Supporting Information

Discovery of Potent, Selective and Orally Bioavailable Small-Molecule Modulators of the Mediator Complex-Associated Kinases CDK8 and CDK19.

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Contents

Compound No	Caco-2	
	Papp A-B (cms^{-1})	Efflux ratio
6	23.7	2.5
17	22.7	19.5
18	32.0	26.1
19	25.4	12.4
20	30.4	5.3
21	18.8	24.0
22	4.9	16.5
23	29.0	3.3
24	33.8	11.0
25	0.03	1275
41	30.6	2.4
42	16.6	4.7
44	19.1	3.7
45	15.9	21.0
46	3.3	126.3
47	19.8	11.2
48	6.7	17.6
49	40.0	4.9
51	35.3	18.76
54	34.3	1.7
61	32.9	3.0
63	16.0	6.5
72	47.4	1.6
85	37.0	4.9
86	25.4	42.7
87	1.3	86.8
88	19.3	5.8
89	48.3	2.0
90	10.3	14.8
91	9.6	21.3
92	23.9	29.5
93	4.0	81
94	20.7	12.5
95	29.1	2.8

Supplementary Table S1. Caco-2 data on compounds from Tables 2 to Table 5.

Assay	% Inhibition of Control Specific Binding
A1 (h) (agonist radioligand)	-4
A2B (h) (antagonist radioligand)	-7
alpha 1B (h) (antagonist radioligand)	15
alpha 2A (h) (antagonist radioligand)	11
alpha 2B (h) (antagonist radioligand)	10
alpha 2C (h) (antagonist radioligand)	25
beta 3 (h) (antagonist radioligand)	-16
AT2 (h) (agonist radioligand)	6
BB3 (h) (agonist radioligand)	-11
CB2 (h) (agonist radioligand)	29
CCK2 (CCKB) (h) (agonist radioligand)	0
CRF1 (h) (agonist radioligand)	-7
D2S (h) (agonist radioligand)	-5
D3 (h) (antagonist radioligand)	7
ETB (h) (agonist radioligand)	-23
GABAA1 (h) (alpha 1,beta 2,gamma 2) (agonist radioligand)	-12
GABAB(1b) (h) (antagonist radioligand)	2
glucagon (h) (agonist radioligand)	-7
AMPA (agonist radioligand)	3
kainate (agonist radioligand)	9
NMDA (antagonist radioligand)	0
glycine (strychnine-insensitive) (antagonist radioligand)	-3
TNF-alpha (h) (agonist radioligand)	-8
CCR2 (h) (agonist radioligand)	-9
H3 (h) (agonist radioligand)	3
H4 (h) (agonist radioligand)	0
BLT1 (LTB4) (h) (agonist radioligand)	16
CysLT1 (LTD4) (h) (agonist radioligand)	12
MCH1 (h) (agonist radioligand)	34
MC1 (agonist radioligand)	-8
MC3 (h) (agonist radioligand)	-24
MT3 (ML2) (agonist radioligand)	71
MAO-A (antagonist radioligand)	8
motilin (h) (agonist radioligand)	12
M4 (h) (antagonist radioligand)	22
NK1 (h) (agonist radioligand)	25
N neuronal alpha 4beta 2 (h) (agonist radioligand)	-6
N muscle-type (h) (antagonist radioligand)	11
PAF (h) (agonist radioligand)	-4
PCP (antagonist radioligand)	-1
FP (h) (agonist radioligand)	-1

Assay	% Inhibition of Control Specific Binding
5-HT2A (h) (agonist radioligand)	-10
5-HT2C (h) (agonist radioligand)	6
5-HT4e (h) (antagonist radioligand)	-3
sigma (non-selective) (h) (agonist radioligand)	12
sst1 (h) (agonist radioligand)	-4
sst4 (h) (agonist radioligand)	9
GR (h) (agonist radioligand)	-1
ERalpha (h) (agonist fluoligand)	0
AR (h) (agonist radioligand)	-2
TR (TH) (agonist radioligand)	-13
UT (h) (agonist radioligand)	33
V2 (h) (agonist radioligand)	2
Ca2+ channel (L, dihydropyridine site) (antagonist radioligand)	-16
Ca2+ channel (L, diltiazem site) (benzothiazepines) (antagonist radioligand)	5
Ca2+ channel (N) (antagonist radioligand)	-12
RY3 (ryanodine) (agonist radioligand)	1
GABA transporter (antagonist radioligand)	3
choline transporter (CHT1) (h) (antagonist radioligand)	4

Supplementary Table S2: *In vitro* pharmacology: binding assays. Activity of compound **109** tested at 10 µM across a panel of 59 receptors and ion channels (CEREP). Results are expressed as percent inhibition of control specific binding.

Assay	% Inhibition of Control Values
COX1 (h)	28
COX2 (h)	-17
inducible NOS	2
PDE2A1 (h)	69
PDE3A (h)	27
PDE4A1A (h)	73
PDE4D2 (h)	68
PDE5 (h) (non-selective)	5
PDE6 (non-selective)	12
ACE (h)	-15
ACE-2 (h)	7
BACE-1 (h) (beta -secretase)	-1
caspase-3 (h)	-8
neutral endopeptidase (h)	-10
MMP-1 (h)	2
MMP-2 (h)	-9
MMP-9 (h)	20
Abl kinase (h)	-22
CaMK2alpha (h)	0
ERK2 (h) (P42mapk)	-4
FLT-1 kinase (h) (VEGFR1)	20
Fyn kinase (h)	-4
Lyn A kinase (h)	10
p38alpha kinase (h)	-1
ZAP70 kinase (h)	-13
acetylcholinesterase (h)	82
COMT (catechol- O-methyl transferase)	11
xanthine oxidase/ superoxide O2- scavenging	4
ATPase (Na+/K+)	-3

Supplementary Table S3: *In vitro* pharmacology: enzyme assays. Activity of compound **109** tested at 10 µM across a panel of 29 enzymes (CEREP). Results are expressed as percent inhibition of control specific binding. Acetylcholinesterase inhibition was followed up with a 5 point IC_{50} determination (IC_{50} = 1.3 µM).

Kinase	% effect	Kinase	% effect	Kinase	% effect
ABL	-15	EPHA1	4	JNK3	-5
ABL(T315I)	4	EPHA2	5	KDR	-26
ALK	4	EPHA4	5	CKIT	-5
ALK4	2	EPHA3	5	CKIT(D816V)	-7
ARG	5	EPHA5	-9	LCK	-18
ARK5	10	EPHA7	13	LIMK1	-13
ASK1	17	EPHA8	-9	LKB1	5
AURKA	-16	EPHB1	3	LOK	11
AXL	-4	EPHB2	-3	LYN	-3
BLK	11	EPHB3	5	MAPK1	7
BMX	-6	EPHB4	-3	MAPK2	-6
BRK	13	ERBB4	-28	MAPKAP-K2	1
BRSK1	7	FER	15	MAPKAP-K3	5
BRSK2	0	FES	-6	MARK1	17
BTK	6	FGFR1	7	MEK1	-13
CAMKI	-3	FGFR2	4	MET	1
CAMKIV	14	FGFR3	-9	MINK	22
CDK1/CYCLINB	-12	FGFR4	6	MKK4	47
CDK2/CYCLINA	1	FGR	-2	MKK6	47
CDK2/CYCLINE	3	FLT1	-8	MKK7BETA	-15
CDK3/CYCLINE	6	FLT3	7	MLCK	3
CDK5/P25	13	FLT3(D835Y)	21	MLK1	-10
CDK5/P35	1	FLT4	-38	MNK2	-3
CDK6/CYCLIND3	5	FMS	-23	MRCKALPHA	-3
CDK7/CYCLINH/MAT1	5	FYN	23	MRCKBETA	-35
CDK9/CYCLINT1	-8	GSK3ALPHA	-18	MSK1	-3
CHK1	-8	GSK3BETA	-11	MSK2	5
CHK2	-2	HCK	-4	MSSK1	-1
CK1(Y)	-1	HIPK1	5	MST1	4
CK1DELTA	18	HIPK2	2	MST2	-11
CK2	3	HIPK3	18	MST3	-11
CK2ALPHA2	-13	IGF-1R	-26	MUSK	3
CSK	8	IKKALPHA	-17	NEK2	4
DAPK1	-8	IKKBETA	-2	NEK3	-11
DAPK2	-7	IR	-5	NEK6	4
DDR2	19	IRR	5	NEK7	15
DMPK	4	IRAK1	15	NEK11	12
DRAK1	1	IRAK4	6	NLK	-5
DYRK2	-9	ITK	-9	P70S6K	-1
EEF-2K	-6	JAK2	-20	PAK2	-10
EGFR	4	JAK3	4	PAK4	-1
EGFR(L858R)	-4	JNK1ALPHA1	-6	PAK5	-11
EGFR(L861Q)	11	JNK2ALPHA2	-5	PAK6	2

Kinase	% effect	Kinase	% effect	Kinase	% effect
PAR-1BALPHA	IC50 > 10 μM	RSK2	-11	EGFR(T790M,L858R)	0
PASK	-20	RSK3	-15	FAK	6
PDGFRALPHA	10	SAPK2A	-6	MER	11
PDGFRBETA	-9	SAPK2A(T106M)	2	PDGFRALPHA(D842V)	-10
PDK1	1	SAPK2B	-3	RSK4	-6
PI3K BETA	2	SAPK3	4	CAMKIDELTA	8
PI3K DELTA	6	SAPK4	-1	CKIT(V654A)	9
PI3K GAMMA	7	SGK	0	FGFR1(V561M)	-25
PIM-1	2	SGK2	-3	VRK2	3
PIM-2	-1	SGK3	13	PDGFRALPHA(V561D)	0
PKA	25	SIK	-1	TAO2	2
PKBALPHA	3	SNK	11	CHK2(R145W)	7
PKBBETA	-21	SRC	7	CHK2(I157T)	-5
PKBGAMMA	7	SRPK1	-8	FGFR2(N549H)	1
PKCALPHA	5	SRPK2	4	GCK	-10
PKCBETAI	-4	STK33	0	HASPIN	26
PKCBII	3	SYK	2	PIM-3	6
PKCDELTA	6	TAK1	-14	TAO3	-11
PKCEPSILON	-21	TBK1	6	TLK2	-5
PKCGAMMA	-6	TIE2	14	SRC(1-530)	0
PKCETA	6	TRKA	2	SRC(T341M)	-8
PKCIOTA	-5	TRKB	-11	TAO1	6
PKCMU	5	TSSK1	-7	ABL (H396P)	-4
PRKCQ	-13	TSSK2	9	ABL (Q252H)	-10
PKCZETA	1	WNK2	27	GRK7	-1
PKG1ALPHA	23	WNK3	6	ACK1	-11
PKG1BETA	-7	YES	-2	ULK3	-21
PKD2	-1	ZAP-70	21	ABL (M351T)	-11
PLK3	-2	ZIPK	6	ABL(Y253F)	1
PRAK	13	CK1GAMMA1	-5	BTK(R28H)	2
PRK2	1	CK1GAMMA2	5	CLK2	-2
PRKX	-9	CK1GAMMA3	-7	RET(V804L)	-7
PTK5	-12	DCAMKL2	-3	RET(V804M)	6
PYK2	-2	GRK5	7	TIE2(R849W)	-9
CRAF	-10	GRK6	5	TIE2(Y897S)	0
RET	7	PHKGAMMA2	11	TXK	-5
RIPK2	1	CAMKIIBETA	19	ULK2	12
ROCK-I	6	CAMKIIGAMMA	8	MTOR	-3
ROCK-II	-10	CAMKIIDELTA	7	PLK1	-3
RON	-1	CLK3	4	MTOR/FKBP12	47
ROS	8	CKIT(D816H)	1	MELK	3
RSE	1	CKIT(V560G)	-5	TEC ACTIVATED	-1
RSK1	13	EGFR(T790M)	11	IGF-1R, ACTIVATED	1

Kinase	% effect
IR, ACTIVATED	-26
PI3 KINASE (P85A)	5
PI3 KINASE (E542K/P85A)	10
PI3 KINASE (E542K/P85A)	4
PI3 KINASE (H1047R/P85A)	7
PI3 KINASE (P65A)	6
PEK	4
cMET (D1246H)	-8
cMET (D1246N)	-2
cMET (M1268T)	1
cMET (Y1248D)	-1
cMET (Y1248H)	-5
FMS(Y969C)	-43
HCK	-7
cMET (Y1248C)	-3
AURKB	-16
AURKC	1
LCK	2
TGFBR1	6
PRKAA1	10
PRKAA2	-6

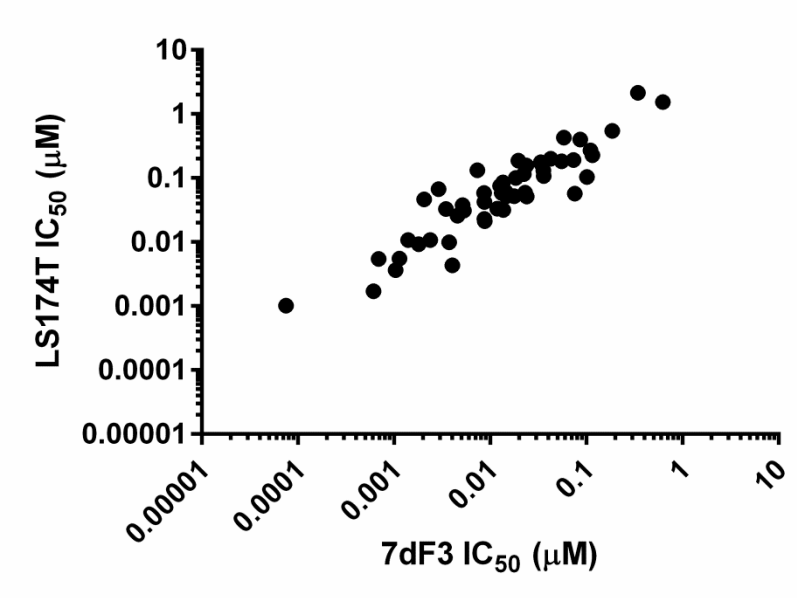
Supplementary Table S4: Activity of compound **109** tested at 1 µM across a panel of 279 kinases (Millipore Panel: data expressed as percentage effect versus control for each kinase tested at its respective Km for ATP). Where >50% inhibition was observed at a single 1 µM concentration, an IC_{50} was obtained as displayed in the Table.

CYP450	IC_{50} (uM)
1A2	>20
2B6	>20
2C8	8.5
2C9	20.5
2C19	>20
2D6	>20
3A4	>20

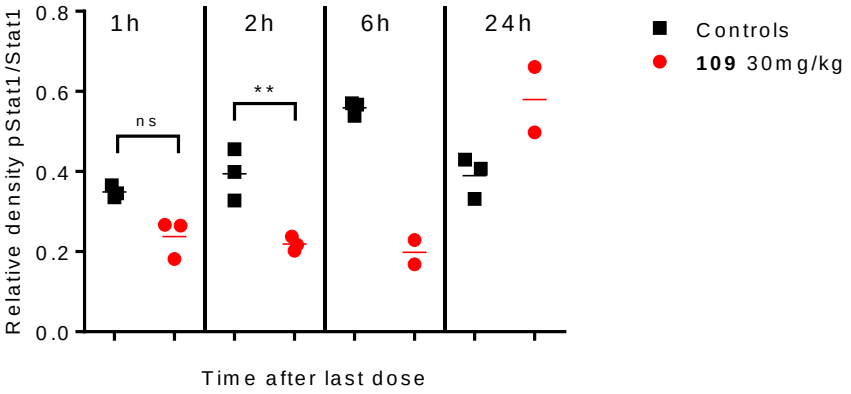
Supplementary Table S5: CYP450 inhibition profile for compound **109**

Time (h)	Total Plasma conc. (nM)	SD	Free Plasma conc. (nM)	SD	Total tumor conc. (nM)	SD	Free tumor conc. (nM)	SD
1	14929	6317	523	221	4875	1329	171	47
2	6860	1900	240	66	3421	1256	120	44
6	822	140	29	5	1572	31	55	1
24	90	133	3	5	796	703	28	25

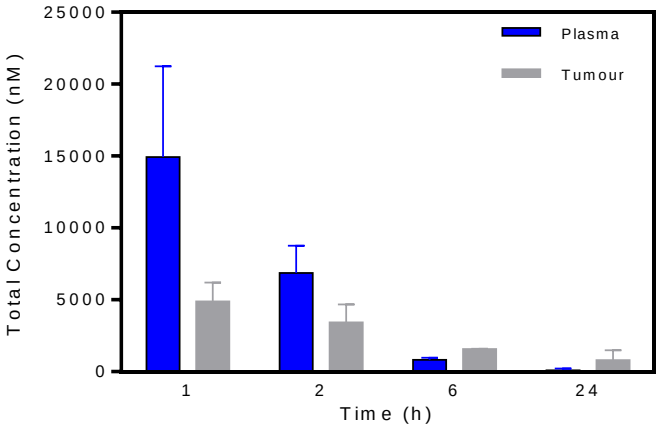
Supplementary Table S6: *APC*-mutant SW620 *in vivo* human colorectal carcinoma xenograft model. Mice were treated orally with **109** (30 mg/kg q.d.) for 15 days. Table shows both total and free concentrations in plasma and tumor (nM) at 1, 2, 6 and 24 hr after the last dose.



Supplementary Figure S1: Correlation of reporter-based IC_{50} data in the 7dF3 and LS174T WNT pathway cellular assays.



Supplementary Figure S2: Western blot analyses of phospho-Stat1^{SER727} expression in an *APC*-mutant SW620 *in vivo* human colorectal carcinoma xenograft model. Mice were treated orally with **109** (30 mg/kg q.d.) for 15 days. Relative ratio of phospho-Stat1^{SER727} to total STAT1 is shown at 1, 2, 6 and 24 h after the last dose. Mean ± SE, n=3, ns (non-significant), $^{**}P < 0.005$ vs vehicle.



Supplementary Figure S3: *APC*-mutant SW620 *in vivo* human colorectal carcinoma xenograft model. Mice were treated orally with compound **109** (30 mg/kg q.d.) for 15 days. Figure shows total plasma and tumor concentration (nM) of **109** at 1, 2, 6 and 24 h after the last dose.

Thermodynamic Solubility Determination

The test substance is dissolved in the solvent system of interest at a constant temperature. HPLC determination of the concentration of the solute in the solution, which must not contain any undissolved particles, is used to quantify the solubility. Composition of standard buffer solutions: Phosphate buffer pH 7.4: 50 mL of 0.2 M monobasic potassium phosphate solution were placed in a 200-mL volumetric flask, 39.1 mL of 0.2 M sodium hydroxide solution was added followed by water to the appropriate volume. Preparation of the standard solution: The test substance (generally 1 mg) was placed into an amber-glass volumetric flask and dissolved completely in a solution of acetonitrile/methanol (1:1; V/V). If the substance is not soluble in this solvent, a different solvent may be used. The target concentration is between 0.1 and 0.2 mg/mL. The standard solution and test sample (see below) use the same test substance. Preparation of the test sample: The test sample (generally 2-3 mg) was placed into a UniPrep syringeless filter (5 mL; 0.45 μm), 2 mL of solvent (generally 50 mM phosphate buffer at pH 7.4) were added and the sample agitated for 24 hours at 37 °C. After 24 hours, the suspension was filtered and the concentration of dissolved substance determined by HPLC (see Chromatographic Conditions). If the substance has completely dissolved, the result is stated as > x μg/mL, calculated from the sample weight taken and the volume of solvent used.

Chromatographic Conditions: Solvent system: Eluent A: Ultrapure water/formic acid for analysis (999:1, V/V); Eluent B: Acetonitrile/formic acid for analysis (999:1, V/V). Equipment settings: Wavelength range of 190 – 400 nm, column: Chromolith RP18e 100 x 3 mm, temperature: 37°C,

Gradient program as follows:

Time [Min.]	Eluent A [%]	Eluent B [%]	Flow [mL/min]
0	90	10	0.85
0.6	90	10	0.85
4	10	90	0.85
5.5	10	90	0.85
5.51	90	10	2.50
8	90	10	2.50

Quantitative determination: The result is determined quantitatively based the external standard method through integration of the peak areas with reference to the figures obtained for the standard substance.

Calculation:

$$L[\mu g/mL] = \frac{a\,(A) \times c\,(S) \times F\,(A)}{a\,(S) \times F\,(S)}$$

a (A) = peak area for analyte/mL; a (S) = peak area for standard/mL; c (S) = concentration of standard (µg/mL); F (A) = dilution factor for analyte; F (S) = dilution factor for standard.

Kinetic Solubility Determination

The following buffers and eluents were used: a) Buffer solution phosphate buffer 20 mM pH 7.4: 100 mL Sorensen phosphate buffer 0.2 M pH 7.4 (EMS, Art.No.11601-40) was placed in a 1000 mL volumetric flask, then add ultrapure water to volume. b) 2% DMSO in phosphate buffer 20 mM pH 7.4: prepared from 1 mL dimethylsulfoxide (Merck, Art. No. 102950) + 49 ml Sorensen phosphate puffer 20 mM pH 7.4; c) Acetonitrile/methanol/eluent A (1:1:2; v/v/v): prepared from 50 mL acetonitrile (Merck, Art.No.100030) + 50 mL methanol (Merck, Art.No.106007) + 100 mL eluent A; d) Eluent A: 1 mL formic acid (Merck, Art.No.100264) + 999 mL Ultrapure water; e) Eluent B: 1 mL formic acid (Merck, Art.No.100264) + 999 mL acetonitrile (Merck, Art.No.100030). A Waters XBridge Column C8 3.5µm (Waters Cat. No. 186003053) was used

Sample Preparation: 98 µL of buffer solution a) was added by pipette into each well of a 96 well filtration plate (double determination). 2 µL of 10 mM compound solution in DMSO was added; the filtration plate was incubated at room temperature for 120 minutes while agitating at 250 rpm. The filtration plate was centrifuged with the polypropylene plate as receiver plate below (2500 rpm, 3 min). The saturated solution in the receiver plate was diluted to a 100 µM sample solution: 50 µL of filtrate from the receiver plate was mixed with 50 µL of 2% DMSO in buffer pH 7.4 solution b (dilution factor= 2) in a HPLC vial.

Standard Preparation: 2 µL of a 10 mM test compound solution was diluted with 198 µL of solution c [acetonitrile/methanol/Eluent A (1:1:2; v/v/v)] to prepare a 100 µM standard solution in a HPLC Vial.

Chromatographic Conditions: Waters XBridge Column C8 3.5µm (Waters Cat. No. 186003053); temperature = 37°C; autosampler temperature ~ 25°C; injection volume = 10 µL; wavelength range = 190 – 400 nm using a DAD detector; gradient as follows:

Time [Min.]	Eluent A (d) [%]	Eluent B (e) [%]	Flow [mL/min]
0.00	90	10	1.7
0.30	90	10	1.7
2.00	10	90	1.7
2.75	10	90	1.7
2.76	90	10	2.5
4.00	90	10	2.5

Calculation:

$$L[\mu g/mL] = \frac{\text{area}_{\text{sample}} * \text{concentration}_{\text{standard}} * \text{dilution factor}_{\text{sample}}}{\text{area}_{\text{standard}} * \text{dilution factor}_{\text{standard}}}$$

$$S[mol/L] = L\ [\mu g/mL] * \text{molar weight}\ [g/mol] / 100$$

Synthetic Procedures and Preparations

For general experimental methods including preparative HPLC method A and B and LCMS/HRMS methods A, B, C and D please see the main manuscript. Additional preparative HPLC methods were carried out as follows: **Method C**, Injections of the sample were made onto a Phenomenex Gemini column (10 µm, 250 x 21.2 mm, C18, Phenomenex, Torrance, USA). Chromatographic separation at room temperature was carried out using Gilson GX-281 Liquid Handler system combined with a Gilson 322 HPLC pump (Gilson, Middleton, USA) over a 15 minute gradient elution from 10:90 to 100:0 MeOH:water (both modified with 0.1% formic acid) at a flow rate of 20 mL/min; **Method D**, Injections of the sample were made onto a Phenomenex Gemini C18 column (5 µm, 250 x 21.2 mm Phenomenex, Torrence, CA, USA). Chromatographic separation at room temperature was carried out using a 1200 Series Preparative HPLC (Agilent, Santa Clara, USA) over a 15 minute gradient elution from 55:45 to 45:55 water:MeOH (both modified with 0.1% formic acid) at a flow rate of 20 mL/min. UV-Vis spectra were acquired at 254nm on a 1200 Series Prep Scale diode array detector (Agilent, Santa Clara, USA). Post-UV & pre-MS splitting was achieved using an Active Split (Agilent, Santa Clara, USA) before being infused into a 6120 Series Quad mass spectrometer fitted with an ESI/APCI Multimode ionisation source (Agilent, Santa Clara, USA). Additional LCMS/HRMS methods were carried out as follows: **Method E**, Analytical separation was carried out at 40°C on a BEH C18 column (2.1 x 50mm, 1.7µm) using a flow rate of 0.9 mL/min in a 2 minute gradient elution with detection at 220 nm. The mobile phase was a mixture of water containing 0.1% formic acid (solvent A) and acetonitrile containing 0.08% formic acid (solvent B). Gradient elution was as follows: 96:4 (A/B) to 0:100 (A/B) over 1.0 min, 0:100 (A/B) for 0.3 min, and then reversion back to 96:4 (A/B) over 0.1 min, finally 96:4 (A/B) for 0.6 min; **Method F**, Analytical separation was carried out at 40 °C on a Merck Purospher STAR column (RP-18e, 30 x 4 mm) using a flow rate of 3 mL/min in a 2 minute gradient elution with detection at 254 nm. The mobile phase was a mixture of MeOH (solvent A) and water (solvent B), both containing 0.1% formic acid. Gradient elution was as follows: 1:9 (A/B) to 9:1 (A/B) over 1.25 min, 9:1 (A/B) for 0.5 min, and then reversion back to 1:9 (A/B) over 0.15 min, finally 1:9 (A/B) for 0.1 min.

Preparation of Compounds in Table 2

8-(3-Chloro-5-(4-(1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one 2,2,2-trifluoroacetate (17)

8-(3-Bromo-5-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one[27] **8** (500 mg, 1.45 mmol), (4-hydroxyphenyl)boronic acid (500 mg, 3.63 mmol) and 0.5 M sodium carbonate in water (5.80 mL, 2.90 mmol) were suspended in acetonitrile (8 mL) under nitrogen atmosphere and Pd(dppf)Cl_2.CH_2Cl_2 (59 mg, 0.072 mmol) was added. The reaction mixture was heated for 1 h at 120 °C under microwave irradiation. EtOAc was added to the reaction mixture; the dark brown residue (402 mg, 85% pure, 66% corrected yield) was filtered and used in the next step without further purification. LC–MS (method A, ESI, m/z) t_R = 1.3 min, 358/360 $(M+H)^+$.

8-(3-Chloro-5-(4-hydroxyphenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (85% pure, 402 mg, 0.957 mmol) was dissolved in DMF (24 mL). *N*,*N*-Diisopropylethylamine (764 µL, 4.49 mmol) was added, followed by the addition of *N*-phenyltrifluoromethanesulfonimide (803 mg, 2.25 mmol). The reaction mixture was stirred for 3 h at rt. Additional *N*-phenyltrifluoromethanesulfonimide (200 mg, 0.560 mmol) was added and the reaction mixture was stirred for another 1.5 h at rt. 150 mL of water were added and the mixture was stirred for 30 min at rt. The resulting precipitate was filtered off, washed with water and dried to yield 4-(5-chloro-4-(1-oxo-2,8-diazaspiro[4.5]decan-8-yl)pyridin-3-yl)phenyl trifluoromethanesulfonate (568 mg, 97% pure) as light pink solid which was used directly in the next step. LC–MS (method A, ESI, m/z) t_R = 2.03 min, 490/492 $(M+H)^+$.

4-(5-Chloro-4-(1-oxo-2,8-diazaspiro[4.5]decan-8-yl)pyridin-3-yl)phenyl trifluoromethanesulfonate (97% pure, 150 mg, 0.297 mmol), 1-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (118 mg, 0.367 mmol) and sodium carbonate (97 mg, 0.92 mmol) were suspended in toluene (5 mL), EtOH (5 mL) and water (1 mL), then Pd(dppf)Cl_2.CH_2Cl_2 (13 mg, 0.015 mmol) was added. The reaction mixture was flushed with nitrogen and stirred for 30 min at 120 °C under microwave irradiation and then filtered over Celite. The filtrate was reduced *in vacuo* and was chromatographed by prep. HPLC (method A, 20 min gradient elution from 2:98 to 25:75 acetonitrile:water) to afford 8-(3-chloro-5-(4-(1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one 2,2,2-trifluoroacetate **17** (33 mg, 19% yield) as a white solid. ^{1}H

NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 0.9 Hz, 1H), 8.32 (d, *J* = 0.9 Hz, 1H), 7.88 (s, 1H), 7.81 (s, 1H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 6.17 (s, 1H), 4.34 – 4.30 (m, 2H), 4.09 – 4.04 (m, 2H), 3.47 – 3.39 (m, 2H), 3.35 (t, *J* = 6.5 Hz, 2H), 2.97 (ddd, *J* = 12.6, 8.5, 3.3 Hz, 2H), 2.02 (t, *J* = 6.5 Hz, 2H), 2.00–1.93 (m, 2H), 1.58 – 1.51 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.3, 157.7, 143.3, 141.8, 137.2, 133.4, 133.1, 132.9, 129.1, 127.6, 127.1, 126.2, 121.8, 61.8, 54.2, 48.4, 41.0, 39.0, 33.1, 32.6; LC–MS (method C, ESI, m/z) t_R = 2.08 min, 452/454 $(M+H)^+$; ESI-HRMS calcd for $C_{24}H_{27}{}^{35}ClN_5O_2$ $(M+H)^+$ 452.1848, found 452.1833.

2-Methyl-1-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazol-1-yl)propan-2-ol (9)

4-(4-Bromophenyl)-1*H*-pyrazole (5.00 g, 22.4 mmol) was dissolved in DMF (50 mL). Potassium carbonate (4.33 g, 31.4 mmol) and 2,2-dimethyl-oxirane (4.00 mL, 44.8 mmol) were added. The reaction mixture was stirred overnight at 100 °C. The reaction mixture was treated with 300 mL of water. A white precipitate was obtained and filtered under vacuum, washed with water and dried to give 1-(4-(4-bromophenyl)-1*H*-pyrazol-1-yl)-2-methylpropan-2-ol (6.6 g, 100% yield) as white crystals which were used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 2.10 min, 295/297 $(M+H)^+$.

1-(4-(4-Bromophenyl)-1*H*-pyrazol-1-yl)-2-methylpropan-2-ol (6.6 g, 22 mmol) was dissolved in THF (300 mL) and bis(pinacolato)diboron (8.5 g, 34 mmol), potassium acetate (6.6 g, 67 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (1.8 g, 2.2 mmol) were added and the red reaction mixture was stirred at 70 °C overnight. The black reaction mixture was treated with water and the organic solvent was distilled off. The aqueous layer was extracted with EtOAc. The organic layer was washed with water, dried, filtered and evaporated to dryness. The dark brown oily residue was purified by flash-chromatography (Companion, n-heptane/EtOAc 100:0 to 0:100) to afford 6.23 g (88% pure, 73% corrected yield) of 2-methyl-1-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazol-1-yl)propan-2-ol **9** as a pale brown solid which was used without further purification. LC–MS (method B, ESI, m/z) t_R = 2.84 min, 342/343 $(M+H)^+$.

8-(3-Chloro-5-(4-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (18)

2-Methyl-1-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazol-1-yl)propan-2-ol **9** (88% pure, 2.69 g, 7.80 mmol) was dissolved in acetonitrile (100 mL). 8-(3-bromo-5-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one[27] **8** (88% pure, 3.06 g, 7.80 mmol), 0.5 M sodium carbonate in water (31.2 ml, 15.6 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (319 mg, 0.390 mmol) were added. The reaction mixture was stirred at 70 °C overnight. After addition of water, ACN was distilled off. The aqueous layer was extracted with EtOAc. The organic layer was dried, filtered and evaporated and the brown residue was purified by flash-chromatography (Companion, DCM/MeOH 100:0 to 88:12). The product was recrystallized from ACN/diethyl ether, the solid was filtered and washed with diethyl ether to afford 8-(3-chloro-5-(4-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **18** (1.40 g, 38% yield) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.45 (s, 1H), 8.19 (s, 1H), 8.16 (d, *J* = 0.8 Hz, 1H), 7.95 (d, *J* = 0.8 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.53 (s, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 4.75 (s, 1H), 4.05 (s, 2H), 3.10 (t, *J* = 6.8 Hz, 2H), 3.07 – 3.00 (m, 2H), 2.70 – 2.63 (m, 2H), 1.83 (t, *J* = 6.8 Hz, 2H), 1.76 – 1.67 (m, 2H), 1.28 – 1.22 (m, 2H), 1.10 (s, 6H); ^{13}C NMR (126 MHz, DMSO-d6) δ 179.8, 152.3, 150.7, 148.7, 135.8, 134.6, 133.4, 132.2, 129.6, 128.4, 127.3, 124.9, 120.9, 69.3, 62.2, 47.5, 41.2, 37.8, 31.8, 30.5, 27.3; LC–MS (method C, ESI, m/z) t_R = 2.39 min, 480/482 $(M+H)^+$; ESI-HRMS calcd for $C_{26}H_{31}{}^{35}ClN_5O_2$ $(M+H)^+$ 480.2161, found 480.2149.

1-(2,2-Diethoxyethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole (10)

To a suspension of 4-(4-bromophenyl)-1*H*-pyrazole (1.48 g, 6.63 mmol) and potassium carbonate (2.75 g, 19.9 mmol) in DMF (22 mL) was added 2-bromo-1,1-diethoxyethane (2.00 mL, 13.3 mmol). The reaction mixture was heated at 70 °C overnight. Two equivalents of 2-bromo-1,1-diethoxyethane were added and the reaction mixture was heated at 70 ºC for 24 h. After addition of water and EtOAc, the aqueous layer was extracted with EtOAc. The organics layers were combined, dried over $MgSO_4$ and concentrated. The crude material was purified by Biotage column chromatography (cyclohexane/EtOAc 90:10 to 50:50) to give 4-(4-

bromophenyl)-1-(2,2-diethoxyethyl)-1*H*-pyrazole as a yellow oil (1.2 g, 53% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.70 (s, 1H), 7.49 – 7.45 (m, 2H), 7.35 – 7.32 (m, 2H), 4.79 (t, *J* = 5.4 Hz, 1H), 4.23 (d, *J* = 5.4 Hz, 2H), 3.77 – 3.65 (m, 2H), 3.50 – 3.39 (m, 2H), 1.16 (t, *J* = 7.0 Hz, 6H); LC–MS (method C, ESI, m/z) t_R = 3.17 min, 339/341 $(M+H)^+$.

4-(4-Bromophenyl)-1-(2,2-diethoxyethyl)-1*H*-pyrazole (1.20 g, 3.54 mmol), bis(pinacolato)diboron (1.35 g, 5.31 mmol), potassium acetate (1.04 g, 10.6 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (0.144 g, 0.177 mmol) were loaded in a microwave vial and DME (26 ml) was added. The reaction was heated in an oil bath at 80 °C overnight. The crude material was concentrated and purified by Biotage column chromatography (Cyclohexane/EtOAc 98:2 to 85:15) to give 1-(2,2-diethoxyethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole **10** as a yellow oil (1.2 g, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.81 – 7.78 (m, 2H), 7.76 (s, 1H), 7.50 – 7.46 (m, 2H), 4.80 (t, *J* = 5.4 Hz, 1H), 4.23 (d, *J* = 5.4 Hz, 2H), 3.76 – 3.67 (m, 2H), 3.49 – 3.41 (m, 2H), 1.34 (s, 12H), 1.16 (t, *J* = 7.0 Hz, 6H); LC–MS (method C, ESI, m/z) t_R = 3.25 min, 386/387 $(M+H)^+$.

8-(3-Chloro-5-(4-(1-(2-(dimethylamino)ethyl)-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (19)

Two microwave vials were prepared as follow: 1-(2,2-diethoxyethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole **10** (235 mg, 0.609 mmol), 8-(3-bromo-5-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one[27] **8** (175 mg, 0.508 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (21 mg, 0.025 mmol) were loaded in a microwave vial and then 0.5 M sodium carbonate in water (1.4 mL, 0.71 mmol) and acetonitrile (9 mL) were added. The reaction mixture was heated at 120 °C for 60 min under microwave irradiation and then concentrated. The crude material was purified by Biotage column chromatography (DCM/EtOH 98:2 to 90:10) to give 8-(3-chloro-5-(4-(1-(2,2-diethoxyethyl)-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (450 mg, 85% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.21 (s, 1H), 7.84 (d, *J* = 0.7 Hz, 1H), 7.79 (d, *J* = 0.8 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 11.9 Hz, 2H), 5.70 (s, 1H), 4.82 (t, *J* = 5.4 Hz, 1H), 4.25 (d, *J* = 5.4 Hz, 2H), 3.74 (dq, *J* = 9.3, 7.0 Hz, 2H), 3.49 (dq, *J* = 9.3, 7.0 Hz, 2H), 3.29 (t, *J* = 6.8 Hz, 2H),

3.26 – 3.18 (m, 2H), 2.79 (t, *J* = 11.7 Hz, 2H), 2.03 – 1.94 (m, 4H), 1.43 – 1.35 (m, 2H), 1.19 (t, *J* = 7.0 Hz, 6H); LC–MS (method C, ESI, m/z) t_R = 2.80 min, 524/526 $(M+H)^+$.

To a solution of 8-(3-chloro-5-(4-(1-(2,2-diethoxyethyl)-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (70 mg, 0.13 mmol) in dry THF (700 μL) was added conc. HCl (0.668 mL, 1.34 mmol) at rt and the reaction mixture was stirred at 60 °C for 1.5 h. The solution was cooled to 0 °C, triethylamine (190 μL, 1.47 mmol) was added. After 5 min at 0 ºC, dimethylamine (2 M in THF, 80 μL, 0.16 mmol) was added and the reaction mixture was stirred at 0 °C for 10 min before sodium cyanoborohydride (10 mg, 0.16 mmol) was added at 0 °C. The reaction mixture was allowed to warm up to rt and was stirred for 5 h before being diluted with 1 M Na_2CO_3 and EtOAc. The layers were separated and the aqueous layer was extracted with DCM three times. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The resulting brown solid was purified by prep. HPLC (method C) to give 8-(3-chloro-5-(4-(1-(2-(dimethylamino)ethyl)-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **19** (12 mg, 18% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.21 (s, 1H), 7.84 (s, 1H), 7.81 (s, 1H), 7.57 (d, *J* = 7.7 Hz, 2H), 7.30 – 7.24 (m, 2H), 5.93 (s, 1H), 4.31 (t, *J* = 6.5 Hz, 2H), 3.28 (t, *J* = 6.8 Hz, 2H), 3.19 – 3.12 (m, 2H), 2.87 (t, *J* = 6.5 Hz, 2H), 2.74 (t, *J* = 12.4 Hz, 2H), 2.33 (s, 6H), 2.05 – 1.90 (m, 4H), 1.38 – 1.29 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.4, 152.8, 150.7, 149.5, 136.8, 135.6, 133.6, 132.2, 129.7, 128.2, 126.8, 125.5, 122.3, 59.0, 50.3, 47.7, 45.6, 41.6, 38.6, 32.3, 31.6; LC–MS (method C, ESI, m/z) t_R = 1.65 min, 479/481 $(M+H)^+$; ESI-HRMS calcd for $C_{26}H_{32}{}^{35}ClN_6O$ $(M+H)^+$ 479.2321, found 479.2311.

1-(2-(Pyrrolidin-1-yl)ethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole (11)

4-(4-Bromophenyl)-1*H*-pyrazole (500 mg, 2.24 mmol), bis(pinacolato)diboron (854 mg, 3.36 mmol), potassium acetate (660 mg, 6.72 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (91 mg, 0.11 mmol) were loaded in a microwave vial and DME (16 mL) was added. The reaction mixture was heated at 80 °C overnight, the solvent was evaporated and the crude material was purified by Biotage column chromatography (cyclohexane/EtOAc 70:30 to 50:50) to give 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole (560 mg, 92% yield) as a white solid. ^{1}H NMR

(500 MHz, $CDCl_3$) δ 7.93 (bs, 2H), 7.83 (d, *J* = 7.8 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 2H), 1.37 (s, 12H); LC–MS (method C, ESI, m/z) t_R = 2.94 min, 270/271 $(M+H)^+$.

4-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole (300 mg, 1.11 mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (283 mg, 1.67 mmol) and cesium carbonate (724 mg, 2.22 mmol) were loaded in a microwave vial and then acetonitrile (3.4 mL) was added. The reaction mixture was heated for 15 h at 80 °C in an oil bath and filtered.

The filtrate was concentrated and purified by Biotage column chromatography (eluting with 2 to 10% MeOH/aq NH_3 (10:1) in DCM) to give 1-(2-(pyrrolidin-1-yl)ethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole **11** (61 mg, 15% yield) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 0.8 Hz, 1H), 7.82 – 7.78 (m, 2H), 7.77 (d, *J* = 0.8 Hz, 1H), 7.52 – 7.47 (m, 2H), 4.33 (t, *J* = 6.9 Hz, 2H), 3.02 (t, *J* = 6.9 Hz, 2H), 2.61 – 2.56 (m, 4H), 1.83 – 1.78 (m, 4H), 1.36 (s, 12H); LC–MS (method C, ESI, m/z) t_R = 2.29 min, 367/368 $(M+H)^+$.

8-(3-Chloro-5-(4-(1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (20)

1-(2-(Pyrrolidin-1-yl)ethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole **11** (61 mg, 0.17 mmol), 8-(3-bromo-5-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one[27] **8** (44 mg, 0.13 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (5.2 mg, 6.4 μmol) were loaded in a microwave vial and then 0.5 M sodium carbonate in water (358 μL, 0.179 mmol) and acetonitrile (2.3 mL) were added. The reaction mixture was heated at 120 °C for 60 min under microwave irradiation. After concentration of the solvent, the crude was purified by Biotage column chromatography (eluting with 3 to 10% MeOH/aq NH_3 (10:1) in DCM) to afford 8-(3-chloro-5-(4-(1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (42 mg, 65% yield) as a beige solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.21 (s, 1H), 7.88 (s, 1H), 7.85 (d, *J* = 0.8 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 5.64 (s, 1H), 4.47 (s, 2H), 3.29 (t, *J* = 6.9 Hz, 2H), 3.21 – 3.13 (m, 4H), 2.80 – 2.65 (m, 6H), 2.02 – 1.94 (m, 4H), 1.91 – 1.83 (m, 4H), 1.40 – 1.33 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.3, 152.8, 150.8, 149.5, 137.2, 135.7, 133.5, 132.0, 129.7, 128.2, 127.3, 125.5, 122.5, 55.5, 54.3, 50.7, 47.7, 41.5, 38.5, 32.3, 31.7, 23.5; LC–MS (method C, ESI, m/z) t_R = 1.79 min, 505/507 $(M+H)^+$; ESI-HRMS calcd for $C_{28}H_{34}{}^{35}ClN_6O$ $(M+H)^+$ 505.2477, found 505.2470.

1,2-Dimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-imidazole (12)

4-Bromo-1,2-dimethyl-1*H*-imidazole (200 mg, 1.14 mmol) and 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (754 mg, 2.29 mmol) were solubilised in acetonitrile (10 mL) and 0.5 M sodium carbonate in water (4.57 mL, 2.29 mmol) and Pd(dppf)Cl_2·CH_2Cl_2 (47 mg, 0.060 mmol) were added. The reaction mixture was stirred for 60 min at 120 ºC under microwave irradiation. After addition of acetonitrile (20 mL), the reaction mixture was filtered and the filtrate was evaporated to dryness. The crude material was purified by flash chromatography (Companion, MeOH/EtOAc/petrol ether gradient) to give a 5:4 mixture of 1,2-dimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-imidazole **12** and [4-(1,2-dimethylimidazol-4-yl)phenyl]boronic acid (44 mg, 90% pure) as colorless solid which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 2.25 min, 298/299 $(M+H)^+$

8-(3-Chloro-5-(4-(1,2-dimethyl-1*H*-imidazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one 2,2,2-trifluoroacetate (21)

8-(3-Bromo-5-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one[27] **8** (45.8 mg, 0.13 mmol) and a 5:4 mixture of 1,2-dimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-imidazole **12** and [4-(1,2-dimethylimidazol-4-yl)phenyl]boronic acid (90 % pure, 44 mg, 0,15 mmol) were dissolved in acetonitrile (4 mL). 0.5 M sodium carbonate in water (534 µL, 0.270 mmol) and Pd(dppf)Cl_2·CH_2Cl_2 (5 mg, 0.01 mmol) were added. The reaction mixture was stirred for 1 h at 120 ºC under microwave irradiation and then diluted with acetonitrile (5 mL), filtered and the filtrate was evaporated. The crude residue was purified by prep HPLC (method A, 20 min gradient elution from 2:98 to 20:80 acetonitrile:water). The pure fractions were combined and lyophilized to give 8-(3-chloro-5-(4-(1,2-dimethyl-1*H*-imidazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one 2,2,2-trifluoroacetate **21** (47 mg, 64% yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.54 (s, 1H), 8.27 (s, 1H), 8.15 (s, 1H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 3.79 (s, 3H), 3.14 – 3.04 (m, 4H), 2.70 (t, *J* = 11.9 Hz, 2H), 2.64 (s, 3H), 1.82 (t, *J* = 6.8 Hz, 2H), 1.73 – 1.64 (m, 2H), 1.29 – 1.22 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d6) δ 180.2, 153.5, 150.0, 148.7, 146.2, 138.1, 133.1, 130.6, 127.6, 126.7, 125.3, 119.9,

48.1, 41.6, 38.2, 34.7, 32.2, 31.1, 11.0 (1Cq missing); LC–MS (method C, ESI, m/z) t_R = 1.71 min, 436/438 $(M+H)^+$. ESI-HRMS calcd for $C_{24}H_{27}{}^{35}ClN_5O$ $(M+H)^+$ 436.1899, found 436.1886.

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide (13)

5-Bromo-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide (200 mg, 0.810 mmol), Pd(dppf)Cl_2.CH_2Cl_2 (33 mg, 0.040 mmol), potassium acetate (238 mg, 2.42 mmol) and bis(pinacolato)diboron (409 mg, 1.61 mmol) were loaded in a microwave vial and THF (10 mL) was added. The reaction mixture was stirred overnight at 80 °C and then concentrated. The crude material was partially purified by column chromatography (Companion, DCM/MeOH 100:0 6 min, than 100:0 to 90:1) to afford 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide **13** (168 mg, 50% pure, 35% corrected yield) as a colorless solid which was used without further purification. LC–MS (method B, ESI, m/z) t_R = 2.73 min, 231/232 $(M+H-SO_2)^+$.

8-(3-Chloro-5-(2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one 2,2,2-trifluoroacetate (22)

8-(3-Bromo-5-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one[27] **8** (79 mg, 0.23 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide **13** (50% pure, 168 mg, 0.285 mmol) und 0.5 M sodium carbonate in water (1.14 mL, 0.57 mmol) were loaded in a microwave vial and acetonitrile (8 mL) and Pd(dppf)Cl_2·CH_2Cl_2 (12 mg, 0.014 mmol) were added. The reaction mixture was stirred for 60 min at 120 °C under microwave irradiation. The solvent was evaporated and the crude material was purified by column chromatography (Companion, MeOH/EtOAc/petrol ether gradient) and by prep HPLC (method A, 20 min gradient elution from 2:98 to 25:75 acetonitrile:water). The fractions containing the product were combined and lyophilised to afford 8-(3-chloro-5-(2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one 2,2,2-trifluoroacetate **22** (26 mg, 21% yield) as a colorless solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.57 (s, 1H), 8.23 (s, 1H), 7.38 – 7.35 (m, 1H), 7.32 – 7.28 (m, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 4.53 (s, 2H), 3.42 (dt, *J* = 13.4, 4.1 Hz, 2H), 3.34 – 3.29 (m, 2H), 3.03 – 2.94 (m, 2H), 2.06 (t, *J* = 6.9

Hz, 2H), 1.96 – 1.87 (m, 2H), 1.51 – 1.43 (m, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 183.2, 158.8, 145.4, 144.2, 142.2, 134.4, 131.1, 130.4, 128.3, 127.4, 122.1, 113.0, 52.9, 49.6, 43.2, 39.8, 33.4, 32.6; LC–MS (method C, ESI, m/z) t_R = 1.80 min, 433/435 $(M+H)^+$; ESI-HRMS calcd for $C_{20}H_{22}{}^{35}ClN_4O_3S$ $(M+H)^+$ 433.1096, found 433.1084.

1-Methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide (15)

To 6-chloro-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide (100 mg, 0.491 mmol) in DMF (3 mL) were added potassium carbonate (170 mg, 1.23 mmol) and iodomethane (30 µL, 0.49 mmol). The reaction mixture was stirred at rt for 1 h. Water was added to the reaction mixture and the solvent was evaporated. The residue was triturated with DCM and the suspension was filtered. The filtrate was concentrated to give 6-chloro-1-methyl-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide (98 mg, 92% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (dt, *J* = 8.0, 1.1 Hz, 1H), 6.98 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.72 (d, *J* = 1.9 Hz, 1H), 4.30 (d, *J* = 1.1 Hz, 2H), 3.12 (s, 3H); LC–MS (method C, ESI, m/z) t_R = 2.43 min, 154/156 $(M+H–SO_2)^+$.

6-Chloro-1-methyl-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide (176 mg, 0.809 mmol), Bis(pinacolato)diboron (246 mg, 0.970 mmol), potassium acetate (238 mg, 2.43 mmol), XPhos (31 mg, 0.065 mmol) and $Pd_2(dba)_3$ (15 mg, 0.016 mmol) were loaded a vial and then dioxane (1.6 mL) was added. The reaction was heated overnight at 85 °C and the solvent was evaporated. The crude material was purified by Biotage column chromatography (cyclohexane/Acetone 97:3 to 85:15) to give 1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide **15** (235 mg, 94% yield) as a cream solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.4, 0.9 Hz, 1H), 7.25 – 7.23 (m, 1H), 7.12 (s, 1H), 4.32 (d, *J* = 0.9 Hz, 2H), 3.15 (s, 3H), 1.35 (s, 12H); LC–MS (method C, ESI, m/z) t_R = 2.83 min, 245/246 $(M+H–SO_2)^+$.

8-(3-Chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-6-yl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (24)

8-(3-Bromo-5-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one[27] **8** (40 mg, 0.12 mmol), 1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole 2,2-

dioxide **15** (51 mg, 0.12 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (4.7 mg, 5.8 µmol) were loaded in a microwave vial and then acetonitrile (2 mL) and 0.5 M sodium carbonate in water (325 µL, 0.162 mmol) were added. The reaction mixture was stirred at 120 ºC for 60 min under microwave irradiation and then concentrated. The crude material was purified by Biotage column chromatography (DCM/EtOH 98:2 to 94:6) and by SCX-2 column to give 8-(3-chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-6-yl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **24** (31 mg, 60% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.19 (s, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 6.94 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.67 (d, *J* = 1.5 Hz, 1H), 6.13 (s, 1H), 4.40 (s, 2H), 3.34 – 3.27 (m, 2H), 3.22 – 3.16 (s, 5H), 2.81 – 2.72 (m, 2H), 2.00 – 1.89 (m, 4H), 1.44 – 1.37 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.4, 152.8, 150.5, 150.1, 142.0, 139.3, 132.9, 128.1, 125.6, 122.7, 116.9, 109.7, 50.7, 47.7, 41.3, 38.6, 32.5, 32.2, 26.5; LC–MS (method C, ESI, m/z) t_R = 2.03 min, 447/449 $(M+H)^+$; ESI-HRMS calcd for $C_{21}H_{24}{}^{35}ClN_4O_3S$ $(M+H)^+$ 447.1252, found 447.1242.

Preparation of Compounds in Table 3

8-(3-Bromo-5-chloropyridin-4-yl)-3-oxa-1,8-diazaspiro[4.5]decan-2-one (26)

4-Amino-1-benzyl-piperidine-4-carboxylic acid (10.0 g, 42.7 mmol) was suspended in THF (90 mL) and 2.0 M lithium aluminium hydride in THF (45 mL, 90 mmol) was added dropwise, then the reaction mixture was stirred for 3 h under reflux and nitrogen. The reaction mixture was cooled down to rt, under stirring and nitrogen, water (5 mL) was added slowly and carefully, then 1 N aqueous sodium hydroxide solution (7.5 mL) was added. The reaction mixture was filtered and washed 3 times with THF (250 mL). The filtrate was concentrated and dried *in vacuo* to afford (4-amino-1-benzylpiperidin-4-yl)methanol (9.47 g, 100% yield) as a colorless solid which was used directly in the next step. LC–MS (method A, ESI, m/z) t_R = 0.38 min, 221 $(M+H)^+$.

(4-Amino-1-benzylpiperidin-4-yl)methanol (9.47 g, 43.0 mmol) and 1,1'-carbonyldiimidazole (7.67 g, 47.3 mmol) was suspended in DCM (145 mL) and stirred for 2 h at room temperature. The reaction mixture was dry loaded and purified by column chromatography (Companion, DCM/MeOH 100:0 to 90:10) to afford 8-benzyl-3-oxa-1,8-diazaspiro[4.5]decan-2-one (8.22 g,

78% yield) as an off-white solid which was used directly in the next step. LC–MS (method A, ESI, m/z) t_R = 0.83 min, 247 $(M+H)^+$.

8-Benzyl-3-oxa-1,8-diazaspiro[4.5]decan-2-one (1.97 g, 8.00 mmol) was dissolved in 1,4-dioxane (50 mL) and MeOH (110 mL). The solution was hydrogenated with an H-cube apparatus using the following conditions: Full H_2, 10% Pd/C cartridge, 70x4 mm, 50 °C, 1 mL/min. The resulting solution was reduced *in vacuo* to afford 3-oxa-1,8-diazaspiro[4.5]decan-2-one (1.25 g, quant. yield) as an off-white solid which was used directly in the next step. LC–MS (method A, ESI, m/z) t_R = 0.34 min, 157 $(M+H)^+$.

3-Bromo-4,5-dichloropyridine[27] **7** (870 mg, 3.84 mmol) and 3-oxa-1,8-diazaspiro[4.5]decan-2-one (600 mg, 3.84 mmol) were diluted in NMP (12 mL) and triethylamine (1.06 mL, 7.67 mmol) was added slowly. The reaction mixture was flushed with N_2 and stirred for 1 h at 220 °C under microwave irradiation. Additional 3-oxa-1,8-diazaspiro[4.5]decan-2-one (338 mg, 2.16 mmol) was added and the reaction mixture was stirred for 1 h at 220 °C. The reaction mixture was put into water; the precipitate was filtered off over Celite and washed with water and DCM, the organic layer was reduced *in vacuo* and purified by column chromatography (Companion, cyclohexane/EtOAc 100:0 to 0:100). The aqueous layer was extracted three time with EtOAc, the organic layer was washed with brine, dried over Na_2SO_4, filtered, reduced *in vacuo* and purified by column chromatography (Companion, cyclohexane/EtOAc 100:0 to 0:100 in 15 min). Combining both samples gave 274 mg of **26** (17% corrected yield) as a white solid which was used directly in the next step. LC–MS (method A, ESI, m/z) t_R = 1.81 min, 346/348 $(M+H)^+$.

8-(3-Chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-3-oxa-1,8-diazaspiro[4.5]decan-2-one (40)

8-(3-Bromo-5-chloropyridin-4-yl)-3-oxa-1,8-diazaspiro[4.5]decan-2-one **26** (79% pure, 50.6 mg, 0.116 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole[27] **37** (50 mg, 0.18 mmol), 0.5 M sodium carbonate in water (700 µL; 0.350 mmol) were suspended in acetonitrile (1.40 mL; 26.8 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 complex (7 mg, 0.009 mmol) was added. The reaction mixture was stirred for 1 h at 120 °C under microwave irradiation. The reaction mixture was filtered over Celite, washed with EtOAc. The filtrate was reduced *in vacuo* and purified by prep. HPLC (method A, 20 min gradient elution from 2:98 to 30:70, then 30:70

to 100:0 in 4 min, acetonitrile:water). The product fractions were combined and lyophilized to give 8-(3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-3-oxa-1,8-diazaspiro[4.5]decan-2-one 2,2,2-trifluoroacetate **40** (98% pure, 37 mg, 58% corrected yield) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.55 (s, 1H), 8.26 (s, 1H), 8.20 (s, 1H), 8.13 (s, 1H), 7.92 (s, 1H), 7.70 – 7.64 (m, 2H), 7.36 – 7.31 (m, 2H), 4.01 (s, 2H), 3.89 (s, 3H), 3.10 – 3.00 (m, 2H), 2.90 – 2.82 (m, 2H), 1.73 – 1.59 (m, 4H); LC–MS (method C, ESI, m/z) t_R = 2.30 min, 424/426 $(M+H)^+$; ESI-HRMS calcd for $C_{22}H_{23}{}^{35}ClN_5O_2$ $(M+H)^+$ 424.1535, found 424.1525.

8-(3-Chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (41)

In a microwave-vial 8-(3-bromo-5-chloropyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one **27** (60 mg, 0.17 mmol) was suspended in acetonitrile (2 mL). 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole[27] **37** (49 mg, 0.17 mmol), 0.5 M sodium carbonate in water (692 µL, 0.346 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 complex (7 mg, 0.009 mmol) were added. The reaction mixture was stirred for 1 h at 120ºC under microwave irradiation and then treated with EtOAc, filtered and evaporated. The crude material was purified by prep. HPLC (method A, 20 min gradient elution from 2:98 to 30:70, then 30:70 to 100:0 in 4 min, acetonitrile:water) to afford 8-(3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one 2,2,2-trifluoroacetate (32 mg, 34% yield) as pale beige solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.63 (s, 1H), 8.32 (s, 1H), 8.24 (d, *J* = 0.8 Hz, 1H), 7.96 (d, *J* = 0.8 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.51 (s, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 3.88 (s, 3H), 3.20 (s, 2H), 3.06 – 2.99 (m, 2H), 2.98 – 2.89 (m, 2H), 1.79 – 1.73 (m, 4H); ^{13}C NMR (126 MHz, DMSO-d6) δ 157.6, 154.3, 147.3, 145.6, 136.2, 133.6, 133.0, 132.6, 129.5, 128.2, 126.7, 125.0, 121.2, 78.4, 50.1, 47.5, 38.7, 35.7; LC–MS (method C, ESI, m/z) t_R = 2.31 min, 424/426 $(M+H)^+$; ESI-HRMS calcd for $C_{22}H_{23}{}^{35}ClN_5O_2$ $(M+H)^+$ 424.1535, found 424.1522.

8-(3-Bromo-5-chloropyridin-4-yl)-4,4-dimethyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one (28)

Butyllithium (1.6 M in hexane, 14.4 mL, 22.8 mmol) was added to a solution of diisopropylamine (3.2 mL, 23 mmol) in THF (15 mL) at 0 °C and the solution was stirred for 5

minutes. Isobutyric acid (950 µL, 10.1 mmol) was added and the reaction mixture was stirred for 15 minutes at 20 °C. The reaction mixture is cooled to -70 °C and a solution of 1-benzyl-piperidin-4-one (2.40 g, 12.7 mmol) in THF (5 mL) was added at such a rate that the temperature remained below -50 °C. The reaction mixture was allowed to warm up to room temperature and poured into 150 mL of diethyl ether. The mixture was extracted twice with 150 mL of water. The organic phase was disposed. The aqueous layer was evaporated to dryness and triturated in MeOH. The solid was filtered off and disposed. The filtrate was evaporated to dryness to yield in 2.20 g (98.5% pure, 62% corrected yield) of 2-(1-benzyl-4-hydroxypiperidin-4-yl)-2-methylpropanoic acid as a yellow solid which was used directly in the next step. LC–MS (method A, ESI, m/z) t_R = 1.11 min, 278 $(M+H)^+$.

A mixture of 2-(1-benzyl-4-hydroxypiperidin-4-yl)-2-methylpropanoic acid (98.5% pure, 1.00 g, 3.55 mmol), diphenylphosphoryl azide (0.630 mL, 2.84 mmol), triethylamine (0.400 mL, 2.84 mmol) and toluene (30 mL) was heated at reflux for 18 h. Evaporation of solvent gave a residue which was taken up in DCM and washed with 1 N hydrochloric acid twice. The organic phase was disposed. The combined aqueous layer was evaporated to dryness and triturated with MeOH. The solid was filtered off and disposed. The filtrate was evaporated to dryness and purified by flash chromatography (DCM/MeOH, gradient) to afford 8-benzyl-4,4-dimethyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one (200 mg, 21% yield) as white crystals which was used directly in the next step. LC–MS (method A, ESI, m/z) t_R = 1.03 min, 275 $(M+H)^+$.

8-Benzyl-4,4-dimethyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one (200 mg, 0.730 mmol) was dissolved in THF (10 mL) and Pd/C-5% (54.1% H_2O, 200 mg) was added. The reaction mixture was stirred at rt for 20 h under hydrogen atmosphere. The catalyst was then filtered off and the filtrate was evaporated to dryness to yield in 98 mg (73% yield) of 4,4-dimethyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one as an off-white solid which was used directly in the next step. LC–MS (method A, ESI, m/z) t_R = 0.45 min, 185 $(M+H)^+$.

In a microwave vial, 3-bromo-4,5-dichloropyridine[27] **7** (80 mg, 0.35 mmol) and 4,4-dimethyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one (98 mg, 0.53 mmol) was suspended in NMP (2 mL), then triethylamine (98 mL, 0.71 mmol) was added. The reaction mixture was stirred at 220 °C for 1 h under microwave irradiation. Ethylacetate and water were added to the mixture, both phases were separated and the organic phase was washed with water (twice), dried with Na_2SO_4, filtered

and evaporated. The residue was dissolved in DMSO, mixed with water, the precipitated crystals were filtered off and dried to afford 8-(3-bromo-5-chloropyridin-4-yl)-4,4-dimethyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one **28** (58 mg, 44% yield) as beige crystals which were used directly in the next step. LC–MS (method A, ESI, m/z) t_R = 2.03 min, 374/376/378 $(M+H)^+$.

8-(3-Chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-4,4-dimethyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one (43)

In a microwave vial 8-(3-bromo-5-chloropyridin-4-yl)-4,4-dimethyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one **28** (58 mg, 0.15 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide **14** (57 mg, 0.18 mmol) were dissolved in acetonitrile (3 mL). 0.5 M sodium carbonate in water (614 mL, 0.307 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 complex (12 mg, 0.015 mmol) were added. The reaction mixture was stirred at 120 °C for 1 h and then concentrated *in vacuo*. The crude product was purified by flash chromatography (DCM/MeOH, gradient) and by prep. HPLC (method A, 15 min gradient elution from 1:99 to 60:40 acetonitrile:water) to afford 8-(3-chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-4,4-dimethyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one **43** (20 mg, 94% pure, 26% corrected yield) as crystals. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.45 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.42 (s, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 4.69 (s, 2H), 3.10 (s, 3H), 3.04 – 2.97 (m, 2H), 2.93 – 2.82 (m, 2H), 1.68 – 1.50 (m, 4H), 1.06 (s, 6H); ^{13}C NMR (126 MHz, DMSO-d6) δ 156.5, 152.0, 150.5, 149.0, 141.2, 133.2, 130.3, 130.1, 127.1, 126.0, 118.6, 109.4, 82.6, 59.0, 50.1, 47.0, 30.4, 26.1, 23.2; LC–MS (method C, ESI, m/z) t_R = 2.17 min, 477/479 $(M+H)^+$; ESI-HRMS calcd for $C_{22}H_{26}{}^{35}ClN_4O_4S$ $(M+H)^+$ 477.1358, found 477.1346.

4-amino-1-(3-bromo-5-chloropyridin-4-yl)piperidine-4-carboxamide (29)

3-Bromo-4,5-dichloropyridine[27] **7** (3.50 g, 15.4 mmol) and *tert*-butyl-4-amino-4-carboamoylpiperidine-1-carboxylate (3.75 g, 15.4 mmol) were loaded in a microwave vial. Triethlyamine (6.9 mL, 54 mmol) and 1-methoxy-2-propanol (35 mL) were added and the light brown solution was degassed. The reaction mixture was heated at 220 °C for 1 h under microwave irradiation. The solvent was evaporated and the crude material was purified by column chromatography (DCM/MeOH, 100:0 to 80:20) to give 4-amino-1-(3-bromo-5-chloropyridin-4-yl)piperidine-4-carboxamide **29** (2.08 g) as a white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.53 (s, 1H), 8.42 (s, 1H), 7.44 (s, 1H), 6.97 (s, 1H), 3.54 (td, *J* = 12.2, 2.7 Hz, 2H), 3.09 (dt, *J* = 12.2, 3.9 Hz, 2H), 2.11 – 2.04 (m, 2H), 1.93 (s, 2H), 1.45 – 1.39 (m, 2H); LC–MS (method C, ESI, m/z) t_R = 1.17 min, 333/335/337 $(M+H)^+$.

8-(3-Chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1,3,8-triazaspiro[4.5]decan-4-one (44)

4-Amino-1-(3-bromo-5-chloropyridin-4-yl)piperidine-4-carboxamide **29** (2.5 g, 7.5 mmol) was dissolved in triethylorthoformate (10 mL, 7.5 mmol) and acetic acid (5.0 mL, 7.5 mmol) using gentle heating with a hot air gun. The reaction mixture was stirred at 100 °C for 5 min under microwave irradiation. The solvent was evaporated and the resulting white solid was purified by column chromatography (CH_2Cl_2/MeOH, 97:3 to 90:10) to give 8-(3-bromo-5-chloropyridin-4-yl)-1,3,8-triazaspiro[4.5]dec-1-en-4-one (2.01 g, 78% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.38 (s, 1H), 7.92 (s, 1H), 3.81 – 3.69 (m, 2H), 3.42 –3.34 (m, 2H), 2.27 – 2.17 (m, 2H), 1.63 – 1.56 (m, 2H); LC–MS (method C, ESI, m/z) t_R = 2.46 min, 343/345/347 $(M+H)^+$.

To a solution of 8-(3-bromo-5-chloropyridin-4-yl)-1,3,8-triazaspiro[4.5]dec-1-en-4-one (2.01 g, 5.85 mmol) in MeOH (60 mL) and DCM (30 mL) was added sodium borohydride (347 mg, 9.17 mmol) at 0 °C and the mixture was stirred at rt for 1 h. The reaction was quenched with 0.5 M NaOH. EtOAc was added and the layers were separated. The aqueous layer was extracted with EtOAc five times. The combined organic layers were dried over $MgSO_4$, concentrated and the resulting white solid was purified by Biotage column chromatography (DCM/EtOH 98:2 to 94:6) to give 8-(3-bromo-5-chloropyridin-4-yl)-1,3,8-triazaspiro[4.5]decan-4-one (1.81 g, 90% yield)

as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.36 (s, 1H), 6.65 (s, 1H), 4.43 (s, 2H), 3.63 – 3.50 (m, 2H), 3.36 – 3.27 (m, 2H), 2.24 – 2.15 (m, 2H), 1.69 – 1.60 (m, 2H); LC–MS (method C, ESI, m/z) t_R = 1.78 min, 345/347/349 $(M+H)^+$.

8-(3-Bromo-5-chloropyridin-4-yl)-1,3,8-triazaspiro[4.5]decan-4-one (180 mg, 0.521 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole[27] **37** (148 mg, 0.521 mmol) and Pd(dppf)Cl_2 CH_2Cl_2 complex (19 mg, 0.026 mmol) were loaded in a microwave vial and acetonitrile (4.5 mL) and 0.5 M aqueous sodium carbonate (1.46 mL, 0.729 mmol) were added. The reaction mixture was stirred at 120 °C for 1 h under microwave irradiation and the solvent was evaporated. The resulting brown solid was purified by Biotage column chromatography (DCM/MeOH, 100:0 to 80:20) and further purified by using a scx2-cartrige (loading with DCM/MeOH, 10:1, elution with DCM/1N NH_3 in MeOH, 9:1) to give 8-(3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1,3,8-triazaspiro[4.5]decan-4-one (165 mg) as a light brown oil which was recrystallized from DCM/Et_2O to give 8-(3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1,3,8-triazaspiro[4.5]decan-4-one **44** (120 mg, 55% yield) as a beige solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.38 (s, 1H), 8.15 (s, 1H), 8.03 (s, 1H), 7.88 (d, *J* = 0.8 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 4.23 (s, 2H), 3.95 (s, 3H), 3.19 – 3.11 (m, 2H), 3.04 – 2.97 (m, 2H), 1.98 – 1.90 (m, 2H), 1.51 – 1.44 (m, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 182.0, 154.9, 151.2, 149.6, 137.5, 136.5, 135.4, 133.7, 130.9, 129.4, 129.2, 126.7, 123.9, 60.3, 57.8, 48.4, 39.0, 32.6; LC–MS (method C, ESI, m/z) t_R = 2.05 min, 423/425 $(M+H)^+$; ESI-HRMS calcd for $C_{22}H_{24}{}^{35}ClN_6O$ $(M+H)^+$ 423.1695, found 423.1691.

8-(3-Bromo-5-chloropyridin-4-yl)-1,3,8-triazaspiro[4.5]decane-2,4-dione (30)

1-Benzylpiperidin-4-one (45.0 g, 228 mmol) was added in portion to a stirring suspension of sodium cyanide (31.5 g, 623 mmol, 97%) and ammonium carbonate (220 g, 1.40 mol) in EtOH (35 mL) and water (35 mL). The reaction mixture was stirred for 2 h at 60ºC. After cooling to rt, the precipitate is filtered and washed with warm water (1.5 L). The solid was dried overnight under vacuum at 50 ºC to give 8-benzyl-1,3,8-triazaspiro[4.5]decane-2,4-dione[44] (53.0 g, 86% yield) as a beige solid which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 1.47 min, 260 $(M+H)^+$.

8-Benzyl-1,3,8-triazaspiro[4.5]decane-2,4-dione (10.0 g, 38.6 mmol) was dissolved in THF (50 mL), MeOH (50 mL), water (25 mL) and conc. HCl (3 mL). Pd/C-5% (54.1% H_2O, 200 g) was added and the reaction mixture was stirred at 50 °C for 18.5 h under hydrogen atmosphere (5 bar). The catalyst was then filtered off and the filtrate was evaporated to dryness to yield in 7.90 g (quant. yield) of 1,3,8-triazaspiro[4.5]decane-2,4-dione hydrochloride[45] as an off-white solid which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 0.39 min, 170 $(M+H)^+$.

In a microwave vial 3-bromo-4,5-dichloropyridine[27] **7** (1.00 g, 4.41 mmol) was dissolved in NMP (10 mL). 1,3,8-triazaspiro[4.5]decane-2,4-dione hydrochloride (1.40 g, 6.61 mmol) and triethylamine (1.80 mL, 13.2 mmol) were added. The reaction mixture was stirred at 220 °C for 1 h under microwave irradiation. The brown mixture was treated with water. The beige precipitate was filtered, washed with water and dried overnight *in vacuo* to afford 8-(3-bromo-5-chloropyridin-4-yl)-1,3,8-triazaspiro[4.5]decane-2,4-dione **30** (1.0 g, 89% pure, 56% corrected yield) as a pale brown solid which was used directly in the next step. LC–MS (method A, ESI, m/z) t_R = 1.88 min, 359/361/363 $(M+H)^+$.

8-(3-Chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1,3,8-triazaspiro[4.5]decane-2,4-dione 2,2,2-trifluoroacetate (45)

8-(3-Bromo-5-chloropyridin-4-yl)-1,3,8-triazaspiro[4.5]decane-2,4-dione **30** (89% pure, 120 mg, 0.296 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole[27] **37** (114 mg, 0.400 mmol) were dissolved in acetonitrile (8 mL). 0.5 M sodium carbonate in water (1.67 mL, 0.830 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (14 mg, 0,020 mmol) were added. The reaction mixture was stirred at 120 °C for 1 h under microwave irradiation. The solvent was evaporated and the crude material was evaporated and purified by prep. HPLC (method A, 20 min gradient elution from 2:98 to 30:70 acetonitrile:water). The product-containing fractions were combined and lyophilized to give 8-(3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1,3,8-triazaspiro[4.5]decane-2,4-dione 2,2,2-trifluoroacetate **45** (36 mg, 20% yield) as a colorless solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 10.66 (s, 1H), 8.59 (s, 2H), 8.28 (s, 1H), 8.21 (d, *J* = 0.8 Hz, 1H), 7.93 (d, *J* = 0.8 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 3.89 (s, 3H), 3.22 – 3.14 (m, 2H), 3.04 – 2.96 (m, 2H), 1.86 (ddd, *J* =

13.9, 10.7, 4.2 Hz, 2H), 1.56 – 1.49 (m, 2H);. LC–MS (method C, ESI, m/z) t_R = 2.29 min, 437/439 $(M+H)^+$; ESI-HRMS calcd for $C_{22}H_{22}{}^{35}ClN_6O_2$ $(M+H)^+$ 437.1487, found 437.1475.

8-(3-Chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-1,3,8-triazaspiro[4.5]decane-2,4-dione (46)

In a microwave vial 8-(3-bromo-5-chloropyridin-4-yl)-1,3,8-triazaspiro[4.5]decane-2,4-dione **30** (89% pure, 100 mg, 0.247 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide **14** (92 mg, 0.30 mmol) were dissolved in 1,4-dioxane (3 mL). 0,5 M sodium carbonate in water (1.00 mL, 0.494 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (18 mg, 0.025 mmol) were added. The reaction mixture was stirred at 120 °C for 1 h. The solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography (DCM/MeOH, gradient) and by prep. HPLC (method A, 15 min gradient elution from 1:99 to 50:50 acetonitrile:water) to afford 8-(3-chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-1,3,8-triazaspiro[4.5]decane-2,4-dione **46** (21 mg, 18% yield) as white crystals. ^{1}H NMR (500 MHz, DMSO-d6) δ 10.67 (s, 1H), 8.49 (s, 1H), 8.45 (s, 1H), 8.18 (s, 1H), 7.35 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.32 (s, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 4.76 (s, 2H), 3.13 – 3.04 (m, 5H), 2.94 – 2.85 (m, 2H), 1.86 – 1.77 (m, 2H), 1.51 – 1.44 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d6) δ 178.2, 156.8, 152.5, 151.0, 149.3, 141.4, 133.2, 130.5, 130.2, 127.4, 126.8, 119.0, 110.0, 60.3, 50.6, 46.9, 33.7, 26.6; LC–MS (method C, ESI, m/z) t_R = 1.84 min, 462/464 $(M+H)^+$; ESI-HRMS calcd for $C_{20}H_{21}{}^{35}ClN_5O_4S$ $(M+H)^+$ 462.0997, found 462.0988.

8-(3-Bromo-5-chloropyridin-4-yl)-2-methyl-1,3,8-triazaspiro[4.5]dec-1-en-4-one (31)

3-Bromo-4,5-dichloropyridine[27] **7** (780 mg, 3.44 mmol) and 2-methyl-1,3,8-triazaspiro[4.5]dec-1-en-4-one dihydrochloride (826 mg, 3.44 mmol) were dissolved in NMP (10 mL) and triethylamine (1.90 mL, 13.8 mmol). The reaction mixture was stirred for 1 h 15 at 220 ºC under microwave irradiation and then poured into water (150 mL). The aqueous layer was extracted with EtOAc (2 x 250 mL). The combined organic layer was dried over Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by flash chromatography (Companion, DCM/MeOH 100:0 2 to 90:10). The product obtained was dissolved in DCM (8 mL) and treated

with diethyl ether (60 mL). The resulting beige precipitate was filtered, washed with diethyl ether (10 mL) and dried at rt under vacuum to give 8-(3-bromo-5-chloropyridin-4-yl)-2-methyl-1,3,8-triazaspiro[4.5]dec-1-en-4-one **31** (238 mg, 19% yield) as a beige solid which was used directly in the next step. LC–MS (method E, ESI, m/z) t_R = 0.78 min, 357/359/361 $(M+H)^+$.

8-(3-Chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-2-methyl-1,3,8-triazaspiro[4.5]dec-1-en-4-one 2,2,2-trifluoroacetate (47)

8-(3-Bromo-5-chloropyridin-4-yl)-2-methyl-1,3,8-triazaspiro[4.5]dec-1-en-4-one **31** (119 mg, 0.330 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide **14** (206 mg, 0.670 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (12 mg, 0.020 mmol) were solubilised in DMF (10 mL) and 0.5 M sodium carbonate solution (2.00 mL, 1.00 mmol) were added. The reaction mixture was stirred for 1 h at 120 ºC under microwave irradiation and then diluted with acetonitrile (5 mL), filtered and and the filtrate was concentrated. The crude product was purified by prep. HPLC (method A, gradient elution from 2:98 to 20:80 acetonitrile/water in 20 min) to give 8-(3-chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-2-methyl-1,3,8-triazaspiro[4.5]dec-1-en-4-one 2,2,2-trifluoroacetate **47** (56 mg, 95% pure, 28% corrected yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.54 (s, 1H), 8.24 (s, 1H), 7.44 (s, 1H), 7.39 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 4.73 (s, 2H), 3.22 – 3.15 (m, 2H), 3.10 (s, 3H), 3.07 – 2.97 (m, 2H), 2.40 (s, 3H), 1.84 – 1.65 (m, 4H); ^{13}C NMR (126 MHz, DMSO-d6) δ 152.7, 149.4, 148.0, 141.2, 133.0, 130.0, 129.7, 126.9, 126.3, 118.6, 109.5, 99.5, 64.7, 50.2, 46.0, 31.0, 26.1, 15.0 (1 Cq not observed); LC–MS (method C, ESI, m/z) t_R = 1.76 min, 460/462 $(M+H)^+$; ESI-HRMS calcd for $C_{21}H_{23}{}^{35}ClN_5O_3S$ $(M+H)^+$ 460.1205, found 460.1195.

9-(3-Bromo-5-chloropyridin-4-yl)-1-(4-methoxybenzyl)-1,4,9-triazaspiro[5.5]undecane-2,5-dione (32)

Aminomethyl polystyrene resin (2.00 g, 2.86 mmol) was washed with DMF (20 mL x 2) and suspended in a mixture of DMF (20 mL) and ethyl formate (30 mL). The suspension was heated to 70 °C without stirring for 15 h. After cooling to RT, the resin was filtered and washed with DMF (2 x 25 mL), DCM (4 x 25 mL), MeOH (4 x 25 mL) and DCM (4 x 25 mL). The resin was

dried under reduced pressure to give the N-formylated aminomethyl resin. The resin was suspended in DCM (50 mL) and successively treated with triethylamine (2.38 mL, 17.2 mmol), carbon tetrachloride (1.67 mL, 17.2 mmol) and triphenylphosphine (4.50 g, 17.2 mmol). The mixture was heated to 50 °C without stirring for 2 h. After cooling to rt, the resin was filtered and washed with DCM (4 x 50 mL), MeOH (2 x 50 mL), and DCM (4 x 50 mL). The resin was dried under reduced pressure to give the yellow methylene-isonitrile resin (2.70 g, 2.86 mmol).

The methylene-isonitrile resin (2.70 g, 2.86 mmol) was washed with THF/MeOH (1:1, 40 mL) and the resin was suspended in THF/MeOH (1:1, 40mL). 1-Boc-4-piperidone (2.85 g, 14.3 mmol), 4-methoxybenzylamine (1.96 g, 14.3 mmol) and *N*-(*tert*-butoxycarbonyl)-glycine (2.51 g, 14.3 mmol) were added. The mixture was heated at 70 °C, without stirring, for 2 days. After cooling to rt, the resin was filtered and washed with MeOH/THF (1:1, 3 x 50 mL) and DCM (4 x 50 mL) The resin was dried under reduced pressure to give polymer bound 4-[(2-*tert*-butoxycarbonylamino-acetyl)-(4-methoxy-benzyl)-amino]-4-carbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester (4.0g, 100%) as a yellow resin.

Polymer bound 4-[(2-*tert*-butoxycarbonylamino-acetyl)-(4-methoxy-benzyl)-amino]-4-carbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester (3.50 g, 2.50 mmol) was suspended in DCM. At 0 °C trifluoroacetic acid (7 mL) was added, the mixture was allowed to warm up to RT and was shaked for 4 h. After filtration, the resin was washed with DCM (3 x 40 mL), toluene (2 x 40 mL), and 1.25 M acetic acid in toluene (50 mL). The resin was suspended in 1.25 M acetic acid in toluene (50 mL) and heated at reflux for 2 days.

The resin was filtered and washed with DCM/ MeOH (1:1, 2 x 40 mL). The filtrates were collected and evaporated to dryness. The residue was dissolved in MeOH and treated slowly with diethyl ether. The resulting precipitate was filtered under reduced pressure, washed with diethyl ether, and dried under reduced pressure to give 1-(4-methoxybenzyl)-1,4,9-triazaspiro[5.5]undecane-2,5-dione acetate (560 mg, 54% yield over 3 steps) as an off-white solid which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 1.77 min, 304 $(M+H)^+$.

3-Bromo-4,5-dichloropyridine[27] **7** (250 mg, 1.10 mmol) and 1-(4-methoxybenzyl)-1,4,9-triazaspiro[5.5]undecane-2,5-dione acetate (400 mg, 1.10 mmol) were dissolved in NMP (8 mL) and triethylamine (0.46 mL, 3.3 mmol) and stirred for 1 h at 220 °C under microwave

irradiation. The mixture was poured into water (80 mL) and extracted with DCM (2 x 100 mL). The organic layer was dried and evaporated to dryness. The oily residue (containing NMP) was purified by flash chromatography (DCM/MeOH, gradient). The product was dissolved in DCM (3 mL) and treated with diethylether (35 mL). The resulting precipitate was filtered and dried under reduced pressure to give 9-(3-bromo-5-chloropyridin-4-yl)-1-(4-methoxybenzyl)-1,4,9-triazaspiro[5.5]undecane-2,5-dione **32** (180 mg, 33% yield) as an off-white solid which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 2.45 min, 493/495/497 $(M+H)^+$.

9-(3-Chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1,4,9-triazaspiro[5.5]undecane-2,5-dione 2,2,2-trifluoroacetate (48)

9-(3-Bromo-5-chloropyridin-4-yl)-1-(4-methoxybenzyl)-1,4,9-triazaspiro[5.5]undecane-2,5-dione **32** (90 mg, 0.18 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole[27] **37** (78 mg, 0.27 mmol) were dissolved in acetonitrile (4 mL). 0.5 M sodium carbonate in water (0.73 mL, 0.36 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (7 mg, 0.01 mmol) were added. The microwave vial was closed, degassed and flushed with nitrogen and stirred under microwave irradiation for 1 h at 120 °C. The mixture was filtered, evaporated and the crude material was purified by flash chromatography (DCM/MeOH, gradient). The product-containing fractions were combined and evaporated to give 9-(3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1-(4-methoxybenzyl)-1,4,9-triazaspiro[5.5]undecane-2,5-dione (61 mg, 59% yield) as a white solid which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 2.18 min, 571/573 $(M+H)^+$.

9-{3-Chloro-5-[4-(1-methyl-1*H*-pyrazol-4-yl)-phenyl]-pyridin-4-yl}-1-(4-methoxy-benzyl)-1,4,9-triaza-spiro[5.5]undecane-2,5-dione (61 mg, 0.11 mmol) was dissolved in trifluoroacetic acid (4 mL) and stirred at rt overnight and then at 70 ºC for another 15 h. The reaction mixture was evaporated and purified by preparative HPLC (method A, 20 min gradient elution from 2:98 to 25:75 acetonitrile:water). The fractions containing desired product were combined and lyophilized to give 9-(3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1,4,9-triazaspiro[5.5]undecane-2,5-dione 2,2,2-trifluoroacetate **48** (32 mg, 52% yield) as white flakes. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.55 (s, 1H), 8.38 (s, 1H), 8.24 (s, 1H), 8.20 (s, 1H), 7.97 – 7.94 (m, 1H), 7.93 (d, *J* = 0.8 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.39 - 7.31 (m, 2H), 3.88 (s, 3H),

3.71 (d, *J* = 2.3 Hz, 2H), 3.20 – 3.04 (m, 4H), 2.05 – 1.93 (m, 2H), 1.67 – 1.56 (m, 2H); LC–MS (method C, ESI, m/z) t_R = 2.07 min, 451/453 $(M+H)^+$; ESI-HRMS calcd for $C_{23}H_{24}{}^{35}ClN_6O_2$ $(M+H)^+$ 451.1644, found 451.1632.

Ethyl 1-(3-bromo-5-chloropyridin-4-yl)piperidine-4-carboxylate (33)

3-Bromo-4,5-dichloropyridine[27] **7** (994 mg, 4.38 mmol) and 1-*tert*-butyl 4-ethyl piperidine-1,4-dicarboxylate (1.24 g, 4,.82 mmol) were solubilised in NMP (10 mL) and triethylamine (1.52 mL, 11.0 mmol) was added. The reaction mixture was stirred for 3 h at 220 °C under microwave irradiation. The solvent was evaporated and the crude material was dissolved in EtOAc, washed four times with water then with brine, dried over sodium sulfate, filtered and evaporated. The red brown oily crude product was purified with flash chromatography (Companion, DCM/MeOH 100:0 to 90:10) to afford ethyl 1-(3-bromo-5-chloropyridin-4-yl)piperidine-4-carboxylate **33** (740 mg, 49% yield) as a colourless oil which was used without further purification. LC–MS (method A, ESI, m/z) t_R = 2.64 min, 347/349/351 $(M+H)^+$.

8-(3-Chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-4-methyl-2,3,8-triazaspiro[4.5]dec-3-en-1-one (49)

To a solution of ethyl 1-(3-bromo-5-chloropyridin-4-yl)piperidine-4-carboxylate **33** (740 mg, 2.13 mmol) in THF (20 mL) was added potassium bis(trimethylsilyl)amide solution 0.5 M in toluene (6.39 mL, 3.19 mmol) dropwise at rt. The reaction mixture was allowed to stir at rt for 30 min, then acetyl chloride (0.200 mL, 2.78 mmol) was added dropwise and the reaction mixture was stirred for another 1 h. The dark yellow solution turned to red. The mixture was quenched with MeOH, diluted with EtOAc and washed with saturated NH_4Cl solution and with brine, dried over sodium sulfate and concentrated. The crude product was purified by flash chromatography (Companion, EtOAc/n-heptane 100:0 to 65:35) to give ethyl 4-acetyl-1-(3-bromo-5-chloropyridin-4-yl)piperidine-4-carboxylate (212 mg, 50% pure, 13 % corrected yield). The crude product was used for the next step without further purification. LC–MS (method A, ESI, m/z) t_R = 2.50 min, 389/391/393 $(M+H)^+$.

Ethyl 4-acetyl-1-(3-bromo-5-chloropyridin-4-yl)piperidine-4-carboxylate (50% pure, 213 mg, 0.273 mmol) was dissolved in 1-butanol (3 mL) and hydrazinium hydroxide (100 μL, 2.06

mmol) was added. The reaction mixture was stirred for 24 h at 115 °C. The solvent was evaporated under reduced pressure, the residue was dissolved in EtOAc and washed with water and brine, dried with sodium sulfate, filtered and purified by flash chromatography (Companion, EtOAc/n-heptane 20:80 to 60:40) to give 8-(3-bromo-5-chloropyridin-4-yl)-4-methyl-2,3,8-triazaspiro[4.5]dec-3-en-1-one (99% pure, 61 mg, 62% corrected yield) as a colorless oil which was used directly in the next step. LC–MS (method A, ESI, m/z) t_R = 1.91 min, 357/359/361 $(M+H)^+$.

To 8-(3-bromo-5-chloro-pyridin-4-yl)-4-methyl-2,3,8-triaza-spiro[4.5]dec-3-en-1-one (99% pure, 61 mg, 0.17 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide **14** (58 mg, 0.19 mmol), potassium carbonate (47 mg, 0.34 mmol) and Pd(dppf)Cl_2·CH_2Cl_2 (7 mg, 0.008 mmol) were added acetonitrile (5 mL) and water (2 mL). The reaction mixture was stirred for 1 h at 120 °C under microwave irradiation. The solvent was evaporated; the residue was dissolved in EtOAc and washed twice with water and brine. The organic layer was dried over sodium sulfate, filtered and evaporated. The crude product was purified by preparative chromatography (method A, 15 min gradient elution from 1:99 to 50:50 acetonitrile:water). The product was dissolved in EtOAc and washed with saturated sodium carbonate solution. The organic layer was dried with sodium sulfate, filtered and concentrated to afford 8-(3-chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-4-methyl-2,3,8-triazaspiro[4.5]dec-3-en-1-one **49** (17 mg, 22% yield) as a colorless solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.48 (s, 1H), 8.23 (s, 1H), 7.43 – 7.36 (m, 2H), 7.08 – 7.04 (m, 1H), 4.71 (s, 2H), 3.41 – 3.28 (m, 2H), 3.10 (s, 3H), 2.87 – 2.80 (m, 2H), 1.89 (s, 3H), 1.74 – 1.64 (m, 2H), 1.50 – 1.39 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d6) δ 179.5, 162.2, 152.6, 150.5, 148.8, 141.1, 133.7, 130.0, 129.7, 127.7, 126.6, 118.5, 109.5, 50.2, 46.9, 44.5, 28.3, 26.1, 14.4; LC–MS (method C, ESI, m/z) t_R = 2.22 min, 460/462 $(M+H)^+$; ESI-HRMS calcd for $C_{21}H_{23}{}^{35}ClN_5O_3S$ $(M+H)^+$ 460.1205, found 460.1191.

8-(3-Chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-4-(trifluoromethyl)-2,3,8-triazaspiro[4.5]dec-3-en-1-one 2,2,2-trifluoroacetate (50)

Ethyl 1-(3-bromo-5-chloropyridin-4-yl)piperidine-4-carboxylate **33** (1.90 g, 5.47 mmol) was dissolved in THF (35 mL). The reaction mixture was cooled to 0 °C and lithium

bis(trimethylsilyl)amide (6.67 mL, 7.11 mmol) was added dropwise at 0 °C over 30 min. After 20 min, trifluoroacetic anhydride (1.14 mL, 8.20 mmol) was added. The reaction mixture was stirred for 2 h at 0 °C and additional 15 h at rt. The reaction mixture was diluted with MeOH (15 mL), filtered and the solvent was evaporated to dryness. The crude residue was dissolved in EtOAc (150 mL) and washed with saturated sodium hydrogen carbonate solution (100 mL). The organic layer was washed with brine (50 mL), dried over sodium sulfate, filtered and evaporated to dryness. The residue was purified by flash chromatography (heptane/EtOAc, gradient) to give ethyl 1-(3-bromo-5-chloropyridin-4-yl)piperidine-4-carboxylate (640 mg, 34% yield) and ethyl 1-(3-bromo-5-chloropyridin-4-yl)-4-(2,2,2-trifluoroacetyl)piperidine-4-carboxylate (350 mg, 14% yield) as colorless oil which was used directly in the next step. LC/MS (Method B): Rt 2.96 min, (M+H) 443/445/447.

In a microwave vial ethyl 1-(3-bromo-5-chloropyridin-4-yl)-4-(2,2,2-trifluoroacetyl)piperidine-4-carboxylate (209 mg, 0.47 mmol) was dissolved in 1-butanol (3 mL), hydrazinium hydroxide (2.00 mL, 41.1 mmol) was added and the reaction mixture was stirred at 100 °C for 1 h under microwave irradiation. The solvent was evaporated and the crude residue was purified by flash chromatography (heptane/EtOAc) to give 8-(3-bromo-5-chloropyridin-4-yl)-4-(trifluoromethyl)-2,3,8-triazaspiro[4.5]dec-3-en-1-one (180 mg, 92% yield) as a white solid which was used directly in the next step. LC/MS (Method B): Rt 2.70 min, (M+H) 411/413/415.

Into a microwave vial, 8-(3-bromo-5-chloropyridin-4-yl)-4-(trifluoromethyl)-2,3,8-triazaspiro[4.5]dec-3-en-1-one (60 mg, 0.15 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide **14** (68 mg, 0.22 mmol) Pd(dppf)Cl_2·CH_2Cl_2 (5 mg, 0.01 mmol) were loaded and then DMF (4 mL) and 0.5 M sodium carbonate solution (0.58 mL, 0.29 mmol, 2.0 eq.) were added. The reaction mixture was stirred for 1 h at 100 ºC and for 1 h at 120 ºC under microwave irradiation. After addition of acetonitrile (5 mL), the reaction mixture was filtered and evaporated to dryness. The crude residue was purified by prep. HPLC (method A, 20 min gradient elution from 1:99 to 35:65 acetonitrile:water) to afford 8-(3-chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-4-(trifluoromethyl)-2,3,8-triazaspiro[4.5]dec-3-en-1-one 2,2,2-trifluoroacetate **50** (27 mg, 29% yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 12.23 (s, 1H), 8.58 (s, 1H), 8.29 (s, 1H), 7.43 – 7.38 (m, 2H), 7.07 (d, *J* = 8.1 Hz, 1H), 4.69 (s, 2H), 3.41 (t, *J* = 11.8

Hz, 2H), 3.10 (s, 3H), 2.96 – 2.88 (m, 2H), 1.97 – 1.88 (m, 2H), 1.78 – 1.71 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d6) δ 178.0, 153.8, 148.7, 147.1, 141.3, 133.4, 129.8, 129.5, 127.4, 126.4, 118.5, 109.5, 50.2, 46.6, 43.9, 28.0, 26.1 (2 Cq not observed); LC–MS (method C, ESI, m/z) t_R = 2.75 min, 514/516 $(M+H)^+$; ESI-HRMS calcd for $C_{21}H_{20}{}^{35}ClF_3N_5O_3S$ $(M+H)^+$ 514.0922, found 514.0910.

1-(3-Bromo-5-chloropyridin-4-yl)-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)piperidine-4-carbonitrile (34)

4-Cyanopiperidine (98% pure, 5.00 g, 0.044 mol) was dissolved in 1,4-dioxane (50 mL) and di-*tert*-butyl dicarbonate (10.4 mL, 0.0490 mol) was added dropwise to the reaction mixture at rt. The mixture was stirred overnight at same temperature. The reaction mixture was diluted with DCM, washed with $NaHCO_3$ solution and NaCl solution, dried over sodium sulfate, filtered and evaporated to dryness to give tert-butyl 4-cyanopiperidine-1-carboxylate[46] (9.10 g, 97% yield) as a light yellow oil, which was used without further purification. LC–MS (method A, ESI, m/z) t_R = 2.00 min, 233 $(M+Na)^+$.

tert-Butyl 4-cyanopiperidine-1-carboxylate (5.10 g, 24.3 mmol) was dissolved in THF (100 mL). At -10 °C lithium bis(trimethylsilyl)amide (1.06 M solution in THF/ethylbenzene, 34.3 mL, 36.4 mmol) was added dropwise. To this solution a solution of (2-bromo-ethoxy)-tert-butyl-dimethyl-silane (7.89 mL, 36.4 mmol) in THF (50 mL) was added dropwise at -10 °C. The reaction mixture was allowed to warm to rt and was stirred for additional 4 h. The reaction mixture was treated with water and EtOAc and the layers were separated. The organic layer was dried over sodium sulfate, filtered and the solvent was evaporated to dryness. The yellow oil was purified by flash chromatography (heptane/DCM, gradient) to obtain *tert*-butyl 4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-cyanopiperidine-1-carboxylate (3.35 g, 92% pure, 34 % corrected yield) as a colorless oil which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 3.83 min, 391 $(M+Na)^+$.

3-Bromo-4,5-dichloropyridine[27] **7** (653 mg, 2.88 mmol) and triethylamine (1.20 mL, 8.64 mmol) was added to a solution of *tert*-butyl 4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-cyanopiperidine-1-carboxylate (92% pure, 2.31 g, 5.76 mmol) in NMP (8 mL). The reaction was stirred for 2 h at 220ºC under microwave irradiation. The dark brown reaction mixture was treated with 100 mL

of water and the aqueous layer was extracted twice with EtOAc. The organic layer was dried, filtered and evaporated to dryness. The dark brown oily residue was purified by flash-chromatography (Companion, heptane/DCM gradient) to afford 1-(3-bromo-5-chloropyridin-4-yl)-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)piperidine-4-carbonitrile **34** (210 mg, 68% pure, 11% corrected yield) as pale brown solid which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 3.92 min, 458/460/462 $(M+H)^+$.

1-(3-Chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-4-(2-(dimethylamino)ethyl)piperidine-4-carbonitrile 2,2,2-trifluoroacetate (51)

1-(3-Bromo-5-chloropyridin-4-yl)-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)piperidine-4-carbonitrile **34** (68% pure, 210 mg, 0.311 mmol) was dissolved in THF (5 mL) and tetrabutylammonium fluoride (244 mg, 0.934 mmol) was added. The reaction mixture was stirred overnight at rt. The solvent was evaporated and the oily residue was diluted with EtOAc and water. The organic layer was washed with water, dried and evaporated to dryness. The brown residue was purified by flash-chromatography (Companion, DCM/MeOH gradient) to give 1-(3-bromo-5-chloropyridin-4-yl)-4-(2-hydroxyethyl)piperidine-4-carbonitrile (115 mg, quant. yield) as a yellow solid which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 2.20 min, 344/346/348 $(M+H)^+$.

1-(3-Bromo-5-chloropyridin-4-yl)-4-(2-hydroxyethyl)piperidine-4-carbonitrile (115 mg, 0.334 mmol) was dissolved in DCM (5 mL). Triethylamine (167 µL, 1.34 mmol) and Methanesulfonyl chloride (38 µL, 0.50 mmol) were added. The reaction solution was stirred overnight at rt and the solvent was evaporated. The residue was diluted with DCM and water and the aqueous layer was extracted with DCM. The organic layer was dried, filtered and evaporated to dryness to yield in 2-(1-(3-bromo-5-chloropyridin-4-yl)-4-cyanopiperidin-4-yl)ethyl methanesulfonate (132 mg, 95% pure, 89% corrected yield) as a pale brown solid which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 2.53 min, 422/424/426 $(M+H)^+$.

2-(1-(3-Bromo-5-chloropyridin-4-yl)-4-cyanopiperidin-4-yl)ethyl methanesulfonate (95% pure, 121 mg, 0.272 mmol) was dissolved in 2 M dimethylamine in THF (10 mL, 20 mmol). The reaction mixture was stirred for 5 day at rt. The solvent was evaporated and the pale brown oily residue was purified by flash-chromatography (Companion, DCM/MeOH gradient) to afford 1-

(3-bromo-5-chloropyridin-4-yl)-4-(2-(dimethylamino)ethyl)piperidine-4-carbonitrile (64 mg, 63% yield) as a colorless oil which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 1.93 min, 371/373/375 $(M+H)^+$.

In a microwave vial 1-(3-bromo-5-chloropyridin-4-yl)-4-(2-(dimethylamino)ethyl)piperidine-4-carbonitrile (32 mg, 0.086 mmol) was suspended in acetonitrile (2 mL). 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide **14** (40 mg, 0.13 mmol), 0.5 M sodium carbonate in water (342 µL, 0.171 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (6 mg, 0,009 mmol) were added. The reaction mixture was stirred for 1 h at 120 ºC under microwave irradiation. After addition of EtOAc, the mixture was filtered and evaporated. The crude brown residue was purified by flash chromatography (Companion, DCM/MeOH gradient) and by prep. HPLC (method A, 18 min gradient elution from 2:98 to 25:75 acetonitrile:water) to afford 1-(3-chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-4-(2-(dimethylamino)ethyl)piperidine-4-carbonitrile 2,2,2-trifluoroacetate **51** (10 mg, 20% yield) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.33 (s, 1H), 7.28 – 7.24 (m, 1H), 7.20 (s, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 4.48 (s, 2H), 3.23 – 3.13 (m, 7H), 3.01 (t, *J* = 12.3 Hz, 2H), 2.86 (s, 6H), 2.13 – 2.03 (m, 2H), 1.91 – 1.84 (m, 2H), 1.68 – 1.59 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.4, 130.4, 126.2, 120.7, 118.8, 109.7, 53.4, 50.6, 48.1, 43.3, 35.6, 34.6, 33.7, 26.6 (4 Cq and 2 pyridine CH missing); LC–MS (method C, ESI, m/z) t_R = 1.60 min, 474/476 $(M+H)^+$; ESI-HRMS calcd for $C_{23}H_{29}{}^{35}ClN_5O_2S$ $(M+H)^+$ 474.1725, found 474.1710.

8-(3-Bromo-5-chloropyridin-4-yl)-1,8-diazaspiro[4.5]decane (35)

3-Bromo-4,5-dichloropyridine[27] **7** (100 mg, 0.441 mmol) and 8-boc-1,8-diazaspiro[4.5]decane oxalate (146 mg, 0.607 mmol) were loaded in a microwave vial. Triethylamine (0.226 mL, 1.76 mmol) and 1-methoxy-2-propanol (1 mL) were added and the light brown solution was degassed. The reaction mixture was heated under microwave irradiation at 220 °C for 2 h. The solvent was evaporated and the crude material was purified by Biotage column chromatography (eluting with 0 to 15 % MeOH/aq NH (9:1) in DCM) to give 8-(3-bromo-5-chloropyridin-4-yl)-1,8-diazaspiro[4.5]decane **35** (100 mg, 69% yield) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.31 (s, 1H), 4.48 (br s, 1H), 3.47 – 3.40 (m, 2H), 3.28 – 3.21 (m, 2H), 3.13 (t, *J* =

7.0 Hz, 2H), 1.94 – 1.72 (m, 8H); LC–MS (method C, ESI, m/z) t_R = 1.82 min, 330/332/334 $(M+H)^+$.

5-(5-Chloro-4-(1-methyl-1,8-diazaspiro[4.5]decan-8-yl)pyridin-3-yl)-1-methyl-1,3-dihydrobenzo[c]isothiazole 2,2-dioxide (52)

To a solution of 8-(3-bromo-5-chloropyridin-4-yl)-1,8-diazaspiro[4.5]decane **35** (40 mg, 0.12 mmol) in MeOH (1.2 mL) was added aqueous formaldehyde solution (37% in water, 0.019 mL, 0.25 mmol), followed by glacial acetic acid (7.6 µL, 0.13 mmol) and sodium triacetoxyborohydride (38.5 mg, 0.181 mmol) and the reaction mixture was stirred at rt for 2 h. To the mixture was added 0.5M NaOH solution and EtOAc. The layers were separated, the aqueous layer was extracted with EtOAc tree times and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuum. The crude product was purified by prep. TLC (DCM/10% NH_4OH (25% in water) in MeOH, 25:1, 2 runs) to give 8-(3-bromo-5-chloropyridin-4-yl)-1-methyl-1,8-diazaspiro[4.5]decane (22 mg, 53% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.33 (s, 1H), 3.37 (td, *J* = 12.5, 2.3 Hz, 2H), 3.28 – 3.22 (m, 2H), 2.85 – 2.79 (m, 2H), 2.36 (s, 3H), 1.93 (td, *J* = 12.5, 4.7 Hz, 2H), 1.87 – 1.79 (m, 4H), 1.38 – 1.30 (m, 2H); LC–MS (method C, ESI, m/z) t_R = 1.78 min, 344/346/348 $(M+H)^+$.

8-(3-Bromo-5-chloropyridin-4-yl)-1-methyl-1,8-diazaspiro[4.5]decane (23 mg, 0.067 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide **14** (21 mg, 0.067 mmol) and $Pd(PPh_3)_4$ (3.9 mg, 3.3 µmol) were loaded in a microwave vial. Acetonitrile (0.65 mL) and 0.5M aqueous sodium carbonate (0.187 mL, 0.093 mmol) were added. The mixture was stirred at 120 °C for 1 h under microwave irradiation, before the mixture was concentrated. The resulting brown solid was purified by Biotage column chromatography (CH_2Cl_2/10% NH_4OH (25% aq.) in MeOH, 100:0 to 90:10) to give 5-(5-chloro-4-(1-methyl-1,8-diazaspiro[4.5]decan-8-yl)pyridin-3-yl)-1-methyl-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide **52** (20 mg, 67% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.14 (s, 1H), 7.23 – 7.17 (m, 2H), 6.80 (d, *J* = 8.1 Hz, 1H), 4.40 (s, 2H), 3.18 (s, 3H), 3.12 – 3.05 (m, 2H), 2.83 (t, *J* = 7.0 Hz, 2H), 2.75 – 2.65 (m, 2H), 2.33 (s, 3H), 1.87 – 1.68 (m, 6H), 1.30 – 1.22 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 150.5, 149.7, 141.4, 133.1, 131.2, 130.5, 128.1, 126.0, 117.8, 109.0, 62.0, 53.0, 50.8, 49.2, 33.6, 32.9, 31.2, 26.5, 20.6; LC–MS (method C, ESI,

m/z) t_R = 1.46 min, 447/449 $(M+H)^+$; ESI-HRMS calcd for $C_{22}H_{28}{}^{35}ClN_4O_2S$ $(M+H)^+$ 447.1616, found 447.1622.

8-(3-Chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1-(2-methoxyethyl)-1,8-diazaspiro[4.5]decane (53)

8-(3-Bromo-5-chloropyridin-4-yl)-1-(2-methoxyethyl)-1,8-diazaspiro[4.5]decane **36** (40 mg, 0.10 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole[27] **37** (35 mg, 0.12 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (4.2 mg, 5.1 µmol) were loaded in a microwave vial and then acetonitrile (1.8 mL) and sodium carbonate in water (288 µL, 0.144 mmol) were added. The reaction mixture was stirred at 120 ºC for 60 min under microwave irradiation. The solvents were evaporated and the crude material was purified by Biotage column chromatography (eluting with 2 to 6 % MeOH/aq NH_3 (10:1) in DCM) and by SCX-2 column chromatography (loading with DCM:MeOH, elution with 1N NH_3 in MeOH) followed by a purification on prep. HPLC (method B). The fractions were concentrated under vacuum and then the product was solubilized in a mixture of DCM and MeOH and filtered on a NH_2 column to afford 8-(3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1-(2-methoxyethyl)-1,8-diazaspiro[4.5]decane **53** (10 mg, 21% yield) as a yellow oil. ^{1}H NMR (500 MHz, acetone-d6) δ 8.39 (s, 1H), 8.19 (s, 1H), 8.06 – 8.04 (s, 1H), 7.87 (d, *J* = 0.9 Hz, 1H), 7.72 – 7.68 (m, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 3.93 (s, 3H), 3.36 (t, *J* = 6.5 Hz, 2H), 3.26 (s, 3H), 3.11 – 3.05 (m, 2H), 2.85 – 2.77 (m, 2H), 2.74 (t, *J* = 7.0 Hz, 2H), 2.60 (t, *J* = 6.5 Hz, 2H), 1.71 – 1.55 (m, 6H), 1.14 – 1.07 (m, 2H); ^{13}C NMR (126 MHz, acetone-d6) δ 152.8, 150.5, 149.1, 136.1, 135.3, 134.4, 132.7, 129.8, 127.8, 127.4, 125.1, 122.1, 72.7, 61.2, 57.8, 51.0, 49.4, 47.2, 38.3, 33.2, 31.9, 20.8; LC–MS (method C, ESI, m/z) t_R = 2.03 min, 466/468 $(M+H)^+$; ESI-HRMS calcd for $C_{26}H_{33}{}^{35}ClN_5O$ $(M+H)^+$ 466.2368, found 466.2375.

5-(5-Chloro-4-(1-(3-methoxypropyl)-1,8-diazaspiro[4.5]decan-8-yl)pyridin-3-yl)-1-methyl-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide (55)

To a solution of 8-(3-bromo-5-chloropyridin-4-yl)-1,8-diazaspiro[4.5]decane **35** (50 mg, 0.15 mmol) in acetonitrile (1.1 mL) was added potassium iodide (25 mg, 0.15 mmol), potassium carbonate (63 mg, 0.45 mmol) and 1-bromo-3-methoxypropane (28 mg, 0.18 mmol) and the

mixture was stirred at 80 °C for 3 h. The reaction mixture was diluted with water and EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuum. The resulting brown oil was purified by Biotage column chromatography (DCM/EtOH, 100:0 to 90:10) to give 8-(3-bromo-5-chloropyridin-4-yl)-1-(3-methoxypropyl)-1,8-diazaspiro[4.5]decane (37 mg, 60% yield) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.31 (s, 1H), 3.44 (t, *J* = 6.2 Hz, 2H), 3.41 – 3.33 (m, 2H), 3.32 (s, 3H), 3.25 – 3.18 (m, 2H), 2.88 – 2.82 (m, 2H), 2.61 (t, *J* = 7.3 Hz, 2H), 1.95 – 1.74 (m, 8H), 1.36 (br d, *J* = 12.3 Hz, 2H); LC–MS (method C, ESI, m/z) t_R = 2.03 min, 402/404/406 $(M+H)^+$.

8-(3-Bromo-5-chloropyridin-4-yl)-1-(3-methoxypropyl)-1,8-diazaspiro[4.5]decane (37 mg, 0.091 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide **14** (28 mg, 0.091 mmol) and Pd(dppf)Cl_2·CH_2Cl_2 (3.3 mg, 4.6 µmol) were loaded in a microwave vial. Acetonitrile (0.8 mL) and 0.5 M aqueous sodium carbonate (0.256 mL, 0.128 mmol) were added and the mixture was stirred at 120 °C for 1 h under microwave irradiation. The volatiles were evaporated and the resulting brown solid was purified by Biotage column chromatography (eluting with 0 to 10 % MeOH/aq NH_3 (9:1) in DCM) to give 5-(5-chloro-4-(1-(3-methoxypropyl)-1,8-diazaspiro[4.5]decan-8-yl)pyridin-3-yl)-1-methyl-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide **55** (20 mg, 43% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.13 (s, 1H), 7.27 – 7.24 (m, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 4.42 (s, 2H), 3.43 (t, *J* = 6.0 Hz, 2H), 3.33 (s, 3H), 3.19 (s, 3H), 3.10 – 3.03 (m, 2H), 2.81 – 2.72 (m, 4H), 2.50 (t, *J* = 7.3 Hz, 2H), 1.80 – 1.62 (m, 8H), 1.21 – 1.13 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9, 150.4, 149.9, 141.4, 133.0, 131.2, 130.5, 127.9, 126.0, 117.7, 109.0, 70.9, 58.6, 50.7, 50.5, 49.5, 45.1, 33.3, 31.7, 29.3, 26.9, 26.5, 20.6; LC–MS (method C, ESI, m/z) t_R = 1.83 min, 505/507 $(M+H)^+$; ESI-HRMS calcd for $C_{25}H_{34}{}^{35}ClN_4O_3S$ $(M+H)^+$ 505.2035, found 505.2032.

5-(5-Chloro-4-(1-(3-(methylsulfonyl)propyl)-1,8-diazaspiro[4.5]decan-8-yl)pyridin-3-yl)-1-methyl-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide (56)

To a solution of 8-(3-bromo-5-chloropyridin-4-yl)-1,8-diazaspiro[4.5]decane **35** (50 mg, 0.15 mmol) in acetonitrile (1.1 mL) was added potassium iodide (25 mg, 0.15 mmol), potassium

carbonate (63 mg, 0.45 mmol) and 1-bromo-3-methansulfonylpropane (37 mg, 0.18 mmol) and the reaction mixture was heated at 80 °C overnight. The mixture was diluted with water and EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuum. The resulting brown oil was purified by Biotage column chromatography (eluting with 0 to 8 % MeOH/aq NH_3 (9:1) in DCM) to give 8-(3-bromo-5-chloropyridin-4-yl)-1-(3-(methylsulfonyl)propyl)-1,8-diazaspiro[4.5]decane (39 mg, 57% yield) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.31 (s, 1H), 3.35 (td, *J* = 12.5, 2.3 Hz, 2H), 3.24 – 3.17 (m, 2H), 3.15 – 3.09 (m, 2H), 2.89 (s, 3H), 2.81 – 2.74 (m, 2H), 2.65 (t, *J* = 6.4 Hz, 2H), 2.03 – 1.95 (m, 2H), 1.85 – 1.77 (m, 6H), 1.34 – 1.27 (m, 2H); LC–MS (method C, ESI, m/z) t_R = 1.77 min, 450/452/454 $(M+H)^+$.

8-(3-Bromo-5-chloropyridin-4-yl)-1-(3-(methylsulfonyl)propyl)-1,8-diazaspiro[4.5]decane (39 mg, 0.087 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide **14** (27 mg, 0.087 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (3.2 mg, 4.3 µmol) were loaded in a microwave vial. Acetonitrile (0.75 mL) and 0.5 M aqueous sodium carbonate (0.242 mL, 0.121 mmol) were added and the mixture was stirred at 120 °C for 1 h under microwave irradiation. The volatiles were evaporated and the resulting brown solid was purified by Biotage column chromatography (DCM/EtOH, 100:0 to 95:5) and further purified by scx_2-cartridge (loading with DCM/MeOH 9/1, elution with DCM/1N NH_3 in MeOH 9/1) to give 5-(5-chloro-4-(1-(3-(methylsulfonyl)propyl)-1,8-diazaspiro[4.5]decan-8-yl)pyridin-3-yl)-1-methyl-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide **56** (37 mg, 77%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.13 (s, 1H), 7.24 – 7.19 (m, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 4.41 (s, 2H), 3.18 (s, 3H), 3.09 (dd, *J* = 9.0, 6.4 Hz, 2H), 3.03 (dt, *J* = 12.4, 2.9 Hz, 2H), 2.89 (s, 3H), 2.82 – 2.66 (m, 4H), 2.56 (t, *J* = 6.5 Hz, 2H), 2.00 – 1.92 (m, 2H), 1.79 – 1.69 (m, 2H), 1.66 –1.60 (m, 2H), 1.58 – 1.49 (s, 2H), 1.16 – 1.09 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9, 150.3, 149.9, 141.4, 131.2, 130.4, 128.1, 126.2, 117.7, 109.0, 52.3, 50.8, 50.0, 49.4, 45.8, 40.6, 33.5, 32.1, 26.5, 21.8, 20.8 (2 Cq missing); LC–MS (method C, ESI, m/z) t_R = 1.50 min, 553/555 $(M+H)^+$; ESI-HRMS calcd for $C_{25}H_{34}{}^{35}ClN_4O_4S_2$ $(M+H)^+$ 553.1705, found 553.1698.

Preparation of Compounds in Table 4

8-(3-Fluoro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (60)

8-(3-Bromo-5-fluoropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **58** (38 mg, 0.12 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole[27] **37** (43 mg, 0.15 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (4.7 mg, 5.8 µmol) were loaded in a microwave vial and acetonitrile (2 mL) and 0.5 M sodium carbonate in water (324 µL, 0.162 mmol) were added. The reaction was stirred at 120 ºC for 60 min under microwave irradiation. After evaporation of the solvents, the crude material was purified by Biotage column chromatography (DCM/EtOH 98:2 to 92:8) followed by a SCX-2 column (loading with DCM/MeOH, elution with 1 N NH_3 in MeOH) to give 8-(3-fluoro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **60** (45 mg, 96% yield) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 4.4 Hz, 1H), 8.14 (s, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 5.97 (s, 1H), 3.97 (s, 3H), 3.34 – 3.23 (m, 4H), 3.03 – 2.94 (m, 2H), 2.05 (t, *J* = 6.8 Hz, 2H), 1.88 (ddd, *J* = 13.1, 11.2, 4.2 Hz, 2H), 1.39 – 1.30 (m, 2H); ^{19}F NMR (500 MHz, $CDCl_3$) δ -139; ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.4, 154.4 (d, *J* = 252.7 Hz), 147.8 (d, *J* = 3.8 Hz), 143.6 (d, *J* = 6.8 Hz), 137.8 (d, *J* = 25.8 Hz), 136.8, 134.7, 132.2, 131.7, 129.2, 127.1, 125.7, 122.6, 47.4 (d, *J* = 5.0 Hz), 41.5, 39.2, 38.6, 32.1, 31.5; LC–MS (method C, ESI, m/z) t_R = 1.98 min, 406 $(M+H)^+$; ESI-HRMS calcd for $C_{23}H_{25}FN_5O$ $(M+H)^+$ 406.2038, found 406.2033.

8-(3-Fluoro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (62)

8-(3-Bromo-5-fluoropyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one **59** (50 mg, 0.15 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole[27] **37** (56 mg, 0.20 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (6.2 mg, 7.6 µmol) were loaded in a microwave vial and acetonitrile (2.6 mL) and 0.5 M sodium carbonate in water (424 µL, 0.212 mmol) were added. The reaction was stirred at 120 ºC for 60 min under microwave irradiation. The solvent was evaporated and the cruder material was purified by Biotage column chromatography (DCM/EtOH 99:1 to 94:6) to afford 8-(3-fluoro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one **62** (50 mg, 81% yield) as a cream solid. ^{1}H NMR

(500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 4.1 Hz, 1H), 8.14 (s, 1H), 7.81 (d, *J* = 0.8 Hz, 1H), 7.67 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 5.51 (s, 1H), 3.97 (s, 3H), 3.31 (s, 2H), 3.30 – 3.22 (m, 2H), 3.09 – 3.01 (m, 2H), 1.90 – 1.84 (m, 2H), 1.74 – 1.65 (m, 2H); ^{19}F NMR (500 MHz, $CDCl_3$) δ -140; ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6, 154.4 (d, *J* = 252.8 Hz), 147.9 (d, *J* = 3.8 Hz), 143.1 (d, *J* = 6.8 Hz), 137.7 (d, *J* = 25.3 Hz), 136.8, 134.6, 132.3, 131.7, 129.2, 127.1, 125.7, 122.5, 80.1, 51.3, 47.0 (d, *J* = 4.6 Hz), 39.2, 36.3; LC–MS (method C, ESI, m/z) t_R = 2.07 min, 408 $(M+H)^+$; ESI-HRMS calcd for $C_{22}H_{23}FN_5O_2$ $(M+H)^+$ 408.1830, found 408.1840.

8-(3,5-Diiodopyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (65)

4-Chloro-3,5-diiodopyridine **64** (1.00 g, 2.74 mmol) and tert-butyl 1-oxo-2,8-diazaspiro[4.5]decane-8-carboxylate (879 mg, 3.28 mmol) were solubilised in NMP (10 mL) and triethylamine for synthesis (759 µL, 5.47 mmol). The reaction mixture was stirred for 1 h at 220 ºC under microwave irradiation and then poured into water (200 mL). The resulting brown precipitate was filtered and washed with water (30 mL). The solid was suspended in diethyl ether (80 mL), filtered and washed with diethyl ether (15 mL) to give 8-(3,5-diiodopyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **65** (576 mg, 79% purity, 34 % corrected yield) as a brown solid which was used without further purification. LC–MS (method E, ESI, m/z) t_R = 1.01 min, 484 $(M+H)^+$.

8-(3-Iodo-5-(trifluoromethyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (67)

Into a 50 mL schlenck vial, silver (I) fluoride (200 mg, 1.57 mmol) was loaded. DMF (20 mL) and (trifluoromethyl)trimethysilane (284 µL, 1.88 mmol) were added at rt and the resulting brown suspension was stirred for 30 min at rt. Then fine powder copper (150 mg, 2.35 mmol) was added and the resulting dark red suspension was stirred for 3 h at rt. The reaction mixture turned green and a silver precipitate was formed on the vessel wall. 8-(3,5-diiodopyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **65** (79% pure, 576 mg, 0.94 mmol) was added and the suspension was stirred at 90 °C for 3 h. The reaction mixture was diluted with DMF (20 mL) and filtered over Celite. The mother liquor was evaporated to dryness. The residue was purified by flash chromatography (Companion, DCM/MeOH 100:0 to 90:10) and by prep. HPLC (method A, gradient elution from 0:100 to 25:75 over 3 min and to 5:50 over 18 min acetonitrile:water) to

give 8-(3-iodo-5-(trifluoromethyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **67** (74 mg, 19% yield) as a yellow crystallized oil which was used directly in the next step. LC–MS (method E, ESI, m/z) t_R = 1.03 min, 426 $(M+H)^+$.

8-(3-(4-(1-Methyl-1*H*-pyrazol-4-yl)phenyl)-5-(trifluoromethyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (70)

1-Methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole[27] **37** (148 mg, 0.520 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (6 mg, 0.01 mmol) were loaded in a microwave vial and a solution of 8-(3-iodo-5-(trifluoromethyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **67** (74 mg, 0.17 mmol) in acetonitrile (4 mL) and 0.5 M sodium carbonate solution (1.0 mL, 0.52 mmol) were added. The reaction mixture was stirred for 1 h at 120ºC under microwave irradiation and then diluted with acetonitrile (5 mL), filtered and the filtrate was evaporated. The crude product was purified by prep. HPLC (method A, gradient elution from 0:100 to 25:75 over 3 min and to 5:50 over 18 min acetonitrile:water) to afford 8-(3-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)-5-(trifluoromethyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one 2,2,2-trifluoroacetate **70** (42 mg, 43% yield) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.84 (s, 1H), 8.53 (s, 1H), 8.23 (d, *J* = 0.8 Hz, 1H), 7.95 (d, *J* = 0.8 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.51 (s, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 3.88 (s, 3H), 3.09 – 3.00 (m, 4H), 2.72 – 2.64 (m, 2H), 1.72 (t, *J* = 6.8 Hz, 2H), 1.67 – 1.58 (m, 2H), 1.20 – 1.14 (m, 2H); ^{19}F NMR (500 MHz, DMSO-d6) δ -74.8; ^{13}C NMR (126 MHz, DMSO-d6) δ 180.2, 156.8, 154.8, 147.1 (d, *J* = 6.7 Hz), 136.8, 136.7, 134.4, 133.0, 130.4, 128.6, 125.3, 123.2, 121.7, 49.0, 41.4, 39.2, 38.2, 31.7, 30.7 (1 Cq not observed); LC–MS (method C, ESI, m/z) t_R = 2.70 min, 456 $(M+H)^+$; ESI-HRMS calcd for $C_{24}H_{25}F_3N_5O$ $(M+H)^+$ 456.2006, found 456.1998.

8-(3-Chloro-5-(trifluoromethyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (69)

Into a 10 mL schlenck, silver (I) fluoride (191 mg, 1.50 mmol) was loaded and DMF (5 mL) and (trifluoromethyl)trimethylsilane (272 uL, 1.80 mmol) were added at rt. The resulting brown suspension was stirred for 20 min at rt, then fine powder copper (144 mg, 2.26 mmol) was added and the resulting dark red suspension was stirred for 1.5 h at rt. The reaction mixture turned dark green / blue and a silver precipitate was formed on the vessel wall. 8-(3-8-(3-bromo-5-

chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one[27] **8** (465 mg, 1.35 mmol) was added and the suspension was stirred at 90 °C for 3 h. The green suspension was diluted with DMF (10 mL) and filtered over Celite. The mother liquor was extracted with DCM (2 x 250 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness. The crude residue was purified by flash chromatography (Companion, DCM/MeOH 100:0 to 90:10) to give 8-(3-chloro-5-(trifluoromethyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **69** (242 mg, 57% pure, 30% corrected yield) as a colorless solid which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 2.27 min, 334/336 $(M+H)^+$.

8-(3-(1-Methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)-5-(trifluoromethyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (71)

To 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole-2,2-dioxide **14** (127 mg, 0.410 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (8 mg, 0.01 mmol) was added a solution of 8-(3-chloro-5-(trifluoromethyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **69** (57% pure, 121 mg, 0.200 mmol) in acetonitrile (4 mL) and 0.5 M sodium carbonate solution (1.2 mL, 0.61 mmol). The reaction mixture was stirred for 1 h at 120ºC under microwave irradiation and then diluted with ACN (5 mL), filtered and the filtrate was concentrate. The crude product was purified by prep. HPLC (method A, 20 min gradient elution from 2:98 to 25:75 acetonitrile:water) to give 8-(3-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)-5-(trifluoromethyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one 2,2,2-trifluoroacetate **71** (36 mg, 29% yield) as a light yellow solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.82 (s, 1H), 8.51 (s, 1H), 7.55 (s, 1H), 7.47 (d, *J* = 1.9 Hz, 1H), 7.40 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 4.78 (s, 2H), 3.12 – 3.07 (m, 5H), 3.07 – 3.00 (m, 2H), 2.76 – 2.68 (m, 2H), 1.79 (t, *J* = 6.8 Hz, 2H), 1.59 – 1.49 (m, 2H), 1.17 – 1.10 (m, 2H); ^{19}F NMR (500 MHz, DMSO-d6) δ -74.9; ^{13}C NMR (126 MHz, DMSO-d6) δ 179.8, 156.4, 154.1, 147.0, 141.4, 135.6, 130.0, 129.4, 126.9, 118.6, 109.6, 50.0, 48.2, 40.9, 37.8, 30.9, 30.4, 26.1 (2 Cq not observed); LC–MS (method C, ESI, m/z) t_R = 2.46 min, 481 $(M+H)^+$; ESI-HRMS calcd for $C_{22}H_{24}F_3N_4O_3S$ $(M+H)^+$ 481.1516, found 481.1505.

Preparation of Compounds in Table 5

8-(2-Amino-3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (85)

8-(2-(bis(4-Methoxybenzyl)amino)-5-bromo-3-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **82** (200 mg, 0.207 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole[27] **37** (59 mg, 0.21 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (8 mg, 10 µmol) were loaded in a microwave vial. Acetonitrile (1.8 mL) and 0.5 M aqueous sodium carbonate (0.579 mL, 0.289 mmol) were added and the mixture was degassed. The mixture was stirred at 120 °C for 1 h under microwave irradiation before the mixture was concentrated. The resulting brown solid was purified by Biotage column chromatography (DCM/EtOH 97:3 to 90:10) to give 8-(2-(bis(4-methoxybenzyl)amino)-3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one as a yellow sticky solid (86 mg) which was used in the next step without further purification. LC–MS (method C, ESI, m/z) t_R = 3.46 min, 677/679 $(M+H)^+$.

8-(2-(bis(4-Methoxybenzyl)amino)-3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (86 mg, 0.13 mmol) was dissolved in trifluoroacetic acid (0.4 mL) and the orange solution was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuum. The residue was dissolved in EtOAc and $NaHCO_3$ was added. The precipitate was filtered off and the aqueous layer was extracted with EtOAc three times. The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated in vacuum. The resulting brown oil was purified by Biotage column chromatography (DCM/EtOH, 97:3 to 90:10) to give a light yellow solid which was further purified by scx_2-cartridge to give 8-(2-amino-3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **85** (39 mg, 70% yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.17 (d, *J* = 0.8 Hz, 1H), 7.89 (d, *J* = 0.8 Hz, 1H), 7.64 (s, 1H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.51 (s, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 6.11 (s, 2H), 3.87 (s, 3H), 3.10 (t, *J* = 6.8 Hz, 2H), 3.00 – 2.92 (m, 2H), 2.72 – 2.61 (m, 2H), 1.81 (t, *J* = 6.8 Hz, 2H), 1.74 – 1.65 (m, 2H), 1.23 – 1.18 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d6) δ 180.4, 156.8, 153.7, 148.2, 136.5, 136.3, 131.5, 130.1, 128.3, 125.1, 124.2, 122.0, 109.2, 47.8, 41.9, 39.1, 38.2, 32.3, 30.5; LC–MS (method C, ESI,

m/z) t_R = 1.99 min, 437/439 $(M+H)^+$; ESI-HRMS calcd for $C_{23}H_{26}{}^{35}ClN_6O$ $(M+H)^+$ 437.1851, found 437.1847.

8-(2-Amino-5-(3-amino-1*H*-indazol-6-yl)-3-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (87)

8-(2-(bis(4-Methoxybenzyl)amino)-5-bromo-3-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **82** (202 mg, 0.340 mmol) and (3-amino-1*H*-indazol-6-yl)boronic acid hydrochloride **16** (86 mg, 0.40 mmol) were dissolved in acetonitrile (8 mL). 0.5 M aqueous sodium carbonate (2.69 mL, 1.35 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (14 mg, 0.020 mmol) were added. The reaction mixture was stirred at 120 ºC for 1 h under microwave irradiation. The solvent was evaporated and the crude product was purified by flash-chromatography (n-heptane/EtOAc/MeOH, gradient) to give 8-(5-(3-amino-1*H*-indazol-6-yl)-2-(bis(4-methoxybenzyl)amino)-3-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (78 mg, 36% yield) as a colorless solid which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 2.68 min, 652/654 $(M+H)^+$.

8-(5-(3-Amino-1*H*-indazol-6-yl)-2-(bis(4-methoxybenzyl)amino)-3-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (78 mg, 0.12 mmol) was solubilised in TFA (4 mL) and the reaction mixture was stirred at rt for 2 days and then concentrated. The crude product was purified by prep. HPLC (method A, 20 min gradient elution from 2:98 to 20:80 acetonitrile:water) to give 8-(2-amino-5-(3-amino-1*H*-indazol-6-yl)-3-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one 2,2,2-trifluoroacetate **87** (43 mg, 68% yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 7.83 (d, *J* = 8.3 Hz, 1H), 7.76 (s, 1H), 7.65 (s, 2H), 7.55 (s, 1H), 7.26 (s, 1H), 6.90 (dd, *J* = 8.3, 1.4 Hz, 1H), 3.26 – 3.18 (m, 2H), 3.09 (t, *J* = 6.8 Hz, 2H), 2.79 – 2.69 (m, 2H), 1.81 (t, *J* = 6.8 Hz, 2H), 1.72 – 1.64 (m, 2H), 1.30 – 1.22 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d6) δ 179.6, 157.3, 152.0, 147.7, 141.7, 138.0, 135.6, 123.2, 120.8, 120.2, 112.7, 109.8, 106.9, 47.7, 41.1, 37.8, 31.8, 30.7; LC–MS (method C, ESI, m/z) t_R = 1.43 min, 412/415 $(M+H)^+$; ESI-HRMS calcd for $C_{20}H_{23}{}^{35}ClN_7O$ $(M+H)^+$ 412.1647, found 412.1632.

8-(2-Amino-5-bromo-3-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (76)

5-Bromo-3,4-dichloropyridin-2-amine **73** (1.0 g, 4.1 mmol), 8-boc-2,8-diaza-spiro-[4.5]decan-1-one (1.16 g, 4.55 mmol) and potassium fluoride (0.480 g, 8.27 mmol) were loaded in a

microwave vial. Triethylamine (1.60 mL, 12.4 mmol) and NMP (10 mL) were added and the light brown solution was degassed and heated at 220 °C for 2 h under microwave irradiation. The reaction mixture was poured onto water (100 mL) and the resulting precipitate was filtered off and washed with water before it was dissolved in $CHCl_3$/MeOH. The dark brown solution was dried over $MgSO_4$, filtered and concentrated in vacuum. The resulting brown solid was purified by Biotage column chromatography (DCM/EtOH 97:3 to 90:10) to give 8-(2-amino-5-bromo-3-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **76** (1.06 g, 71% yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 7.92 (s, 1H), 7.59 (s, 1H), 6.34 (s, 2H), 3.37 – 3.11 (m, 6H), 2.01 (t, *J* = 6.8 Hz, 2H), 1.95 – 1.81 (m, 2H), 1.43 – 1.36 (m, 2H); LC–MS (method C, ESI, m/z) t_R = 2.09 min, 359/361 $(M+H)^+$.

8-(2-Amino-3-chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (88)

8-(2-Amino-5-bromo-3-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **76** (40 mg, 0.11 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole-2,2-dioxide **14** (41 mg, 0.13 mmol) and $Pd(PPh_3)_4$ (6.4 mg, 5.6 µmol) were loaded in a microwave vial and degassed acetonitrile (2 mL) and 0.5 M aqueous sodium carbonate (310 µL, 0.156 mmol) were added. The reaction mixture was heated at 120 °C under microwave irradiation for 60 min. Then, the reaction mixture was concentrated and purified by Biotage column chromatography (DCM/EtOH 99:1 to 93:7) to afford 8-(2-amino-3-chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **88** as a white solid (22 mg, 43% yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 7.62 (s, 1H), 7.53 (s, 1H), 7.28 (s, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H), 4.71 (s, 2H), 3.11 (t, *J* = 6.8 Hz, 2H), 3.07 (s, 3H), 2.98 – 2.92 (m, 2H), 2.77 – 2.65 (br s, 2H), 1.84 (t, *J* = 6.8 Hz, 2H), 1.69 – 1.60 (m, 2H), 1.22 – 1.15 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d6) δ 180.5, 156.8, 153.9, 147.9, 140.8, 132.0, 130.0, 127.0, 123.9, 118.8, 109.7, 109.2, 50.6, 47.7, 41.8, 38.3, 32.2, 31.2, 26.6; LC–MS (method C, ESI, m/z) t_R = 1.76 min, 462/464 $(M+H)^+$; ESI-HRMS calcd for $C_{21}H_{25}{}^{35}ClN_5O_3S$ $(M+H)^+$ 462.1361, found 462.1352.

8-(2-(bis(4-Methoxybenzyl)amino)-5-bromo-3-chloropyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (83)

5-Bromo-3,4-dichloro-*N*,*N*-bis(4-methoxybenzyl)pyridin-2-amine **81** (1.15 g, 2.39 mmol) was suspended in NMP (10 mL). 1-oxa-3,8-diazaspiro[4.5]decan-2-one acetate **38** (619 mg, 2.86 mmol) and sodium bicarbonate (801 mg, 9.54 mmol) were added. The reaction mixture was stirred at 220 ºC for 1 h. After addition of 100 mL of water, the grey precipitate was filtered and washed with water. The precipitate was impure and was purified by flash-chromatography (Companion, DCM/MeOH gradient) to give 8-(2-(bis(4-methoxybenzyl)amino)-5-bromo-3-chloropyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one **83** (69% pure, 654 mg, 31% corrected yield) as light-yellow solid. Using the same condition, a second reaction were set up on 1.0 g of 5-bromo-3,4-dichloro-*N*,*N*-bis(4-methoxybenzyl)pyridin-2-amine and 590 mg (68% pure, 31% corrected yield) were obtained. Both samples were combined and used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 3.52 min, 601/603 $(M+H)^+$.

8-(2-Amino-3-chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (90)

8-(2-(bis(4-Methoxybenzyl)amino)-5-bromo-3-chloropyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one **83** (69% pure, 1.24 g, 1.42 mmol) was solubilised in acetonitrile (10 mL). 1-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole-2,2-dioxide **14** (441 mg, 1.43 mmol), 0.5 M aqueous sodium carbonate (5.70 ml, 2.85 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (58 mg, 0.071 mmol) were added. The reaction mixture was stirred at 120 ºC for 1 h and diluted with EtOAc, filtered through Celite and the filtrate was concentrated. The brown residue was purified by flash-chromatography (Companion, n-heptane/EtOAc gradient) to afford 8-(2-(bis(4-methoxybenzyl)amino)-3-chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (588 mg, 100% pure and 144 mg, 76% pure, 69% corrected yield) as a brown solid. LC–MS (method B, ESI, m/z) t_R = 2.92 min, 704/706 $(M+H)^+$.

8-(2-(bis(4-Methoxybenzyl)amino)-3-chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (100% pure, 588 mg, 0.835 mmol) was dissolved in TFA (20 mL). The brown reaction solution was stirred

overnight at rt and then evaporated under vacuum to dryness. The dark red resin was dissolved in DCM (50 mL) and treated with water (50 mL). The stirred mixture was adjusted to pH= 9 with solid sodium hydrogencarbonate. The mixture was filtered through a phase-separator. The DCM phase was evaporated and the residue was purified by flash-chromatography (Companion, DCM/MeOH gradient). The aqueous phase from the phase-separator was treated with diethyl ether and filtered. The solid was washed with water and ether. The product was then dissolved in 40 mL of water containing 10 ml of 2 M HCl and ca. 4 mL of MeOH. The solution was treated with solid sodium hydrogen carbonate to pH=9. The resulting precipitate was filtered, washed with water and dried at 70 °C under vacuum for 2 days to give 8-(2-amino-3-chloro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one **90** (254 mg, 65% yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 7.62 (s, 1H), 7.48 (s, 1H), 7.27 (s, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.18 (s, 2H), 4.68 (s, 2H), 3.18 (s, 2H), 3.07 (s, 3H), 2.99 – 2.87 (m, 2H), 2.86 – 2.77 (m, 2H), 1.74 – 1.61 (m, 4H); ^{13}C NMR (126 MHz, DMSO-d6) δ 157.8, 156.3, 153.0, 147.5, 140.4, 131.4, 129.9, 126.1, 123.3, 118.4, 109.3, 108.6, 78.9, 50.5, 50.2, 47.0, 35.9, 26.1; LC–MS (method C, ESI, m/z) t_R = 1.60 min, 464/466 $(M+H)^+$; ESI-HRMS calcd for $C_{20}H_{23}{}^{35}ClN_5O_4S$ $(M+H)^+$ 464.1154, found 464.1141.

8-(2-Amino-3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (89)

8-(2-(bis(4-Methoxybenzyl)amino)-5-bromo-3-chloropyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one **83** (87% pure, 250 mg, 0.36 mmol) was solubilised in acetonitrile (8 mL). 1-Methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole[27] **37** (155 mg, 0.547 mmol), 0.5 M aqueous sodium carbonate (1.46 mL, 0.729 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (15 mg, 0.018 mmol) were added. The reaction mixture was stirred for 1 h at 120ºC, diluted with EtOAc, filtered and the filtrate was concentrated. The dark brown residue was purified by flash-chromatography (Companion, DCM/MeOH gradient) to give 8-(2-(bis(4-methoxybenzyl)amino)-3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (200 mg, 81% yield) as a brown solid which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 2.85 min, 679/681 $(M+H)^+$.

TFA (4 mL) was added to 8-(2-(bis(4-methoxybenzyl)amino)-3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (200 mg, 0.294 mmol). The brown solution was stirred for 2 h at rt and the red reaction mixture was concentrated. The residue was dissolved in 100 mL of water, solid sodium carbonate was added to adjust to the pH to 8. The mixture was extracted with EtOAc twice. The organic layer was dried and evaporated to dryness. The residue was triturated with diethyl ether and acetonitrile. The precipitate was filtered, washed with ether and dried to give 8-(2-amino-3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one **89** (56 mg, 43% yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.18 (d, *J* = 0.8 Hz, 1H), 7.91 (d, *J* = 0.8 Hz, 1H), 7.65 (s, 1H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.46 (s, 1H), 7.24 (d, *J* = 8.2 Hz, 2H), 6.17 (s, 2H), 3.87 (s, 3H), 3.17 (s, 2H), 2.95 – 2.82 (m, 4H), 1.74 – 1.66 (m, 4H); ^{13}C NMR (126 MHz, DMSO-d6) δ 153.8, 152.2, 149.1, 143.4, 132.0, 131.6, 127.1, 125.6, 123.8, 120.8, 119.6, 117.5, 104.5, 74.9, 46.1, 43.1, 34.7, 31.9; LC–MS (method C, ESI, m/z) t_R = 1.87 min, 439/441 $(M+H)^+$; ESI-HRMS calcd for $C_{22}H_{24}{}^{35}ClN_6O_2$ $(M+H)^+$ 439.1644, found 439.1630.

8-(2-(bis(4-methoxybenzyl)amino)-5-bromo-3-chloropyridin-4-yl)-1,3,8-triazaspiro[4.5]decane-2,4-dione (84)

1,3,8-Triazaspiro[4.5]decane-2,4-dione hydrochloride (638 mg, 3.11 mmol) and 5-bromo-3,4-dichloro-*N*,*N*-bis(4-methoxybenzyl)pyridin-2-amine **81** (1.50 g, 3.11 mmol) were solubilised in NMP (10 mL) and triethylamine (1.00 mL, 9.33 mmol). The solution was divided in three microwave vials and the reaction mixture was stirred for 1 h at 220ºC. The reaction mixture was added to a saturated sodium carbonate solution (300 mL) and the precipitate formed was filtered off, redissolved in DCM, dried and purified by flash chromatography (Companion, petrol ether/MeOH/DCM gradient). The product was suspended in MeOH (8 mL) and diethyl ether (30 mL) overnight. The precipitate was then filtered, washed with diethyl ether and dried to give 8-(2-(bis(4-methoxybenzyl)amino)-5-bromo-3-chloropyridin-4-yl)-1,3,8-triazaspiro[4.5]decane-2,4-dione **84** (380 mg, 20% yield) as light-yellow solid which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 3.24 min, 614/616/618 $(M+H)^+$.

8-(2-Amino-3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1,3,8-triazaspiro[4.5]decane-2,4-dione 2,2,2-trifluoroacetate (91)

8-(2-(bis(4-Methoxybenzyl)amino)-5-bromo-3-chloropyridin-4-yl)-1,3,8-triazaspiro[4.5]decane-2,4-dione **84** (180 mg, 0.290 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole[27] **37** (125 mg, 0.440 mmol) were solubilised in acetonitrile (4 mL). 0.5 M aqueous sodium carbonate (1.00 mL, 0.730 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (12 mg, 0.015 mmol) were added. The reaction mixture was stirred at 120ºC for 1 h under microwave irradiation. The crude mixture was filtered and the filtrate was evaporated. The residue was purified by flash chromatography to give 8-(2-(bis(4-methoxybenzyl)amino)-3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1,3,8-triazaspiro[4.5]decane-2,4-dione (64 mg, 32% yield) as a colorless solid which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 2.82 min, 692/694 $(M+H)^+$.

8-(2-(bis(4-Methoxybenzyl)amino)-3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1,3,8-triazaspiro[4.5]decane-2,4-dione (64 mg, 0.090 mmol) was dissolved in TFA (4 mL) and stirred overnight at rt. The TFA was evaporated and the crude residue was purified by prep. HPLC (method A, 20 min gradient elution from 2:98 to 30:70 acetonitrile:water) to give 8-(2-amino-3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1,3,8-triazaspiro[4.5]decane-2,4-dione 2,2,2-trifluoroacetate **91** (31 mg, 58% yield) as a light-yellow solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 10.67 (s, 1H), 8.60 (s, 1H), 8.20 (d, *J* = 0.8 Hz, 1H), 7.92 (d, *J* = 0.8 Hz, 1H), 7.71 (s, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.50 (s, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 3.89 (s, 3H), 3.26 – 3.19 (m, 2H), 3.11 – 3.02 (m, 2H), 1.87 – 1.78 (m, 2H), 1.55 – 1.47 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d6) δ 177.5, 156.6, 156.2, 152.4, 138.8, 136.1, 133.5, 131.9, 129.4, 127.9, 125.1, 122.7, 121.3, 106.8, 59.7, 46.8, 38.7, 33.2; LC–MS (method C, ESI, m/z) t_R = 1.82 min, 452/454 $(M+H)^+$; ESI-HRMS calcd for $C_{22}H_{23}{}^{35}ClN_7O_2$ $(M+H)^+$ 452.1596, found 452.1583.

8-(2-Amino-5-chloro-3-fluoropyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (78)

4,5-Dichloro-3-fluoropyridin-2-amine **74** (100 mg, 0.553 mmol) and 2-oxo-1-oxa-3,8-diazaspiro[4.5]decan-8-ium acetate **38** (178 mg, 0.829 mmol) were introduced in a microwave vial. NMP (1.4 mL) and triethylamine (233 µL, 1.66 mmol) were added and the reaction mixture was stirred for 2*2h30 at 220°C under microwave irradiation. The reaction mixture was concentrated, and the residue was washed successively with DCM and MeOH to give 8-(2-

amino-5-chloro-3-fluoropyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one **78** (60 mg, 36% yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 7.68 (s, 1H), 7.55 (s, 1H), 6.21 (s, 2H), 3.33 – 3.24 (m, 4H), 3.22 – 3.13 (m, 2H), 1.93 – 1.79 (m, 4H); ^{19}F NMR (500 MHz, DMSO-d6) δ -149; LC–MS (method C, ESI, m/z) t_R = 1.63 min, 301/303 $(M+H)^+$.

8-(2-Amino-3-fluoro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (93)

8-(2-Amino-5-chloro-3-fluoropyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one **78** (30 mg, 0.10 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydrobenzo[*c*]isothiazole-2,2-dioxide **14** (62 mg, 0.20 mmol) and $PdCl_2(Pcy_3)_2$ (3.7 mg, 5.0 µmol) were loaded in a microwave vial and acetonitrile (1.7 mL) and 0.5 M sodium carbonate in water (279 µL, 0.140 mmol) were added. The reaction mixture was stirred at 150 ºC for 30 min under microwave irradiation. The solvent was concentrated and purified by Biotage column chromatography (DCM/EtOH 98:2 to 92:8) to afford 8-(2-amino-3-fluoro-5-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[*c*]isothiazol-5-yl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one **93** (15 mg, 34% yield) as a cream solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 7.48 (s, 2H), 7.44 – 7.40 (m, 2H), 6.98 (d, *J* = 8.7 Hz, 1H), 6.05 (s, 2H), 4.69 (s, 2H), 3.22 (s, 2H), 3.11 – 3.03 (m, 2H), 3.06 (s, 3H), 2.97 – 2.89 (m, 2H), 1.69 – 1.55 (m, 4H); ^{19}F NMR (500 MHz, DMSO-d6) δ -152; ^{13}C NMR (126 MHz, DMSO-d6) δ 157.8, 149.8 (d, *J* = 14.1 Hz), 143.0, 142.0 (d, *J* = 5.1 Hz), 140.3, 140.6 (d, *J* = 246 Hz), 130.6, 129.1, 125.6, 121.3, 118.5, 109.5, 78.7, 50.1, 49.9, 46.7 (d, *J* = 5.0 Hz), 35.6, 26.1; LC–MS (method C, ESI, m/z) t_R = 1.63 min, 448 $(M+H)^+$; ESI-HRMS calcd for $C_{20}H_{23}FN_5O_4S$ $(M+H)^+$ 448.1449, found 448.1447.

8-(2-Amino-5-bromo-3-(trifluoromethyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (79)

5-Bromo-4-chloro-3-(trifluoromethyl)pyridin-2-amine **75** (800 mg, 2.90 mmol) and tert-butyl 1-oxo-2,8-diazaspiro[4.5]decane-8-carboxylate (1.10 g, 4.36 mmol) were solubilised in NMP (8 mL) and triethylamine (1.21 mL, 8.71 mmol) was added. The reaction mixture was stirred at 220 ºC for 3 h under microwave irradiation. The black reaction mixture was poured into water (150 mL). The brown precipitate was filtered and washed with water and purified by flash-chromatography (Companion, DCM/MeOH gradient) to give 8-(2-amino-5-bromo-3-

(trifluoromethyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **79** (455 mg, 79% pure, 32% corrected yield) as a pale brown solid which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 1.92 min, 393/395 $(M+H)^+$.

8-(2-Amino-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)-3-(trifluoromethyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one 2,2,2-trifluoroacetate (94)

8-(2-Amino-5-bromo-3-(trifluoromethyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **79** (79% pure, 70 mg, 0.14 mmol) was suspended in acetonitrile (2 mL). 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole[27] **37** (60 mg, 0.21 mmol), 0.5 M sodium carbonate (562 µL, 0.281 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (8 mg, 0.007 mmol) were added. The reaction mixture was stirred for 1 h at 120 ºC under microwave irradiation. After addition of EtOAc, the mixture was filtered and the filtrate was concentrated. The brown oily residue was purified by prep. HPLC (method A, 20 min gradient elution from 0:100 to 15:85 over 3 min and to 35:65 over 17 min acetonitrile:water) to give 8-(2-amino-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)-3-(trifluoromethyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one 2,2,2-trifluoroacetate **94** (13 mg, 16% yield) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.19 (d, *J* = 0.8 Hz, 1H), 7.91 (d, *J* = 0.8 Hz, 1H), 7.72 (s, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.51 (s, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 3.87 (s, 3H), 3.25 – 3.17 (m, 2H), 3.07 (t, *J* = 6.8 Hz, 2H), 2.90 (t, *J* = 12.2 Hz, 2H), 1.79 (t, *J* = 6.8 Hz, 2H), 1.56 – 1.47 (m, 2H), 1.14 – 1.06 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d6) δ 179.5, 160.9, 154.2, 143.8, 136.1, 133.2, 132.2, 130.1, 128.0, 124.9, 124.6 (q, *J* = 270 Hz), 124.0, 121.3, 48.5, 40.6, 38.7, 37.7, 30.7; LC–MS (method C, ESI, m/z) t_R = 2.11 min, 471 $(M+H)^+$; ESI-HRMS calcd for $C_{24}H_{26}F_3N_6O$ $(M+H)^+$ 471.2115, found 471.2104.

Preparation of Compounds in Table 7

1-(3-Bromo-5-chloropyridin-4-yl)-4-(methylamino)piperidine-4-carboxamide (96)

3-Bromo-4,5-dichloropyridine[27] **7** (400 mg, 1.76 mmol) was dissolved in NMP (5 mL). 4-(methylamino)piperidine-4-carboxamide (416 mg, 2.64 mmol) and triethylamine (730 µL, 5.29 mmol) were added. The reaction mixture was stirred at 220 °C for 1 h and concentrated. The crude product was purified by flash chromatography (DCM/MeOH, gradient) to give 1-(3-

bromo-5-chloropyridin-4-yl)-4-(methylamino)piperidine-4-carboxamide **96** (467 mg, 95% pure, 72% corrected yield) as brown crystals which were used directly in the next step. LC–MS (method A, ESI, m/z) t_R = 1.20 min, 347/349/351 $(M+H)^+$.

8-(3-Chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1-methyl-1,3,8-triazaspiro[4.5]decane-2,4-dione 2,2,2-trifluoroacetate (103)

1-(3-Bromo-5-chloropyridin-4-yl)-4-(methylamino)piperidine-4-carboxamide **96** (95% pure, 233 mg, 0.637 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole[27] **37** (271 mg, 0.955 mmol) were dissolved in acetonitrile (5 mL). 0.5 M aqueous sodium carbonate (2.60 mL, 1.27 mmol) and Pd(dppf)Cl_2·CH_2Cl_2 (47 mg, 0.064 mmol) were added. The reaction mixture was stirred at 120 °C for 1 h under microwave irradiation and concentrated in vacuo. The crude product was purified by flash chromatography (DCM/MeOH, gradient) and by prep. HPLC (method A, 13 minute gradient elution from 1:99 to 45:55 acetonitrile:water) to afford 1-(3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-4-(methylamino)piperidine-4-carboxamide (57 mg, 21% yield) as beige crystals which were used directly in the next step. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.40 (s, 1H), 8.20 (s, 1H), 8.16 – 8.15 (m, 2H), 7.93 (d, *J* = 0.8 Hz, 1H), 7.68 – 7.63 (m, 2H), 7.32 – 7.27 (m, 2H), 7.15 (s, 1H), 6.91 (s, 1H), 3.88 (s, 3H), 3.02 – 2.92 (m, 2H), 2.85 – 2.75 (m, 2H), 2.03 (s, 3H), 1.85 – 1.75 (m, 2H), 1.49 – 1.38 (m, 2H); LC–MS (method A, ESI, m/z) t_R = 1.26 min, 425/427 $(M+H)^+$.

1-(3-Chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-4-(methylamino)piperidine-4-carboxamide (20 mg, 0.047 mmol) was solubilized in THF (3 mL). N-Ethyldiisopropylamine (16 µL, 0.094 mmol) and 1,1'-carbonyldiimidazole (7.6 mg, 0.047 mmol) were added and the reaction solution was stirred overnight at 60 °C. Sodium hydride (60% suspension in paraffin oil) (4.5 mg, 0.11 mmol) was added and stirred at rt for 3 days. The reaction mixture was then stirred at 60 °C overnight. Additional sodium hydride (60% suspension in paraffin oil) (5.0 mg, 0.13 mmol) and 1,1'-carbonyldiimidazole (4.0 mg, 0.025 mmol) were added and the reaction mixture was stirred at 70 °C overnight. To improve the conversion, additional sodium hydride (5.0 mg, 0.13 mmol) and 1,1'-carbonyldiimidazole (4.0 mg, 0.025 mmol) were added and the reaction mixture was stirred at 70 °C for 4 h and then concentrated. The crude material was purified by prep HPLC to give 8-(3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1-methyl-

1,3,8-triazaspiro[4.5]decane-2,4-dione 2,2,2-trifluoroacetate **103** (4 mg, 16% yield) as a white fluffy solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.77 (s, 1H), 8.55 (s, 1H), 8.27 (s, 1H), 8.21 (s, 1H), 7.93 (s, 1H), 7.72 – 7.67 (m, 2H), 7.41 –- 7.36 (m, 2H), 3.88 (s, 3H), 3.40 - 3.30 (m, 2H), 3.12 - 3.04 (m, 2H), 2.66 (s, 3H), 1.90 – 1.78 (m, 2H), 1.56 (d, *J* = 13.1 Hz, 2H); LC–MS (method C, ESI, m/z) t_R = 2.44 min, 451/453 $(M+H)^+$; ESI-HRMS calcd for $C_{23}H_{24}{}^{35}ClN_6O_2$ $(M+H)^+$ 451.1644, found 451.1629.

8-(3-Chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1-methyl-1,3,8-triazaspiro[4.5]decan-4-one (104)

To a solution of 8-(3-bromo-5-chloropyridin-4-yl)-1,3,8-triazaspiro[4.5]decan-4-one (200 mg, 0.579 mmol) in MeOH (6 mL) was added formaldehyde (37% in water, 0.078 mL, 1.0 mmol), followed by glacial acetic acid (0.040 mL, 0.69 mmol) and sodium triacetoxyborohydride (368 mg, 1.74 mmol) and the reaction mixture was stirred at rt overnight. Additional sodium triacetoxyborohydride (61 mg, 0.29 mmol) was added and the colourless suspension was stirred for 1 h at rt before the mixture was diluted with water and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$, concentrated and the resulting colourless oil was purified by Biotage column chromatography (DCM/MeOH, 100:0 to 94:6) to give 8-(3-bromo-5-chloropyridin-4-yl)-1-methyl-1,3,8-triazaspiro[4.5]decan-4-one (167 mg, 80% yield) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.49 (s, 1H), 8.36 (s, 1H), 4.15 (s, 2H), 3.99 – 3.90 (m, 2H), 3.36 – 3.27 (m, 2H), 2.43 (s, 3H), 2.06 – 1.99 (m, 2H), 1.86 – 1.77 (m, 2H); LC–MS (method C, ESI, m/z) t_R = 2.20 min, 359/361/363 $(M+H)^+$.

8-(3-Bromo-5-chloropyridin-4-yl)-1-methyl-1,3,8-triazaspiro[4.5]decan-4-one (40 mg, 0.11 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole[27] **37** (32 mg, 0.11 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (4.1 mg, 5.6 µmol) were loaded in a microwave vial and acetonitrile (1.0 mL) and 0.5 M aqueous sodium carbonate (0.311 mL, 0.156 mmol) were added and the reaction mixture was stirred at 120 °C for 1 h under microwave irradiation. After evaporation of the solvent, the crude material was purified by Biotage column chromatography (DCM/EtOH, 100:0 to 86:14), followed by purification on a scx_2-cartrige (loading with DCM/:MeOH, 10:1, elution with DCM/1N NH_3 in MeOH, 9:1) and by prep. TLC (DCM/EtOH,

94:6) to give 8-(3-chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1-methyl-1,3,8-triazaspiro[4.5]decan-4-one **104** (30 mg, 62% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.21 (s, 1H), 7.80 (d, *J* = 0.8 Hz, 1H), 7.66 (s, 1H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.09 (s, 1H), 4.06 (d, *J* = 0.9 Hz, 2H), 3.95 (s, 3H), 3.44 – 3.36 (m, 2H), 3.05 – 2.98 (m, 2H), 2.32 (s, 3H), 1.82 – 1.73 (m, 2H), 1.63 – 1.56 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.2, 152.9, 150.7, 149.3, 136.8, 135.4, 133.4, 132.1, 129.7, 127.7, 127.1, 125.5, 122.6, 63.2, 59.2, 47.2, 39.1, 33.2, 28.6; LC–MS (method C, ESI, m/z) t_R = 2.26 min, 437/439 $(M+H)^+$; ESI-HRMS calcd for $C_{23}H_{26}{}^{35}ClN_6O$ $(M+H)^+$ 437.1851, found 437.1861.

8-(3-Chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1-(2,2,2-trifluoroethyl)-1,3,8-triazaspiro[4.5]decan-4-one (105)

A solution of trifluoroacetaldehyde methyl hemiacetal (1.11 mL, 11.6 mmol) and conc. sulfuric acid (9 mL) was heated to 70 °C. Nitrogen gas was bubbled through the solution and the outlet gas stream of this capped vial was passed through a second vial filled with a solution of 8-(3-bromo-5-chloropyridin-4-yl)-1,3,8-triazaspiro[4.5]decan-4-one (200 mg, 0.579 mmol) in TFA (7 mL) at rt. Whilst keeping a constant stream of nitrogen, the first vial was stirred for 30 min. Then, the reaction mixture from the second vial was carefully added dropwise to sat. $NaHCO_3$, EtOAc was added and the layers were separated. The aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The resulting brown oil was purified by Biotage column chromatography (DCM/EtOAc, 90:1 to 70:30) and by prep. TLC (DCM/EtOAc, 2:1, 3 runs) to give 8-(3-bromo-5-chloropyridin-4-yl)-1-(2,2,2-trifluoroethyl)-1,3,8-triazaspiro[4.5]decan-4-one (180 mg) as a colourless oil which slowly solidified and was used in the next step without further purification.

8-(3-Bromo-5-chloropyridin-4-yl)-1-(2,2,2-trifluoroethyl)-1,3,8-triazaspiro[4.5]decan-4-one (60 mg, 0.14 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole[27] **37** (40 mg, 0.14 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5.1 mg, 7.0 µmol) were loaded in a microwave vial. Acetonitrile (1.1 mL) and 0.5 M aqueous sodium carbonate (0.393 mL, 0.196 mmol) were added. The reaction mixture was stirred at 120 °C for 1 h under microwave irradiation before it was concentrated. The resulting brown solid was purified by Biotage column chromatography (DCM/EtOH, 100:0 to 94:6) and by prep. HPLC (method D) to give 8-(3-

chloro-5-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-1-(2,2,2-trifluoroethyl)-1,3,8-triazaspiro[4.5]decan-4-one **105** (8 mg, 12% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.23 (s, 1H), 7.80 (d, *J* = 0.8 Hz, 1H), 7.66 (d, *J* = 0.8 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 5.65 (s, 1H), 4.27 (s, 2H), 3.96 (s, 3H), 3.44 (t, *J* = 11.7 Hz, 2H), 3.11 (q, *J* = 9.1 Hz, 2H), 3.05 – 2.97 (m, 2H), 1.71 – 1.59 (m, 4H); LC–MS (method C, ESI, m/z) t_R = 2.85 min, 505/507 $(M+H)^+$; ESI-HRMS calcd for $C_{24}H_{25}{}^{35}ClF_3N_6O$ $(M+H)^+$ 505.1725, found 505.1731.

Preparation of Compounds in Table 8

1-Isopropyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole (106)

To a solution of 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole (387 mg, 1.43 mmol) in DMF (7 mL) was added potassium carbonate (515 mg, 3.72 mmol) and 2-iodopropane (180 µL, 1.80 mmol). The reaction mixture was stirred at rt for 2 days before the addition of an additional 1.3 eq of 2-iodopropane. After 16 h, 2.6 eq of iodopropane were added and the reaction mixture was stirred at rt for 72 h. The mixture was filtered and the filtrate was concentrated and purified by Biotage column chromatography (cyclohexane/EtOAc 90:10 to 60:40) to give 1-isopropyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole **106** (150 mg, 34% yield) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 0.8 Hz, 1H), 7.81 – 7.78 (m, 2H), 7.71 (d, *J* = 0.8 Hz, 1H), 7.50 – 7.48 (m, 2H), 4.52 (sept., *J* = 6.7 Hz, 1H), 1.54 (d, *J* = 6.7 Hz, 6H), 1.35 (s, 12H); LC–MS (method F, ESI, m/z) t_R = 1.71 min, 312/313 $(M+H)^+$.

8-(2-Amino-3-chloro-5-(4-(1-isopropyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (108)

8-(2-Amino-5-bromo-3-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **76** (48 mg, 0.13 mmol), 1-isopropyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole **106** (50 mg, 0.16 mmol) and $Pd(PPh_3)_4$ (7.7 mg, 6.7 µmol) were loaded in a microwave vial and acetonitrile (2.3 mL) and 0.5 M sodium carbonate in water (374 µL, 0.187 mmol) were added. The reaction mixture was heated at 120 ºC for 60 min. The solvent was evaporated and the crude

material was purified by Biotage column chromatography (DCM/EtOH 98:2 to 95:5) and by SCX-2 column (loading with DCM/MeOH, elution with 1 N NH_3 in MeOH) to afford 8-(2-amino-3-chloro-5-(4-(1-isopropyl-1*H*-pyrazol-4-yl)phenyl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **108** (23 mg, 37% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 0.8 Hz, 1H), 7.75 (s, 1H), 7.72 (d, *J* = 0.8 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.25 – 7.20 (m, 2H), 6.42 (s, 1H), 4.93 (s, 2H), 4.53 (sept, *J* = 6.7 Hz, 1H), 3.26 (t, *J* = 6.9 Hz, 2H), 3.14 – 3.08 (m, 2H), 2.72 (s, 2H), 2.05 – 1.90 (m, 4H), 1.55 (d, *J* = 6.7 Hz, 6H), 1.35 – 1.26 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.8, 155.5, 154.0, 147.9, 136.3, 136.1, 131.6, 129.8, 125.5, 125.2, 123.4, 122.0, 110.3, 54.0, 47.6, 42.0, 38.7, 32.3, 31.2, 23.0; LC–MS (method C, ESI, m/z) t_R = 2.26 min, 465/467 $(M+H)^+$; ESI-HRMS calcd for $C_{25}H_{30}{}^{35}ClN_6O$ $(M+H)^+$ 465.2164, found 465.2168.

8-(2-Amino-3-chloro-5-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (110)

8-(2-(bis(4-Methoxybenzyl)amino)-5-bromo-3-chloropyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one **83** (164 mg, 0.272 mmol) was suspended in acetonitrile (5 mL). 1-Methylindazole-5-boronic acid **39** (72 mg, 0.41 mmol), 0.5 M aqueous sodium carbonate (1.09 mL, 0.545 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (11 mg, 0. 14 mmol) were added. The reaction mixture was stirred at 120 ºC for 1 h and then diluted with acetonitrile and filtered. The filtrate was concentrated and the crude product was purified by flash-chromatography (Companion, n-heptane/EtOAc gradient) to give 8-(2-(bis(4-methoxybenzyl)amino)-3-chloro-5-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (139 mg, 78% yield) as a brown solid which was used directly in the next step. LC–MS (method B, ESI, m/z) t_R = 2.87 min, 653/655 $(M+H)^+$.

8-(2-(bis(4-Methoxybenzyl)amino)-3-chloro-5-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (139 mg, 0.213 mmol) was dissolved in TFA (5 mL). The brown reaction solution was stirred overnight at rt and then concentrated. The red residue was purified by flash-chromatography (Companion, DCM/MeOH gradient). The product was recrystallized in diethyl ether to give 8-(2-amino-3-chloro-5-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one **110** (48 mg, 55% yield) as a beige solid. ^{1}H NMR (500 MHz,

DMSO-d6) δ 8.06 (d, *J* = 1.0 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 1H), 7.66 (s, 1H), 7.63 (s, 1H), 7.44 (s, 1H), 7.27 (dd, *J* = 8.6, 1.7 Hz, 1H), 6.15 (s, 2H), 4.08 (s, 3H), 3.13 (s, 2H), 2.84 (s, 4H), 1.68 – 1.62 (m, 4H); ^{13}C NMR (126 MHz, DMSO-d6) δ 157.7, 156.2, 153.3, 147.9, 138.7, 132.4, 130.5, 128.3, 124.2, 123.7, 120.3, 109.3, 108.6, 78.9, 50.1, 47.0, 35.9, 35.5; LC–MS (method C, ESI, m/z) t_R = 1.69 min, 413/415 $(M+H)^+$; ESI-HRMS calcd for $C_{20}H_{22}{}^{35}ClN_6O_2$ $(M+H)^+$ 413.1487, found 413.1476.

1-Isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (107)

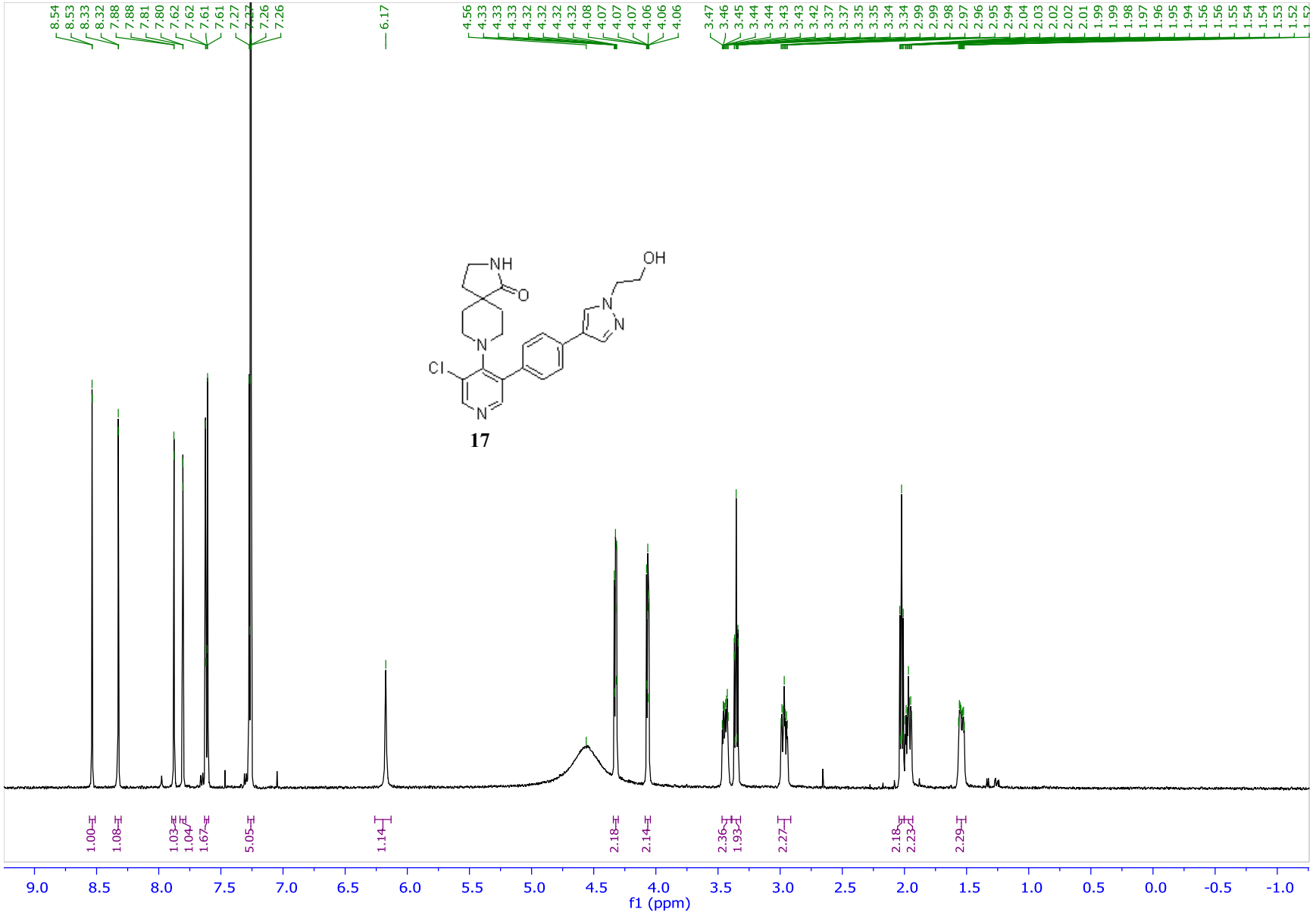
A mixture of 1*H*-indazole-6-boronic acid, pinacol ester (500 mg, 2.05 mmol), 2-bromopropane (0.352 mL, 4.10 mmol) and potassium carbonate (849 mg, 6.15 mmol) in DMF (8 mL) was heated at 80 °C for 24 h. Additional 2-bromopropane (0.352 mL, 4.10 mmol) was added and the mixture was stirred at 85 °C for 2 days. Water and EtOAc were added and the layers were separated. The aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuum. The resulting brown oil was purified by Biotage column chromatography (cyclohexane/EtOAc, 95:5 to 70:30) to give 1-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole **107** (232 mg, 40% yield) and 2-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole (99 mg, 17%) as colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.98 (s, 1H), 7.71 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.56 (dd, *J* = 8.1, 0.8 Hz, 1H), 4.93 (sept, *J* = 6.7 Hz, 1H), 1.57 (d, *J* = 6.7 Hz, 6H), 1.36 (s, 12H); LC–MS (method C, ESI, m/z) t_R = 3.26 min, 286/287 $(M+H)^+$.

8-(2-Amino-3-chloro-5-(1-isopropyl-1*H*-indazol-6-yl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one (111)

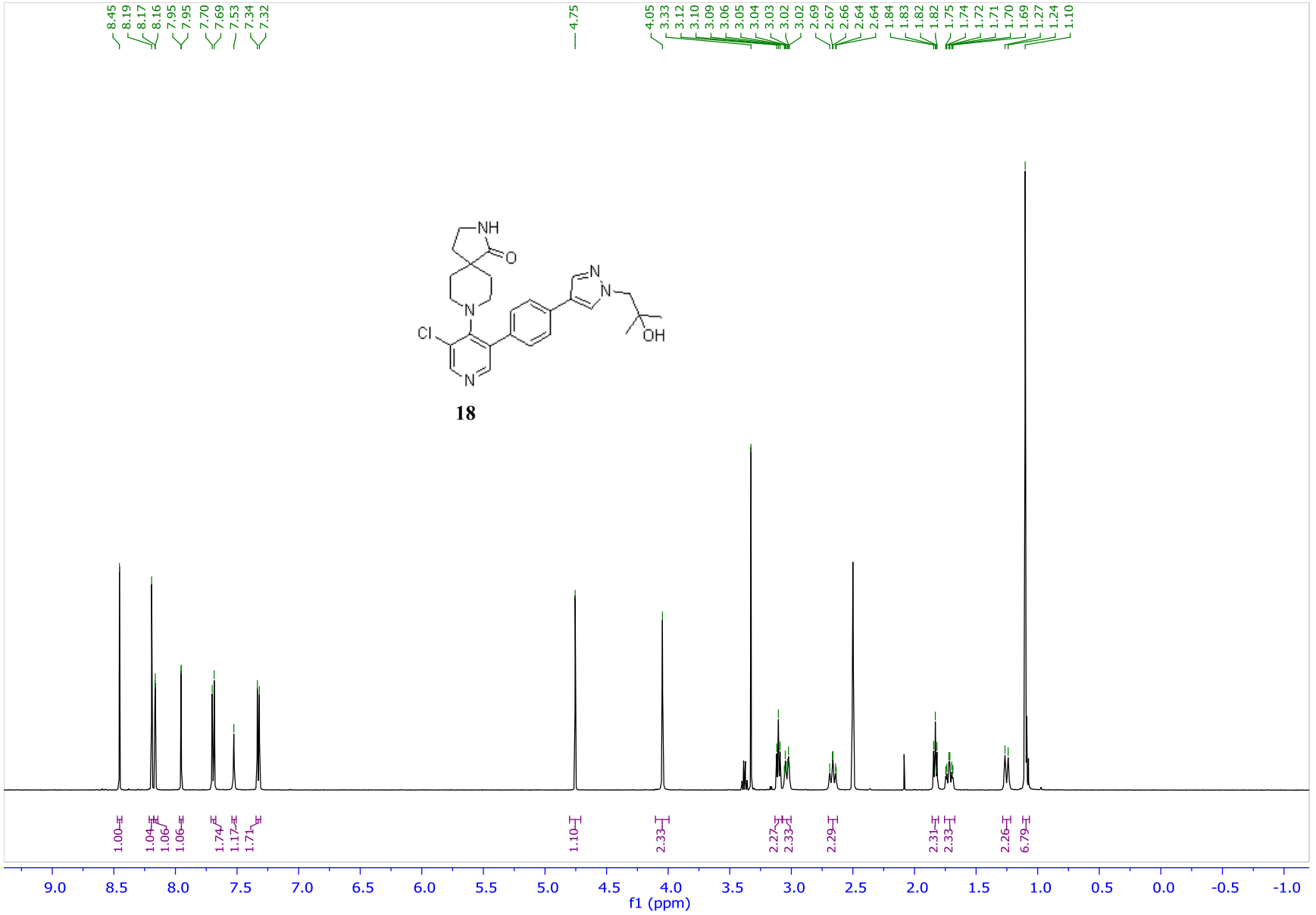
8-(2-Amino-5-bromo-3-chloropyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **76** (40 mg, 0.11 mmol), 1-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole **106** (32 mg, 0.11 mmol) and $Pd(PPh_3)_4$ (6.4 mg, 5.6 µmol) were loaded in a microwave vial. Acetonitrile (1.0 mL) and 0.5 M aqueous sodium carbonate (0.311 mL, 0.156 mmol) were added and the mixture was stirred at 120 °C for 1 h under microwave irradiation. The resulting brown solid was purified by Biotage column chromatography (DCM/EtOH, 100:0 to 96:4) to give 8-(2-amino-3-chloro-5-(1-isopropyl-1*H*-indazol-6-yl)pyridin-4-yl)-2,8-diazaspiro[4.5]decan-1-one **111** (22 mg, 45%

yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.07 (s, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.73 (s, 1H), 7.53 (s, 1H), 7.49 (s, 1H), 7.03 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.16 (s, 2H), 5.02 (sept, *J* = 6.6 Hz, 1H), 3.07 (t, *J* = 6.8 Hz, 2H), 3.02 – 2.96 (m, 2H), 2.70 – 2.57 (m, 2H), 1.75 (t, *J* = 6.8 Hz, 2H), 1.72 – 1.62 (m, 2H), 1.50 (d, *J* = 6.6 Hz, 6H), 1.21 – 1.15 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d6) δ 179.9, 156.4, 153.5, 148.2, 138.5, 136.0, 132.2, 124.0, 122.7, 122.3, 120.4, 109.3, 108.5, 49.2, 47.4, 41.4, 37.7, 31.8, 30.3, 22.2; LC–MS (method C, ESI, m/z) t_R = 2.13 min, 439/441 $(M+H)^+$; ESI-HRMS calcd for $C_{23}H_{28}{}^{35}ClN_6O$ $(M+H)^+$ 439.2008, found 439.2010.

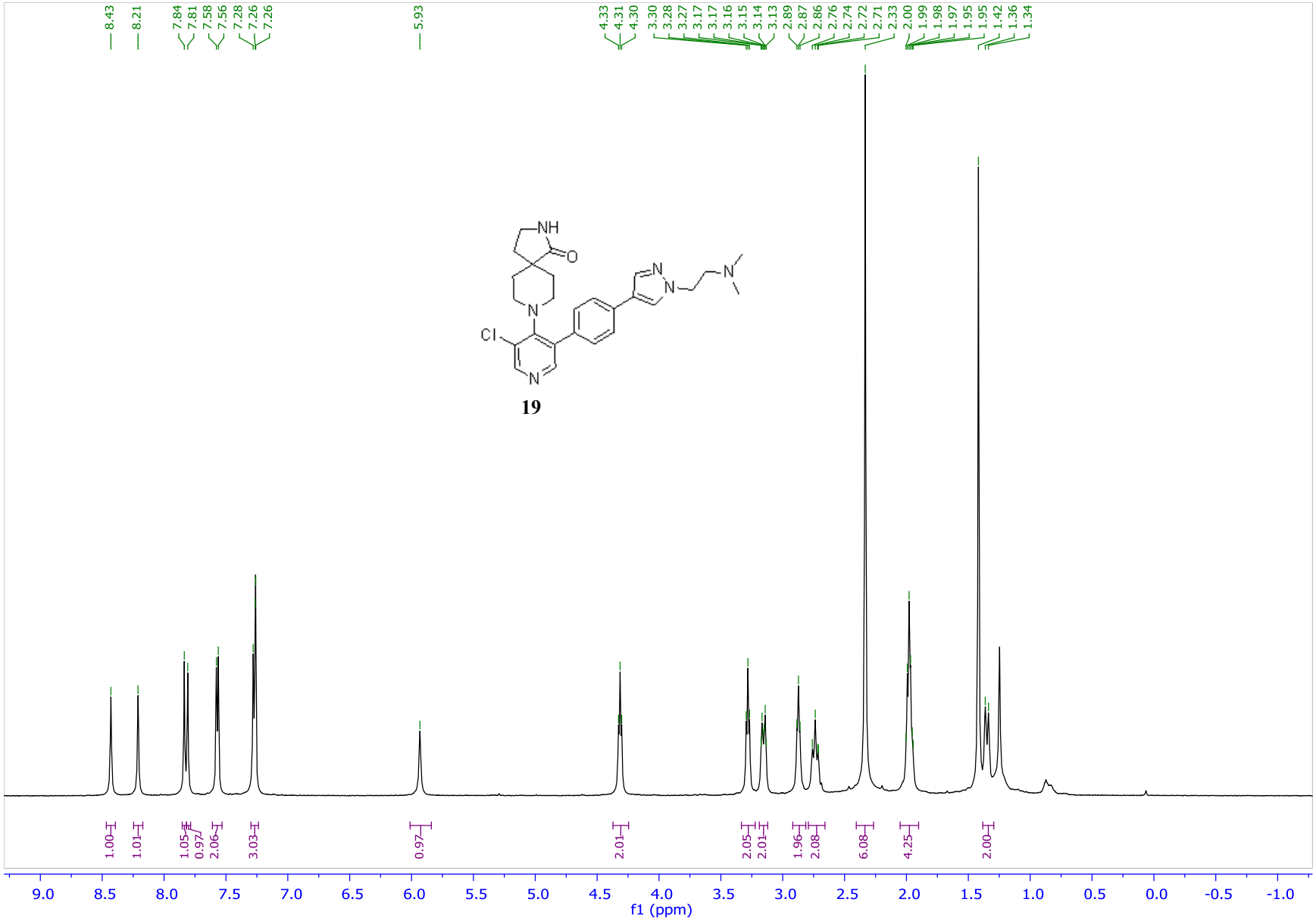
^{1}H NMR ($CDCl_3$, 500 MHz)



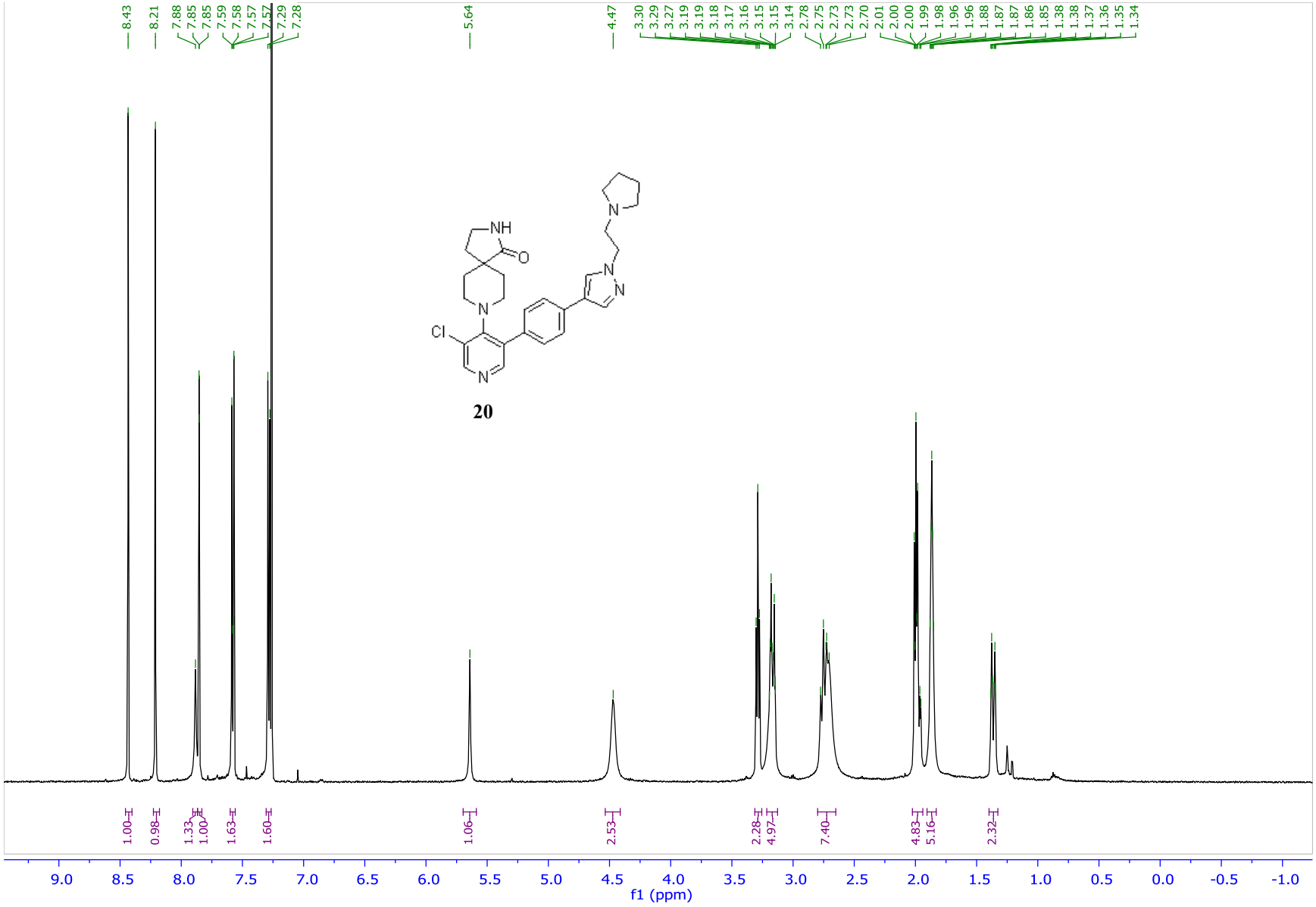
^{1}H NMR (DMSO-d6, 500 MHz)



^{1}H NMR ($CDCl_3$, 500 MHz)

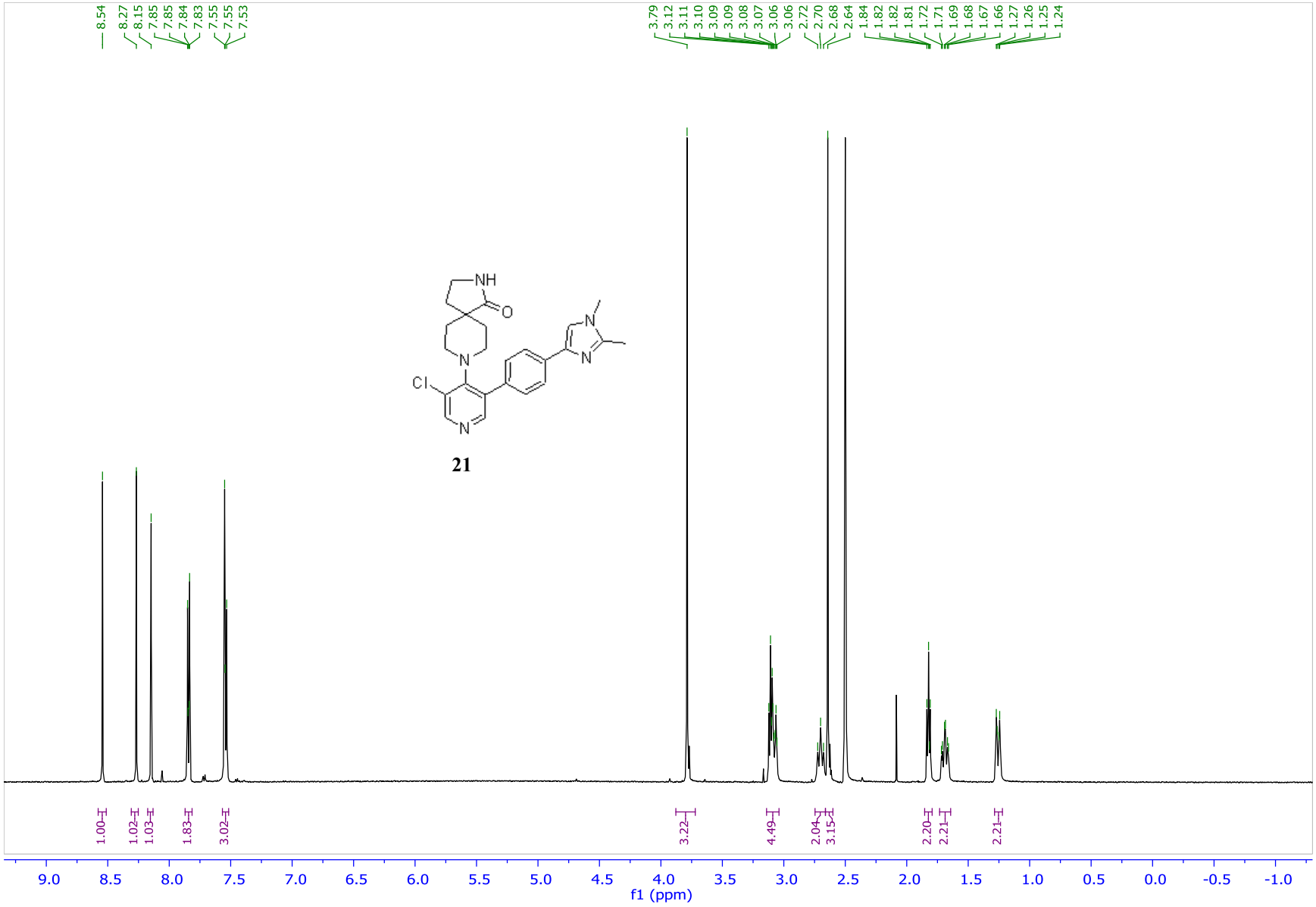


^{1}H NMR ($CDCl_3$, 500 MHz)

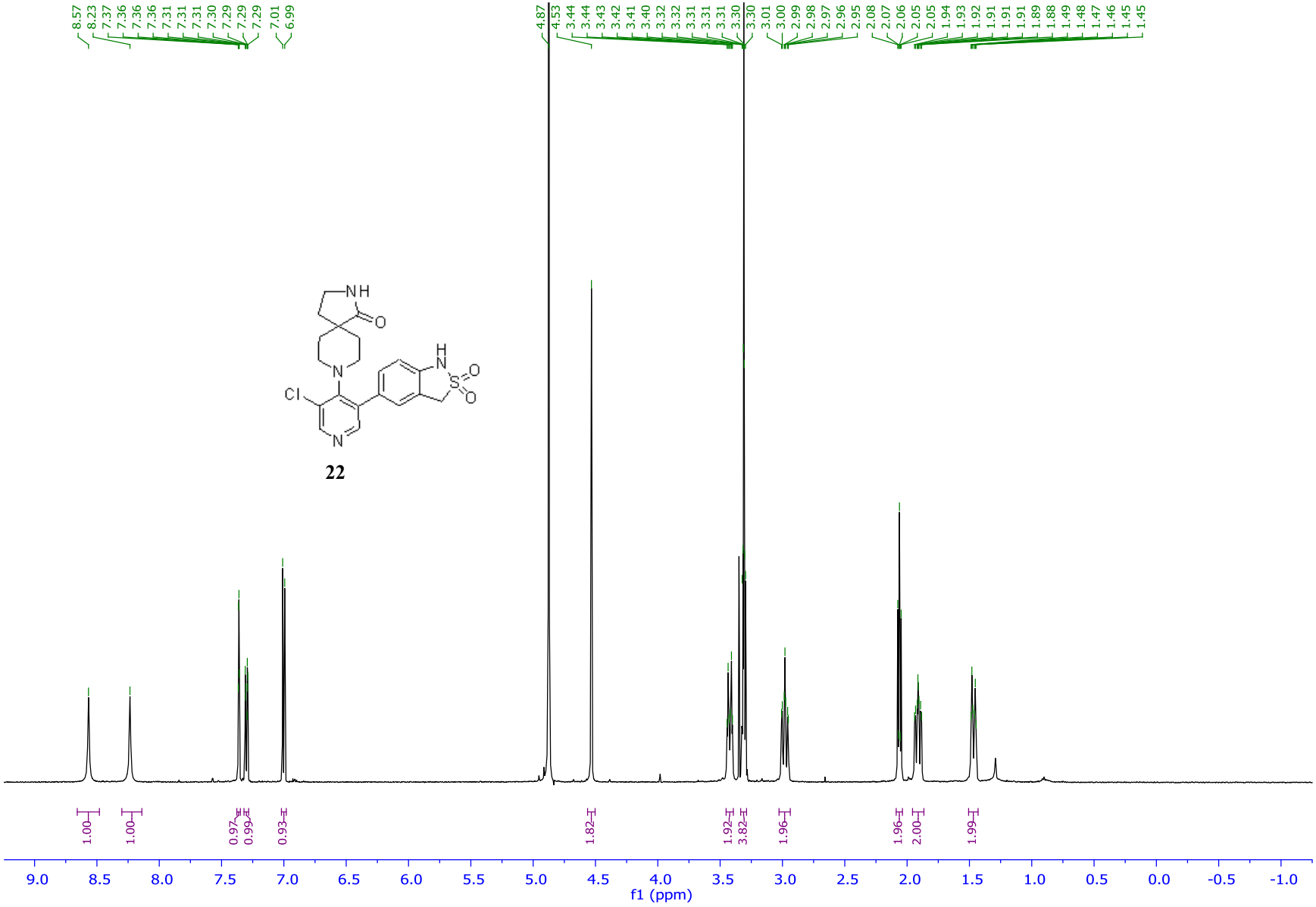


20

^{1}H NMR (DMSO-d6, 500 MHz)

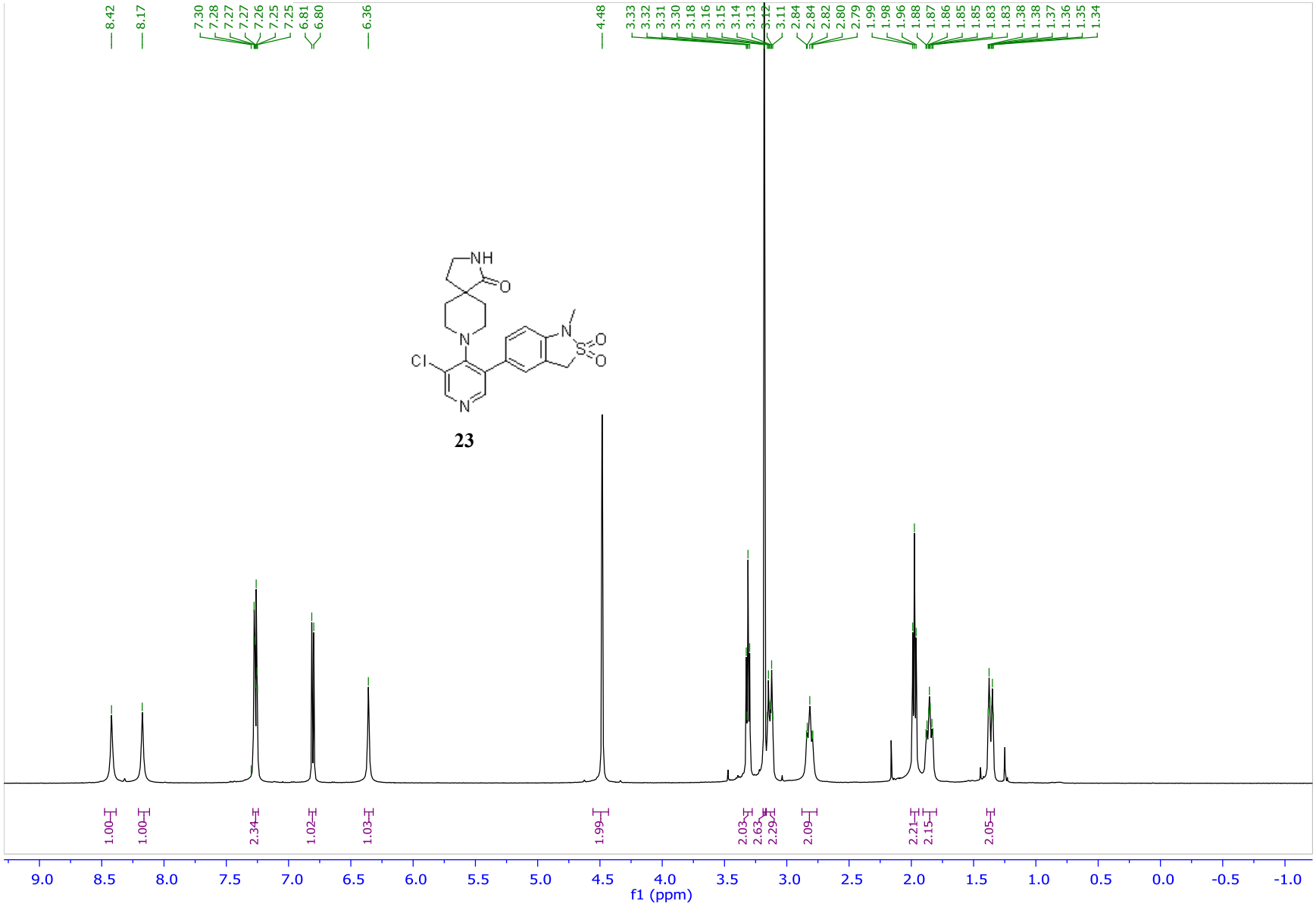


^{1}H NMR (CD_3OD, 500 MHz)



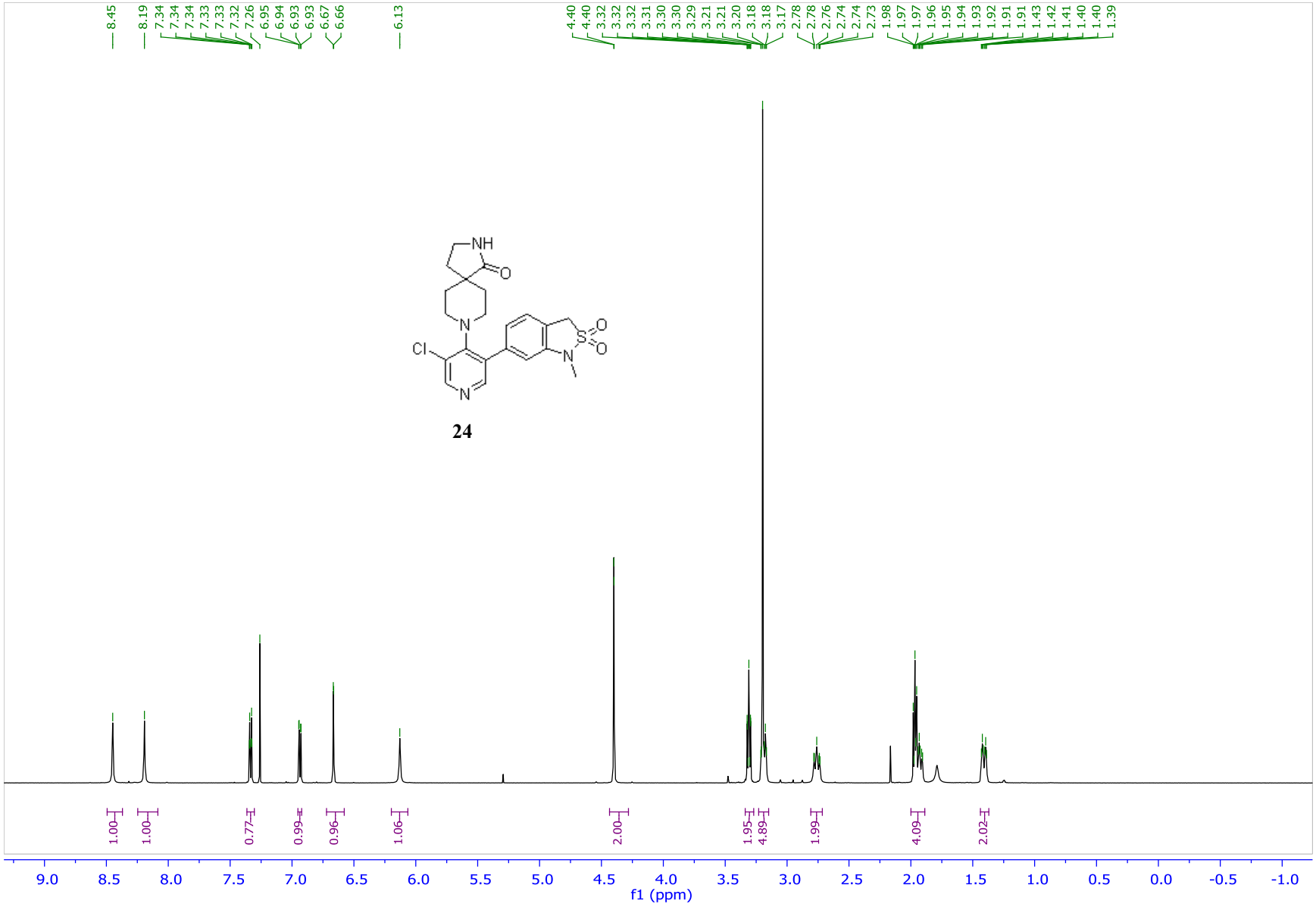
22

^{1}H NMR ($CDCl_3$, 500 MHz)



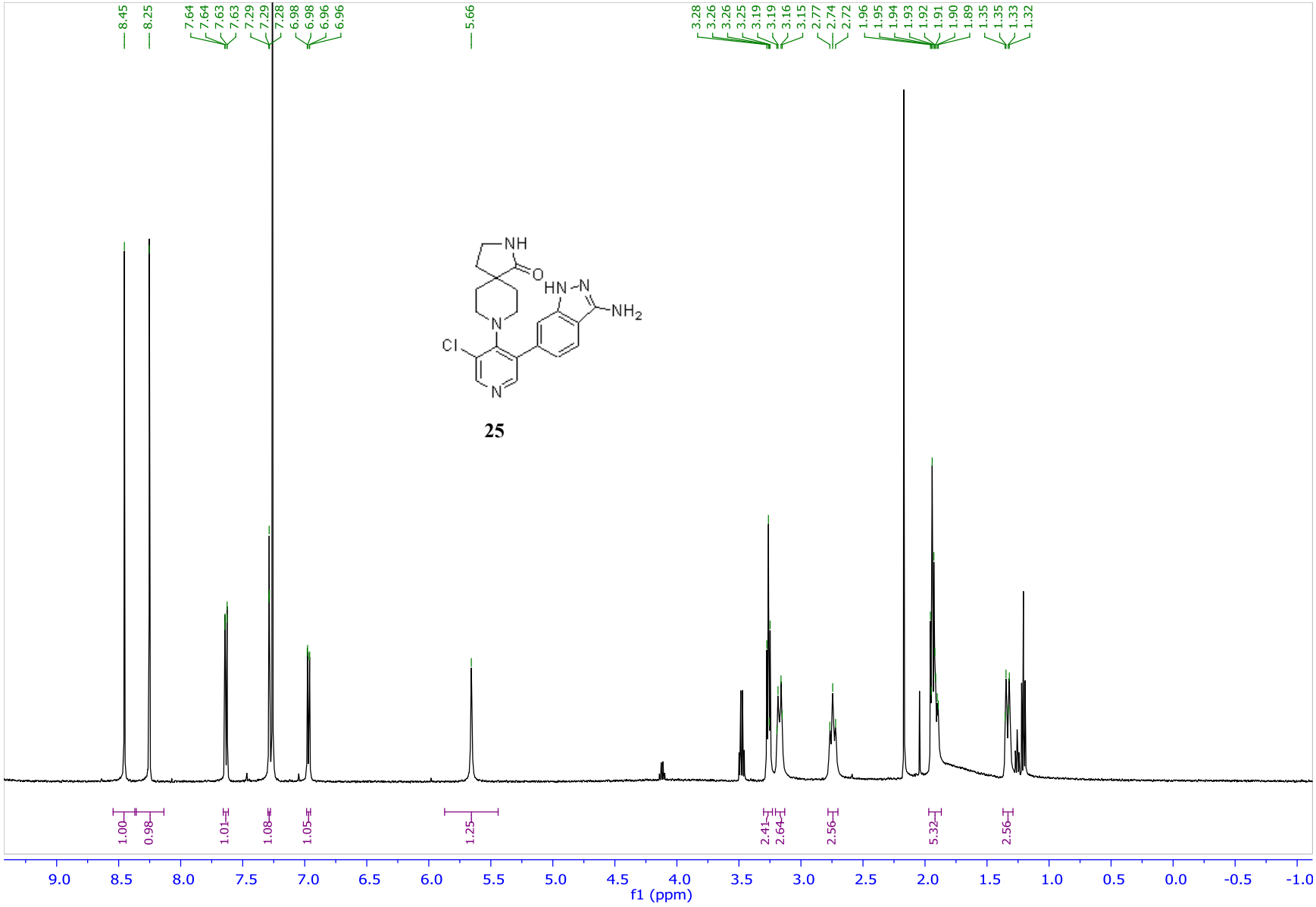
23

^{1}H NMR ($CDCl_3$, 500 MHz)



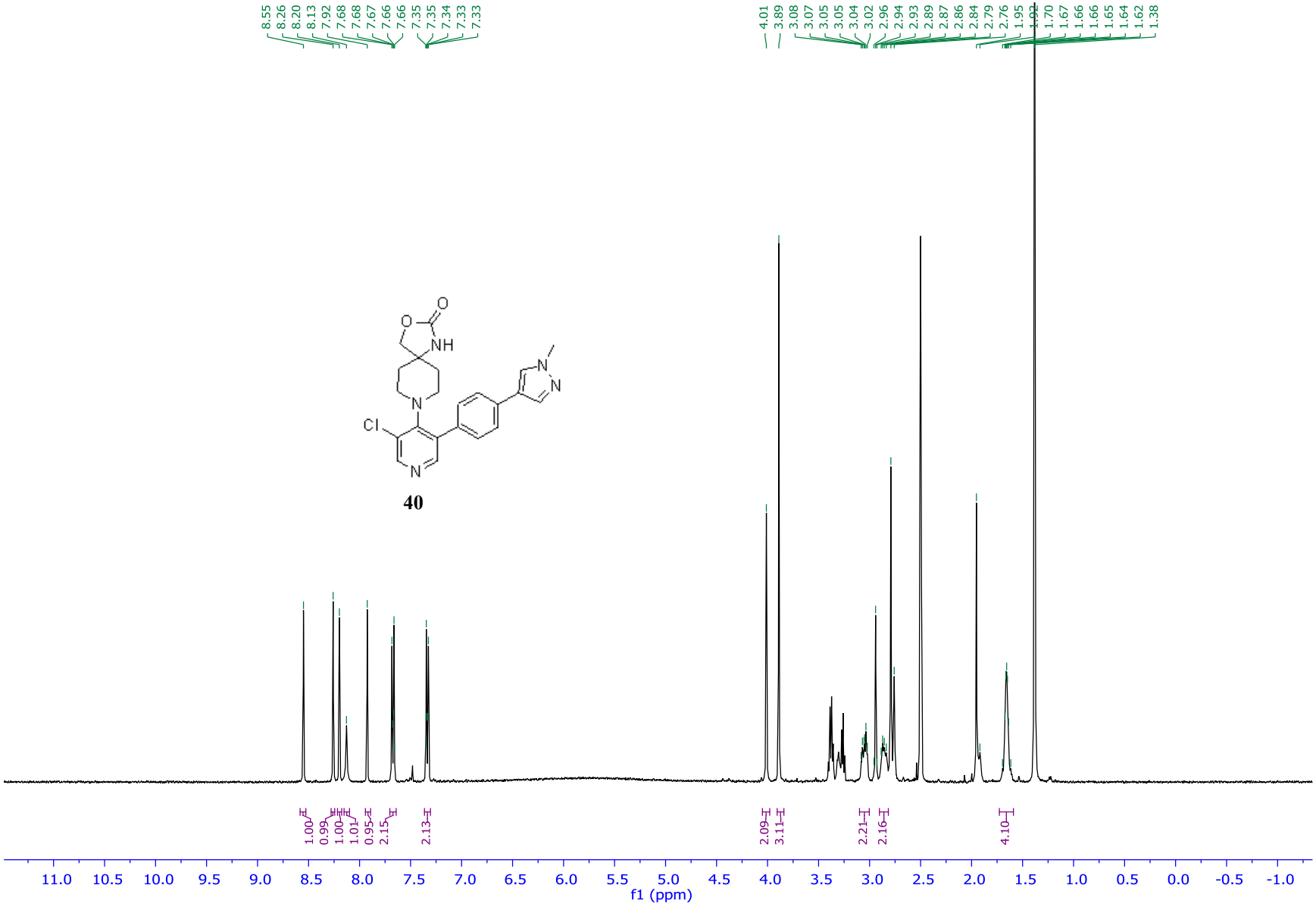
24

^{1}H NMR ($CDCl_3$, 500 MHz)



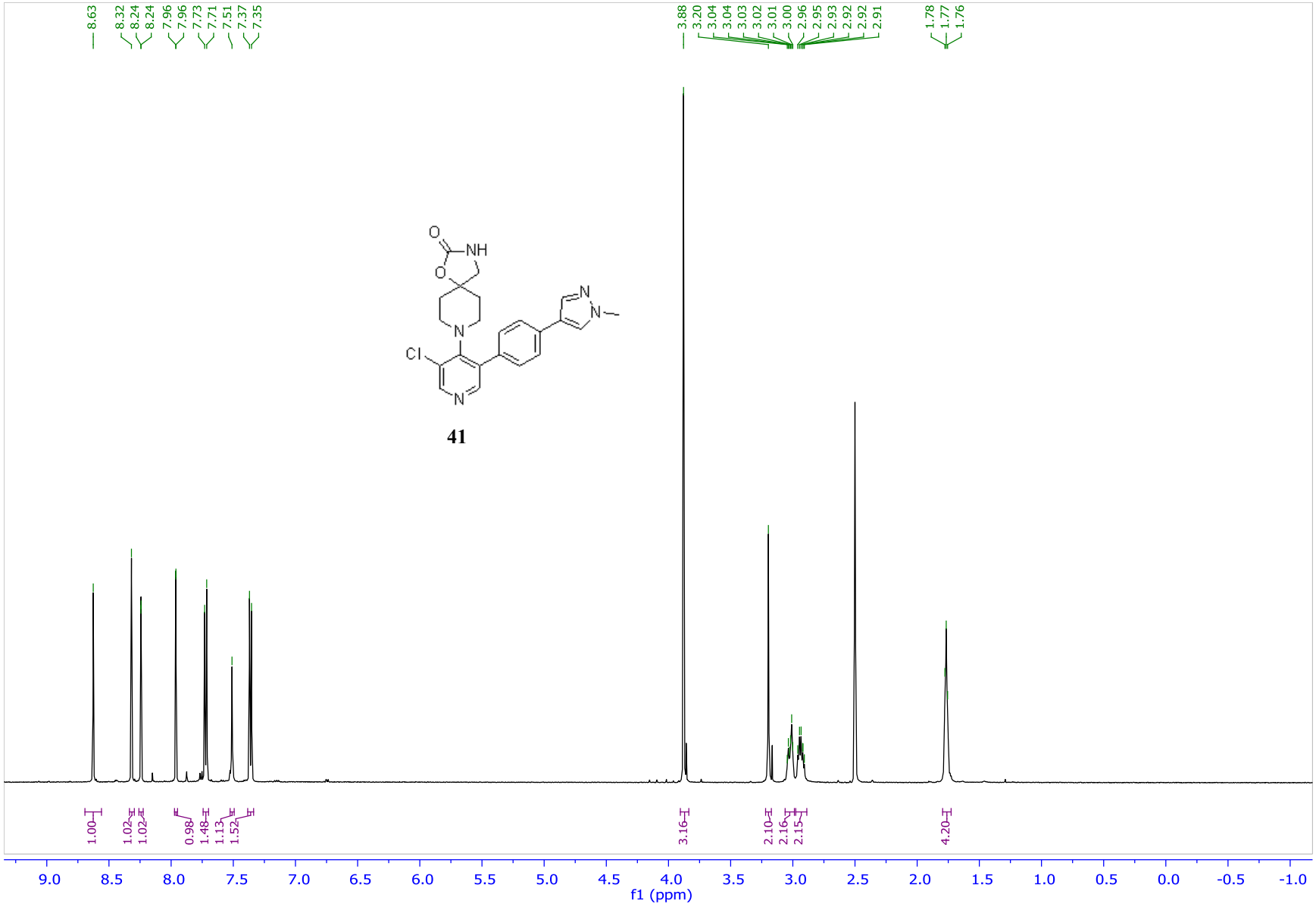
25

^{1}H NMR (DMSO-d6, 400 MHz)



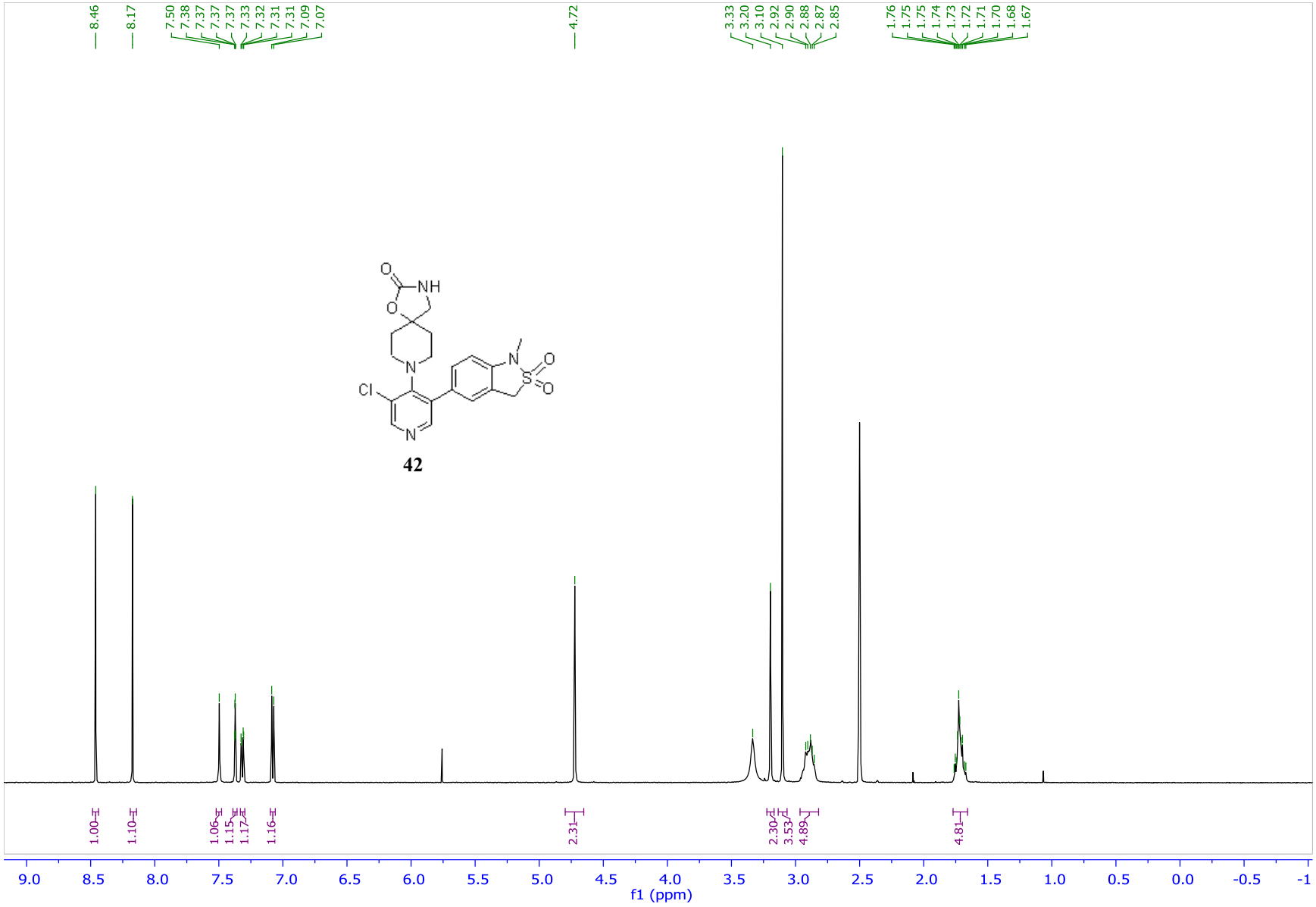
40

^{1}H NMR (DMSO-d6, 500 MHz)



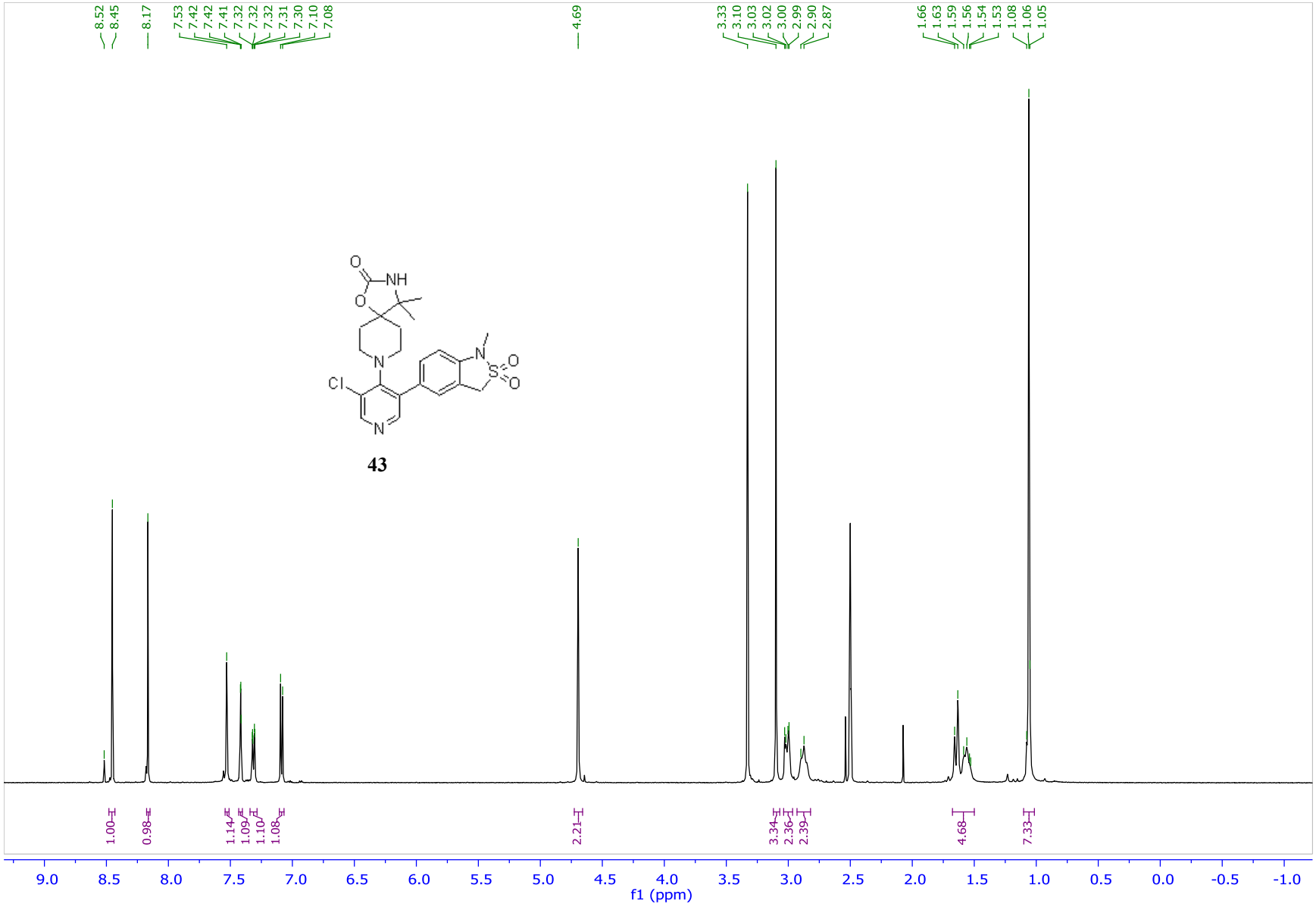
41

^{1}H NMR (DMSO-d6, 500 MHz)



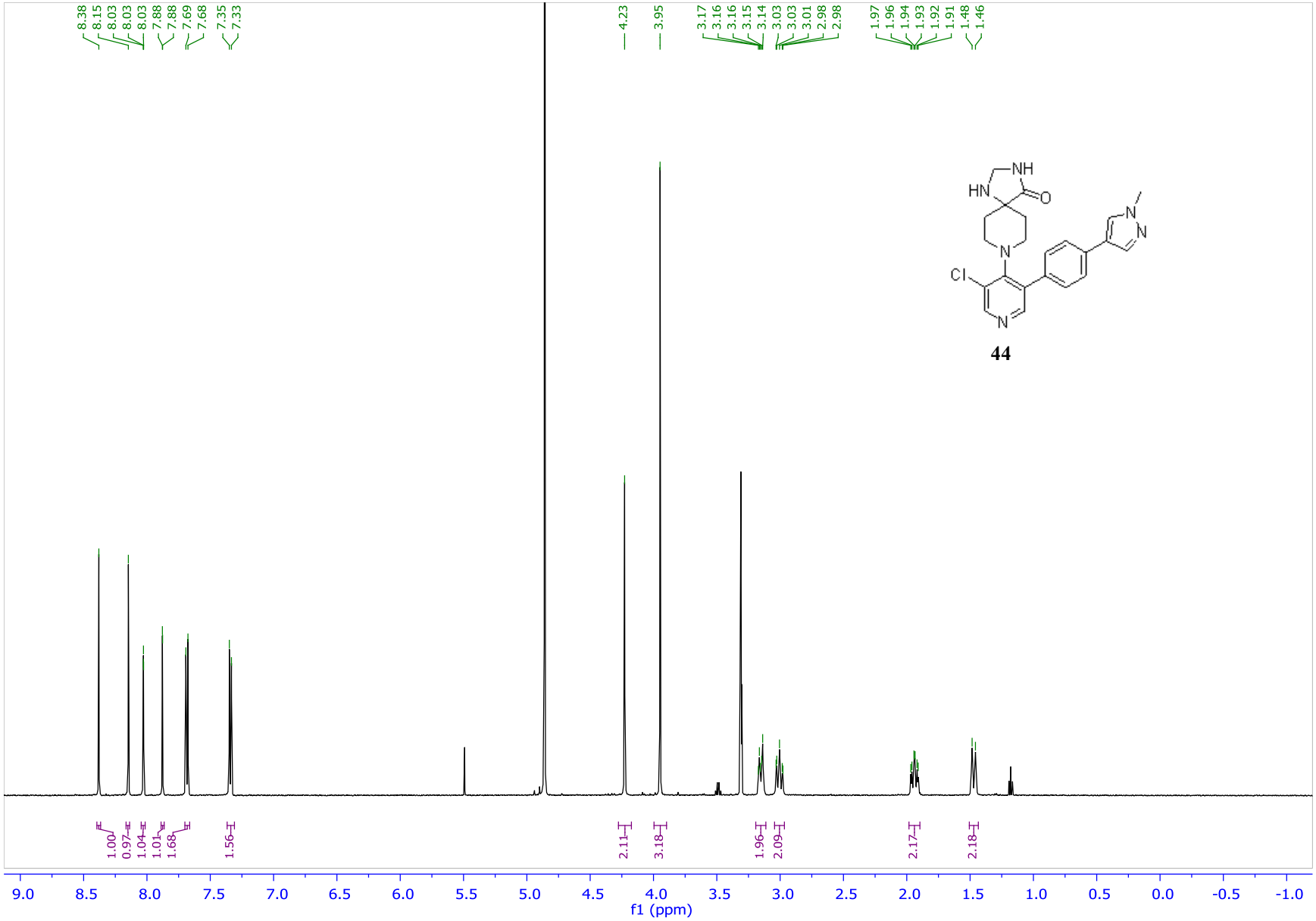
42

^{1}H NMR (DMSO-d6, 500 MHz)



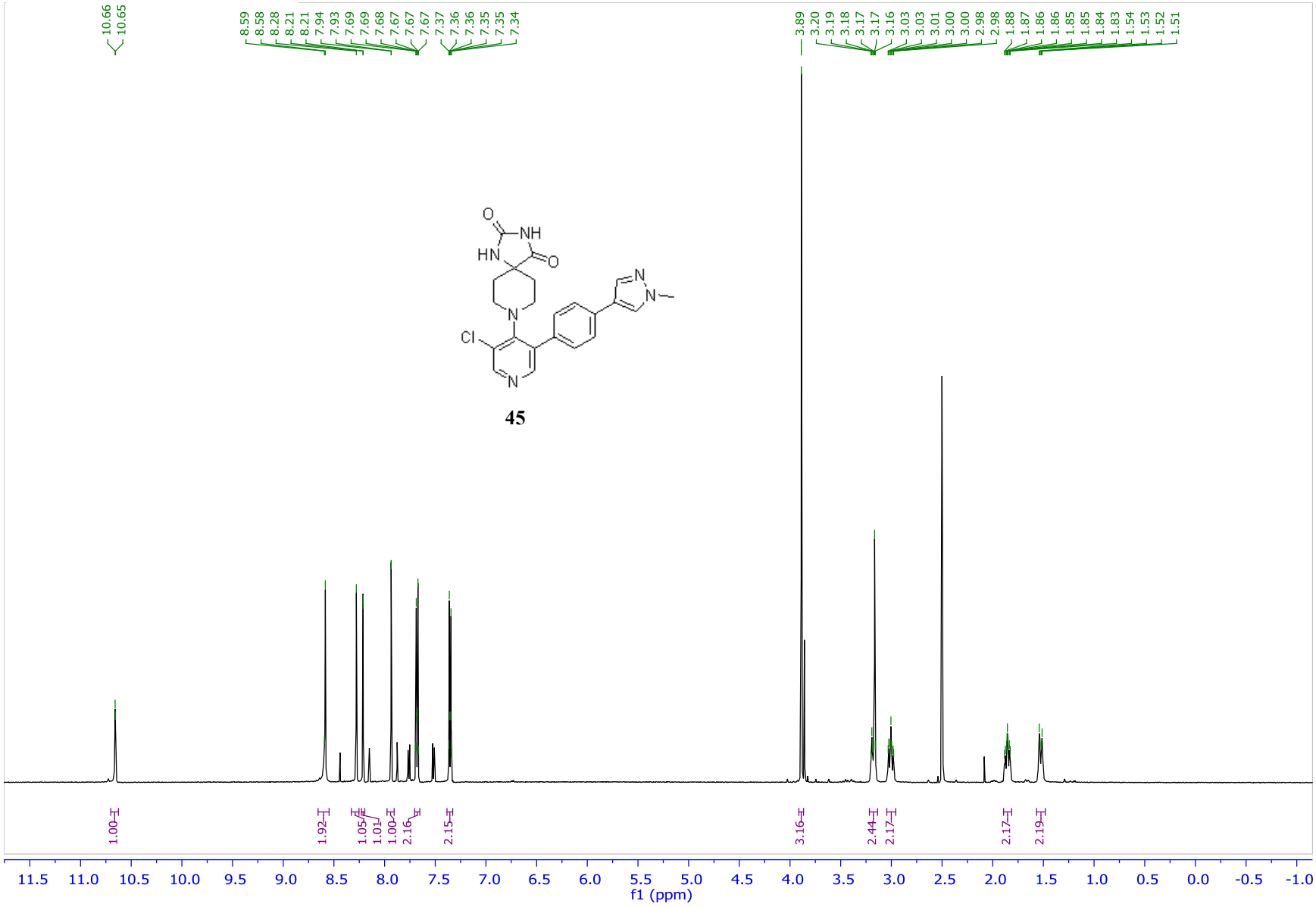
43

^{1}H NMR (CD_3OD, 500 MHz)

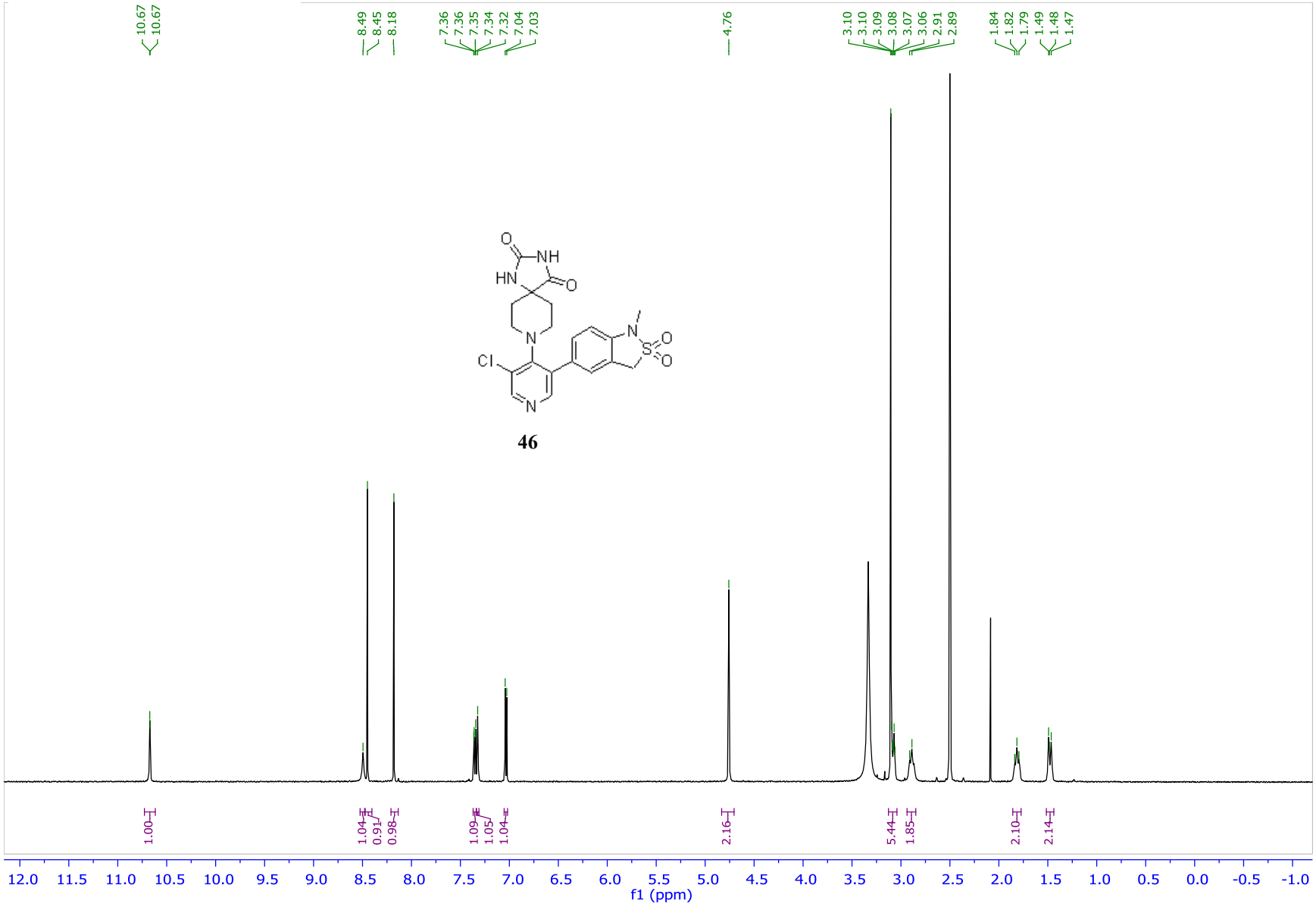


44

^{1}H NMR (DMSO-d6, 500 MHz)

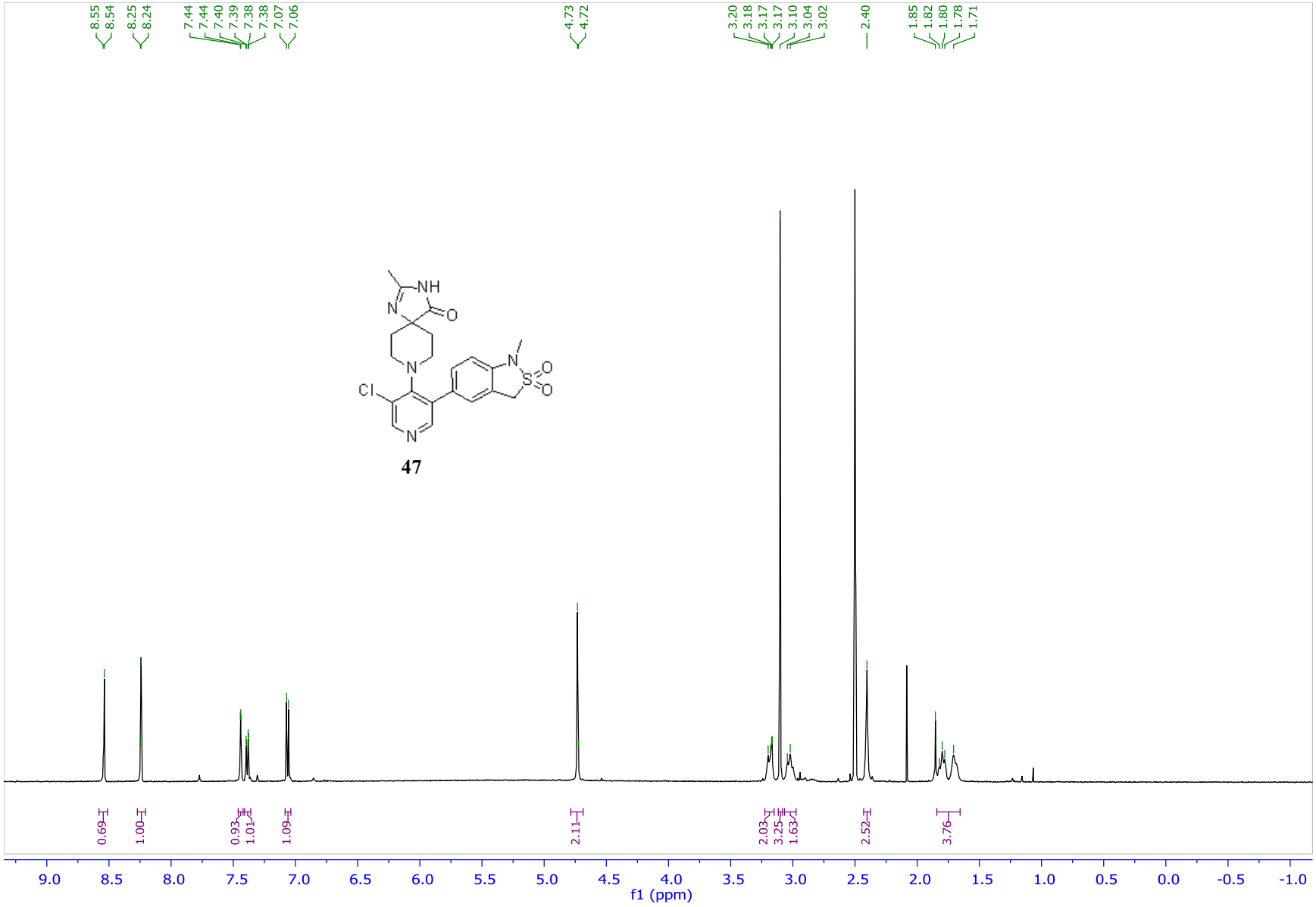


^{1}H NMR (DMSO-d6, 500 MHz)



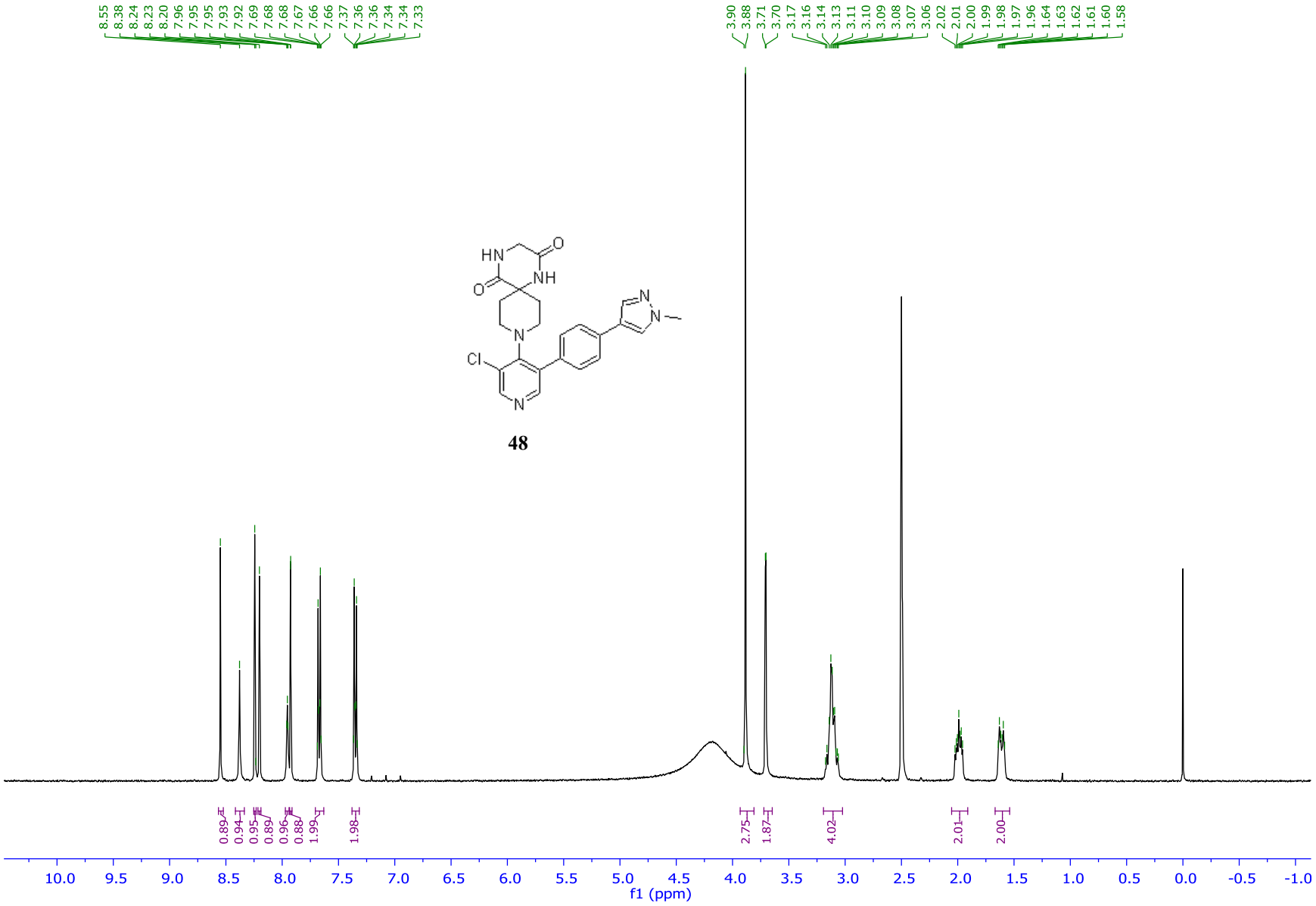
46

^{1}H NMR (DMSO-d6, 500 MHz)



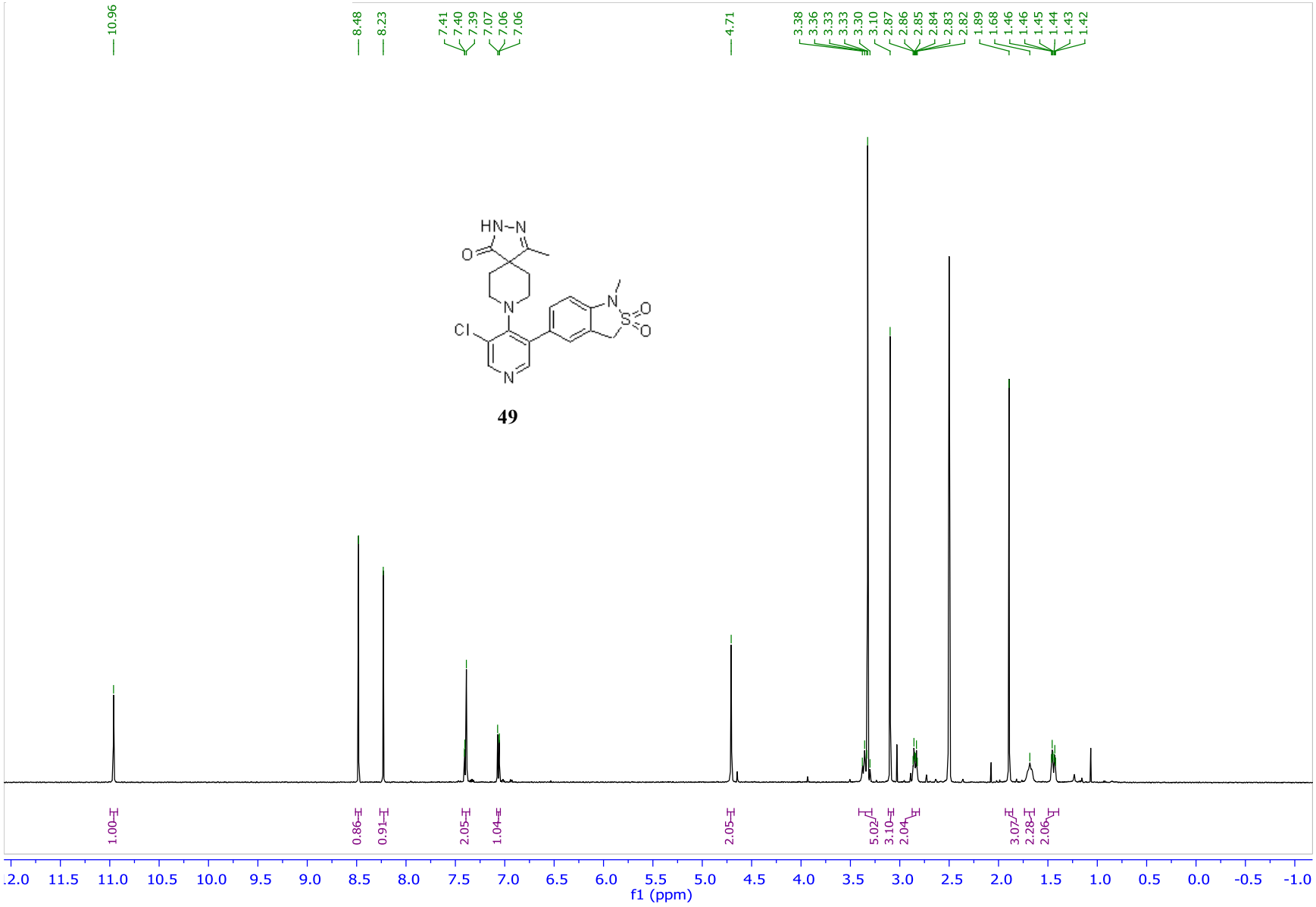
47

^{1}H NMR (DMSO-d6, 400 MHz)



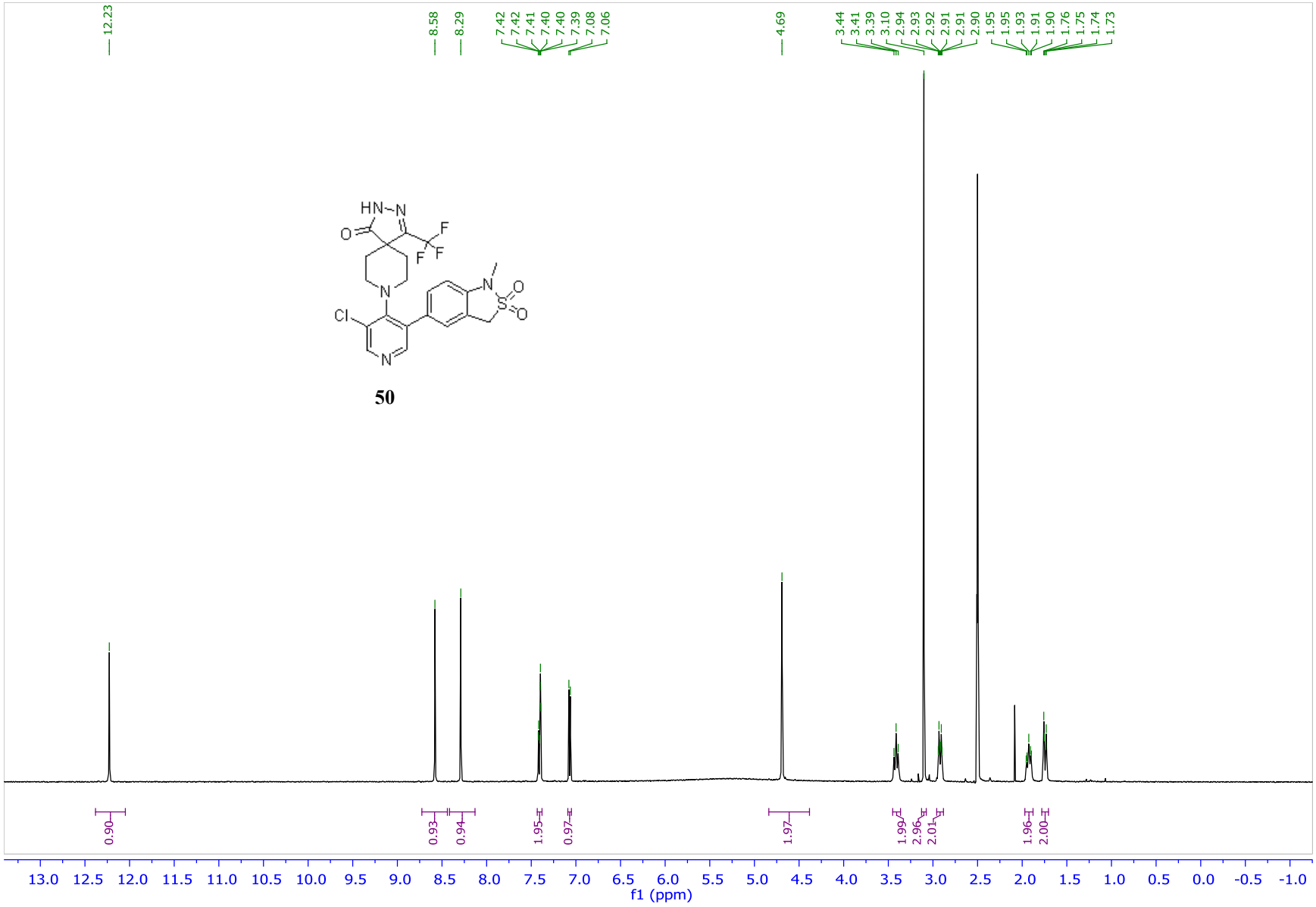
48

^{1}H NMR (DMSO-d6, 500 MHz)



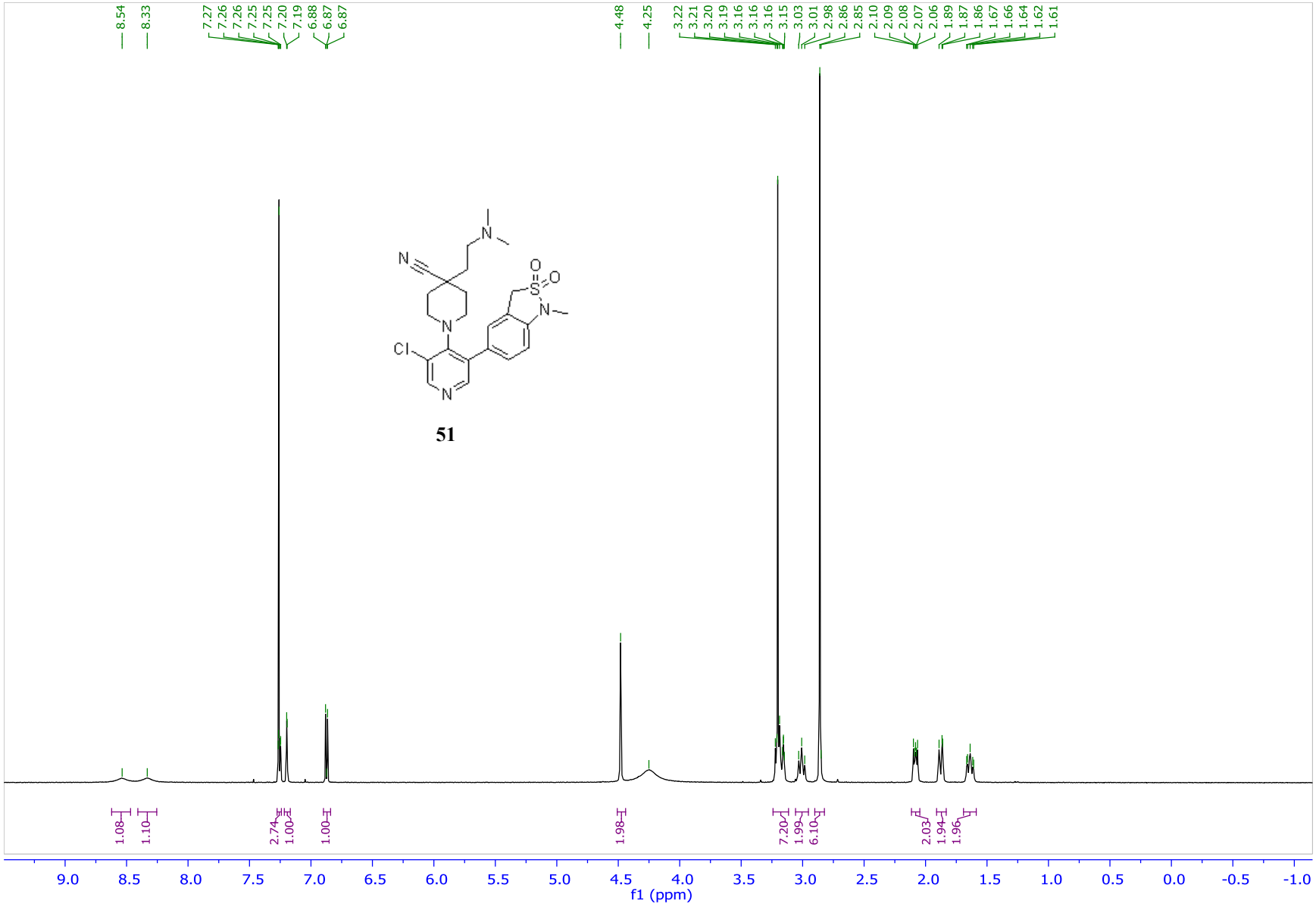
49

^{1}H NMR (DMSO-d6, 500 MHz)



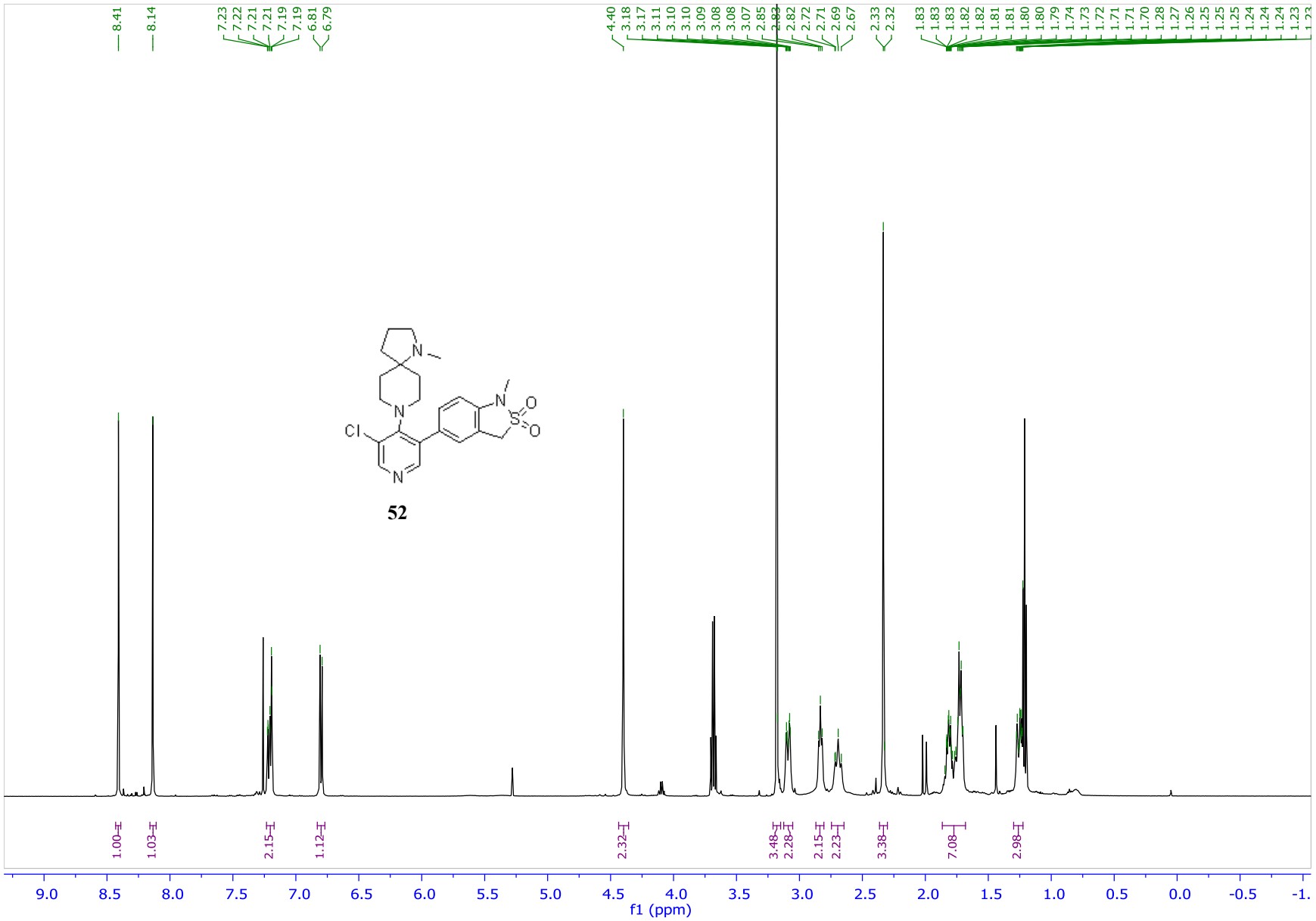
50

^{1}H NMR ($CDCl_3$, 500 MHz)



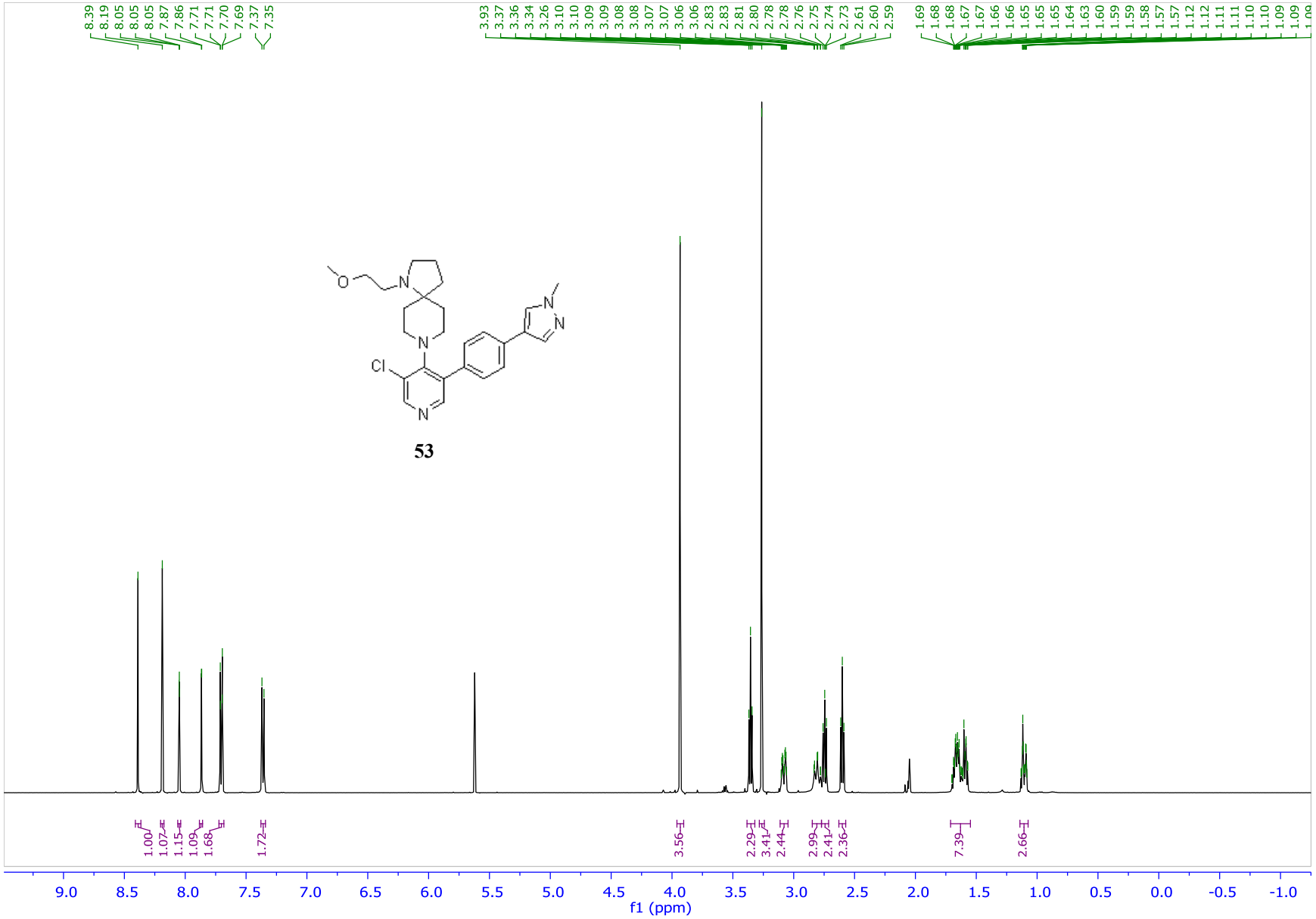
51

^{1}H NMR ($CDCl_3$, 500 MHz)

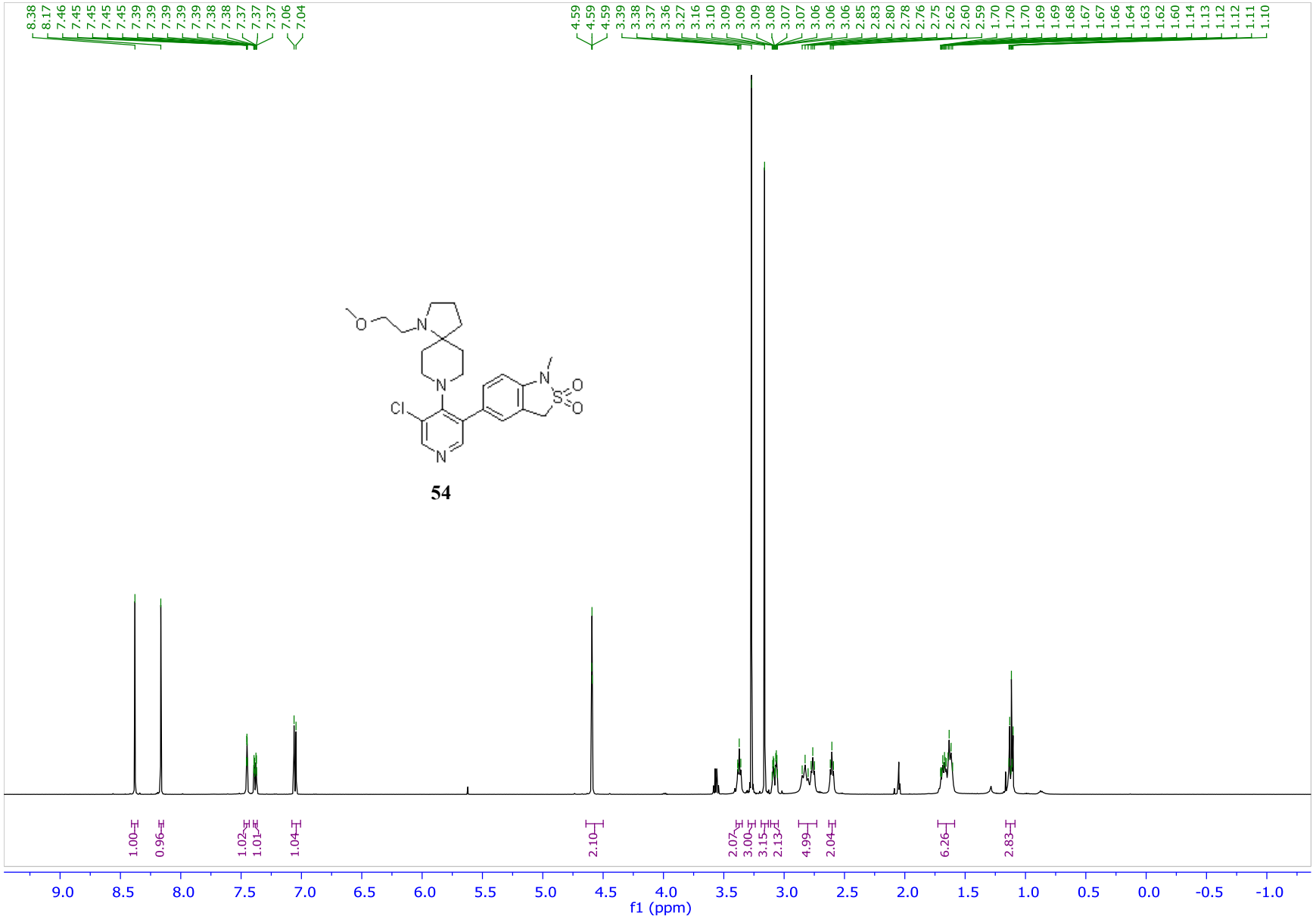


52

^{1}H NMR (acetone-d6, 500 MHz)

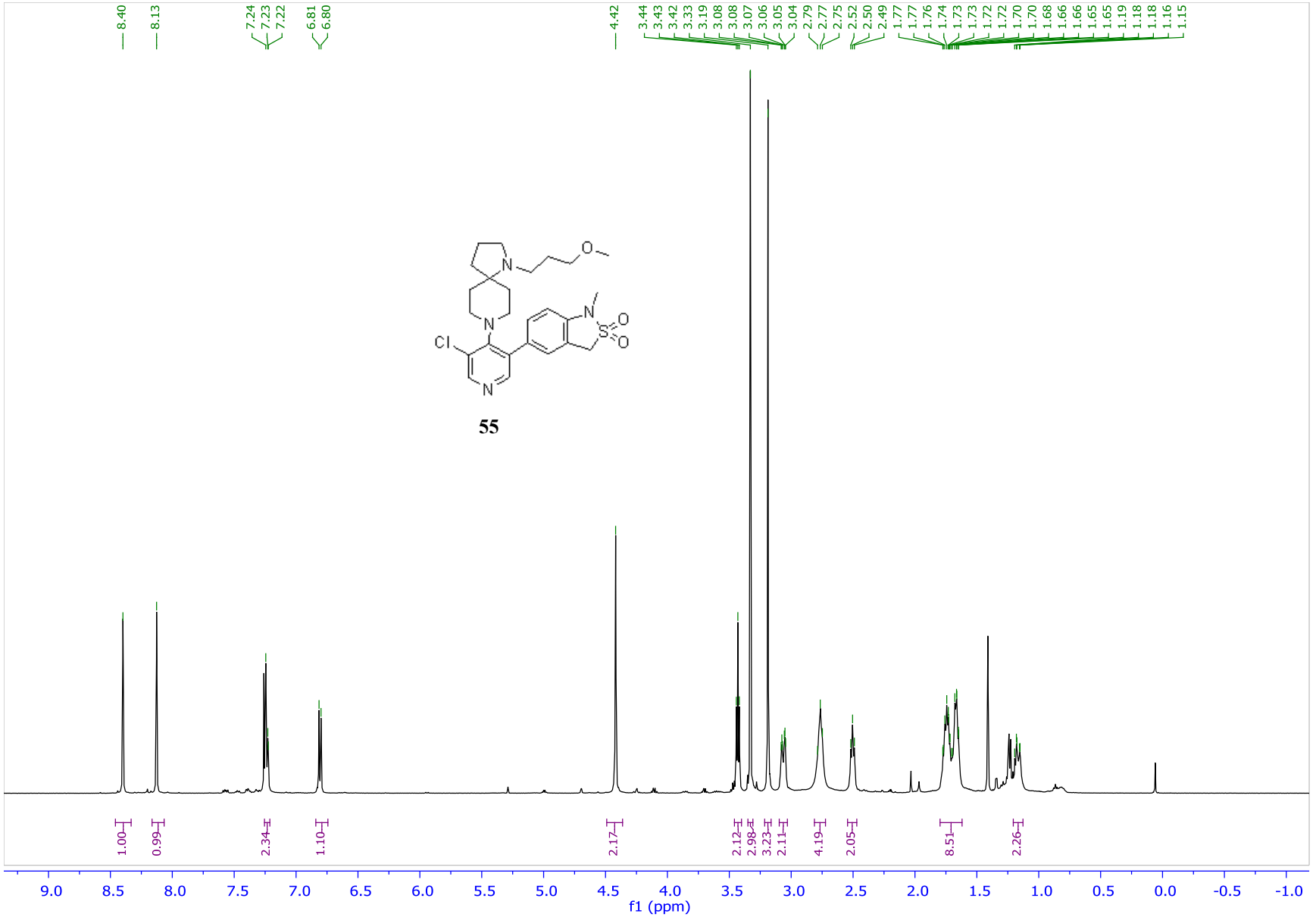


^{1}H NMR (acetone-d6, 500 MHz)



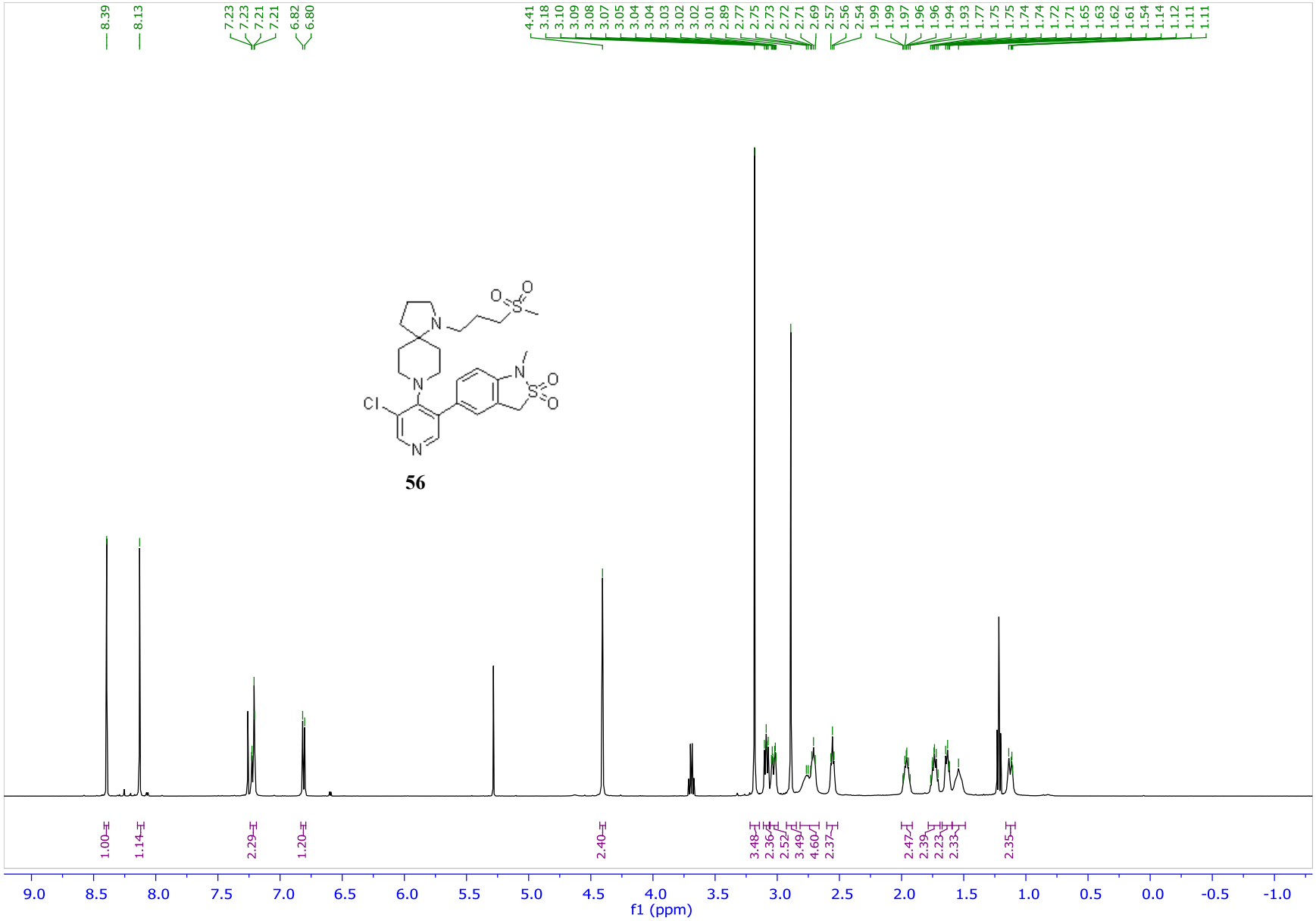
54

^{1}H NMR ($CDCl_3$, 500 MHz)

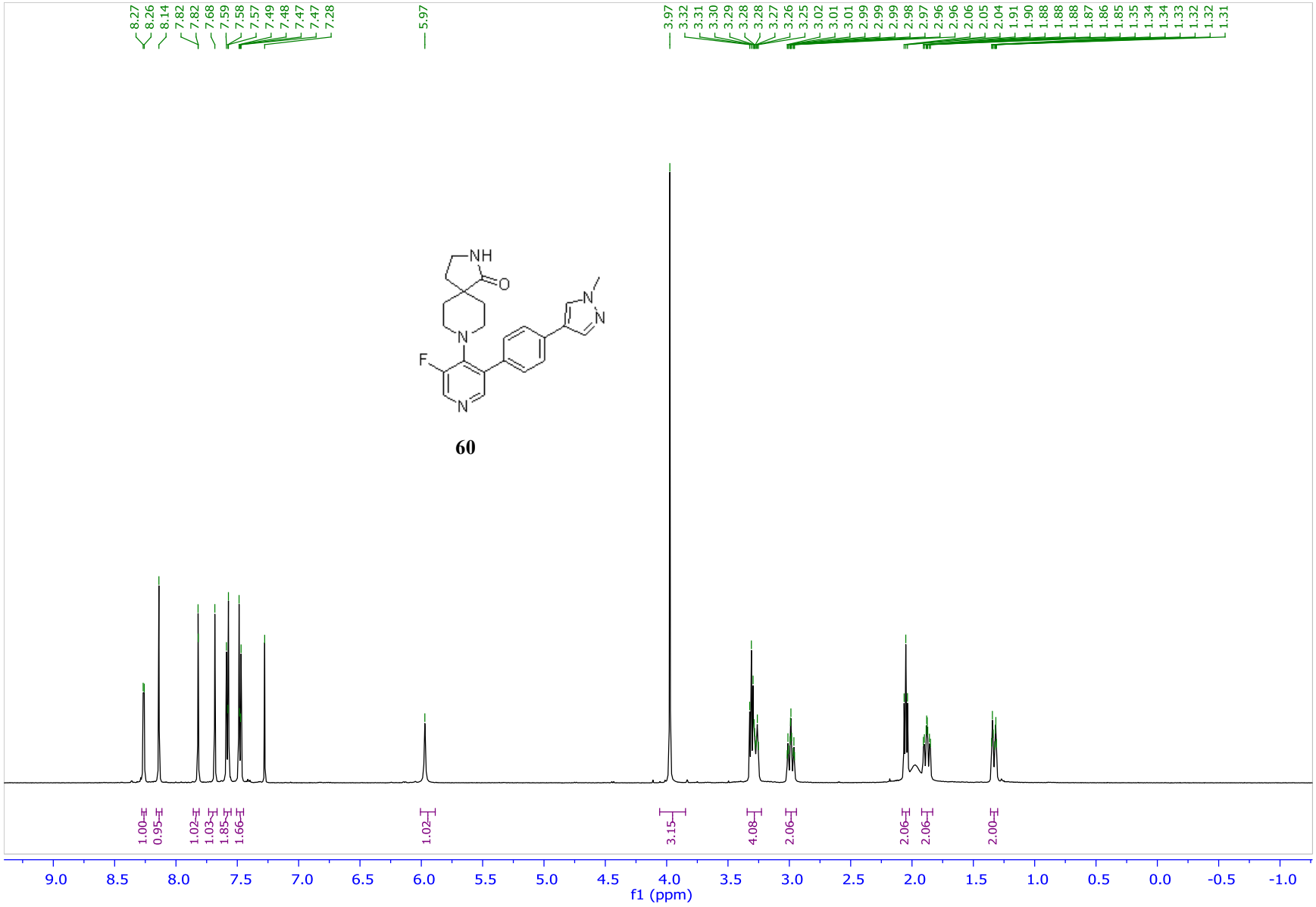


55

^{1}H NMR ($CDCl_3$, 500 MHz)

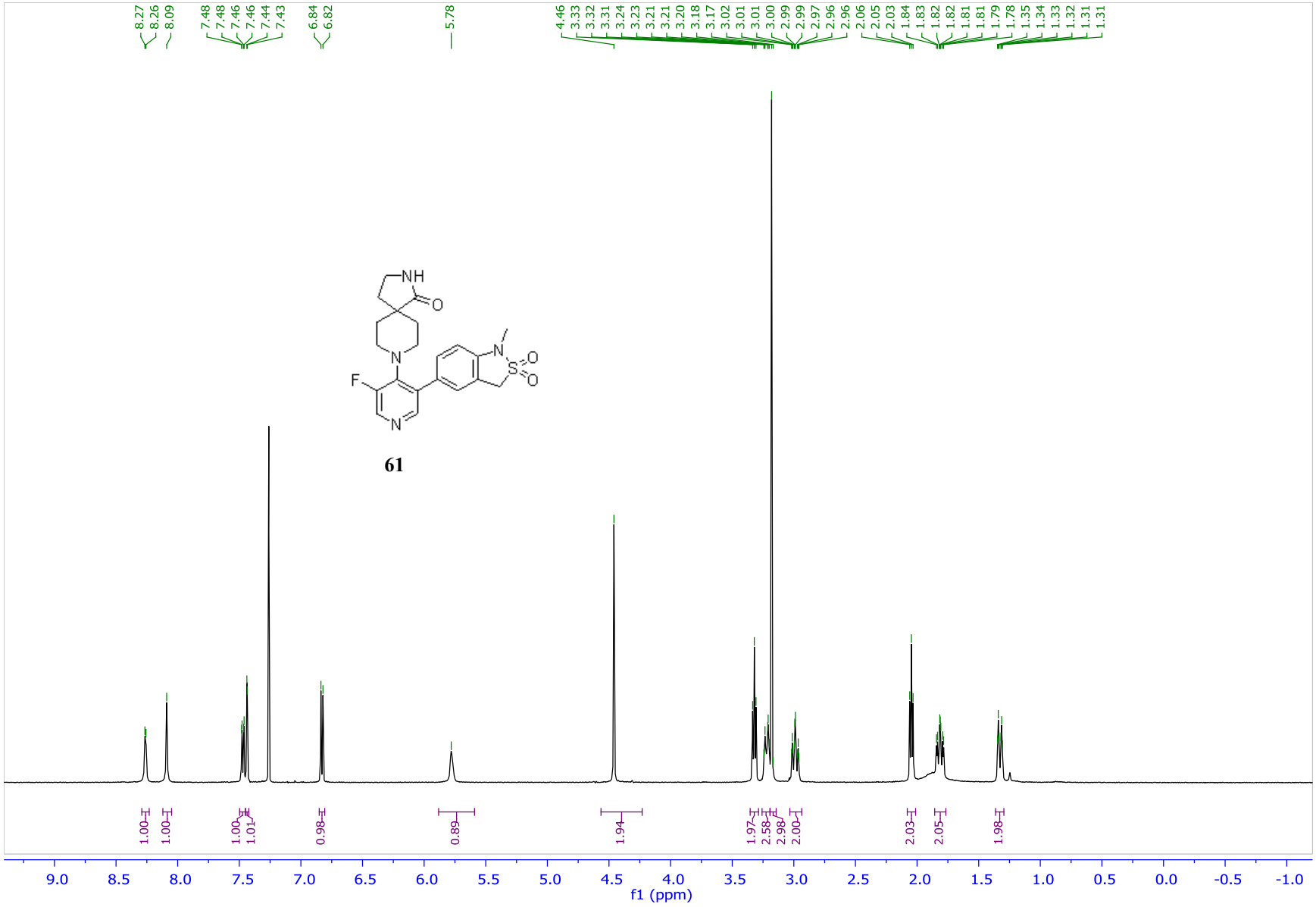


^{1}H NMR ($CDCl_3$, 500 MHz)



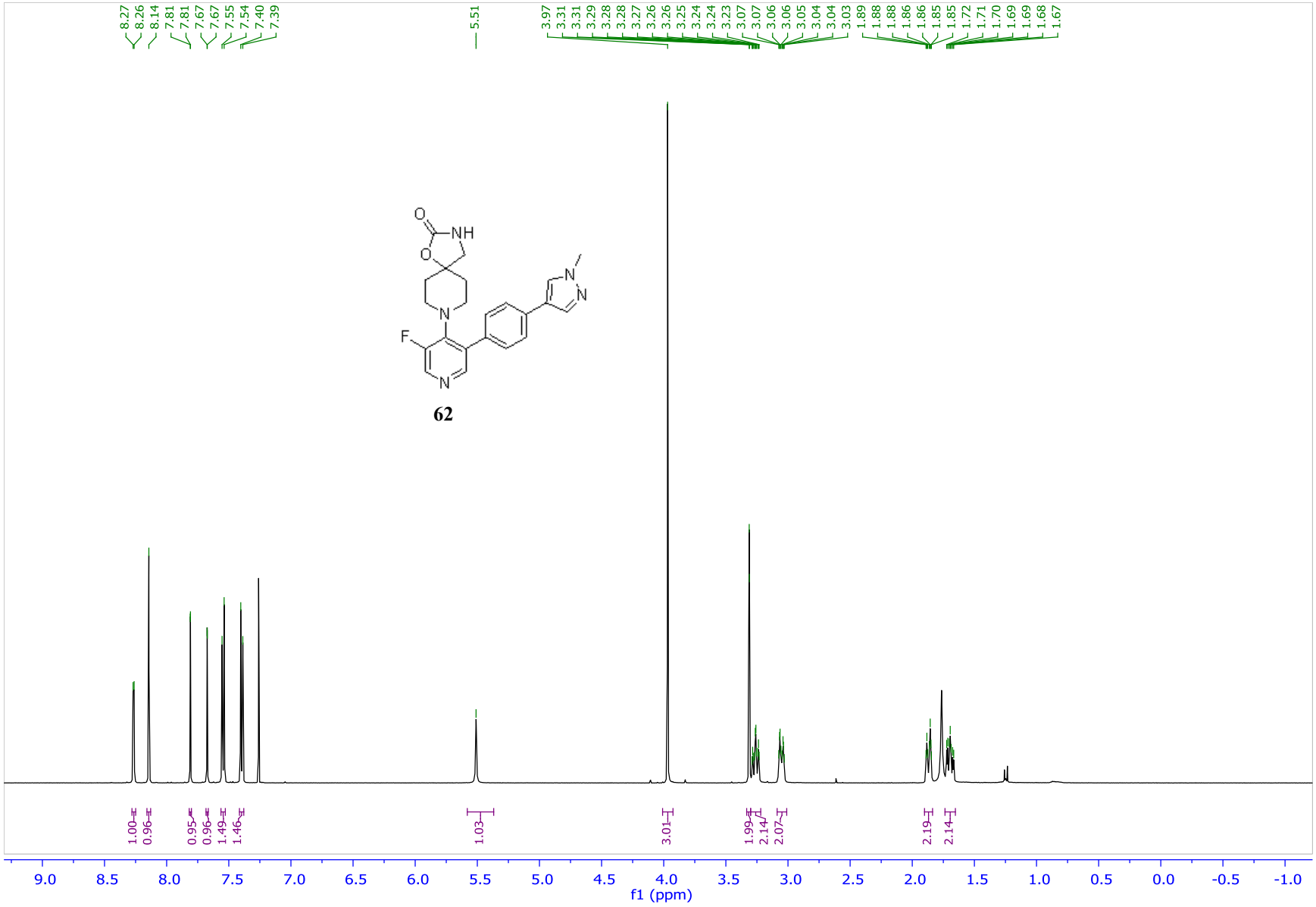
60

^{1}H NMR ($CDCl_3$, 500 MHz)



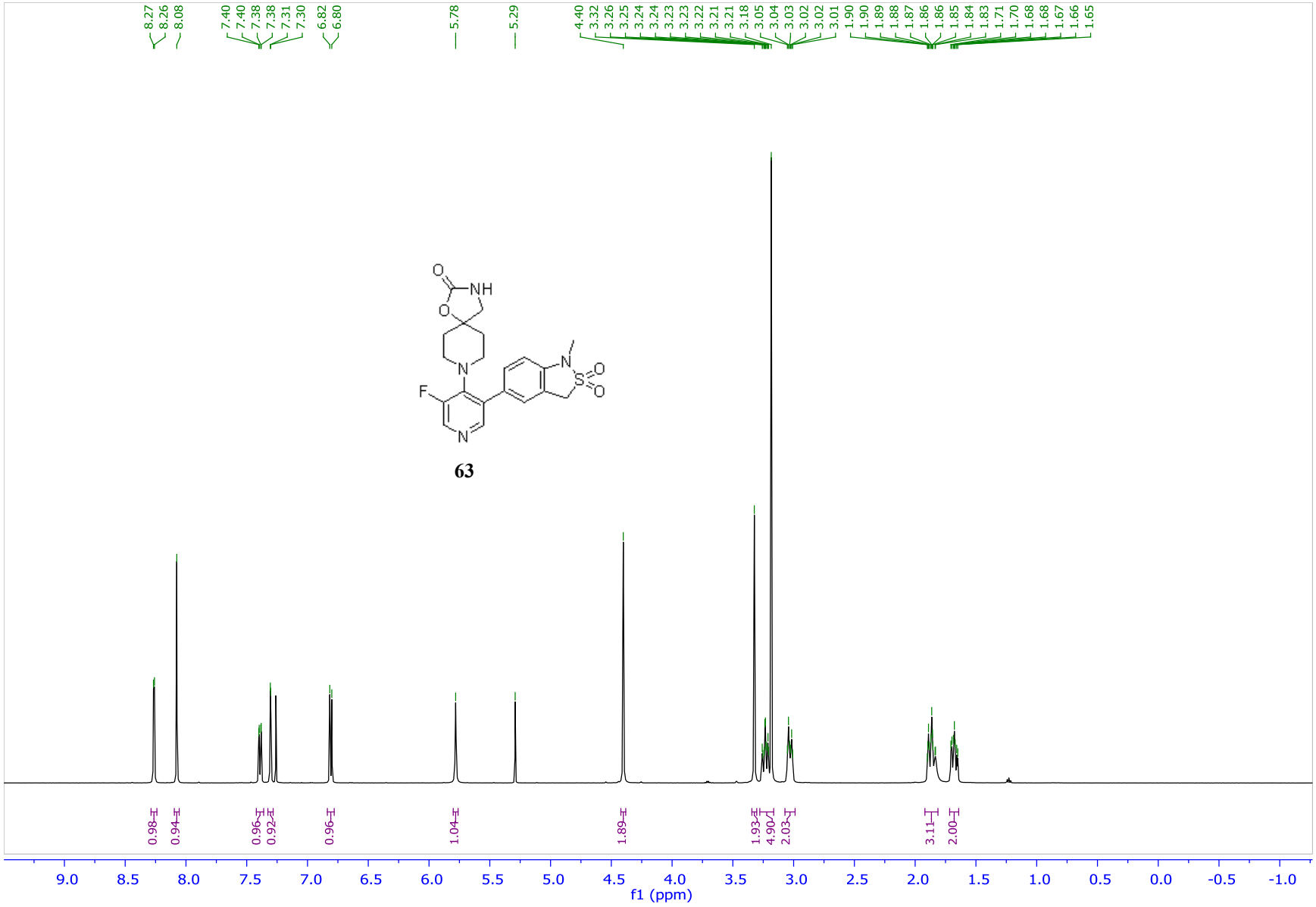
61

^{1}H NMR ($CDCl_3$, 500 MHz)



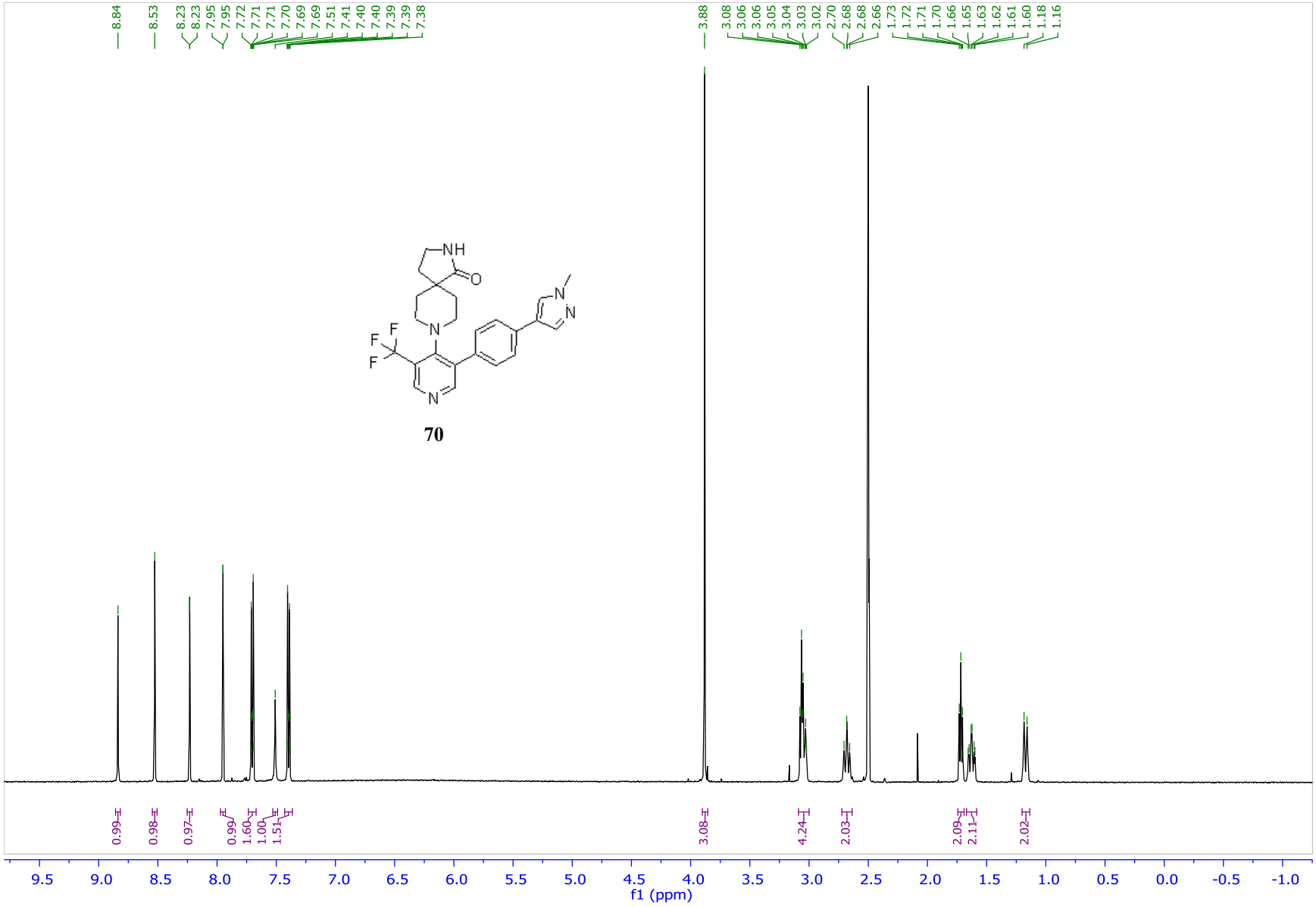
62

^{1}H NMR ($CDCl_3$, 500 MHz)



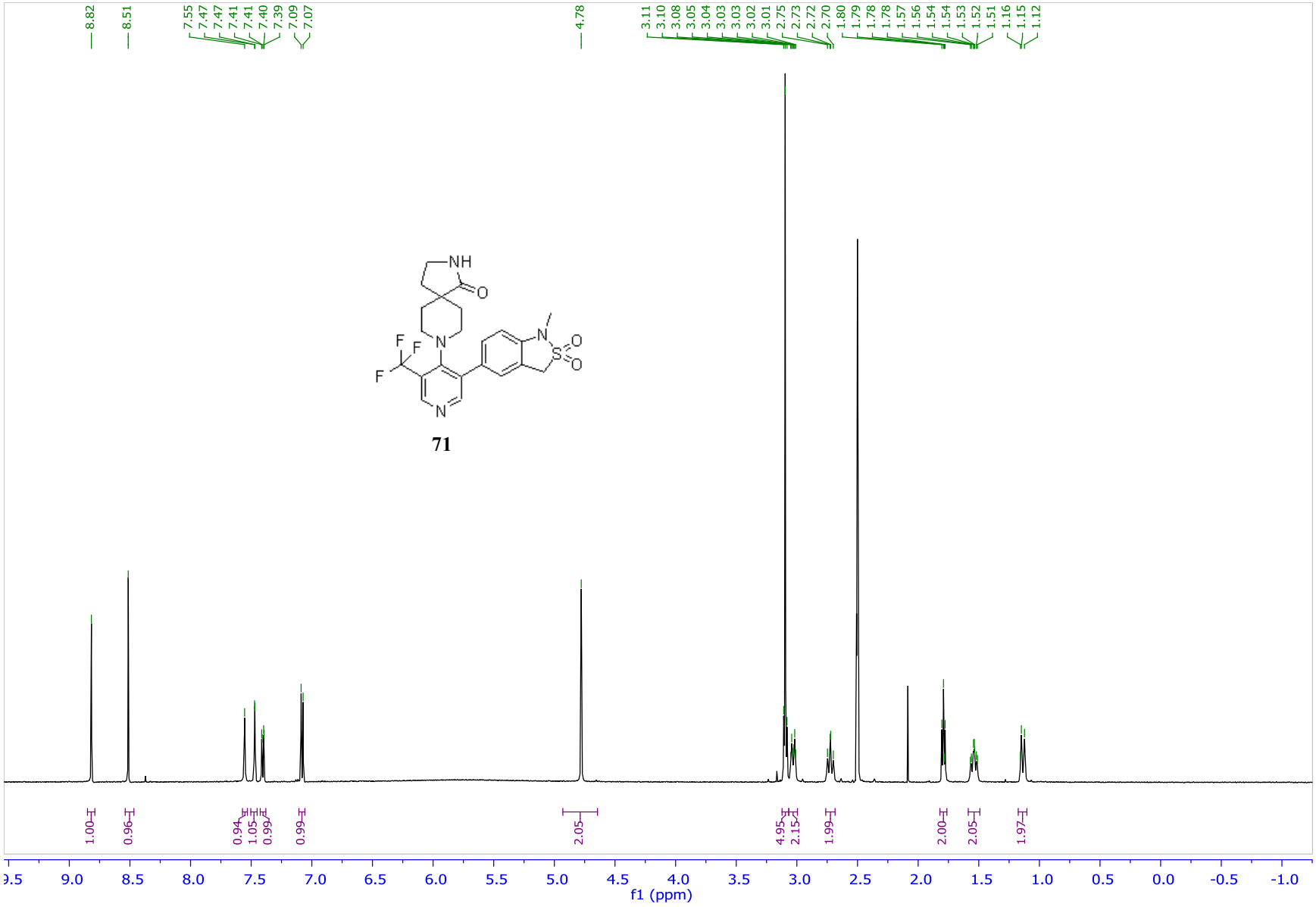
63

^{1}H NMR (DMSO-d6, 500 MHz)



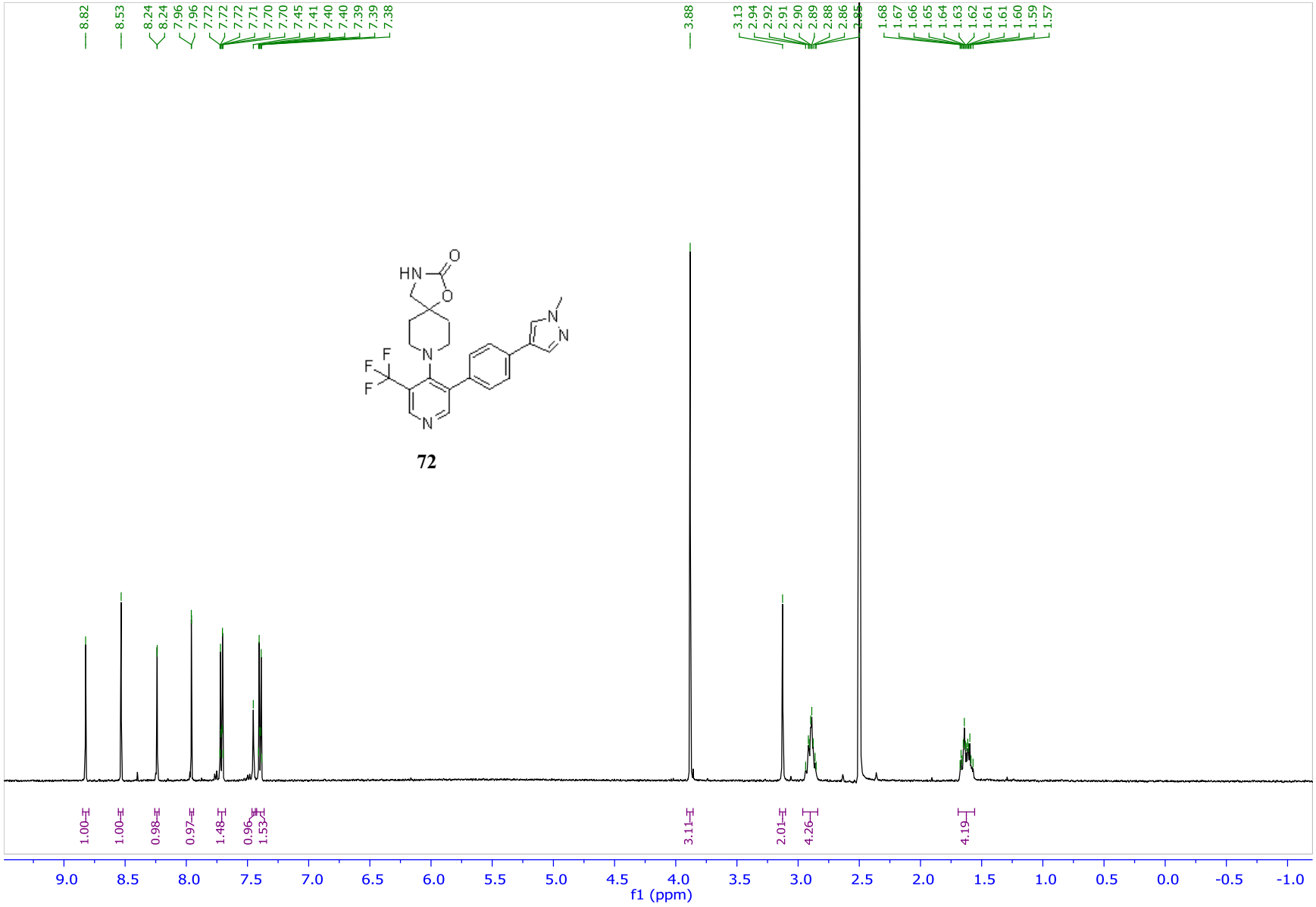
70

^{1}H NMR (DMSO-d6, 500 MHz)



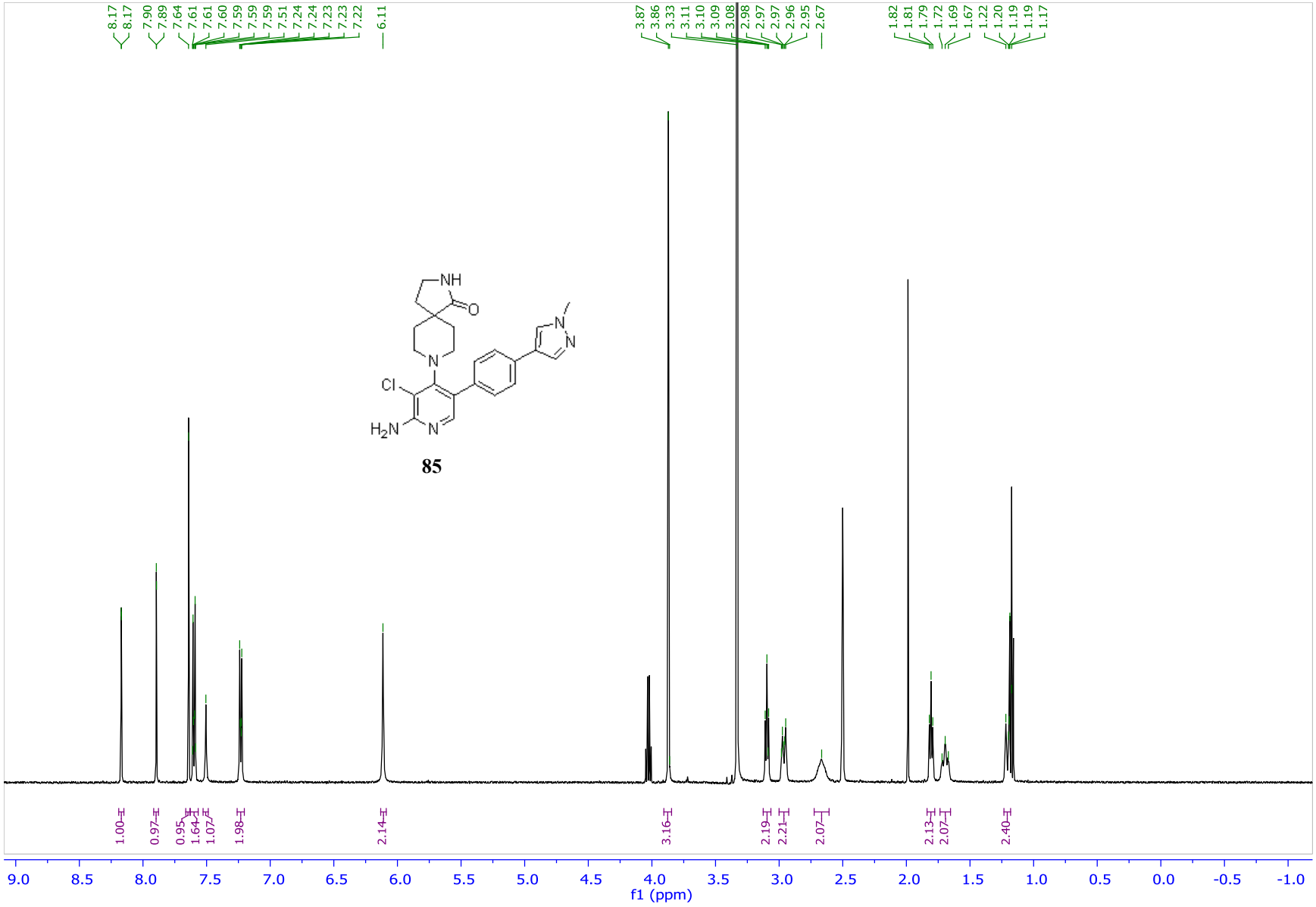
71

^{1}H NMR (DMSO-d6, 500 MHz)



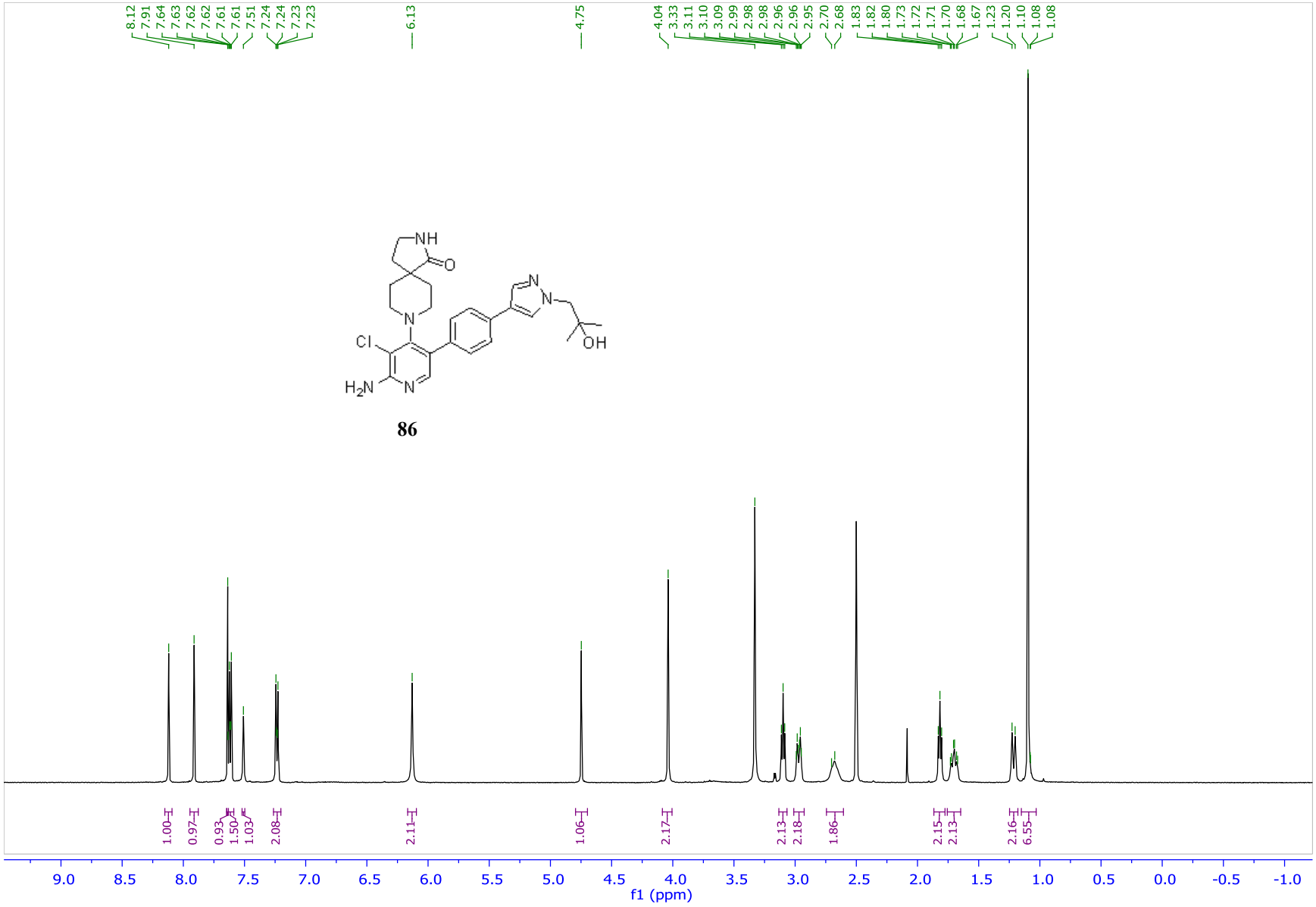
72

[1]H NMR (DMSO-d6, 500 MHz)



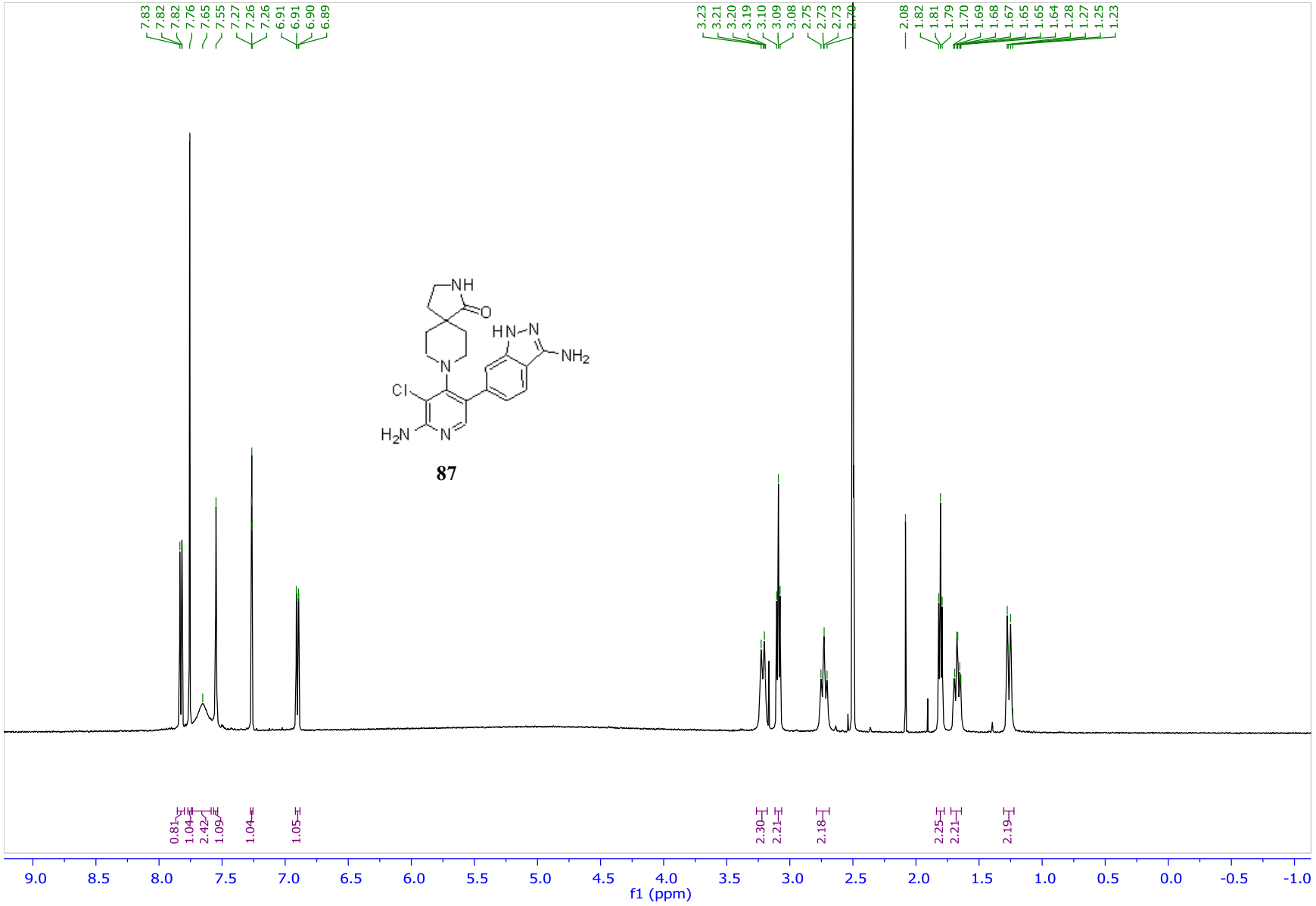
85

^{1}H NMR (DMSO-d6, 500 MHz)



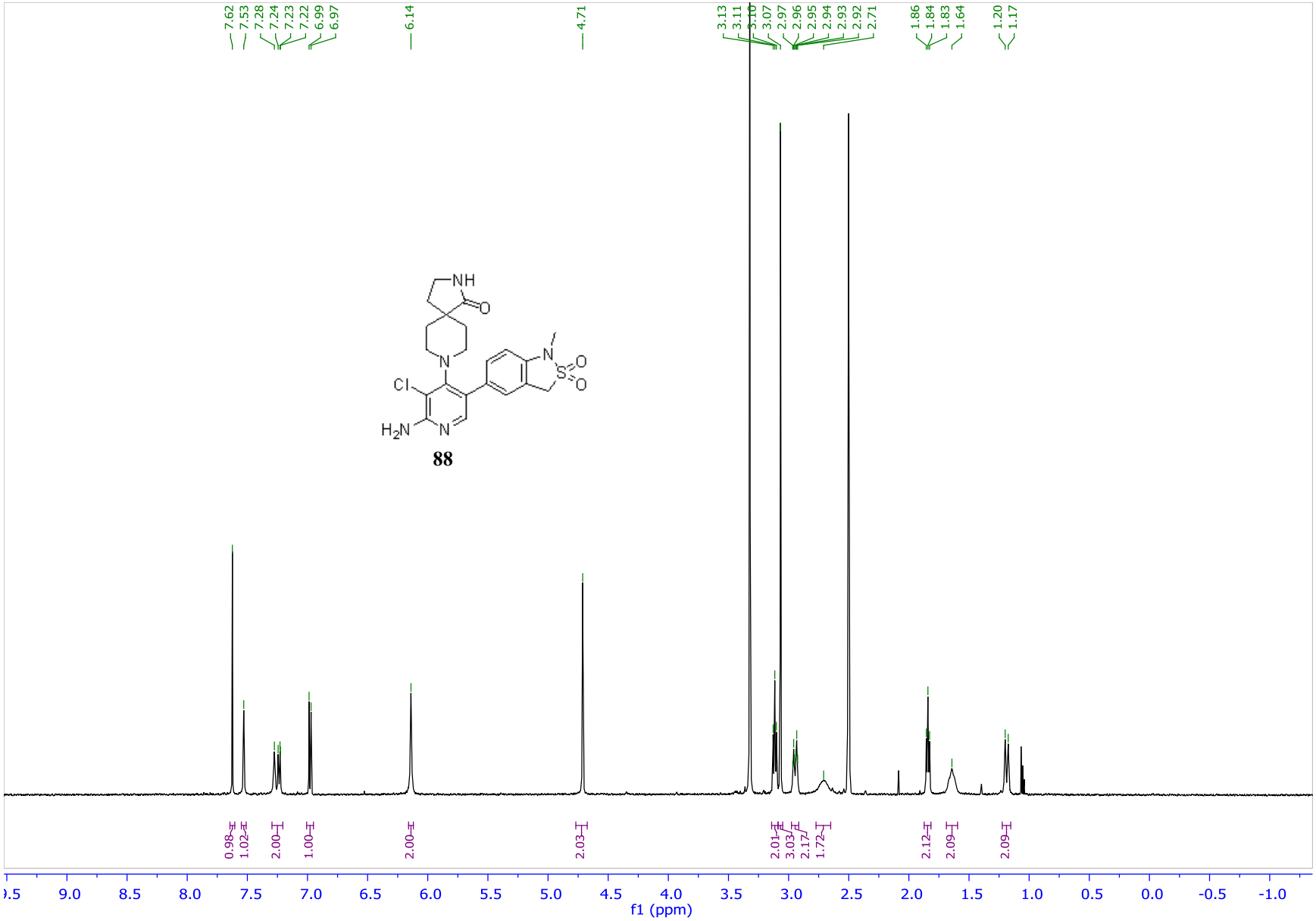
86

^{1}H NMR (DMSO-d6, 500 MHz)

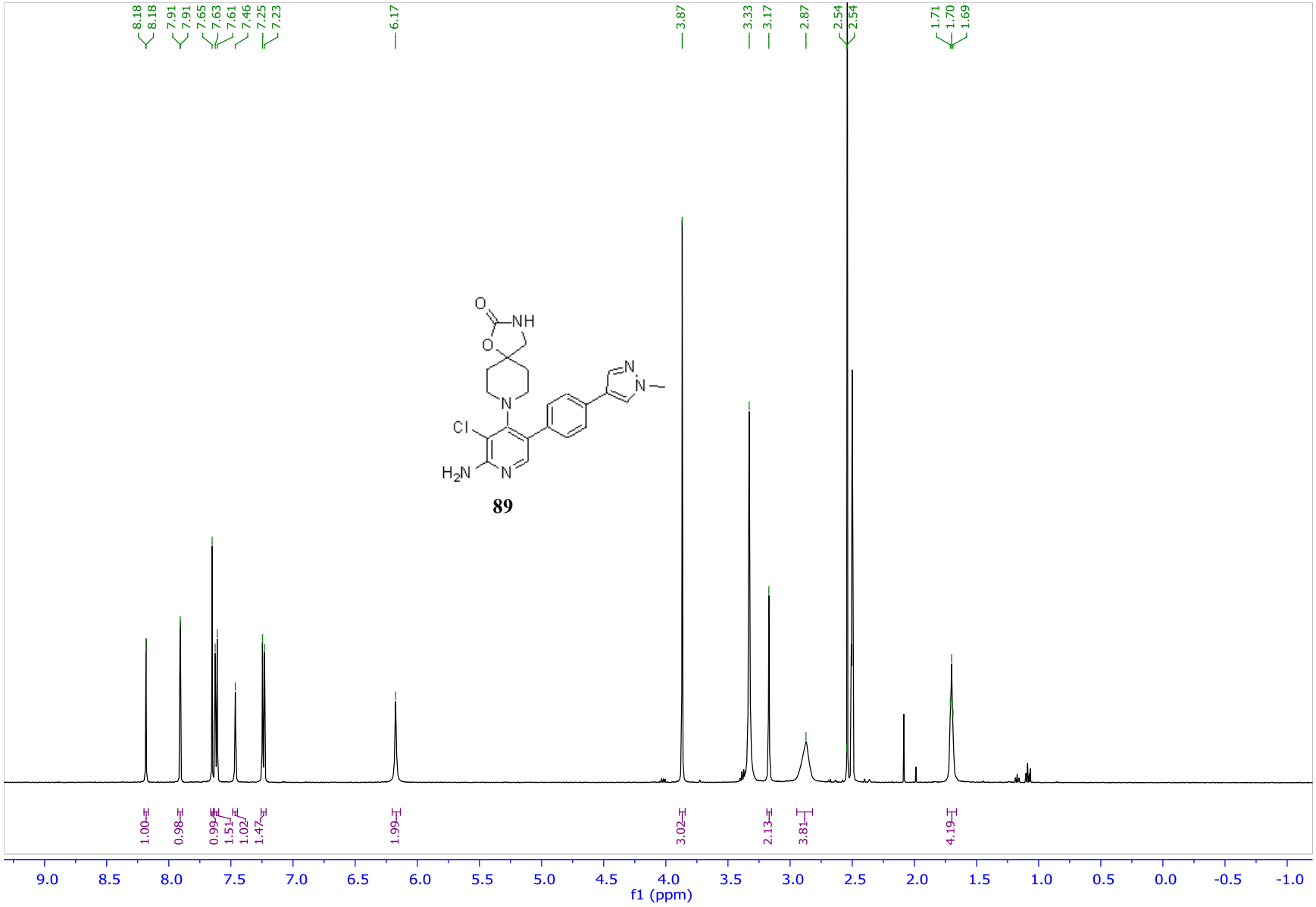


87

^{1}H NMR (DMSO-d6, 500 MHz)

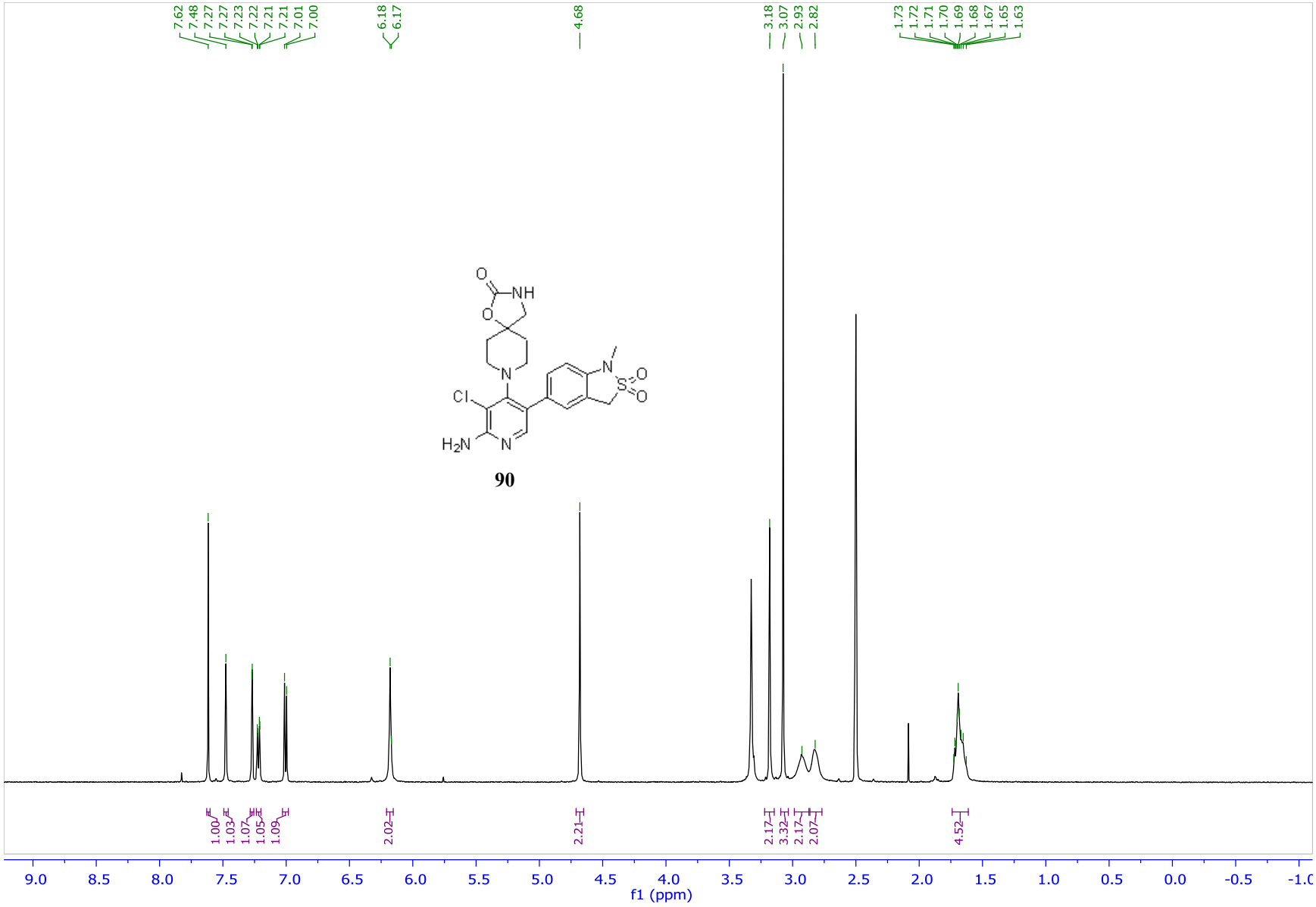


^{1}H NMR (DMSO-d6, 500 MHz)



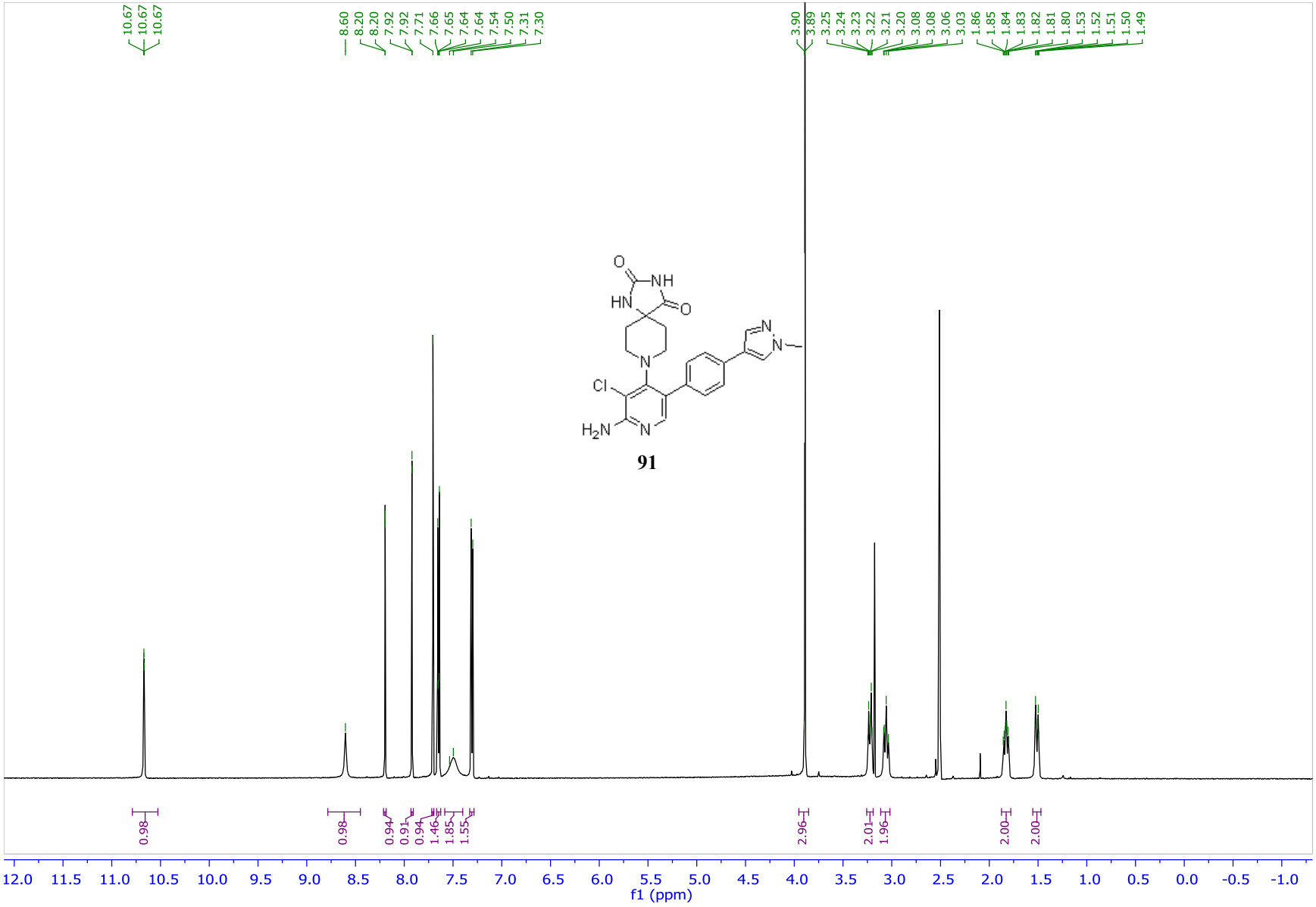
89

^{1}H NMR (DMSO-d6, 500 MHz)



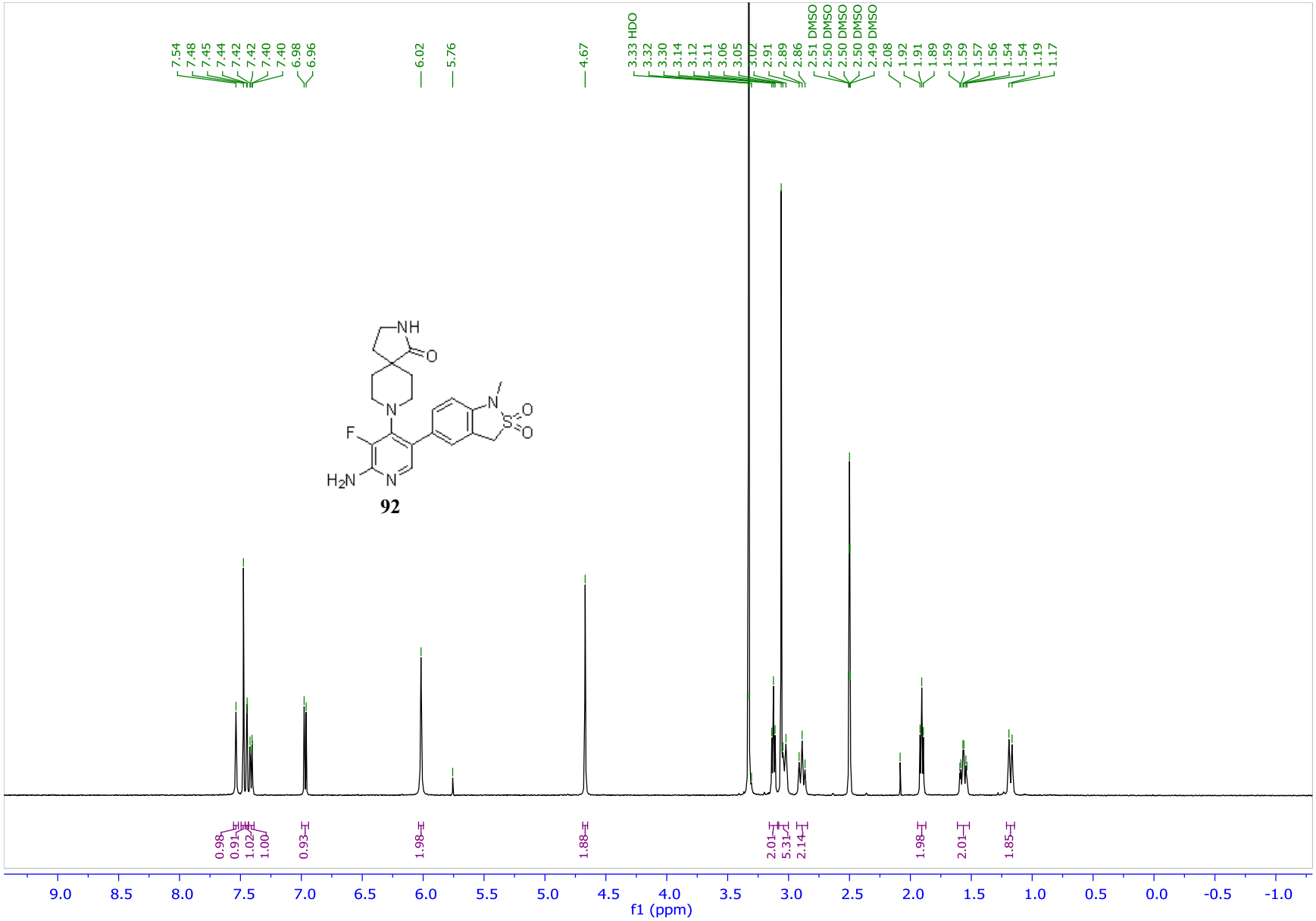
90

^{1}H NMR (DMSO-d6, 500 MHz)



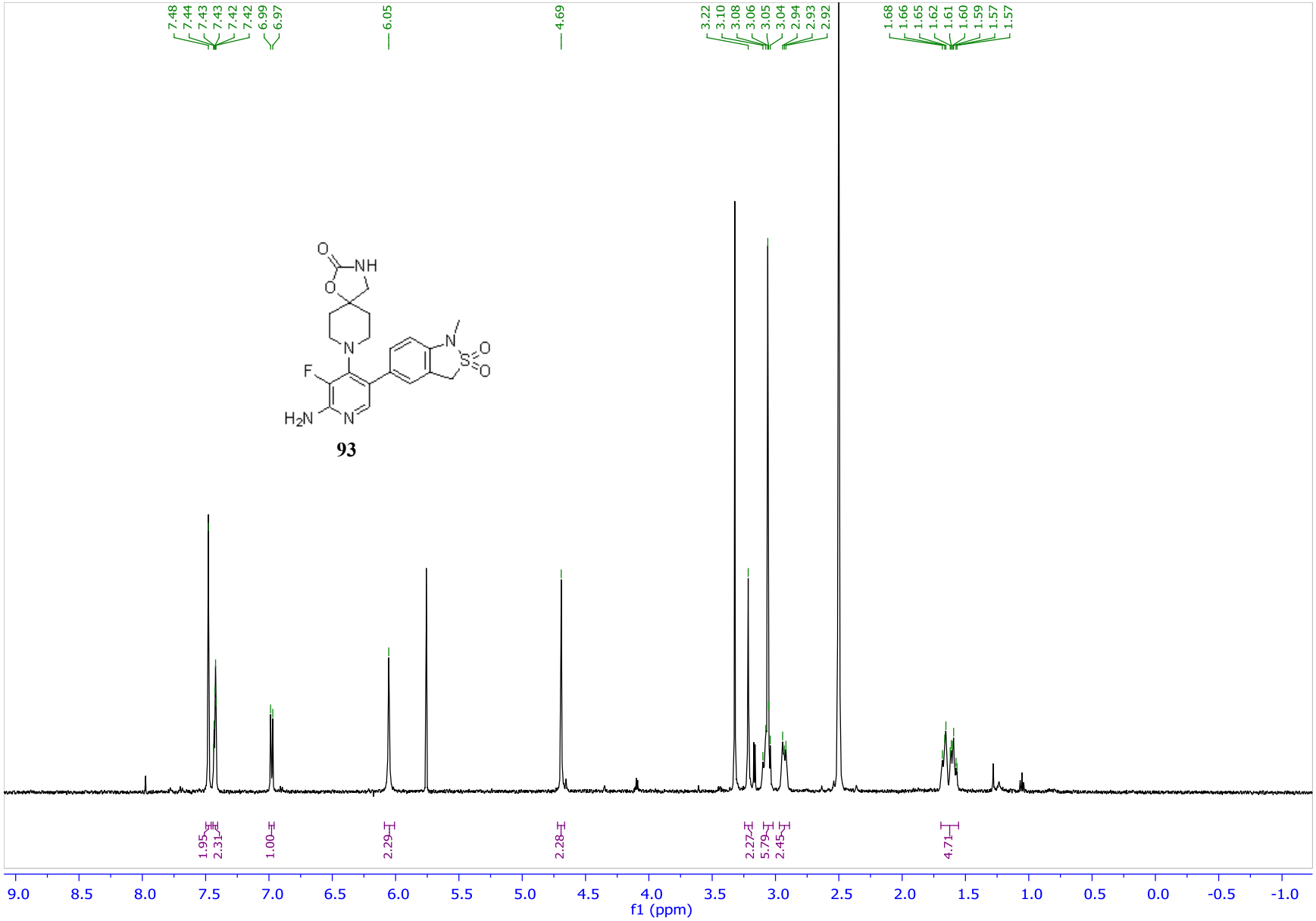
91

^{1}H NMR (DMSO-d6, 500 MHz)



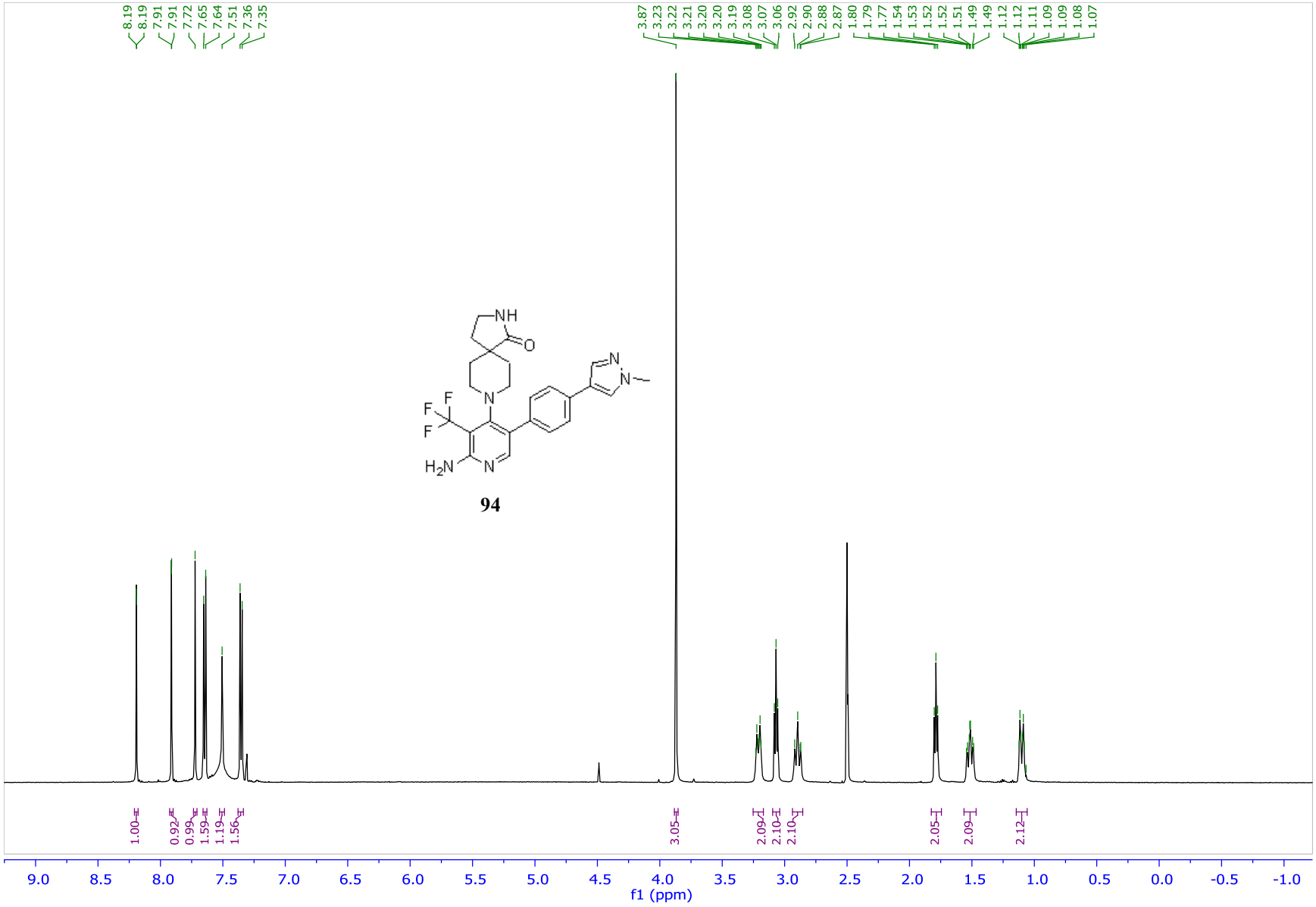
92

^{1}H NMR (DMSO-d6, 500 MHz)



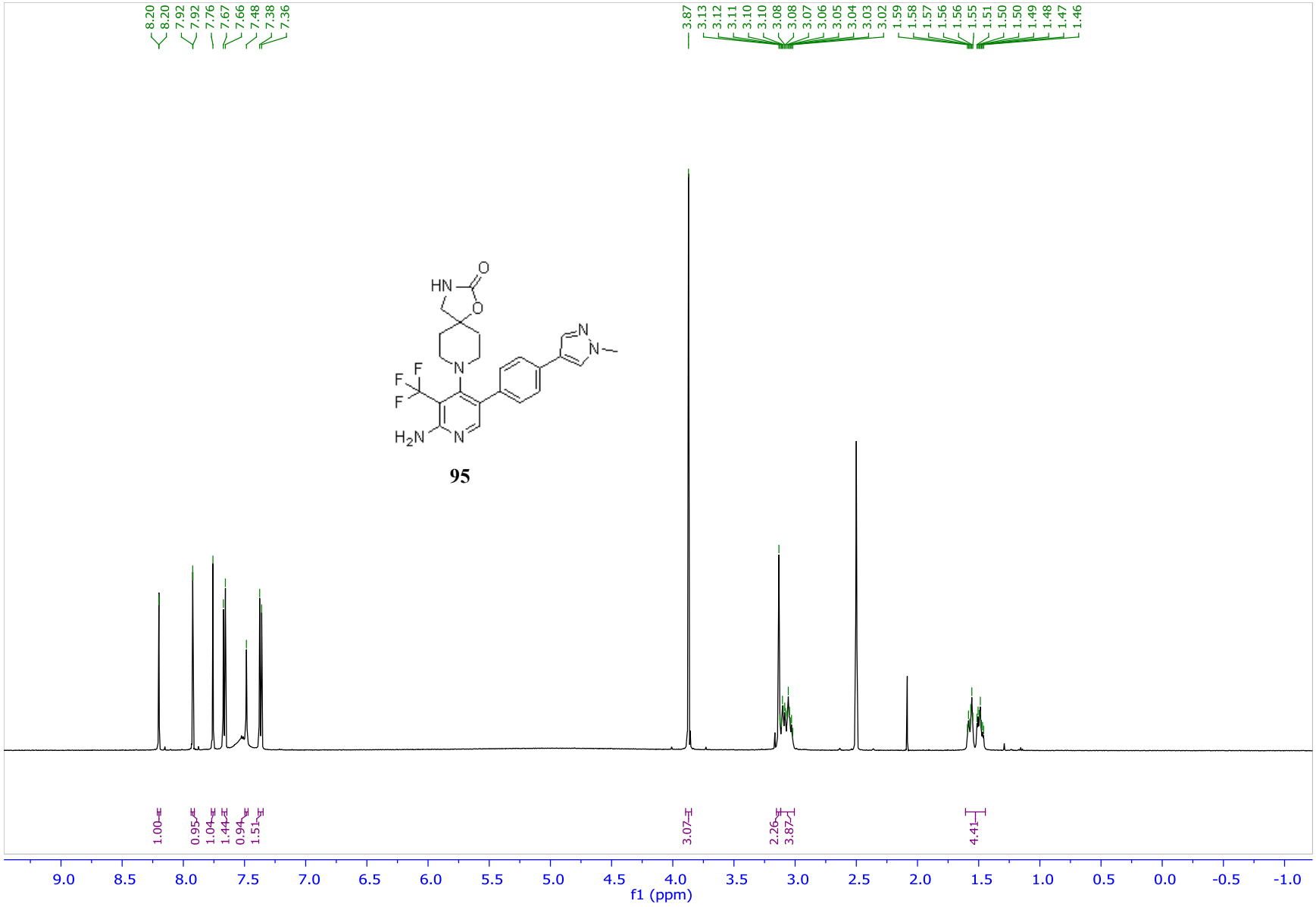
93

^{1}H NMR (DMSO-d6, 500 MHz)



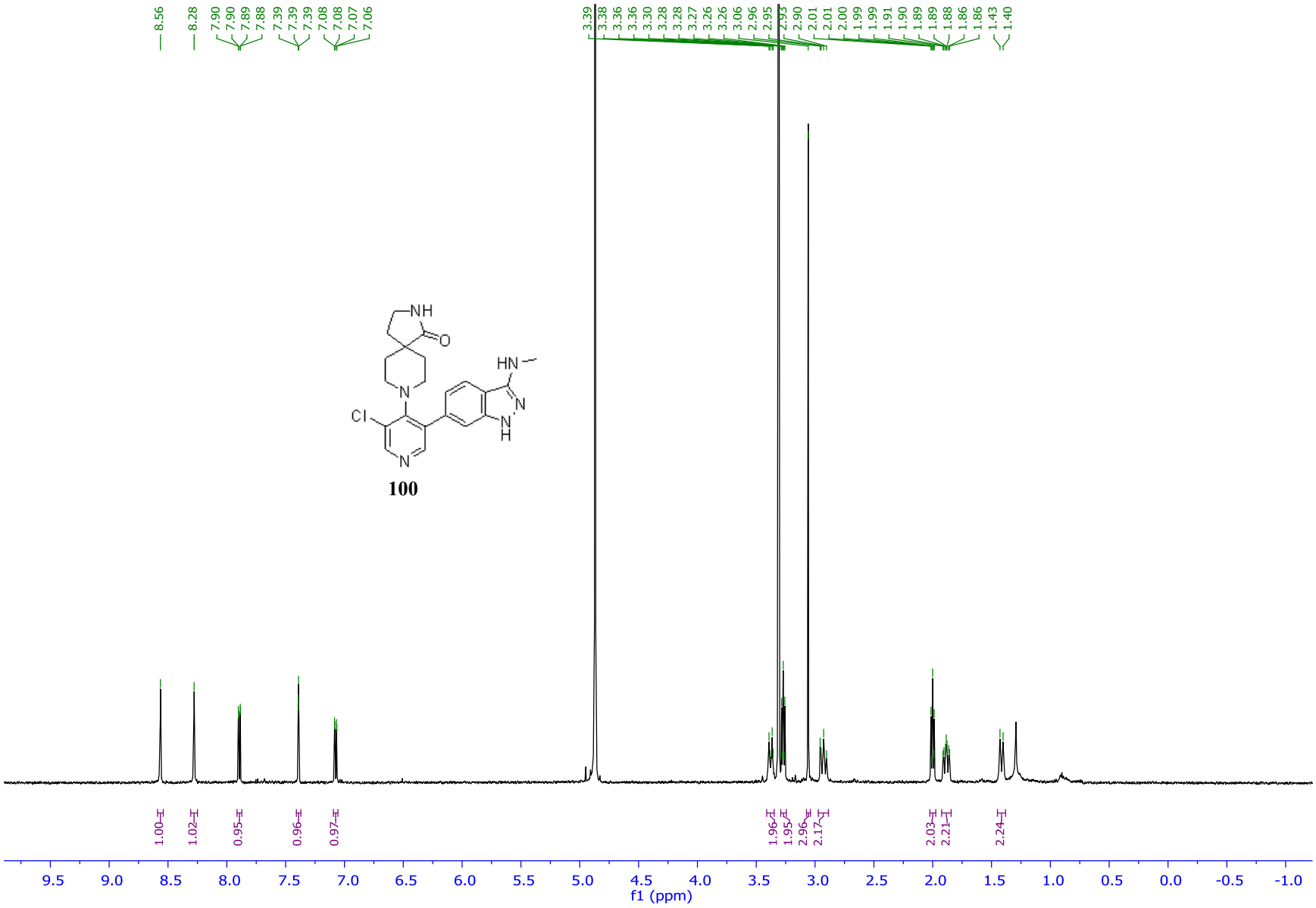
94

^{1}H NMR (DMSO-d6, 500 MHz)



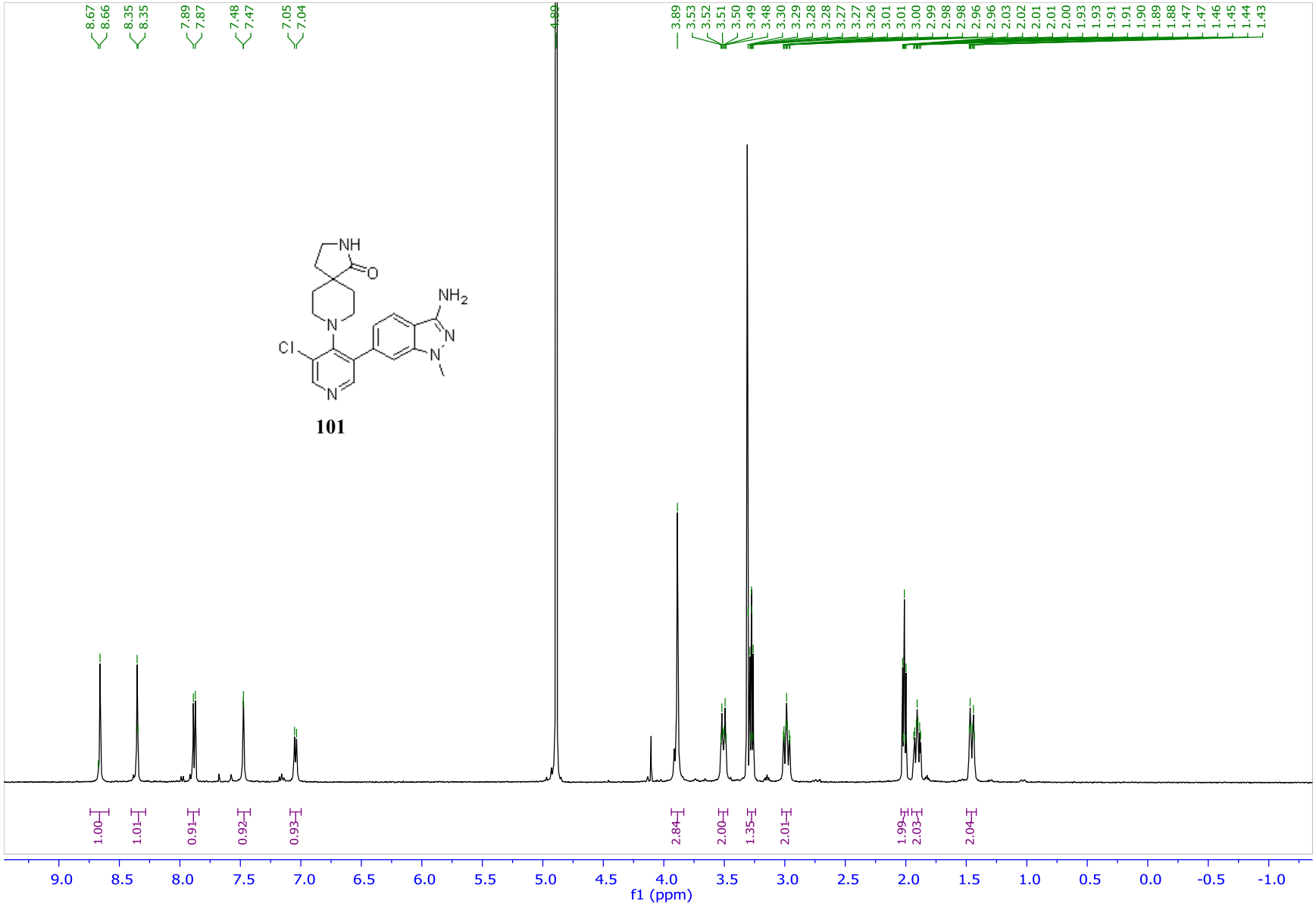
95

^{1}H NMR (CD_3OD, 500 MHz)



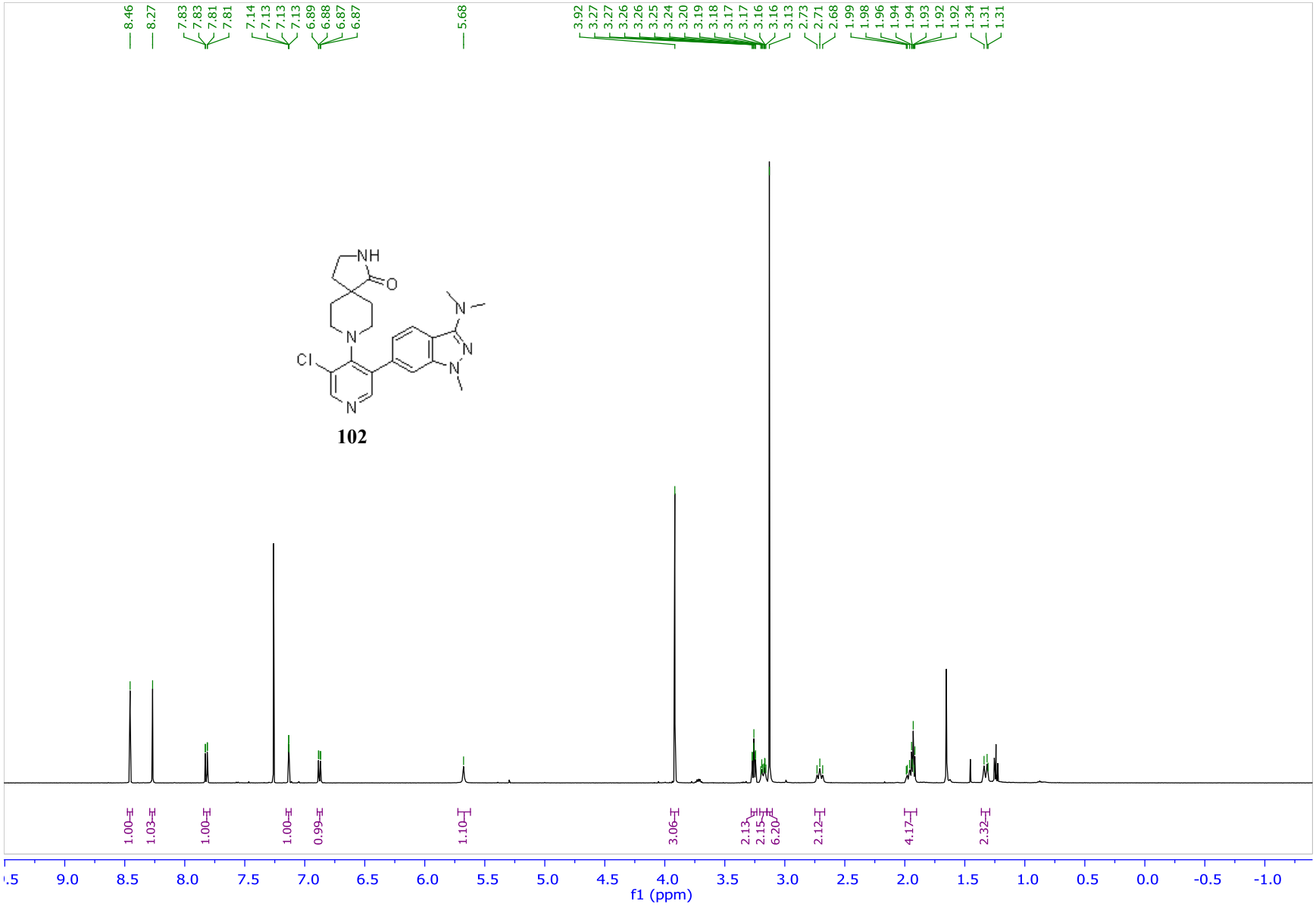
100

^{1}H NMR (CD_3OD, 500 MHz)

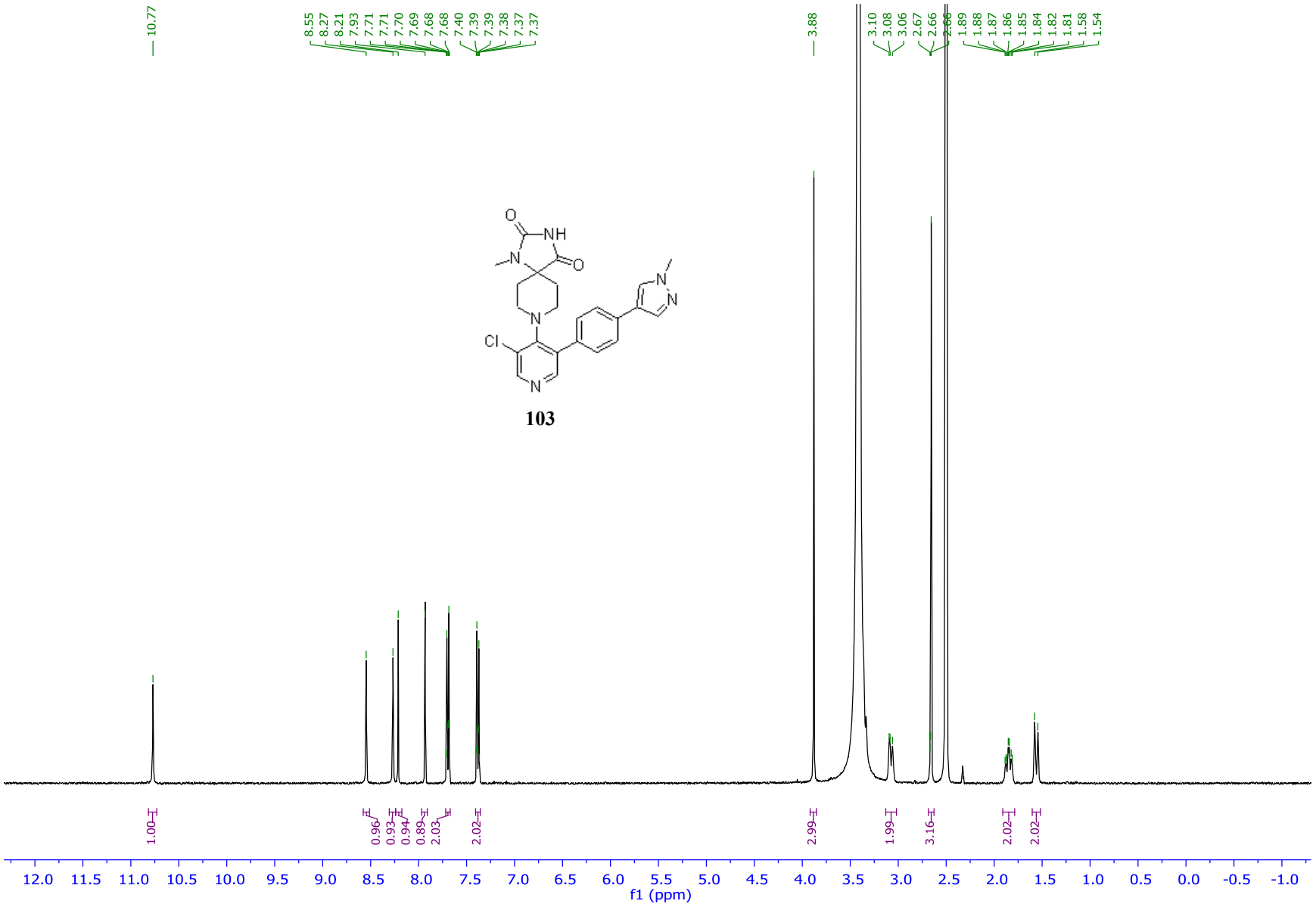


101

^{1}H NMR ($CDCl_3$, 500 MHz)

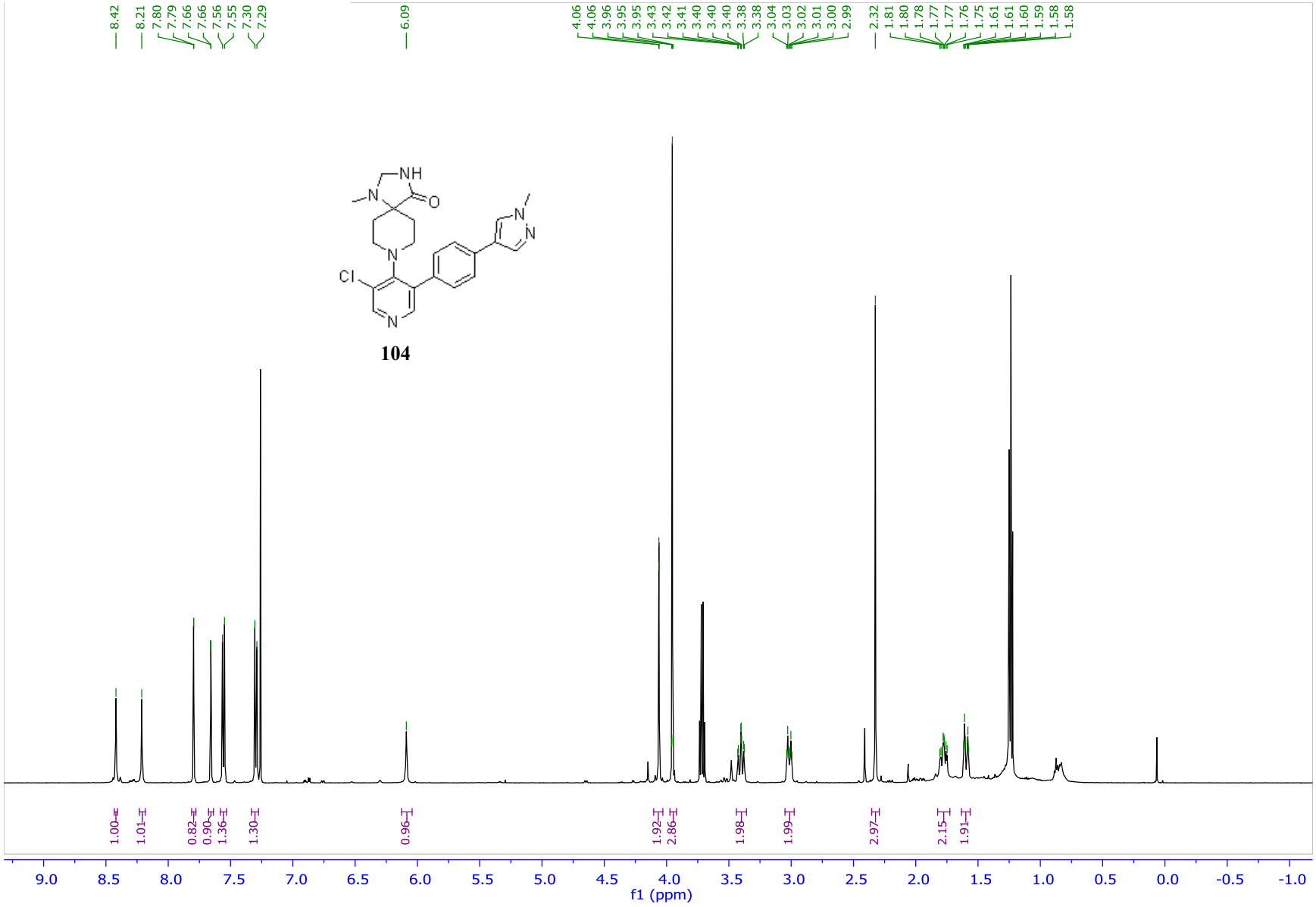


^{1}H NMR (DMSO-d6, 400 MHz)



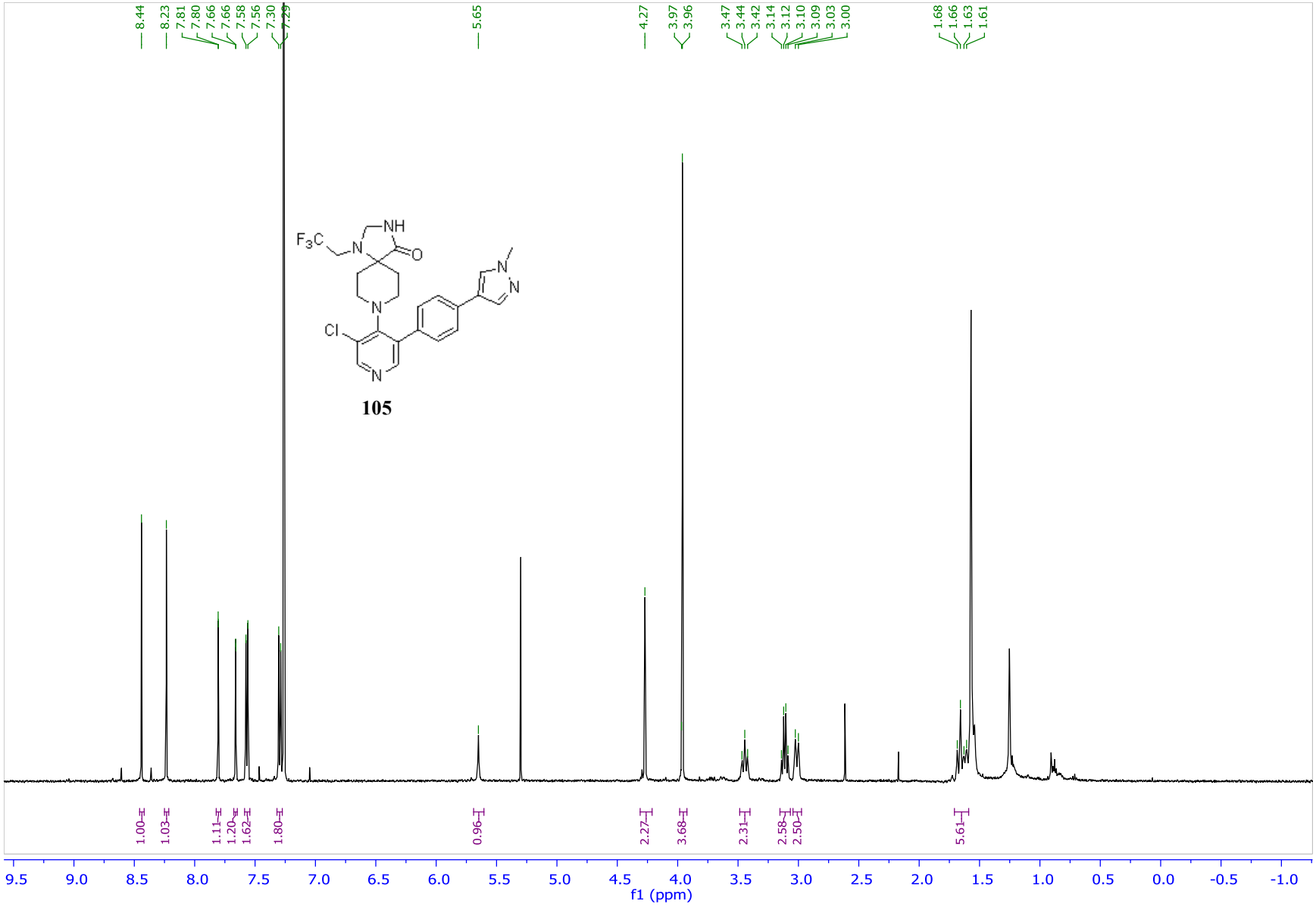
103

^{1}H NMR ($CDCl_3$, 500 MHz)



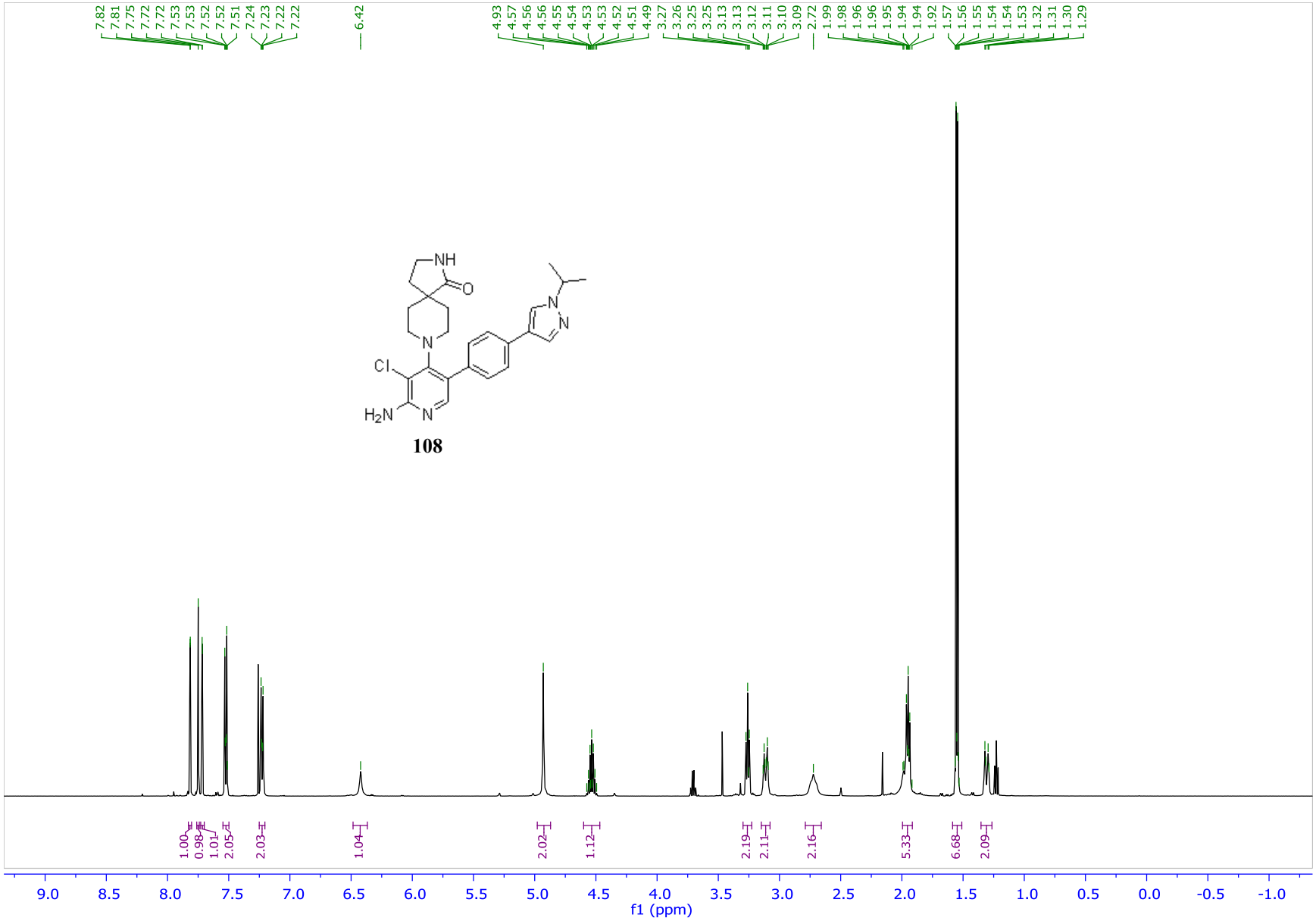
104

^{1}H NMR ($CDCl_3$, 500 MHz)

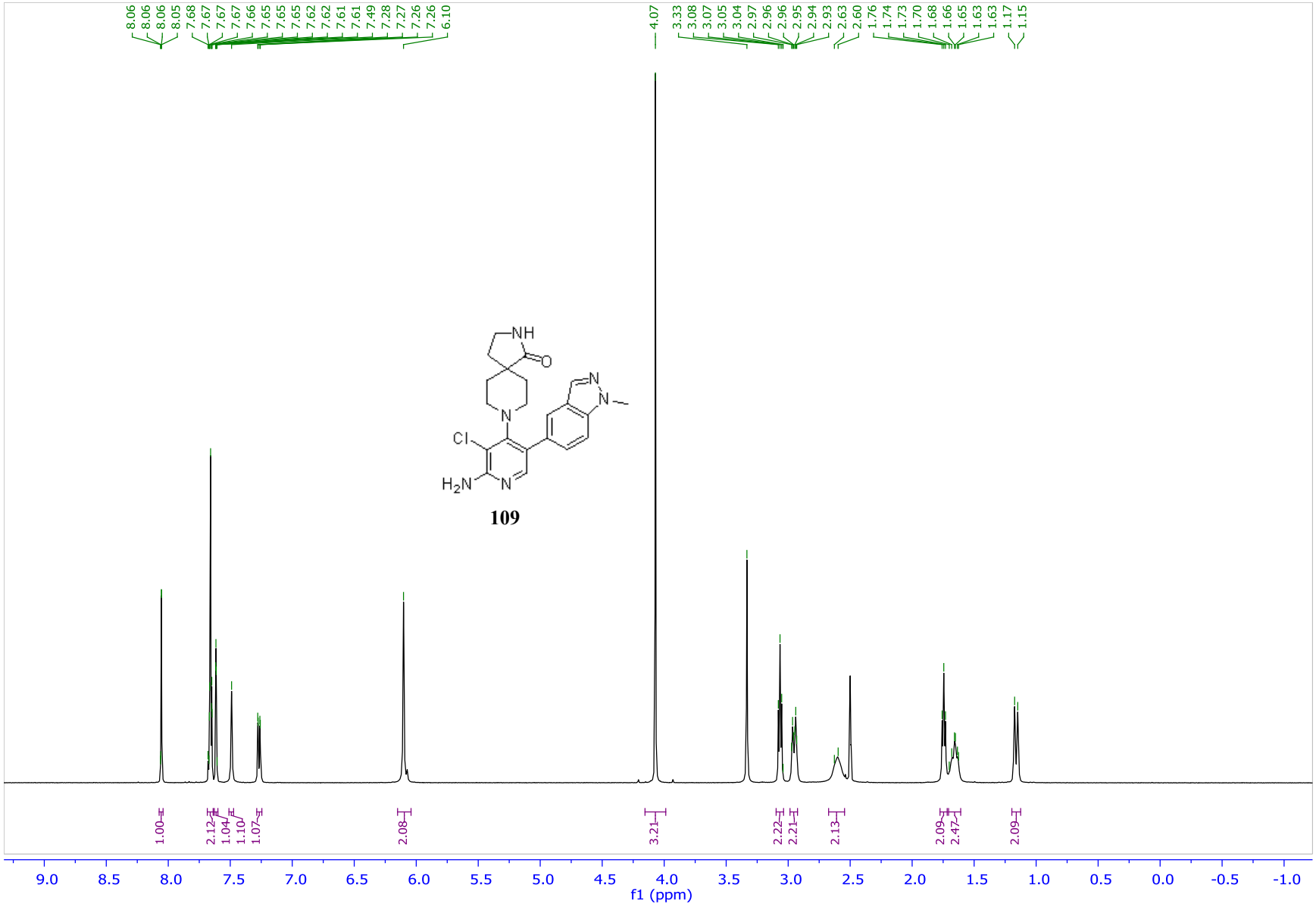


105

^{1}H NMR ($CDCl_3$, 500 MHz)

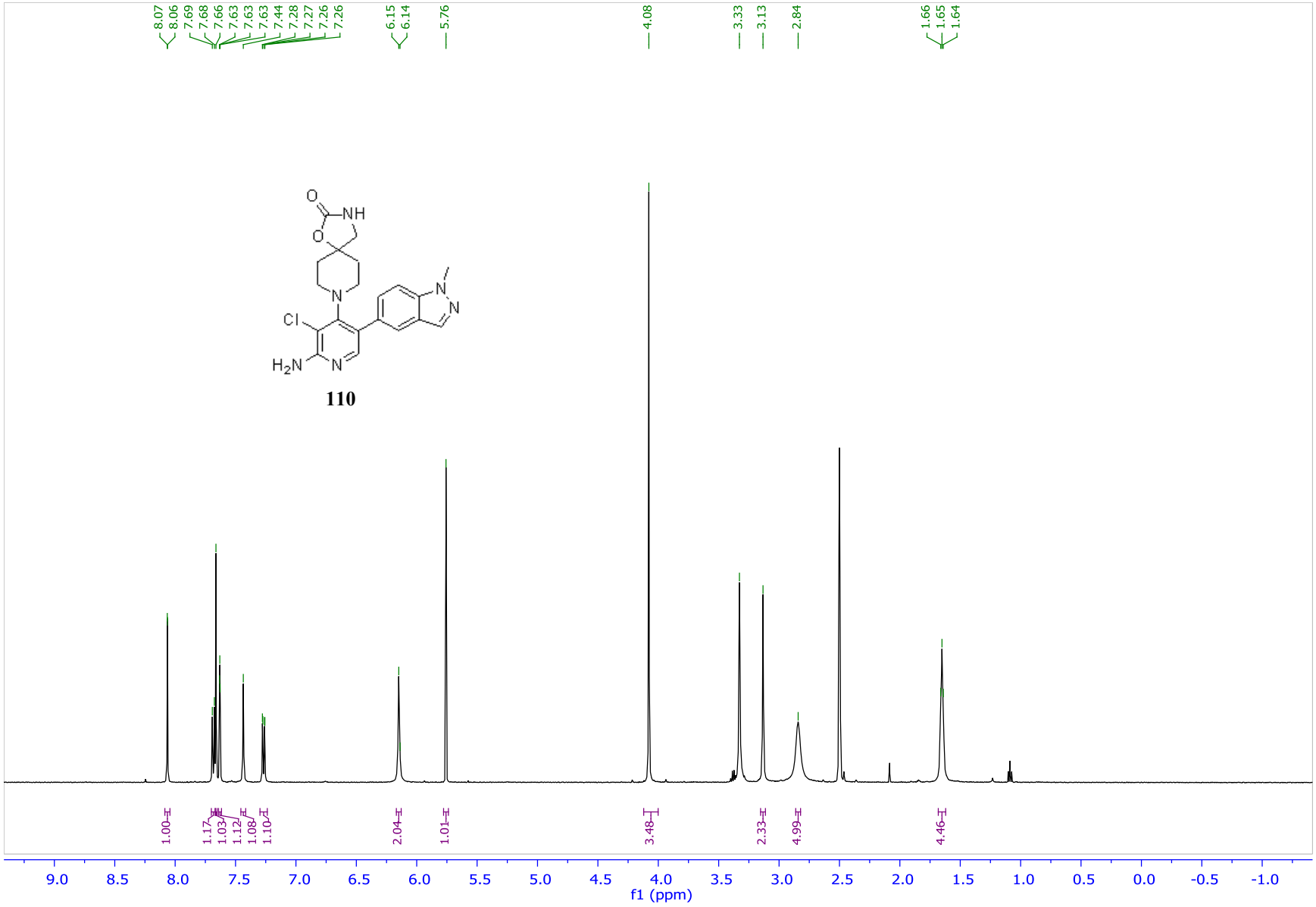


^{1}H NMR (DMSO-d6, 500 MHz)



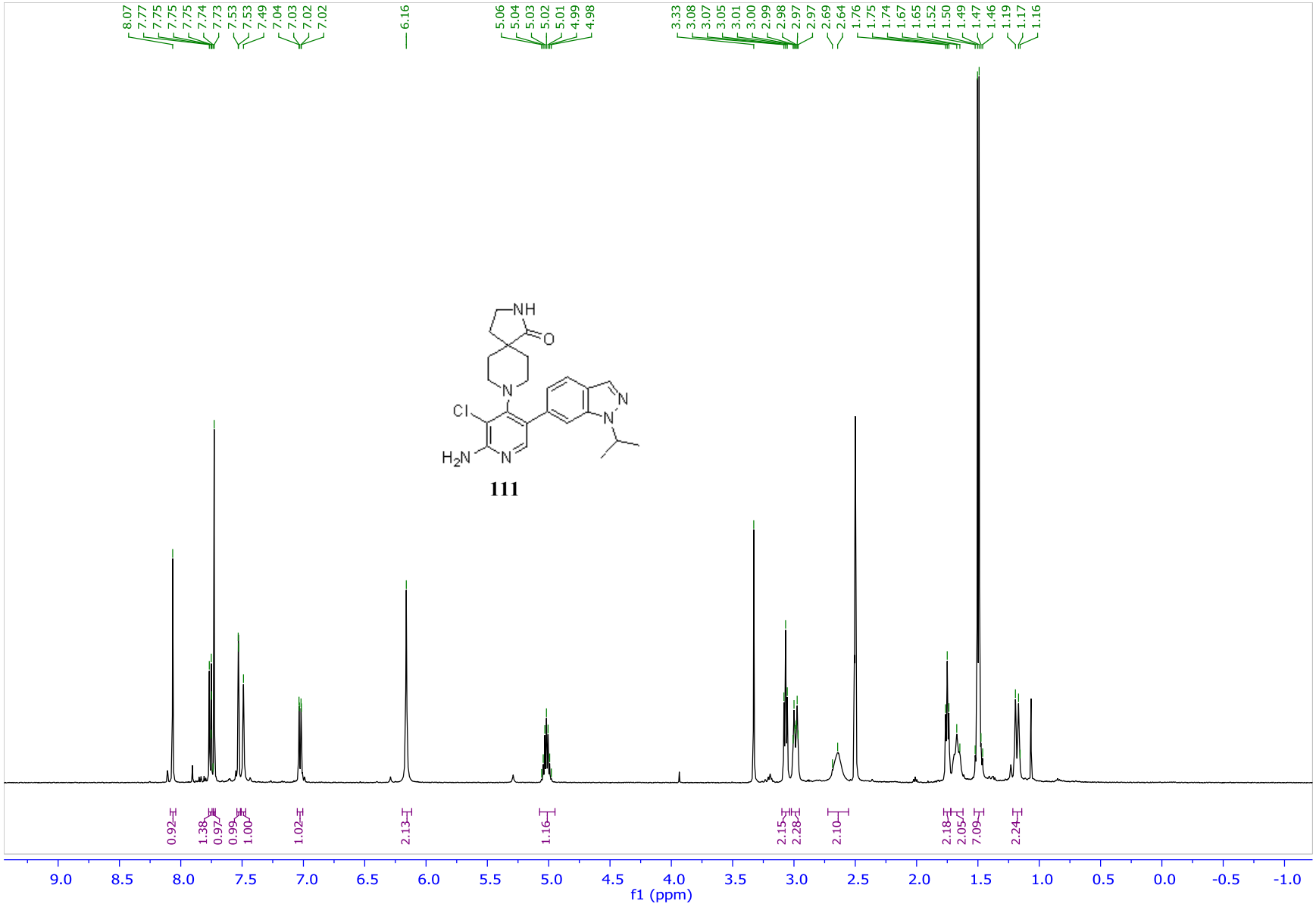
109

^{1}H NMR (DMSO-d6, 500 MHz)



110

^{1}H NMR (DMSO-d6, 500 MHz)



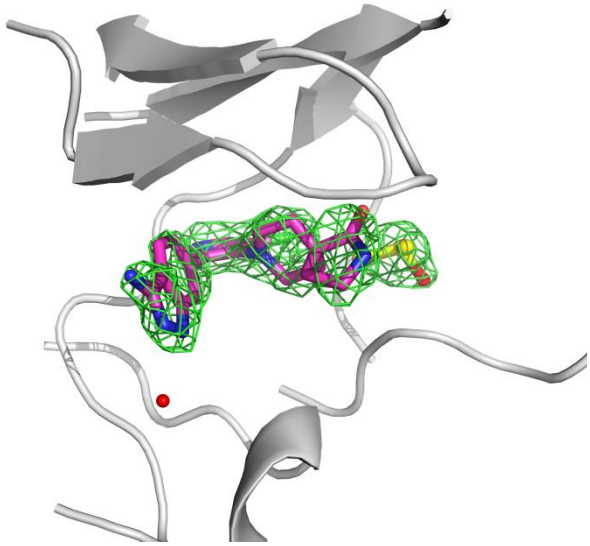
Crystallographic data and refinement parameters

Data-collection details	Compound **25**	Compound **42**	Compound **54**	Compound **109**
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Unit-Cell parameters [Å, °]	a=70.94, b= 71.93, c= 177.93; α = 90.0 β = 90.0 γ = 90.0	a=71.01, b= 71.11, c= 173.15; α = 90.0 β = 90.0 γ = 90.0	a=70.14, b= 70.66, c= 169.47; α = 90.0 β = 90.0 γ = 90.0	a=70.75, b= 71.79, c= 176.42; α = 90.0 β = 90.0 γ = 90.0
Resolution [Å] [a]	2.36 (2.61-2.36)	2.38 (2.63-2.38)	2.50 (2.56-2.50)	3.00 (3.25-3.00)
Data collection wavelength [Å]	1.00008	1.00000	1.00000	0.99997
Number of measurements [a]	105854 (27407)	165126 (35696)	238730 (16719)	53920 (11302)
Number of unique reflections [a]	37664 (9794)	35696 (9131)	29394 (2101)	17593 (3684)
Completeness[%] [a]	97.4 (99.1)	99.2 (99.6)	98.1 (97.5)	94.6 (94.6)
R_{merge} [%][a]	8.2 (48.3)	6.0 (51.6)	9.8 (51.0)	8.4 (48.2)
Mean(I)/sd [a]	9.17 (2.31)	18.73 (3.36)	10.8 (2.9)	10.0 (57.6)
Refinement				
Resolution [Å]	88.96-2.36	86.58-2.38	84.73-2.50	11302
R_{work}/R_{free}	0.208 / 0.237[b]	0.229 / 0.256[c]	0.234 / 0.268[d]	0.216 / 0289[e]
Rmsd bond length [Å]	0.011	0.009	0.010	0.009
Rmsd bond angle [°]	1.25	1.16	1.37	1.08
Average B-factor [Å^2]				
Protein	43.5	36.8	67.6	58.4
Ligand	55.5	70.7	59.4	62.6
Water	43.8	30.2	48.6	7.7
Formic acid	84.1	81.7	67.7	59.1
All atoms	43.9	37.1	67.5	58.3
Number of atoms				
Protein atoms	4974	5096	5026	5056
Ligand	28	30	33	29
Water	190	55	21	16
Formic acid	21	12	9	3
DMSO	4	4	-	-
1,2-Ethanediol	8	4	4	4
All atoms	5225	5201	5103	5108
Ramachandran				
Core [%]	94.1	93.8	90.3	90.7
Allowed [%]	5.8	6.2	9.1	8.8
Generously allowed [%]	0.2	0.0	0.5	0.5
Dissallowed [%]	0.0	0.0	0.0	0.0

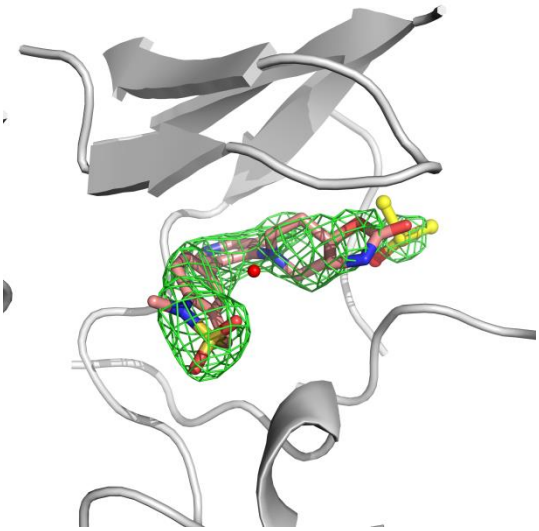
[a]Values for the last resolution shell shown in brackets; [b]Using randomly selected 3.2% of data; [c]Using randomly selected 2.4% of data; [d]Using randomly selected 2.4% of data; [e]Using randomly selected 3.4% of data

Fo-Fc Omit maps at 2.5 σ cutoff for protein crystal structures of CDK8/cyclin C bound to: Compound **25** (Panel A), **42** (Panel B), **54** (Panel C), and **109** (Panel D).

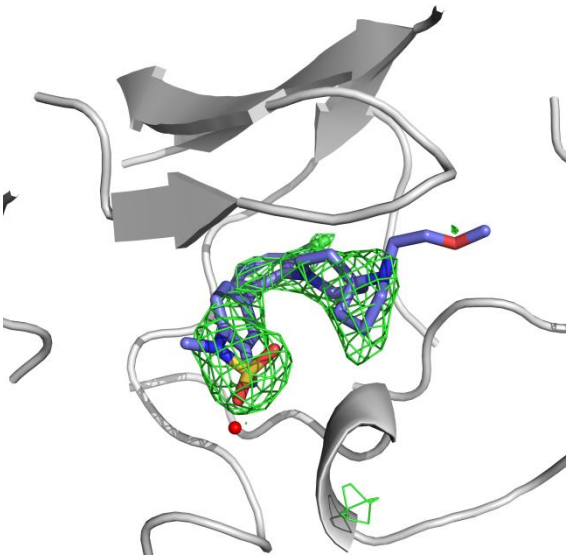
A



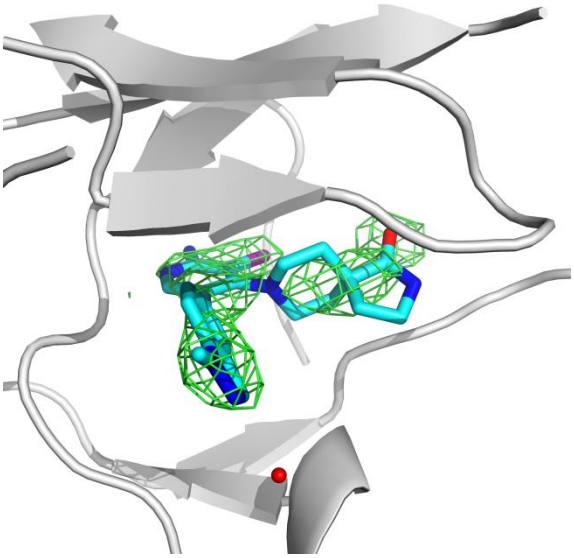
B



C



D



Supplementary References

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