4. X-Ray Crystal Structures

Crystals of compounds **4** and **5** were obtained by dissolving in a minimum amount of solvent(s), and allowing the solvent(s) to slowly evaporate at room temperature. The structures were solved by direct methods and refined by full-matrix least-squares analysis (SHELXTL).²⁵ Data were corrected for absorption effects using the multi-scan method (SADABS). Unless otherwise indicated below, all non-hydrogen atoms were refined anisotropically. All hydrogen atoms, except for the ones on nitrogen atoms, were constrained to ideal geometries and refined with fixed isotropic displacement parameters (in terms of a riding model). CCDC-1913486 (**4**) and -1913485 (**5**) contain the supplementary crystallographic data for this publication. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

S4.1. X-Ray Crystal Data of Compound **4**

Table S6. Crystal data, data collection, and structure refinement for **4** (CCDC-1913486).

Crystal data	
Empirical formula	C ₁₆ H ₁₁ ClFN ₃ O ₂
Formula weight (<i>M_r</i>)	331.73
Crystal system, space group	Orthorhombic, <i>Pna</i> 2 ₁
Temperature	100(2) K
Unit cell dimensions	<i>a</i> = 12.4287 (19) Å
	<i>b</i> = 16.933 (3) Å
	<i>c</i> = 6.578 (1) Å
Volume	1384.3 (4) Å ³
<i>Z</i>	4
Radiation type	CuKα radiation, λ = 1.54178 Å
Crystal size (mm)	0.20 × 0.10 × 0.04 mm ³
Density (calculated)	1.592 mg mm ⁻³
Absorption coefficient μ	2.690 mm ⁻¹
F(000)	680

Data collection	
Diffractometer	Bruker APEX-II CCD
Theta range for data collection	4.4 to 69.9°
Index ranges	$-15 \leq h \leq 14$, $-20 \leq k \leq 20$, $-7 \leq l \leq 7$
Reflections collected	8518
Independent reflections	2385 ($R_{\text{int}} = 0.041$)
Absorption correction	multi-scan
Max. and min. transmission	0.75 and 0.63
Refinement	
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2385 / 1 / 211
Goodness-of-fit on F^2	1.100
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0254$, $wR_2 = 0.0619$
R indices (all data)	$R_1 = 0.0263$, $wR_2 = 0.0625$
Largest diff. peak and hole	0.19 and $-0.24 \text{ e}\text{\AA}^{-3}$

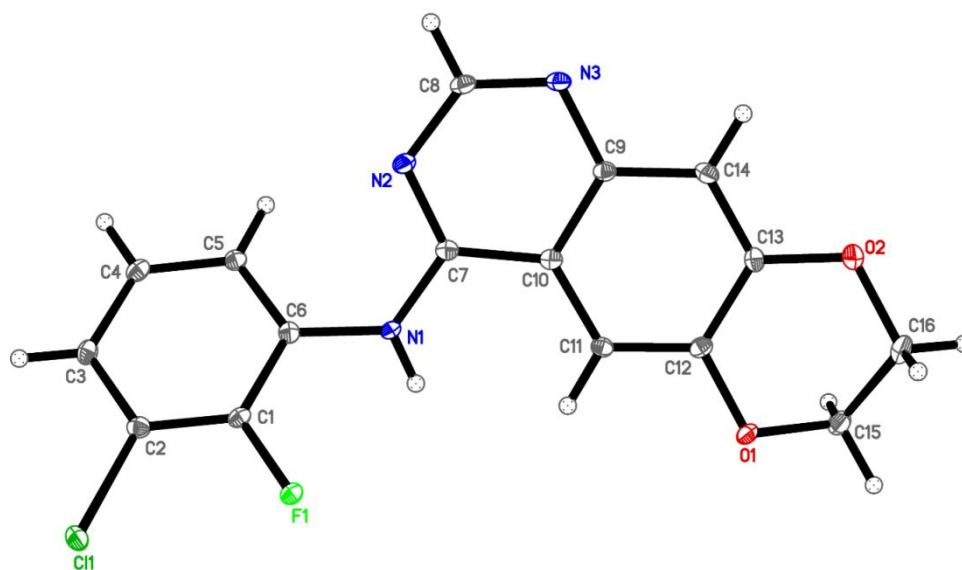


Figure S14. ORTEP representation of **4**, arbitrary numbering. Atomic displacement parameters at 100 K are drawn at 50% probability level. Color code: grey = C, white = H, blue = N, red = O, pale green = F, dark green = Cl. Selected bond lengths (Å), and torsional angles (°): F1–C1 1.355(2), C11–C2 1.733(2), N1–C6 1.415(3), N1–C7 1.358(3), O1–C12 1.376(3), O2–C13 1.363(3), N2–C7–N1–C6 1.0(3), C5–C6–N1–C7 30.3(3).

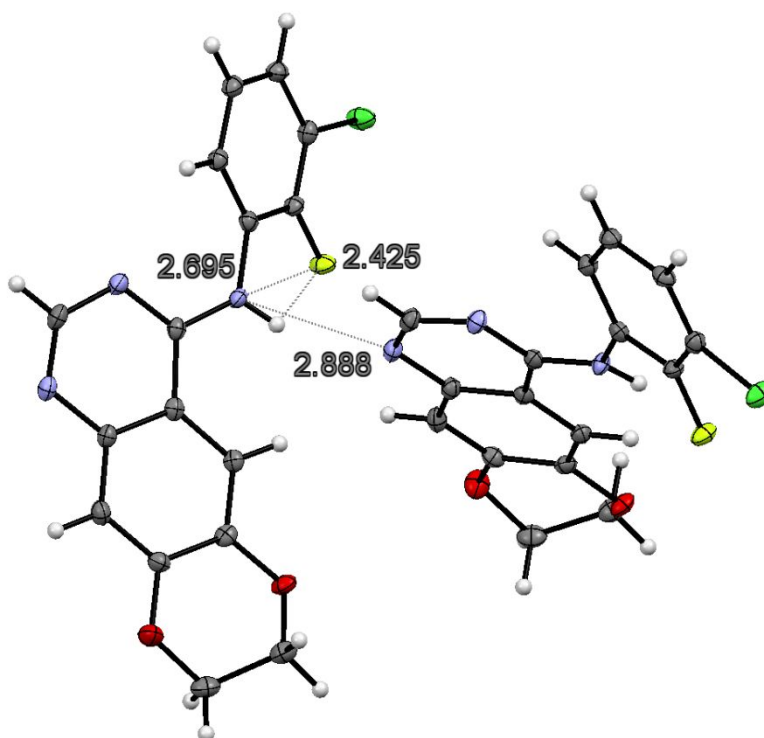


Figure S15. Distances of inter- and intramolecular hydrogen bonding interactions involving the N-H proton in the crystal packing of **4**. Distances (in Å) are shown as dashed grey lines.

S4.2. X-Ray Crystal Data of Compound **5**

Table S7. Crystal data, data collection, and structure refinement for **5** (CCDC-1913485).

Crystal data	
Empirical formula	C ₁₆ H ₁₁ BrFN ₃ O ₂
Formula weight (<i>M_r</i>)	376.19
Crystal system, space group	Orthorhombic, <i>Pna</i> 2 ₁
Temperature	100(2) K
Unit cell dimensions	<i>a</i> = 12.4531 (10) Å <i>b</i> = 17.0793 (13) Å <i>c</i> = 6.6267 (5) Å
Volume	1409.43 (19) Å ³
<i>Z</i>	4
Radiation type	MoK α radiation, λ = 0.71073 Å
Crystal size (mm)	0.30 × 0.25 × 0.10 mm ³
Density (calculated)	1.773 mg mm ⁻³
Absorption coefficient μ	2.942 mm ⁻¹
F(000)	752

Data collection	
Diffractometer	Bruker APEX-II CCD
Theta range for data collection	2.0 to 31.0°
Index ranges	$-17 \leq h \leq 17$, $-24 \leq k \leq 23$, $-9 \leq l \leq 9$
Reflections collected	17842
Independent reflections	4154
Absorption correction	multi-scan
Max. and min. transmission	0.74 and 0.57
Refinement	
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4154 / 1 / 211
Goodness-of-fit on F^2	1.034
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0217$, $wR_2 = 0.0530$
R indices (all data)	$R_1 = 0.0239$, $wR_2 = 0.0537$
Largest diff. peak and hole	0.41 and -0.42 eÅ^{-3}

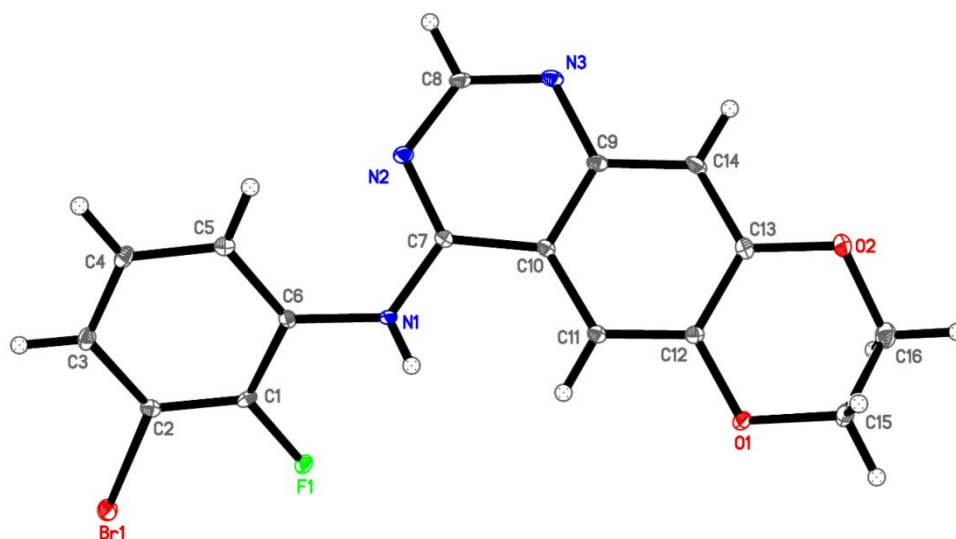


Figure S16. ORTEP representation of **5**, arbitrary numbering. Atomic displacement parameters at 100 K are drawn at 50% probability level. Color code: grey = C, white = H, blue = N, red = O, pale green = F, dark green = Cl. Selected bond lengths (Å), and torsional angles (°): F1–C1 1.351(2), Br1–C2 1.883(2), N1–C6 1.409(3), N1–C7 1.362(3), O1–C12 1.371(2), O2–C13 1.371(3), N2–C7–N1–C6 $-0.7(3)$, C5–C6–N1–C7 $-30.9(3)$.

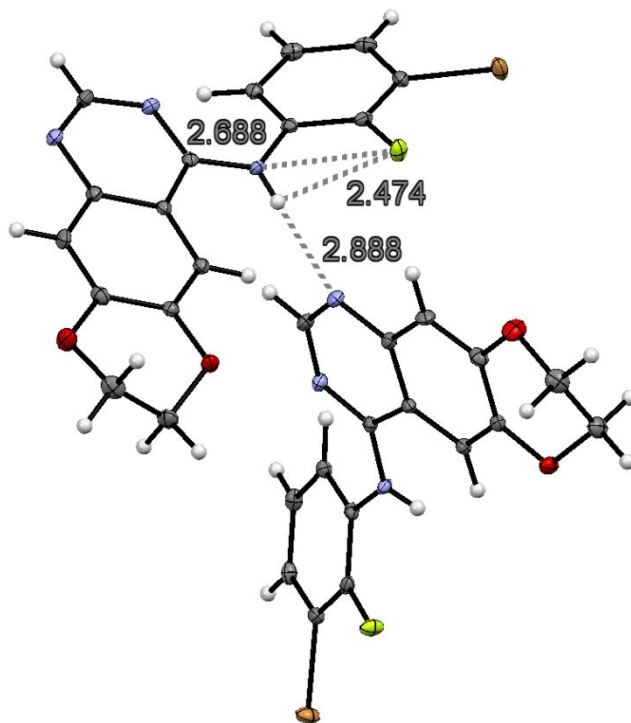


Figure S17. Distances of inter- and intramolecular hydrogen bonding interactions involving the N-H proton in the crystal packing of **5**. Distances (in Å) are shown as dashed grey lines.

S5. List of Kinase Inhibitors

The data of the kinase inhibitors in the following tables were compiled from ²⁶⁻²⁹. Properties were adopted from the original sources, individually verified, and in some cases manually recalculated (HBD, HBA, NRB, NArR, NChn, C/Het, BasAmn, noncon), or calculated with MarvinSketch 17.11 from ChemAxon (cLogD, TPSA, pKa).

Abbreviations of molecular properties: MW: molecular weight; HBD: number of hydrogen bond donors; HBA: number of hydrogen bond acceptors; NRB: number of rotatable bonds; TPSA: topological polar surface area (in Å); NArR: number of aromatic rings; NChn: number of chains; C/Het: ratio of carbon atoms to non-carbon-non-hydrogen atoms; BasAmn: number of aliphatic amines, for piperazine rings only one nitrogen atom was counted; noncon: number of saturated carbon atoms in rings.

Table S8. FDA-approved kinase inhibitors.

Drug	SMILES	MW	HBD	HBA	cLogP	cLogD	NRB	TPSA	Most basic center (pKa)	NArR	NChn	C/Het	BasAmn	noncon
Abemaciclib	<chem>CCN1CCN(CC1)Cc2ccc(nc2)Nc3ncc(c(n3)c4cc5c(c(c4)F)nc(n5C(C)C)C)F</chem>	507	1	8	5.16	4.15	7	75.00	7.94	4	9	2.70	1	4
Acalabrutinib	<chem>CC#CC(=O)N1CCC[C@H]1c2nc(c3n2ccnc3N)c4ccc(cc4)C(=O)Nc5ccccc5</chem>	466	2	6	1.14	1.14	4	118.51	4.63	4	7	2.89	0	4
Afatinib	<chem>CN(C)C/C=C/C(=O)Nc1cc2c(cc1O[C@H]3CCOC3)ncnc2Nc4ccc(c(c4)Cl)F</chem>	486	2	7	3.97	3.02	8	88.61	8.81	3	7	2.40	0	4
Alectinib	<chem>CCc1cc2c(cc1N3CCC(CC3)N4CCOCC4)C(c5c(c6ccc(cc6[nH]5)C#N)C2=O)(C)C</chem>	483	1	5	4.69	4.46	3	72.36	6.97	3	7	5.00	1	10
Axitinib	<chem>CNC(=O)c1cccc1Sc2ccc3c(c2)[nH]nc3/C=C/c4ccccc4</chem>	386	2	4	3.82	3.81	5	95.97	4.61	4	4	3.67	0	0
Baricitinib	<chem>CCS(=O)(=O)N1CC(C1)(CC#N)n2cc(en2)c3e4cc[nH]c4nen3</chem>	371	1	7	0.33	0.33	5	128.94	3.91	3	6	1.60	0	3
Binimetinib	<chem>Cn1cnc2c1cc(c(c2F)Nc3ccc(cc3F)Br)C(=O)NOCCO</chem>	441	3	5	2.64	2.64	6	88.41	5.06	3	7	1.70	0	0
Bosutinib	<chem>CN1CCN(CC1)CCCOc2cc3c(cc2OC)c(c(en3)C#N)Nc4cc(c(cc4Cl)Cl)OC</chem>	530	1	8	4.96	4.12	9	82.88	8.03	3	8	2.60	1	4
Brigatinib	<chem>CN1CCN(CC1)C2CCN(CC2)c3ccc(c(c3)OC)Nc4ncc(c(n4)Nc5ccccc5P(=O)(C)C)Cl</chem>	584	2	9	5.17	4.16	8	85.86	8.54	3	10	2.64	1	9
Cabozantinib	<chem>COc1cc2c(ccnc2cc1OC)Oc3ccc(cc3)NC(=O)C4(CC4)C(=O)Nc5ccc(cc5)F</chem>	501	2	6	4.47	4.29	8	98.78	5.90	4	7	3.11	0	3
Ceritinib	<chem>Cc1cc(c(cc1C2CCNCC2)OC(C)C)Nc3ncc(c(n3)Nc4ccccc4S(=O)(=O)C(C)C)Cl</chem>	558	3	8	6.09	3.89	9	113.62	10.07	3	11	2.80	1	5
Cobimetinib	<chem>c1c(cc(c(c1)Nc2c(c(ccc2C(=O)N3C[C@H](C3)O)[C@H]4NC(CCC4)F)F)I</chem>	531	3	4	5.09	3.97	4	64.60	9.76	2	9	2.33	1	8
Crizotinib	<chem>C[C@H](c1c(ccc(c1Cl)F)Cl)Oc2cc(cnc2N)c3cnn(c3)C4CCNC4</chem>	450	2	5	4.39	2.66	5	77.99	10.12	3	8	2.33	1	5
Dabrafenib	<chem>CC(C)(C)c1nc(c(s1)c2cncnc2N)c3ccccc3F)NS(=O)(=O)c4c(cccc4F)F</chem>	520	2	7	4.51	2.64	6	147.48	2.91	4	12	1.92	0	0
Dacomitinib	<chem>COc1cc2c(cc1NC(=O)/C=C/CN3CCCC3)c(nen2)Nc4ccc(c(c4)Cl)F</chem>	470	2	6	4.76	3.88	7	79.38	8.55	3	6	2.67	1	5

Dasatinib	<chem>Cc1cccc(c1NC(=O)c2cnc(s2)Nc3cc(ne(n3)C)N4CCN(CC4)CCO)Cl</chem>	488	3	8	2.97	2.81	7	134.75	7.18	3	8	2.00	1	4
Encorafenib	<chem>C[C@@H](CNc1cccc(n1)c2en(nc2c3cc(cc3F)NS(=O)(=O)C)Cl)C(C)C)NC(=O)OC</chem>	540	3	9	3.12	2.89	10	148.51	3.08	3	12	1.57	0	0
Erdafitinib	<chem>CC(C)NCCN(c1ccc2c(c1)nc(en2)c3cnn(c3)C)c4ccc(cc4)OC)OC</chem>	447	1	7	4.6	1.3	9	77.33	9.72	4	7	3.125	1	0
Erlotinib	<chem>COCCOc1cc2c(cc1OCCOC)ncnc2Nc3cccc(c3)C#C</chem>	393	1	7	3.14	3.12	10	74.73	4.62	3	4	3.14	0	0
Everolimus	<chem>C[C@@H]1CC[C@H]2C[C@@H](/C(=C/C=C/C(=O)[C@H](C[C@H](C(=O)[C@H]([C@@H](C[C@@H](C(=O)C[C@H](OC(=O)[C@H]3CCCCN3C(=O)C(=O)[C@@H]1(O2)O)[C@H](C)C[C@@H]4CC[C@H]([C@@H](C4)OC)OCCO)C)/C)O)OC)C)/C)OC</chem>	958	3	14	4.47	4.47	9	204.66	N/A	0	19	3.53	0	25
Fostamatinib	<chem>CC1(C(=O)N(c2c(ccc(n2)Nc3c(cnc(n3)Nc4ccc(c(c4)OC)OC)OC)F)O1)COP(=O)(O)O)C</chem>	580	4	14	1.70	-2.25		186.72	1.90	3	12	1.35	0	1
Gefitinib	<chem>COc1cc2c(cc1OCCCN3CCOCC3)c(cncn2)Nc4ccc(c4)Cl)F</chem>	447	1	7	4.50	4.33	8	68.74	6.85	3	5	2.44	1	4
Gilteritinib	<chem>CCc1c(nc(c1)C(=O)N)Nc2ccc(c(c2)OC)N3CCC(CC3)N4CCN(CC4)C)NC5CCOCC5</chem>	553	3	10	2.95	1.83	9	121.11	8.47	2	9	2.64	2	13
Ibrutinib	<chem>C=CC(=O)N1CCC[C@H](C1)n2c3c(c(n2)c4ccc(cc4)Oc5cccc5)c(nen3)N</chem>	441	1	6	3.12	3.12	5	99.16	4.06	4	6	3.13	0	5
Imatinib	<chem>Cc1ccc(cc1Nc2nccc(n2)c3ccnc3)NC(=O)c4ccc(cc4)CN5CCN(CC5)C</chem>	494	2	7	4.15	3.29	7	86.28	7.84	4	7	3.63	1	4
Lapatinib	<chem>CS(=O)(=O)CCNCc1ccc(o1)c2ccc3c(c2)c(nen3)Nc4ccc(c4)Cl)OCc5cccc(c5)F</chem>	581	2	8	4.97	4.92	11	114.73	7.26	5	8	2.64	1	0
Larotrectinib	<chem>c1cc(c(c1F)[C@H]2CCCN2c3ccn4c(n3)c(cn4)NC(=O)N5CC[C@@H](C5)O)F</chem>	428	2	6	2.61	2.61	3	86.00	0.70	3	7	2.10	0	8
Lenvatinib	<chem>COc1cc2c(cc1C(=O)N)c(cen2)Oc3ccc(c(c3)Cl)NC(=O)NC4CC4</chem>	427	3	5	3.57	3.56	6	115.57	5.40	3	7	2.33	0	3
Lorlatinib	<chem>C[C@@H]1c2cc(ccc2C(=O)N(Cc3c(c(n3)C)C#N)-c4cc(c(nc4)N)O1)C)F</chem>	406	1	6	1.96	1.95	0	110.06	5.71	3	7	2.33	0	2
Midostaurin	<chem>C[C@@@]12[C@@H]([C@@H]([C@H]([C@@H](O1)n3c4cccc4c5c3c6n2c7cccc7c6c8c5C(=O)NC8)N(C)C(=O)c9cccc9)OC</chem>	571	1	4	5.31	5.31	3	77.73	N/A	6	6	4.38	0	6
Neratinib	<chem>CCOc1cc2c(cc1NC(=O)/C=C/CN(C)C)c(cen2)C#N)Nc3ccc(c(c3)Cl)OCc4ccccn4</chem>	557	2	8	5.09	4.13	11	112.40	8.81	4	8	3.00	1	0
Netarsudil	<chem>Cc1ccc(c(c1)C)C(=O)OCc2ccc(cc2)[C@@H](CN)C(=O)Nc3ccc4cncccc4c3</chem>	453	2	5	4.19	3.15	8	94.31	8.69	4	7	4.67	1	0
Nilotinib	<chem>Cc1ccc(cc1Nc2nccc(n2)c3ccnc3)C(=O)Nc4cc(cc4)n5cc(nc5)C)C(F)F</chem>	530	2	6	4.96	4.48	6	97.62	5.92	5	10	2.55	0	0
Nintedanib	<chem>CN1CCN(CC1)CC(=O)N(C)c2ccc(cc2)N/C(=C)/c4ccc(cc4NC3=O)C(=O)OC/c5cccc5</chem>	540	2	7	3.94	3.15	8	94.22	7.23	3	9	3.44	1	4
Osimertinib	<chem>CN1C=C(C2=CC=CC=C2)C3=NC(=NC=C3)NC4=C(C=C(C(=C4)NC(=O)C=N(C)CCN(C)C)OC</chem>	500	2	7	3.38	2.07	10	87.55	8.87	4	9	3.11	1	0
Palbociclib	<chem>Cc1c2cnc(nc2n(c(=O)c1C(=O)C3CCCC3)Nc4ccc(cn4)N5CCNCC5</chem>	447	2	8	0.30	1.87	5	103.35	8.86	2	7	2.67	1	9
Pazopanib	<chem>Cc1ccc(cc1S(=O)(=O)N)Nc2nccc(n2)N(C)c3ccc4c(n(c4c3)C)C</chem>	437	2	8	3.81	3.18	5	127.41	4.36	4	9	2.10	0	0
Ponatinib	<chem>Cc1ccc(cc1C#Cc2nc3n2cccc3)C(=O)Nc4ccc(c4)C(F)(F)CN5CCN(CC5)C</chem>	533	1	5	4.68	3.83	6	65.77	7.62	4	9	2.90	1	4
Regorafenib	<chem>CNC(=O)c1cc(cen1)Oc2ccc(c(c2)F)NC(=O)Nc3ccc(c(c3)C(F)(F)F)Cl</chem>	483	3	4	4.80	4.74	5	92.35	2.02	3	10	1.75	0	0
Ribociclib	<chem>CN(C)C(=O)c1cc2cnc(nc2n1C3CCCC3)Nc4ccc(cn4)N5CCNCC5</chem>	435	2	7	2.62	0.97	5	91.21	8.86	3	6	2.56	1	9

Ruxolitinib	<chem>c1c[nH]c2c1c(ncn2)c3enn(c3)[C@H](CC#N)C4CCCC4</chem>	306	1	4	2.02	2.02	4	83.18	3.91	3	3	2.83	0	5
Sirolimus	<chem>C[C@@H]1CC[C@H]2C[C@@H](/C=C/C=C/C/[C@H](C[C@H](C=O)[C@@H](C[C@@H](/C=C/[C@H](C=O)C[C@H](OC(=O)[C@@H]3CCCCN3C(=O)C(=O)[C@@H]1(O2)O)[C@H](C)C[C@@H]4CC[C@H](C[C@@H](C4)OC)O)C)OC)OC</chem>	914	3	13	4.46	4.46	6	195.43	N/A	0	19	3.64	0	25
Sorafenib	<chem>CNC(=O)c1cc(cen1)Oc2ccc(cc2)NC(=O)Nc3ccc(c(c3)C(F)(F)F)Cl</chem>	465	3	4	4.61	4.59	5	92.35	2.03	3	9	1.91	0	0
Sunitinib	<chem>CCN(CC)CCNC(=O)c1c(c([nH]c1C)/C=C/2/c3cc(ccc3NC2=O)F)C</chem>	398	3	3	3.17	1.68	7	77.23	9.04	2	8	3.14	1	0
Temsirolimus	<chem>C[C@@H]1CC[C@H]2C[C@@H](/C=C/C=C/C/[C@H](C[C@H](C=O)[C@@H](C[C@@H](/C=C/[C@H](C=O)C[C@H](OC(=O)[C@@H]3CCCCN3C(=O)C(=O)[C@@H]1(O2)O)[C@H](C)C[C@@H]4CC[C@H](C[C@@H](C4)OC)OC(=O)C(C)(CO)CO)C)O)OC)C)OC</chem>	1029	4	16	4.29	4.29	11	241.96	N/A	0	22	3.29	0	16
Tofacitinib	<chem>C[C@@H]1CCN(C[C@@H]1N(C)C2c3cc[nH]c3ncn2)C(=O)C#N</chem>	312	1	5	1.01	-0.02	3	88.91	6.44	2	5	2.29	0	5
Trametinib	<chem>Cc1c2c(c(n(c1=O)C)Nc3ccc(cc3F)I)c(=O)n(c(=O)n2c4cccc(c4)NC(=O)C)C5CC5</chem>	615	2	5	3.41	3.41	5	102.06	N/A	3	12	2.36	0	3
Vandetanib	<chem>CN1CCC(CC1)COc2cc3c(cc2OC)c(ncn3)Nc4ccc(cc4F)Br</chem>	475	1	6	5.34	3.89	6	59.51	9.13	3	6	2.75	1	5
Vemurafenib	<chem>CCCS(=O)(=O)Nc1ccc(c(c1F)C(=O)c2c[nH]c3c2cc(cn3)c4ccc(cc4)Cl)F</chem>	489	2	4	4.85	3.38	7	100.30	2.30	4	9	2.30	0	0

Table S9. FDA-approved EGFR kinase inhibitors.

Drug	SMILES	MW	HBD	HBA	cLogP	cLogD	NRB	TPSA	Most basic center (pKa)	NArR	NChn	C/Het	BasAmn	noncon
Afatinib	<chem>CN(C)C/C=C/C(=O)Nc1cc2c(cc1O)[C@H]3CCOC3)ncnc2Nc4ccc(c(c4)Cl)F</chem>	486	2	7	3.97	3.02	8	88.61	8.81	3	7	2.40	0	4
Brigatinib	<chem>CN1CCN(CC1)C2CCN(CC2)c3ccc(c(c3)OC)Nc4ncc(c(n4)Nc5cccc5P(=O)(C)C)Cl</chem>	584	2	9	5.17	4.16	8	85.86	8.54	3	10	2.64	1	9
Dacomitinib	<chem>COc1cc2c(cc1NC(=O)/C=C/CN3CCCC3)c(ncn2)Nc4ccc(c(c4)Cl)F</chem>	470	2	6	4.76	3.88	7	79.38	8.55	3	6	2.67	1	5
Erlotinib	<chem>COCCOc1cc2c(cc1OCCOC)ncnc2Nc3cccc(c3)C#C</chem>	393	1	7	3.14	3.12	10	74.73	4.62	3	4	3.14	0	0
Gefitinib	<chem>COc1cc2c(cc1OCCCN3CCOCC3)c(ncn2)Nc4ccc(c(c4)Cl)F</chem>	447	1	7	4.5	4.33	8	68.74	6.85	3	5	2.44	1	4
Lapatinib	<chem>CS(=O)(=O)CCNCc1ccc(o1)c2ccc3c(c2)c(ncn3)Nc4ccc(c(c4)Cl)OCc5cccc(c5)F</chem>	581	2	8	4.97	4.92	11	114.73	7.26	5	8	2.64	1	0
Neratinib	<chem>CCOc1cc2c(cc1NC(=O)/C=C/CN(C)C)c(c(n2)C#N)Nc3ccc(c(c3)Cl)OCc4ccccn4</chem>	557	2	8	5.09	4.13	11	112.40	8.81	4	8	3.00	1	0
Osimertinib	<chem>CN1C=C(C2=CC=CC=C21)C3=NC(=NC=C3)NC4=C(C=C(C(=C4)NC(=O)C=C)N(C)CCN(C)C)OC</chem>	500	2	7	3.38	2.07	10	87.55	8.87	4	9	3.11	1	0
Vandetanib	<chem>CN1CCC(CC1)COc2cc3c(cc2OC)c(ncn3)Nc4ccc(cc4F)Br</chem>	475	1	6	5.34	3.89	6	59.51	9.13	3	6	2.75	1	5

Table S10. EGFR kinase inhibitors, which are approved by any agency or are in clinical development.

Drug	SMILES	MW	HBD	HBA	cLogP	cLogD	NRB	TPSA	Most basic center (pKa)	NArR	NChn	C/Het	BasAmm	noncon
Afatinib	<chem>CN(C)C/C=C/C(=O)Nc1cc2c(cc1O[C@H]3CCOC3)nenc2Nc4ccc(c(c4)Cl)F</chem>	486	2	7	3.97	3.02	8	88.61	8.81	3	7	2.40	0	4
Brigatinib	<chem>CN1CCN(CC1)C2CCN(CC2)c3ccc(c(c3)OC)Nc4ncc(c(n4)Nc5ccccc5P(=O)(C)C)Cl</chem>	584	2	9	5.17	4.16	8	85.86	8.54	3	10	2.64	1	9
Dacomitinib	<chem>COc1cc2c(cc1NC(=O)/C=C/CN3CCCC3)c(nen2)Nc4ccc(c(c4)Cl)F</chem>	470	2	6	4.76	3.88	7	79.38	8.55	3	6	2.67	1	5
Erlotinib	<chem>COCCOc1cc2c(cc1OCCOC)nenc2Nc3cccc(c3)C#C</chem>	393	1	7	3.14	3.12	10	74.73	4.62	3	4	3.14	0	0
Gefitinib	<chem>COc1cc2c(cc1OCCCN3CCOCC3)c(nen2)Nc4ccc(c(c4)Cl)F</chem>	447	1	7	4.50	4.33	8	68.74	6.85	3	5	2.44	1	4
Lapatinib	<chem>CS(=O)(=O)CCNCc1ccc(o1)c2ccc3c(c2)c(nen3)Nc4ccc(c(c4)Cl)OCc5cccc(c5)F</chem>	581	2	8	4.97	4.92	11	114.73	7.26	5	8	2.64	1	0
Neratinib	<chem>CCOc1cc2c(cc1NC(=O)/C=C/CN(C)C)c(c(en2)C#N)Nc3ccc(c(c3)Cl)OCc4ccccn4</chem>	557	2	8	5.09	4.13	11	112.40	8.81	4	8	3.00	1	0
Osimertinib	<chem>CN1C=C(C2=CC=CC=C21)C3=NC(=NC=C3)NC4=C(C=C(C(=C4)NC(=O)C=C)N(C)CCN(C)C)OC</chem>	500	2	7	3.38	2.07	10	87.55	8.87	4	9	3.11	1	0
Vandetanib	<chem>CN1CCC(CC1)COc2cc3c(cc2OC)c(nen3)Nc4ccc(cc4F)Br</chem>	475	1	6	5.34	3.89	6	59.51	9.13	3	6	2.75	1	5
Varlitinib	<chem>C[C@H]1N=C(NC2=CC3=C(NC4=CC=C(OCC5=NC=CS5)C(Cl)=C4)N=CN=C3C=C2)OC1</chem>	467	2	8	4.20	4.67	7	121.79	4.64	4	5	2.20	0	2
Olmутinib	<chem>C=CC(NC1=CC=CC(OC2=C3C(C=CS3)=NC(NC4=CC=C(C=C4)N5CCN(CC5)C)=N2)=C1)=O</chem>	487	2	7	4.70	4.81	7	110.86	7.96	4	6	2.89	1	4
BMS-599626	<chem>FC1=CC=CC(CN2N=CC3=C2C=CC(NC4=NC=NN5C4=C(C)C(NC(OC[C@H]6NCCOC6)=O)=C5)=C3)=C1</chem>	531	3	8	2.80	3.65	8	119.63	7.49	5	6	2.25	1	4
Icotinib	<chem>C#CC1=CC=CC(NC2=C3C=C4OCCOCCOCCOC4=CC3=NC=N2)=C1</chem>	391	1	7	3.10	3.03	2	74.73	4.62	3	2	3.14	0	6
Pelitinib	<chem>O=C(NC1=C(OCC)C=C2N=CC(C#N)=C(NC3=CC=C(F)C(Cl)=C3)C2=C1)/C=C/CN(C)C</chem>	468	2	6	4.50	2.76	8	90.28	8.81	3	8	2.67	1	0
Canertinib	<chem>C=CC(=O)NC1=C(C=C2C(=C1)C(=NC=N2)NC3=CC(=C(C(=C3)F)Cl)OCCCN4CCOCC4</chem>	486	2	7	3.90	3.79	9	88.61	6.87	3	6	2.40	1	4
Naquotinib	<chem>CCC1=NC(=C(N=C1OC2CCN(C2)C(=O)C=C)NC3=CC=C(C(=C3)N4CCC(CC4)N5CCN(CC5)C)C(=O)N</chem>	563	2	9	3.40	2.11	9	120.16	8.57	2	10	2.73	1	12
AV-412	<chem>CC(C)(C#CC1=CC2=C(C=C1NC(=O)C=C)C(=NC=N2)NC3=CC(=C(C(=C3)F)Cl)N4CCN(CC4)C</chem>	507	2	6	4.50	4.71	7	73.39	7.65	3	9	3.00	1	4
Tesevatinib	<chem>CN1CC2CC(C2C1)COC3=C(C=C4C(=C3)N=CN=C4NC5=C(C(=C(C(=C5)Cl)Cl)F)OC</chem>	491	1	6	5.80	2.84	6	59.51	9.84	3	7	2.67	1	7
Allitinib	<chem>C=CC(=O)NC1=CC2=C(C=C1)N=CN=C2NC3=CC(=C(C(=C3)OCC4=CC(=CC=C4)F)Cl</chem>	449	2	5	5.40	5.77	7	76.14	3.99	4	6	3.00	0	0
Poziotinib	<chem>COC1=C(C=C2C(=C1)N=CN=C2NC3=C(C(=C(C(=C3)Cl)Cl)F)OC4CCN(CC4)C(=O)C=C</chem>	491	1	6	5.40	4.50	6	76.58	4.49	3	8	2.30	0	5
Pyrotinib	<chem>CCOC1=C(C=C2C(=C1)N=CC(=C2NC3=CC(=C(C(=C3)OCC4=CC=CC=N4)Cl)C#N)NC(=O)C=CC5CCCN5C</chem>	583	2	8	5.40	3.61	10	112.40	8.71	4	8	3.20	1	4

Rociletinib	<chem>CC(=O)N1CCN(CC1)C2=CC(=C(C=C2)NC3=NC=C(C(=N3)NC4=CC(=CC=C4)NC(=O)C=C)C(F)(F)F)OC</chem>	556	3	8	4.00	4.10	9	111.72	3.62	3	11	2.08	0	4
Sapitinib	<chem>CNC(=O)CN1CCC(CC1)OC2=C(C=C3C(=C2)C(=NC=N3)NC4=C(C(=CC=C4)Cl)F)OC</chem>	474	2	7	4.00	2.67	7	88.61	6.98	3	7	2.30	1	5
Selatinib	<chem>CS(=O)CCNCC1=CC=C(O1)C2=CC3=C(C=C2)N=CN=C3NC4=CC(=C(C=C4)OCC5=CC(=CC=C5)F)Cl</chem>	565	2	7	4.80	3.88	11	108.49	7.94	5	7	2.90	1	0
Simotinib	<chem>COC1=C(C=C2C(=C1)N=CN=C2NC3=CC(=C(C=C3)F)Cl)OCCN4CC5(CC5)C6(C4)OCCO6</chem>	501	1	8	4.00	4.47	7	77.97	6.95	3	5	2.50	1	8

S6. References

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S7. NMR Spectra of Final Compounds

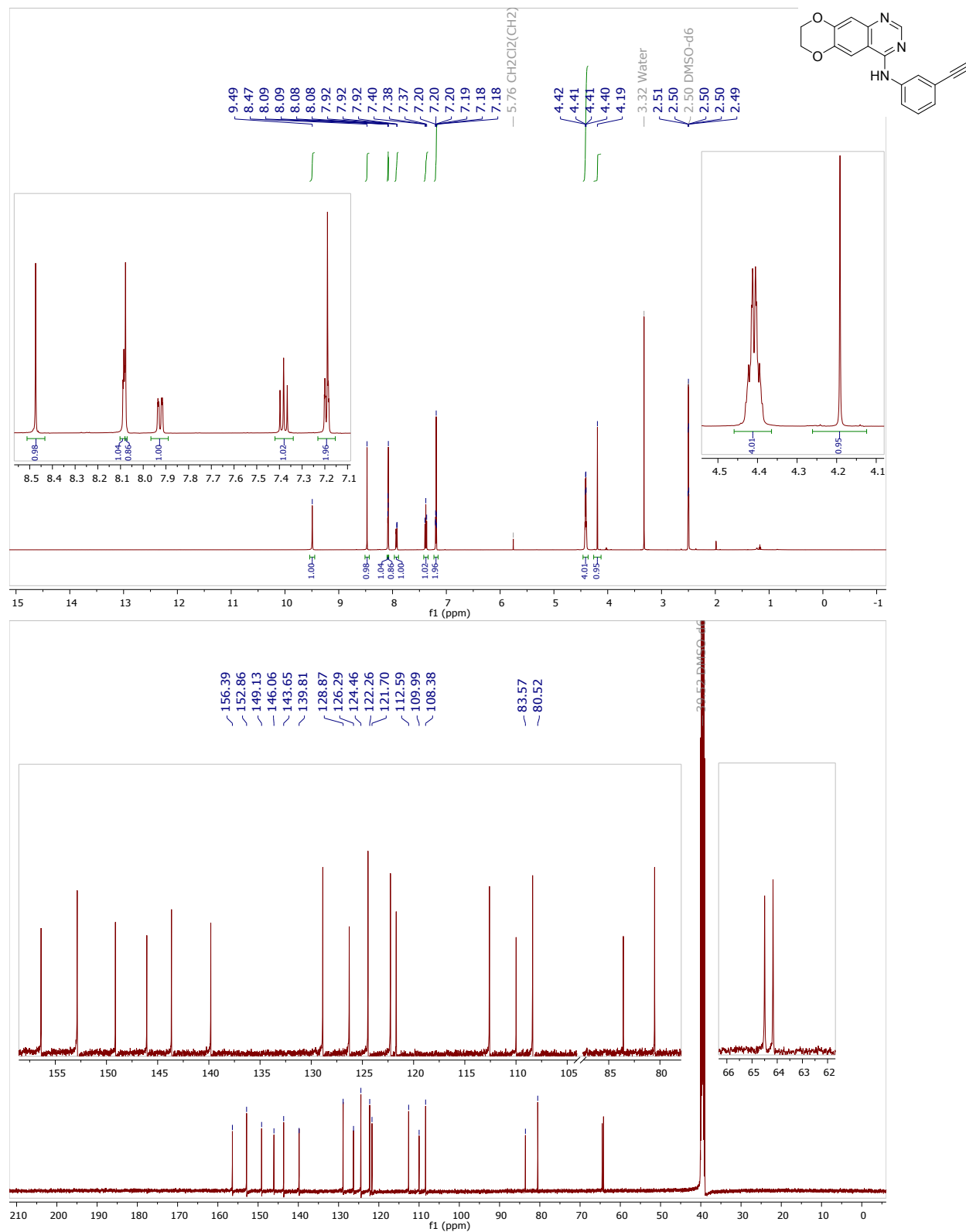


Figure S18. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **1** in DMSO-*d*₆ at 298 K.

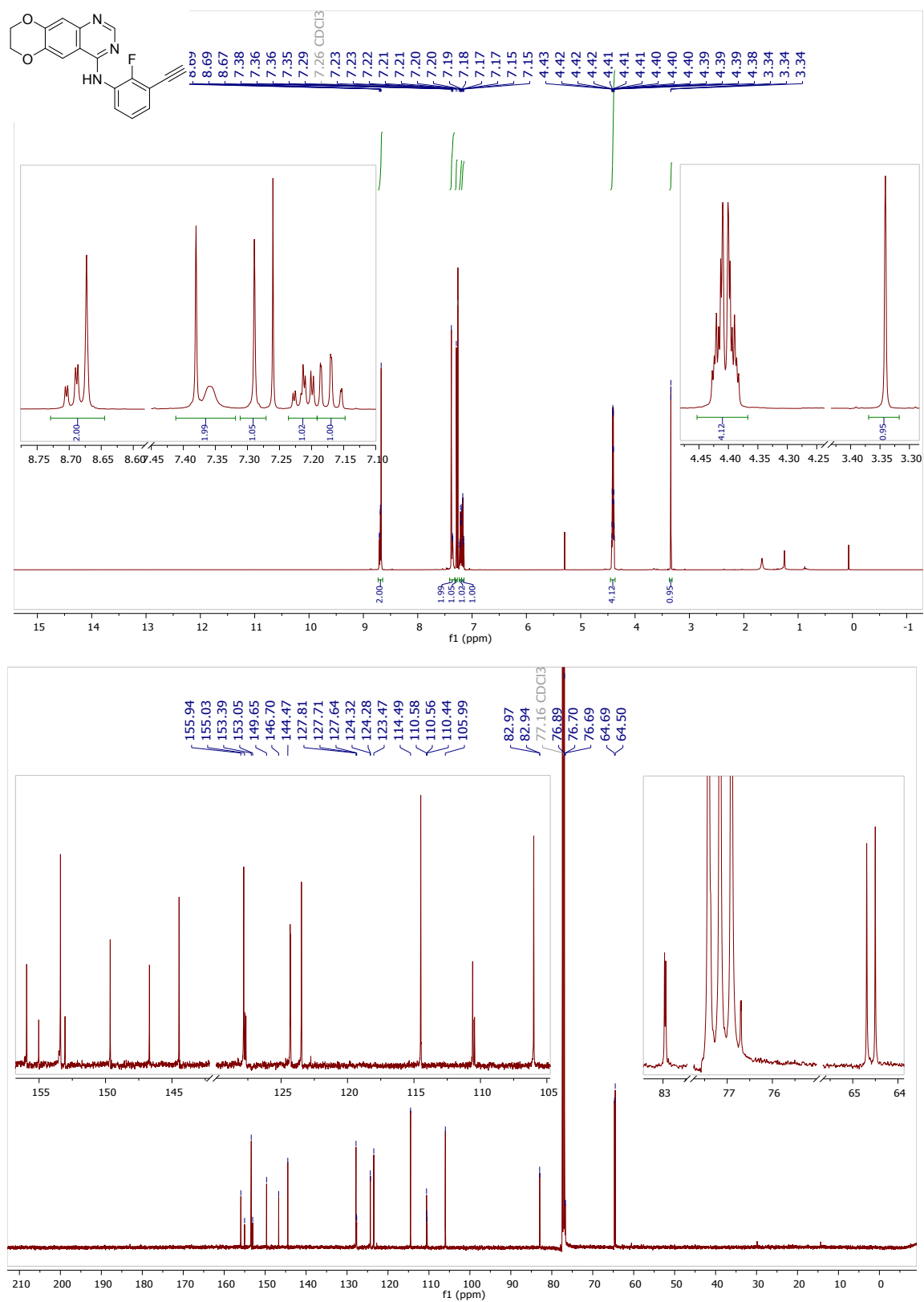


Figure S19. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **2** in CDCl₃ at 298 K.

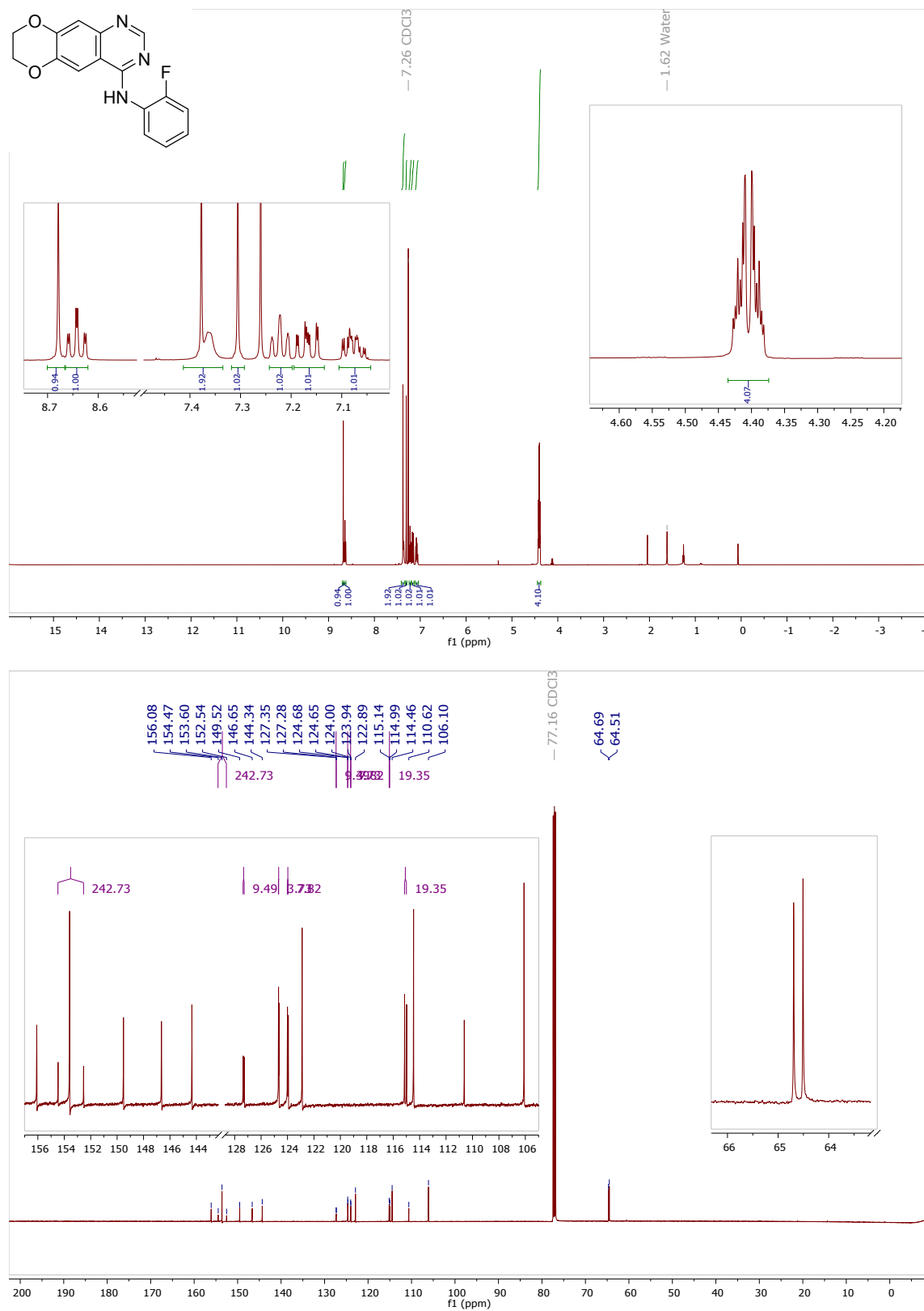


Figure S20. ^1H NMR (top) and ^{13}C NMR (bottom) spectra of **S1** in CDCl_3 at 298 K.

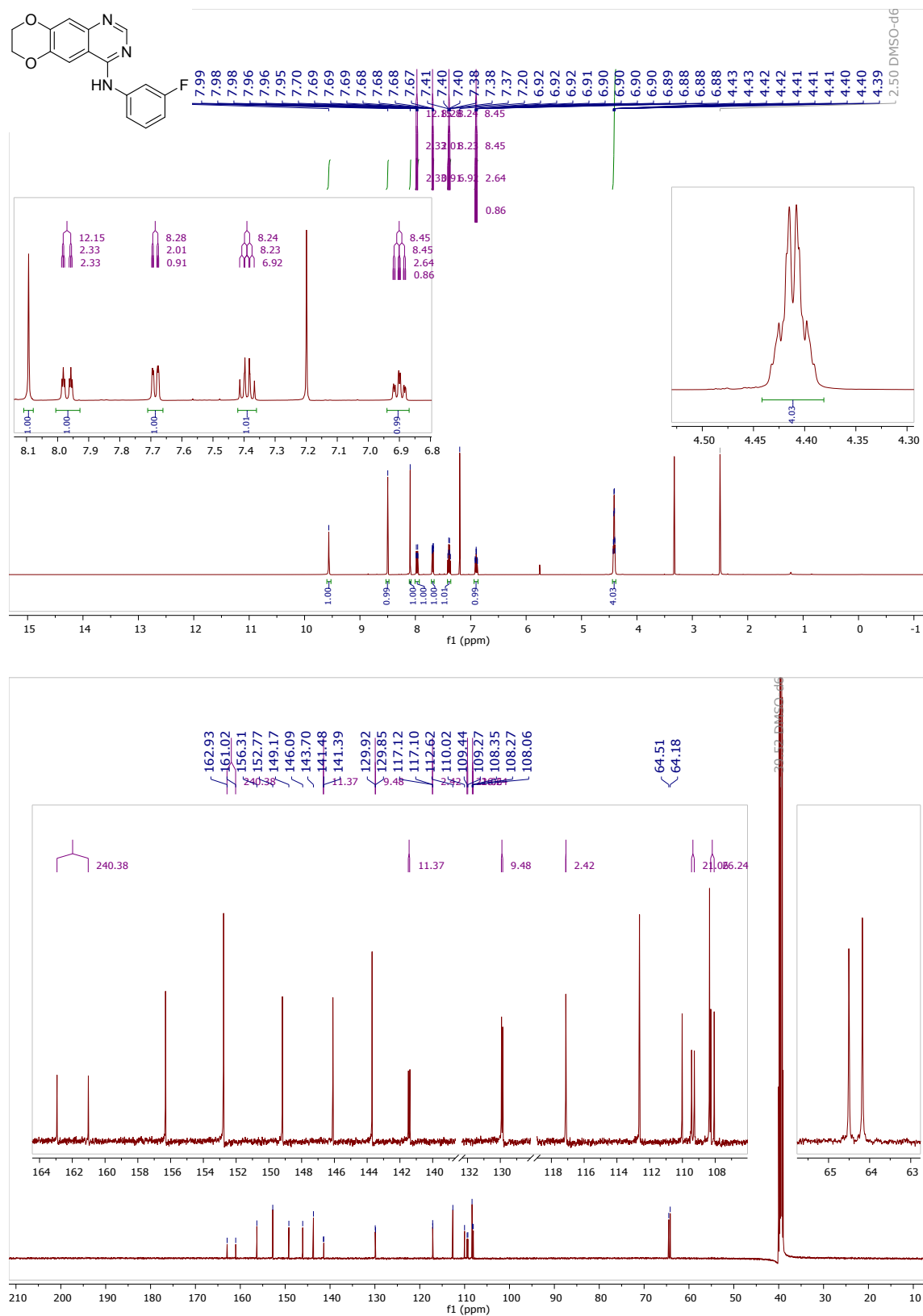


Figure S21. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **S2** in DMSO-*d*₆ at 298 K.

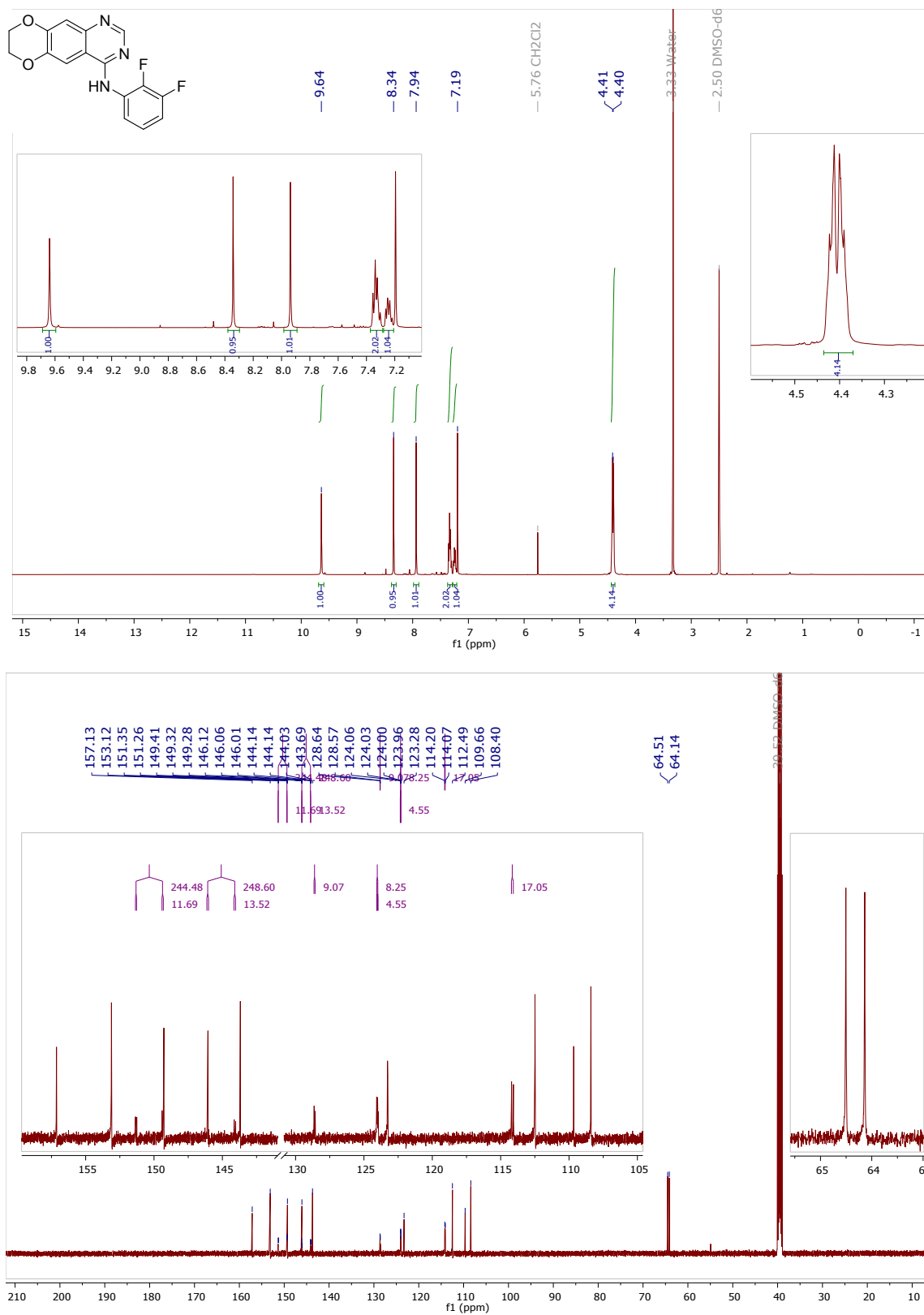


Figure S22. ¹H NMR (top) and ¹³C NMR (bottom) spectra of S3 in DMSO-*d*₆ at 298 K.

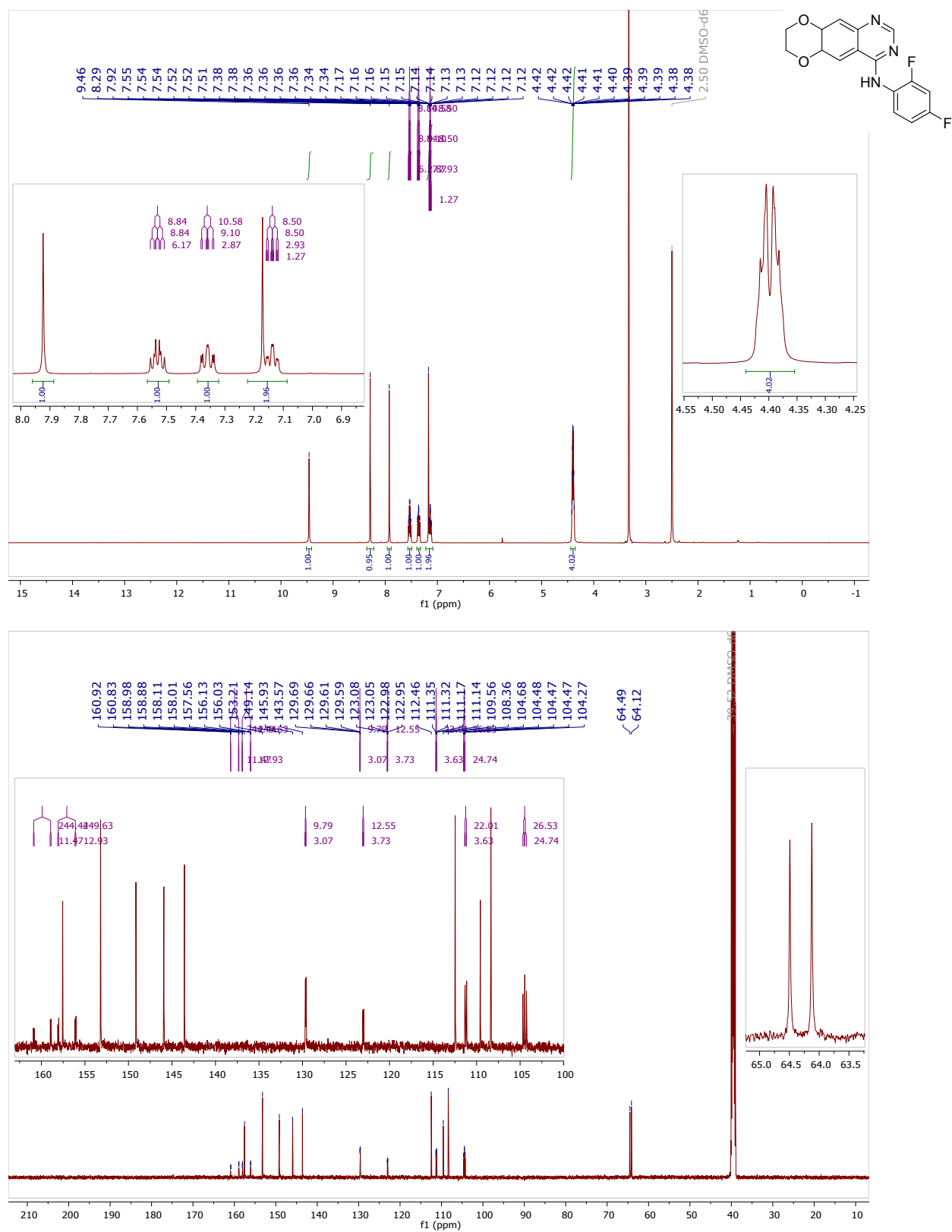


Figure S23. ¹H NMR (top) and ¹³C NMR (bottom) spectra of S4 in DMSO-*d*₆ at 298 K.

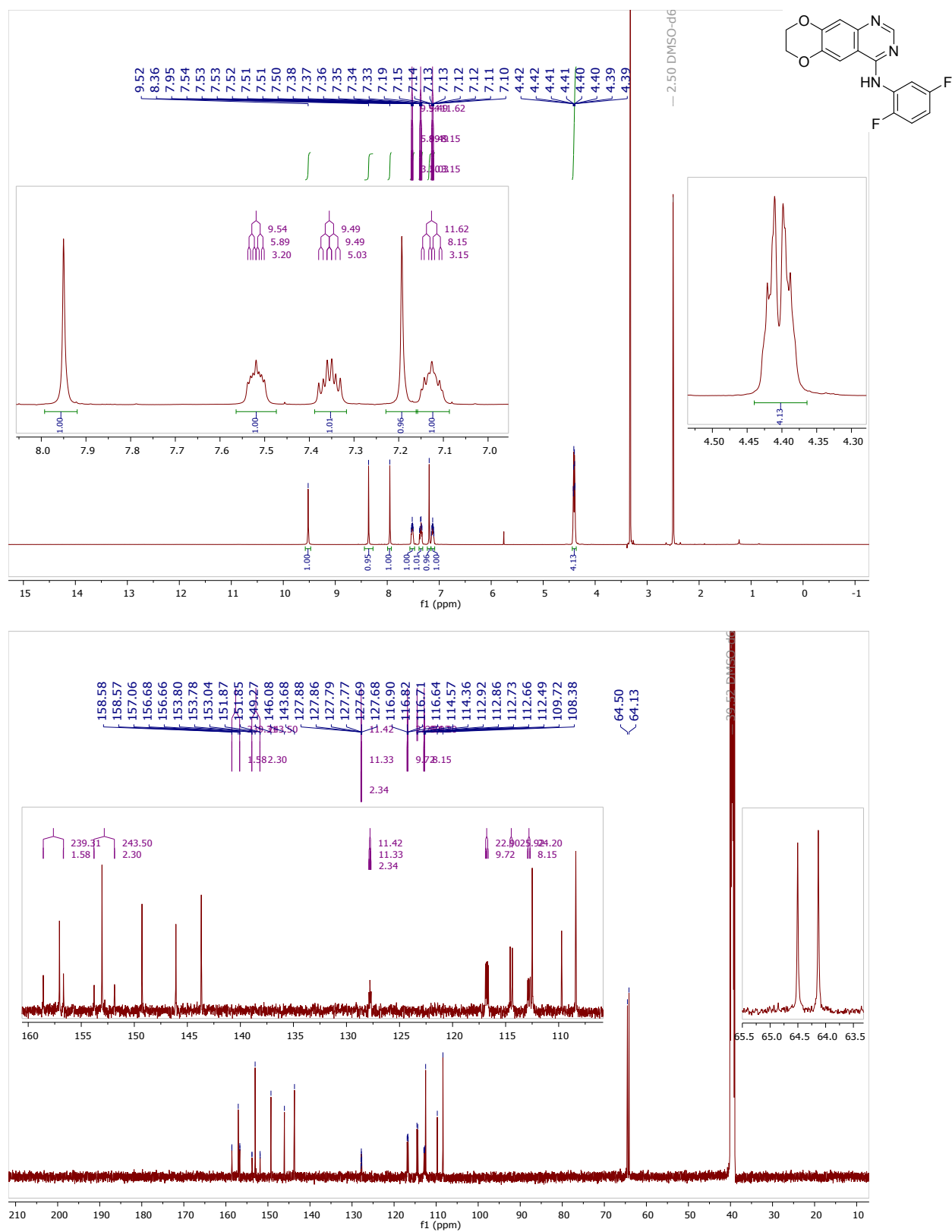


Figure S24. ¹H NMR (top) and ¹³C NMR (bottom) spectra of S5 in DMSO-*d*₆ at 298 K.

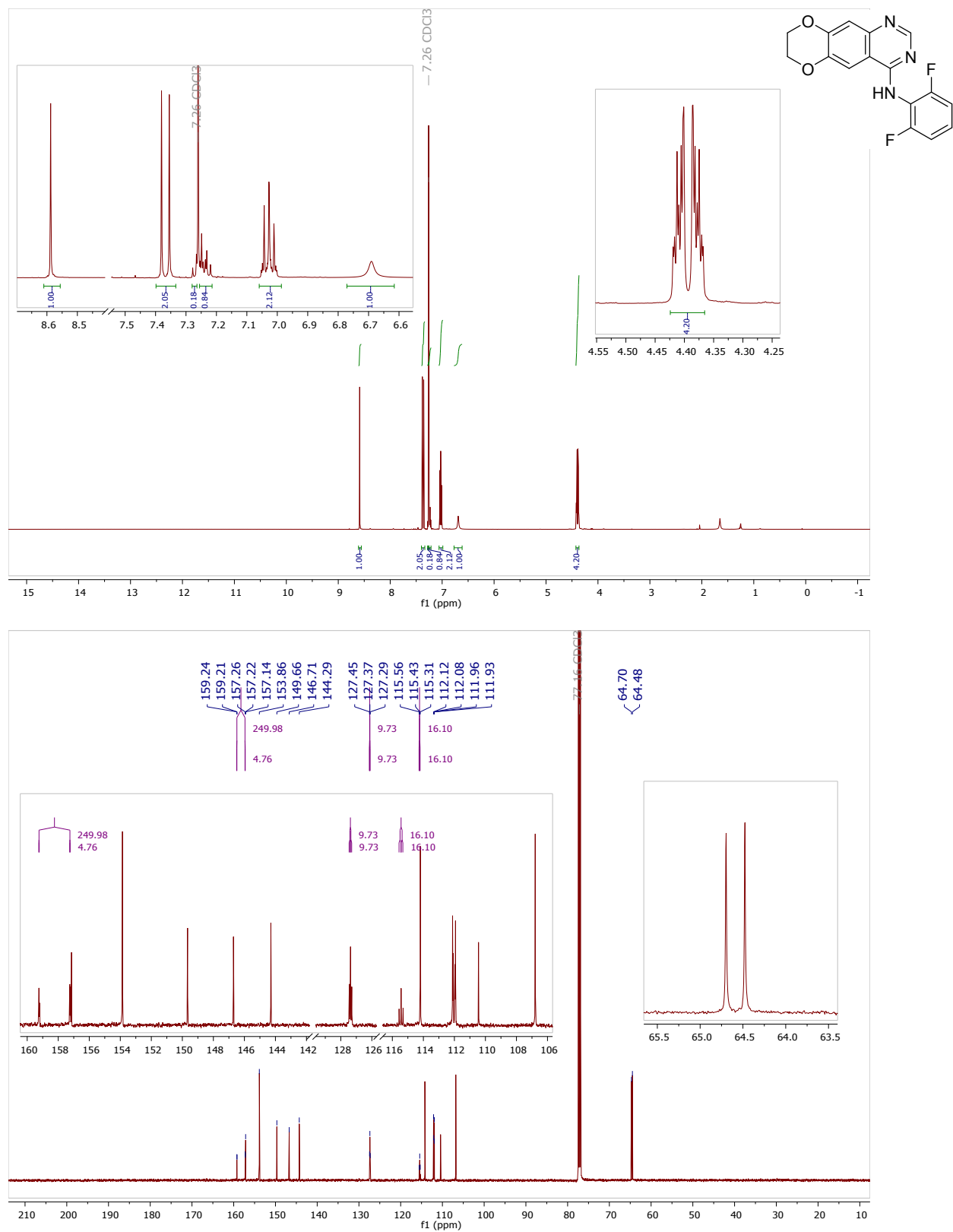


Figure S25. ¹H NMR (top) and ¹³C NMR (bottom) spectra of S6 in CDCl₃ at 298 K.

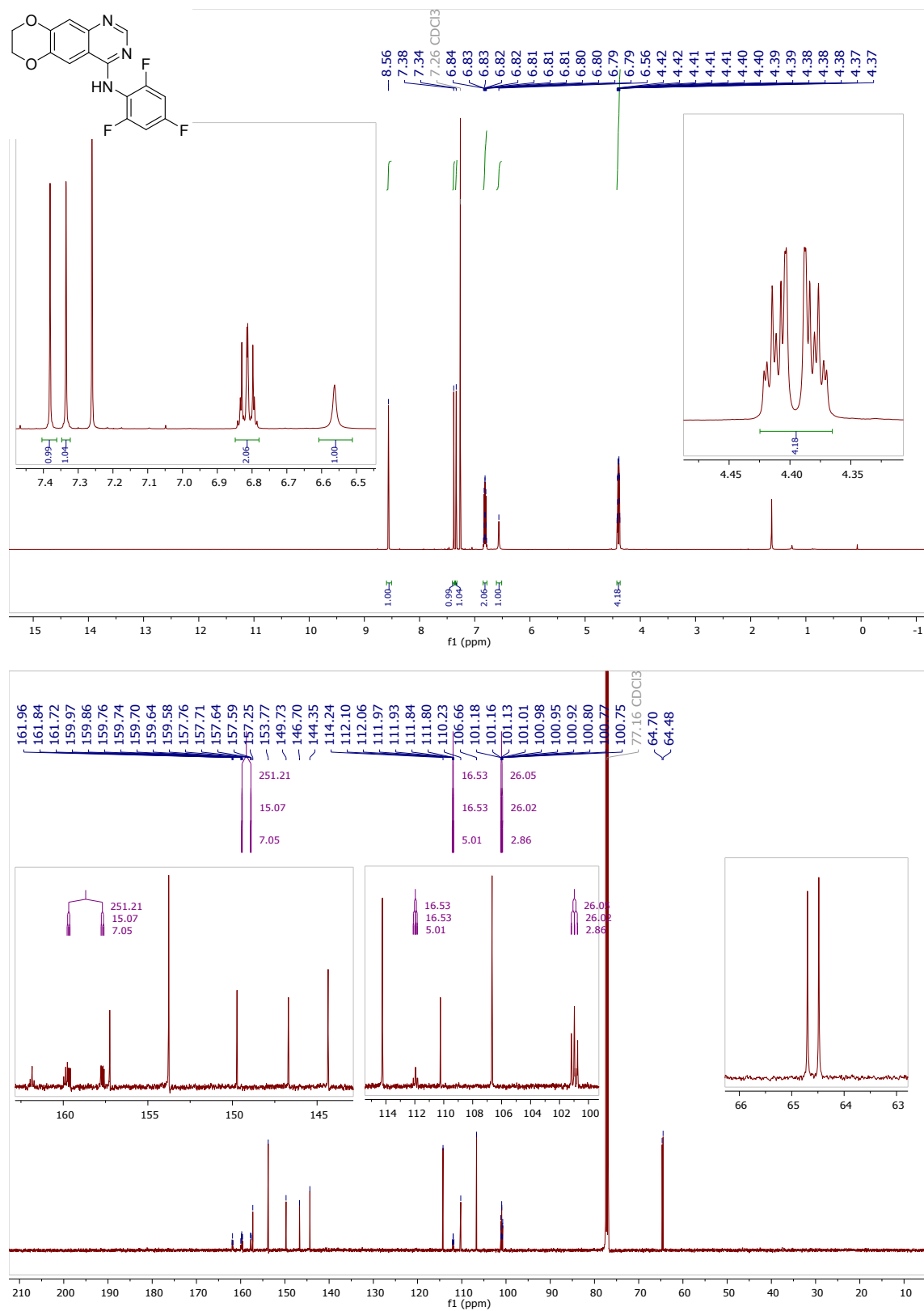


Figure S26. ¹H NMR (top) and ¹³C NMR (bottom) spectra of S7 in CDCl₃ at 298 K.

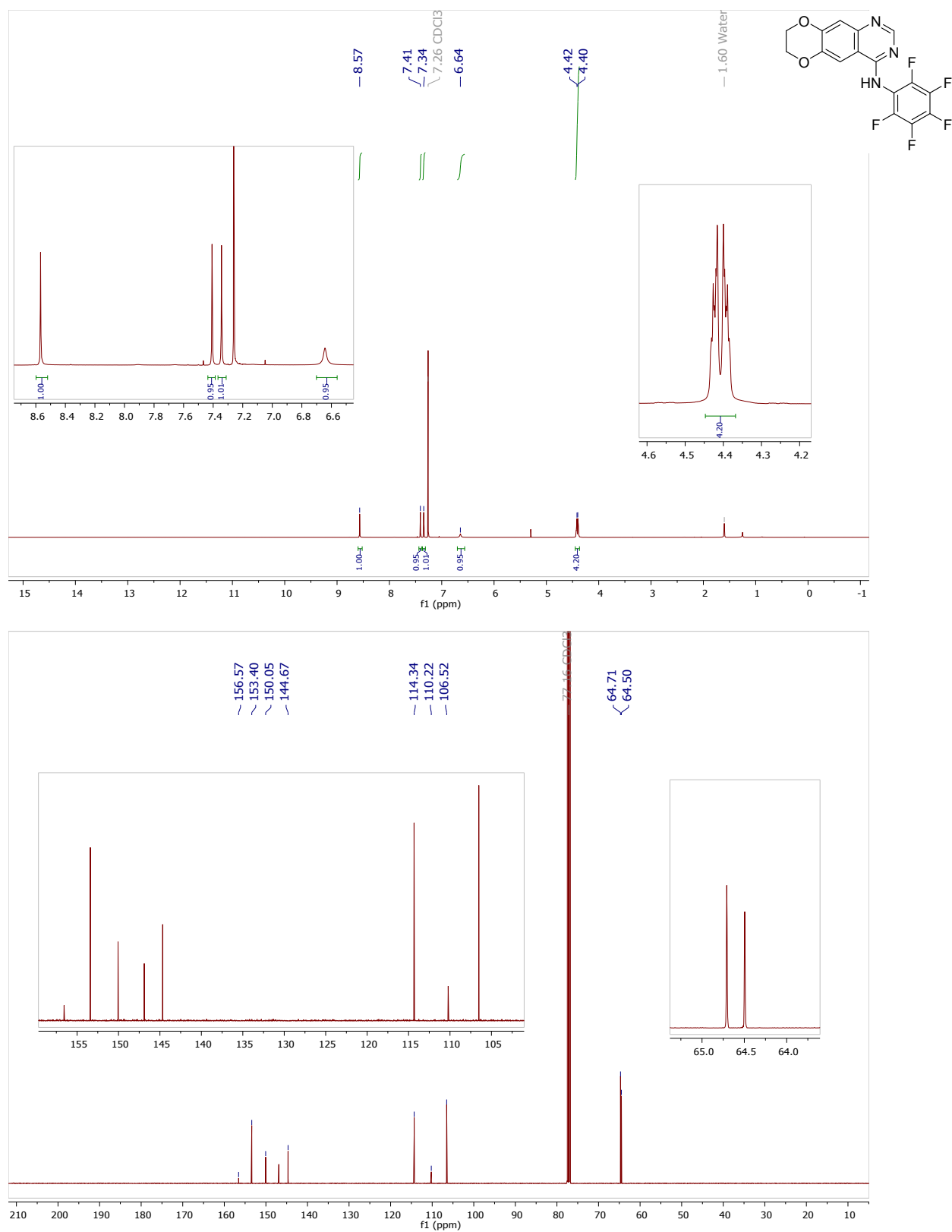


Figure S27. ^1H NMR (top) and ^{13}C NMR (bottom) spectra of **S8** in CDCl_3 at 298 K.

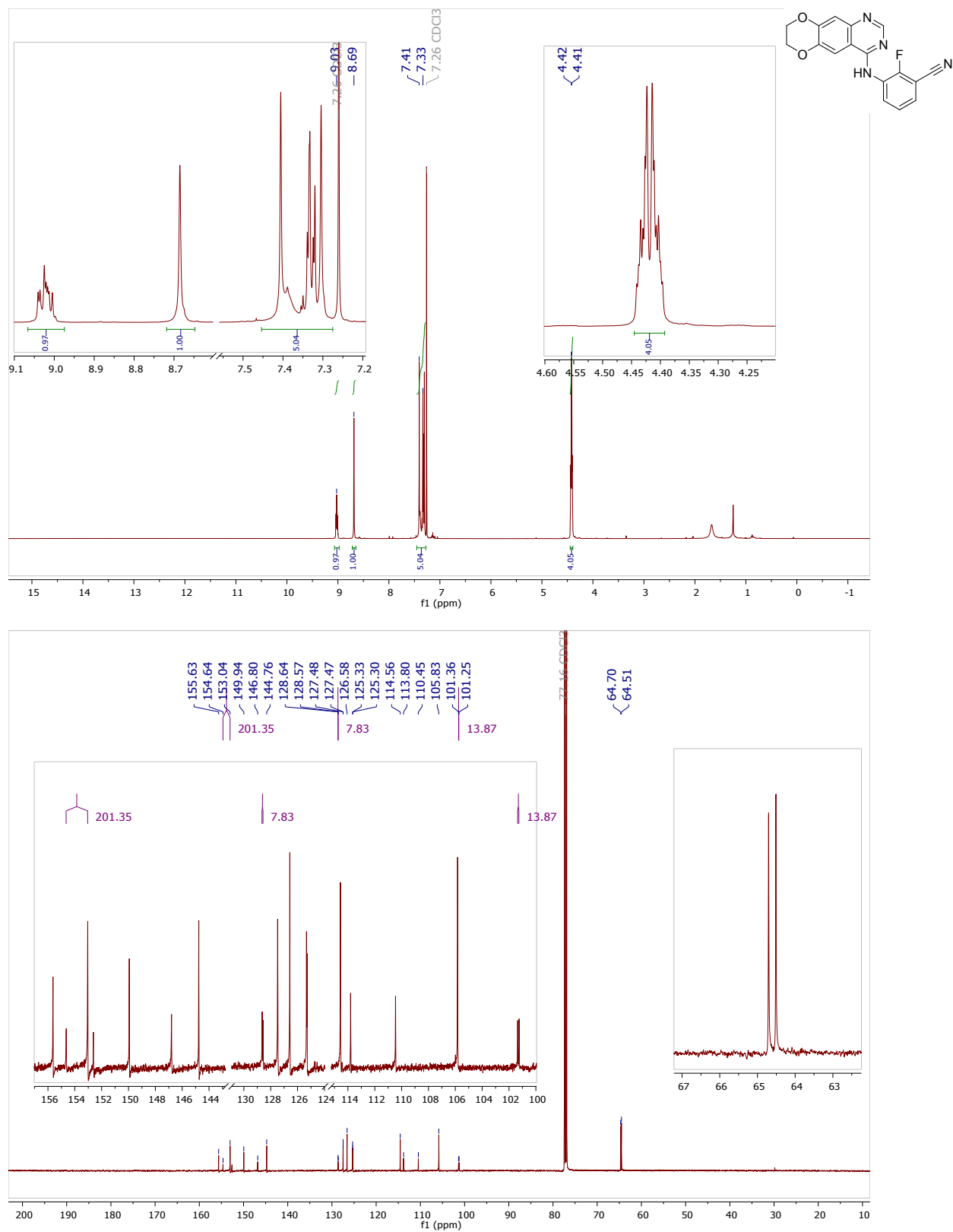


Figure S28. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **3** in CDCl₃ at 298 K.

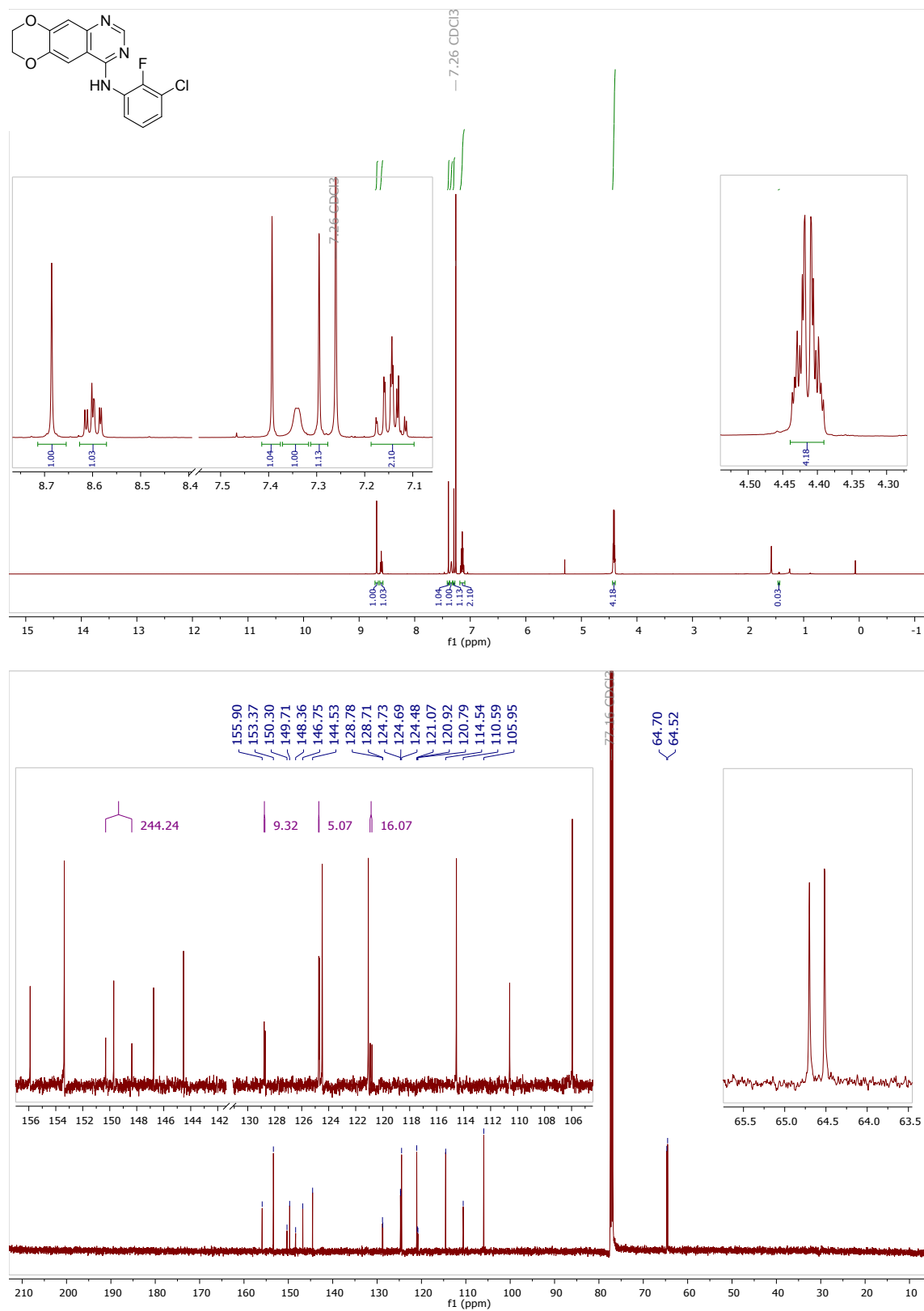


Figure S29. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **4** in CDCl₃ at 298 K.

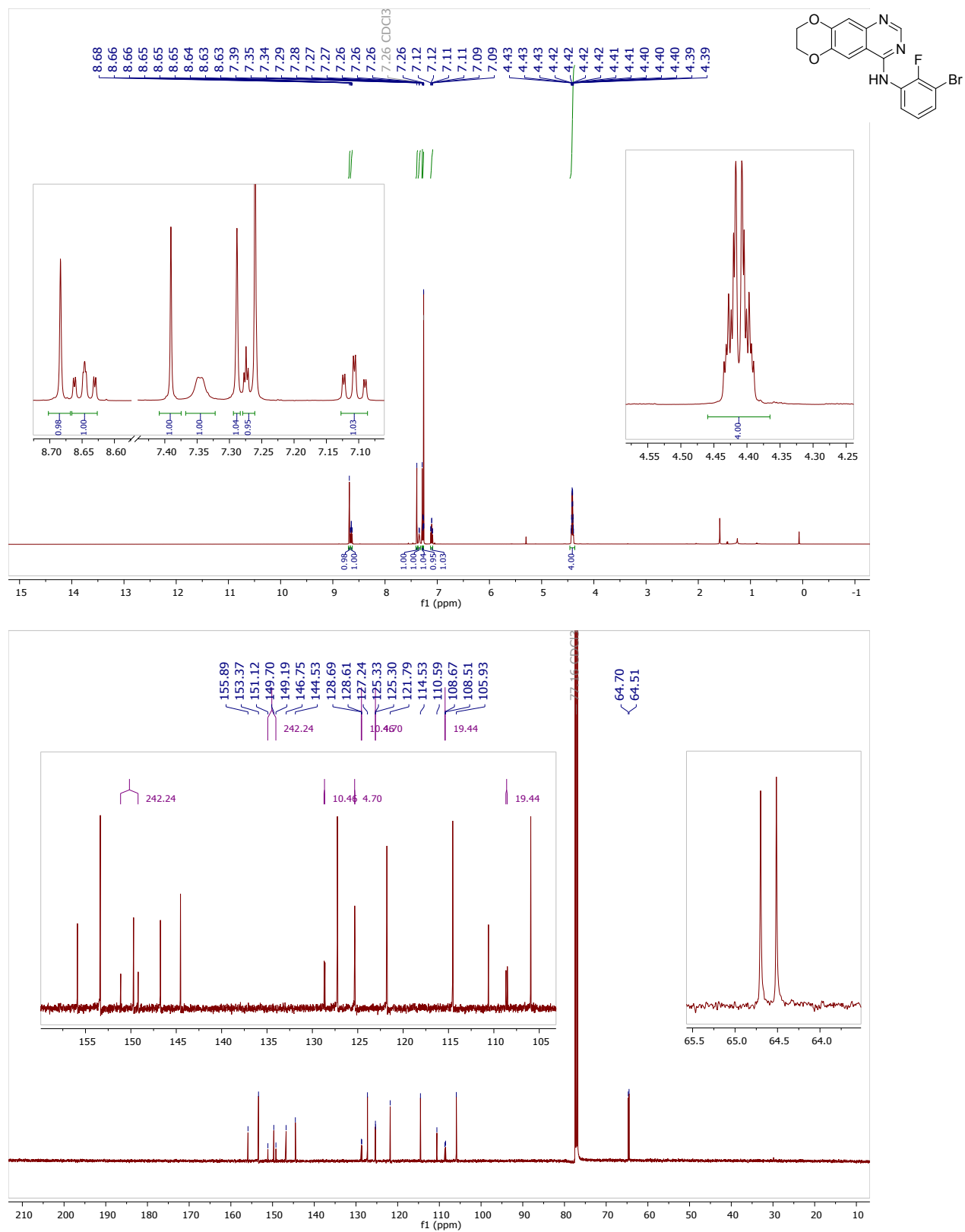


Figure S30. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **5** in CDCl₃ at 298 K.

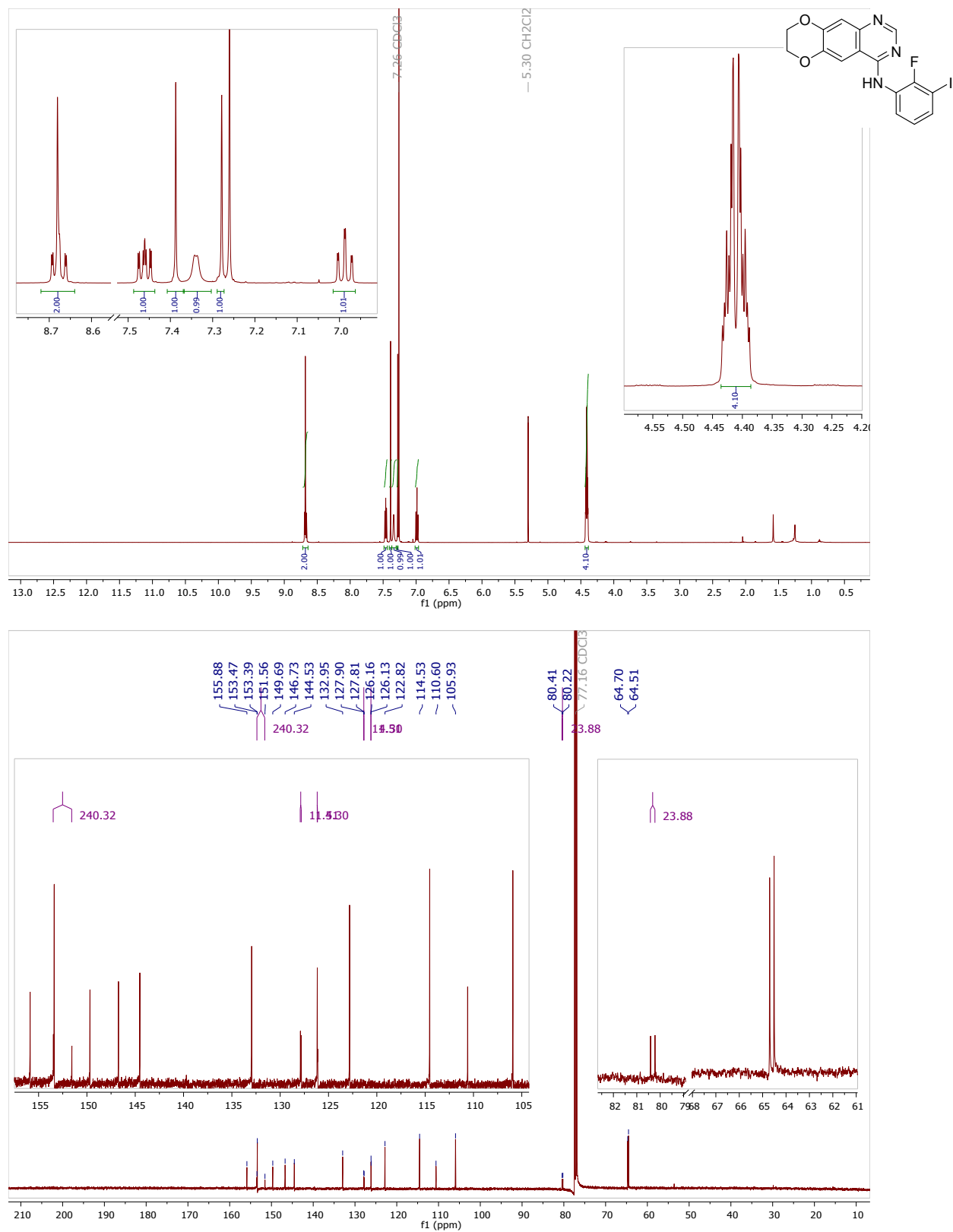


Figure S31. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **6** in CDCl₃ at 298 K.

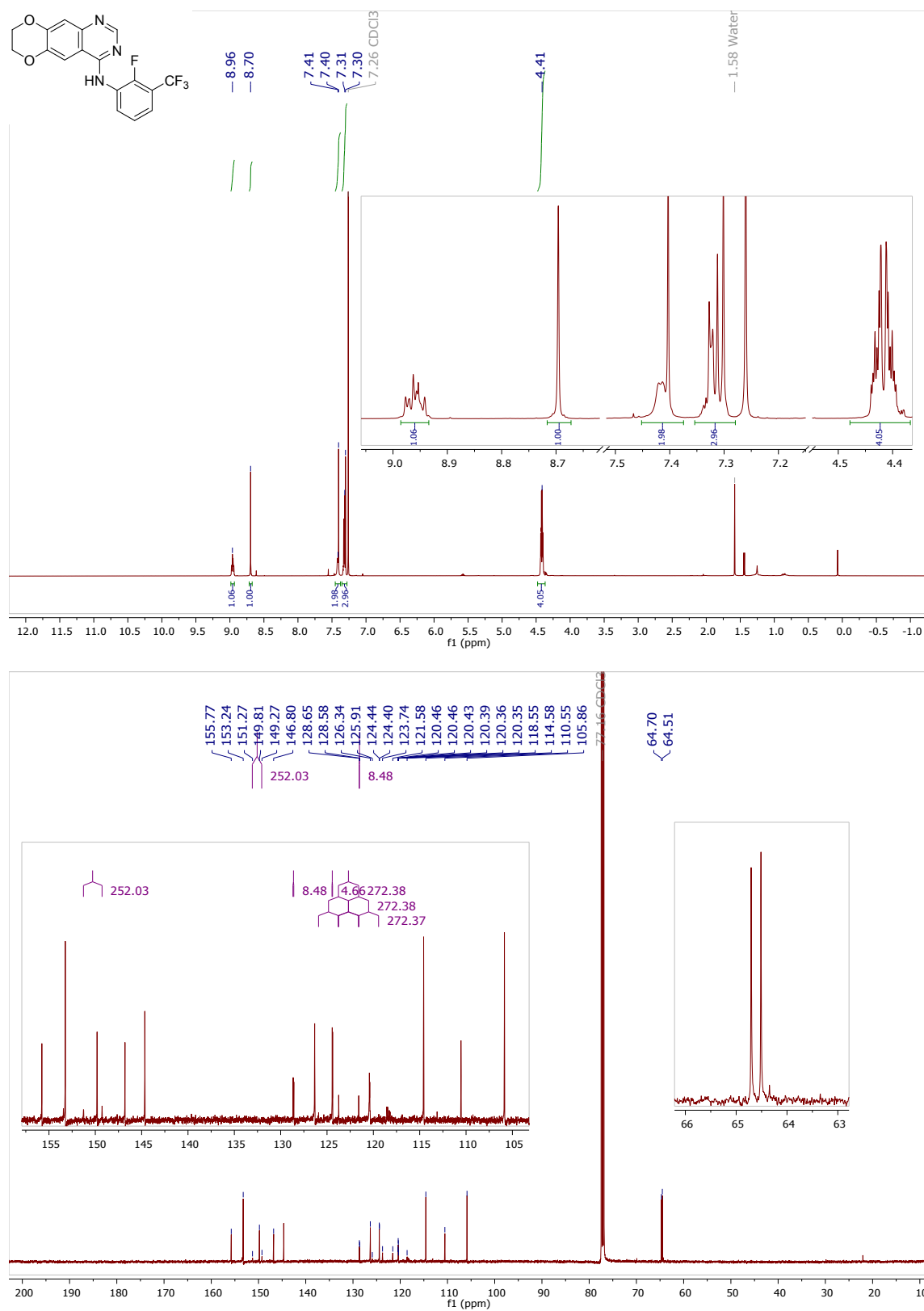


Figure S32. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **7** in CDCl₃ at 298 K.

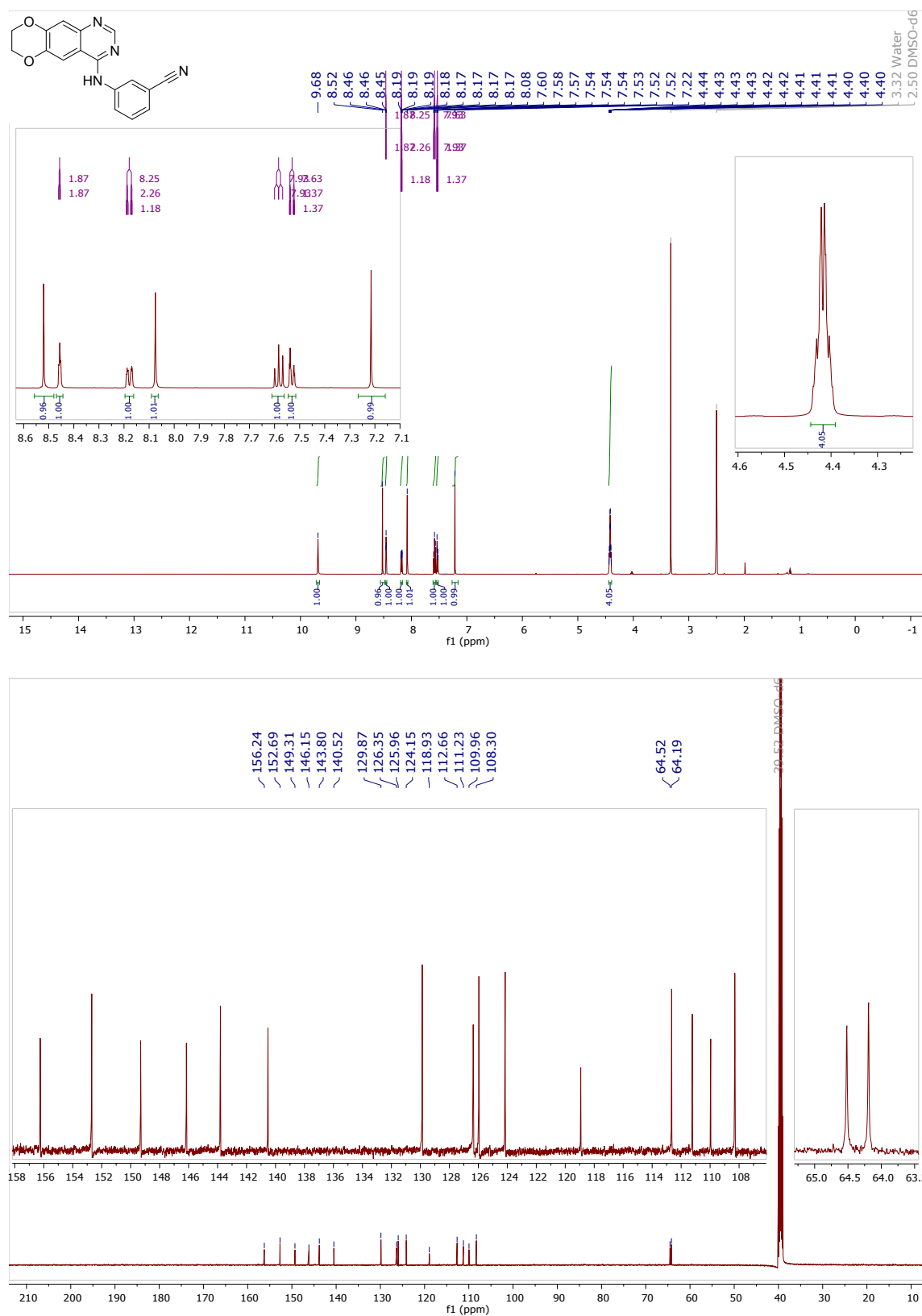


Figure S33. ^1H NMR (top) and ^{13}C NMR (bottom) spectra of **8** in $\text{DMSO}-d_6$ at 298 K.

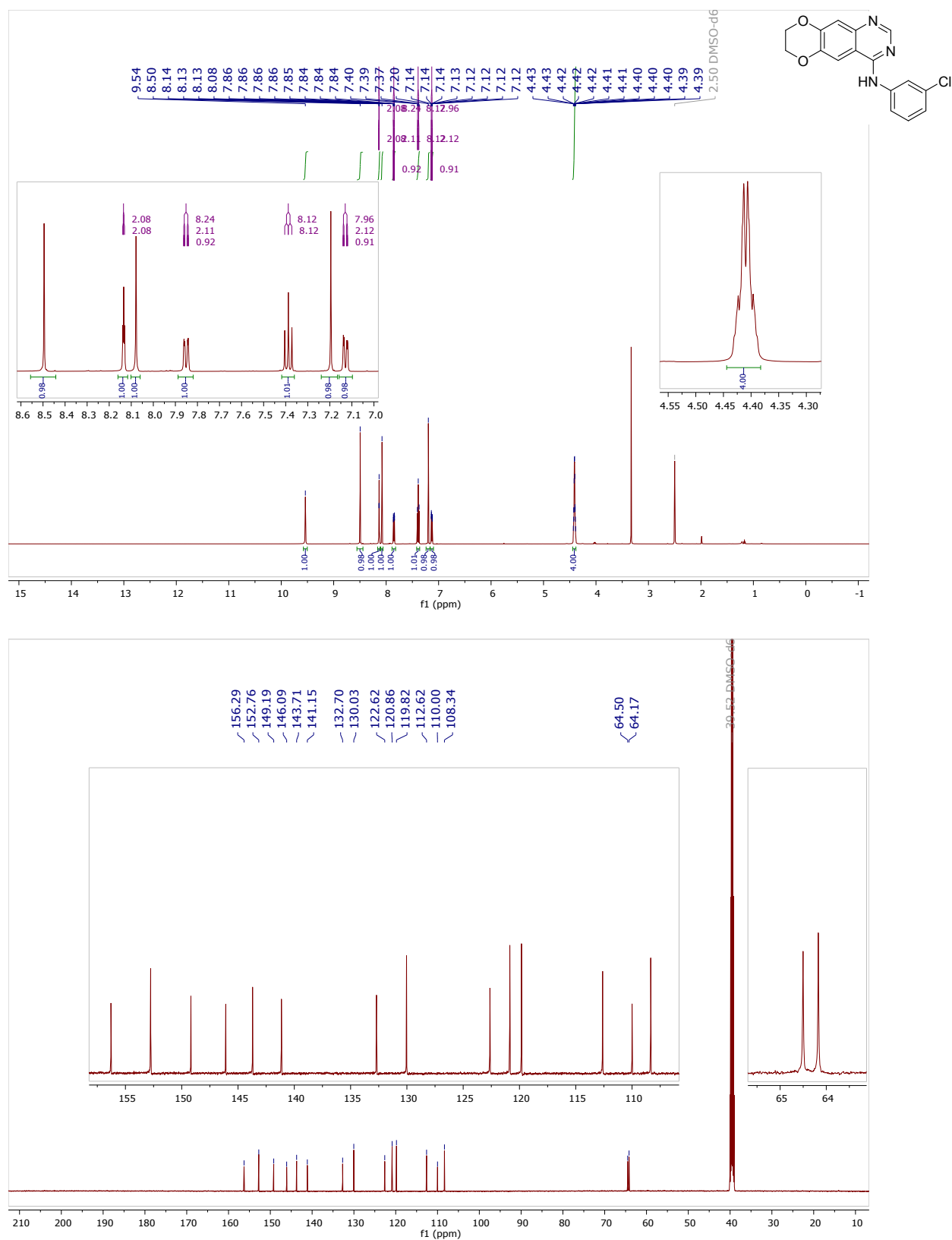


Figure S34. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **9** in DMSO-*d*₆ at 298 K.

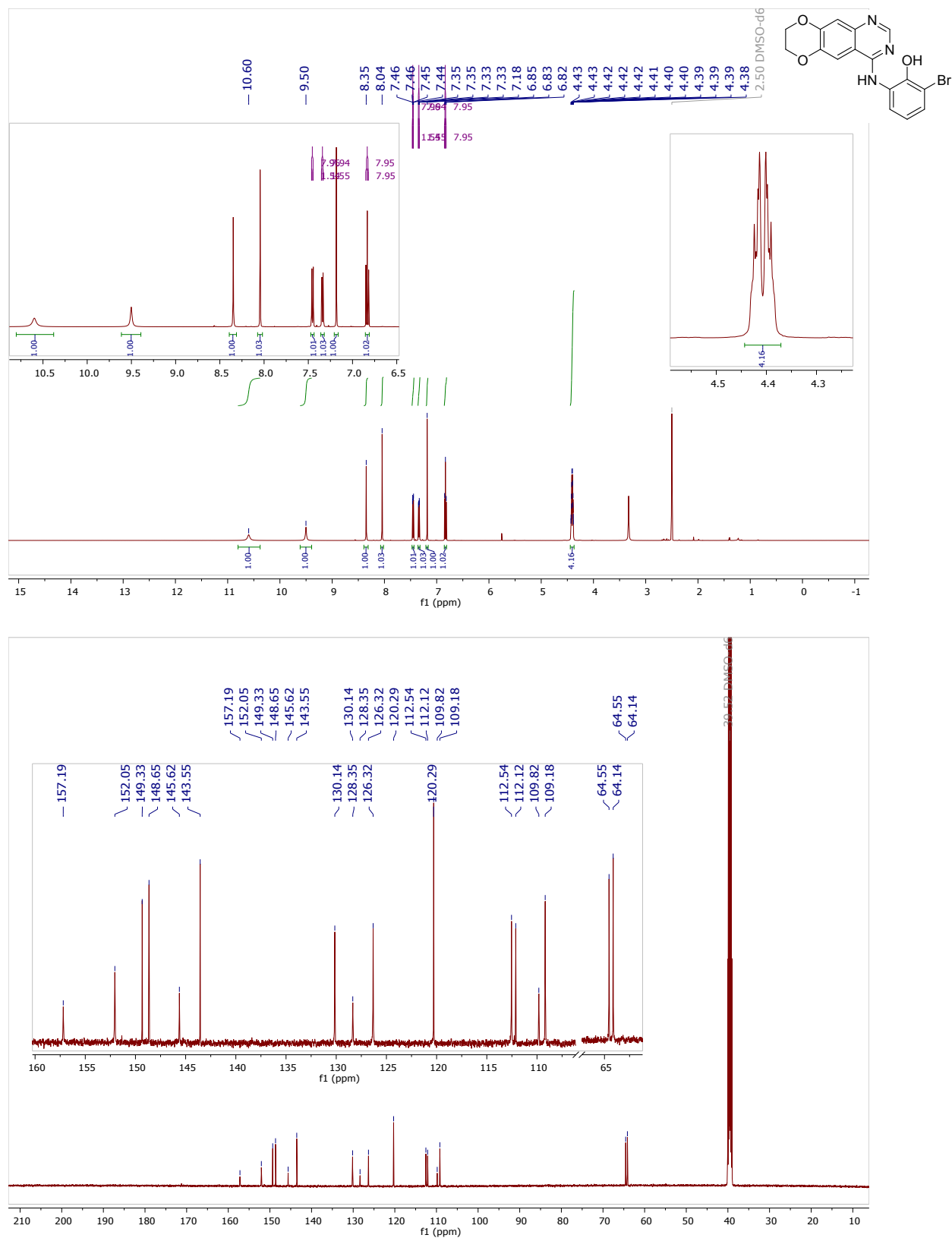


Figure S36. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **11** in DMSO-*d*₆ at 298 K.

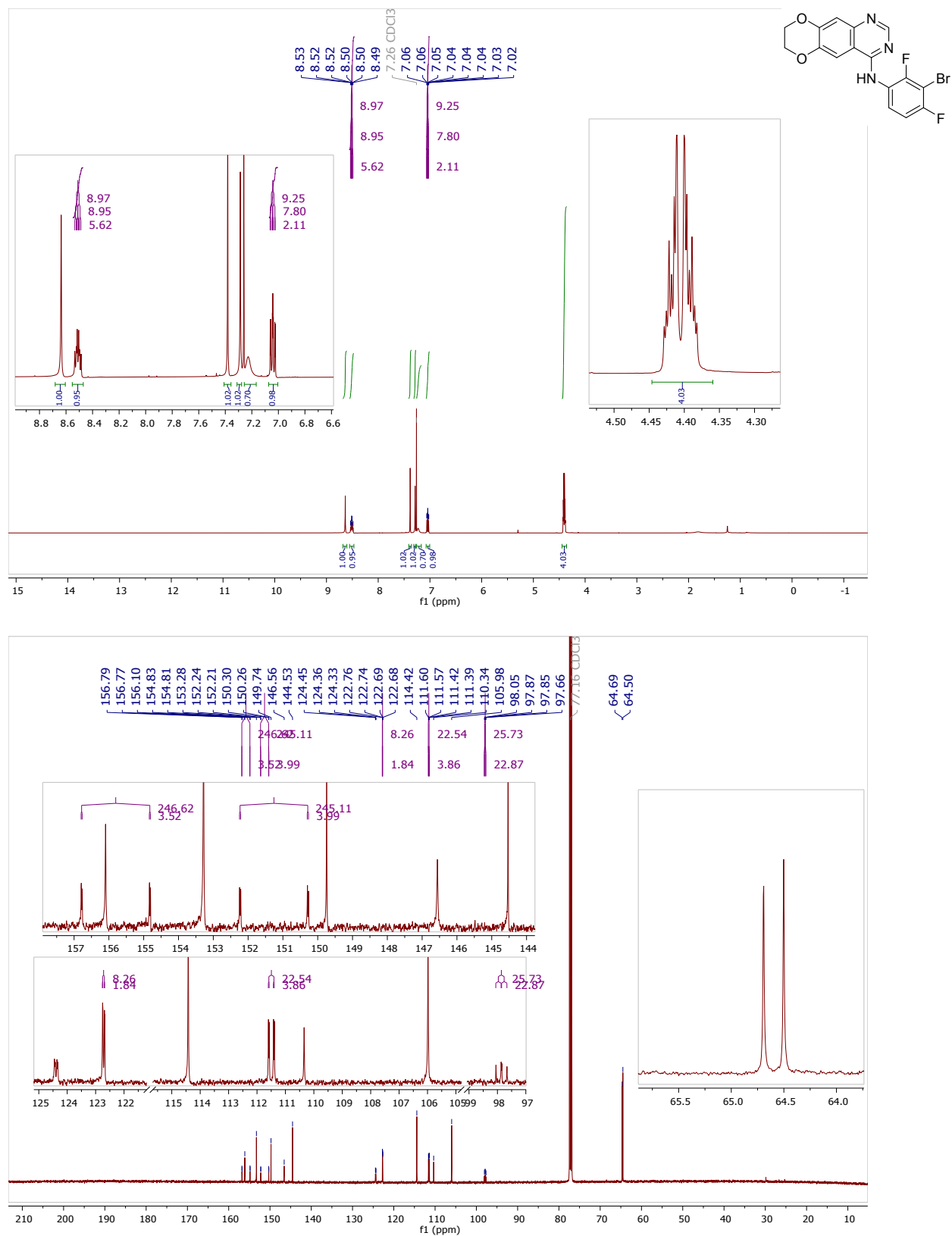


Figure S37. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **12** in CDCl₃ at 298 K.

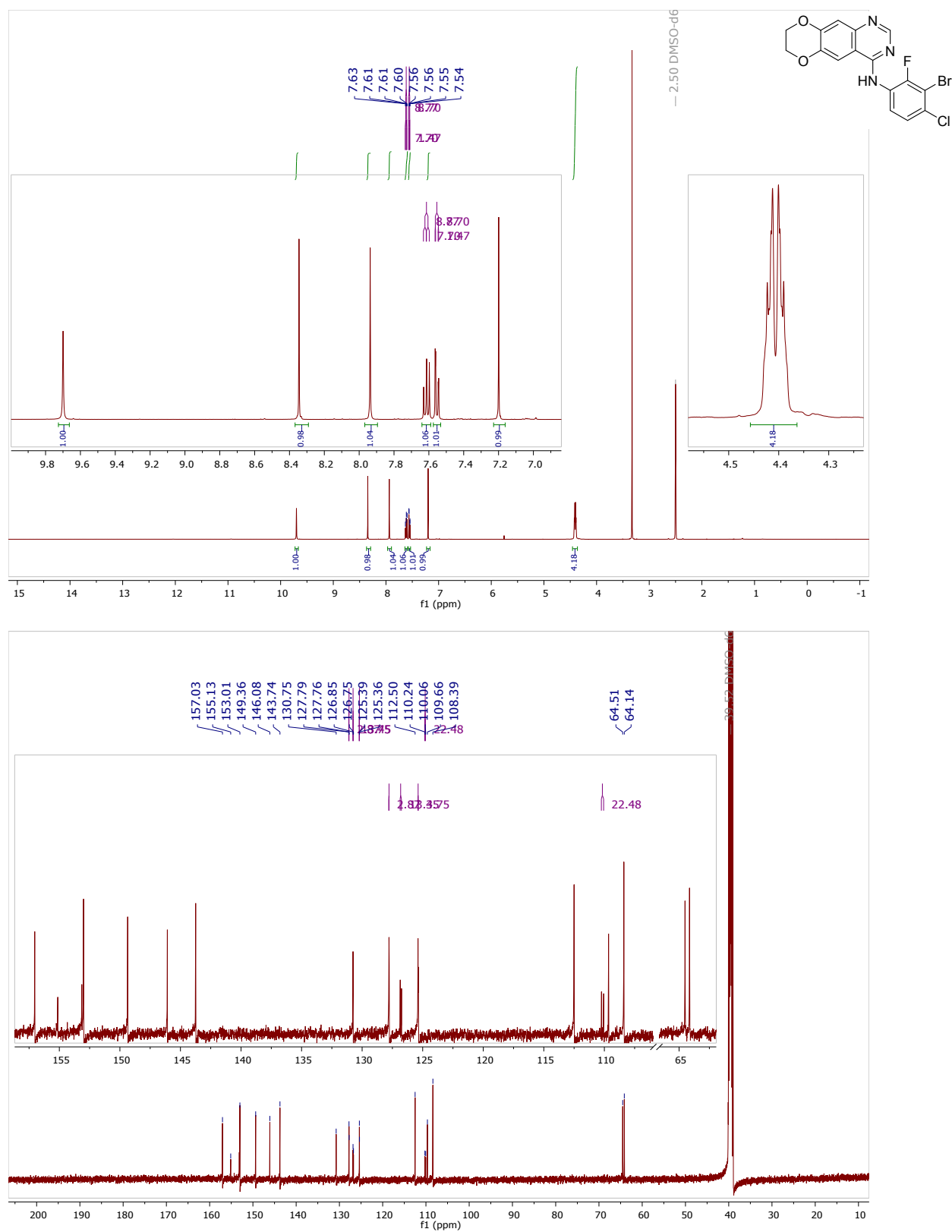


Figure S38. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **13** in DMSO-*d*₆ at 298 K.

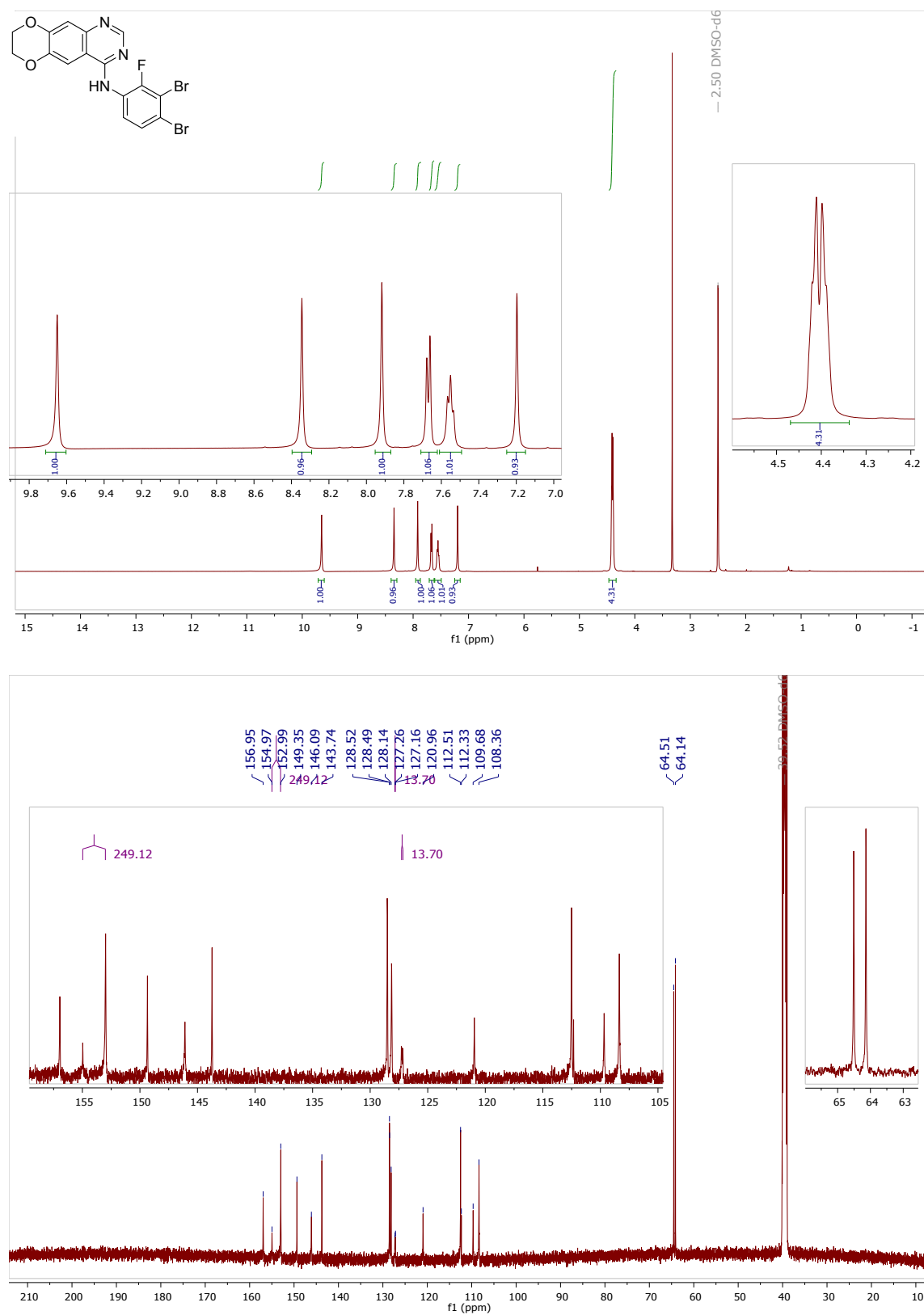


Figure S39. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **14** in DMSO-*d*₆ at 298 K.

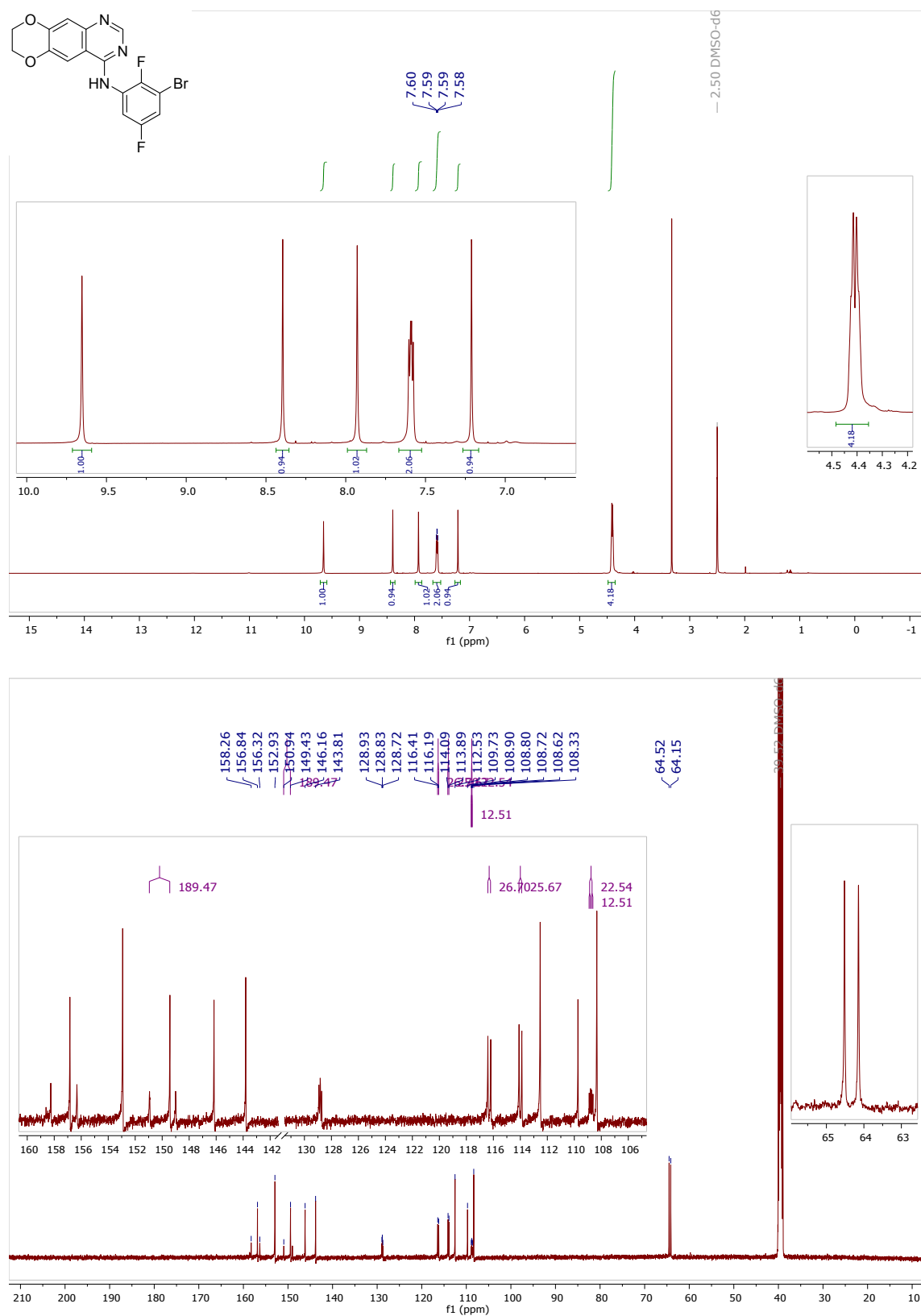


Figure S40. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **15** in DMSO-*d*₆ at 298 K.

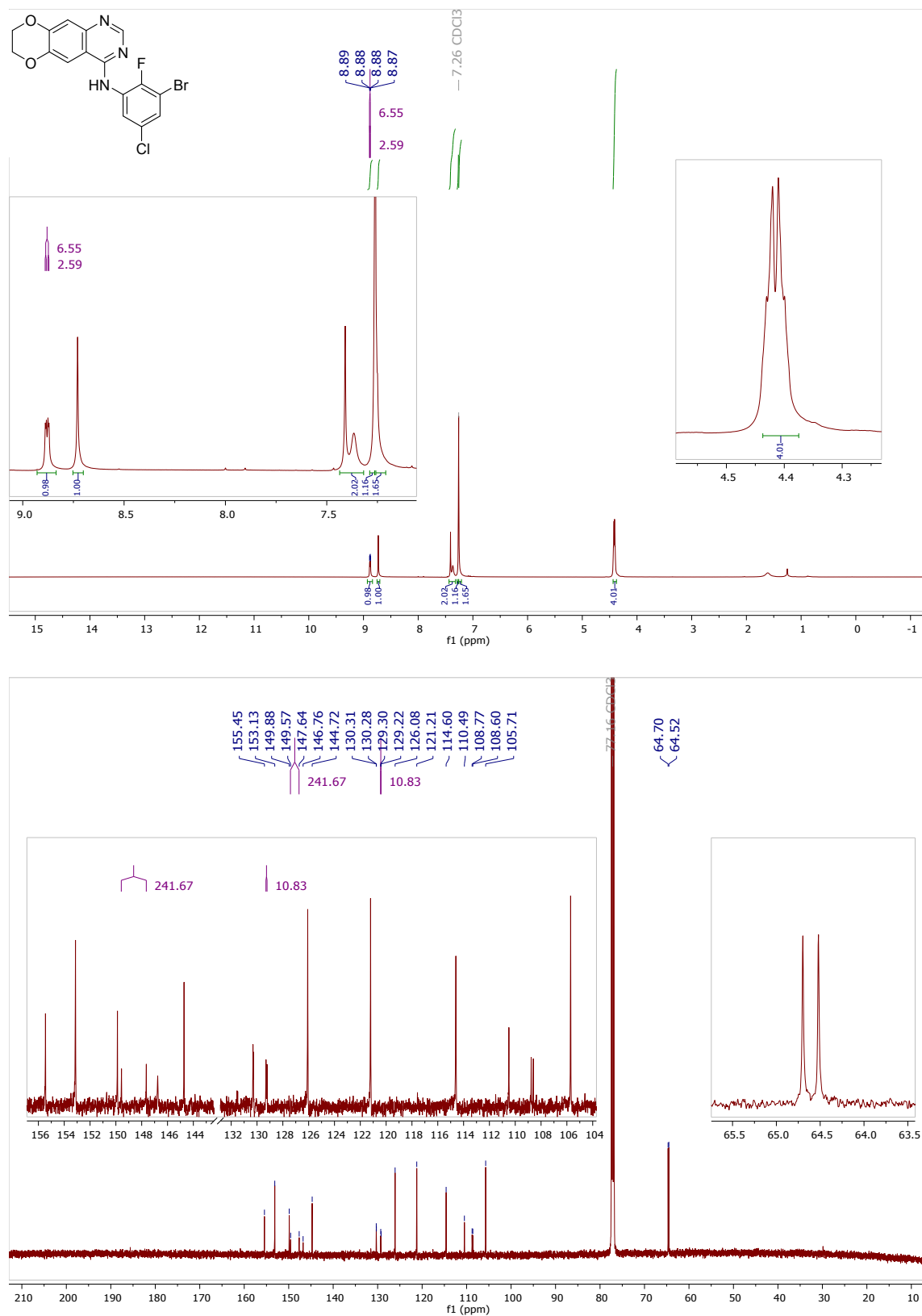


Figure S41. ^1H NMR (top) and ^{13}C NMR (bottom) spectra of **16** in CDCl_3 at 298 K.

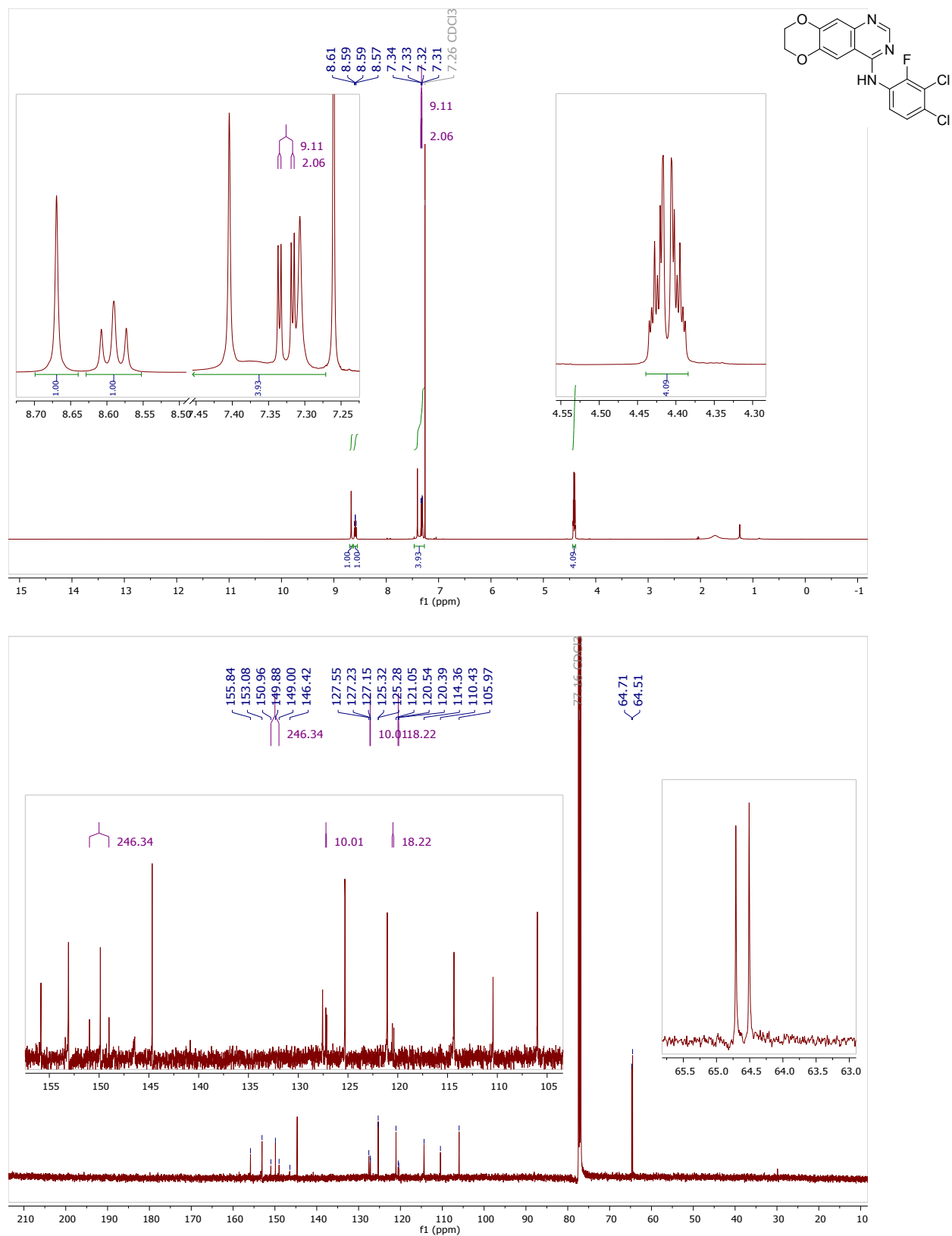


Figure S42. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **17** in CDCl₃ at 298 K.

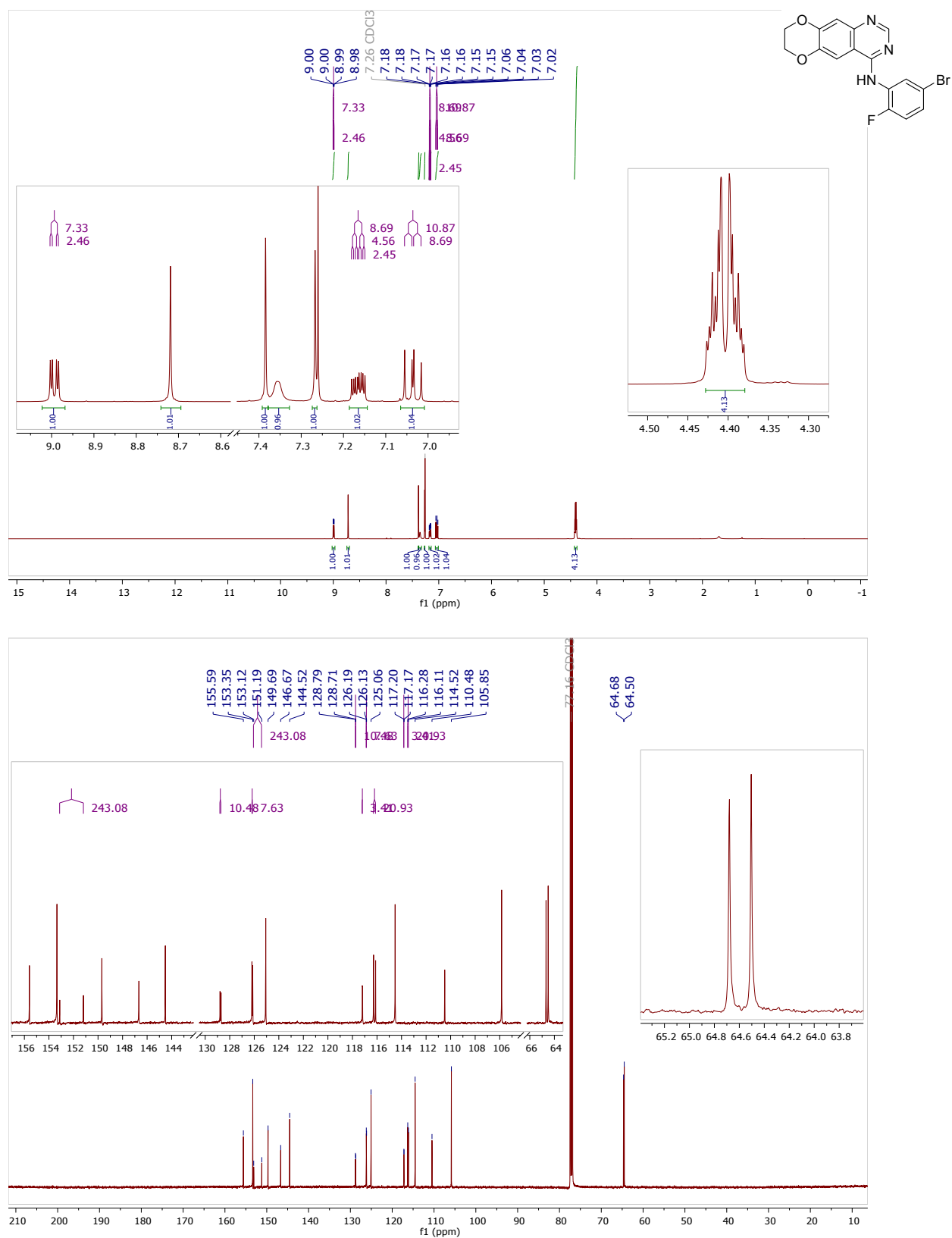


Figure S43. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **18** in CDCl₃ at 298 K.

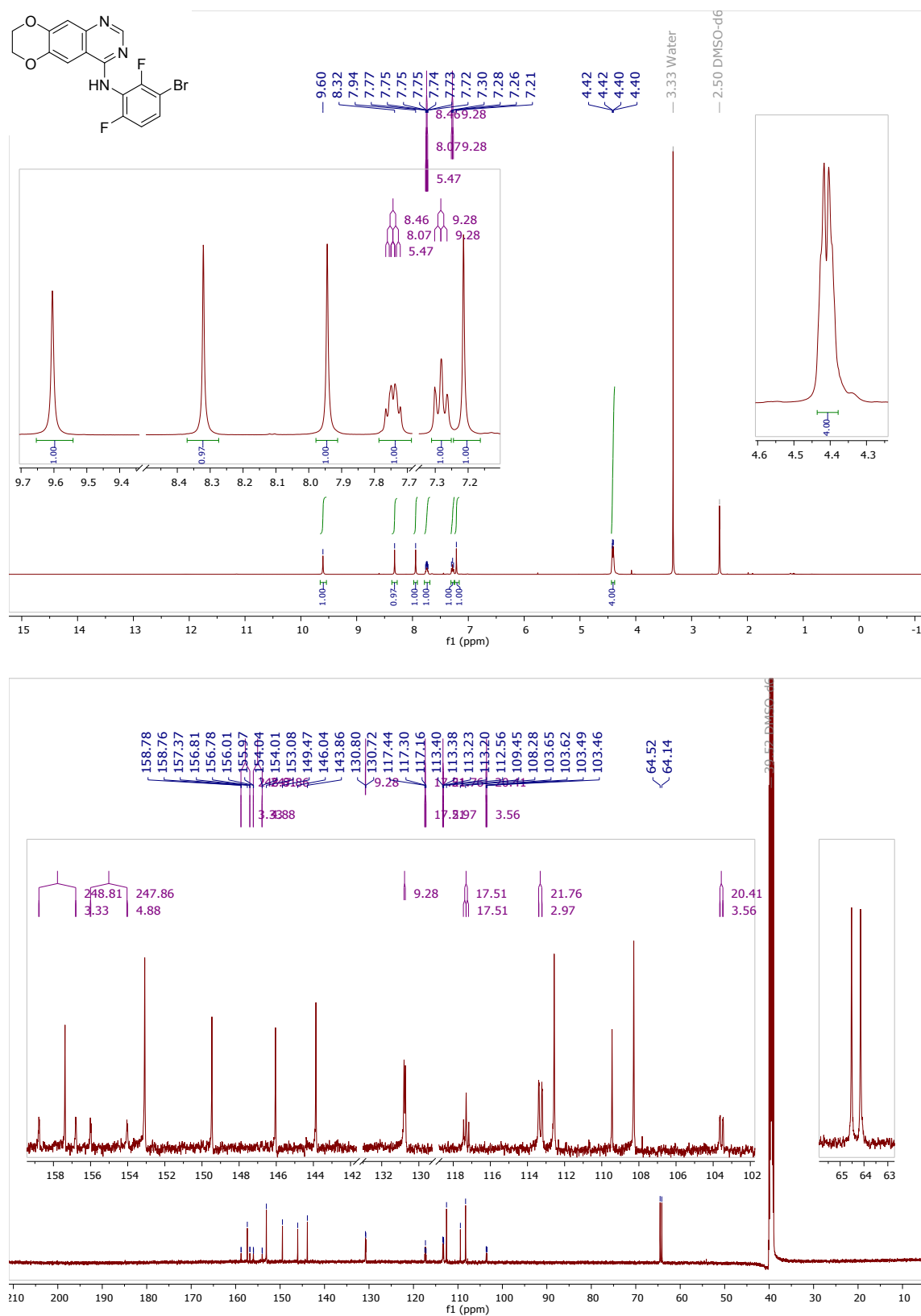


Figure S44. ^1H NMR (top) and ^{13}C NMR (bottom) spectra of **19** in DMSO- d_6 at 298 K.

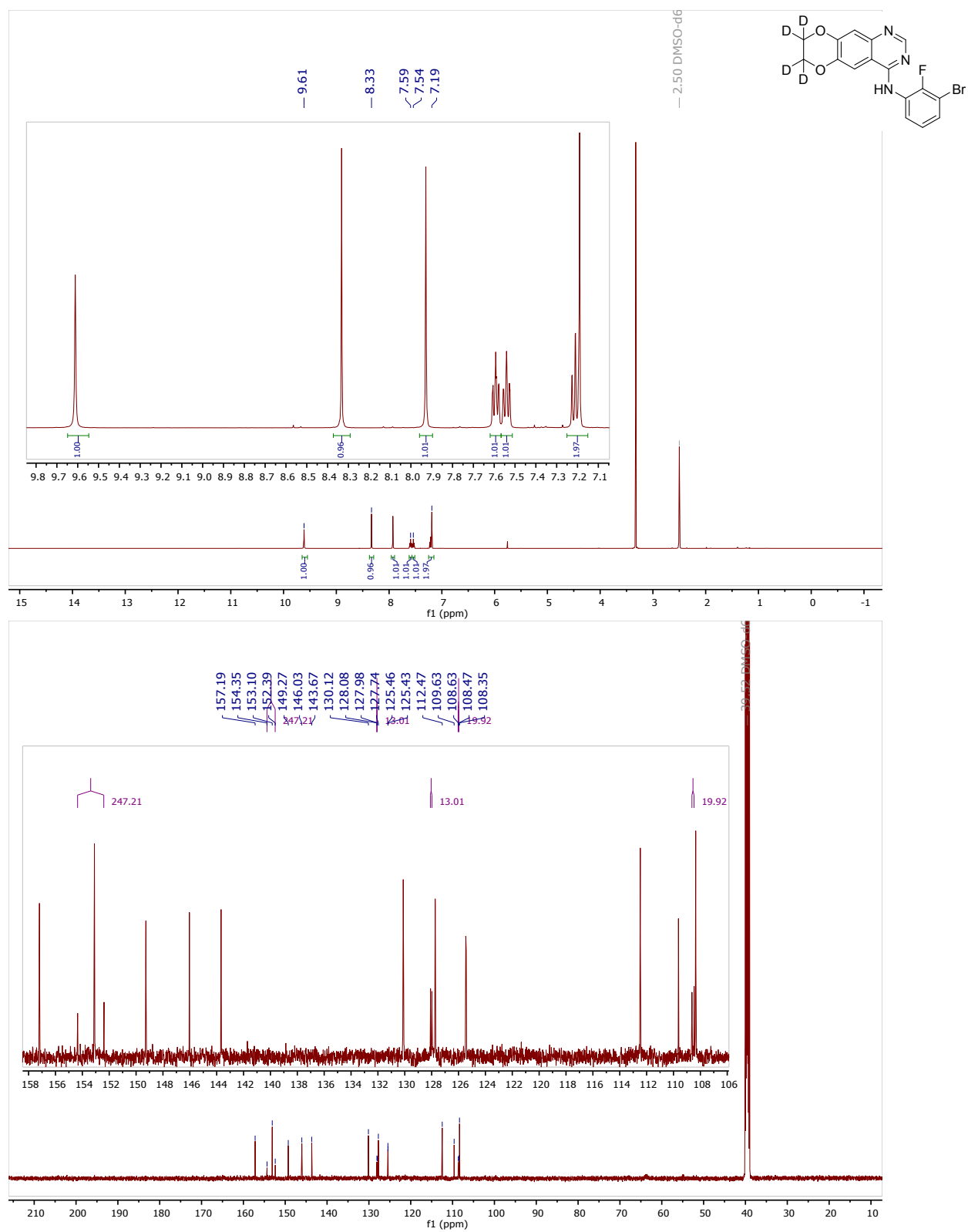


Figure S45. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **S9** in DMSO-*d*₆ at 298 K.

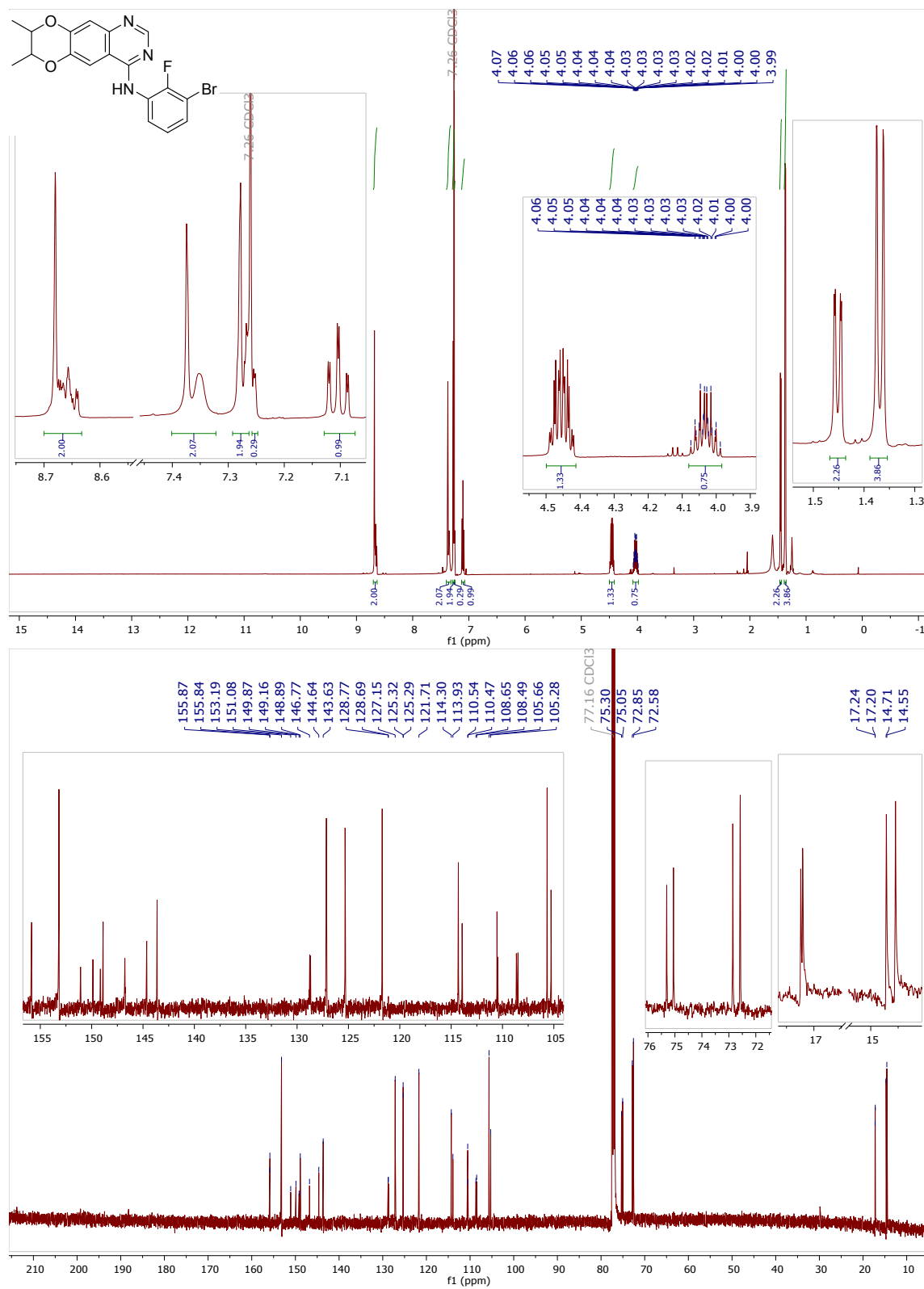


Figure S46. ¹H NMR (top) and ¹³C NMR (bottom) spectra of **S10** in CDCl₃ at 298 K.