

## Supporting Information

### Identification of pyrimidine-based lead compounds for understudied kinases implicated in driving neurodegeneration

David H. Drewry<sup>⊥,†,‡</sup>, Joel K. Annor-Gyamfi<sup>⊥,†</sup>, Carrow I. Wells<sup>⊥,†</sup>, Julie E. Pickett<sup>⊥,†</sup>, Verena Dederer<sup>†,§</sup>, Franziska Preuss<sup>†,§</sup>, Sebastian Mathea<sup>†,§</sup>, Alison D. Axtman<sup>\*,⊥,†</sup>

<sup>⊥</sup>Structural Genomics Consortium, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599, USA

<sup>†</sup>Division of Chemical Biology and Medicinal Chemistry, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599, USA

<sup>‡</sup>UNC Lineberger Comprehensive Cancer Center, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599, USA

<sup>§</sup>Institute for Pharmaceutical Chemistry, Johann Wolfgang Goethe-University, Max-von-Laue-Str. 9, 60438 Frankfurt am Main, Germany

<sup>§</sup>Structural Genomics Consortium, Buchmann Institute for Molecular Life Sciences, Johann Wolfgang Goethe-University, Max-von-Laue-Str. 15, 60438 Frankfurt am Main, Germany

\*Corresponding Author E-mail: [alison.axtman@unc.edu](mailto:alison.axtman@unc.edu).

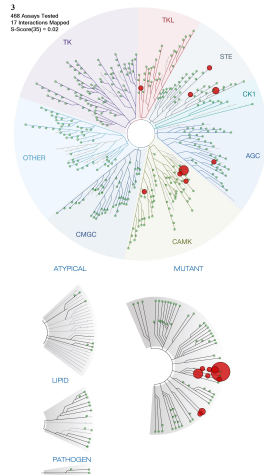
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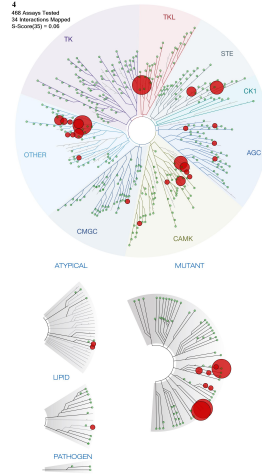
**Table S1.** Enzymatic profiling of aminopyrimidine library.

Compound	% control at 1 $\mu$ M <sup>[a]</sup>															
	AAK1	AURKB	BMP2K	DRAK1 <sup>[b]</sup>	DRAK2 <sup>[b]</sup>	IKK $\epsilon$	JAK2	MARK1 <sup>[b]</sup>	MARK2	MARK3 <sup>[b]</sup>	MARK4 <sup>[b]</sup>	MLK1	MLK3	NUAK1	TBK1	ULK1
3	90	82	96	107	59	95	123	71	90	96	88	72	91	73	81	78
4	61	102	73	25	13	12	99	79	93	96	100	78	94	82	4	58
5	101	102	94	105	88	43	100	108	100	111	110	90	89	97	10	106
6	12	7	7	58	39	32	3	66	65	68	61	25	34	23	4	50
7	7	38	19	5	5	1	67	8	19	35	27	21	36	22	-1	3
8	81	90	101	106	60	63	114	108	103	126	113	85	106	86	61	96
9	4	1	1	8	4	36	6	-3	5	16	3	-1	2	1	21	3
10	54	22	47	63	12	55	106	49	55	68	49	30	60	13	21	20
11	70	51	68	108	84	43	87	100	98	109	98	72	68	83	10	88
12	82	82	86	103	92	73	95	107	108	122	101	97	95	94	49	99
13	8	6	1	41	23	35	12	57	57	63	42	30	24	11	1	66
14	49	2	18	50	14	55	82	1	14	0	4	7	27	6	43	24
15	82	71	104	99	91	83	89	109	104	126	99	77	94	90	87	88
16	73	53	80	82	96	79	62	104	115	115	99	86	89	78	68	97
17	33	56	56	18	17	33	88	72	82	92	85	79	86	87	36	75
18	1	5	-1	0	0	-2	10	-6	2	-3	-1	0	-3	0	-2	2
19	61	48	51	93	96	78	54	102	102	113	98	81	95	79	33	92
20	59	5	58	78	65	80	81	75	93	78	68	73	82	14	50	85
21	73	61	64	79	77	52	107	94	93	112	89	89	72	89	6	82
22	12	11	8	2	3	3	68	-4	6	0	7	31	27	51	-4	17
MRT67307	6	5	3	3	7	4	46	-5	4	-1	5	19	38	31	-1	9
MRT68921	4	8	3	3	4	4	44	-1	3	-4	3	14	44	6	1	1
BX-795	2	3	1	2	4	2	6	-5	3	-4	2	4	1	2	-3	4
BX-912	5	2	2	6	1	44	24	-4	5	-1	2	5	2	1	10	6
GSK8612	37	87	30	93	47	23	70	90	89	105	79	80	82	58	5	77

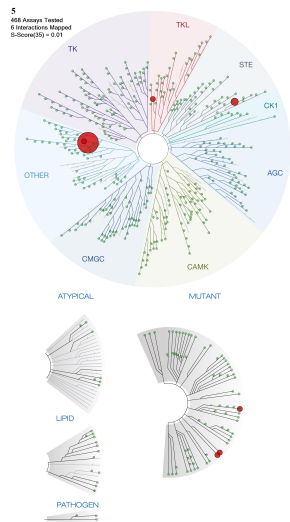
<sup>a</sup>Compounds tested at a single concentration (1  $\mu$ M) in duplicate. <sup>b</sup>IDG kinase; DRAK1 = STK17A and DRAK2 = STK17B.



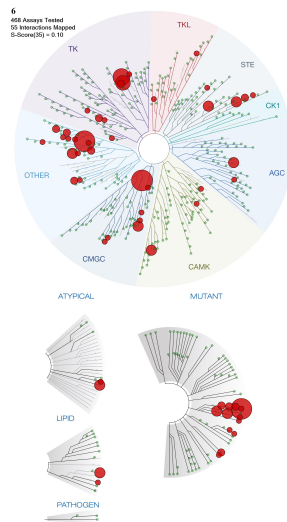
WT kinase	% control at 1000nM
DRAK2	4.8
YSK4	5.4
LRRK2	11
NIM1	14
MEK5	23
MYLK2	24
RSK4(Kin.Dom.1-N-terminal)	28
MLCK	30
MINK	31



WT kinase	% control at 1000nM
LRRK2	0
IKK-epsilon	0
YSK4	0.4
DRAK1	0.5
ULK2	1.3
MKNK2	1.5
TBK1	1.7
GAK	2.2
MEK5	3.6
DRAK2	4.7
ULK1	9.5
ULK3	11
GRK4	13
SRPK3	14
RIOK3	16
PIPSK1A	20
BMP2K	22
SNARK	23
RSK4(Kin.Dom.1-N-terminal)	24
CIT	24
DCAMKL3	25
DAPK1	26
RIOK1	26
ROCK2	28
AAK1	29
TTK	30
DAPK3	34



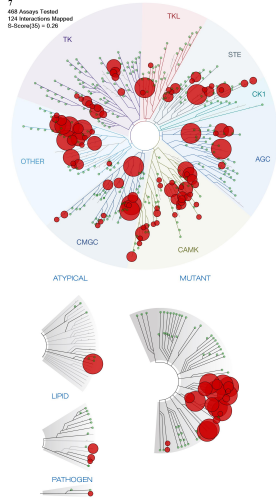
WT kinase	% control at 1000nM
IKK-epsilon	0
YSK4	8.5
TBK1	25
LRRK2	28



WT kinase	% control at 1000nM
TBK1	0
PRP4	0
JAK3(JH1domain-catalytic)	0.1
JAK2(JH1domain-catalytic)	0.9
MEK5	1.2
YSK4	1.4
BMP2K	1.4
GRK4	2.1
SRPK3	3.4
RIOK1	3.6
PIPSK1A	4.7
SNARK	4.8
STK16	5.4
CSF1R-autoinhibited	5.8
TYK2(JH1domain-catalytic)	7.6
CSNK2A2	9
AURKA	9.2
MAP3K2	9.3
AURKB	9.6
AAK1	11
CSNK2A1	12
TRKA	12
SRPK1	13
SRPK2	17
ULK3	18
IKK-epsilon	20
VEGFR2	21
MKNK2	21
RIOK3	22
LRRK2	25
DRAK2	25
FLT3	25
ULK2	26
PIPSK2B	28
MAP3K3	29
TAK1	30
JNK1	30
MAP4K2	31
ULK1	31
JNK3	31
RSK4(Kin.Dom.1-N-terminal)	32
CDKL5	34
ZAP70	35
NEK3	35

7

488 Assays Tested  
124 Interactions Mapped  
S-score(3) = 0.29



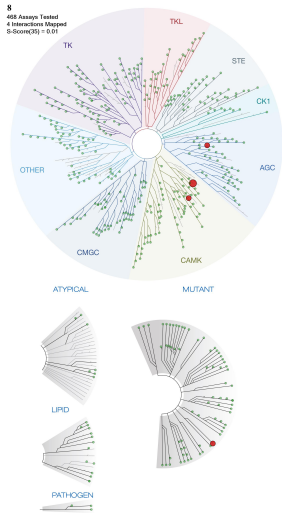
WT kinase	% control at 1000nM
PRP4	0
MEK5	0
BMP2K	0
GRK4	0
SRPK3	0
RIOK1	0
SRPK2	0
ULK3	0
IKK-epsilon	0
LRRK2	0
CIT	0
ULK2	0.1
ULK1	0.1
DRAK1	0.1
BUB1	0.1
JAK3(JH1domain-catalytic)	0.2
YSK4	0.3
DRAK2	0.4
DCAMKL3	0.5
MKNK2	0.6
SBK1	0.7
PDGFRB	0.7
SNARK	0.8
ROCK2	0.8
GAK	0.9
TAOK3	1
FLT4	1
CDK7	1.2
CAMK2A	1.4
TBK1	1.5
MEK4	1.7
TAOK1	1.7
PIPSK1A	1.8
MARK3	2.1
ROCK1	2.2
ALRKA	2.4
AAK1	3.3
CAMK2D	3.3
ERK8	3.4
SRPK1	3.5
DCAMKL1	3.5
JAK2(JH1domain-catalytic)	3.8
TTK	3.9
DAPK1	4.4

WT kinase	% control at 1000nM
MAP4K2	4.5
JAK1(JH1domain-catalytic)	5.1
PCTK1	5.8
MAP3K15	6
AURKC	6.2
PIP5K2B	6.5
CAMK2G	6.9
KIT	7.5
ASK1	7.6
FLT3	8.1
PDGFRA	8.2
TNK1	8.5
RSK4(Kin.Dom.1-N-terminal)	8.7
CAMK2B	8.7
DAPK3	8.8
TYK2(JH1domain-catalytic)	9
RSK3(Kin.Dom.2-C-terminal)	9.2
LKB1	9.4
ANKK1	11
JNK3	13
RIPK5	13
RSK1(Kin.Dom.2-C-terminal)	14
JNK1	15
TSSK3	15
PAK3	16
FLT1	17
ERN1	17
VEGFR2	18
DAPK2	18
DMMPK	18
IKK-alpha	19
RP56KA4(Kin.Dom.2-C-terminal)	20
CSF1R	20
JNK2	21
Sgk110	21
PRKD2	21
DCAMKL2	21
ARK5	22
CASK	22
TAOK2	24
PRKD1	24
HUNK	25
HPK1	25
CLK2	26

WT kinase	% control at 1000nM
NIK	26
SIK2	26
RSK4(Kin.Dom.2-C-terminal)	26
MEK1	27
MEK2	27
QSK	28
TSSK1B	28
PCTK2	28
CLK1	29
CAMK1B	31
STK16	32
PIPSK2C	33
CSNK2A1	34
BRSK2	34
IRAK4	35
RP56KA5(Kin.Dom.2-C-terminal)	35
PLK4	35
NIK	26
SIK2	26
RSK4(Kin.Dom.2-C-terminal)	26
MEK1	27
MEK2	27
QSK	28
TSSK1B	28
PCTK2	28
CLK1	29
CAMK1B	31
STK16	32
PIPSK2C	33
CSNK2A1	34
BRSK2	34
IRAK4	35
RP56KA5(Kin.Dom.2-C-terminal)	35
PLK4	35

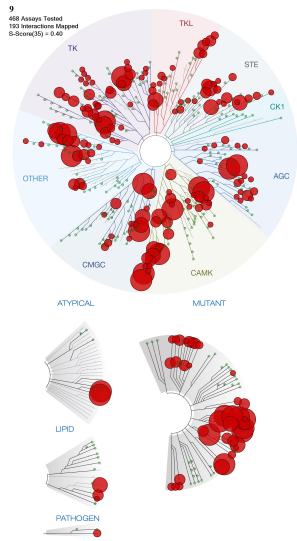
8

468 Assays Tested  
4 Interactions Mapped  
S-score(3) = 0.01



WT kinase	% control at 1000nM
DRAK2	6.6
YANK2	22
MKNK2	24

9  
488 Assays Tested  
193 Interactions Mapped  
S-Score(C) = 0.40



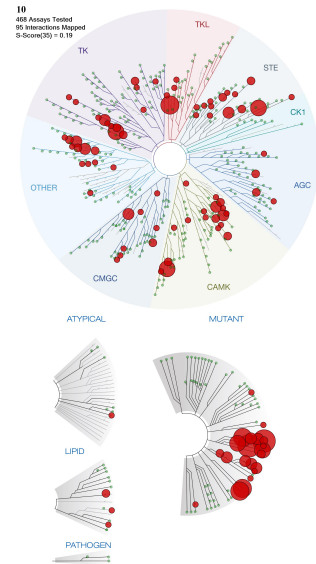
WT kinase	% control at 1000nM
JAK3(JH1domain-catalytic)	0
DRAK2	0
BMP2K	0
GRK4	0
AURKA	0
SRPK3	0
RIOK1	0
PRKD3	0
PRP4	0
RIOK3	0
AURKC	0
PRX	0
DRAK1	0
MARK3	0
MARK1	0
AMPK-alpha2	0
PDGFRB	0.1
YSK4	0.2
SRPK2	0.2
NIM1	0.2
CDKL5	0.3
LRRK2	0.4
MEK5	0.4
SNARK	0.4
AURKB	0.4
ARK5	0.5
JAK2(JH1domain-catalytic)	0.6
SRPK1	0.6
FLT3	0.7
MAP4K2	0.7
PIPSK1A	0.9
ULK3	1
CHEK1	1.1
ULK2	1.2
ULK1	1.3
PRKD2	1.4
MLK1	1.8
PIPSK2B	1.8
HPK1	2.1
GAK	2.4
FGFR1	2.4
JAK1(JH2domain-pseudokinase)	2.6
MARK4	2.7
EPHB6	2.8

WT kinase	% control at 1000nM
TRKA	2.9
OSK	3
STK33	3.1
MYLK2	3.1
MST4	3.2
LKB1	3.2
VEGFR2	3.3
CSNK2A1	3.3
TAK1	3.4
IRAK4	3.5
MELK	3.6
FLT4	3.7
ITK	3.7
AAK1	3.9
CSNK2A2	3.9
MEK2	3.9
FGFR3	3.9
CDK7	4.3
DLK	4.3
MLCK	4.3
SGK	4.6
MAP3K2	5
MAST1	5.1
JNK1	5.2
MLK2	5.4
IRAK1	5.7
TAOK3	5.9
TYK2(JH1domain-catalytic)	6
LZK	6
MINK	6.1
MKNK2	6.9
PDGFRA	6.9
MAP3K3	6.9
ANKK1	7.1
ABL1-phosphorylated	7.1
TBK1	7.3
TRKB	7.3
RET	7.5
FGFR2	7.5
JNK3	7.6
TYK2(JH2domain-pseudokinase)	8
KIT	8.1
CAMKK2	8.2
RSK2(Kin.Dom.1-N-terminal)	8.5

WT kinase	% control at 1000nM
TNIK	8.8
STK16	9.2
AMPK-alpha1	9.6
RSK4(Kin.Dom.1-N-terminal)	9.7
MLK3	9.7
PHKG2	10
PKN1	10
SIK	10
FLT1	11
MEK1	11
PHKG1	11
JNK2	12
ABL1-nonphosphorylated	12
ROCK2	12
TAOK1	12
SYK	13
RIPK4	14
Sgk110	14
ROCK1	15
SGK3	15
CSF1R	15
CSF1R-autoinhibited	16
LATS2	16
NEKS	16
ZAP70	17
CLK2	17
PRKD1	17
TIE1	17
PKAC-beta	17
SGK2	17
SRC	17
PAK3	18
RPS6KA4(Kin.Dom.2-C-terminal)	19
INSR	19
AXL	20
MERTK	20
SIK2	20
PDPK1	20
NIK	21
CIT	21
PKN2	21
PIPSK2C	22
CDK4-cyclinD3	22
CDK4-cyclinD1	22

WT kinase	% control at 1000nM
IKK-epsilon	23
DAPK3	23
MARK2	23
BMPR1B	23
BLK	23
LCK	23
BMPR2	24
MAP4K3	25
MEK4	26
TNK1	26
DAPK1	26
HIPK1	26
NEK3	26
SGK1	27
SLK	27
FGR	28
IKK-alpha	29
ABL2	30
CAMKK1	30
MAPKAPK5	30
TRCK	31
IRAK3	31
CDK1	32
PAK2	33
MAP4K5	33
MAP3K15	33
PKAC-alpha	33
FYN	34
DYRK1B	34
CHEK2	34
YES	35

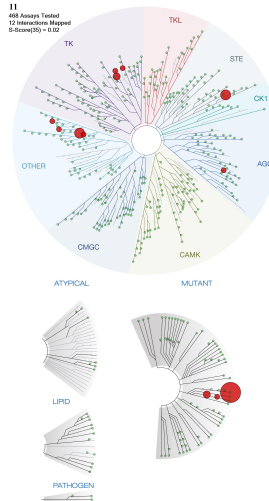
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488 Assays Tested  
93 Interactions Mapped  
S-Score(S) = 0.19



WT kinase	% control at 1000nM
LRRK2	0.1
PDGFRB	0.5
YSK4	0.5
SNARK	0.8
MYLK2	1.1
MEK5	1.3
MLCK	1.5
ULK3	3.1
AURKA	3.2
FLT4	4.2
CDK7	4.8
JAK3(JH1domain-catalytic)	5.1
ULK1	5.4
HPK1	5.4
RSK4(Kin.Dom.1-N-terminal)	5.5
DRAK2	6.2
ARK5	6.2
RPS6KA4(Kin.Dom.2-C-terminal)	6.5
FLT3	6.6
AURKC	6.8
MKNK2	6.8
GRK4	7.3
MINK	7.3
PDGFRA	7.6
PIK4CB	8.2
TBK1	8.7
SRPK3	9.1
MEK4	9.3
BMP2K	12
DRAK1	12
NIM1	12
MAP4K2	12
PIPSK1A	12
VEGFR2	12
TNIK	12
RIOK1	13
RSK2(Kin.Dom.1-N-terminal)	13
ULK2	14
PAK3	14
PIPSK2C	14
SRPK1	15
CSNK2A1	16
GAK	19
KIT	19

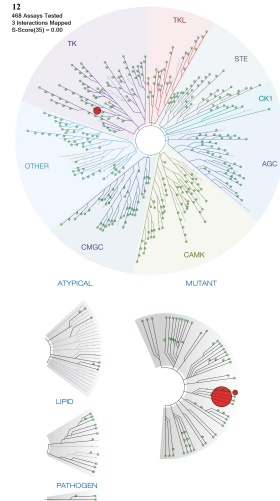
WT kinase	% control at 1000nM
TNK1	19
PRKD3	20
STK33	21
ANKK1	21
JAK2(JH1domain-catalytic)	22
JNK1	23
JNK3	24
INSR	24
AURKB	26
TAOK3	27
DAPK3	27
ERK8	27
MARK4	28
CSF1R	28
RIPK4	30
DAPK1	30
SLK	30
MST2	30
AAK1	31
ROCK1	31
MAP3K15	31
PRP4	32
IRAK1	32
PHKG1	32
SBK1	32
FGFR3	33
JNK2	33
TAOK1	33
RPS6KAS(Kin.Dom.2-C-terminal)	33
RSK3(Kin.Dom.2-C-terminal)	33
MYO3B	34
FGFR2	35
PHKG2	35

11  
408 Assays Tested  
12 Interactions Mapped  
S-Score(95) = 0.02



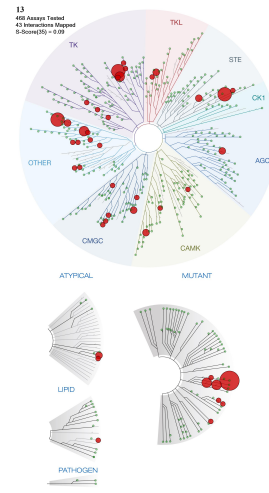
WT kinase	% control at 1000nM
TBK1	3.8
YSK4	4.1
JAK2(JH1domain-catalytic)	8.6
IKK-epsilon	13
TRKA	20
RSK4(kin.Dom.1-N-terminal)	25
AURKB	27
JAK3(JH1domain-catalytic)	29
ULK2	33

12  
408 Assays Tested  
13 Interactions Mapped  
S-Score(95) = 0.00



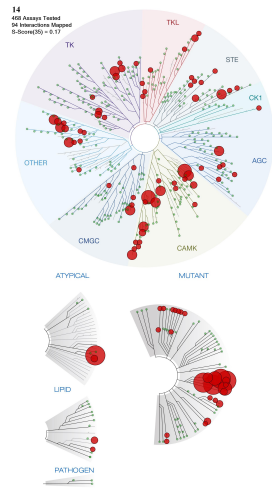
WT kinase	% control at 1000nM
CSF1R-autoinhibited	6.6

13  
408 Assays Tested  
43 Interactions Mapped  
S-Score(95) = 0.00



WT kinase	% control at 1000nM
JAK3(JH1domain-catalytic)	0.4
AURKB	0.8
YSK4	0.9
TBK1	3
JAK2(JH1domain-catalytic)	3
AURKA	5.6
BMPR2	5.7
RIOK3	5.7
SNARK	6
MEK5	8.3
GRK4	8.6
SRPK3	9.4
VEGFR2	11
BMP2K	11
RIPK4	12
CSNK2A2	12
JNK3	14
PIPSK1A	14
TYK2(JH1domain-catalytic)	16
MNPK2	16
AAK1	16
STK16	17
CDK7	19
TRKA	19
RIOK1	19
JNK2	21
JNK1	23
HUNK	24
SBK1	24
PDGFRA	28
CSNK2A1	29
MAP3K2	29
CSF1R-autoinhibited	30
SRPK1	31
IKK-epsilon	32
TRKB	35

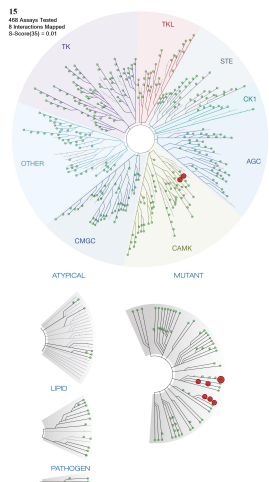
14  
408 Assays Tested  
50 Interactions Mapped  
S-Score(95) = 0.1



WT kinase	% control at 1000nM
RIOK3	0
DRAK1	0.5
NIM1	0.6
DRAK2	1
YSK4	1.1
AURKB	1.2
GRK4	1.4
MARK3	1.7
BMP2K	2.2
ARK5	2.6
JAK3(JH1domain-catalytic)	2.7
SRPK3	2.9
SRPK3	3
ULK2	3.6
CHEK1	4.3
DAPK3	5.3
PDGFRB	5.6
AURKC	6.4
SNARK	6.5
RIOK1	6.8
JAK2(JH1domain-catalytic)	7.2
MEK5	7.4
PIPSK1A	7.6
ULK1	8.2
FLT3	8.3
MLK1	8.6
TRKA	9.6
RSK4(kin.Dom.1-N-terminal)	11
LRRK2	13
TBK1	14
AURKA	14
MLK3	14
VRK2	14
SRPK1	16
TAK1	17
MINK	17
SIK2	17
PRP4	18
MST4	18
RSK2(kin.Dom.1-N-terminal)	18
PRKD2	18
MELK	20
TRKB	21
GAK	21

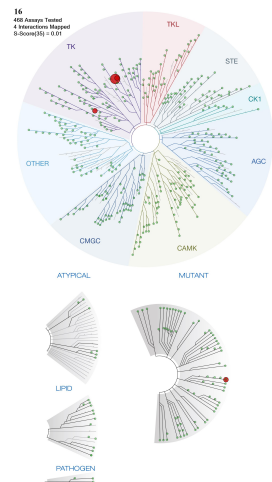
WT kinase	% control at 1000nM
SRPK2	22
MAP3K2	23
RP56KA4(kin.Dom.2-C-terminal)	24
PKN1	24
PRKCQ	26
MAP3K3	27
MARK2	27
IRAK4	28
IRAK1	28
MARK1	28
IKK-epsilon	30
HPK1	30
PHKG1	30
MAP4K2	31
TNIK	32
CDK7	33
S6K1	33
CAMKK2	33
MERTK	33
SIK	33
SIK	33
AAK1	34
PDGFRA	34
MYLK2	34
ANKK1	35
PIPSK2B	35
PHKG2	35

15  
408 Assays Tested  
8 Interactions Mapped  
S-Score(95) = 0.01



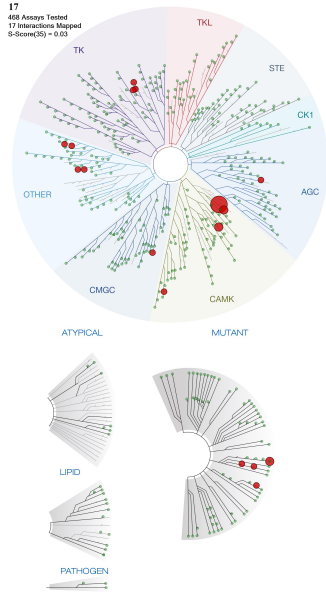
WT kinase	% control at 1000nM
MYLK2	15
DRAK2	32

16  
408 Assays Tested  
4 Interactions Mapped  
S-Score(95) = 0.01



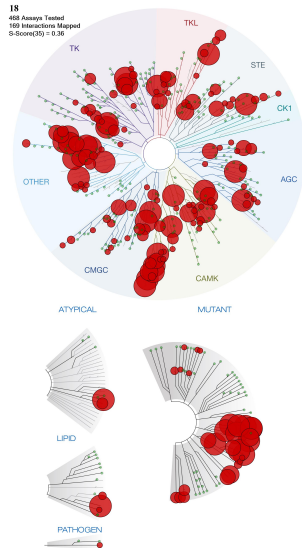
WT kinase	% control at 1000nM
TYK2(JH1domain-catalytic)	1
JAK2(JH1domain-catalytic)	13
CSF1R-autoinhibited	18

17  
493 Assays Tested  
17 Interactions Mapped  
S-Score(3) = 0.03



WT kinase	% control at 1000nM
DRAK1	0.8
DRAK2	5.3
MKNK2	9
TYK2(JH1domain-catalytic)	11
AAK1	22
AURKC	24
SIK2	24
AURKA	26
JAK2(JH1domain-catalytic)	27
BMP2K	30
GRK4	30
SRPK3	33
JAK3(JH1domain-catalytic)	35

18  
468 Assays Tested  
192 Interactions Mapped  
S-Score(3) = 0.36

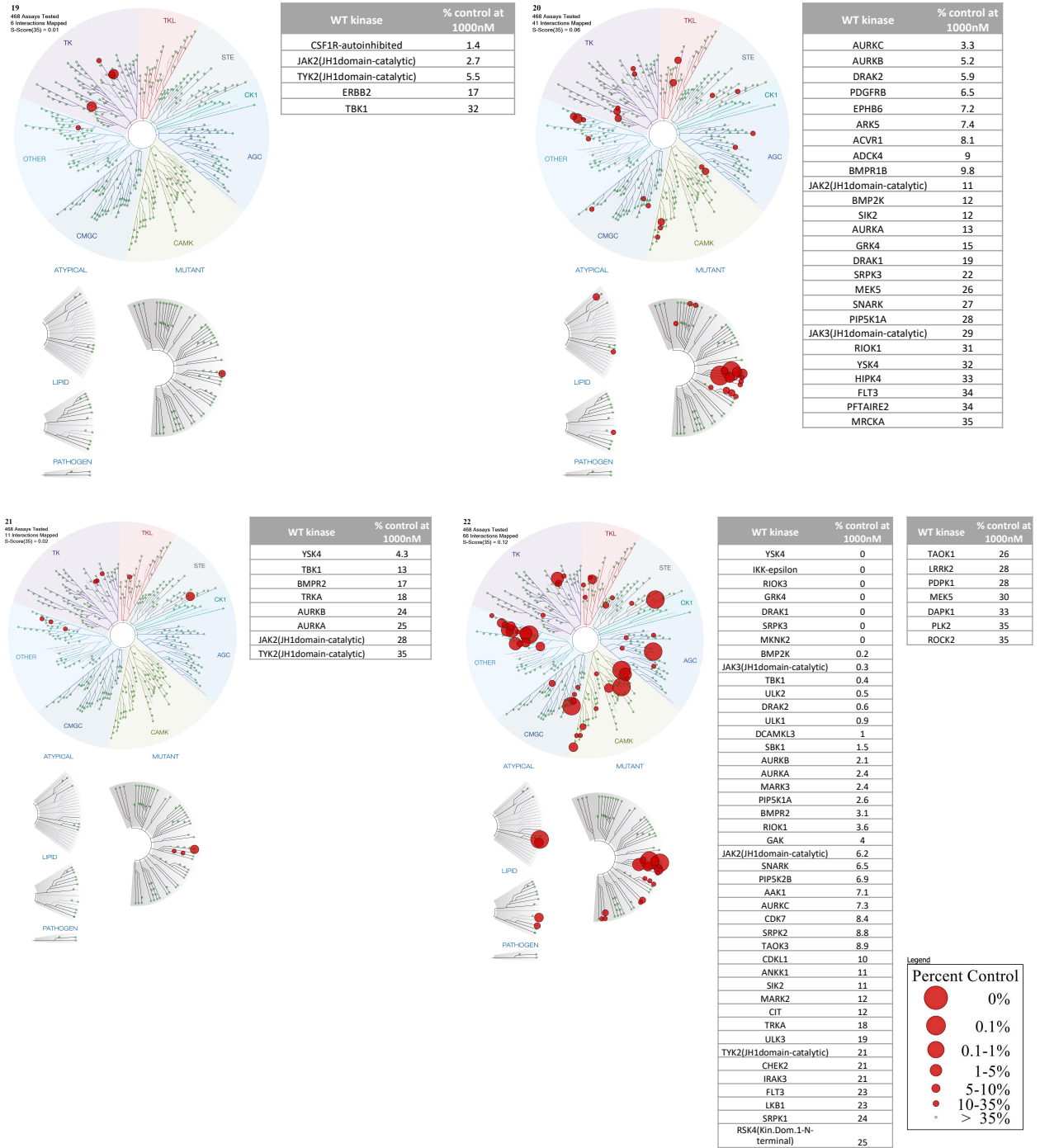


WT kinase	% control at 1000nM
DRAK1	0
MKNK2	0
SIK2	0
AURKA	0
JAK2(JH1domain-catalytic)	0
BMP2K	0
JAK3(JH1domain-catalytic)	0
SRPK1	0
TBK1	0
PIP5K2B	0
CHEK2	0
ULK1	0
IRAK3	0
ULK2	0
BUB1	0
YSK4	0
IKK-epsilon	0
PDGFRB	0
CDK11	0
OSK	0
FLT3	0
MLK2	0
RIOK3	0
ARKS	0
SBK1	0
PRKX	0
CHEK1	0
MARK1	0
PKN1	0
MARK3	0
DRAK2	0.1
TAOK3	0.1
MARK2	0.1
DCAMKL3	0.1
TYK2(JH1domain-catalytic)	0.2
AURKC	0.2
AURKB	0.2
SNARK	0.3
MEK5	0.3
ULK3	0.3
GAK	0.3
BMPR2	0.4
CIT	0.5
LRRK2	0.6

WT kinase	% control at 1000nM
CDK7	0.6
ROCK2	0.6
TAOK1	0.6
AAK1	0.7
JAK1(JH1domain-catalytic)	1.1
ERK8	1.1
Sgk110	1.4
CDKL5	1.7
MARK4	1.8
LKB1	2.2
MELK	2.3
RIOK1	2.8
PLK4	3
RET	3.1
SRPK2	3.2
SRPK3	3.3
FLT4	3.3
MLK3	3.3
PDGFRA	3.4
ANKK1	3.6
ROCK1	3.6
MAP4K2	3.8
CLK2	4.5
FYN	4.9
PCTK1	5.1
CDK4-cyclinD3	5.4
MEK4	5.4
PIP5K1A	5.8
NEK5	5.8
TRKA	6
CAMK2A	6.1
MAP3K3	6.3
GRK4	6.4
PKN2	6.8
TAK1	6.9
CSNK2A2	7.2
PAK3	7.2
JAK1(JH2domain-pseudokinase)	7.6
KIT	7.7
FLT1	8.2
DAPK1	8.2
MAP3K2	8.4
SIK	8.4
STK16	8.4

WT kinase	% control at 1000nM
MLK1	9.1
CDC2L5	9.9
SYK	10
MEK2	11
IRAK4	11
TNK1	11
TAOK2	11
CAMKK2	11
JNK3	11
CASK	11
AMPK-alpha2	11
MEK1	12
CDK4-cyclinD1	12
RIPK4	13
AMPK-alpha1	13
SGK	14
JNK1	14
PIP5K2C	15
MAP3K15	16
ZAK	16
VEGFR2	17
BRSK2	17
IRAK1	18
DMPK	18
TIE1	19
CAMK2D	19
JNK2	19
TTK	20
CSF1R	20
PHKG2	20
PHKG1	21
TRKB	24
PRP4	24
CSNK2A1	25
RSK4(Kin.Dom.1-N-terminal)	25
FGFR1	25
HPK1	26
DAPK3	26
MKNK1	27
CAMK2G	28
DYRK2	28
TGFBF2	28
IKK-alpha	29
ICK	29

WT kinase	% control at 1000nM
SGK3	29
ERN1	29
BRSK1	30
DCAMKL1	31
PRKD1	31
MAST1	32
SGK2	33
PDPK1	33
PCTK2	34
CDK2	34
TSSK3	35
LATS2	35



**Figure S1.** Treepots and all WT kinases inhibited > 90% at 1  $\mu$ M by compounds 3-22.



Kinase	Above outer lipophilic pocket	Turn in Gly-rich loop	Turn in Gly-rich loop	Conserved Val above purine	Conserved Ala above purine	Conserved Lys	Conserved Glu on C-helix	On C-helix	Back pocket on C-helix	Back pocket	Back pocket	Gatekeeper	Hinge inner H-bond acceptor	Hinge	Hinge donor & outer H-bond acceptor	Outer hinge	Outer hinge	Solvent front	Solvent front & sugar pocket sidechain	Surface helix	Surface helix	Gamma-phosphate region	Sugar pocket carbonyl	Mg binding	Outer hydrophobe below purine	Inner hydrophobe below purine	DFG Asp	DFG Phe
TBK1	L	A	T	V	A	K	E	F	L	V	L	M	E	F	C	P	C	G	S	Y	T	K	G	N	M	T	D	F
ULK2	V	A	F	V	A	K	E	I	L	V	L	M	E	Y	C	N	G	G	D	A	D	K	Q	N	L	A	D	F
PDK1	L	S	F	V	A	K	E	R	M	V	F	L	S	Y	A	K	N	-	E	L	K	K	E	N	L	T	D	F
DRAK1	L	K	F	V	A	K	E	I	L	I	L	L	E	Y	A	A	G	G	E	F	D	K	Q	N	L	V	D	F
MARK3	I	N	F	V	A	K	E	V	M	V	L	M	E	Y	A	S	G	G	K	F	D	K	E	N	L	A	D	F
MARK4	I	N	F	V	A	K	E	V	M	V	L	M	E	Y	A	S	A	G	E	F	D	Q	E	N	L	A	D	F
BMP2K	L	G	F	L	V	N	E	I	M	V	I	M	E	Y	C	R	A	G	Q	V	N	K	E	N	L	C	D	F

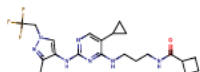
**Figure S2.** Sequence alignment of solved and understudied kinases that bind aminopyrimidines with high affinity.

**Table S2.** X-Ray crystallography data collection and refinement statistics.

MARK3-Compound 9	
<b>PDB ID</b>	7P1L
<b>Space group</b>	P 1 2 <sub>1</sub> 1
<b>Cell parameters</b>	
a, b, c (Å)	50.99, 95.73, 68.58
α, β, γ (°)	90, 91.98, 90
<b>Resolution (Å)</b>	47.87 - 1.95 (2.02 - 1.95)*
<b>Unique reflexions</b>	47368 (4760)*
<b>Completeness for range (%)</b>	98.7 (99.4)*
<b>Multiplicity</b>	3.5 (3.6)*
<b>R<sub>merge</sub></b>	0.079 (0.543)*
<b>CC1/2</b>	0.996 (0.782)*
<b>I/σ(I)</b>	11.8 (2.5)*
<b>Wavelength (Å)</b>	1.00002
<b>Phasing</b>	MR
<b>R<sub>work</sub>, R<sub>free</sub> (%)</b>	21.0, 24.2
<b>Number of atoms</b>	
protein, inhibitor, ethylene glycol, solvent	4578, 58, 12, 103
<b>B-factors (Å<sup>2</sup>)</b>	
protein, inhibitor, ethylene glycol, solvent	34.3, 33.5, 26.8, 31.0
<b>rmsd bond (Å)</b>	0.01
<b>rmsd angle (°)</b>	1.05
<b>Ramachandran statistics</b>	
favored, outliers (%)	97.6, 0

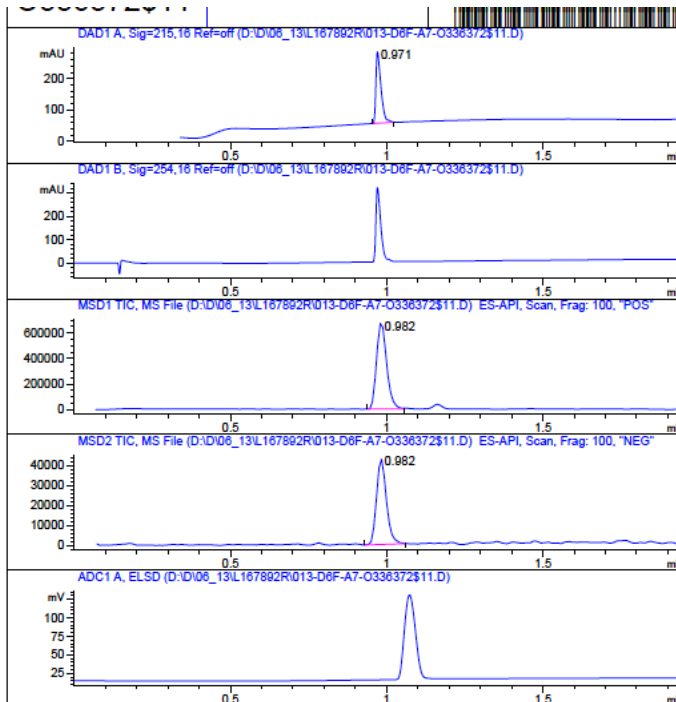
\*Values in parentheses correspond to the highest resolution shell

MaxPeak: 100.00%  
Ret\_Time: 0.971 min



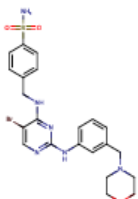
Mol Wt 451.49  
Exact Mass 451.27

#	Time	Area%
1	0.971	100.00



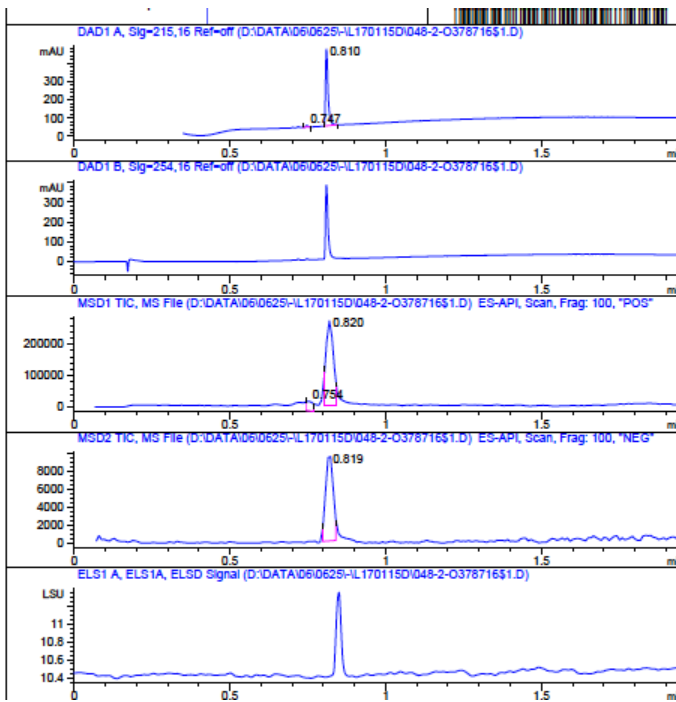
LC Chromatogram for 4

MaxPeak: 98.96%  
Ret\_Time: 0.810 min



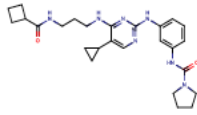
Mol Wt 533.44  
Exact Mass 534.11

#	Time	Area%
1	0.747	1.64
2	0.810	98.96



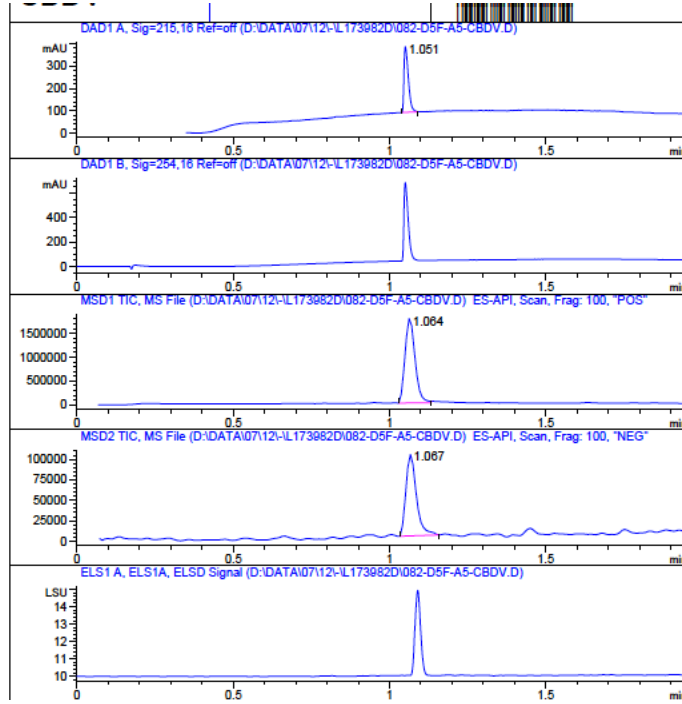
LC Chromatogram for 6

MaxPeak: 100.00%  
Ret\_Time: 1.051 min



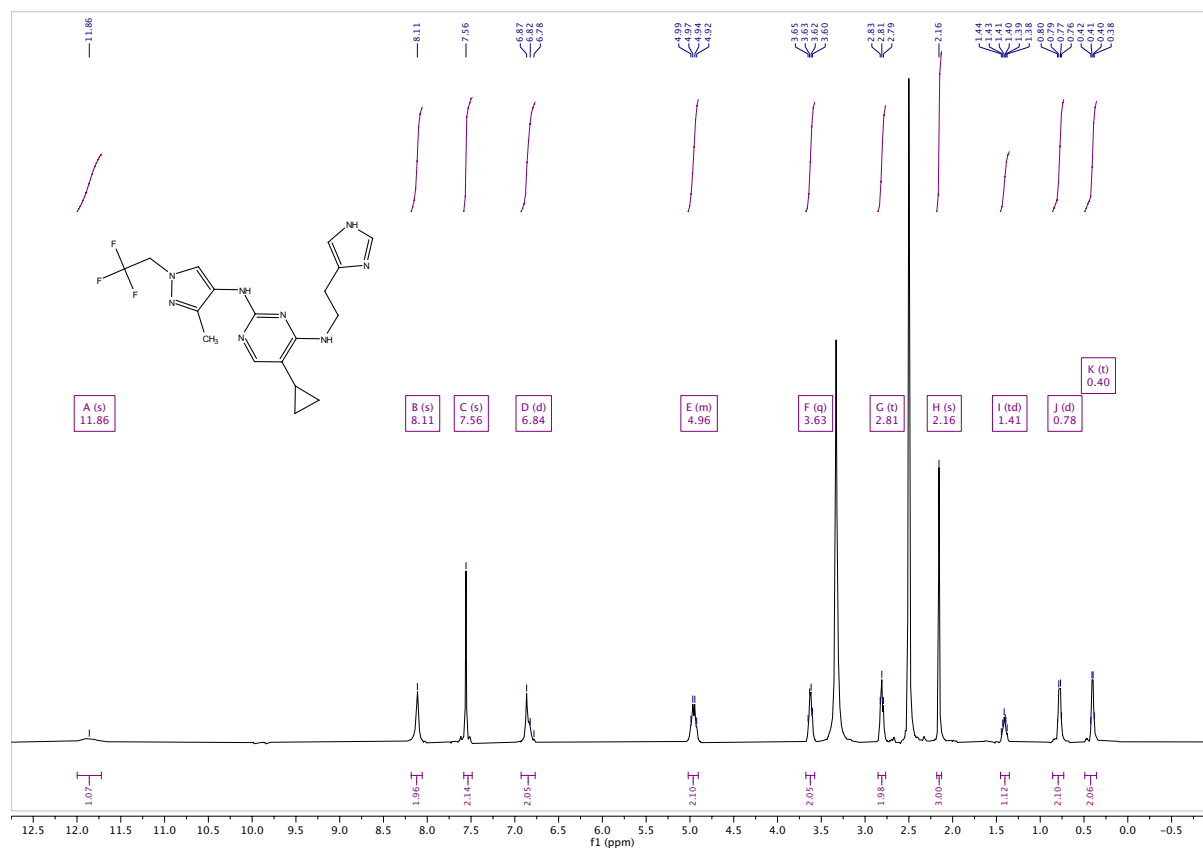
Mol Wt 477.6  
Exact Mass 477.33

#	Time	Area%
1	1.051	100.00

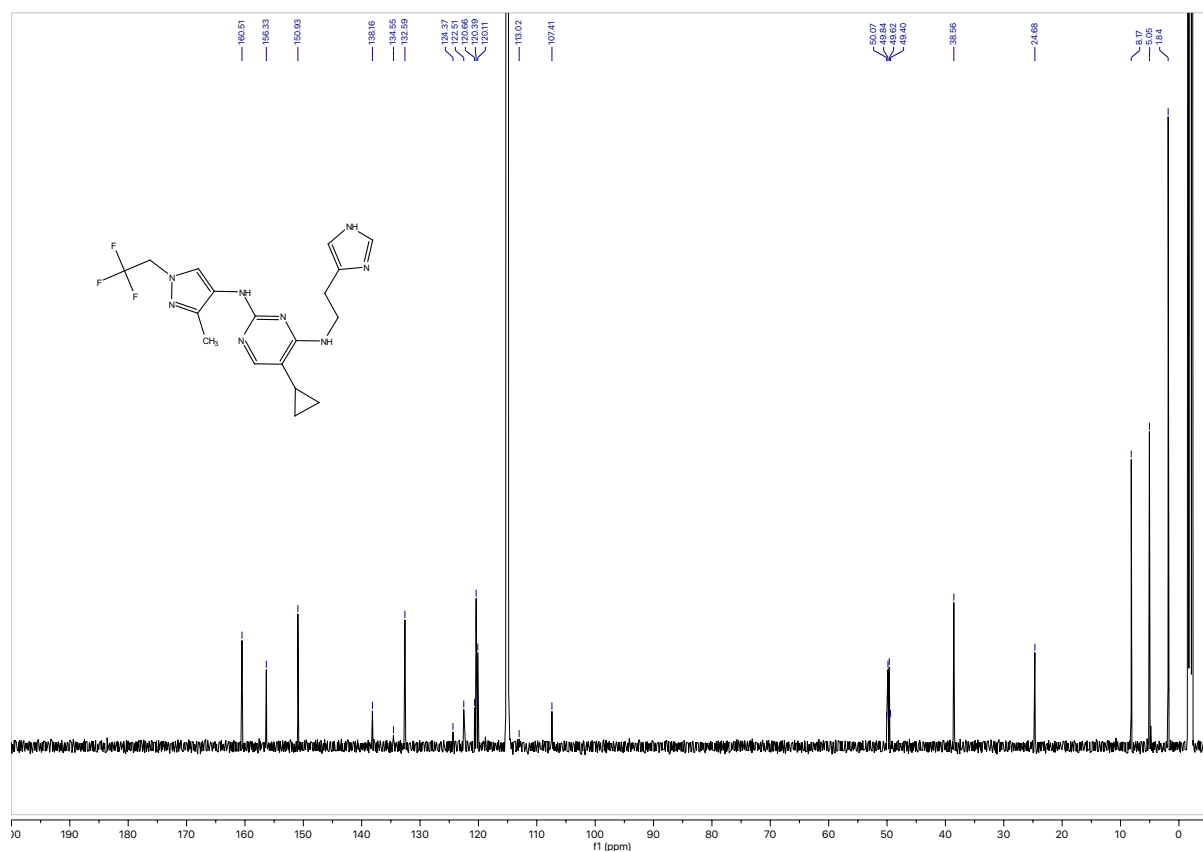


LC Chromatogram for 22

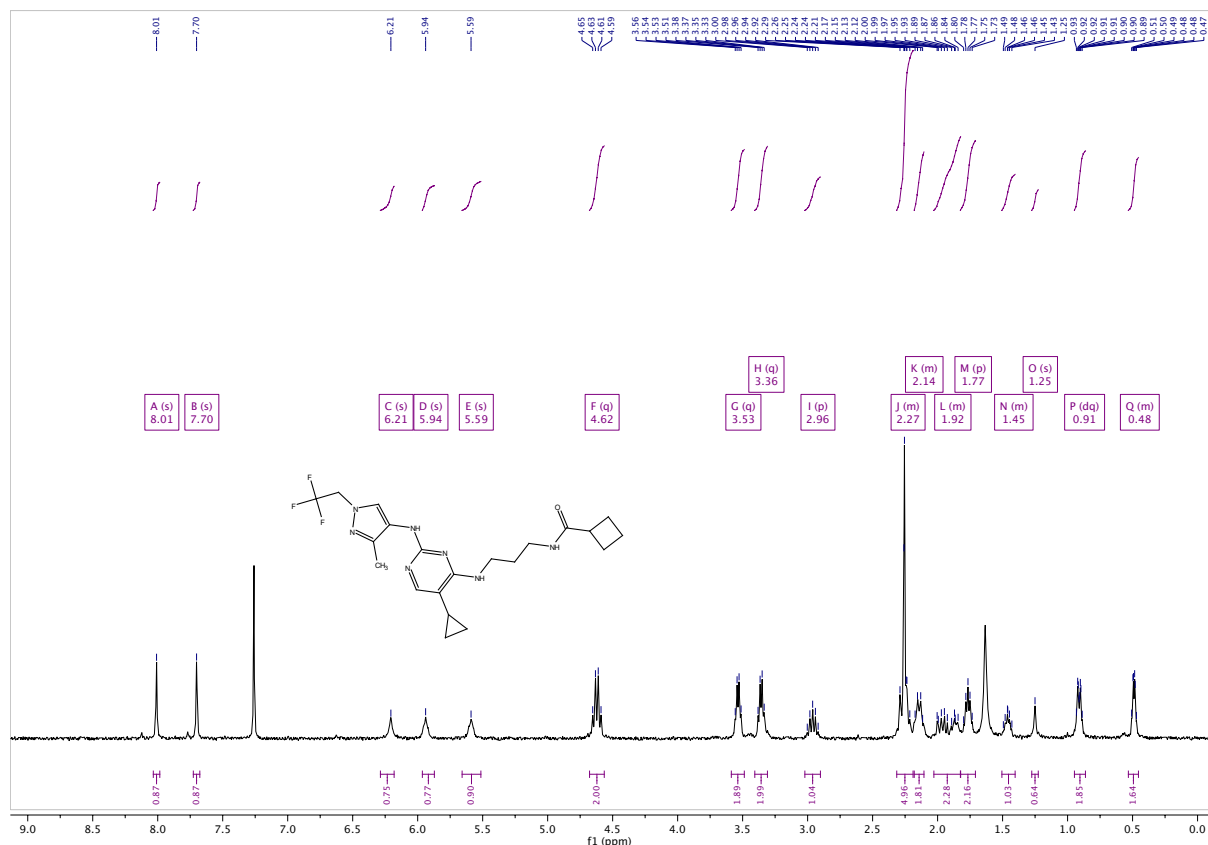
**<sup>1</sup>H NMR of N<sup>4</sup>-(2-(1H-imidazol-4-yl)ethyl)-5-cyclopropyl-N<sup>2</sup>-(3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)pyrimidine-2,4-diamine (3)**



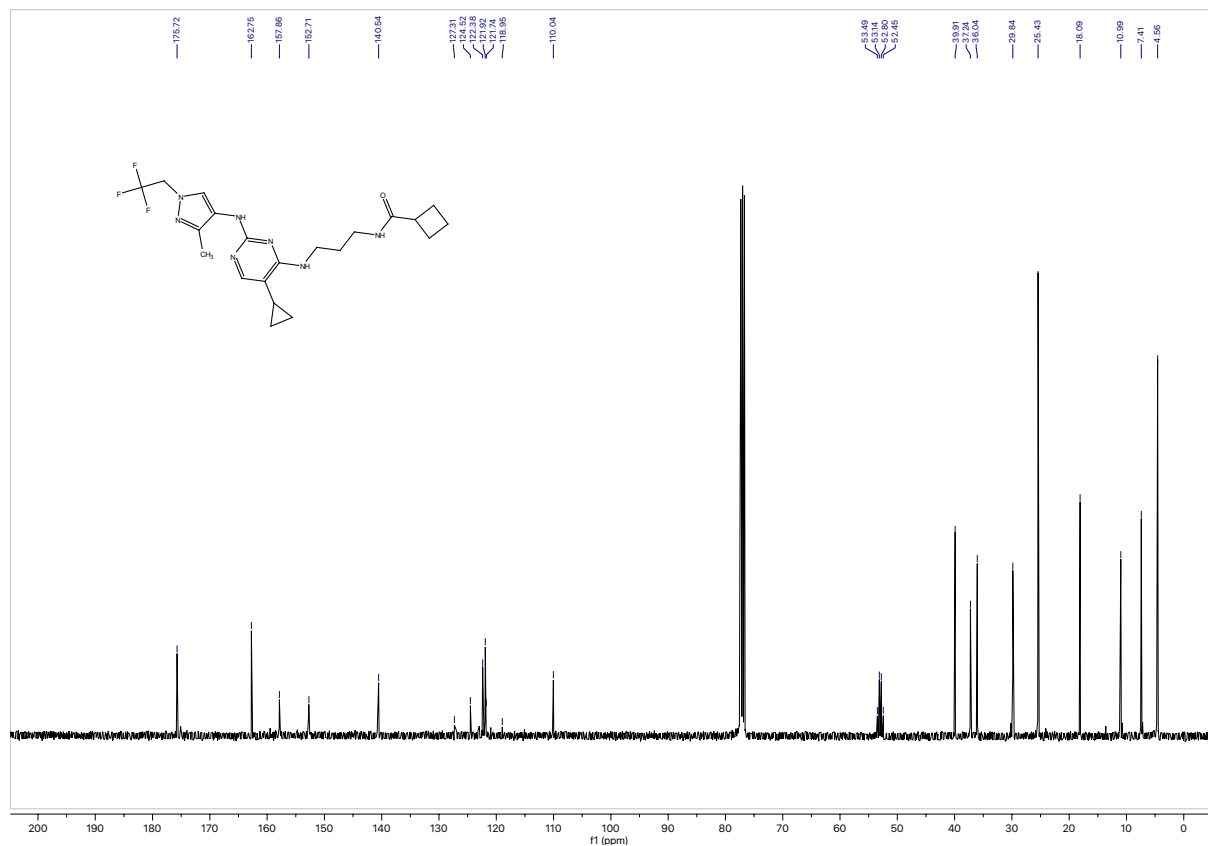
**<sup>13</sup>C NMR of N<sup>4</sup>-(2-(1H-imidazol-4-yl)ethyl)-5-cyclopropyl-N<sup>2</sup>-(3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)pyrimidine-2,4-diamine (3)**



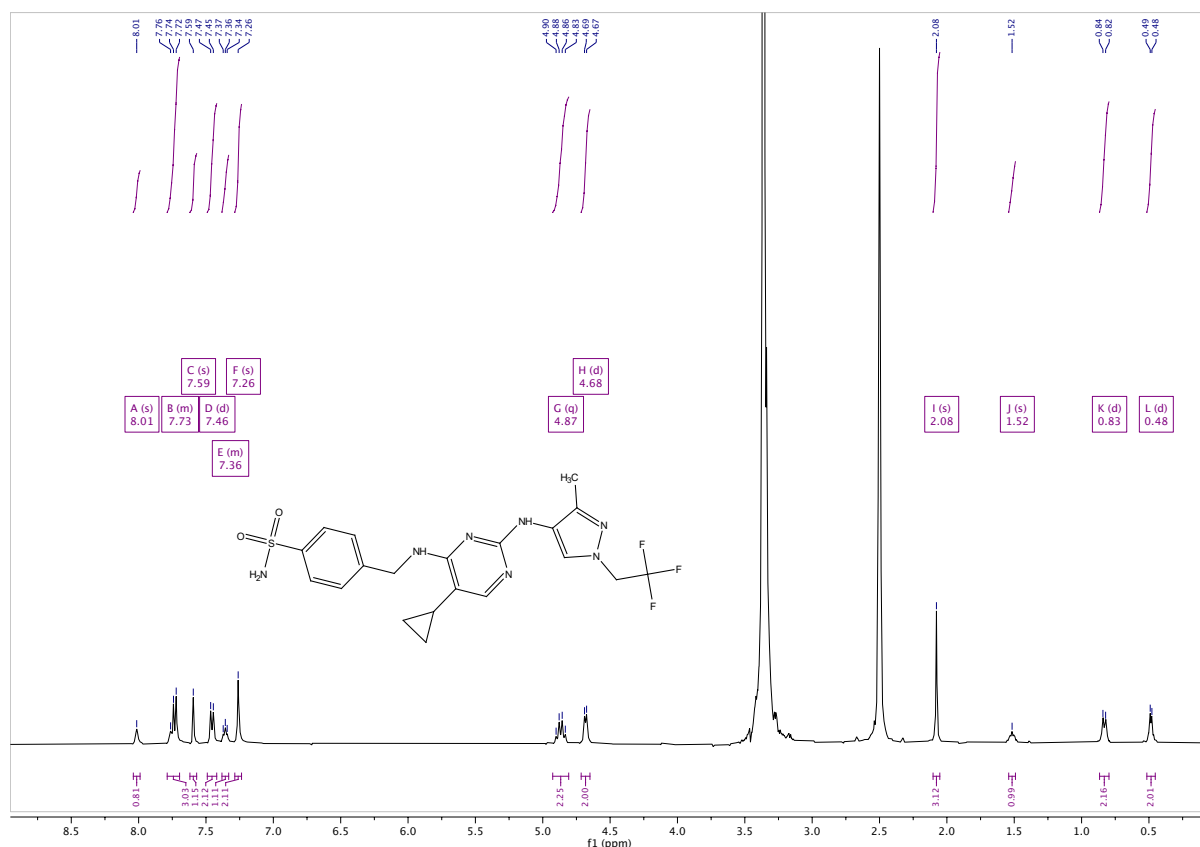
**<sup>1</sup>H NMR of N-(3-((5-cyclopropyl-2-((3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide (4)**



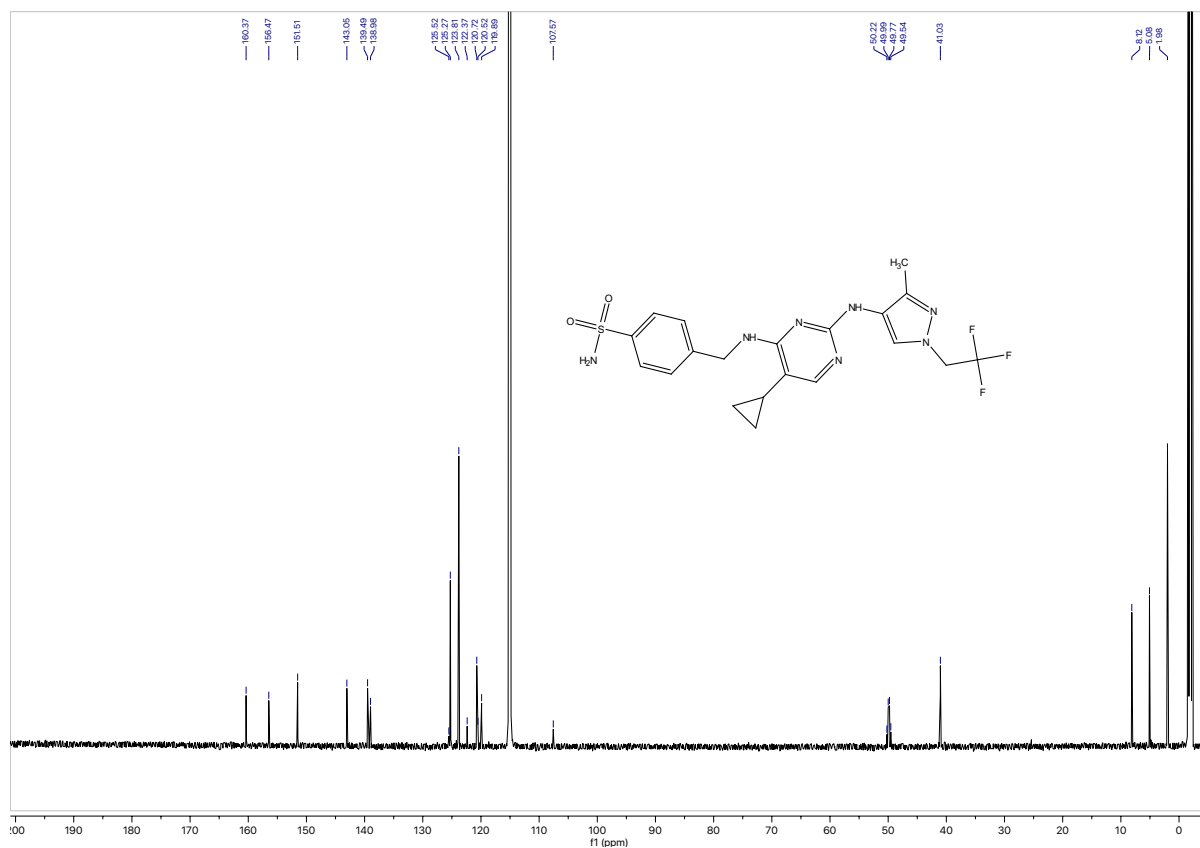
**<sup>13</sup>C NMR of N-(3-((5-cyclopropyl-2-((3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide (4)**



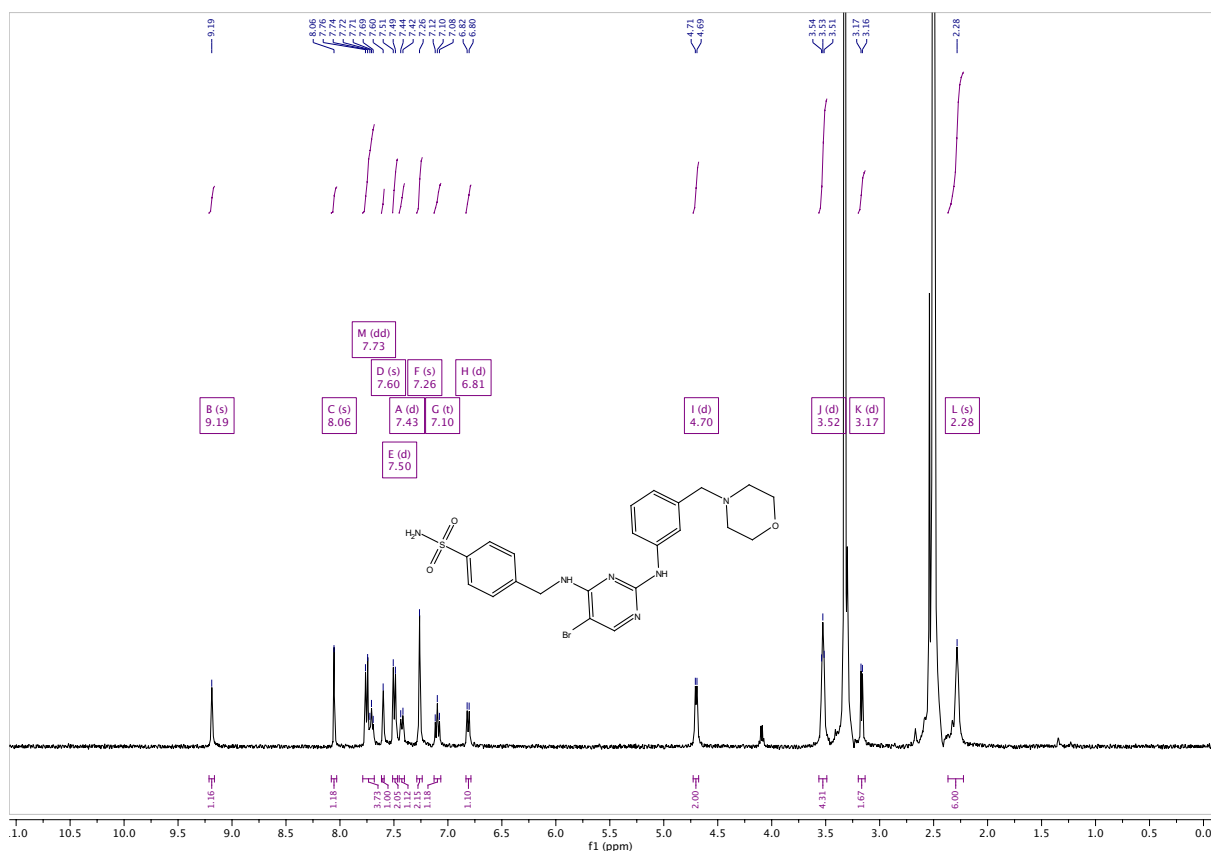
**<sup>1</sup>H NMR of 4-(((5-cyclopropyl-2-((3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)methyl)benzenesulfonamide (5)**



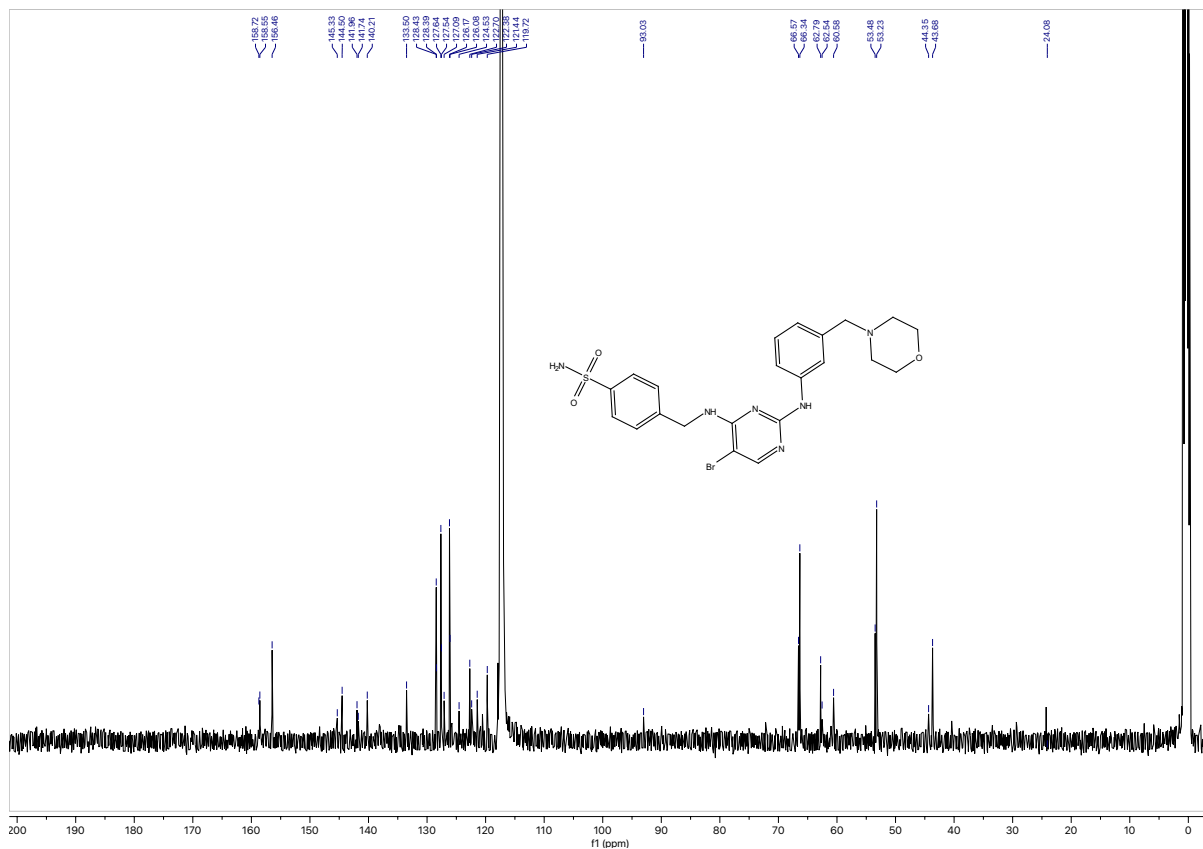
**<sup>13</sup>C NMR of 4-(((5-cyclopropyl-2-((3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)methyl)benzenesulfonamide (5)**



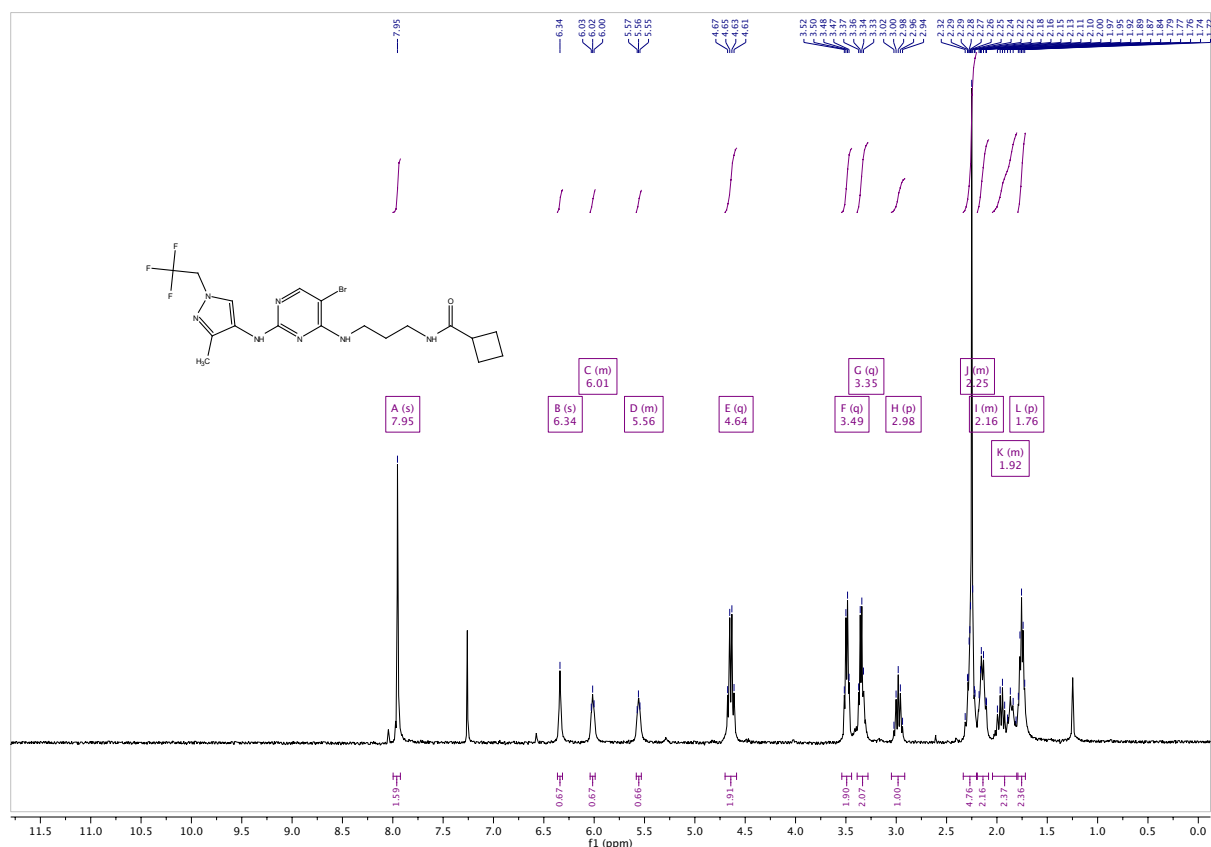
**<sup>1</sup>H NMR of 4-(((5-bromo-2-((3-(morpholinomethyl)phenyl)amino)pyrimidin-4-yl)amino)methyl)benzenesulfonamide (6)**



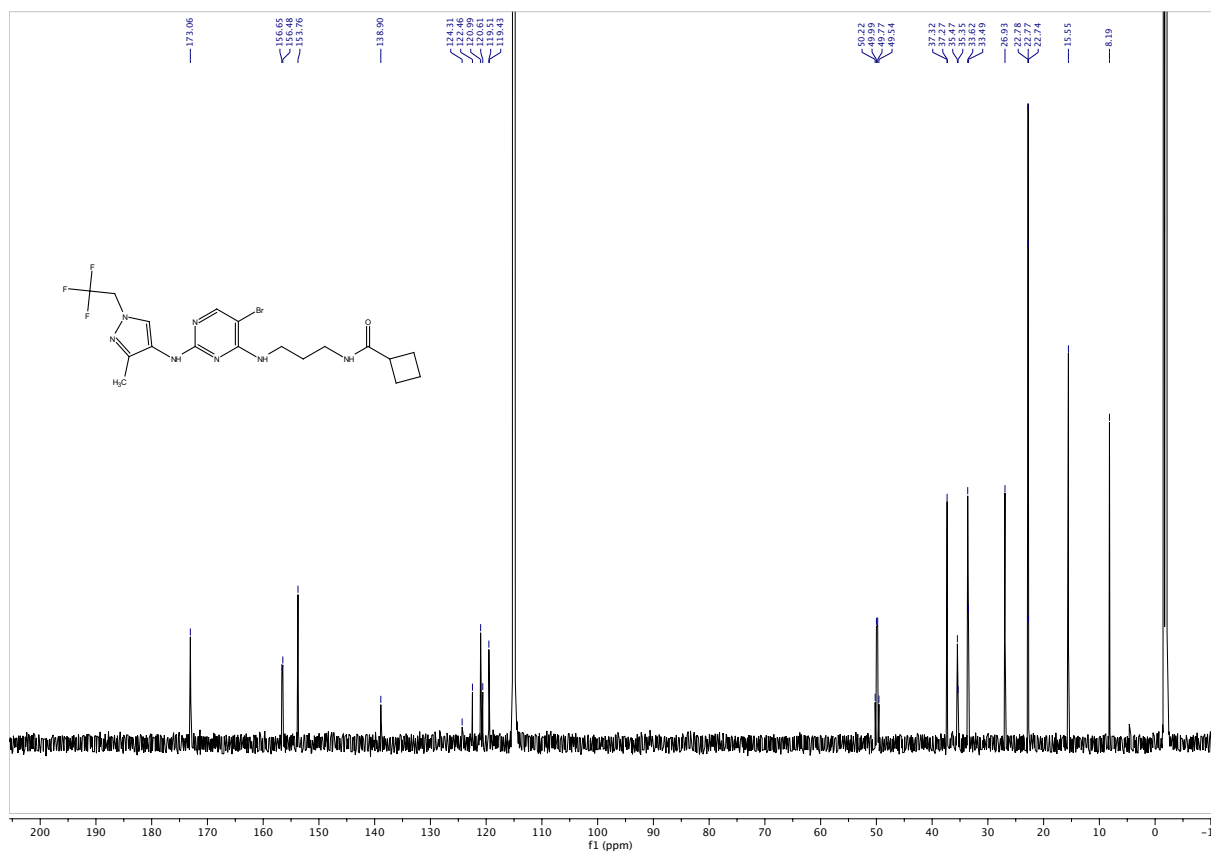
**<sup>13</sup>C NMR of 4-(((5-bromo-2-((3-(morpholinomethyl)phenyl)amino)pyrimidin-4-yl)amino)methyl)benzenesulfonamide (6)**



**<sup>1</sup>H NMR of N-(3-((5-bromo-2-((3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide (7)**

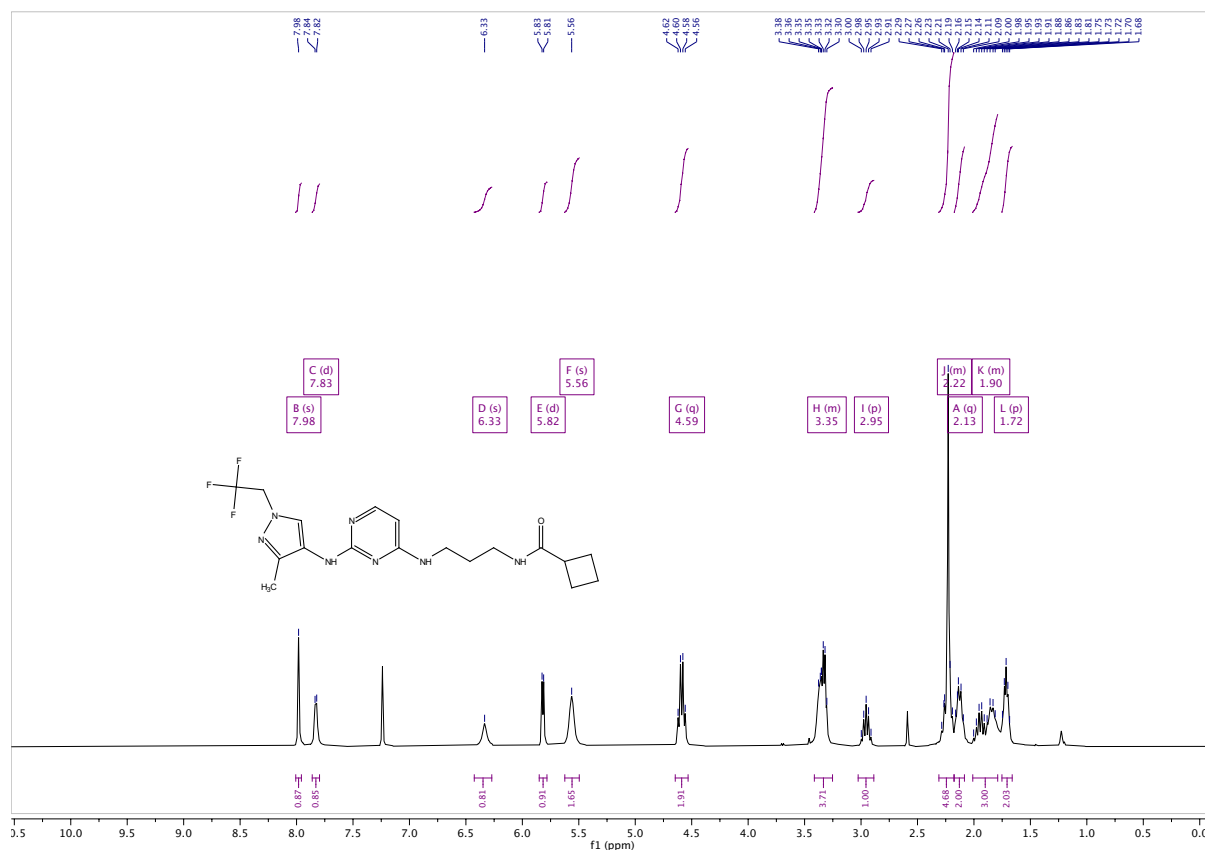


**<sup>13</sup>C NMR of N-(3-((5-bromo-2-((3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide (7)**

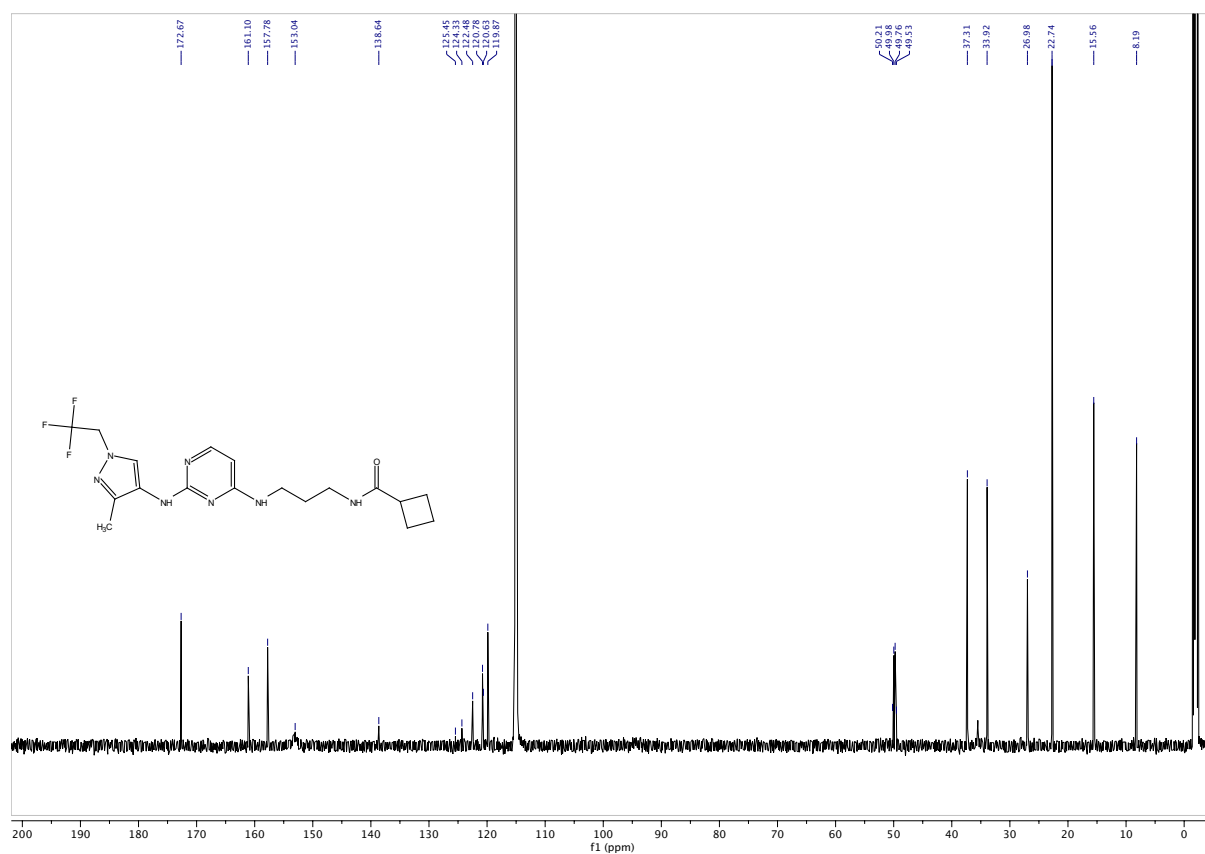




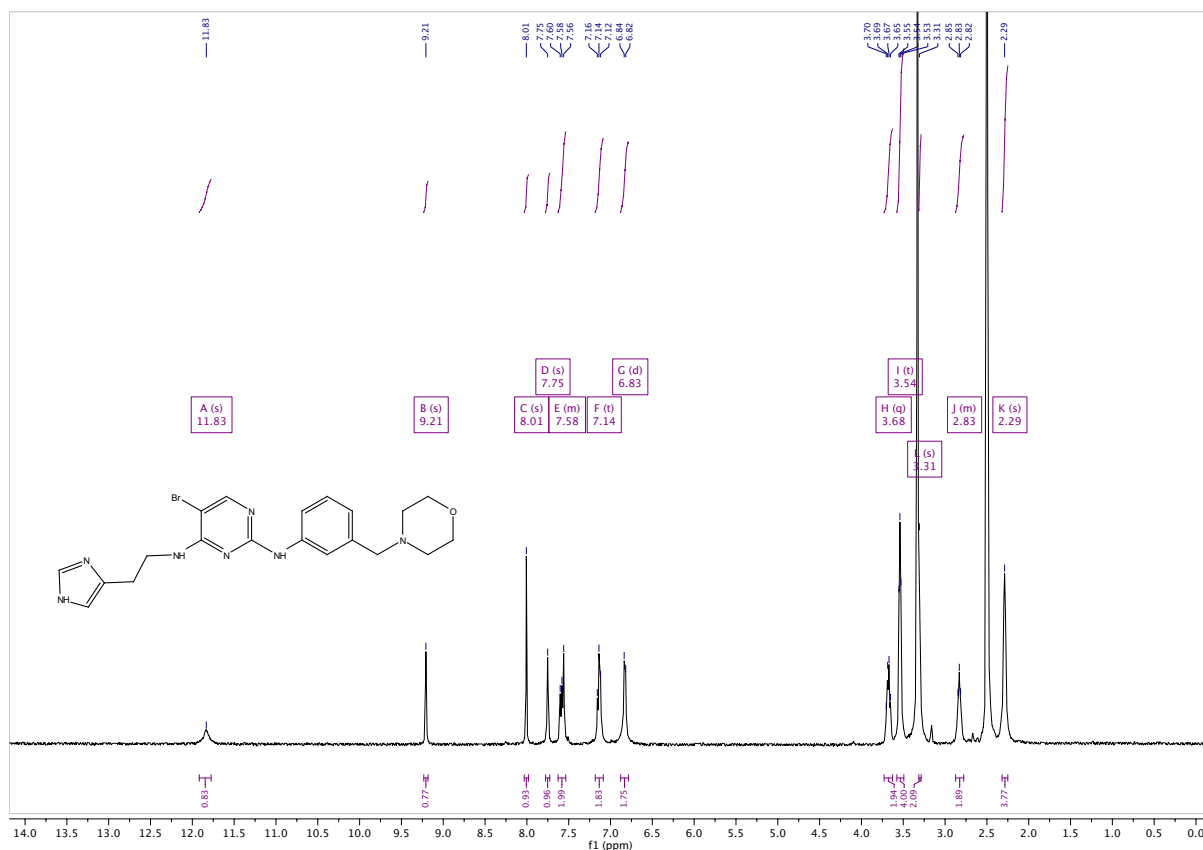
**$^1\text{H}$  NMR of N-(3-((2-((3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)-propyl)cyclobutanecarboxamide (8)**



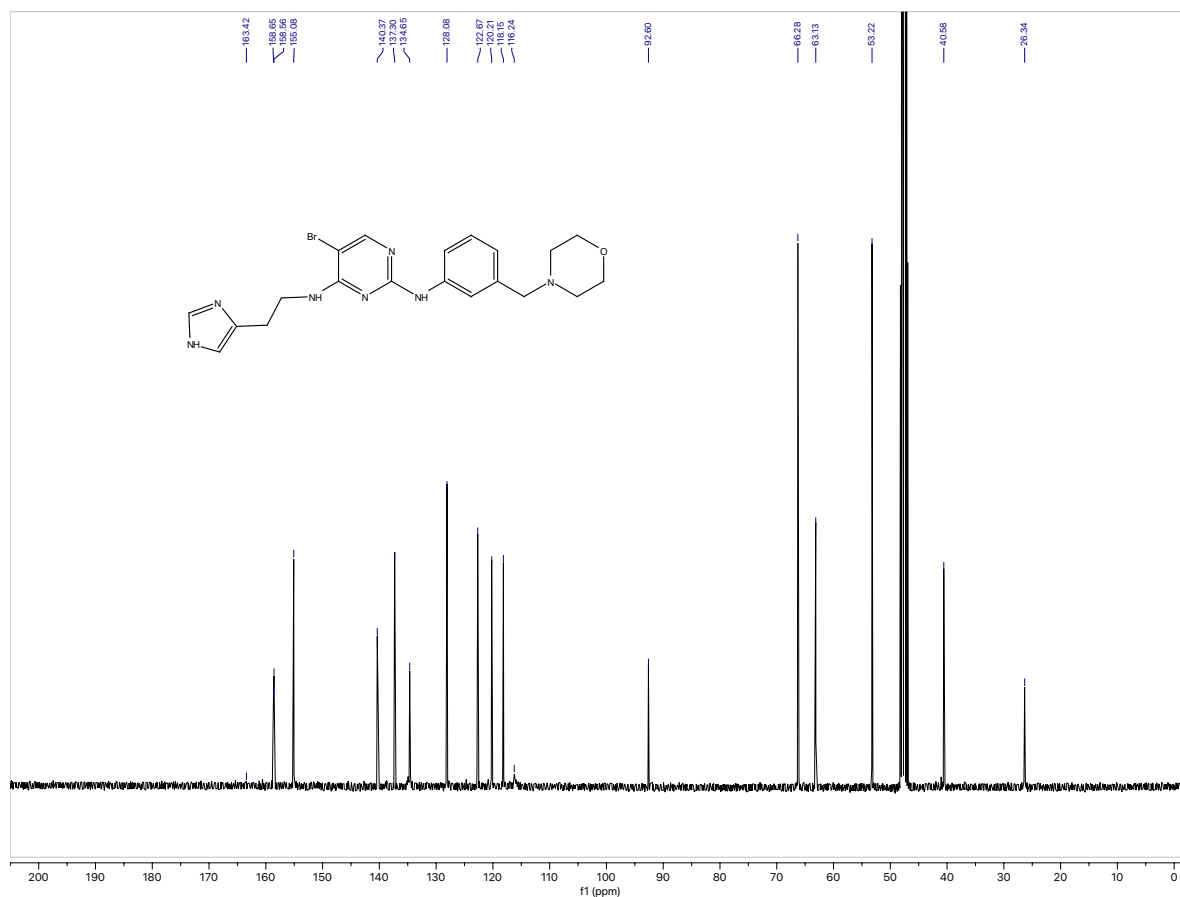
**$^{13}\text{C}$  NMR of N-(3-((2-((3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)-propyl)cyclobutanecarboxamide (8)**



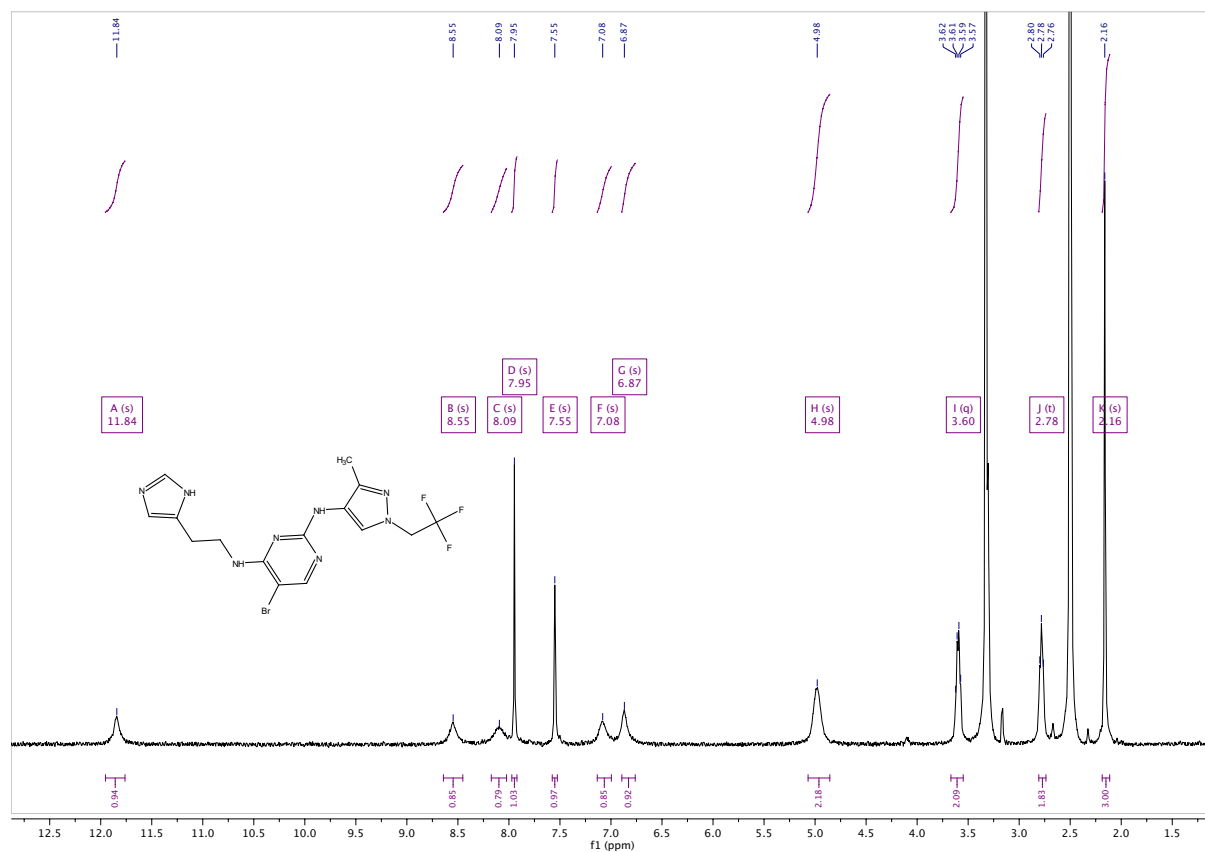
**<sup>1</sup>H NMR of N<sup>4</sup>-(2-(1H-imidazol-4-yl)ethyl)-5-bromo-N<sup>2</sup>-(3-(morpholinomethyl)phenyl)pyrimidine-2,4-diamine (9)**



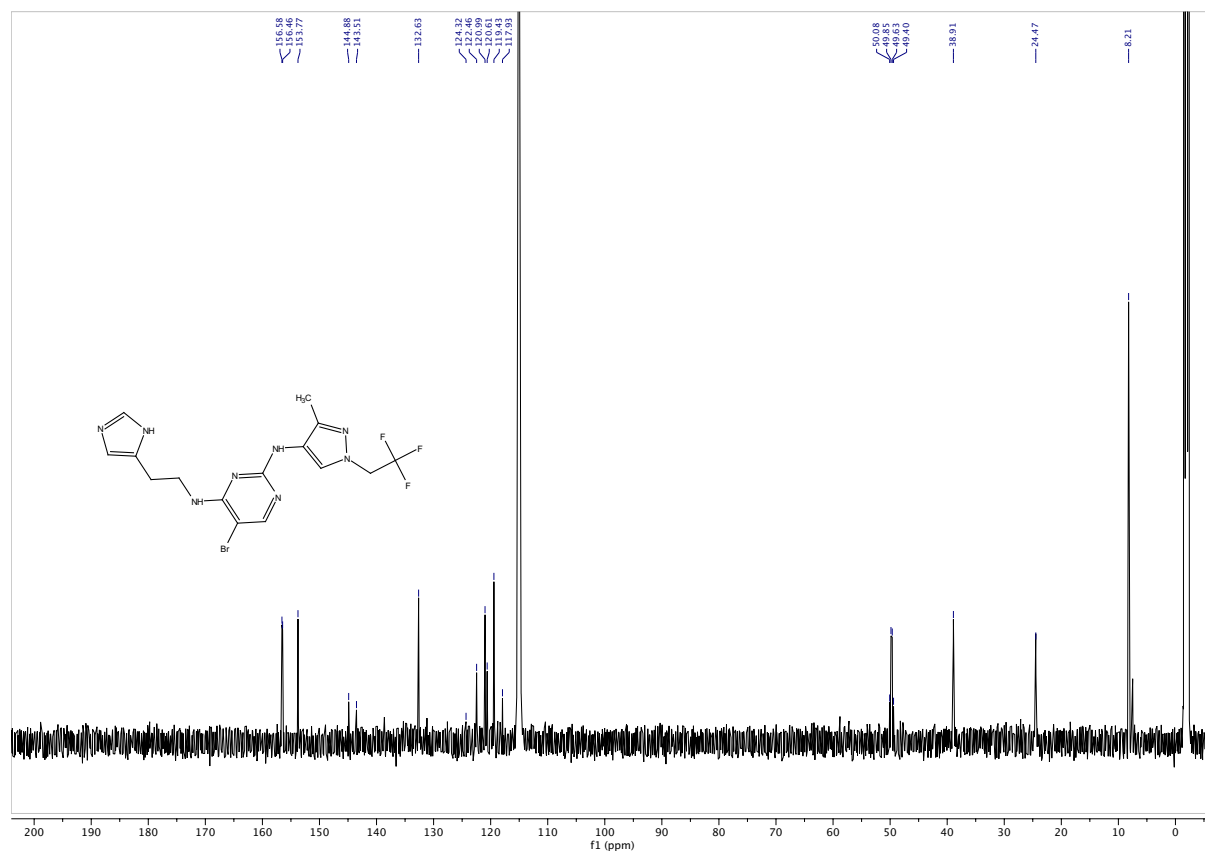
**<sup>13</sup>C NMR of N<sup>4</sup>-(2-(1H-imidazol-4-yl)ethyl)-5-bromo-N<sup>2</sup>-(3-(morpholinomethyl)phenyl)pyrimidine-2,4-diamine (9)**



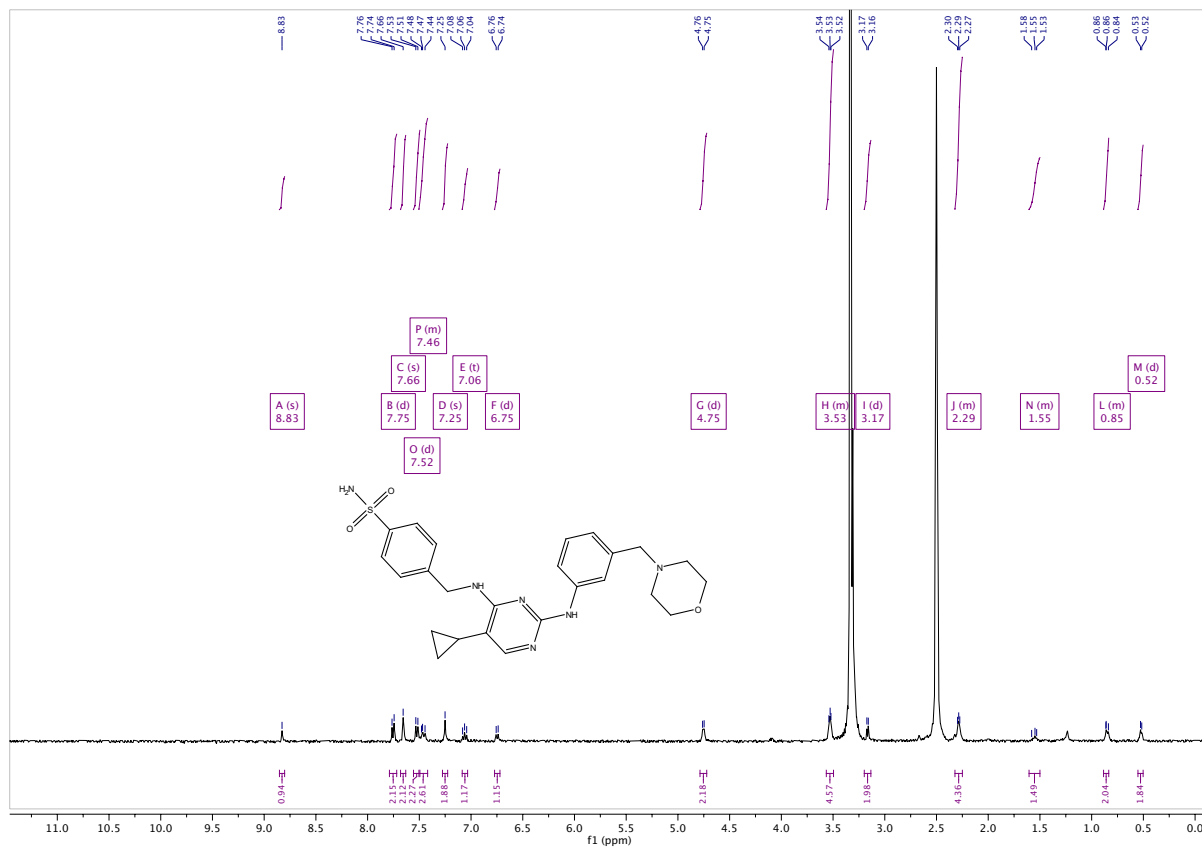
**$^1\text{H}$  NMR of  $\text{N}^4$ -(2-(1H-imidazol-5-yl)ethyl)-5-bromo- $\text{N}^2$ -(3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)pyrimidine-2,4-diamine (10)**



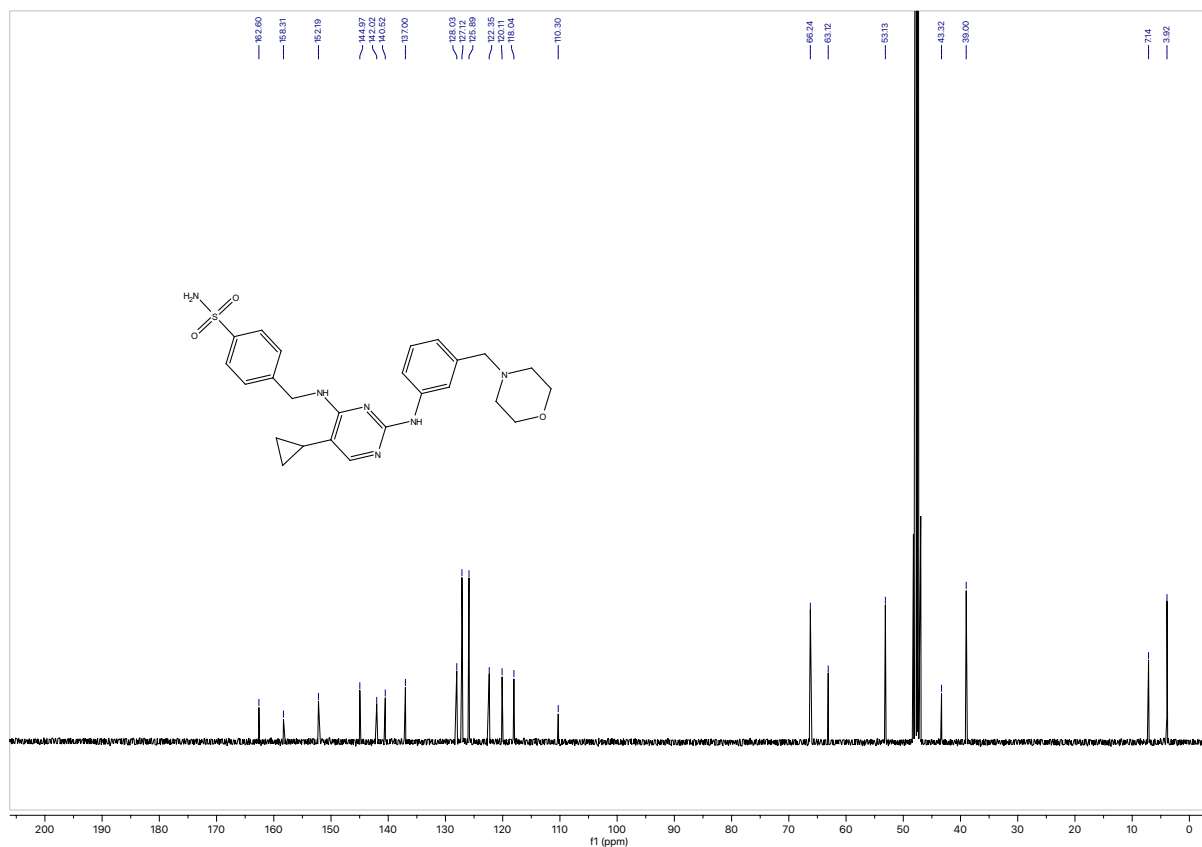
**$^{13}\text{C}$  NMR of  $\text{N}^4$ -(2-(1H-imidazol-5-yl)ethyl)-5-bromo- $\text{N}^2$ -(3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)pyrimidine-2,4-diamine (10)**



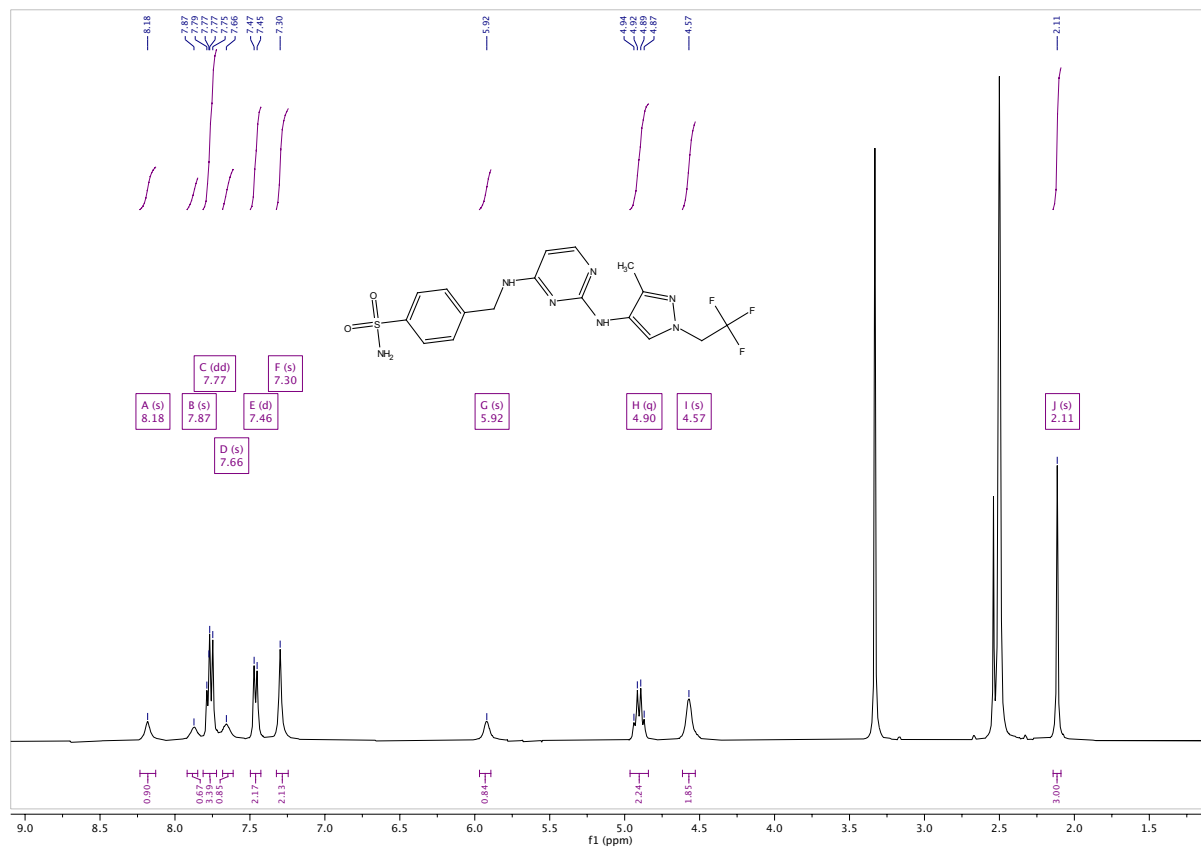
**<sup>1</sup>H NMR of 4-(((5-cyclopropyl-2-((3-(morpholinomethyl)phenyl)amino)pyrimidin-4-yl)amino)methyl)benzenesulfonamide (11)**



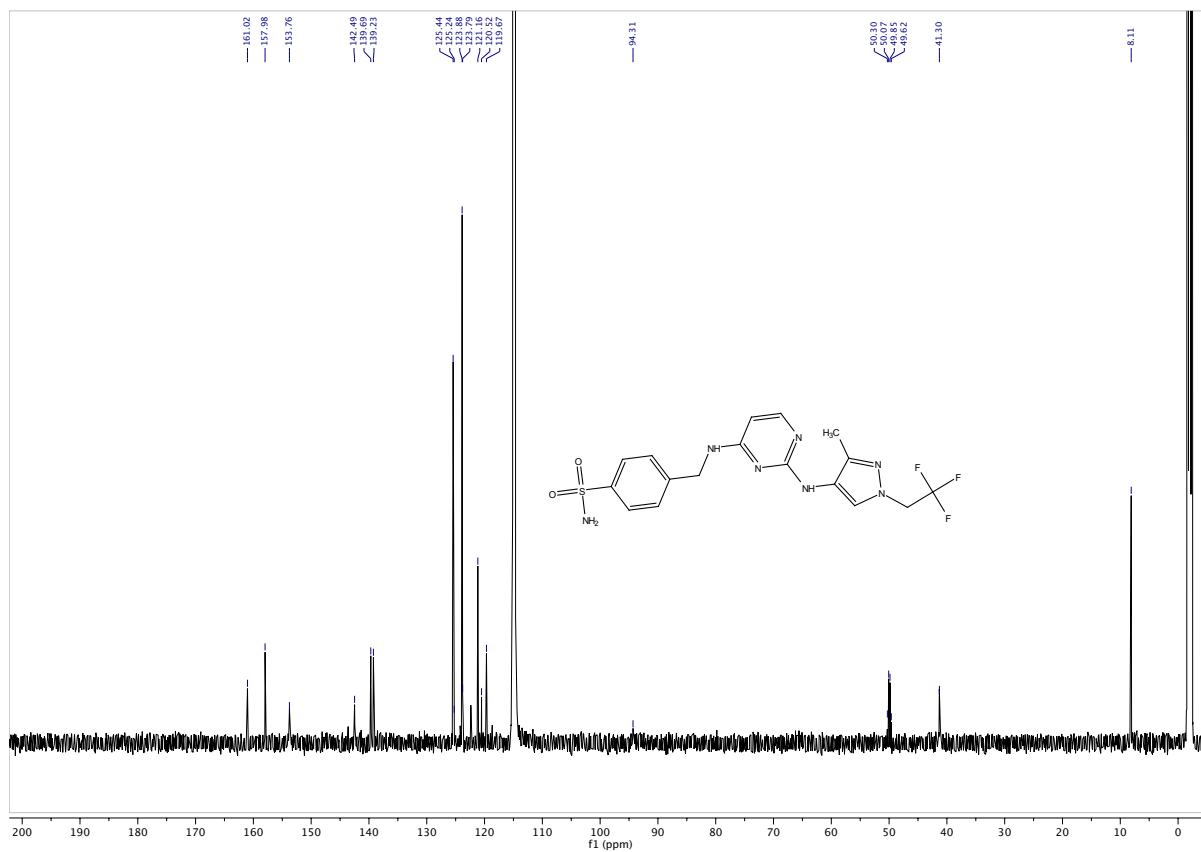
**<sup>13</sup>C NMR of 4-(((5-cyclopropyl-2-((3-(morpholinomethyl)phenyl)amino)pyrimidin-4-yl)amino)methyl)benzenesulfonamide (11)**



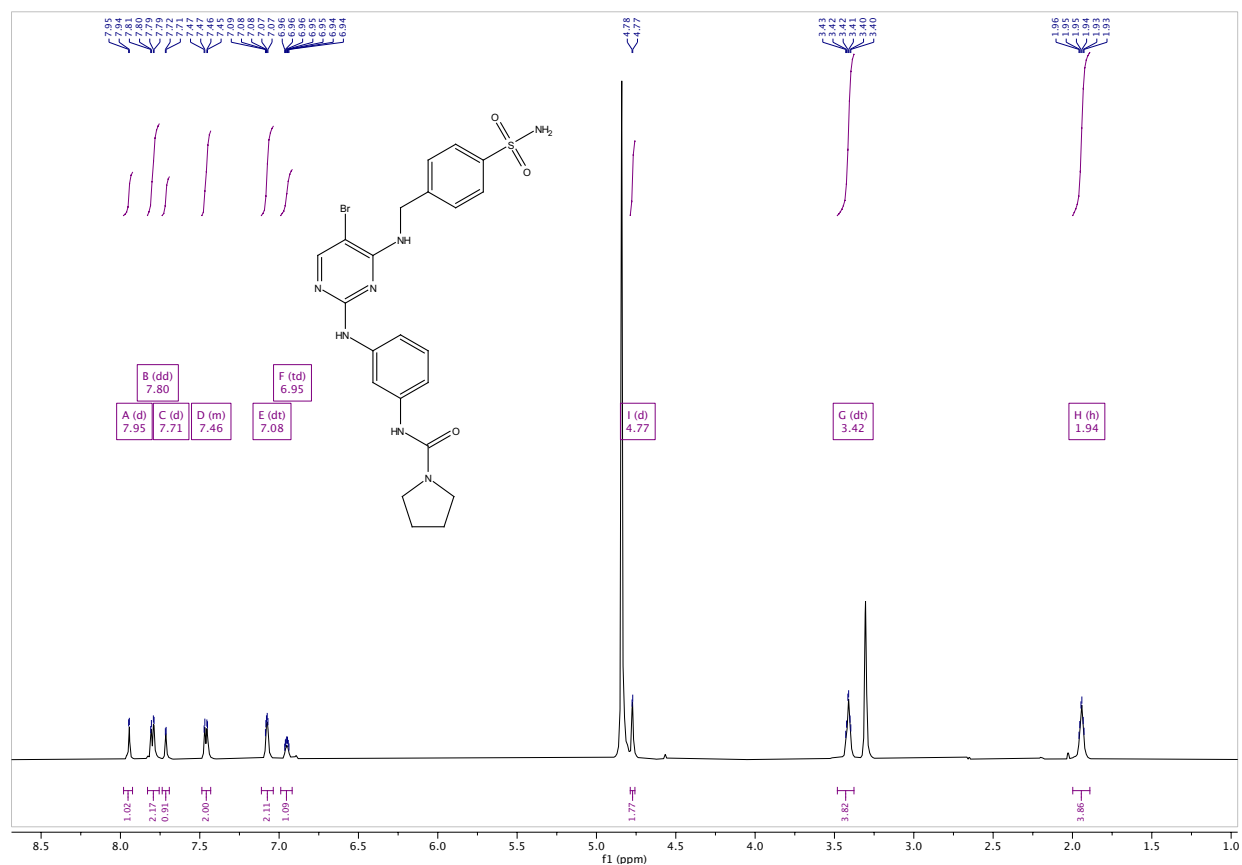
**<sup>1</sup>H NMR of 4-(((2-((3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)methyl)benzenesulfonamide (12)**



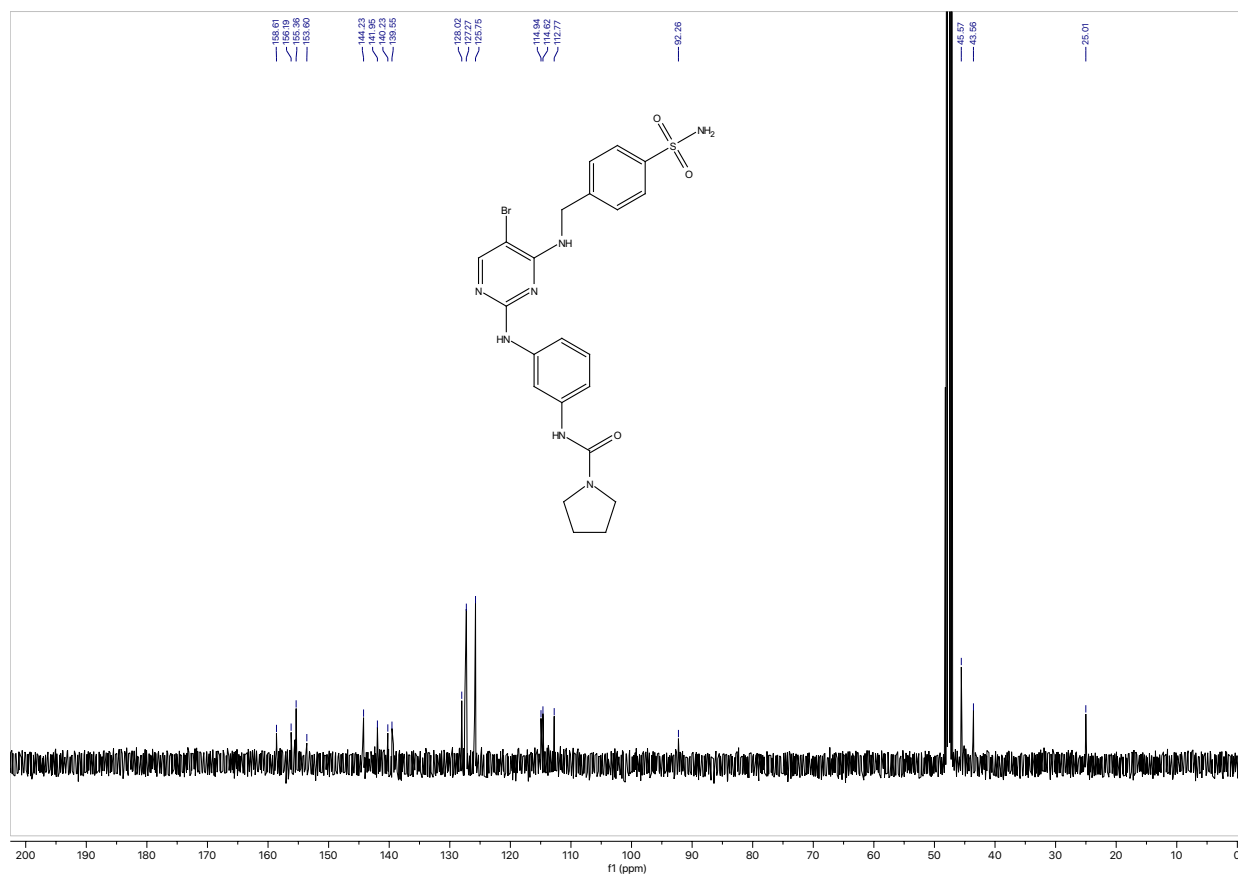
**<sup>13</sup>C NMR of 4-(((2-((3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)methyl)benzenesulfonamide (12)**



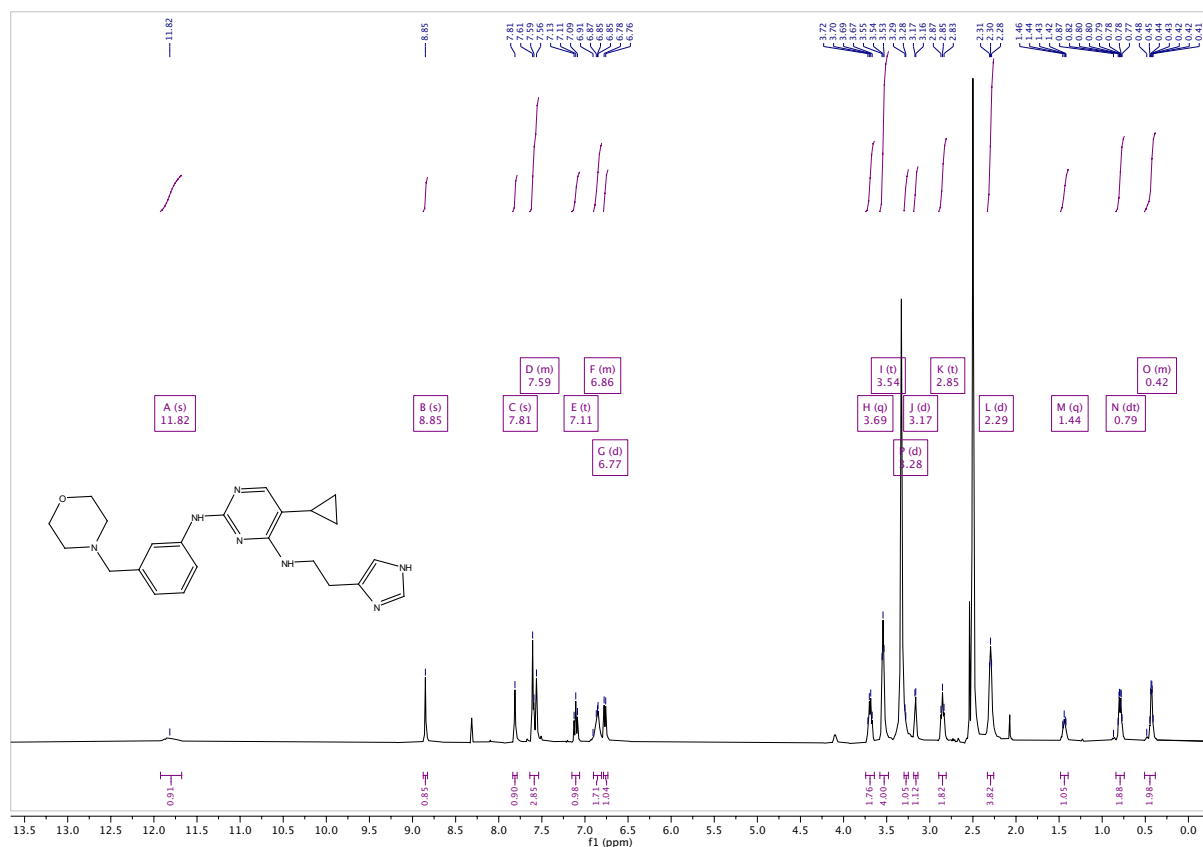
**<sup>1</sup>H NMR of N-(3-((5-bromo-4-((4-sulfamoylbenzyl)amino)pyrimidin-2-yl)amino)phenyl)pyrrolidine-1-carboxamide (13)**



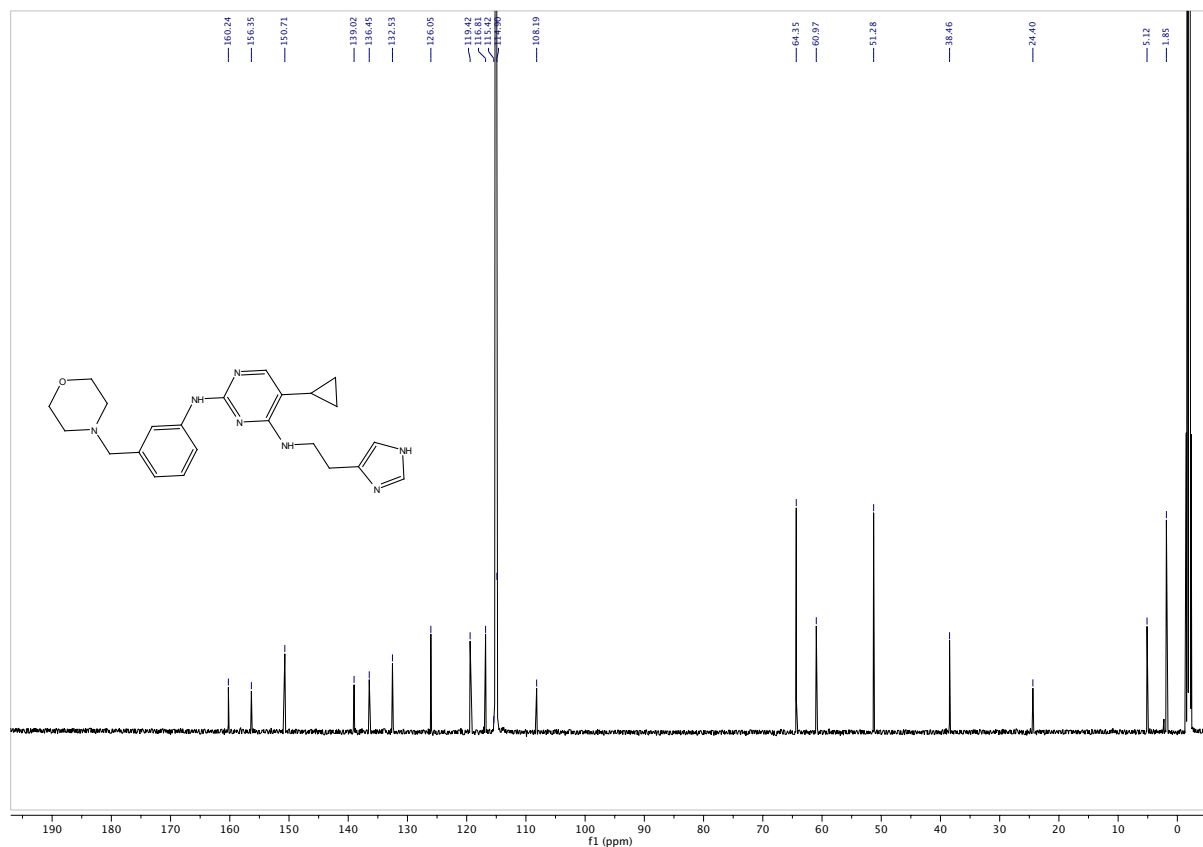
**<sup>13</sup>C NMR of N-(3-((5-bromo-4-((4-sulfamoylbenzyl)amino)pyrimidin-2-yl)amino)phenyl)pyrrolidine-1-carboxamide (13)**



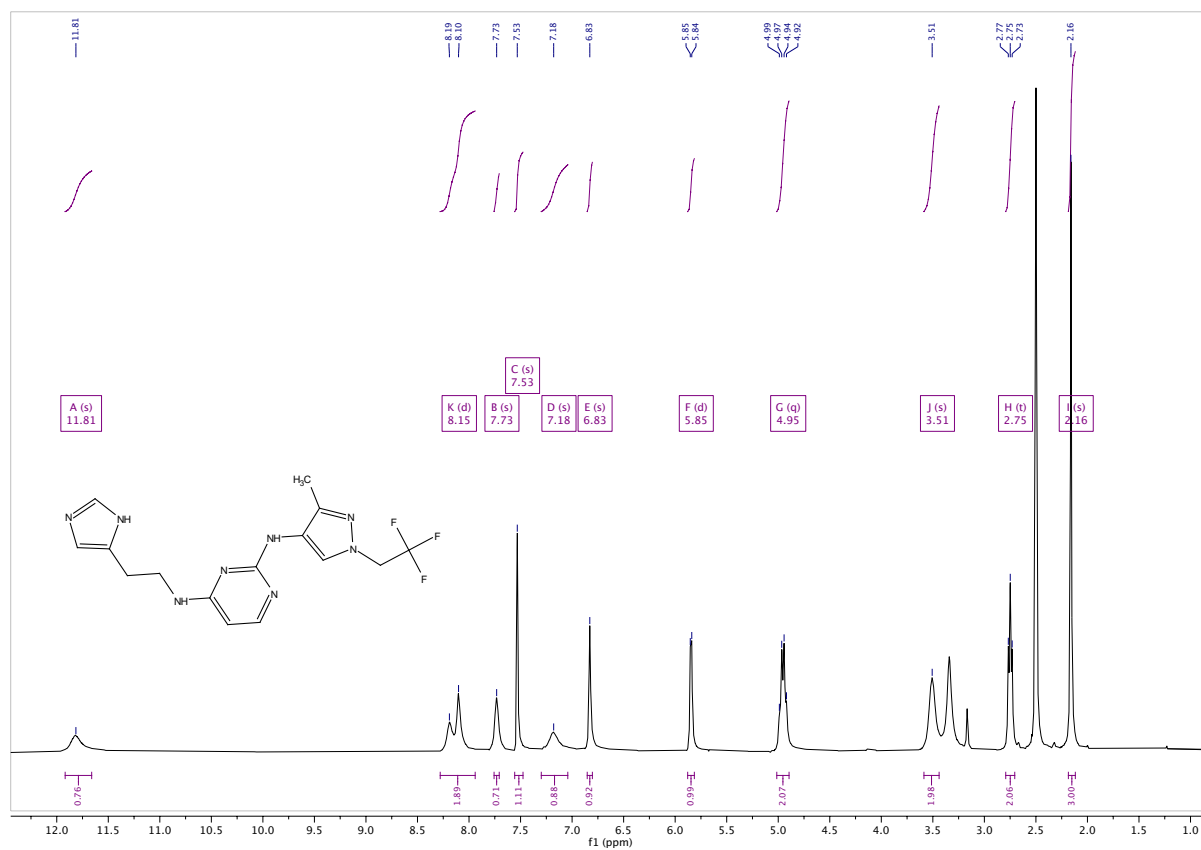
**<sup>1</sup>H NMR of N<sup>4</sup>-(2-(1H-imidazol-4-yl)ethyl)-5-cyclopropyl-N<sup>2</sup>-(3-(morpholinomethyl)phenyl)pyrimidine-2,4-diamine (14)**



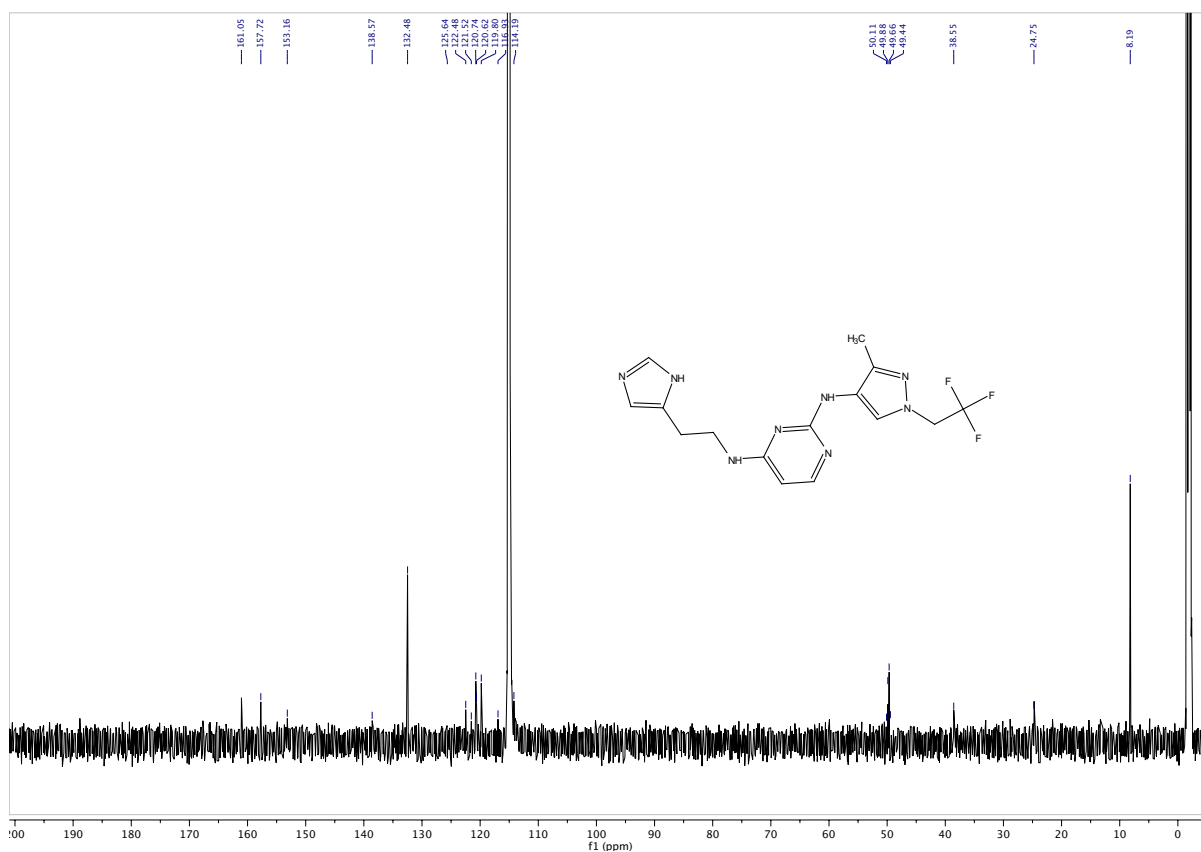
**<sup>13</sup>C NMR of N<sup>4</sup>-(2-(1H-imidazol-4-yl)ethyl)-5-cyclopropyl-N<sup>2</sup>-(3-(morpholinomethyl)phenyl)pyrimidine-2,4-diamine (14)**



**$^1\text{H}$  NMR of  $\text{N}^4$ -(2-(1H-imidazol-5-yl)ethyl)- $\text{N}^2$ -(3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)pyrimidine-2,4-diamine (15)**

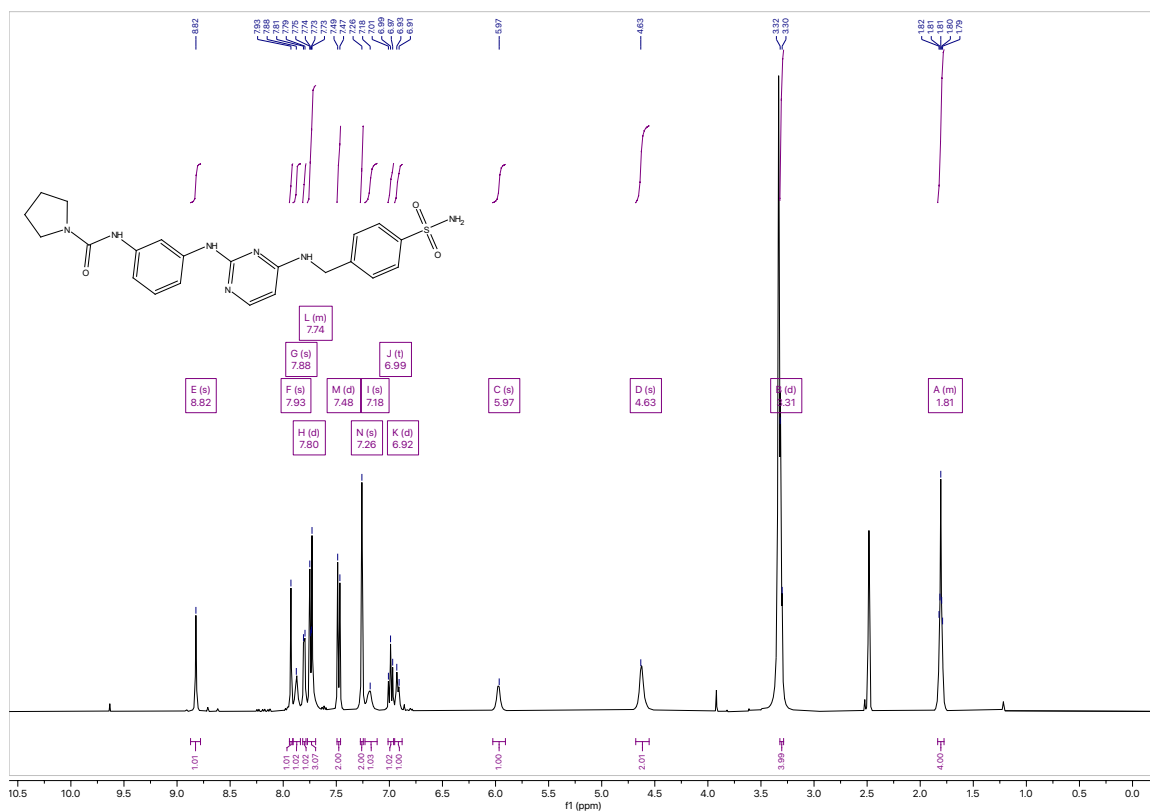


**$^{13}\text{C}$  NMR of  $\text{N}^4$ -(2-(1H-imidazol-5-yl)ethyl)- $\text{N}^2$ -(3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)pyrimidine-2,4-diamine (15)**

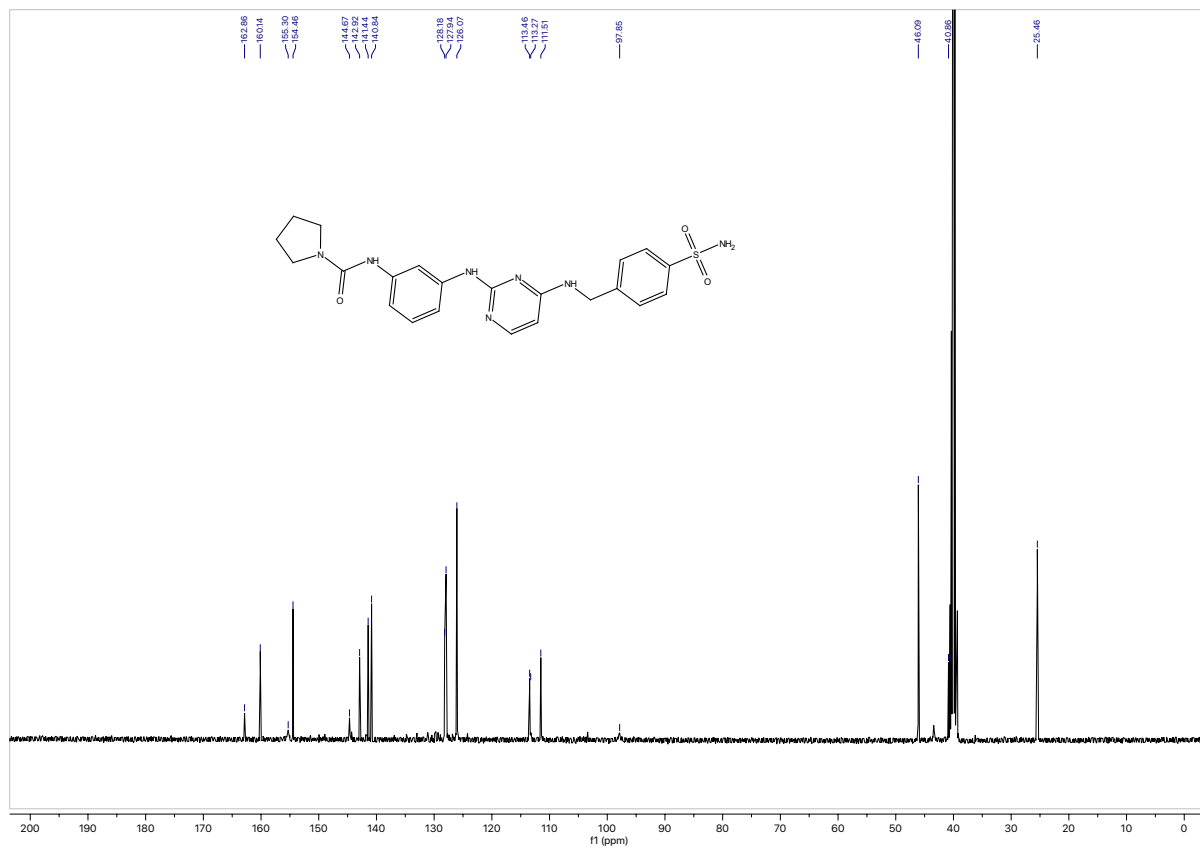




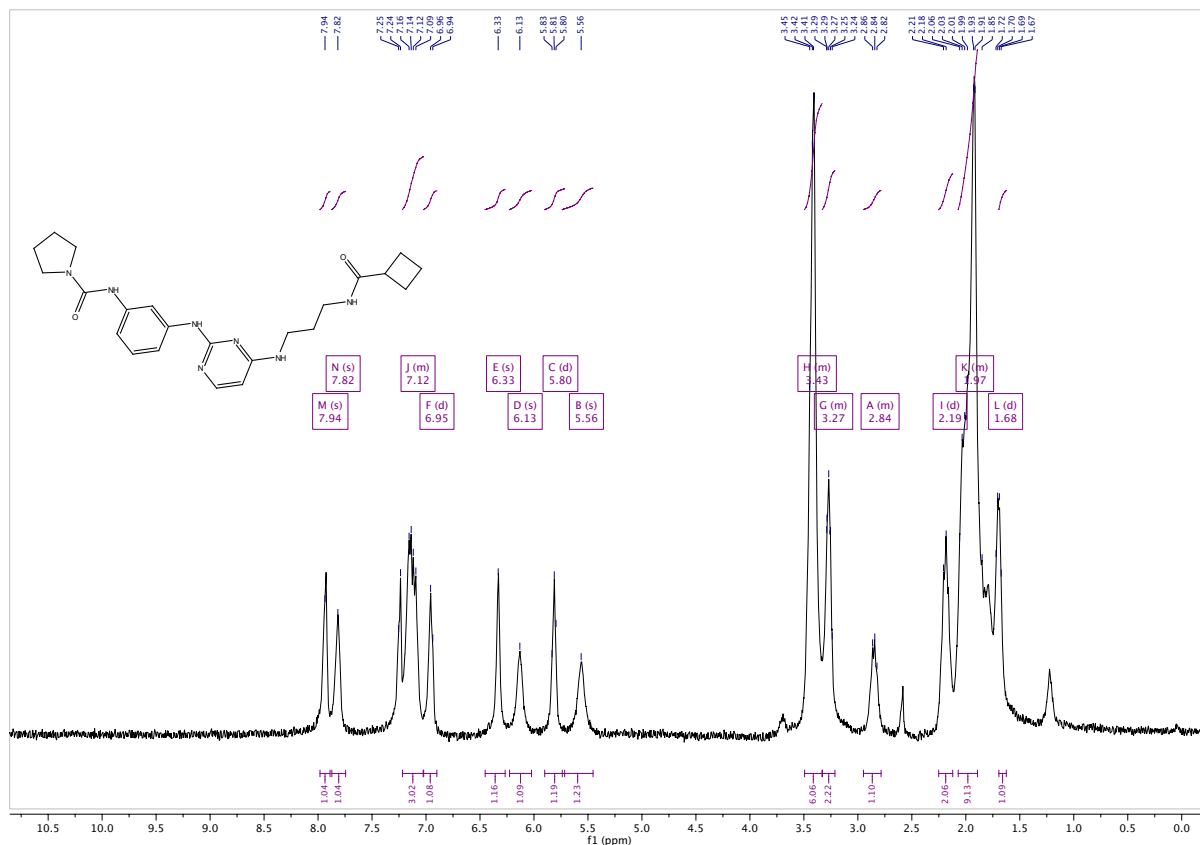
**<sup>1</sup>H NMR of N-(3-((4-((4-sulfamoylbenzyl)amino)pyrimidin-2-yl)amino)phenyl)pyrrolidine-1-carboxamide (16)**



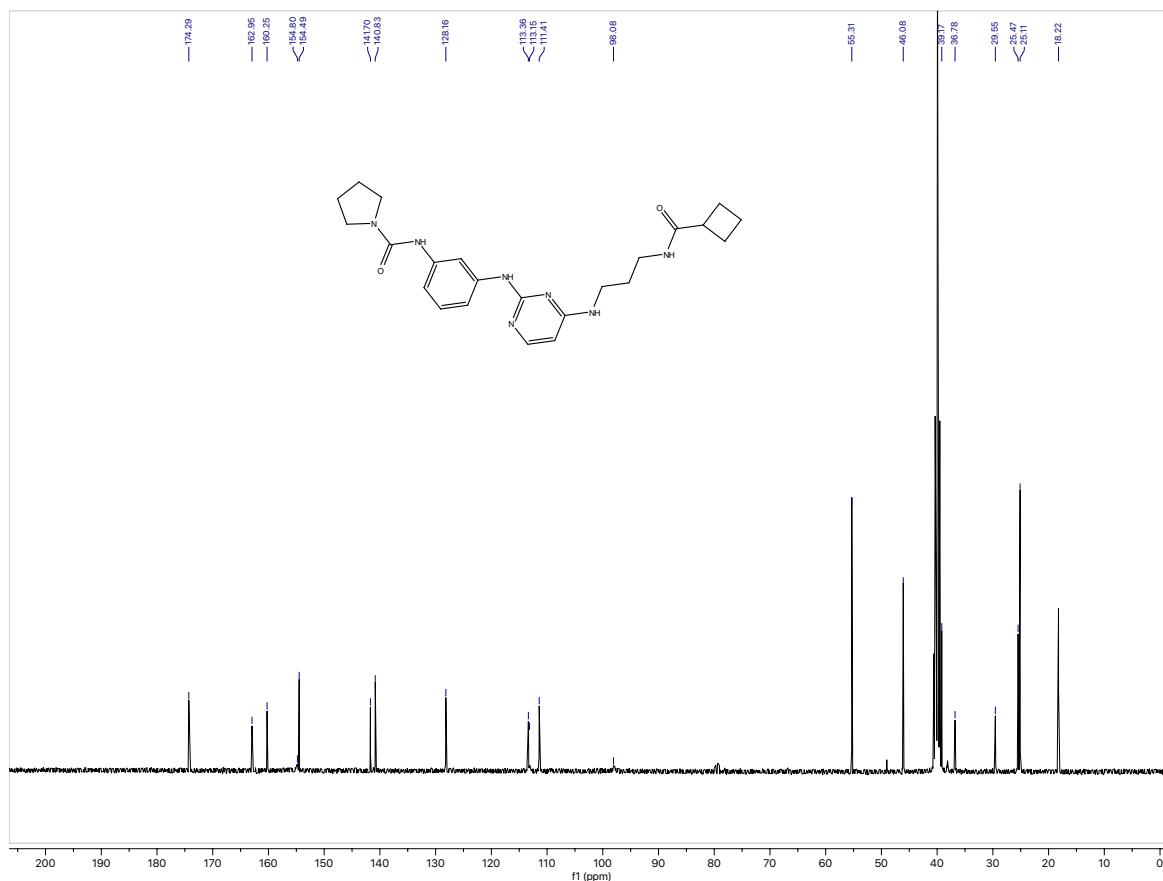
**<sup>13</sup>C NMR of N-(3-((4-((4-sulfamoylbenzyl)amino)pyrimidin-2-yl)amino)phenyl)pyrrolidine-1-carboxamide (16)**



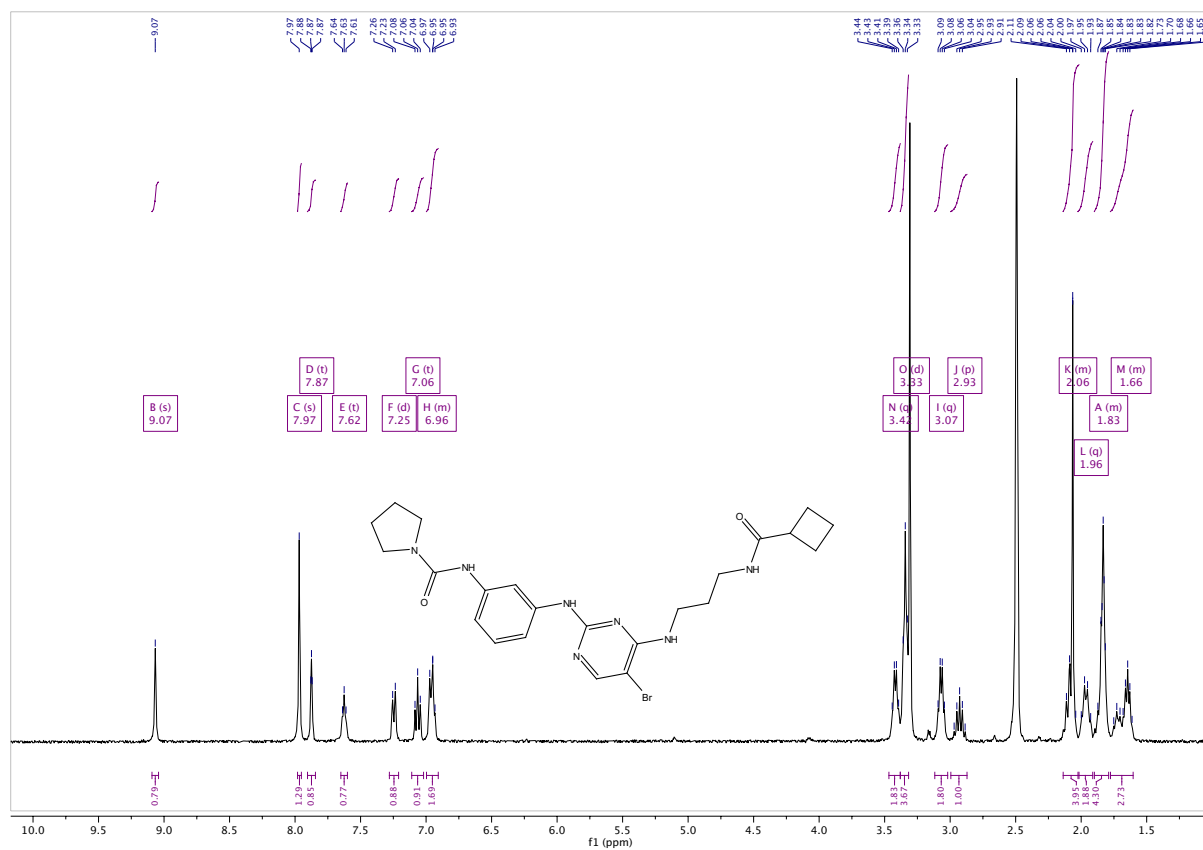
**<sup>1</sup>H NMR of N-(3-((4-((3-(cyclobutanecarboxamido)propyl)amino)pyrimidin-2-yl)amino)phenyl)pyrrolidine-1-carboxamide (17)**



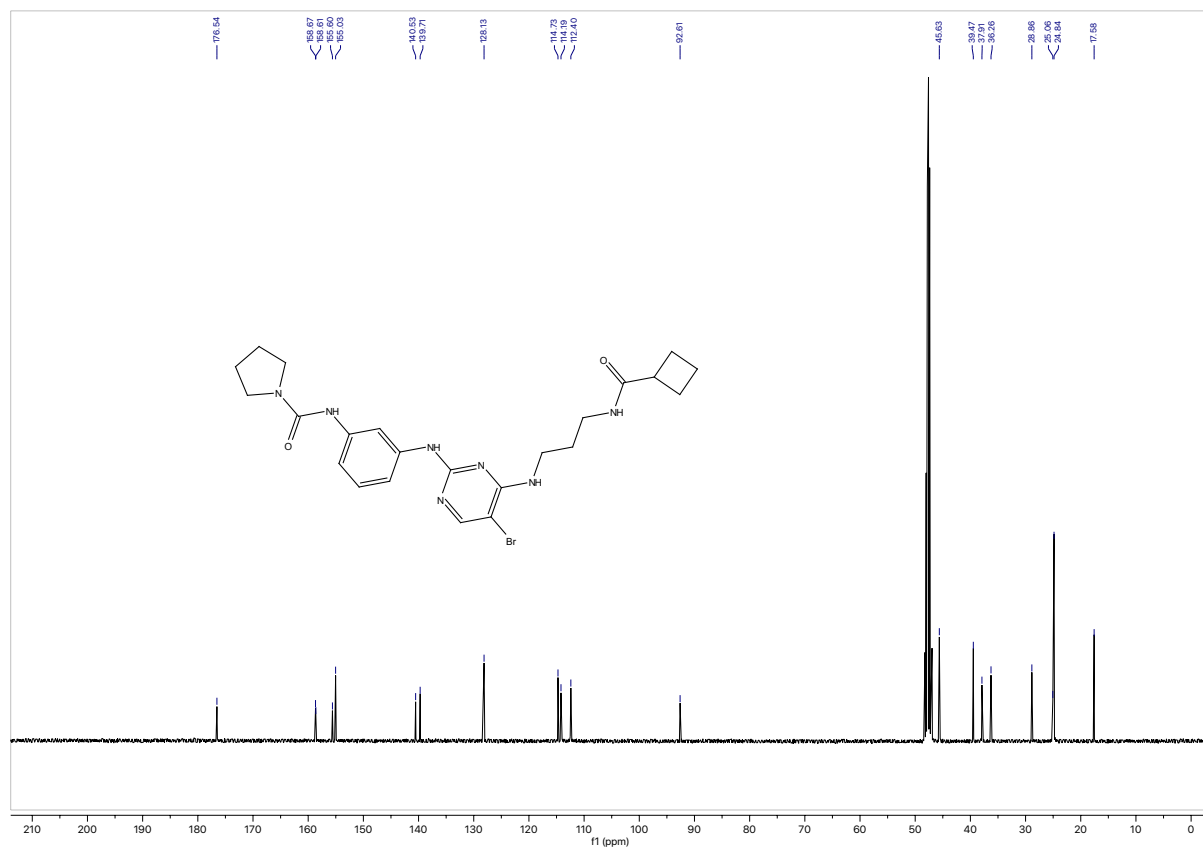
**<sup>13</sup>C NMR of N-(3-((4-((3-(cyclobutanecarboxamido)propyl)amino)pyrimidin-2-yl)amino)phenyl)pyrrolidine-1-carboxamide (17)**



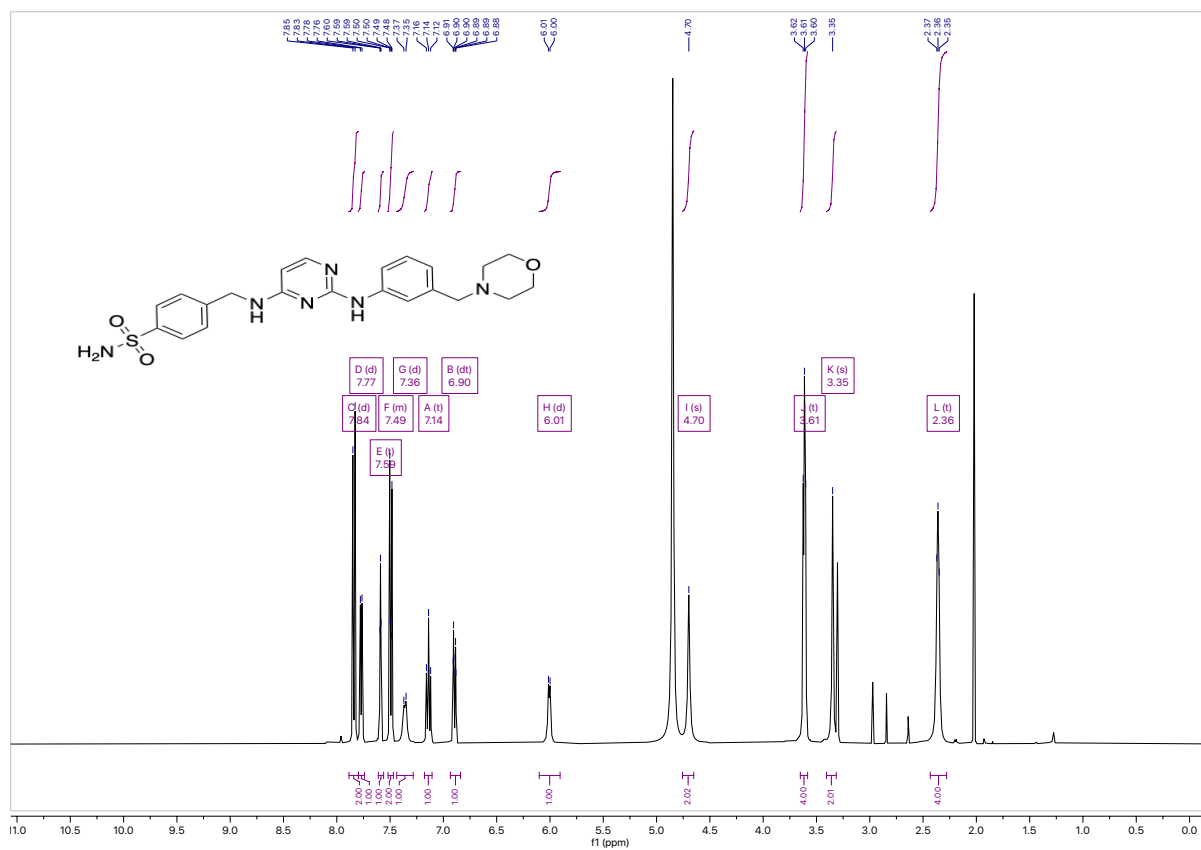
**<sup>1</sup>H NMR of N-(3-((5-bromo-4-((3-(cyclobutanecarboxamido)propyl)amino)pyrimidin-2-yl)amino)phenyl)pyrrolidine-1-carboxamide (18)**



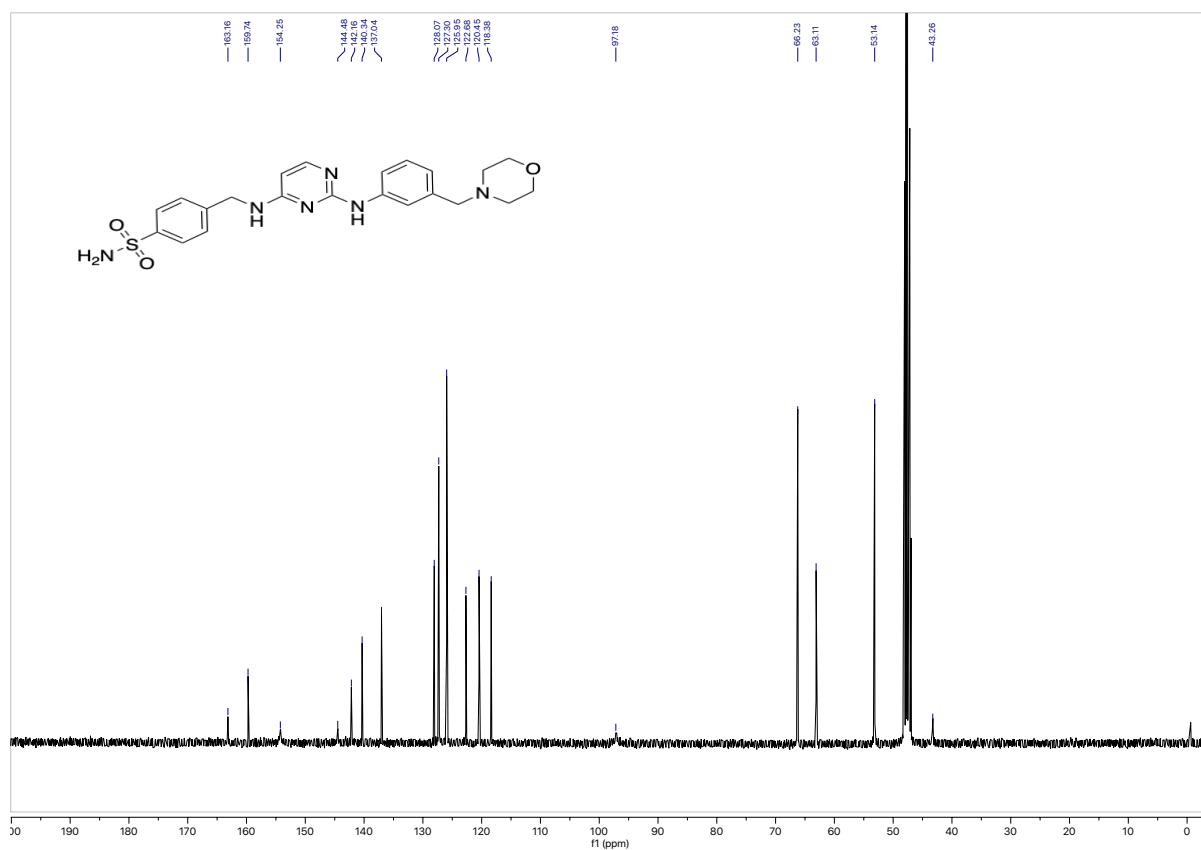
**<sup>13</sup>C NMR of N-(3-((5-bromo-4-((3-(cyclobutanecarboxamido)propyl)amino)pyrimidin-2-yl)amino)phenyl)pyrrolidine-1-carboxamide (18)**



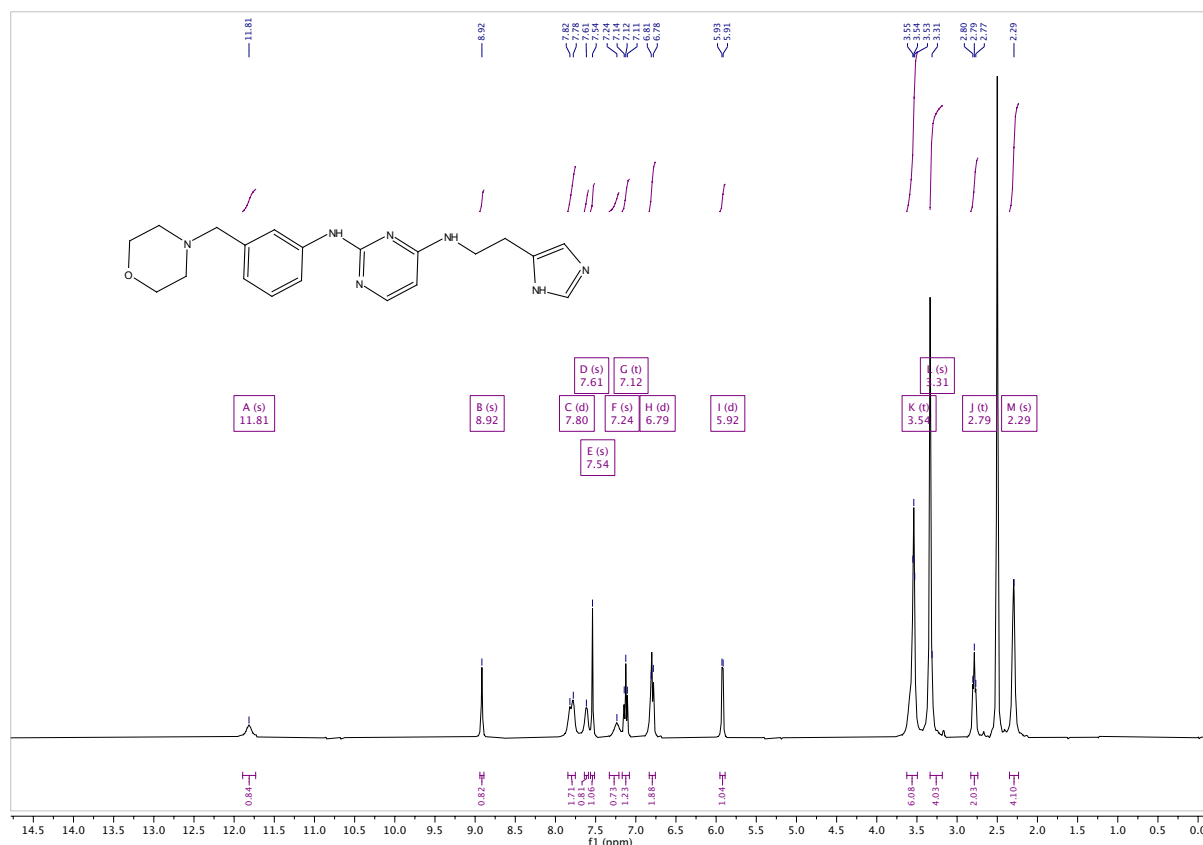
**<sup>1</sup>H NMR of 4-(((2-((3-(morpholinomethyl)phenyl)amino)pyrimidin-4-yl)amino)methyl)benzenesulfonamide (19)**



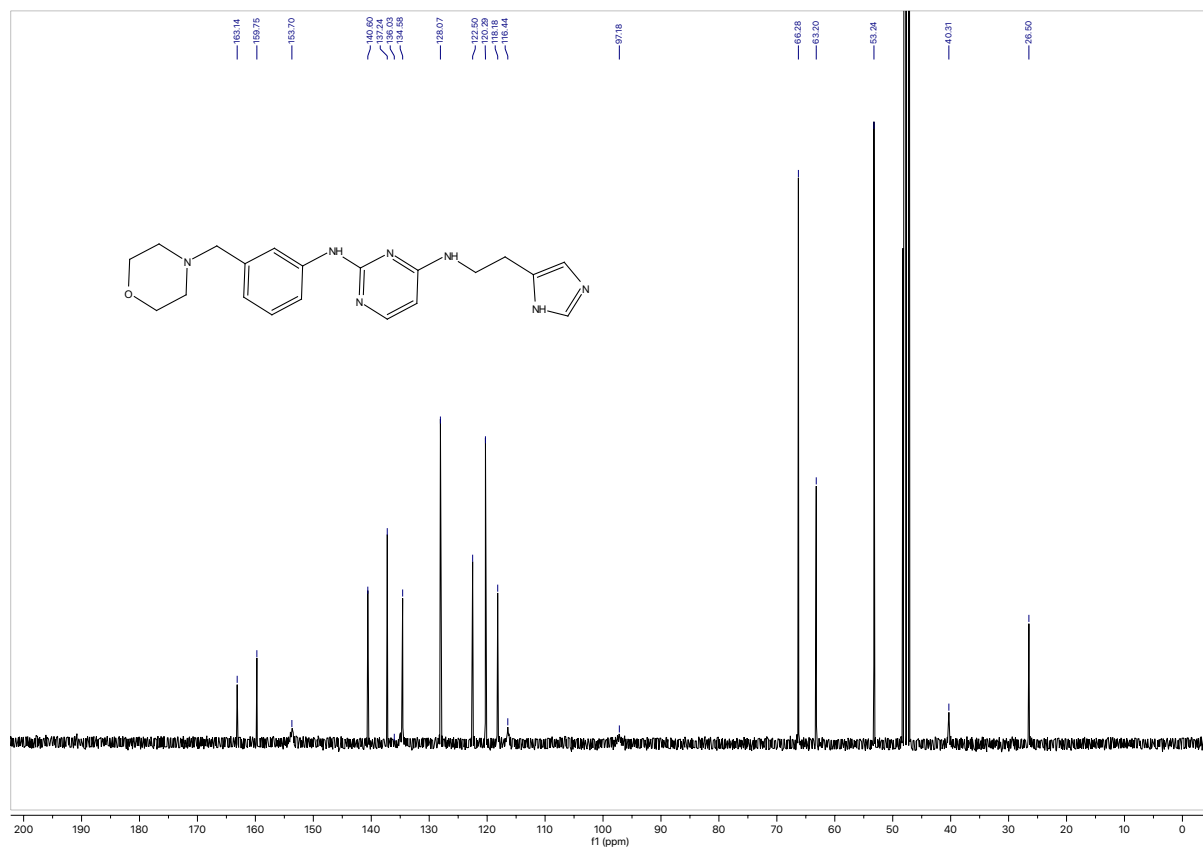
**<sup>13</sup>C NMR of 4-(((2-((3-(morpholinomethyl)phenyl)amino)pyrimidin-4-yl)amino)methyl)benzenesulfonamide (19)**



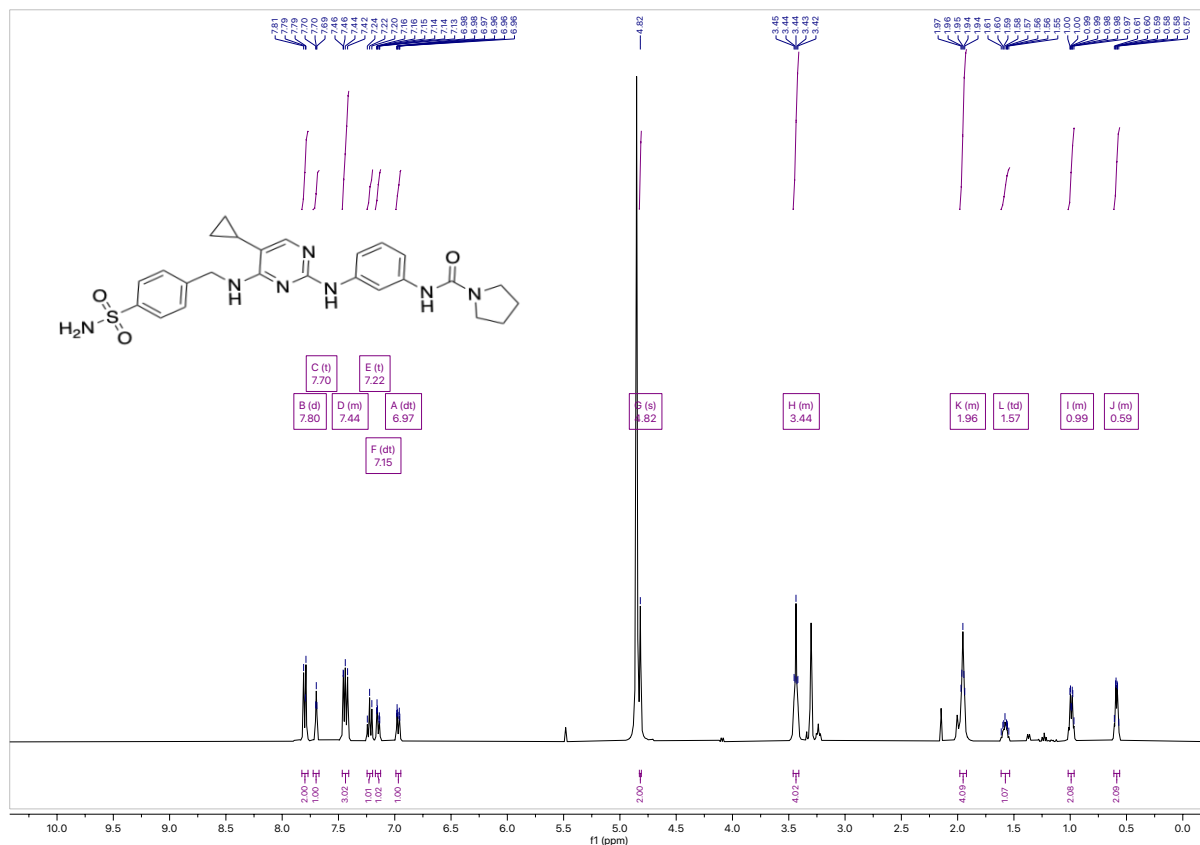
**<sup>1</sup>H NMR of N<sup>4</sup>-(2-(1H-imidazol-5-yl)ethyl)-N<sup>2</sup>-(3-(morpholinomethyl)phenyl)pyrimidine-2,4-diamine (20)**



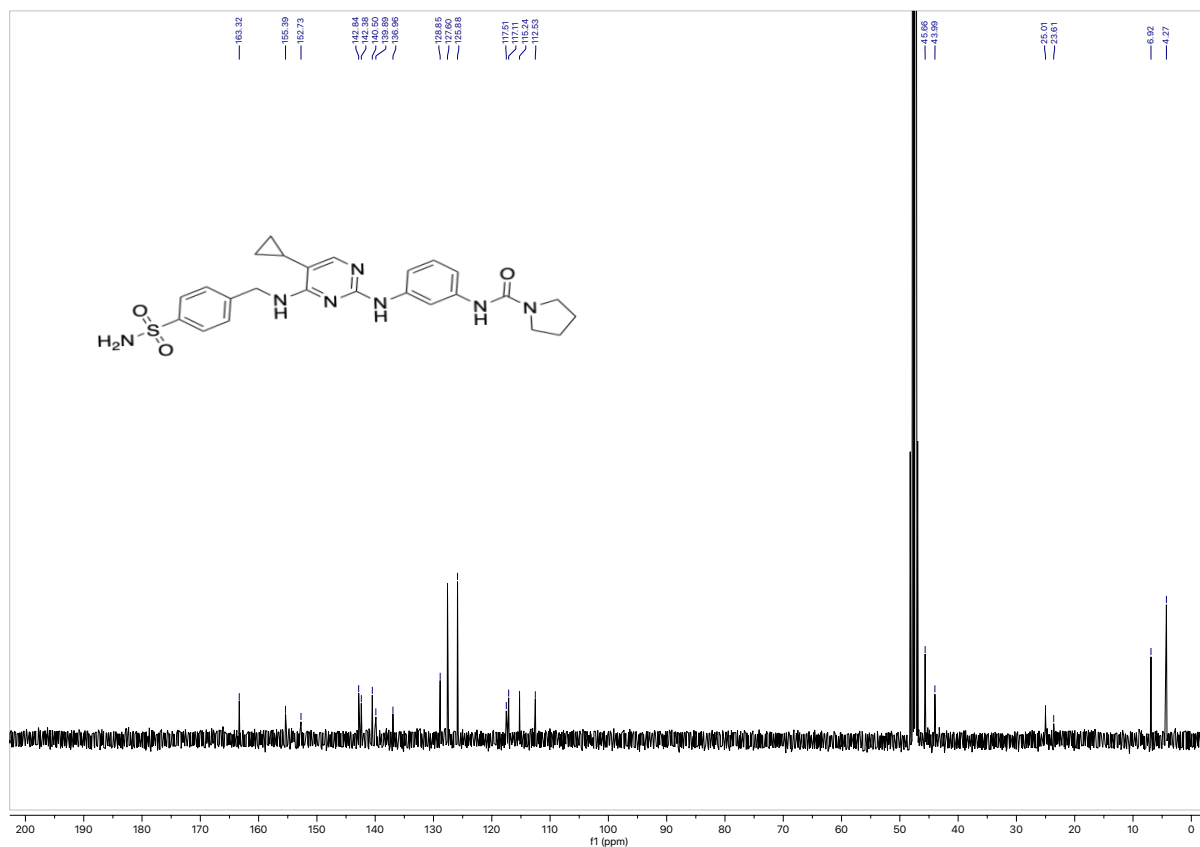
**<sup>13</sup>C NMR of N<sup>4</sup>-(2-(1H-imidazol-5-yl)ethyl)-N<sup>2</sup>-(3-(morpholinomethyl)phenyl)pyrimidine-2,4-diamine (20)**



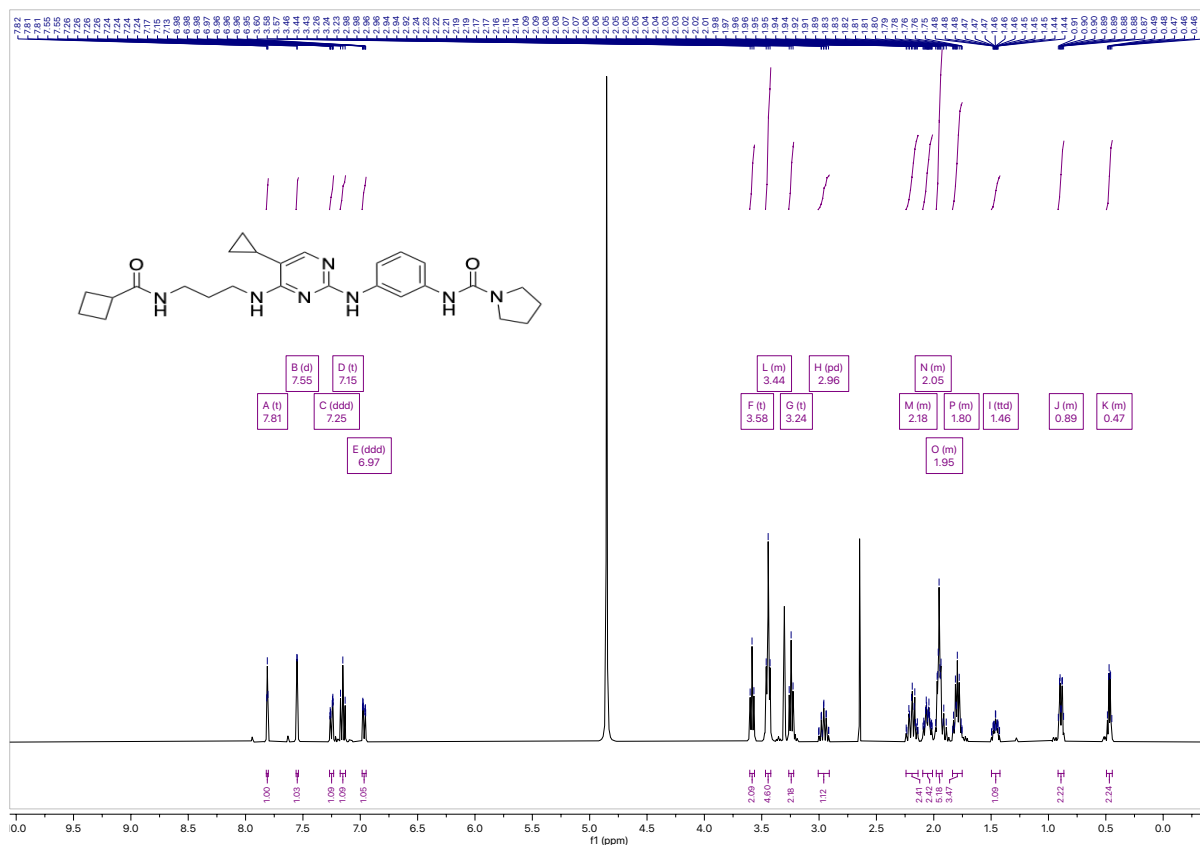
**<sup>1</sup>H NMR of N-(3-((5-cyclopropyl-4-((4-sulfamoylbenzyl)amino)pyrimidin-2-yl)amino)phenyl)pyrrolidine -1-carboxamide (21)**



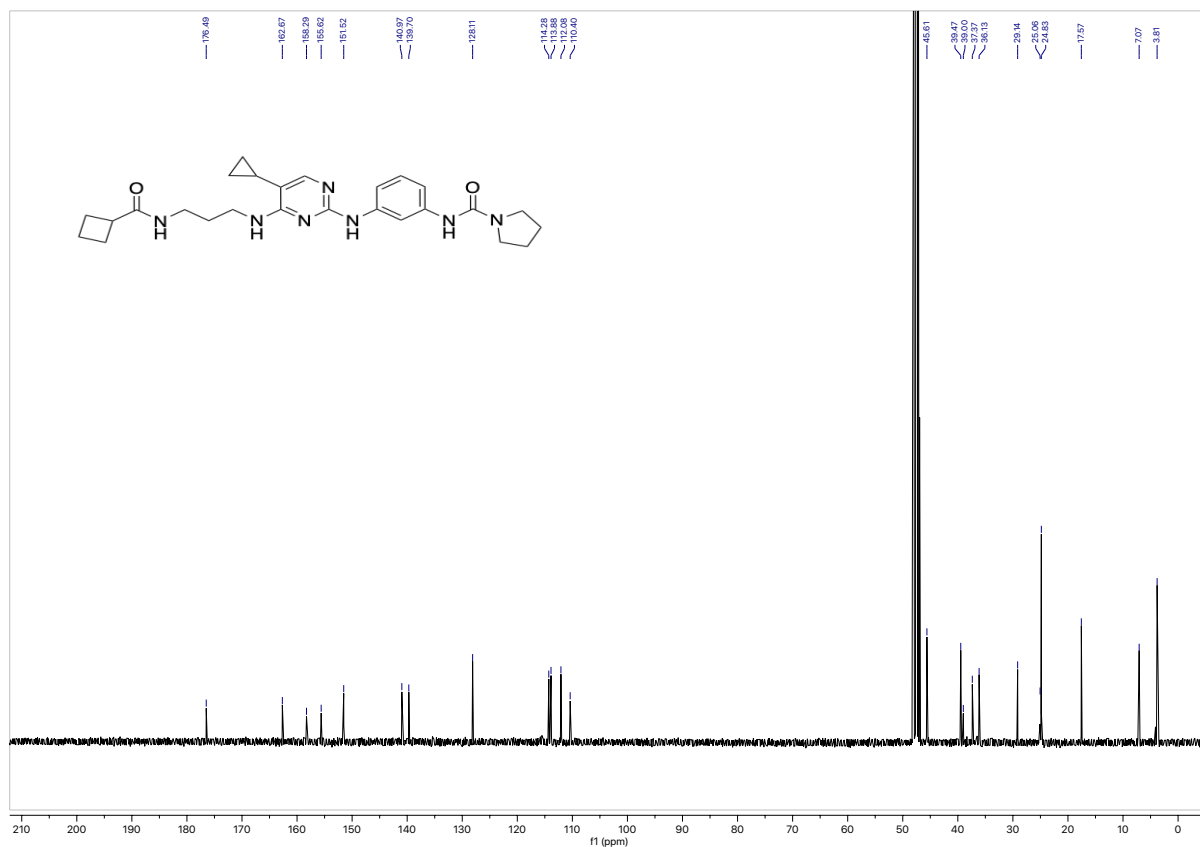
**<sup>13</sup>C NMR of N-(3-((5-cyclopropyl-4-((4-sulfamoylbenzyl)amino)pyrimidin-2-yl)amino)phenyl)pyrrolidine -1-carboxamide (21)**



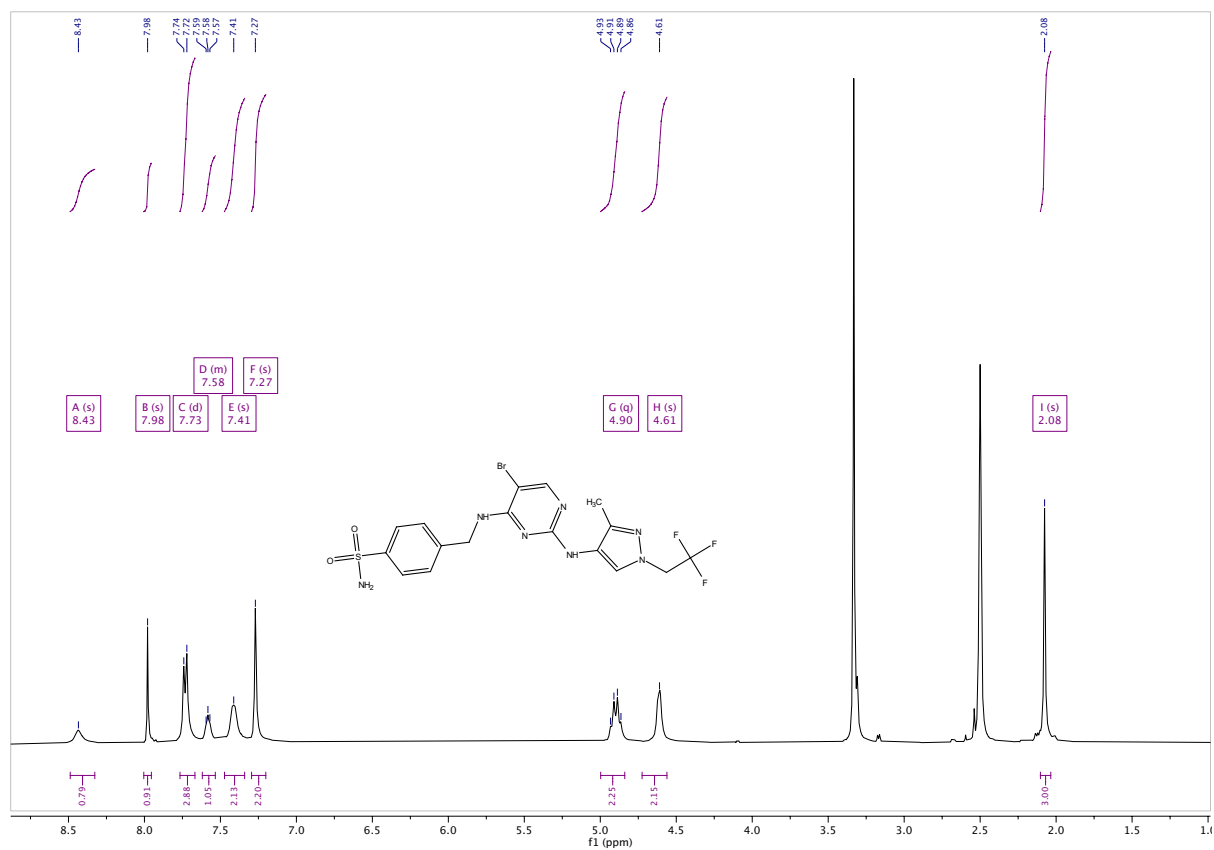
**<sup>1</sup>H NMR of N-(3-((4-((3-(cyclobutanecarboxamido)propyl)amino)-5-cyclopropylpyrimidin-2-yl)amino)phenyl)pyrrolidine-1-carboxamide (22)**



**<sup>13</sup>C NMR of N-(3-((4-((3-(cyclobutanecarboxamido)propyl)amino)-5-cyclopropylpyrimidin-2-yl)amino)phenyl)pyrrolidine-1-carboxamide (22)**



**$^1\text{H}$  NMR of 4-(((5-bromo-2-((3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-amino)methyl)benzenesulfonamide (GSK8612)**



**$^{13}\text{C}$  NMR of 4-(((5-bromo-2-((3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-amino)methyl)benzenesulfonamide (GSK8612)**

