Supporting Information:

Design and Synthesis of Pyrazole-based Macrocyclic Kinase Inhibitors targeting BMPR2

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Table of Content:

Table S1: DSF data from **8a-e**, **1** and staurosporine (**9**) as a positive control against 90 kinases.

8a		8b		8c		8d		8e		1		9	
Kinase	ΔTm [°C]	Kinase	ΔTm [°C]	Kinase	ΔTm [°C]	Kinase	ΔTm [°C]	Kinase	ΔTm [°C]	Kinase	ΔTm [°C]	Kinase	ΔTm [°C]
GSK3B	8,4	BMP2K	11,2	BMP2K	10,4	BMP2K	5,7	BMP2K	7,9	BMP2K	18,8	CAMKK2B	24,6
BMP2K	5,8	STK3	7,2	STK3	8,4	GSK3B	4,9	GSK3B	6,8	MAPK15	17,4	STK10	23,3
BMPR2	5,3	GSK3B	7,2	STK4	6,5	STK3	4,0	STK3	5,8	UKL3	15,5	PHKG2	21,2
FLT1	4,8	RIOK1	6,8	MELK	6,2	MELK	3,9	MST3	4,9	CDK2	15,2	PIM3	19,7
MARK3	4,2	MELK	6,6	RIOK1	5,9	CLK1	3,0	STK4	4,8	STK6	14,3	UKL3	19,6
MARK4	3,9	AAK1	6,6	MARK3	5,4	MARK4	2,9	RIOK1	3,7	GSK3B	14,0	BMP2K	19,1
MAPK15	3,8	GAK	6,3	MAPK15	5,3	FLT1	2,6	CDK2	3,7	AAK1	13,8	MARK3	19,0
CDK2	3,8	STK6	6,3	CLK1	5,2	MAPK15	2,5	PIM1	3,4	CLK1	12,2	MAP3K5	18,5
STK4	3,3	UKL3	5,9	UKL3	5,1	MARK3	2,4	UKL3	3,3	CAMKK2B	12,0	SLK	18,0
MST3	3,2	MARK4	5,4	MARK4	5,1	AAK1	2,2	AAK1	3,2	MAP3K5	12,0	STK6	17,1
MERTK	3,2	MAPK15	5,4	GSK3B	4,9	FGFR3	2,2	MARK4	3,2	STK3	11,6	CHEK2	17,1
UKL3	2,9	CDK2	5,3	AAK1	4,9	DYRK2	2,1	PCTK1	3,1	CLK3	11,3	STK3	16,6
CAMK1D	2,7	CLK1	5,3	BMPR2	4,6	RIOK1	2,1	STK17B	2,9	PLK4	11,1	MARK4	16,4
MAP2K4	2,6	SLK	5,2	CDK2	4,4	BMPR2	2,0	BMPR2	2,8	DYRK2	11,0	CAMK2D	16,2
MAPK10	2,6	STK4	5,0	MST3	4,3	GSG2	1,9	MAPK15	2,8	FLT1	10,6	PLK4	16,0
PCTK1	2,6	FLT1	5,0	STK39	3,7	SLK	1,9	STK39	2,7	MAP2K6	10,4	DAPK3	15,8
PIM1	2,3	BMPR2	5,0	STK17B	3,7	STK4	1,9	MST4	2,7	PCTK1	10,3	AAK1	15,6
FGFR2	2,2	STK17A	4,9	FLT1	3,7	UKL3	1,7	MAPK10	2,5	STK10	10,1	CDK2	15,5
AAK1	2,2	MARK3	4,9	ULK1	3,6	BRAF	1,7	CHEK2	2,4	MAP2K4	10,0	STK4	14,9
CHEK2	2,2	CK2A2	4,8	DYRK2	3,6	STK39	1,7	GAK	2,2	MELK	9,8	MAPK15	14,7
FGFR3	2,1	DAPK3	4,4	GAK	3,6	CDK2	1,7	CLK1	2,2	FGFR3	9,8	MELK	13,8
MELK	2,0	GSG2	4,4	SLK	3,5	CSNK1D	1,7	FLT1	2,2	STK17B	9,7	FLT1	13,6
GAK	2,0	MAP2K4	4,1	FGFR3	3,5	CLK3	1,6	MELK	2,1	DAPK3	9,7	CAMK2B	13,3
VRK1	2,0	STK39	4,1	BRAF	3,2	MAP3K5	1,6	MAP2K4	1,9	STK17A	9,6	FGFR3	13,3
RIOK1	2,0	DYRK2	4,0	MAP3K5	3,1	CK2A2	1,5	CLK3	1,6	STK4	9,6	STK38L	12,6
CAMK1G	2,0	FGFR3	3,8	VRK1	3,0	ULK1	1,4	DYRK1A	1,5	MST3	9,3	PIM1	12,5
CAMKK2B	1,9	PLK4	3,8	MST4	3,0	FGFR2	1,1	FES	1,5	BMPR2	9,2	DCAMKL1	12,4
STK3	1,8	CAMKK2B	3,7	MAP2K4	2,9	MAP2K4	1,1	PDK4	1,5	DCAMKL1	8,9	MAP2K6	12,3
SLK	1,8	MST3	3,7	GSG2	2,9	STK17B	1,1	STK17A	1,4	PHKG2	8,8	PAK4	12,2
DYRK1A	1,7	CHEK2	3,5	STK17A	2,9	PCTK1	1,1	GSG2	1,4	TTK	8,8	MAP2K4	12,0
EPHA7	1,7	EPHA5	3,2	CLK3	2,8	GPRK5	1,0	ULK1	1,3	SLK	8,8	CLK1	11,9
CLK1	1,6	ABL1	3,2	CK2A2	2,7	STK17A	1,0	STK6	1,3	STK38L	8,7	STK17A	11,8
DYRK2	1,6	EPHA2	3,1	STK6	2,7	GAK	1,0	MAP3K5	1,3	ABL1	8,7	GSK3B	11,8
CAMK2D	1,6	CLK3	3,0	CHEK2	2,6	MERTK	1,0	TTK	1,3	CHEK2	8,6	STK17B	11,5
PHKG2	1,5	MAPK10	3,0	PCTK1	2,6	MST3	0,9	MERTK	1,2	MAPK1	8,5	ULK1	11,3
STK17B	1,5	PCTK1	3,0	PIM3	2,3	RPS6KA1	0,9	OSR1	1,2	CK2A2	8,5	TTK	11,2
CLK3	1,5	CAMK1D	3,0	FGFR2	2,3	CHEK2	0,9	FGFR2	1,1	EPHA2	8,4	CAMK1G	10,9
MAPK9	1,5	SRC	2,9	RPS6KA1	2,2	FGFR1B	0,9	FGFR3	1,1	ULK1	8,3	EPHA7	10,3
CSNK1D	1,5	STK17B	2,8	PIM1	2,1	PDK4	0,8	STK10	1,1	MARK4	8,2	ABL1	10,3
FGFR1B	1,4	ULK1	2,8	CSNK1D	2,1	VRK1	0,8	GPRK5	1,1	DYRK1A	8,2	CAMK1D	10,0
TTK	1,4	STK10	2,6	MAPK10	1,9	CAMK2B	0,7	MAP2K6	1,1	MARK3	8,1	DAPK1	9,8
STK17A	1,4	DYRK1A	2,6	PLK4	1,9	EPHA7	0,7	CAMK2D	1,1	MAPK13	8,0	STK39	9,6
STK6	1,3	DCAMKL1	2,6	MERTK	1,8	STK6	0,7	PKMYT1	1,1	GAK	8,0	PCTK1	9,1
STK38L	1,3	FES	2,5	PHKG2	1,8	PLK4	0,6	MAPK9	1,1	PAK4	7,7	FGFR2	9,0
STK39	1,2	PIM3	2,5	ABL1	1,6	DYRK1A	0,6	PIM3	1,1	STK39	7,6	GAK	9,0
WNK1	1,2	FGFR2	2,5	FES	1,6	MST4	0,6	DYRK2	1,1	MAPK10	7,2	DYRK1A	8,7
FES	1,2	MERTK	2,5	STK38L	1,6	CAMK2D	0,6	CK2A2	1,0	MST4	7,1	DMPK1	8,7
CAMK2B	1,1	PIM1	2,4	FGFR1B	1,6	WNK1	0,5	DAPK3	0,9	CDKL1	6,8	CAMK4	8,6
MST4	1,1	STK38L	2,4	CAMKK2B	1,6	MAP2K6	0,5	VRK1	0,9	MAPK9	6,5	EPHA2	8,3
BRAF	1,1	OSR1	2,3	GPRK5	1,4	FES	0,5	SRPK1	0,9	EPHA5	6,3	EPHA5	7,9
ULK1	1,1	DAPK1	2,3	CAMK2D	1,4	STK38L	0,5	CAMK1D	0,9	VRK1	5,9	GPRK5	7,7
BRD4	1,0	MAPK9	2,3	MAP2K6	1,3	DAPK1	0,5	MARK3	0,9	FGFR2	5,9	OSR1	7,7
EPHB3	0,9	MST4	2,3	SRC	1,2	DAPK3	0,5	BMX	0,8	OSR1	5,6	MAPK13	7,5
GSG2	0,9	MAP2K6	2,3	DAPK1	1,2	SRC	0,4	STK38L	0,8	CAMK1G	5,5	MAPK10	7,4
MAP3K5	0,9	MAPK13	2,2	OSR1	1,2	OSR1	0,4	EPHB3	0,8	CAMK1D	5,4	MST3	7,3
MAP2K1	0,9	MAP3K5	2,1	EPHA2	1,1	NEK1	0,4	PLK4	0,8	CAMK4	5,4	GSG2	7,2
PAK1	0,9	BRAF	2,1	DCAMKL1	1,1	MAPK13	0,4	CAMKK2B	0,8	GPRK5	5,2	BMX	7,1
PDK4	0,8	PHKG2	2,1	STK10	1,1	EPHB3	0,4	DMPK1	0,8	RPS6KA1	5,1	DYRK2	7,0
SRPK1	0,8	BMX	2,1	MAPK13	1,1	MAPK9	0,3	PAK1	0,7	EPHB3	5,1	SRPK1	6,9
PLK4	0,7	TTK	2,0	PDK4	1,1	PIM3	0,3	DCAMKL1	0,7	DAPK1	4,9	PAK1	6,6
MAP2K6	0,7	PAK4	1,9	CAMK2B	1,1	PKMYT1	0,3	EPHA2	0,7	EPHA7	4,9	MERTK	6,6
CK2A2	0,7	CAMK1G	1,9	MAPK9	1,0	EPHA2	0,2	BRAF	0,7	RIOK1	4,9	AKT3	6,6
PKMYT1	0,7	CSNK1D	1,8	BRD4	1,0	ABL1	0,2	EPHA7	0,7	BRAF	4,6	FES	6,2
ABL1	0,5	VRK1	1,8	TTK	0,9	BRD4	0,2	WNK1	0,7	FGFR1B	4,5	MST4	6,1
DAPK3	0,5	FGFR1B	1,8	PAK4	0,9	MAPK1	0,2	SLK	0,7	FES	4,5	FGFR1B	5,9
DMPK1	0,5	EPHB3	1,7	EPHB3	0,7	BMX	0,1	SRC	0,6	CAMK2D	4,5	SRC	5,9
DAPK1	0,5	RPS6KA1	1,7	BMX	0,7	RPS6KA6	0,1	FGFR1B	0,6	SRC	4,4	CK2A2	5,6
CDC42BPA	0,5	PKMYT1	1,6	DAPK3	0,7	CAMKK2B	0,1	DAPK1	0,6	BMX	4,4	CLK3	5,6
BMX	0,4	GPRK5	1,5	DYRK1A	0,7	CASK	0,1	ABL1	0,5	CAMK2B	4,4	EPHB3	5,0
MAPK13	0,3	EPHA7	1,4	DMPK1	0,7	PAK4	0,1	EPHA5	0,5	MERTK	4,4	CASK	4,8
RPS6KA1	0,3	DMPK1	1,4	SRPK1	0,6	PHKG2	0,1	CSNK1D	0,5	SRPK1	4,1	RPS6KA1	3,9
MAPK1	0,3	CAMK2B	1,3	NEK1	0,6	CAMK4	0,0	AKT3	0,5	PIM3	3,8	MAPK9	3,7
AKT3	0,3	PDK4	1,2	PKMYT1	0,5	PAK1	0,0	CAMK2B	0,4	PAK1	3,3	CDKL1	3,1
TAF1	0,3	CAMK2D	1,2	MAPK1	0,5	DMPK1	0,0	MAP2K1	0,4	PIM1	3,3	CDC42BPA	2,8
CAMK4	0,2	CAMK4	1,1	WNK1	0,4	SRPK1	0,0	MAPK13	0,4	DMPK1	3,2	VRK1	2,8
EPHA5	0,2	BRD4	0,9	PAK1	0,4	AKT3	0,0	MAPK1	0,3	CSNK1D	3,1	BMPR2	2,6
EPHA2	0,2	SRPK1	0,8	TAF1	0,3	TAF1	0,0	CDC42BPA	0,3	GSG2	2,9	CSNK1D	1,8
STK10	0,2	WNK1	0,7	CAMK4	0,3	TTK	-0,1	CASK	0,2	MAPK14	2,5	MAPK1	1,4
NEK1	0,1	NEK1	0,7	CDKL1	0,2	STK10	-0,1	CDKL1	0,2	CASK	2,0	MAP2K1	1,3
SRC	0,1	PAK1	0,7	CASK	0,2	CAMK1G	-0,3	PHKG2	0,1	MAP2K1	1,4	BRD4	1,1
DCAMKL1	0,1	MAPK1	0,7	MAP2K1	0,1	DCAMKL1	-0,3	RPS6KA1	0,1	AKT3	1,4	WNK1	0,9
OSR1	0,1	CASK	0,4	CAMK1G	0,1	CDKL1	-0,3	BRD4	0,1	BRD4	1,3	BRAF	0,8
CDKL1	0,1	AKT3	0,4	EPHA5	0,1	PIM1	-0,3	RPS6KA6	0,1	PDK4	1,2	MAPK14	0,3
PIM3	0,1	TAF1	0,3	AKT3	-0,1	MAPK14	-0,3	TAF1	0,1	NEK1	1,1	PDK4	0,2
CASK	0,0	CDC42BPA	0,3	CDC42BPA	-0,2	EPHA5	-0,3	PAK4	0,1	WNK1	1,1	PKMYT1	0,2
PAK4	0,0	RPS6KA6	0,3	MAPK14	-0,2	CDC42BPA	-0,4	CAMK4	0,1	PKMYT1	1,0	TAF1	0,2
MAPK14	-0,1	CDKL1	0,2	RPS6KA6	-0,4	MAP2K1	-0,4	NEK1	0,0	RPS6KA6	0,4	RIOK1	0,0
GPRK5	-0,2	MAP2K1	0,0	EPHA7	-0,5	MAPK10	-0,8	MAPK14	-0,1	TAF1	0,1	RPS6KA6	-0,5
RPS6KA6	-0,3	MAPK14	0,0	CAMK1D	-0,6	CAMK1D	-1,6	CAMK1G	-0,6	CDC42BPA	-0,1	NEK1	-0,6

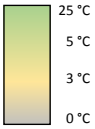


Table S2. Selectivity screening results of **8a** at 1 μM screening concentration.

Kinase	Percent Control
FLT3(D835V)	4.5
BMPR2	8.3
GSK3A	16
JNK1	27
RIOK2	27
FLT3(ITD,F691L)	37
JNK3	38
PIP5K1C	39
RSK4(Kin.Dom.1-N-terminal)	42
VRK2	44
FLT3(ITD,D835V)	46
STK16	46
FLT3(D835H)	47
FLT3(N841I)	50
ERBB2	52
YSK4	52
PIP5K2C	53
PCTK1	54
CDK4-cyclinD1	57
MYLK	58
BRSK2	59
CDK4-cyclinD3	59
PAK6	59
AMPK-alpha1	60

EGFR(S752-I759del)	60
FGFR1	60
PIK3CA(H1047Y)	60
CSNK1E	61
MARK4	61
MARK1	62
MTOR	62
BRAF(V600E)	63
IRAK1	63
MET	63
RAF1	63
TBK1	63
TSSK1B	64
WNK4	64
BMPR1A	65
RPS6KA5(Kin.Dom.2-C-terminal)	65
TSSK3	65
BLK	66
CAMK2B	66
CDC2L5	66
IRAK4	66
PRKCD	66
SYK	66
CIT	67
CSNK1D	67
DYRK1A	67

HIPK1	67
ICK	67
JNK2	67
PRKCE	67
EGFR(L747-T751del,Sins)	68
EPHB6	68
MLK1	68
PIK3C2G	68
SLK	68
TYK2(JH2domain-pseudokinase)	68
FLT3(K663Q)	69
GRK3	69
MYLK2	69
p38-beta	69
PDPK1	69
PIK3CD	69
TEC	69
ABL1-phosphorylated	70
EGFR(G719S)	70
LKB1	70
p38-gamma	70
PKN2	70
RSK1(Kin.Dom.1-N-terminal)	70
CSNK1G2	71
EGFR(G719C)	71
EPHA7	71

ERK8	71
MEK5	71
PIK3CA(E545A)	71
PIK3CG	71
PIK4CB	71
TAOK2	71
ABL1-nonphosphorylated	72
CLK4	72
MEK3	72
NIK	72
SGK2	72
ABL2	73
AMPK-alpha2	73
CAMK2A	73
CAMK2G	73
CSK	73
DAPK2	73
ERK1	73
MLK3	73
MYO3B	73
PIK3CA(M1043I)	73
PKNB(M.tuberculosis)	73
SGK	73
STK36	73
TAOK3	73
TIE2	73
PRKD1	74

BUB1	75
CDK2	75
CSNK2A1	75
DCAMKL3	75
PIM1	75
SNARK	75
TAK1	75
YSK1	75
AAK1	76
ACVR1B	76
ACVRL1	76
DYRK1B	76
EGFR(L747-E749del, A750P)	76
JAK3(JH1domain-catalytic)	76
MAP3K2	76
MAP3K3	76
MYLK4	76
PKAC-alpha	76
PRKCI	76
RSK2(Kin.Dom.1-N-terminal)	76
CAMK1G	77
CDK5	77
DAPK3	77
HCK	77
MAP3K15	77
p38-alpha	77

PHKG2	77
PIK3CA	77
PIM3	77
ABL1(E255K)-phosphorylated	78
CDKL5	78
CTK	78
FLT3	78
LCK	78
MELK	78
MKNK2	78
MST4	78
MYO3A	78
SIK	78
AKT1	79
CAMK1	79
CDK8	79
CSNK1A1L	79
GRK2	79
OSR1	79
PAK4	79
PFCDPK1(P.falciparum)	79
PIK3CA(C420R)	79
RET(V804L)	79
TAOK1	79
TGFBR1	79
YANK3	79

CSNK1A1	80
EPHA5	80
FLT4	80
GSK3B	80
HASPIN	80
ITK	80
KIT(V559D,V654A)	80
MEK6	80
NEK6	80
PIK3C2B	80
RET(M918T)	80
ANKK1	81
AXL	81
FLT1	81
LYN	81
MAP3K1	81
MINK	81
PAK3	81
PCTK2	81
PIK3CA(H1047L)	81
RPS6KA5(Kin.Dom.1-N-terminal)	81
ULK1	81
EPHA8	82
LZK	82
MET(M1250T)	82
SRC	82

VEGFR2	82
ABL1(T315I)-phosphorylated	83
AKT3	83
CAMKK2	83
EGFR(L861Q)	83
IGF1R	83
KIT(D816V)	83
MST1R	83
MST3	83
SgK110	83
TLK2	83
CDK9	84
FLT3(ITD)	84
LATS1	84
MAP4K5	84
NDR2	84
PDGFRA	84
PRKCH	84
RET	84
RIPK1	84
ROCK1	84
TNNI3K	84
ABL1(F317L)-phosphorylated	85
ABL1(Q252H)-nonphosphorylated	85
EGFR(E746-A750del)	85

ERK2	85
LIMK2	85
LOK	85
MAPKAPK5	85
PRKR	85
RPS6KA4(Kin.Dom.2-C-terminal)	85
TGFBR2	85
ULK3	85
WEE2	85
ACVR2A	86
ASK1	86
BIKE	86
CAMK1D	86
CAMK2D	86
CDC2L2	86
CLK1	86
CSF1R	86
CSF1R-autoinhibited	86
FER	86
FLT3-autoinhibited	86
JAK1(JH1domain-catalytic)	86
KIT(D816H)	86
ROS1	86
AKT2	87
EGFR(L747-S752del, P753S)	87

EGFR(L858R,T790M)	87
EPHB2	87
ERN1	87
IKK-beta	87
KIT	87
LIMK1	87
MERTK	87
MST1	87
NEK7	87
PAK1	87
PYK2	87
ABL1(H396P)-nonphosphorylated	88
ABL1(H396P)-phosphorylated	88
CAMKK1	88
CLK3	88
DMPK2	88
DRAK1	88
ERK5	88
FGFR3	88
FGFR3(G697C)	88
FGFR4	88
INSR	88
MAP4K2	88
NEK3	88
PLK1	88

QSK	88
RSK3(Kin.Dom.1-N-terminal)	88
ADCK4	89
AURKC	89
CDKL2	89
CLK2	89
EPHA2	89
GCN2(Kin.Dom.2,S808G)	89
HIPK3	89
HPK1	89
KIT(V559D,T670I)	89
MKNK1	89
PAK2	89
PFPK5(P.falciparum)	89
PRKCQ	89
RIPK2	89
RSK3(Kin.Dom.2-C-terminal)	89
TRKA	89
TRPM6	89
WNK2	89
ABL1(M351T)-phosphorylated	90
CDK11	90
CSNK1G3	90
DAPK1	90
EPHB1	90
MET(Y1235D)	90

NEK9	90
NIM1	90
NLK	90
PIK3CA(E542K)	90
PRKG1	90
RSK1(Kin.Dom.2-C-terminal)	90
TTK	90
ACVR2B	91
BMPR1B	91
CDK3	91
MKK7	91
MST2	91
NDR1	91
NEK1	91
NEK5	91
PIKFYVE	91
S6K1	91
TLK1	91
ULK2	91
CHEK2	92
DDR2	92
FGFR2	92
IRAK3	92
JAK2(JH1domain-catalytic)	92
PCTK3	92
PIP5K2B	92
BMX	93

CHEK1	93
DCAMKL2	93
FYN	93
KIT(A829P)	93
KIT-autoinhibited	93
MEK1	93
MRCKA	93
PFTAIRE2	93
PIM2	93
RPS6KA4(Kin.Dom.1-N-terminal)	93
SRPK1	93
STK35	93
GRK1	94
GRK4	94
IKK-epsilon	94
KIT(L576P)	94
MAP4K4	94
PIK3CA(E545K)	94
PLK4	94
RET(V804M)	94
RIPK4	94
SIK2	94
SRMS	94
STK33	94
TIE1	94
VPS34	94

WEE1	94
ACVR1	95
BRSK1	95
CDC2L1	95
CDKL1	95
EGFR	95
ERBB3	95
GAK	95
PDGFRB	95
PIK3CA(I800L)	95
ABL1(Y253F)-phosphorylated	96
DRAK2	96
EGFR(L858R)	96
EPHA4	96
MAK	96
NEK11	96
PRKD3	96
PRKG2	96
TESK1	96
TNK1	96
TRKC	96
EGFR(T790M)	97
ERK3	97
GRK7	97
IKK-alpha	97
KIT(V559D)	97

PAK7	97
PRKD2	97
TNIK	97
ADCK3	98
EPHA3	98
MARK3	98
MAST1	98
PIP5K1A	98
TNK2	98
EPHB4	99
MAP3K4	99
MAPKAPK2	99
MRCKB	99
PKN1	99
ZAP70	99
ABL1(F317I)-nonphosphorylated	100
ABL1(F317I)-phosphorylated	100
ABL1(F317L)-nonphosphorylated	100
ABL1(Q252H)-phosphorylated	100
ABL1(T315I)-nonphosphorylated	100
ALK	100
ALK(C1156Y)	100
ALK(L1196M)	100

ARK5	100
ASK2	100
AURKA	100
AURKB	100
BRAF	100
BRK	100
BTK	100
CAMK1B	100
CAMK4	100
CASK	100
CDK4	100
CDK7	100
CDKL3	100
CSNK1G1	100
CSNK2A2	100
DCAMKL1	100
DDR1	100
DLK	100
DMPK	100
DYRK2	100
EIF2AK1	100
EPHA1	100
EPHA6	100
EPHB3	100
ERBB4	100
ERK4	100
FAK	100

FES	100
FGR	100
FLT3(D835Y)	100
FLT3(R834Q)	100
FRK	100
HIPK2	100
HIPK4	100
HUNK	100
INSRR	100
JAK1(JH2domain-pseudokinase)	100
LATS2	100
LRRK2	100
LRRK2(G2019S)	100
LTK	100
MAP4K3	100
MARK2	100
MEK2	100
MEK4	100
MLCK	100
MLK2	100
MUSK	100
NEK10	100
NEK2	100
NEK4	100
p38-delta	100
PFTK1	100

PHKG1	100
PIK3CA(Q546K)	100
PIK3CB	100
PKAC-beta	100
PKMYT1	100
PLK2	100
PLK3	100
PRKX	100
PRP4	100
RIOK1	100
RIOK3	100
RIPK5	100
ROCK2	100
RSK2(Kin.Dom.2-C-terminal)	100
RSK4(Kin.Dom.2-C-terminal)	100
SBK1	100
SGK3	100
SNRK	100
SRPK2	100
SRPK3	100
STK39	100
TRKB	100
TXK	100
TYK2(JH1domain-catalytic)	100
TYRO3	100
WNK1	100
WNK3	100

YANK1	100
YANK2	100
YES	100
ZAK	100

Table S3. Off-target evaluation of **8a** against JNK1 & RIOK2 by DSF and NanoBRET.

Compound	DSF ΔTm [°C]		NanoBRET™ EC_{50}	
	JNK1	RIOK2	JNK1	RIOK2
1	6.70	9.40	n.d.	76 nM
8a	1.40	0.70	> 50 µM	> 50 µM
8b	n.d.	3.90	n.d.	n.d.
8c	1.95	3.20	n.d.	3.7 µM

Experimental Section

Differential Scanning Fluorimetry Assay. Recombinant protein kinase domains with a concentration of 2 µM were mixed with a 10 µM compound solution in DMSO, using a final buffer consisting of 20 mM HEPES, pH 7.5, and 500 mM NaCl. SYPRO Orange (5000×, Invitrogen) was added as a fluorescence probe (1 µl per mL) in a final concentration of 5x. Subsequently, temperature-dependent protein unfolding profiles were measured, using the QuantStudio™ 5 realtime PCR machine (Thermo Fisher). Excitation and emission filters were set to 465 nm and 590 nm. The temperature was raised with a step rate of 3°C per minute. Data points were analysed with the internal software (Thermal Shift SoftwareTM Version 1.4, Thermo Fisher) using the Boltzmann equation to determine the inflection point of the transition curve. Differences in melting temperature are given as ΔTm values in °C. Measurements were performed in duplicates.

Isothermal titration calorimetry (ITC): Thermodynamic parameters of the interactions were measured by ITC for compounds **1** and **8a** with BMPR2 (residues 189–517). Sample cell and injection syringe were equilibrated with gel filtration buffer, the compound solution (12.5µM of **1** and **8a**, prepared in gel filtration buffer) was added into the sample cell and the protein (71µM for **1** and **8a**, in gel filtration buffer) filled into an injection syringe. The experiments were performed at 20 °C for **1** and **8a** with 35 injections of 2 µL each using a Nano ITC device (TA Instruments).

ADP-Glo™. The assay was performed as per the manufacturer's instructions (Promega, Catalog No VA7389) using 1x Kinase Reaction buffer and a final concentration of 10 µM ATP, 2 µg/µL (17.4 nM) BMPR2 (aa174-end, MW 115 kDa) and 0.1 µg/µL Native Swine Myelin Basic Protein (MBP) as Substrate. For the assay, inhibitor was titrated into white 384 small volume assay plates (Greiner 784075) as an 11-point dose-response in technical duplicates in a final concentration range of 45 µM to 830 pM using an Echo 550 acoustic dispenser (Beckman) including a no inhibitor control (DMSO only) that was used as an uninhibited control reaction. ATP was added using the Echo 550 and the reaction was started by adding 5 µL BMPR2 in

1x kinase buffer including a no kinase control that was used as a background control. The reaction was allowed to continue at RT for 60 min before adding 5 µL of the stopping reagent. After an incubation of 40 min at RT, 10 µL of the detection reagent was added and the plate incubated for 30 min at RT. Luminescence of the plate was then detected using a PHERAstar FSX Platereader (BMG Labtech) and the data normalized to background and uninhibited control and graphed using GraphPad Prism 9 using the normalized 3-parameter-fit with the following equation: Y=100/(1+10^(X-LogIC$_{50}$))

NanoBRET™: The assay was performed as described previously.[1] In brief: full-length kinases were obtained as plasmids cloned in frame with a N-terminal NanoLuc-fusion for GSK3A (Promega, NV3191), GSK3B (Promega, NV3201) JNK1 (Promega, NV1701) and RIOK2 (Promega, NV1961). Plasmids were transfected into HEK293T cells using FuGENE HD (Promega, E2312), and proteins were allowed to express for 20 h. Serially diluted inhibitor and NanoBRET™ Kinase Tracer K8 (Promega, N2820) at a concentration determined previously as the Tracer $K_{D, app}$ (GSK3A 150 nM and GSK3B 200 nM) or NanoBRET™ Kinase Tracer K10 (Promega, N2840) at a concentration determined previously as the Tracer $K_{D, app}$ (JNK1 130 nM and RIOK2 500 nM) were pipetted into white 384-well plates (Greiner 781207) using an Echo acoustic dispenser (Labcyte). The corresponding protein-transfected cells were added and reseeded at a density of 2.5 x 10^5 cells/mL after trypsinization and resuspending in Opti-MEM without phenol red (Life Technologies). The system was allowed to equilibrate for 2 hours at 37 °C/5% CO_2 prior to BRET measurements. To measure BRET, NanoBRET™ NanoGlo Substrate + Extracellular NanoLuc Inhibitor (Promega, N2540) was added as per the manufacturer's protocol, and filtered luminescence was measured on a PHERAstar plate reader (BMG Labtech) equipped with a luminescence filter pair (450 nm BP filter (donor) and 610 nm LP filter (acceptor)). Competitive displacement data were then graphed using GraphPad Prism 9 software using a normalized 3-parameter curve fit with the following equation: Y=100/(1+10^(X-LogIC$_{50}$)).

Docking. The protein structure BMPR2 (PDB:6UNP) was used for docking. The protein structures and ligands were prepared according to the standard protocol of Autodock Vina.[2,3] Briefly, the protein structures were added hydrogen atoms by REDUCE at neural pH and allowed the Asn, Gln and His sidechains to flip,[4] then the protein structures were converted to PDBQT format using the script prepare_receptor from ADFR suite,[5,6] hetero-atoms including water, cofactors, ions and any other non-protein atoms contained in the protein structures were removed before docking. Ligands were converted to PDBQT format in the default setting using the script prepare_ligand from ADFR suite,[5,6] with addition to add hydrogens, merge non-polar hydrogens, merge charges and remove lone pairs. PyMOL were used to view the docking results in PDBQT formats,[7] PLIP web-server was used to analyze the protein-ligand interactions with all parameters in default setting.[8]

Kinome-Wide Selectivity Profile. Compounds **1** and **8a** were tested at a concentration of 1 μM against a panel of 468 kinases in the KINOMEscan assay performed by Eurofins Scientific.

Chemistry. The synthesis of compounds will be explained in the following and the analytical data for them can be found in the Supporting Information. All commercial chemicals were purchased from common suppliers with a purity ≥ 95% and were used without further purification. The solvents with an analytical grade were obtained from VWR Chemicals and Merck and all dry solvents from Acros Organics. All reactions were proceeded under an argon atmosphere. The thin layer chromatography was done with silica gel on aluminum foils (60 Å pore diameter) obtained from Macherey-Nagel and visualized with ultraviolet light (λ = 254 and 365 nm). The purification of the compounds was done by flash chromatography. A puriFlash XS 420 device with a UV-VIS multiwave detector (200−400 nm) from Interchim was used with pre-packed normal-phase PF-SIHP silica columns with particle sizes of 15 and 30 μm (Interchim). Preparative purification by HPLC was carried out on an Agilent 1260 Infinity II device using an Eclipse XDB-C18 (Agilent, 21.2 x 250mm, 7μm) reversed phase column. A suitable gradient (flow rate 21 ml/min.) was used, with 0.1% TFA in water (A) and 0.1% TFA

in acetonitrile (B), as a mobile phase. The nuclear magnetic resonance spectroscopy (NMR) was performed with DPX250, AV300, AV400 or AV500 MHz spectrometers from Bruker. Chemical shifts (δ) are reported in parts per million (ppm). DMSO-d6, chloroform-d and methylene chloride-d2 was used as a solvent, and the spectra were calibrated to the solvent signal: 2.50 ppm (1H NMR) or 39.52 ppm (13C NMR) for DMSO-d6, 7.26 ppm (1H NMR) or 77.16 ppm (13C NMR) for chloroform-d and 5.32 ppm (1H NMR) or 54.00 ppm (13C NMR) for methylene chloride-d2. Coupling constants (J) were reported in hertz (Hz) and multiplicities were designated as followed: s (singlet), d (doublet), dd (doublet of doublet), t (triplet), dt (doublet of triplets), td (triplet of doublets), ddd (doublet of doublet of doublet), q (quartet), m (multiplet). Mass spectra were measured on a Surveyor MSQ device from ThermoFisher measuring in the positive- or negative-ion mode. Final compounds were additionally characterized by HRMS using a MALDI LTQ Orbitrap XL from ThermoScientific. The purity of the final compounds was determined by HPLC using an Agilent 1260 Infinity II device with a 1260 DAD HS detector (G7117C; 254 nm, 280 nm, 310 nm) and a LC/MSD device (G6125B, ESI pos. 100-1000). The compounds were analyzed on a Poroshell 120 EC-C18 (Agilent, 3 x 150 mm, 2.7 µm) reversed phase column using 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B) as a mobile phase. The following gradient was used: 0 min 5% B - 2 min 5% B - 8 min 98% B - 10 min 98% B (flow rate of 0.5 mL/min). UV-detection was performed at 254, 280 and 310 nm and all compounds used for further biological characterizations showed a purity ≥95%. No unexpected or unusually high safety hazards were encountered.

Synthesis of methyl 5-((2-chloropyrimidin-4-yl)amino)-1*H*-pyrazole-3-carboxylate (4).

3-amino-1*H*-pyrazole-5-carboxylate (500 mg, 3.54 mmol, 1.1 eq) and 2,4-dichloropyrimidine (480 mg, 3.22 mmol, 1.0 eq) were dissolved in 15 mL anhydrous isopropanol. TEA (978 mg, 9.66 mmol, 3.0 eq) was added and the mixture was stirred at 50 °C for 72 h. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography using n-hexane/ ethyl acetate as an eluent to obtain the product (132 mg, 16%) as a white solid. Molecular formula: $C_9H_8ClN_5O_2$. ^{1}H NMR (250 MHz, DMSO-d6) δ 13.70

(s, 1H), 10.63 (s, 1H), 8.20 (d, J = 5.9 Hz, 1H), 7.19 – 6.81 (m, 2H), 3.86 (s, 3H). ^{13}C NMR (151 MHz, DMSO) δ 160.56, 159.39, 147.77, 133.08, 128.15, 127.41, 99.45, 52.04. MS-ESI m/z $[M + Na]^+$: calcd 276.7, found 276.1.

Synthesis of methyl 5-((2-((4-(2-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)amino)-pyrimidin-4-yl)amino)-1*H*-pyrazole-3-carboxylate (5a).

4 (214 mg, 0.84 mmol, 1.0 eq) and *tert*-butyl 4-aminophenethylcarbamate (181 mg, 0.77 mmol, 1.0 eq) were dissolved in 13 mL anhydrous ethanol. An catalytic amount of 1 M HCl was added and the mixture was stirred under reflux for 18 h. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography using DCM/ methanol as an eluent to obtain the product (219 mg, 63%) as a light yellow solid. Molecular formula: $C_{22}H_{27}N_7O_4$. ^{1}H NMR (250 MHz, DMSO-d6) δ 13.87 (s, 1H), 11.29 (s, 1H), 10.50 (s, 1H), 8.00 (d, J = 6.9 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 7.06 (s, 1H), 6.90 (t, J = 5.3 Hz, 1H), 6.52 (s, 1H), 3.87 (s, 3H), 3.22 – 3.10 (m, 2H), 2.80 – 2.65 (m, 2H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 160.11, 155.54, 146.85, 136.35, 133.35, 129.22, 122.79, 100.87, 99.04, 77.52, 52.04, 41.52, 35.06, 28.24. MS-ESI m/z $[M + H]^+$: calcd 454.5, found 454.1. HRMS m/z $[M + Na]^+$: calcd 476.2017, found 476.2038. HPLC: t_R = 6.09, purity ≥ 95% (UV: 254/ 280 nm).

Synthesis of methyl 5-((2-((3-(2-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)amino)-pyrimidin-4-yl)amino)-1*H*-pyrazole-3-carboxylate (5b).

The title compound was prepared according to the procedure of **5a**, using **4** (225 mg, 0.89 mmol) and *tert*-butyl 3-aminophenethylcarbamate (191 mg, 0.81 mmol). The mixture was stirred for 18 h under reflux to obtain the product (178 mg, 49%) as a light yellow solid. Molecular formula: $C_{22}H_{27}N_7O_4$. ^{1}H NMR (250 MHz, DMSO-d6) δ 13.85 (s, 1H), 11.33 (s, 1H), 10.54 (s, 1H), 8.01 (d, J = 6.7 Hz, 1H), 7.54 – 7.28 (m, 3H), 7.08 (d, J = 7.1 Hz, 1H), 6.98 (s, 1H), 6.85 (t, J = 5.6 Hz, 1H), 6.52 (s, 1H), 3.84 (s, 3H), 3.16 – 3.06 (m, 2H), 2.75 – 2.64 (m, 2H), 1.34 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 160.28, 159.49, 155.52, 153.45, 147.09, 140.65, 136.85, 133.51, 129.09, 125.61, 123.38, 121.02, 100.73, 99.19, 77.53, 51.93, 41.30,

35.37, 28.22. MS-ESI m/z $[M + H]^+$: calcd 454.5, found 454.3. HRMS m/z $[M + H]^+$: calcd 454.2197, found 454.2182. HPLC: t_R = 6.07, purity ≥ 95% (UV: 254/ 280 nm).

Synthesis of methyl 5-((2-((5-((*tert*-butoxycarbonyl)amino)pentyl)amino)pyrimidin-4-yl)amino)-1*H*-pyrazole-3-carboxylate (5c).

4 (180 mg, 0.71 mmol, 1.0 eq) and *tert*-butyl (5-aminopentyl)carbamate (144 mg, 0.71 mmol, 1.0 eq) were dissolved in 12 mL anhydrous ethanol. TEA (215 mg, 2.13 mmol, 3.0 eq) was added and the mixture was stirred at 120 °C for 5 h under micowave irradiation. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography using DCM/ methanol as an eluent to obtain the product (142 mg, 45%) as a white solid. Molecular formula: $C_{19}H_{29}N_7O_4$. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.38 (s, 1H), 9.91 (d, J = 185.8 Hz, 1H), 7.83 (s, 1H), 7.21 (s, 1H), 6.75 (s, 2H), 6.04 (d, J = 53.4 Hz, 1H), 3.82 (s, 3H), 3.23 (q, J = 6.3 Hz, 2H), 2.91 (q, J = 6.4 Hz, 2H), 1.61 – 1.46 (m, 2H), 1.36 (s, 13H). ^{13}C NMR (101 MHz, DMSO) δ 162.50, 160.04, 157.02, 156.06, 150.13, 142.02, 100.07, 96.24, 77.78, 52.27, 41.26, 40.66, 29.78, 29.39, 28.74, 24.33. MS-ESI m/z $[M + H]^+$: calcd 420.5, found 420.9. HRMS m/z $[M + H]^+$: calcd 420.2354, found 420.2350. HPLC: t_R = 5.57, purity ≥ 95% (UV: 254/ 280 nm).

Synthesis of methyl 5-((2-((2-(2-((*tert*-butoxycarbonyl)amino)ethoxy)ethyl)amino)-pyrimidin-4-yl)amino)-1*H*-pyrazole-3-carboxylate (5d).

The title compound was prepared according to the procedure of **5c**, using **4** (200 mg, 0.79 mmol) and *tert*-butyl (2-(2-aminoethoxy)ethyl)carbamate (161 mg, 0.79 mmol). The mixture was stirred for 5 h at 120 °C to obtain the product (10 mg, 31%) as a colorless oil. Molecular formula: $C_{18}H_{27}N_7O_5$. ^{1}H NMR (500 MHz, DMSO-d6) δ 13.39 (s, 1H), 9.91 (d, J = 245.4 Hz, 1H), 7.86 (s, 1H), 7.54 – 5.86 (m, 4H), 3.82 (s, 3H), 3.60 – 3.49 (m, 2H), 3.46 – 3.38 (m, 4H), 3.09 (q, J = 5.9 Hz, 2H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 162.14, 159.69, 156.87, 155.63, 149.28, 141.64, 132.78, 99.45, 96.01, 92.69, 77.62, 69.08, 51.72, 40.48, 28.22. MS-

ESI m/z $[M + H]^+$: calcd 422.5, found 422.9. HRMS m/z $[M + H]^+$: calcd 422.2146, found 422.2135. HPLC: t_R = 5.18, purity ≥ 95% (UV: 254/ 280 nm).

Synthesis of methyl 5-((2-((6-((*tert*-butoxycarbonyl)amino)hexyl)amino)pyrimidin-4-yl)amino)-1*H*-pyrazole-3-carboxylate (5e).

The title compound was prepared according to the procedure of **5c**, using **4** (50 mg, 0.20 mmol) and *tert*-butyl (6-aminohexyl)carbamate (43 mg, 0.20 mmol). The mixture was stirred for 5 h at 120 °C to obtain the product (36 mg, 42%) as a colorless oil. Molecular formula: $C_{20}H_{31}N_7O_4$. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.37 (s, 1H), 9.90 (d, J = 169.7 Hz, 1H), 7.85 (s, 1H), 7.17 (s, 1H), 6.94 – 6.58 (m, 2H), 6.07 (s, 1H), 3.81 (s, 3H), 3.23 (q, J = 6.7 Hz, 2H), 2.98 – 2.83 (m, 2H), 1.57 – 1.45 (m, 2H), 1.40 – 1.23 (m, 15H). ^{13}C NMR (101 MHz, DMSO) δ 162.04, 159.47, 156.64, 155.60, 149.06, 140.95, 132.46, 99.15, 95.72, 77.29, 51.72, 40.65, 29.53, 29.24, 28.27, 26.31, 26.18. MS-ESI m/z $[M + H]^+$: calcd 434.5, found 435.0. HRMS m/z $[M + H]^+$: calcd 434.2510, found 434.2500. HPLC: t_R = 5.86, purity ≥ 95% (UV: 254/ 280 nm).

Synthesis of methyl 3-((2-((4-(2-aminoethyl)phenyl)amino)pyrimidin-4-yl)amino)-1*H*-pyrazole-5-carboxylate (6a).

5a (50 mg, 0.1 mmol, 1.0 eq) was dissolved in 4 mL anhydrous DCM. TFA (503 mg, 4.4 mmol, 40.0 eq) was added at 0°C and the reaction mixture was allowed to warm up to rt overnight. The solvent was evaporated under reduced pressure. The residue was dissolved in methanol and neutralized with saturated K_2CO_3 solution. The solvent was again evaporated under reduced pressure and the crude product was used without further purification to obtain the desired product as a white solid together with salts.

Synthesis of methyl 5-((2-((3-(2-aminoethyl)phenyl)amino)pyrimidin-4-yl)amino)-1*H*-pyrazole-3-carboxylate (6b).

The title compound was prepared according to the procedure of **6a**, using **5b** (178 mg, 0.39 mmol). The desired product was obtained as a white solid with salts.

Synthesis of methyl 5-((2-((5-aminopentyl)amino)pyrimidin-4-yl)amino)-1*H*-pyrazole-3-carboxylate (6c).

The title compound was prepared according to the procedure of **6a**, using **5c** (142 mg, 0.34 mmol). The desired product was obtained as a white solid with salts.

Synthesis of methyl 5-((2-((2-(2-aminoethoxy)ethyl)amino)pyrimidin-4-yl)amino)-1*H*-pyrazole-3-carboxylate (6d).

The title compound was prepared according to the procedure of **6a**, using **5d** (100 mg, 0.24 mmol). The desired product was obtained as a white solid with salts.

Synthesis of methyl 5-((2-((6-aminohexyl)amino)pyrimidin-4-yl)amino)-1*H*-pyrazole-3-carboxylate (6e).

The title compound was prepared according to the procedure of **6a**, using **5e** (95 mg, 0.22 mmol). The desired product was obtained as a white solid with salts.

Synthesis of 5-((2-((4-(2-aminoethyl)phenyl)amino)pyrimidin-4-yl)amino)-1*H*-pyrazole-3-carboxylic acid (7a).

6a (160 mg, 0.45 mmol, 1.0 eq) and lithium hydroxide monohydrate (95 mg, 2.26 mmol, 5.0 eq) were dissolved in 8.9 mL THF and 2.3 mL H_2O. The resulting mixture was strirred at 50 °C for 16 h. The solvent was removed under reduced pressure, the residue was dissolved in H_2O and it was neutralized with a 10% HCl. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using acetonitile/ water as an eluent to obtain the desired product (116 mg, 75%) as a white solid. Molecular formula: $C_{16}H_{17}N_7O_2$. MS-ESI m/z $[M + H]^+$: calcd 340.4, found 340.6.

Synthesis of 5-((2-((3-(2-aminoethyl)phenyl)amino)pyrimidin-4-yl)amino)-1*H*-pyrazole-3-carboxylic acid (7b).

The title compound was prepared according to the procedure of **7a**, using **6b** (139 mg, 0.39 mmol). The desired product was obtained as a white solid with salts. Molecular formula: $C_{16}H_{17}N_7O_2$. MS-ESI m/z $[M + H]^+$: calcd 340.4, found 340.2.

Synthesis of 5-((2-((5-aminopentyl)amino)pyrimidin-4-yl)amino)-1*H*-pyrazole-3-carboxylic acid (7c).

The title compound was prepared according to the procedure of **7a**, using **6c** (108 mg, 0.34 mmol). The desired product was obtained as a white solid with salts. Molecular formula: $C_{13}H_{19}N_7O_2$. MS-ESI m/z $[M + H]^+$: calcd 306.3, found 306.2.

Synthesis of 5-((2-((2-(2-aminoethoxy)ethyl)amino)pyrimidin-4-yl)amino)-1*H*-pyrazole-3-carboxylic acid (7d).

The title compound was prepared according to the procedure of **7a**, using **6d** (84 mg, 0.24 mmol). The desired product was obtained as a white solid with salts. Molecular formula: $C_{12}H_{17}N_7O_3$. MS-ESI m/z $[M + H]^+$: calcd 308.3, found 308.2.

Synthesis of 5-((2-((6-aminohexyl)amino)pyrimidin-4-yl)amino)-1*H*-pyrazole-3-carboxylic acid (7e).

The title compound was prepared according to the procedure of **7a**, using **6e** (73 mg, 0.22 mmol). The desired product (41 mg, 59%) was obtained as a white solid with salts. Molecular formula: $C_{14}H_{21}N_7O_2$. MS-ESI m/z $[M + H]^+$: calcd 320.4, found 320.6.

Synthesis of (Z)-1^{1}H-2,4,8-triaza-3(4,2)-pyrimidina-1(3,5)-pyrazola-5(1,4)-benzena-cyclononaphan-9-one (8a).

7a (100 mg, 0.29 mmol, 1.0 eq) and HATU (134 mg, 0.35 mmol, 1.2 eq) were dissolved in 100 mL anhydrous DMF. DIPEA (99 mg, 0.77 mmol, 2.6 eq) was added to the resulting mixture

and it was stirred at 70 °C for 16 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using acetonitrile/ water as an eluent and by preparative HPLC to obtain the product (2 mg, 2%) as a white solid. Molecular formula: $C_{16}H_{15}N_7O_1$. ^{1}H NMR (250 MHz, DMSO-d6) δ 13.12 (s, 1H), 11.06 (s, 1H), 9.99 (s, 1H), 7.92 (d, J = 7.1 Hz, 1H), 7.25 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.97 (t, J = 6.0 Hz, 1H), 6.30 (d, J = 7.0 Hz, 1H), 5.74 (s, 1H), 3.54 (dd, J = 13.0, 6.7 Hz, 2H), 2.98 (t, J = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 159.55, 159.46, 157.93, 157.68, 145.58, 137.73, 137.58, 135.42, 130.67, 128.68, 102.65, 98.42, 37.78, 32.52. MS-ESI m/z $[M + H]^+$: calcd 322.3, found 322.6. HRMS m/z $[M + H]^+$: calcd 322.1411, found 322.1403. HPLC: t_R = 10.36, purity ≥ 95% (UV: 254/ 280 nm).

Synthesis of (Z)-1^{1}H-2,4,8-triaza-3(4,2)-pyrimidina-1(3,5)-pyrazola-5(1,3)-benzena-cyclononaphan-9-one (8b).

The title compound was prepared according to the procedure **8a**, using **7b** (20 mg, 0.06 mmol). The mixture was stirred for 16 h at 70 °C to obtain the product (8 mg, 42%) as a white solid. Molecular formula: $C_{16}H_{15}N_7O_1$. ^{1}H NMR (250 MHz, DMSO-d6) δ 13.01 (s, 1H), 9.88 (s, 1H), 9.25 (s, 1H), 8.46 (s, 1H), 8.16 (s, 1H), 7.98 (d, J = 5.7 Hz, 1H), 7.32 (s, 1H), 7.15 (t, J = 7.7 Hz, 1H), 6.97 (d, J = 7.7 Hz, 1H), 6.76 (d, J = 7.3 Hz, 1H), 6.24 (d, J = 5.7 Hz, 1H), 3.53 – 3.42 (m, 4H), 2.86 – 2.70 (m, 4H). ^{13}C NMR (126 MHz, DMSO) δ 161.19, 160.84, 160.18, 159.76, 156.30, 148.09, 140.92, 138.67, 134.70, 128.48, 121.12, 117.42, 98.58, 97.99, 45.20, 44.58. MS-ESI m/z $[M + H]^+$: calcd 322.3, found 322.2. HRMS m/z $[M + H]^+$: calcd 322.1411, found 322.1409. HPLC: t_R = 10.57, purity ≥ 95% (UV: 254/ 280 nm).

Synthesis of (Z)-3^{1}H-2,5,11-triaza-1(4,2)-pyrimidina-3(3,5)-pyrazolacycloundecaphan-4-one (8c).

The title compound was prepared according to the procedure **8a**, using **7c** (100 mg, 0.33 mmol). The mixture was stirred for 16 h at rt to obtain the product (10 mg, 10%) as a white solid. Molecular formula: $C_{13}H_{17}N_7O_1$. ^{1}H NMR (500 MHz, DMSO-d6) δ 13.40 (s, 1H), 11.44 (s, 1H), 8.56 (t, J = 6.0 Hz, 1H), 8.10 (t, J = 7.3 Hz, 1H), 7.86 (d, J = 7.1 Hz, 1H), 7.35 (s, 1H),

6.32 (d, J = 7.1 Hz, 1H), 3.57 – 3.34 (m, 2H), 3.34 – 3.18 (m, 2H), 1.74 – 1.61 (m, 4H), 1.55 – 1.39 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 160.34, 159.81, 153.79, 146.73, 143.04, 134.63, 98.11, 97.62, 42.12, 41.20, 27.92, 25.17, 22.35. MS-ESI m/z $[M + H]^+$: calcd 288.2, found 288.2. HRMS m/z $[M + H]^+$: calcd 288.1567, found 288.1569. HPLC: t_R = 9.81, purity ≥ 95% (UV: 254/ 280 nm).

Synthesis of (Z)-3^{1}H-8-oxa-2,5,11-triaza-1(4,2)-pyrimidina-3(5,3)-pyrazolacyclo-undecaphan-4-one (8d).

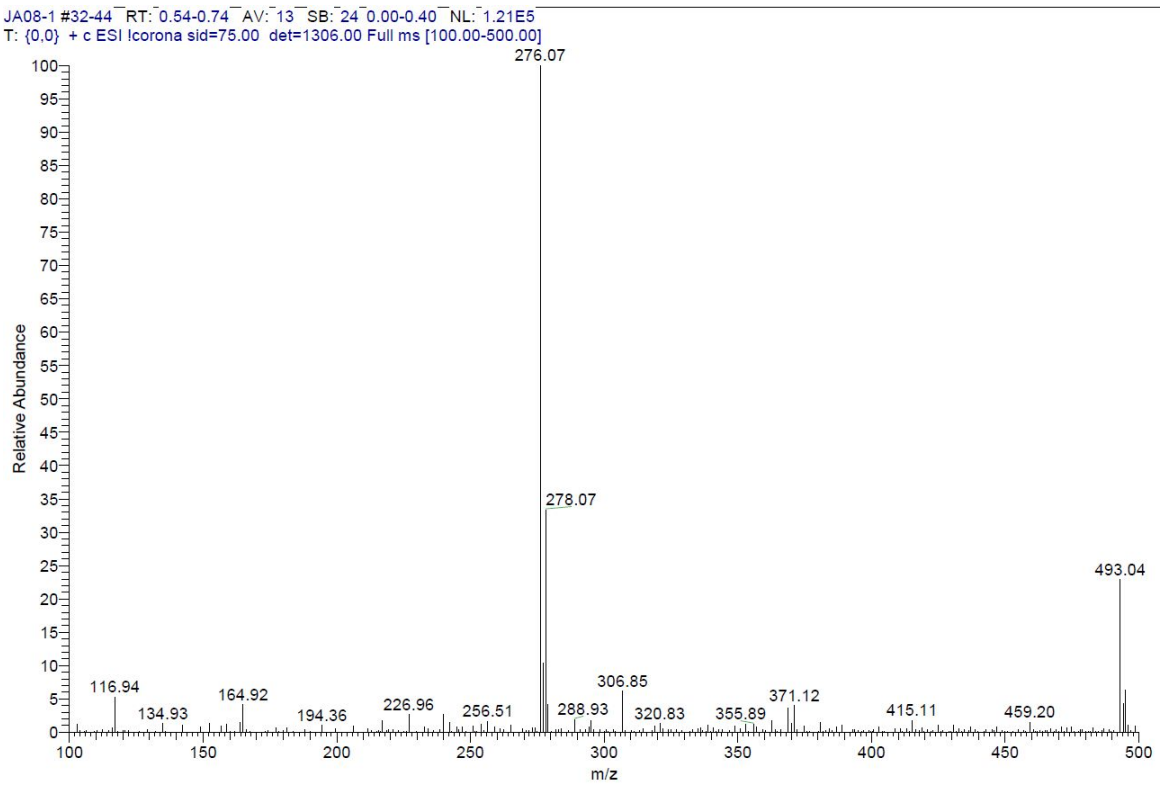
The title compound was prepared according to the procedure **8a**, using **7d** (73 mg, 0.24 mmol). The mixture was stirred for 16 h at 70 °C to obtain the product (2 mg, 3%) as a light yellow solid. Molecular formula: $C_{12}H_{15}N_7O_2$. ^{1}H NMR (250 MHz, DMSO-d6) δ 13.13 (s, 1H), 10.75 (s, 1H), 7.85 (s, 2H), 7.67 (s, 1H), 7.55 (s, 1H), 6.21 (s, 1H), 3.73 – 3.58 (m, 4H), 3.53 – 3.42 (m, 4H). MS-ESI m/z $[M + H]^+$: calcd 290.3, found 290.2. HRMS m/z $[M + Na]^+$: calcd 312.1179, found 312.1177. HPLC: t_R = 9.86, purity ≥ 95% (UV: 254/ 280 nm).

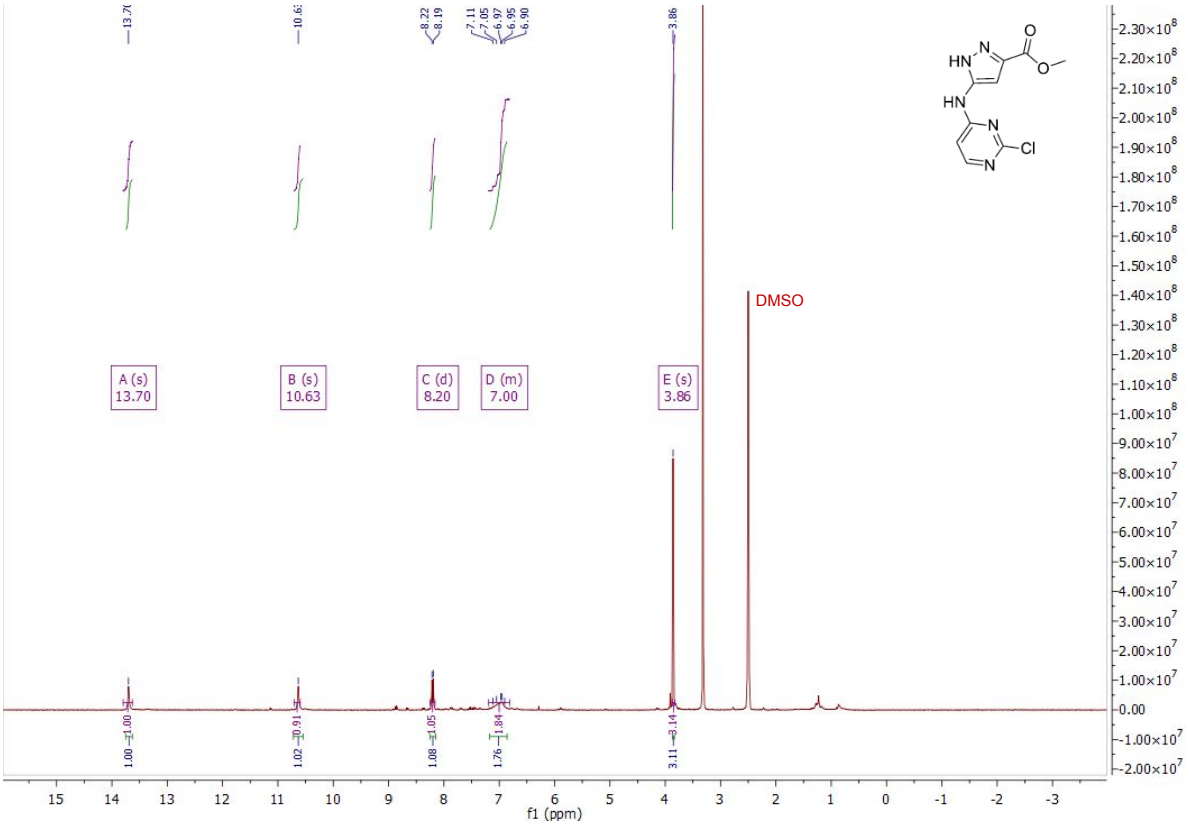
Synthesis of (Z)-3^{1}H-2,5,12-triaza-1(4,2)-pyrimidina-3(3,5)-pyrazolacyclododecaphan-4-one (8e).

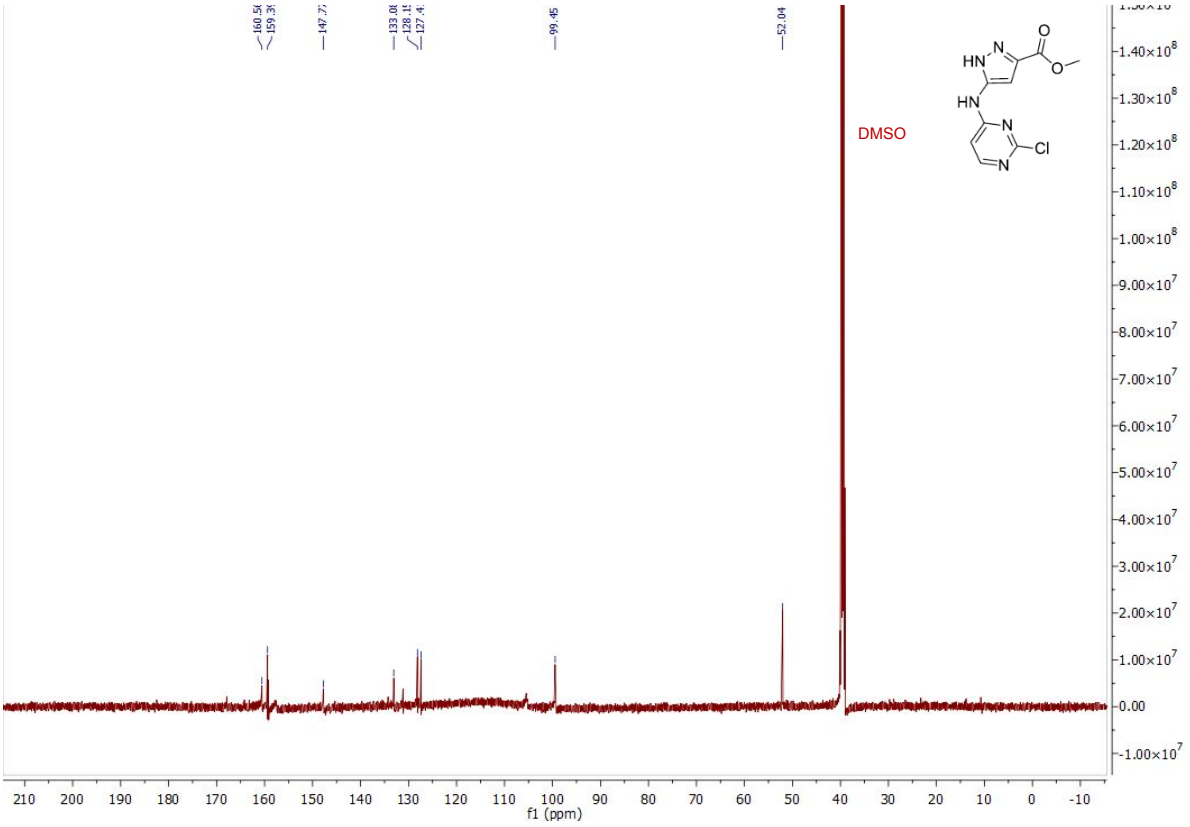
The title compound was prepared according to the procedure **8a**, using **7e** (31 mg, 0.10 mmol). The mixture was stirred for 16 h at 35 °C to obtain the product (5 mg, 17%) as a white solid. Molecular formula: $C_{14}H_{19}N_7O_1$. ^{1}H NMR (500 MHz, DMSO-d6) δ 13.35 (s, 1H), 11.01 (s, 1H), 8.25 (s, 1H), 8.00 (s, 1H), 7.83 (d, J = 6.9 Hz, 1H), 7.23 (s, 1H), 6.24 (d, J = 6.8 Hz, 1H), 3.28 – 3.25 (m, 4H), 1.60 – 1.53 (m, 2H), 1.52 – 1.46 (m, 2H), 1.42 – 1.34 (m, 3H), 1.31 – 1.21 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 161.33, 159.65, 154.90, 146.16, 145.27, 138.29, 102.55, 97.76, 42.01, 38.76, 29.61, 27.88, 27.64, 24.81. MS-ESI m/z $[M + H]^+$: calcd 302.4, found 302.5. HRMS m/z $[M + H]^+$: calcd 302.1724, found 302.1730. HPLC: t_R = 10.46, purity ≥ 95% (UV: 254/ 280 nm).

Analytical data of compounds **4 – 8e**.

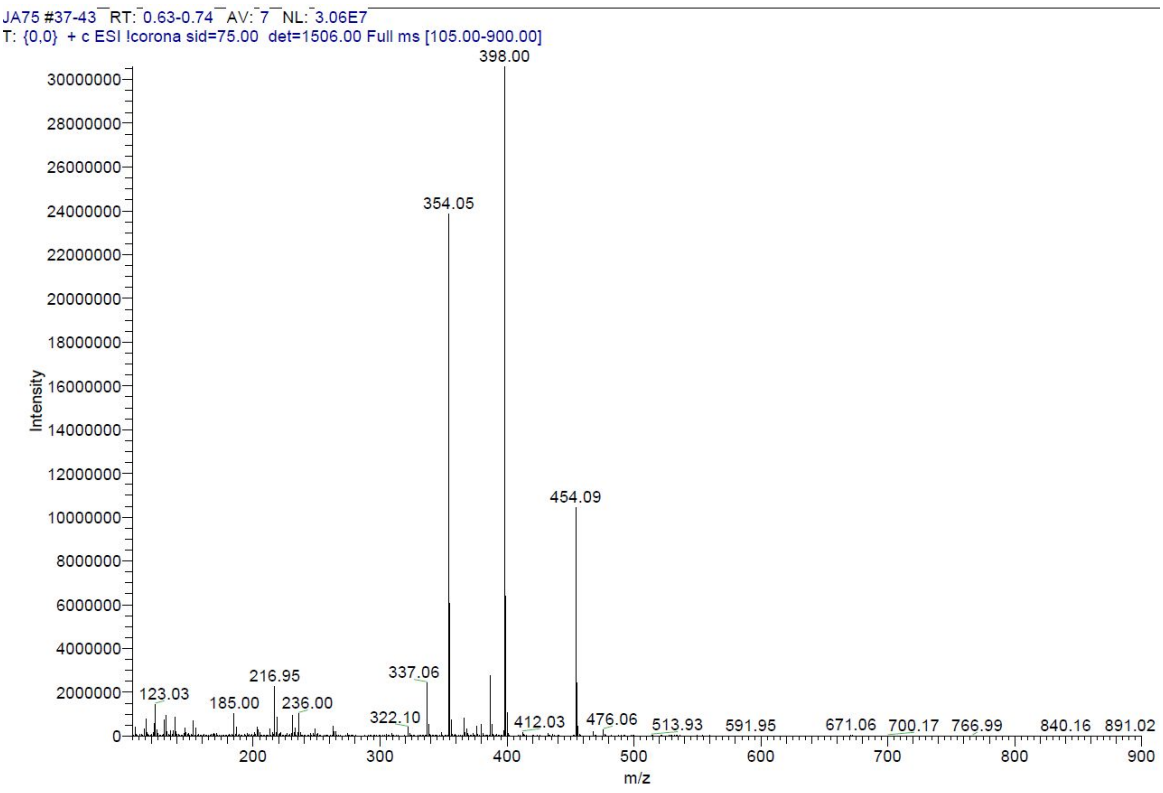
ESI, ^{1}H and ^{13}C NMR data of compound **4**.

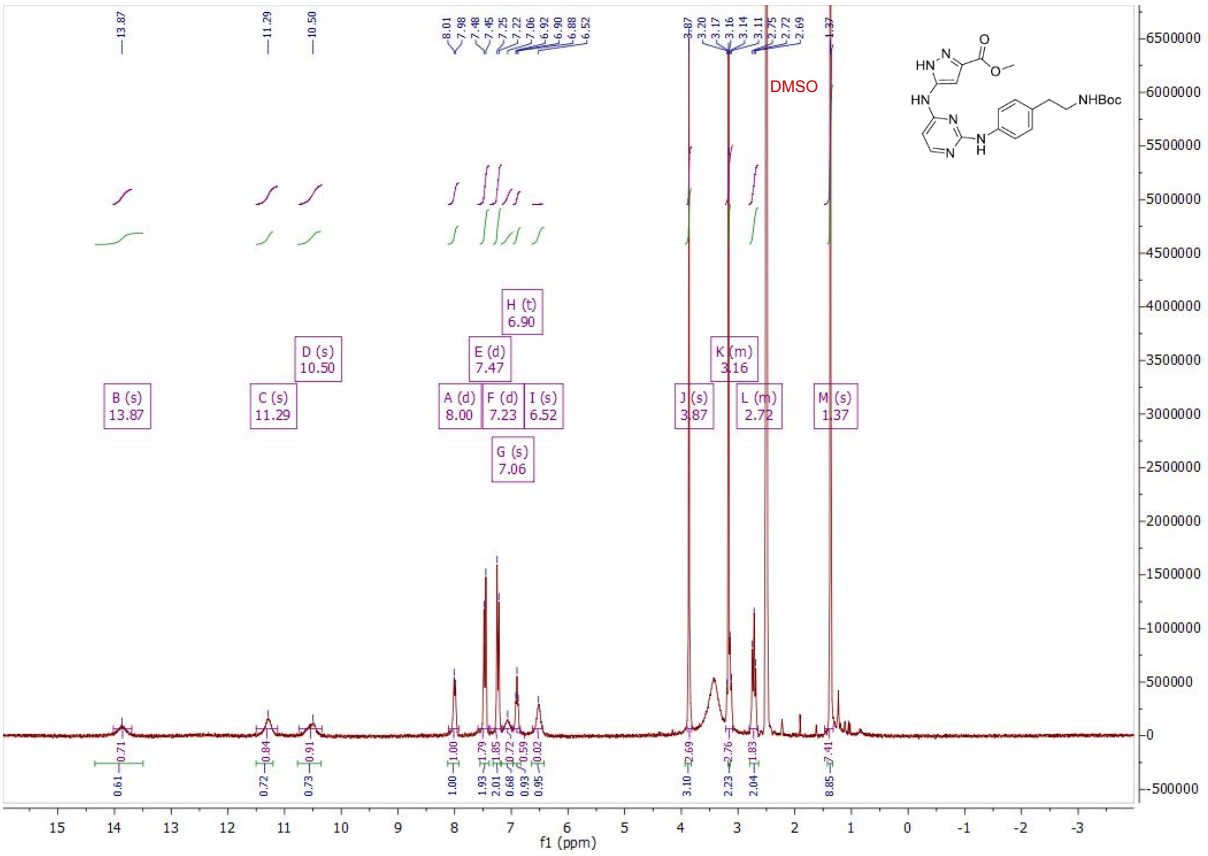


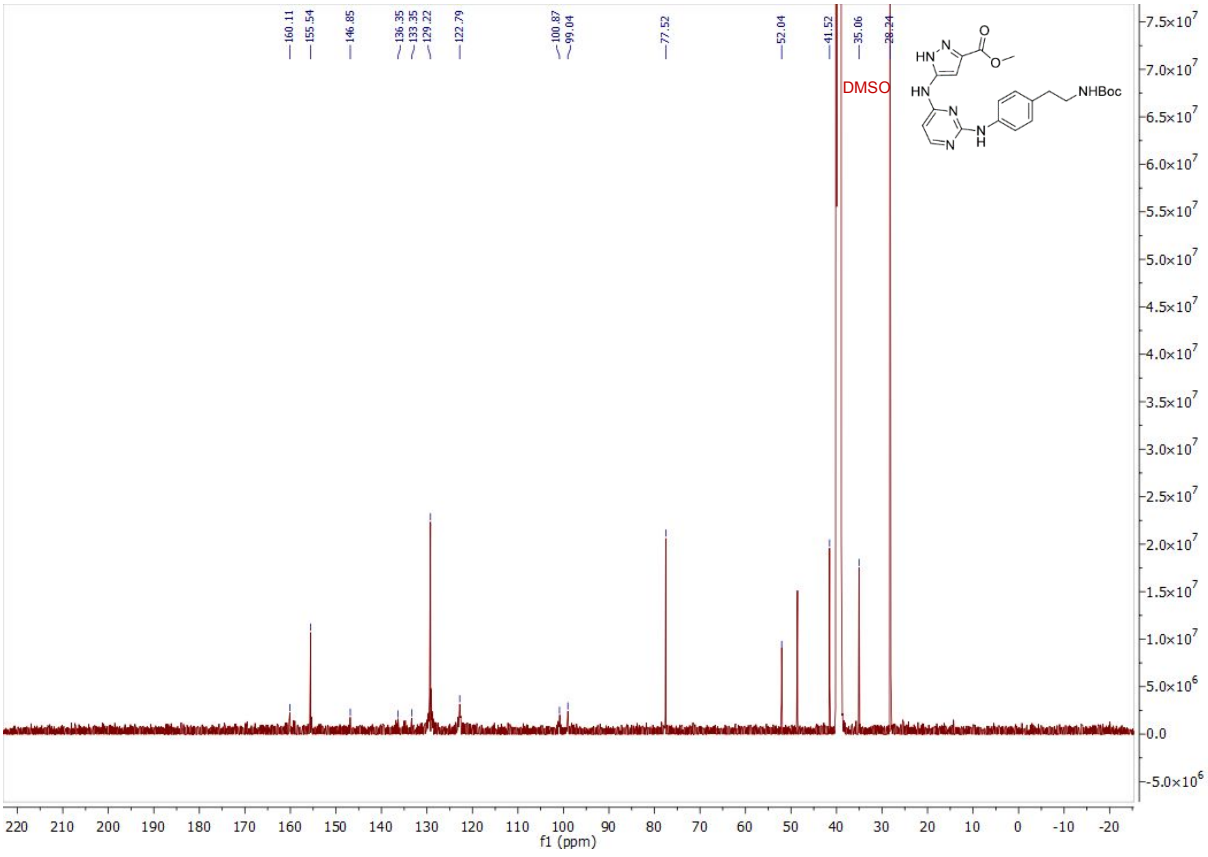


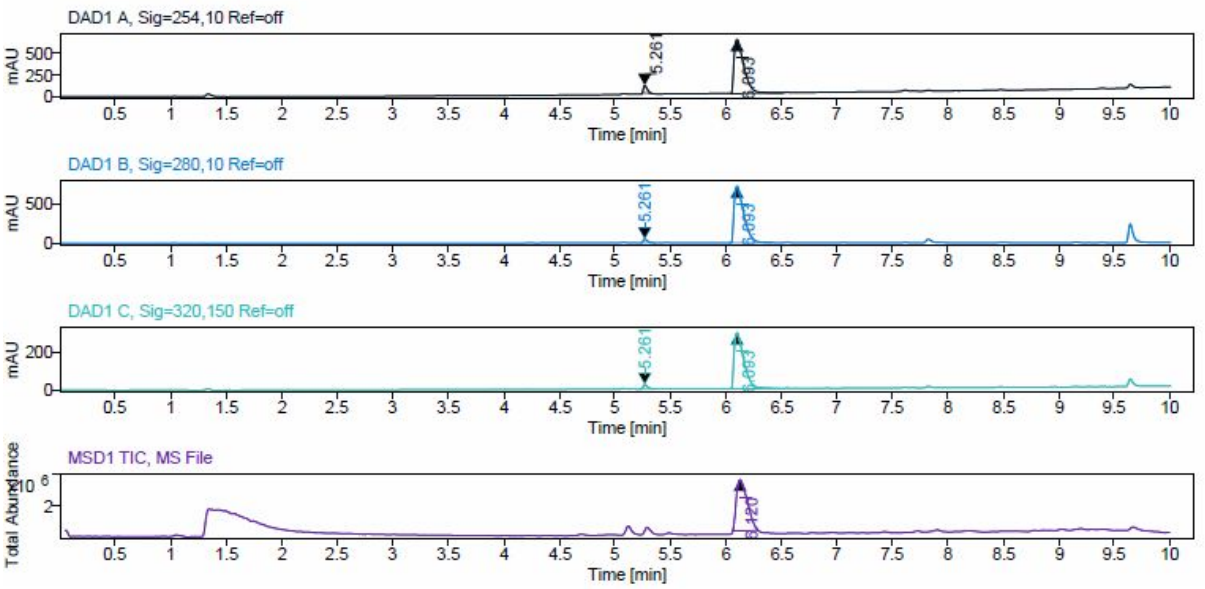


ESI, ^{1}H, ^{13}C NMR and HPLC data of compound **5a**.




DMSO
NHBoc
B (s) 13.87
C (s) 11.29
D (s) 10.50
A (d) 8.00
F (d) 7.23
I (s) 6.52
H (t) 6.90
E (d) 7.47
G (s) 7.06
J (s) 3.87
K (m) 3.16
L (m) 2.72
M (s) 1.37
f1 (ppm)


DMSO
NHBoc
f1 (ppm)



Sample Purity

Signal Description DAD1 A, Sig=254,10 Ref=off

Sample Name	Name	RT	Width	Area	Area%	Height
JA86		5.261	0.037	203.0431	4.92	89.4782
JA86		6.093	0.093	3921.0303	95.08	629.5381

Max Area% 95.077

UV Signal Purity>95% Pass

Signal Description DAD1 B, Sig=280,10 Ref=off

Sample Name	Name	RT	Width	Area	Area%	Height
JA86		5.261	0.040	122.6163	2.71	46.4638
JA86		6.093	0.093	4409.0713	97.29	732.4024

Max Area% 97.294

UV Signal Purity>95% Pass

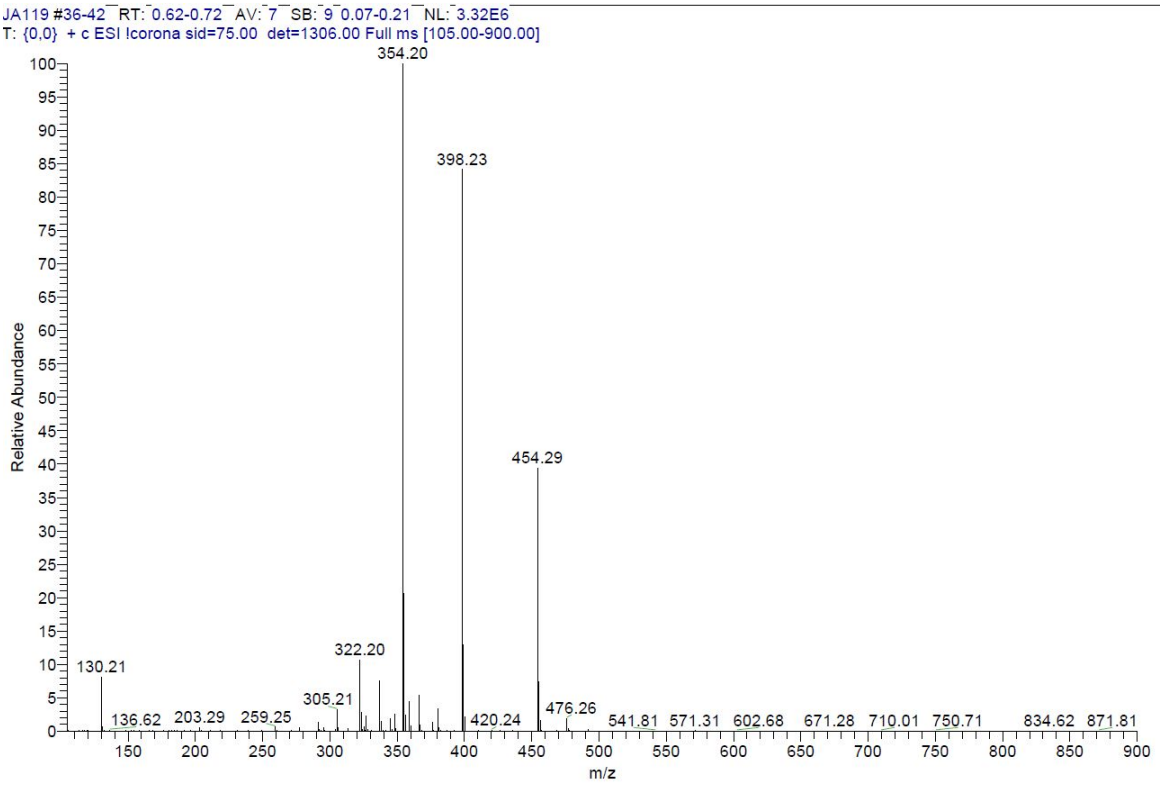
Signal Description DAD1 C, Sig=320,150 Ref=off

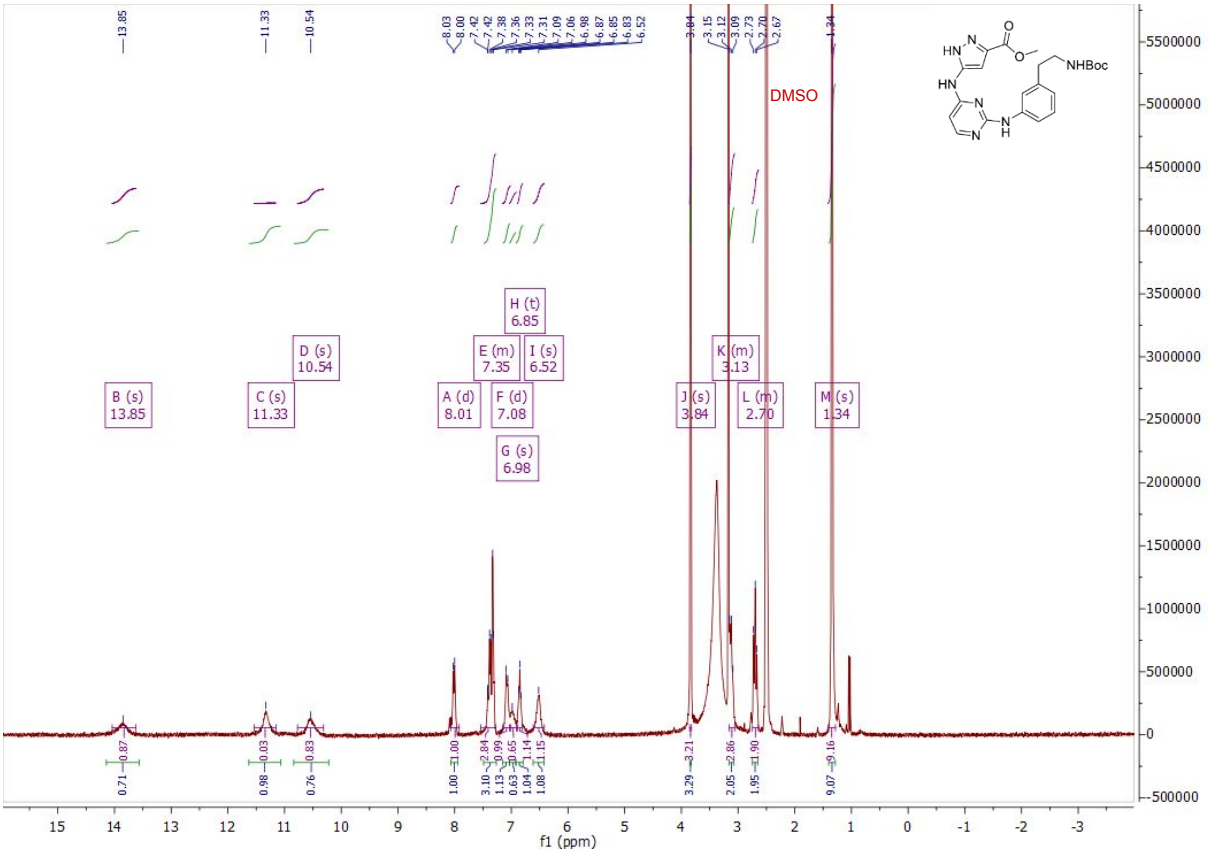
Sample Name	Name	RT	Width	Area	Area%	Height
JA86		5.261	0.041	68.8697	3.56	24.5446
JA86		6.093	0.093	1865.4775	96.44	307.2874

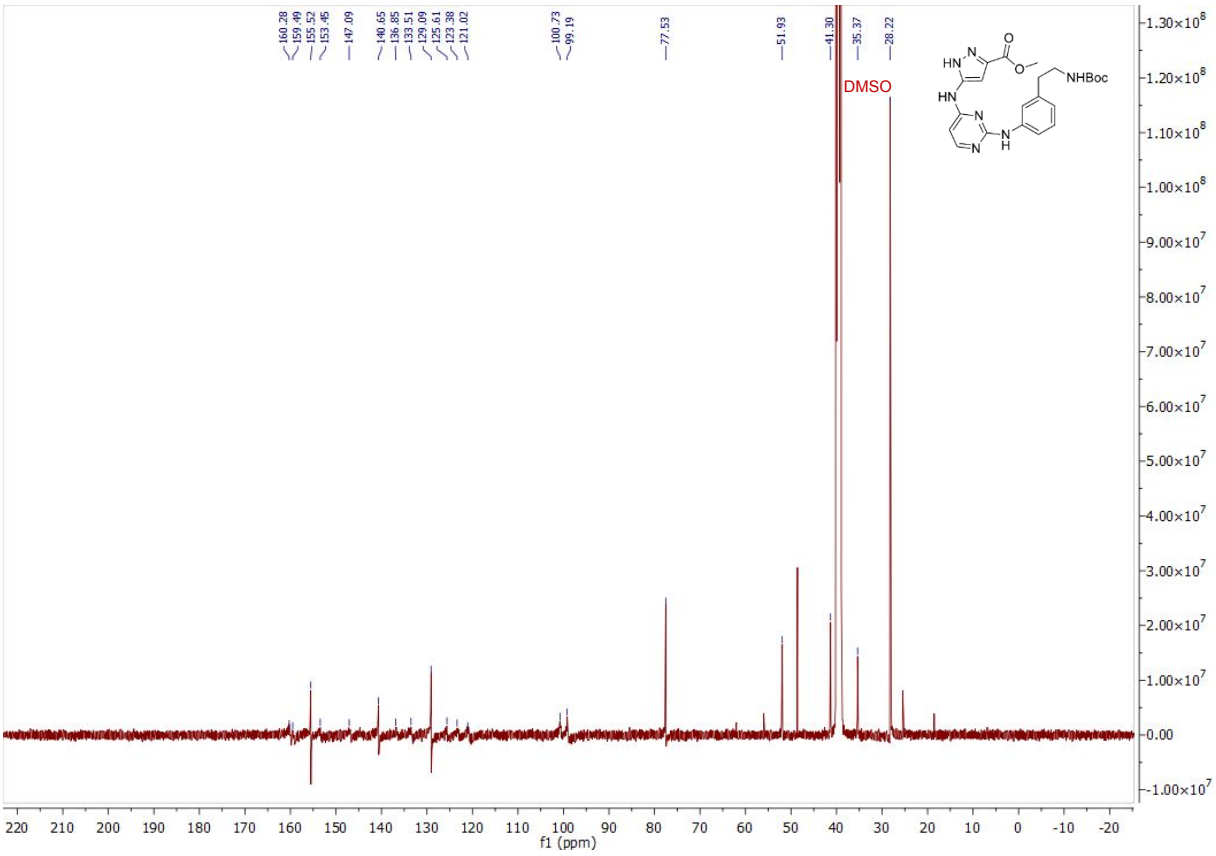
Max Area% 96.440

UV Signal Purity>95% Pass

ESI, ^{1}H, ^{13}C NMR and HPLC data of compound **5b**.



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159.49
155.52
153.45
147.09
140.65
136.85
133.51
129.09
125.61
123.38
121.02
100.73
99.19
77.53
51.93
41.30
39.37
28.22
DMSO
HN
N
O
O
NHBoc
HN
N
N
H
1.30×10^8
1.20×10^8
1.10×10^8
1.00×10^8
9.00×10^7
8.00×10^7
7.00×10^7
6.00×10^7
5.00×10^7
4.00×10^7
3.00×10^7
2.00×10^7
1.00×10^7
0.00
-1.00×10^7
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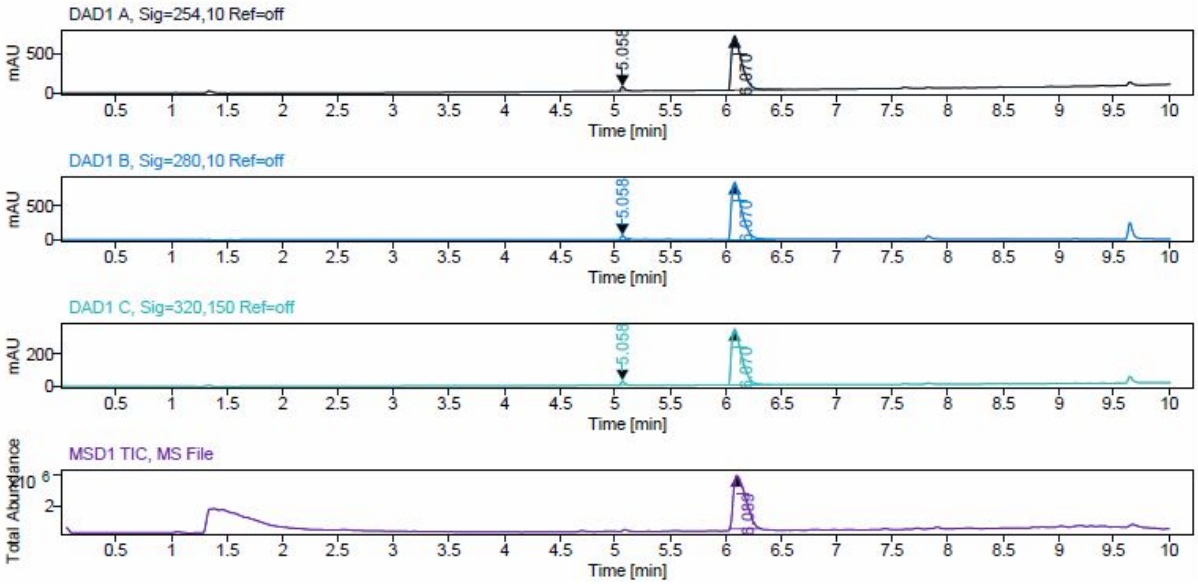
f1 (ppm)



Sample Purity

Signal Description DAD1 A, Sig=254,10 Ref=off

Sample Name	Name	RT	Width	Area	Area%	Height
JA119		5.058	0.034	126.3551	2.73	58.4173
JA119		6.070	0.100	4507.8599	97.27	702.8458

Max Area% 97.273

UV Signal Purity>95% Pass

Signal Description DAD1 B, Sig=280,10 Ref=off

Sample Name	Name	RT	Width	Area	Area%	Height
JA119		5.058	0.033	119.3543	2.15	54.4841
JA119		6.070	0.099	5443.5239	97.85	838.2568

Max Area% 97.854

UV Signal Purity>95% Pass

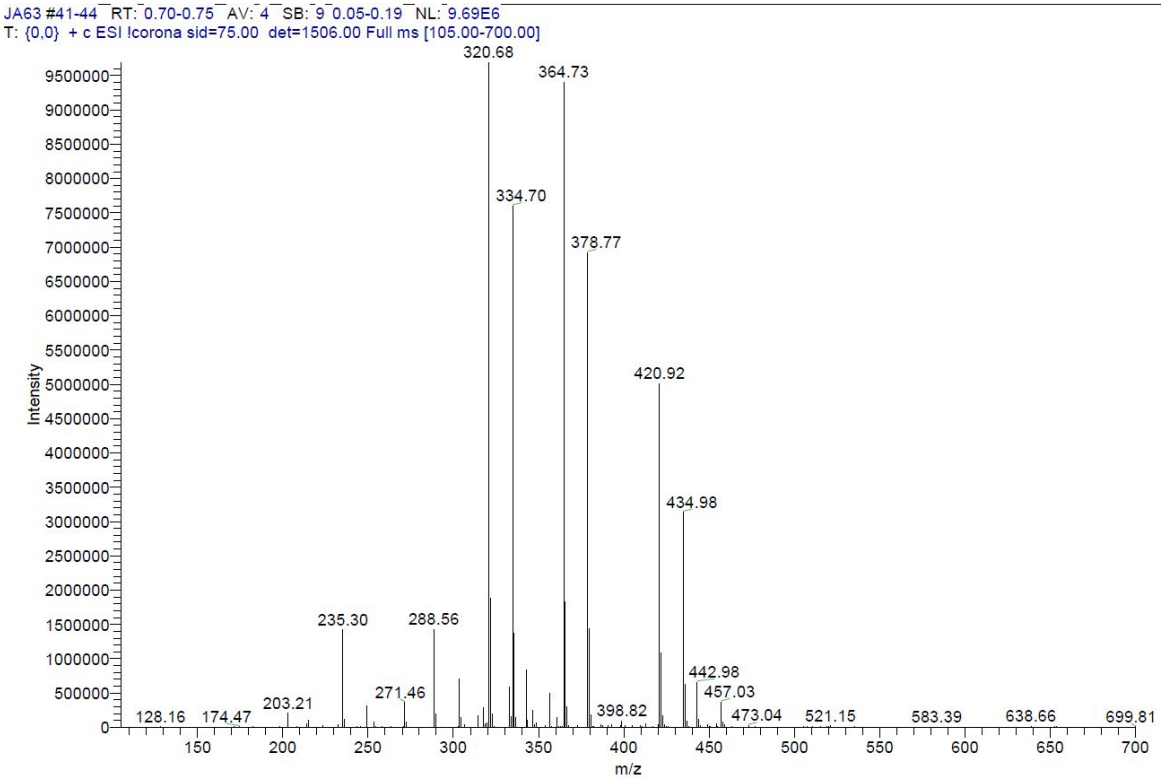
Signal Description DAD1 C, Sig=320,150 Ref=off

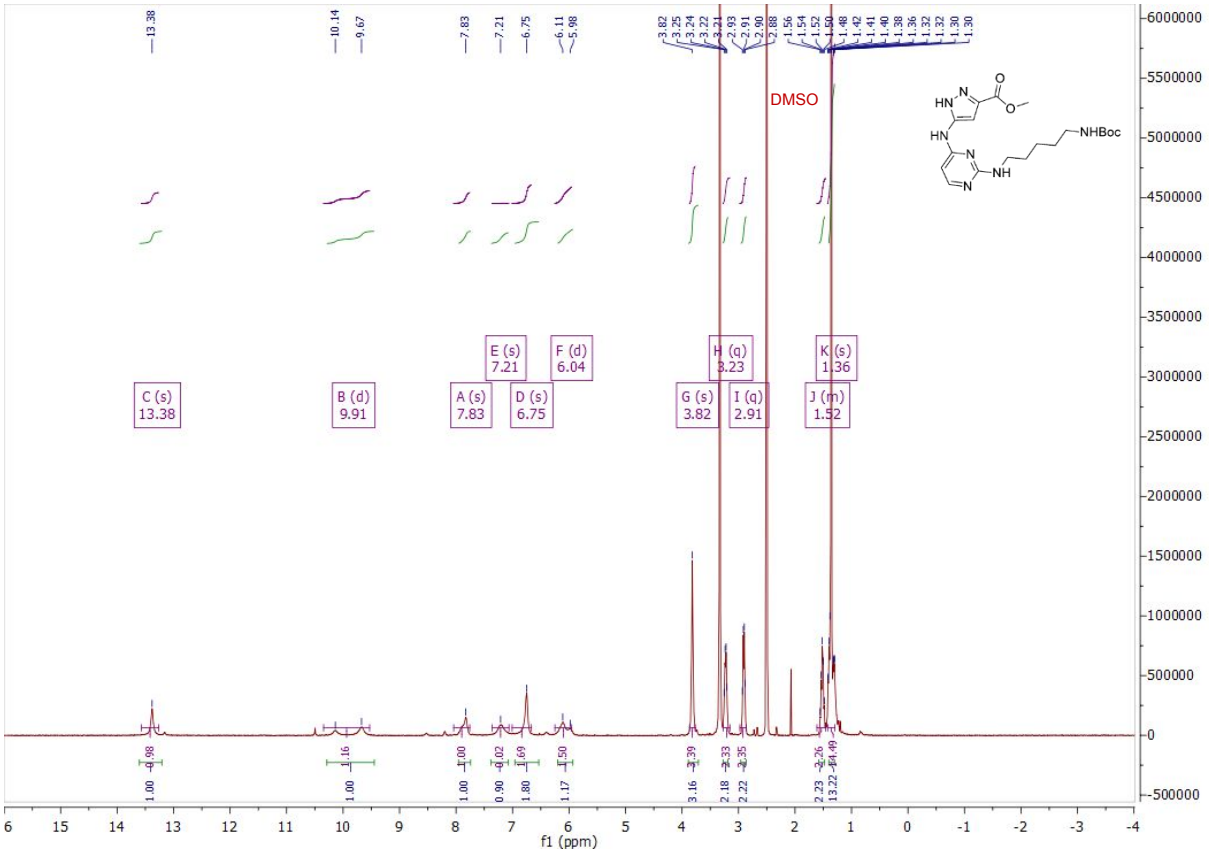
Sample Name	Name	RT	Width	Area	Area%	Height
JA119		5.058	0.035	63.1891	2.70	27.0492
JA119		6.070	0.100	2277.7769	97.30	352.8789

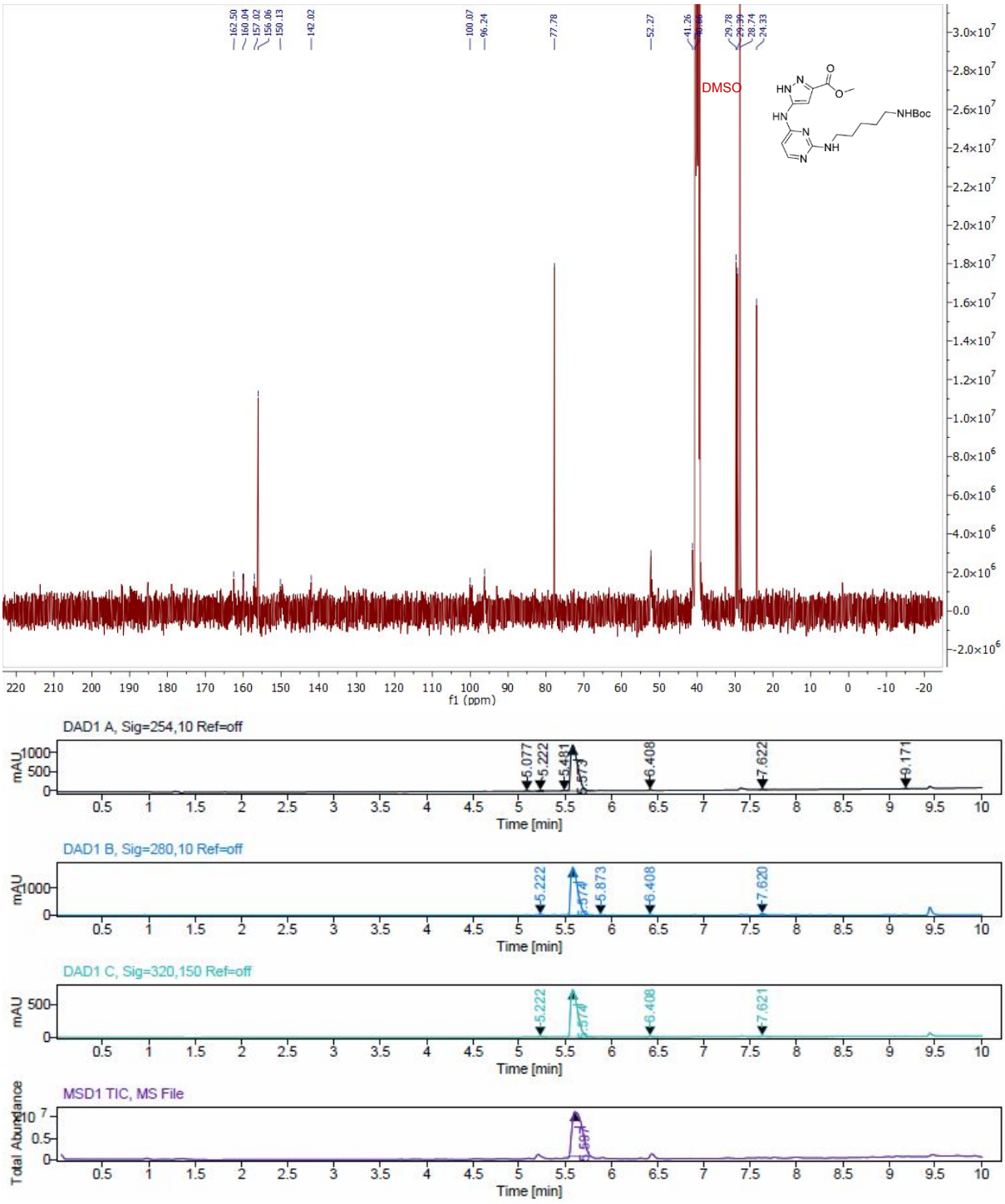
Max Area% 97.301

UV Signal Purity>95% Pass

ESI, ^{1}H, ^{13}C NMR and HPLC data of compound **5c**.






DMSO
NHBoc
f1 (ppm)
DAD1 A, Sig=254,10 Ref=off
DAD1 B, Sig=280,10 Ref=off
DAD1 C, Sig=320,150 Ref=off
MSD1 TIC, MS File
Time [min]
mAU
Total Abundance

Sample Purity

Signal Description DAD1 A, Sig=254,10 Ref=off

Sample Name	Name	RT	Width	Area	Area%	Height
JA103_prep_f14		5.077	0.045	38.5699	0.59	15.0074
JA103_prep_f14		5.222	0.037	45.0486	0.69	20.1107
JA103_prep_f14		5.481	0.051	35.7459	0.54	12.2971
JA103_prep_f14		5.573	0.085	6298.5713	95.97	1187.9170
JA103_prep_f14		6.408	0.032	66.7007	1.02	31.0731
JA103_prep_f14		7.622	0.051	45.3789	0.69	13.4217
JA103_prep_f14		9.171	0.045	33.1855	0.51	13.6909

Max Area% 95.968
UV Signal Purity>95% Pass

Signal Description DAD1 B, Sig=280,10 Ref=off

Sample Name	Name	RT	Width	Area	Area%	Height
JA103_prep_f14		5.222	0.033	34.3728	0.35	16.0165
JA103_prep_f14		5.574	0.085	9455.1982	97.52	1790.9185
JA103_prep_f14		5.873	0.031	23.3287	0.24	10.3943
JA103_prep_f14		6.408	0.032	34.2773	0.35	14.8231
Sample Name	**Name**	**RT**	**Width**	**Area**	**Area%**	**Height**
JA103_prep_f14		7.620	0.042	148.5687	1.53	53.3182

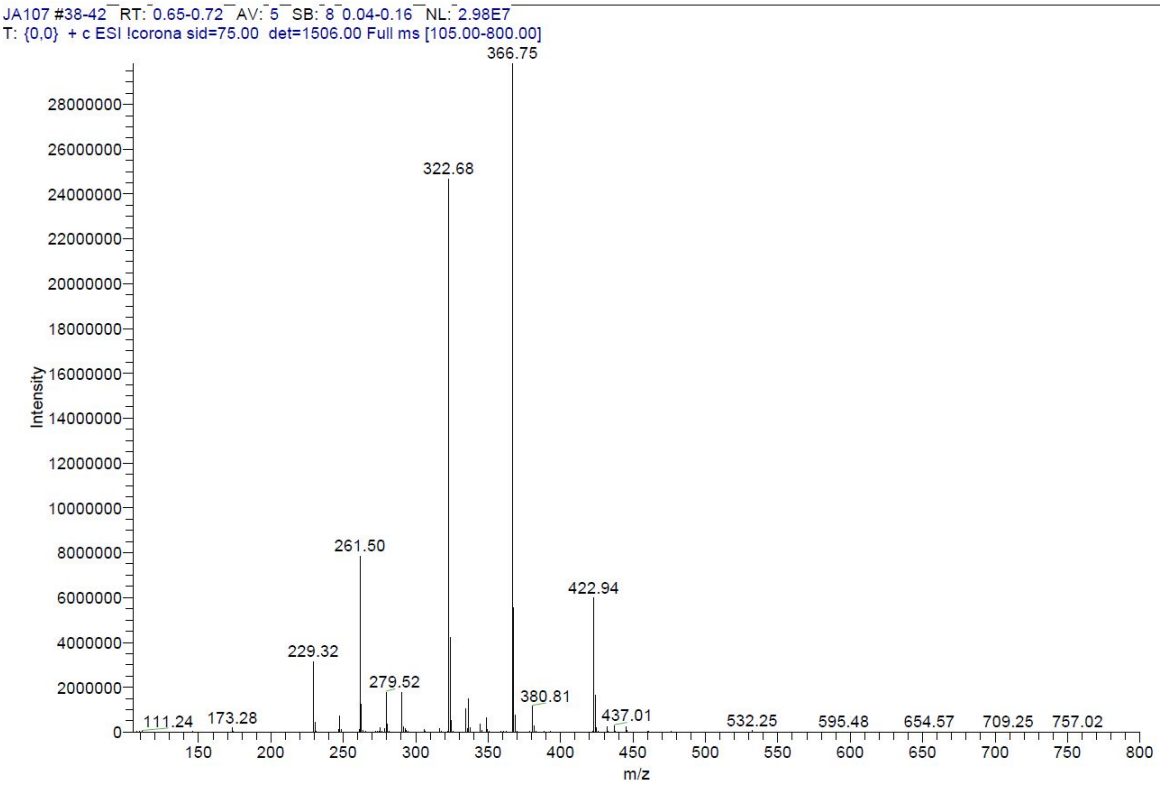
Max Area% 97.519
UV Signal Purity>95% Pass

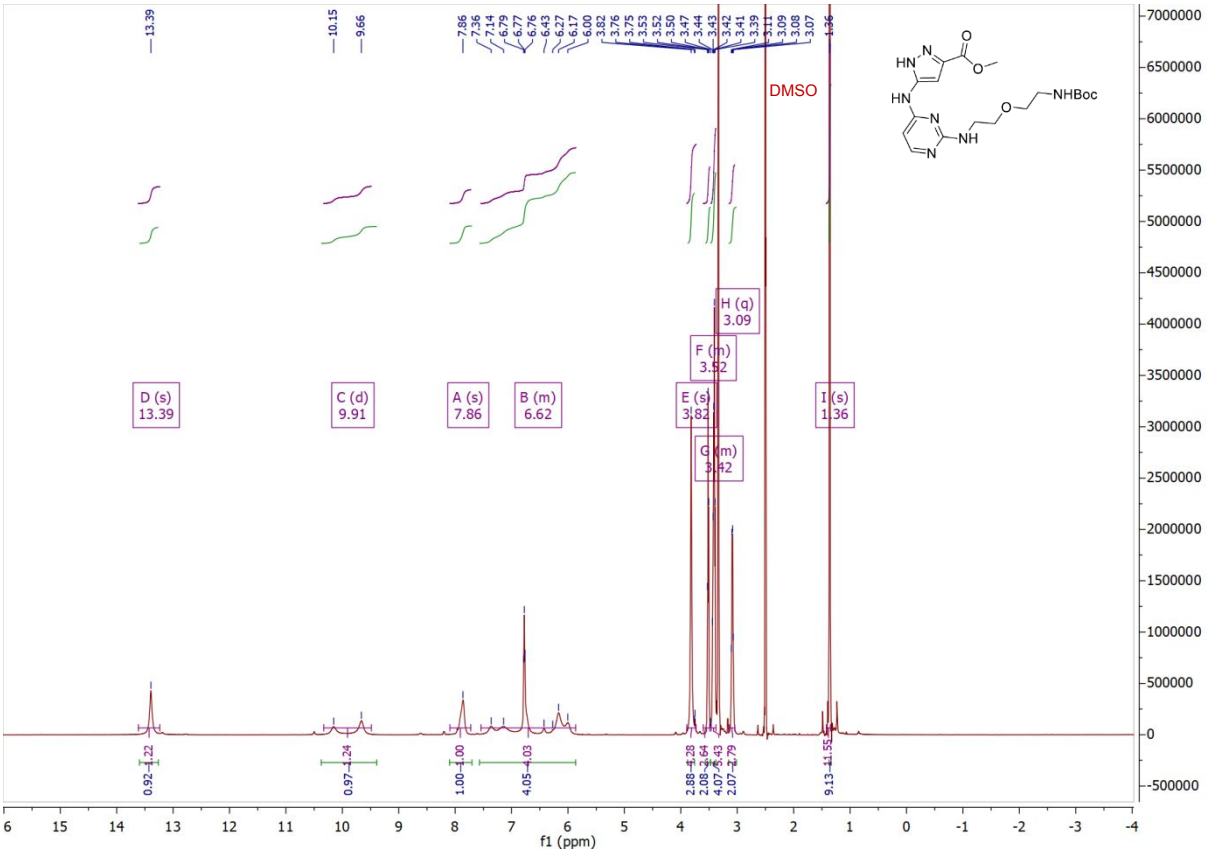
Signal Description DAD1 C, Sig=320,150 Ref=off

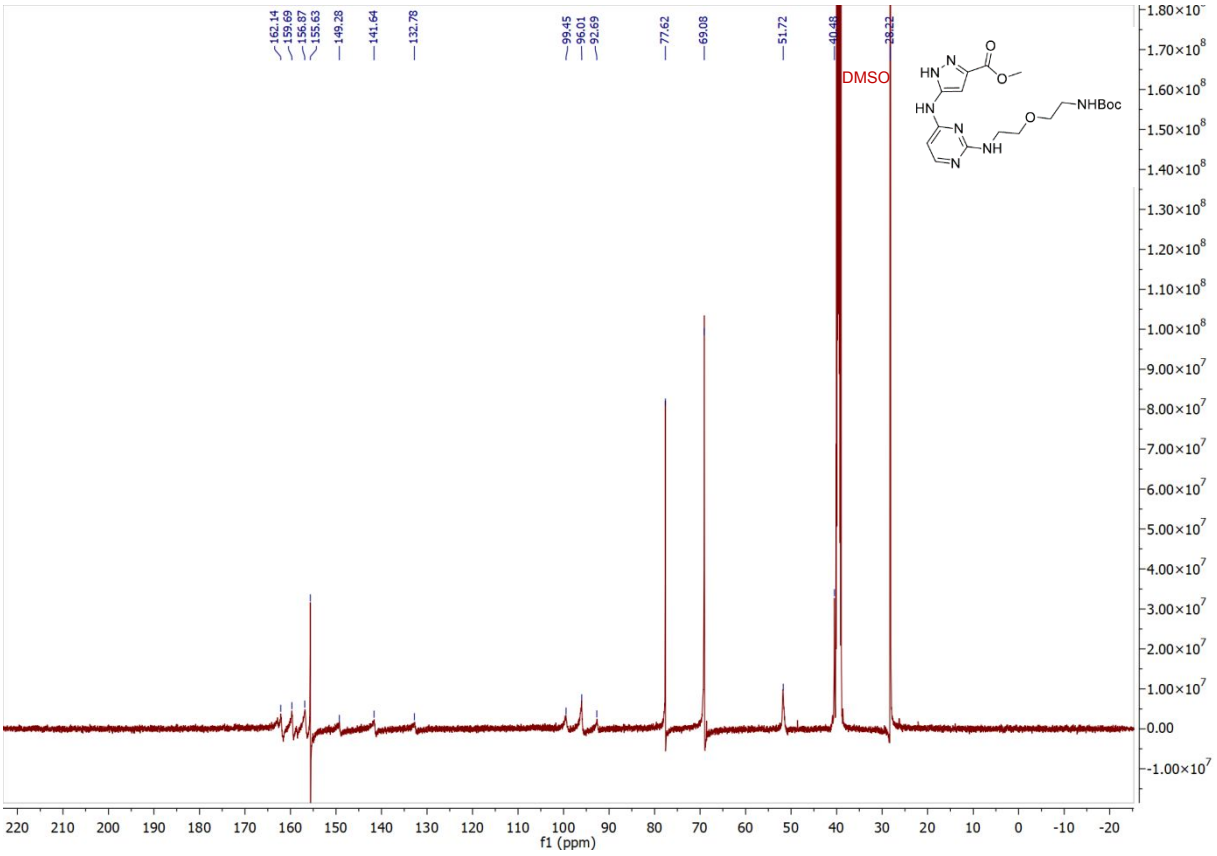
Sample Name	Name	RT	Width	Area	Area%	Height
JA103_prep_f14		5.222	0.033	16.8287	0.44	7.7458
JA103_prep_f14		5.574	0.086	3789.2156	98.13	718.6230
JA103_prep_f14		6.408	0.033	28.5044	0.74	12.9056
JA103_prep_f14		7.621	0.042	26.7143	0.69	9.4558

Max Area% 98.134
UV Signal Purity>95% Pass

ESI, ^{1}H, ^{13}C NMR and HPLC data of compound **5d**.



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155.63
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141.64
132.78
99.45
96.01
92.69
77.62
69.08
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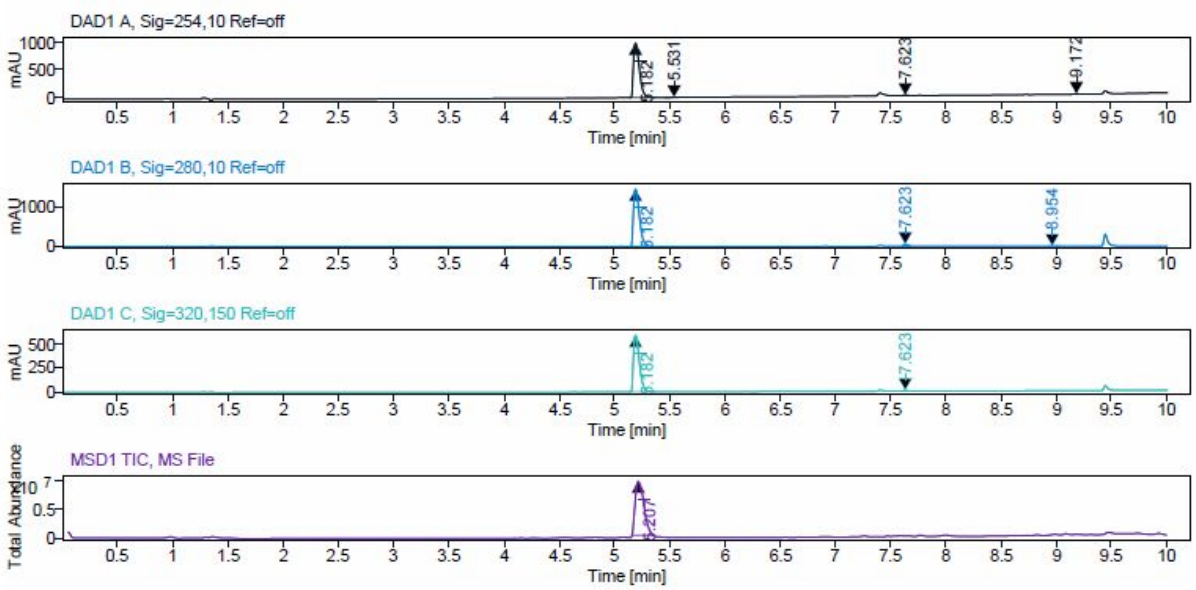
O
HN
N
O
NHBoc
N
NH
f1 (ppm)



Sample Purity

Signal Description DAD1 A, Sig=254,10 Ref=off

Sample Name	Name	RT	Width	Area	Area%	Height
JA107_prepF1		5.182	0.059	3622.2283	98.01	971.3520
JA107_prepF1		5.531	0.037	15.2247	0.41	6.1775
JA107_prepF1		7.623	0.043	31.5078	0.85	11.2794
JA107_prepF1		9.172	0.036	26.8967	0.73	11.0198

Max Area% 98.008

UV Signal Purity>95% Pass

Signal Description DAD1 B, Sig=280,10 Ref=off

Sample Name	Name	RT	Width	Area	Area%	Height
JA107_prepF1		5.182	0.059	5476.6074	97.28	1467.6888
JA107_prepF1		7.623	0.040	127.1096	2.26	50.6332
JA107_prepF1		8.954	0.038	25.9763	0.46	10.3502

Max Area% 97.281

UV Signal Purity>95% Pass

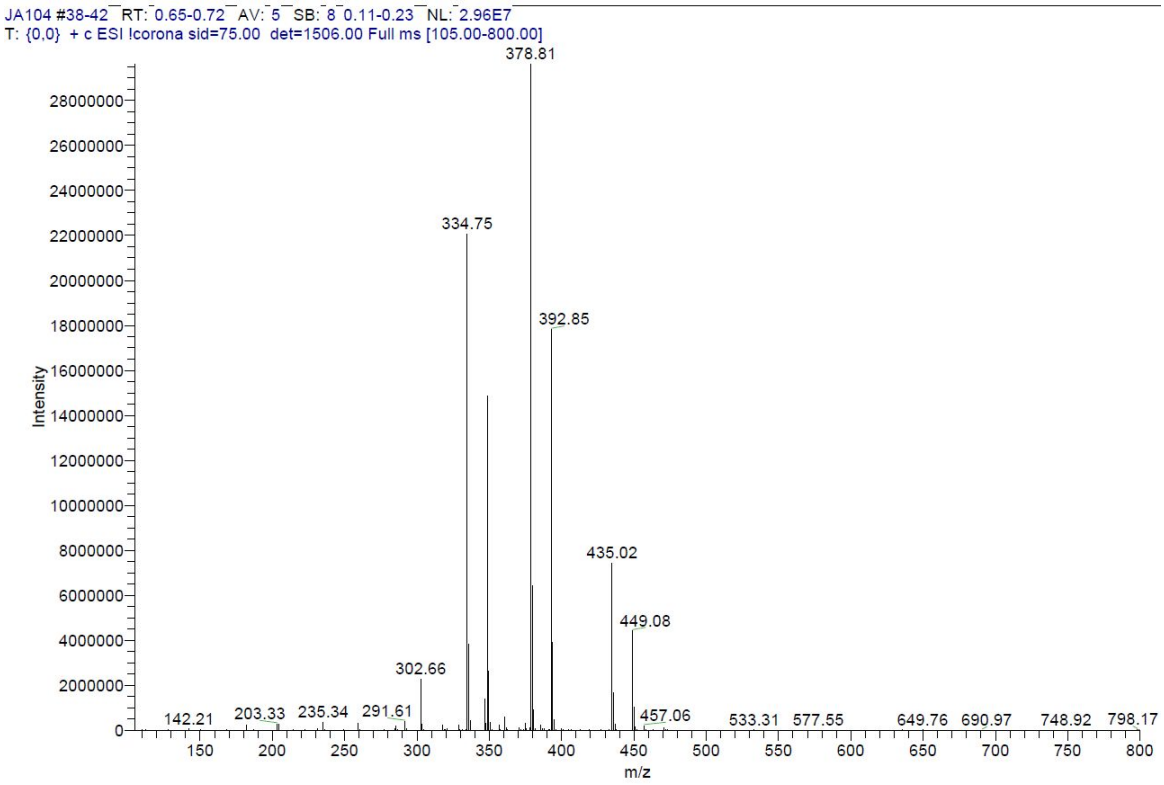
Signal Description DAD1 C, Sig=320,150 Ref=off

Sample Name	Name	RT	Width	Area	Area%	Height
JA107_prepF1		5.182	0.059	2234.7620	98.84	598.5150
JA107_prepF1		7.623	0.043	26.2908	1.16	9.6527

Max Area% 98.837

UV Signal Purity>95% Pass

ESI, ^{1}H, ^{13}C NMR and HPLC data of compound **5e**.


JA104 #38-42 RT: 0.65-0.72 AV: 5 SB: 8 0.11-0.23 NL: 2.96E7
T: {0,0} + c ESI !corona sid=75.00 det=1506.00 Full ms [105.00-800.00]
Intensity
m/z
378.81
334.75
392.85
435.02
449.08
302.66
457.06
142.21
203.33
235.34
291.61
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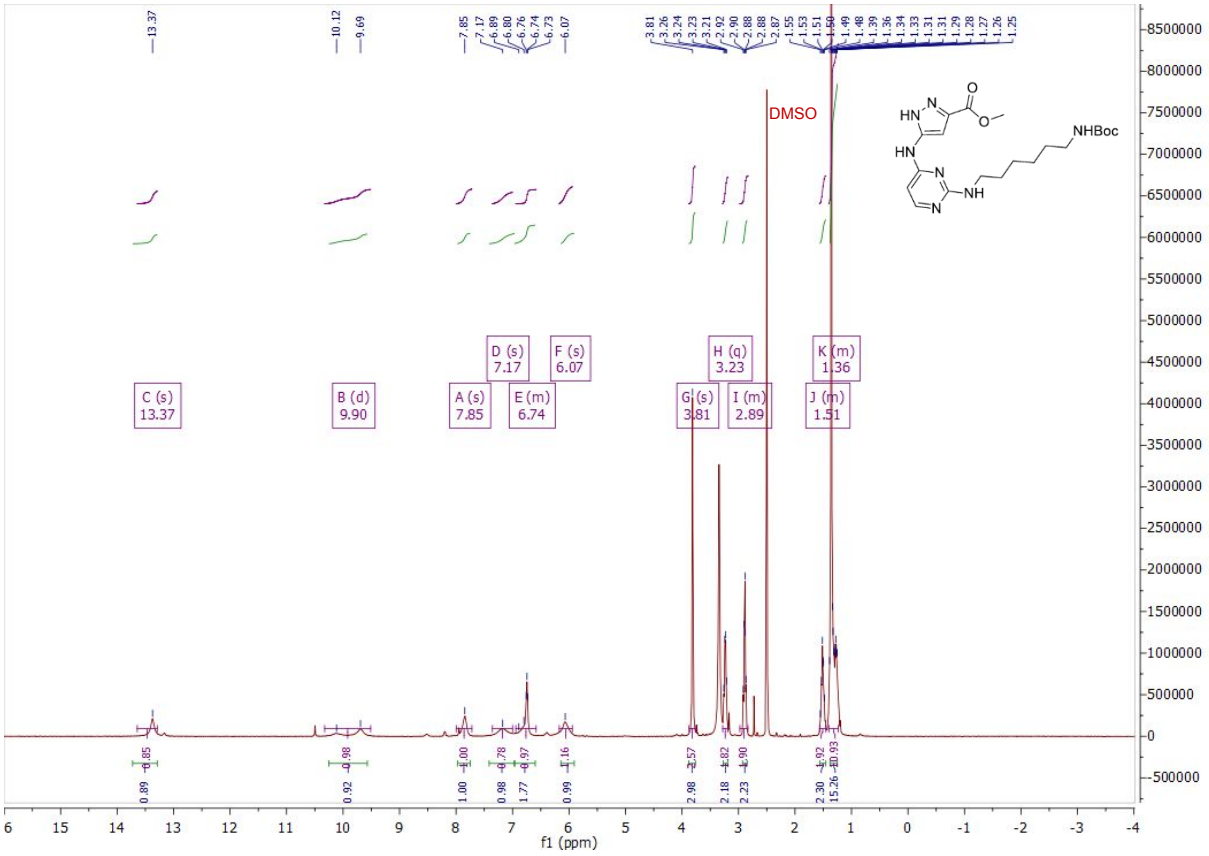
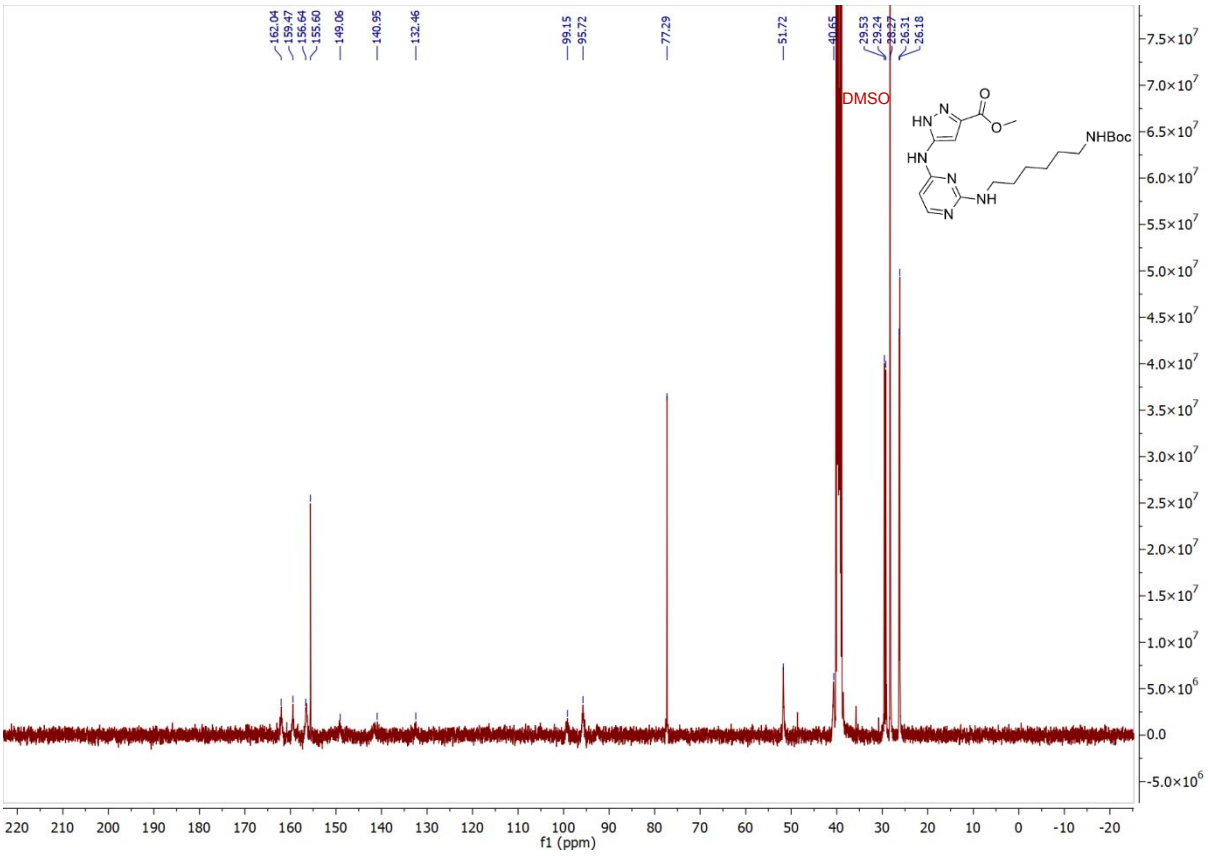
577.55
649.76
690.97
748.92
798.17


DMSO
NHBoc
C (s) 13.37
B (d) 9.90
A (s) 7.85
E (m) 6.74
D (s) 7.17
F (s) 6.07
G (s) 3.81
I (m) 2.89
H (q) 3.23
J (m) 1.51
K (m) 1.36
f1 (ppm)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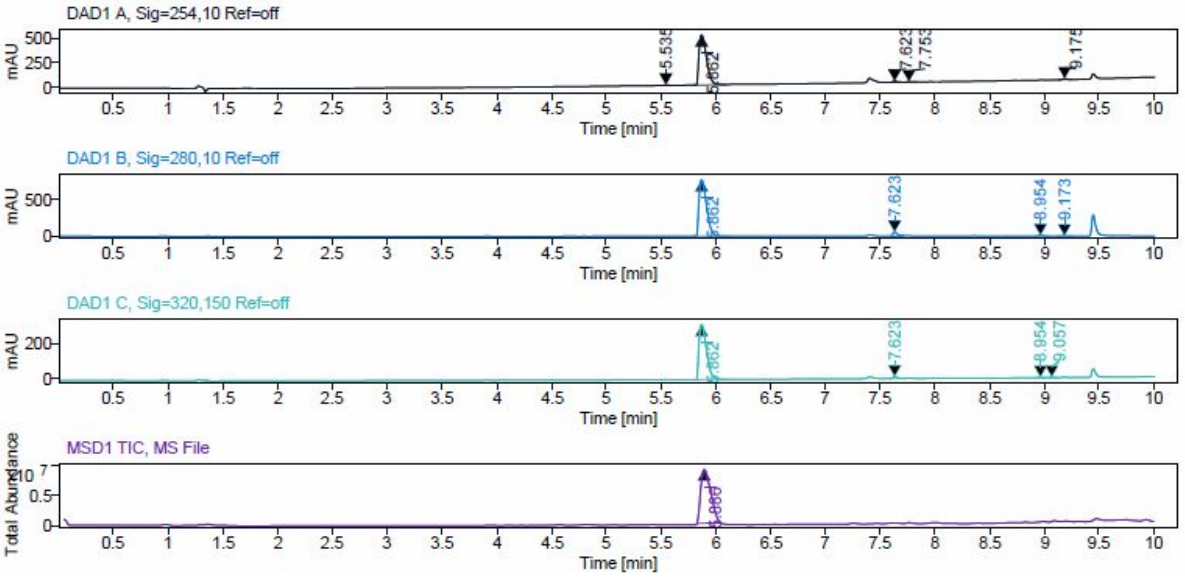
95.72
77.29
51.72
40.65
29.53
29.24
28.27
26.31
26.18
DMSO
HN
N
O
O
HN
NHBoc
N
NH
N
7.5×10^7
7.0×10^7
6.5×10^7
6.0×10^7
5.5×10^7
5.0×10^7
4.5×10^7
4.0×10^7
3.5×10^7
3.0×10^7
2.5×10^7
2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0
-5.0×10^6
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)



Sample Purity

Signal Description DAD1 A, Sig=254,10 Ref=off

Sample Name	Name	RT	Width	Area	Area%	Height
JA104_prep_F16		5.535	0.043	12.0778	0.49	4.3697
JA104_prep_F16		5.862	0.077	2387.1487	96.52	503.9031
JA104_prep_F16		7.623	0.044	31.3098	1.27	10.9434
JA104_prep_F16		7.753	0.043	12.9726	0.52	4.7900
JA104_prep_F16		9.175	0.038	29.5919	1.20	11.8123

Max Area% 96.525

UV Signal Purity>95% Pass

Signal Description DAD1 B, Sig=280,10 Ref=off

Sample Name	Name	RT	Width	Area	Area%	Height
JA104_prep_F16		5.862	0.075	3681.2483	95.67	775.2848
JA104_prep_F16		7.623	0.042	134.1460	3.49	49.4574
JA104_prep_F16		8.954	0.039	23.7454	0.62	9.2409
JA104_prep_F16		9.173	0.041	8.7145	0.23	2.9845

Max Area% 95.670

UV Signal Purity>95% Pass

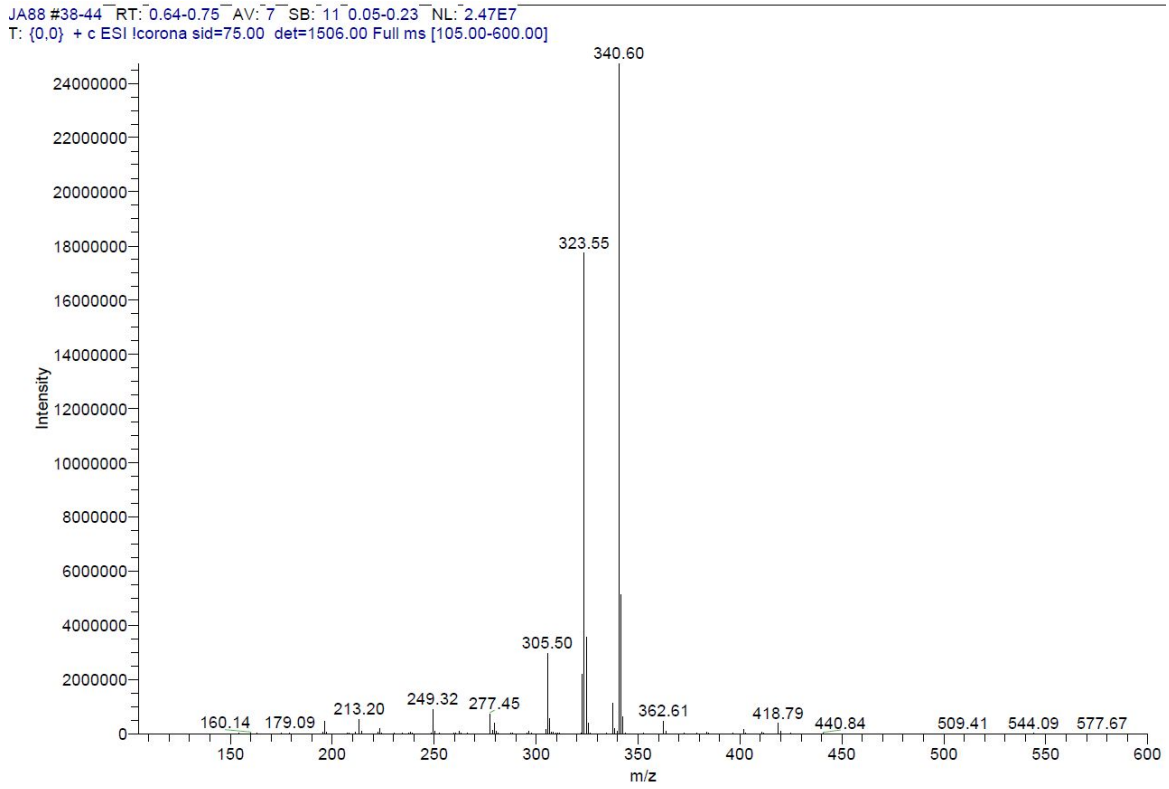
Signal Description DAD1 C, Sig=320,150 Ref=off

Sample Name	Name	RT	Width	Area	Area%	Height
JA104_prep_F16		5.862	0.076	1472.0709	97.47	310.0414
JA104_prep_F16		7.623	0.044	26.6122	1.76	9.2569
JA104_prep_F16		8.954	0.041	6.2512	0.41	2.4823
JA104_prep_F16		9.057	0.034	5.3317	0.35	2.4078

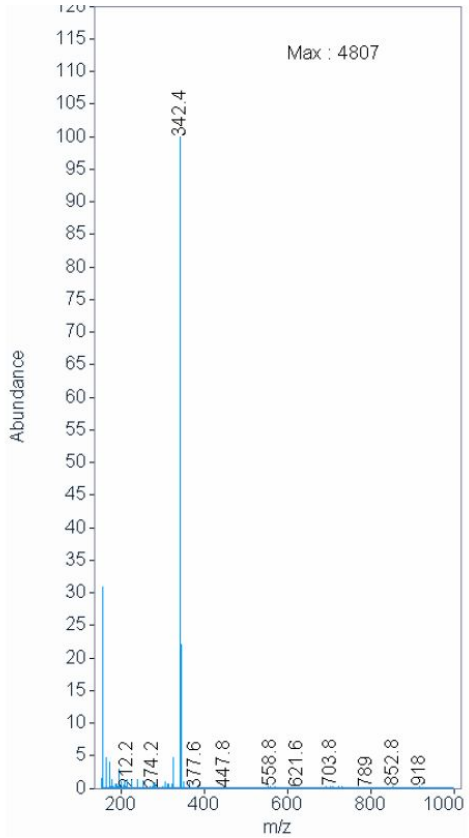
Max Area% 97.471

UV Signal Purity>95% Pass

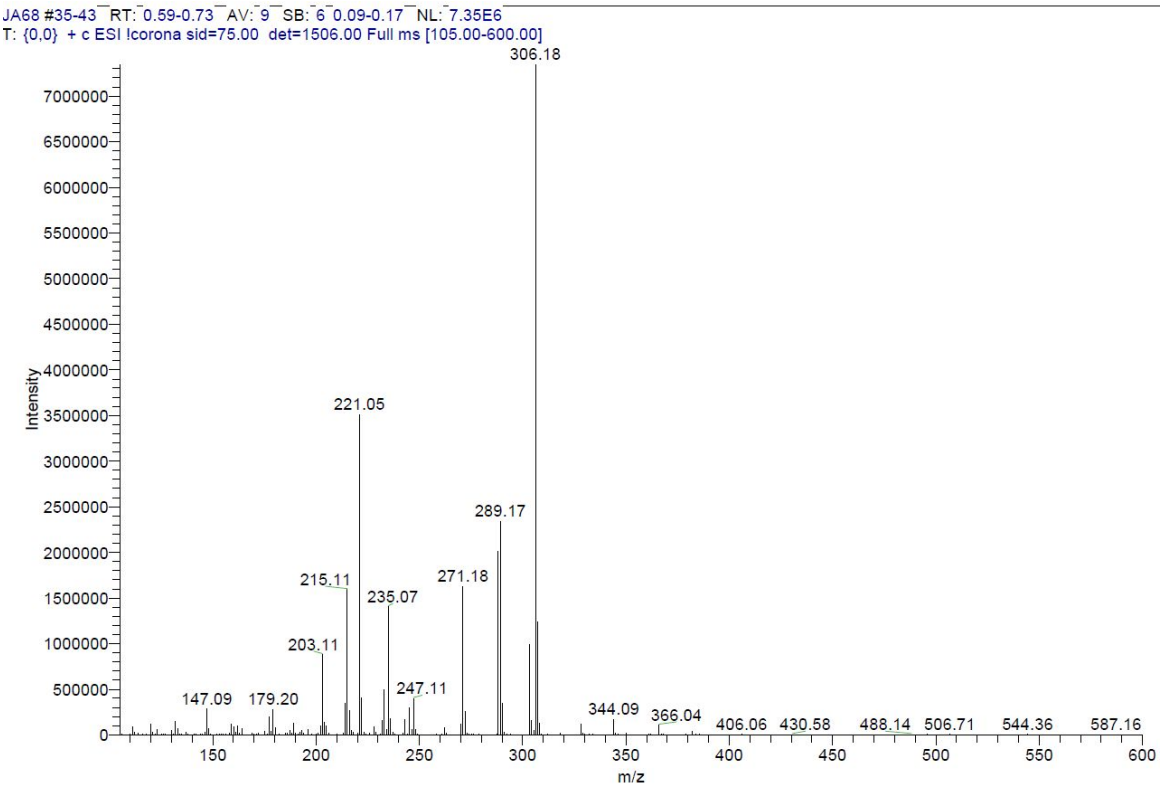
ESI data of compound **7a**.



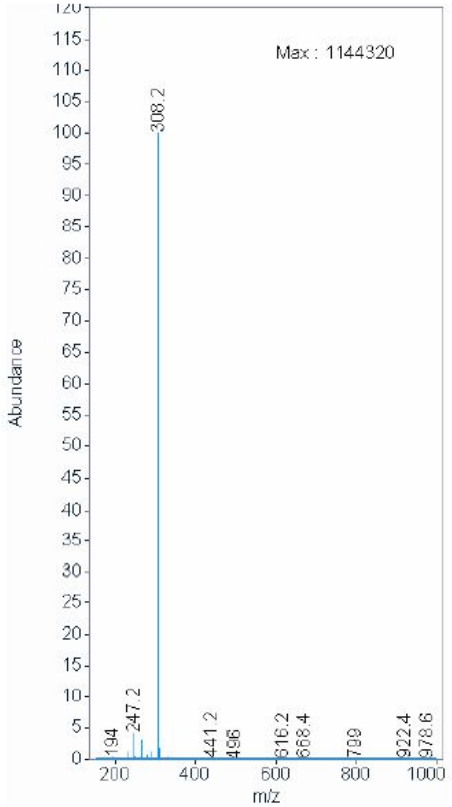
ESI data of compound **7b**.



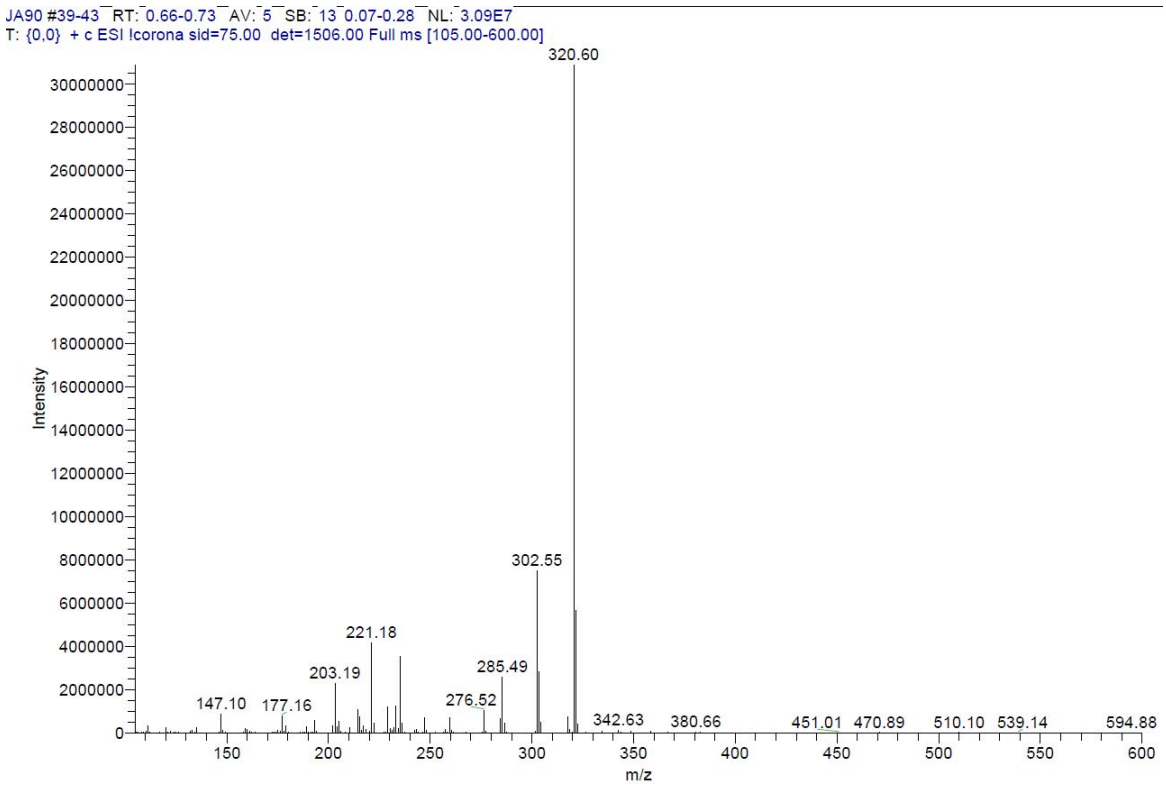
ESI data of compound **7c**.



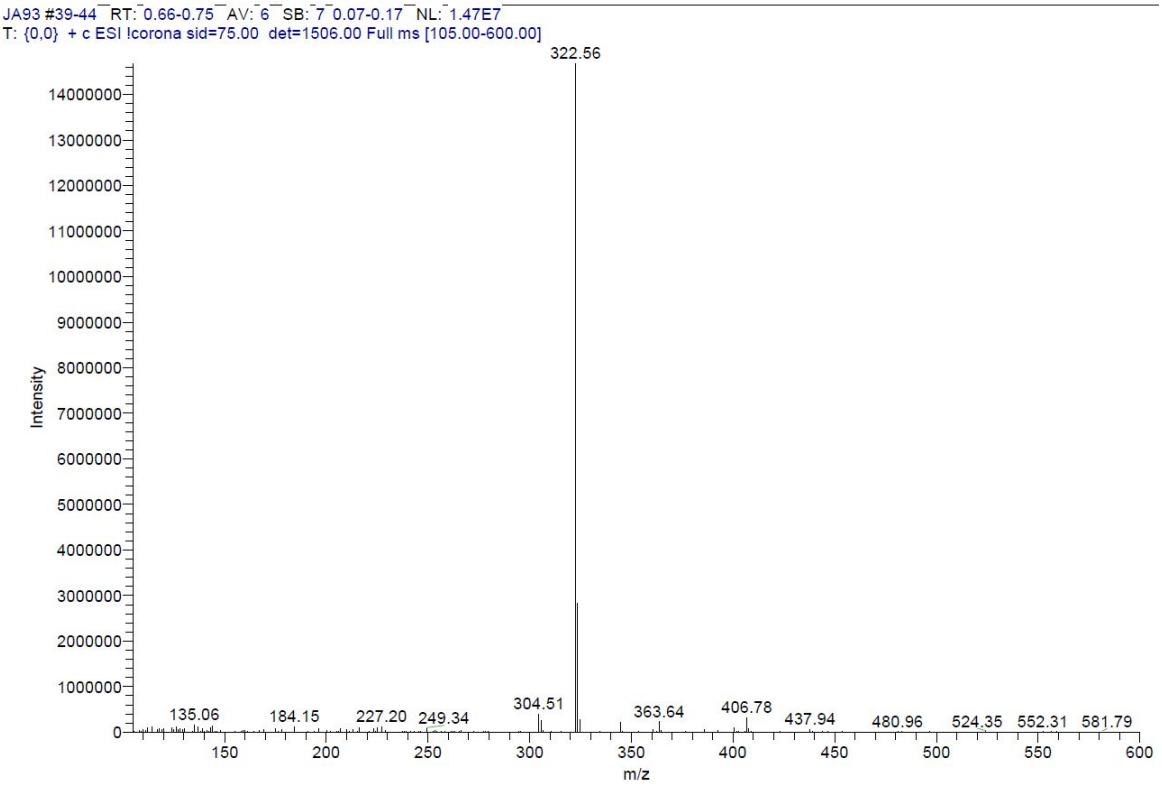
ESI data of compound **7d**.

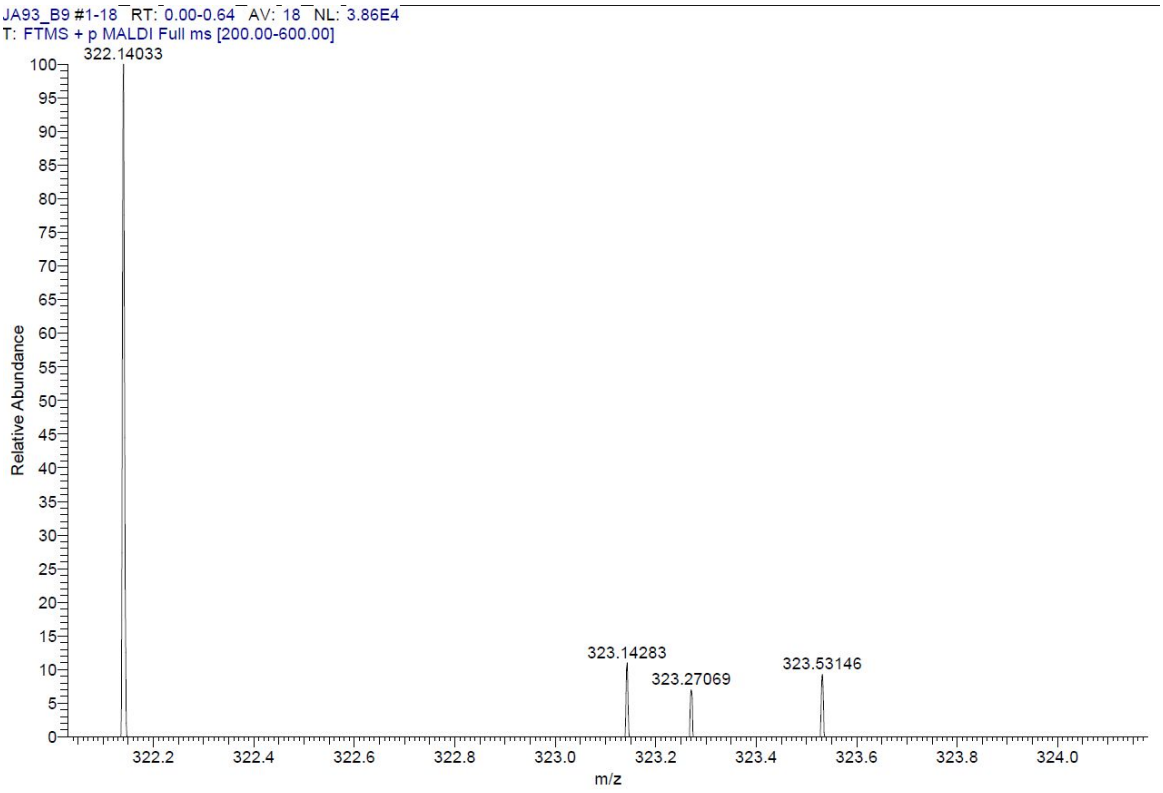


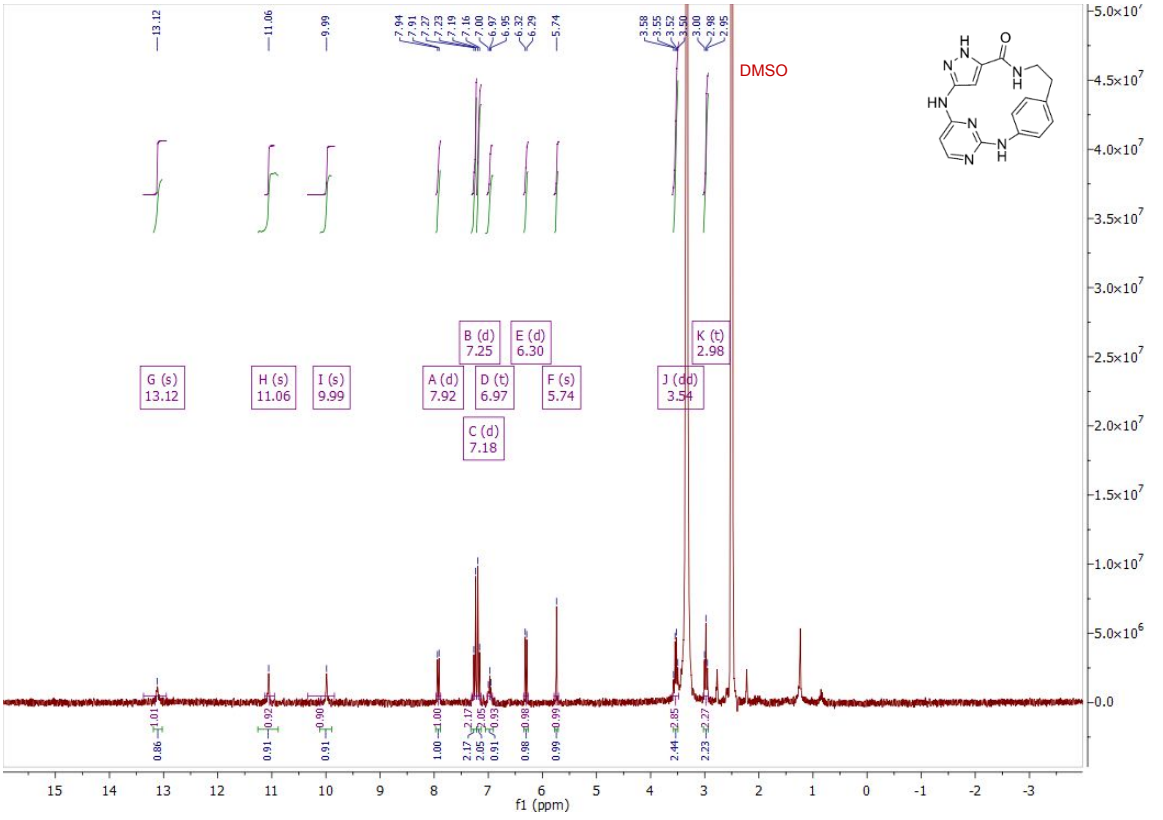
ESI data of compound **7e**.

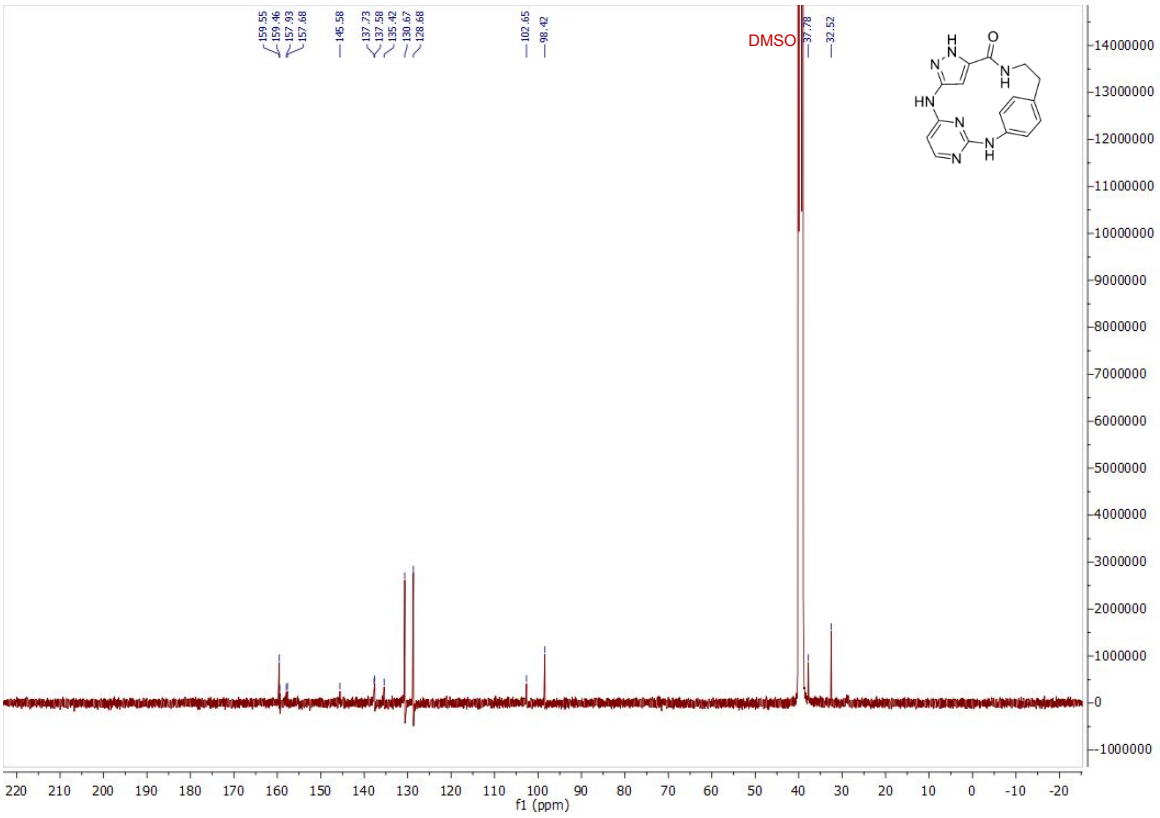


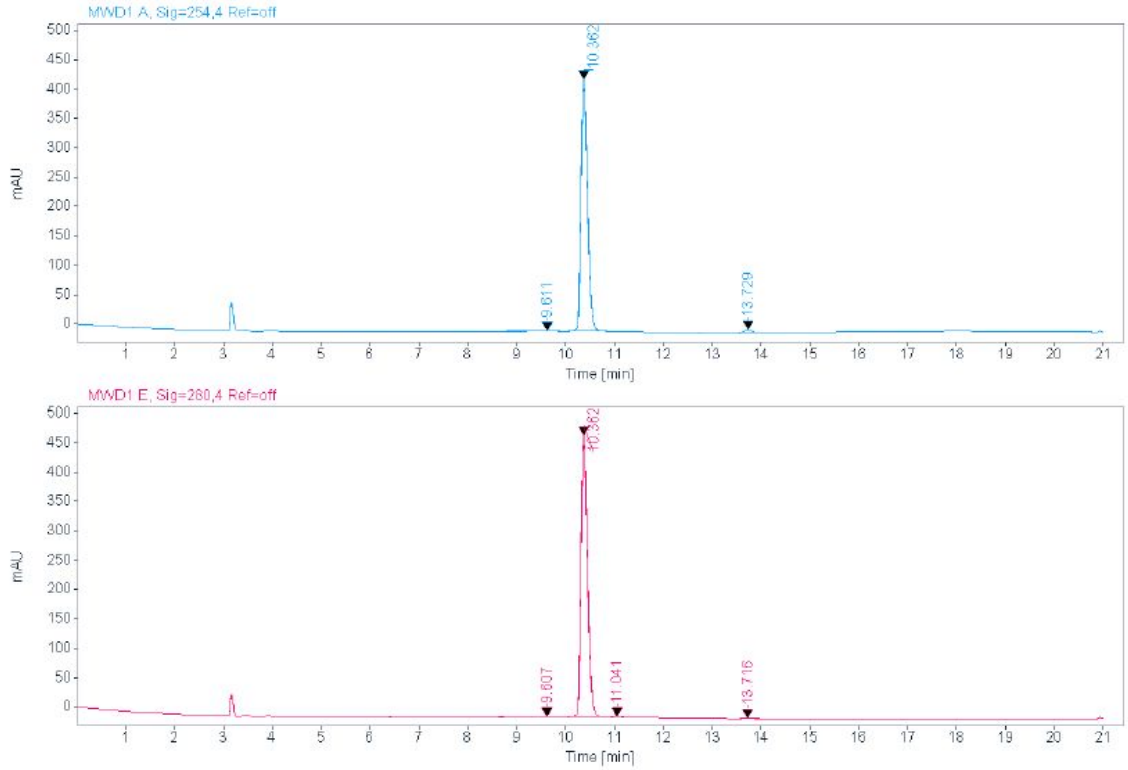
ESI, HRMS, ^{1}H, ^{13}C NMR and HPLC data of compound **8a**.




JA93_B9 #1-18 RT: 0.00-0.64 AV: 18 NL: 3.86E4
T: FTMS + p MALDI Full ms [200.00-600.00]
322.14033
323.14283
323.27069
323.53146
Relative Abundance
m/z


DMSO
G (s) 13.12
H (s) 11.06
I (s) 9.99
A (d) 7.92
B (d) 7.25
C (d) 7.18
D (t) 6.97
E (d) 6.30
F (s) 5.74
J (dd) 3.54
K (t) 2.98
f1 (ppm)


159.55
159.46
157.93
157.68
145.58
137.73
137.58
135.42
130.67
128.68
102.65
98.42
DMSO
39.78
32.52
f1 (ppm)


MWD1 A, Sig=254,4 Ref=off
10.362
9.611
13.729
mAU
Time [min]
MWD1 E, Sig=280,4 Ref=off
10.362
9.607
11.041
13.716
mAU
Time [min]

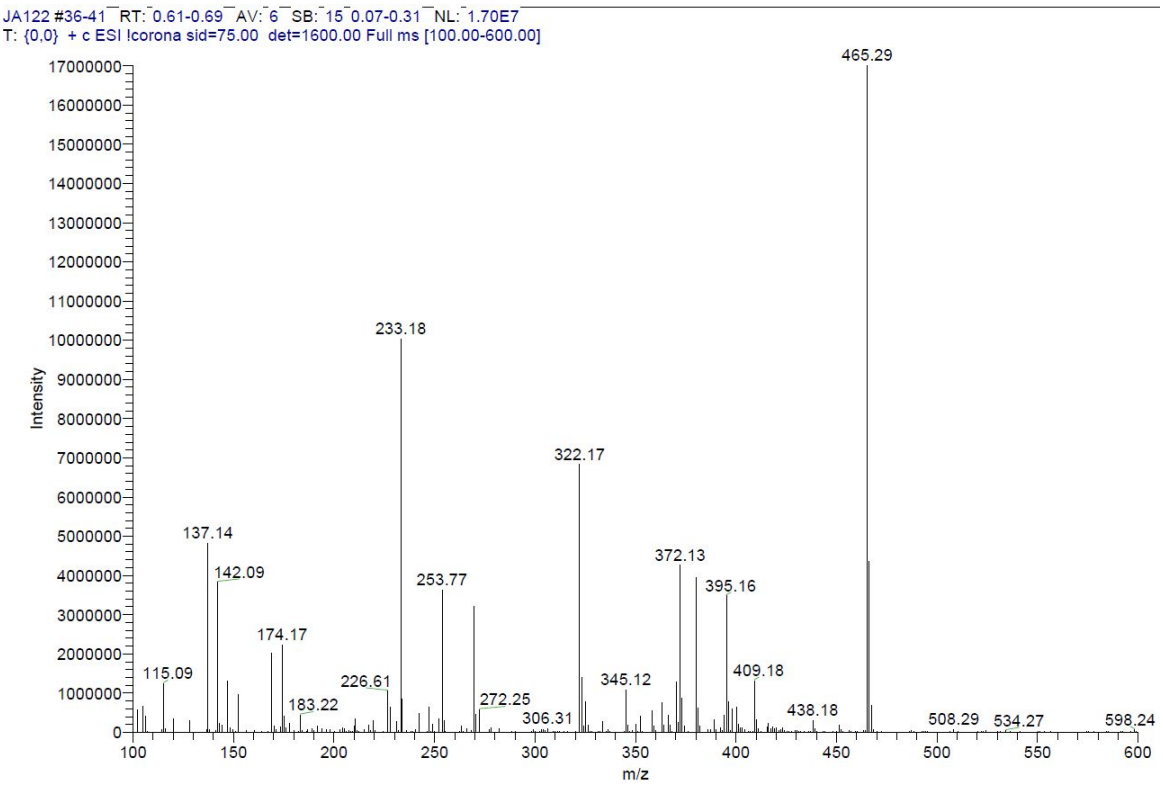
Signal: MWD1 A, Sig=254,4 Ref=off

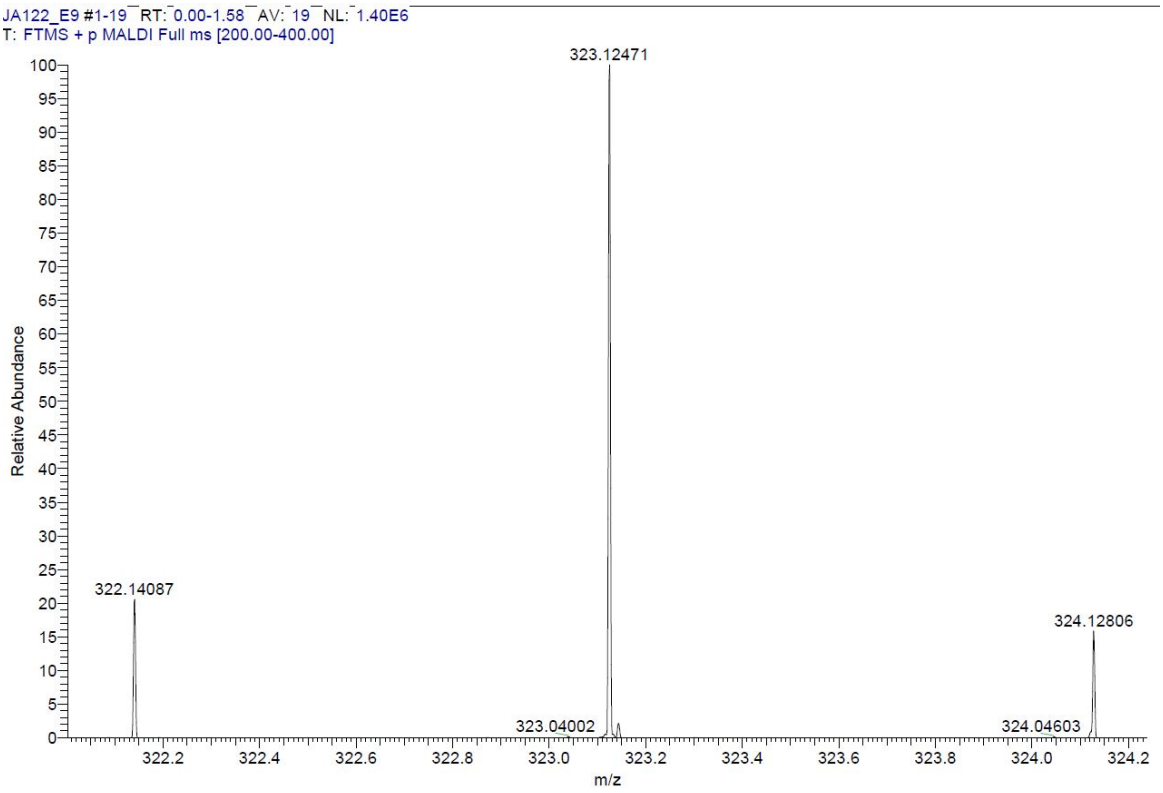
RT [min]	Type	Width [min]	Area	Height	Area%	Name
9.611	MM	0.8894	77.9974	1.4616	1.8454	
10.362	MM	0.1588	4086.1445	428.9523	96.6753	
13.729	MM	0.1831	62.5284	5.6921	1.4794	
		Sum	4226.6704			

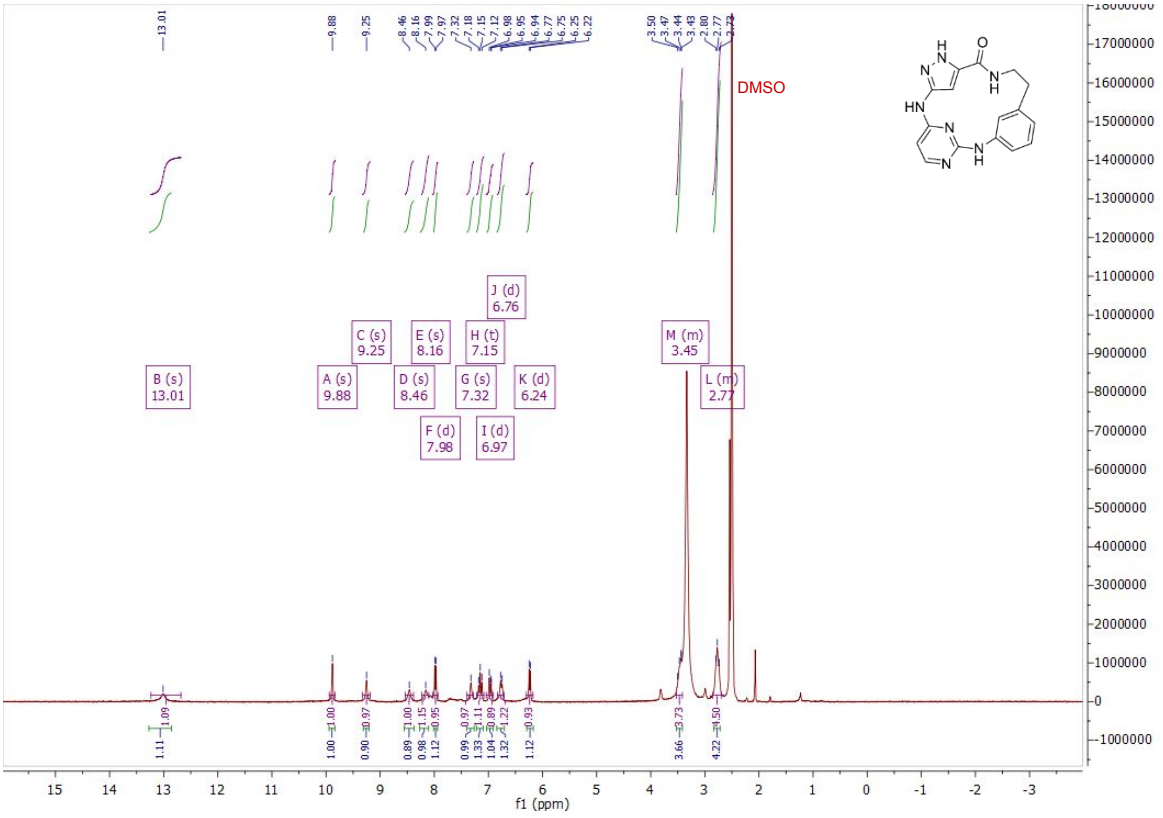
Signal: MWD1 E, Sig=280,4 Ref=off

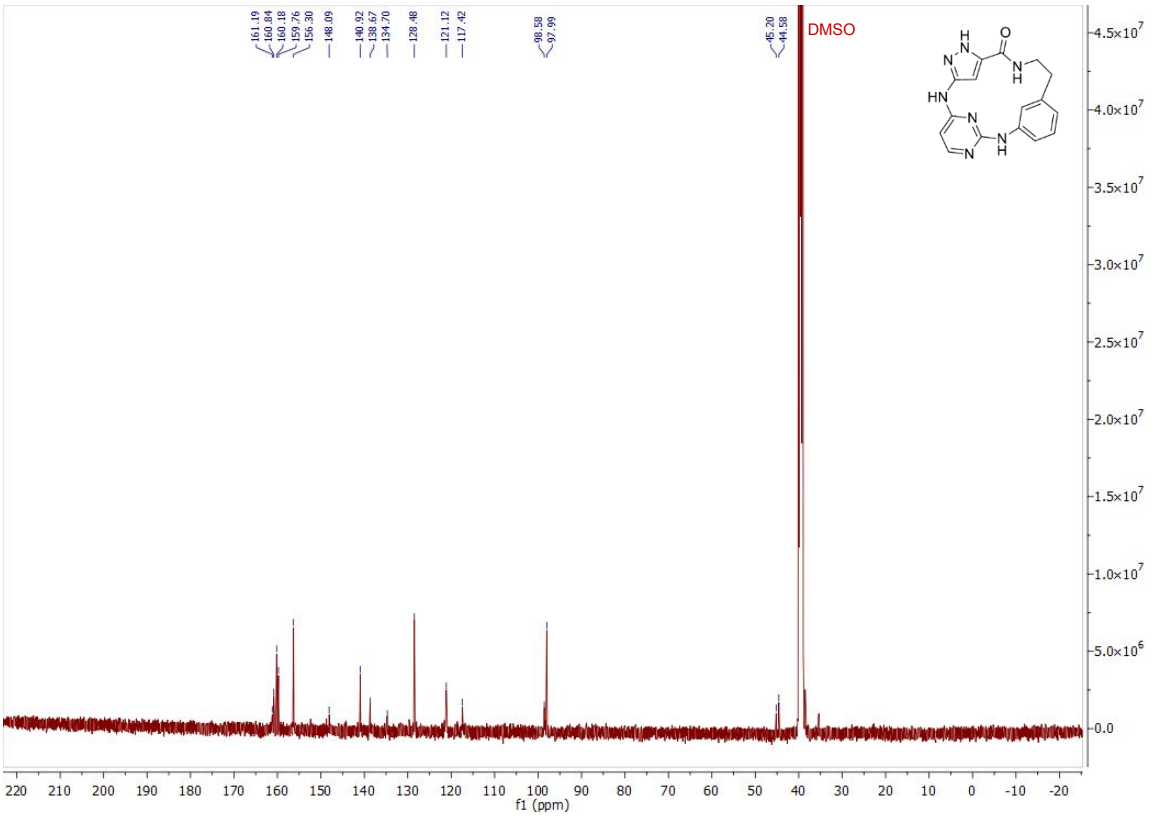
RT [min]	Type	Width [min]	Area	Height	Area%	Name
9.607	MM	0.5428	44.7534	1.3741	0.9677	
10.362	MM	0.1581	4548.1382	479.3879	98.3392	
11.041	MM	0.1443	11.2091	1.2948	0.2424	
13.716	MM	0.1889	20.8503	1.8393	0.4508	
		Sum	4624.9509			

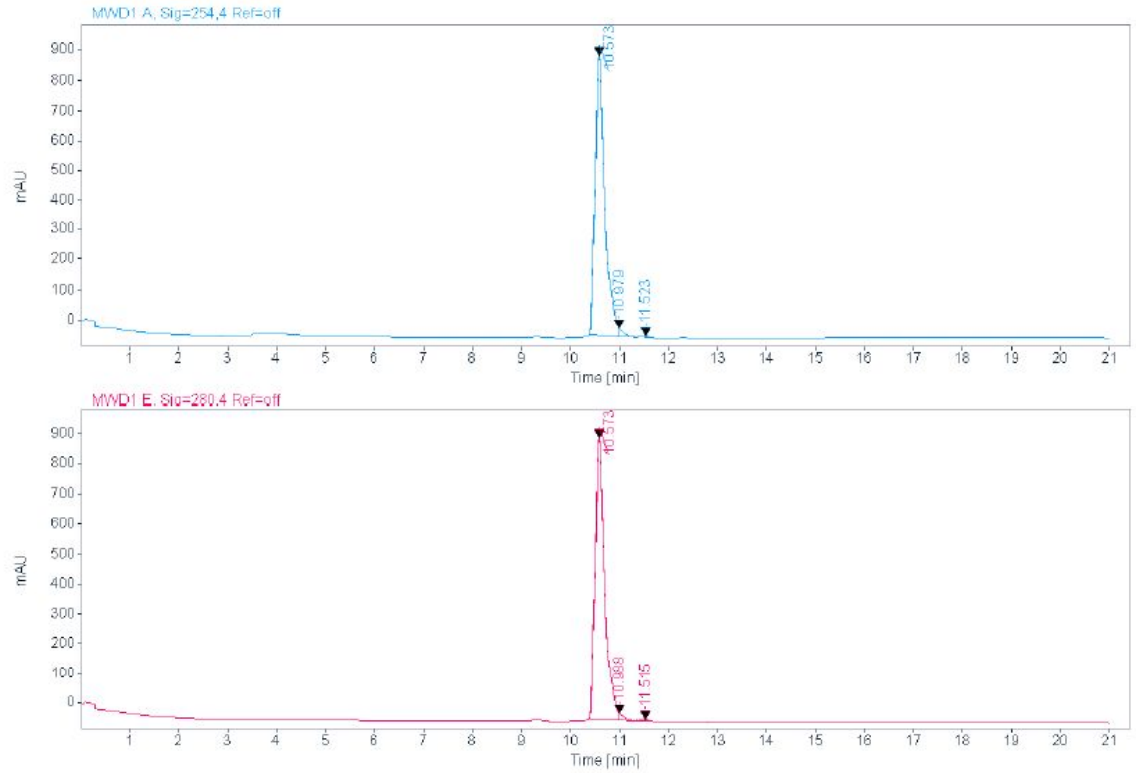
ESI, HRMS, ^{1}H, ^{13}C NMR and HPLC data of compound **8b**.




JA122_E9 #1-19 RT: 0.00-1.58 AV: 19 NL: 1.40E6
T: FTMS + p MALDI Full ms [200.00-400.00]
323.12471
322.14087
324.12806
323.04002
324.04603
Relative Abundance
m/z


DMSO
B (s) 13.01
A (s) 9.88
C (s) 9.25
D (s) 8.46
E (s) 8.16
F (d) 7.98
G (s) 7.32
H (t) 7.15
I (d) 6.97
J (d) 6.76
K (d) 6.24
M (m) 3.45
L (m) 2.77
f1 (ppm)

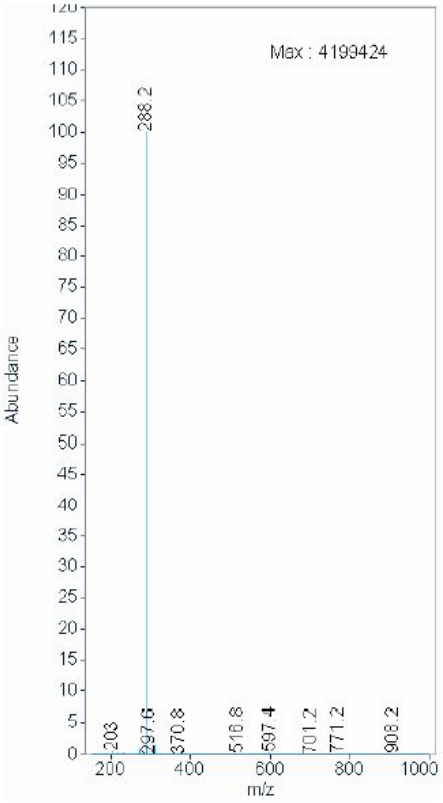

161.19
160.84
160.18
159.76
156.30
148.09
140.92
138.67
134.70
128.48
121.12
117.42
98.58
97.99
65.20
44.58
DMSO
f1 (ppm)

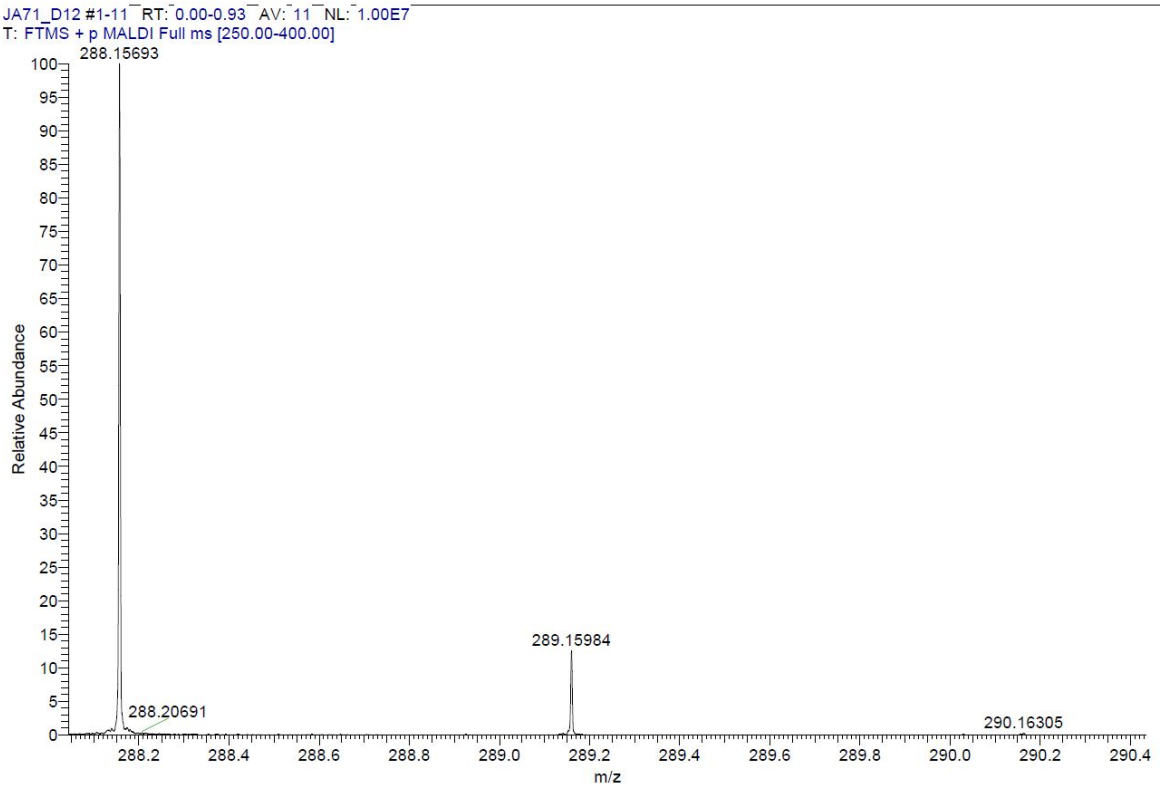

MWD1 A, Sig=254,4 Ref=off
10.573
10.879
11.523
mAU
Time [min]
MWD1 E, Sig=280,4 Ref=off
10.573
10.868
11.545
mAU
Time [min]

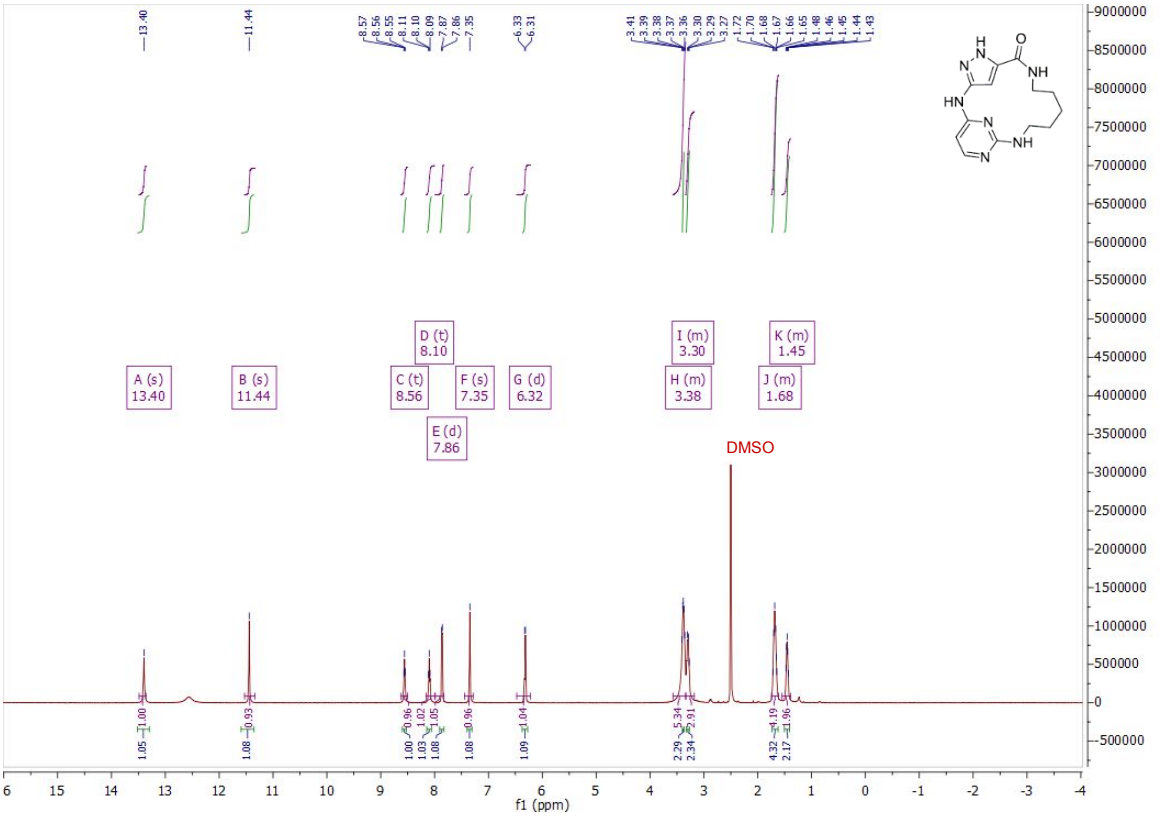
Signal:	MWD1 A, Sig=254,4 Ref=off				
RT [min]	Type	Width [min]	Area	Height	Area% Name
10.573	MF	0.2262	12645.9326	931.8766	98.1447
10.979	FM	0.1185	186.5474	26.2475	1.4478
11.523	MM	0.1820	52.5069	4.8093	0.4075
		Sum	12884.9869		

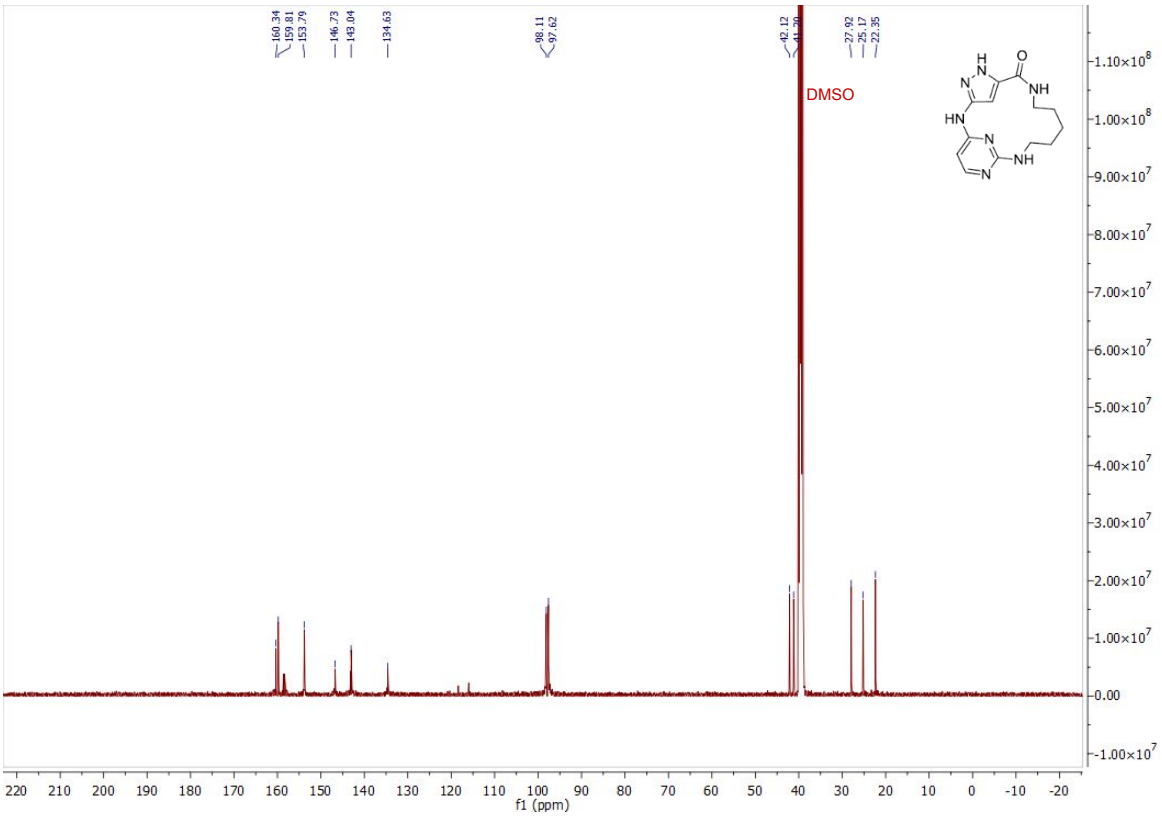
Signal:	MWD1 E, Sig=280,4 Ref=off				
RT [min]	Type	Width [min]	Area	Height	Area% Name
10.573	MF	0.2245	12704.6367	943.0483	98.3864
10.988	FM	0.1119	147.2023	21.9317	1.1400
11.515	MM	0.1890	61.1598	5.3930	0.4736
		Sum	12912.9988		

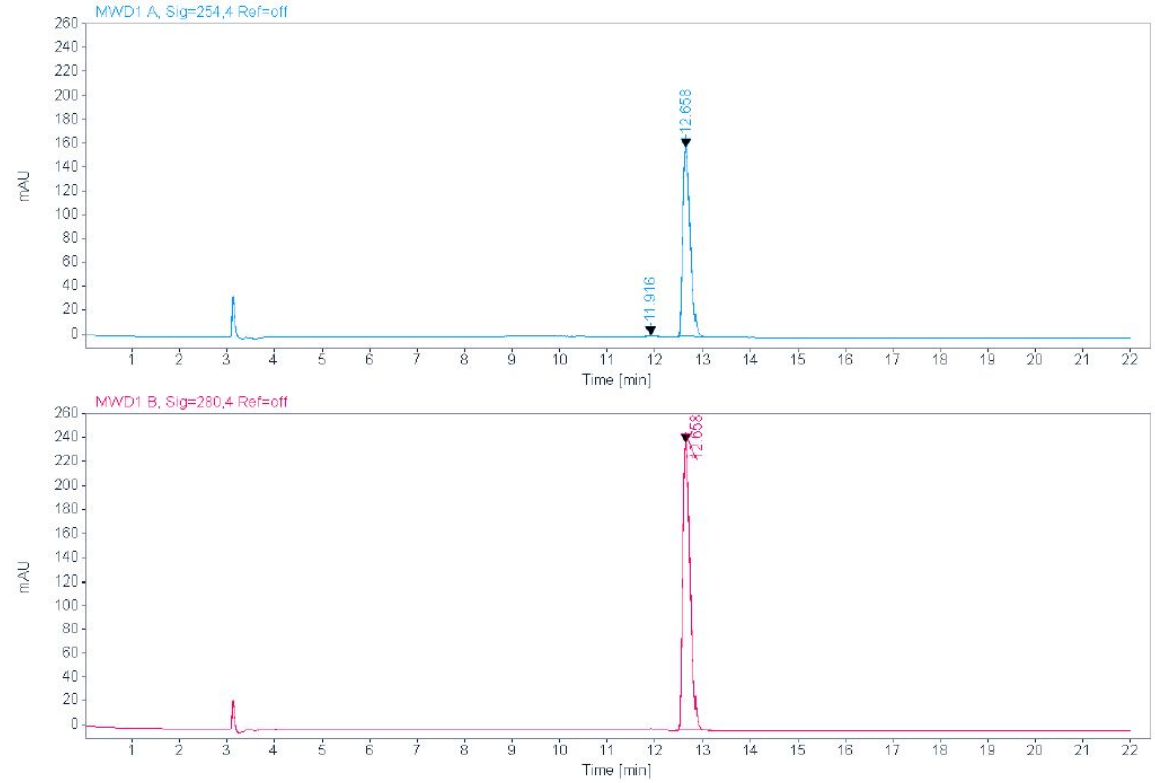
ESI, HRMS, ^{1}H, ^{13}C NMR and HPLC data of compound **8c**.




JA71_D12 #1-11 RT: 0.00-0.93 AV: 11 NL: 1.00E7
T: FTMS + p MALDI Full ms [250.00-400.00]
288.15693
289.15984
288.20691
290.16305
Relative Abundance
m/z


A (s) 13.40
B (s) 11.44
C (t) 8.56
D (t) 8.10
E (d) 7.86
F (s) 7.35
G (d) 6.32
H (m) 3.38
I (m) 3.30
J (m) 1.68
K (m) 1.45
DMSO
f1 (ppm)


160.34
159.81
153.79
146.73
143.04
134.63
98.11
97.62
42.12
41.80
27.92
25.17
22.35
DMSO
f1 (ppm)


MWD1 A, Sig=254,4 Ref=off
12.658
11.916
mAU
Time [min]
MWD1 B, Sig=280,4 Ref=off
12.658
mAU
Time [min]

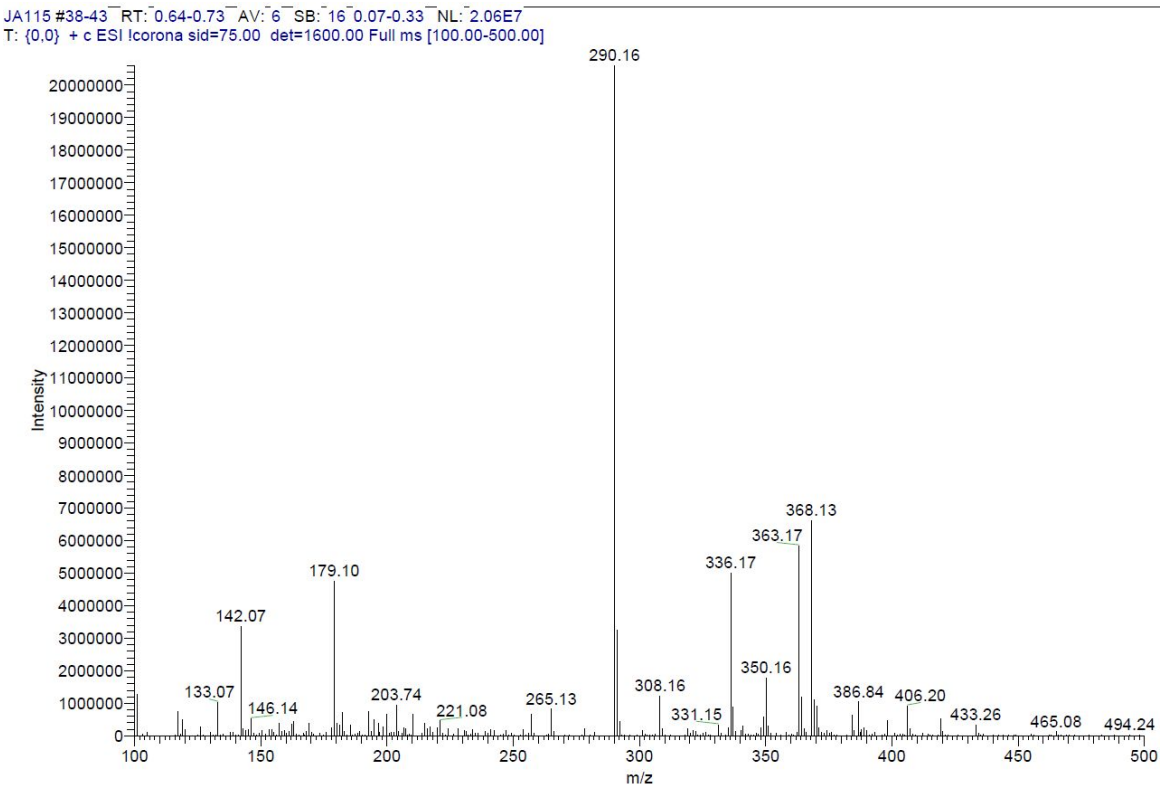
Signal: MWD1 A, Sig=254,4 Ref=off

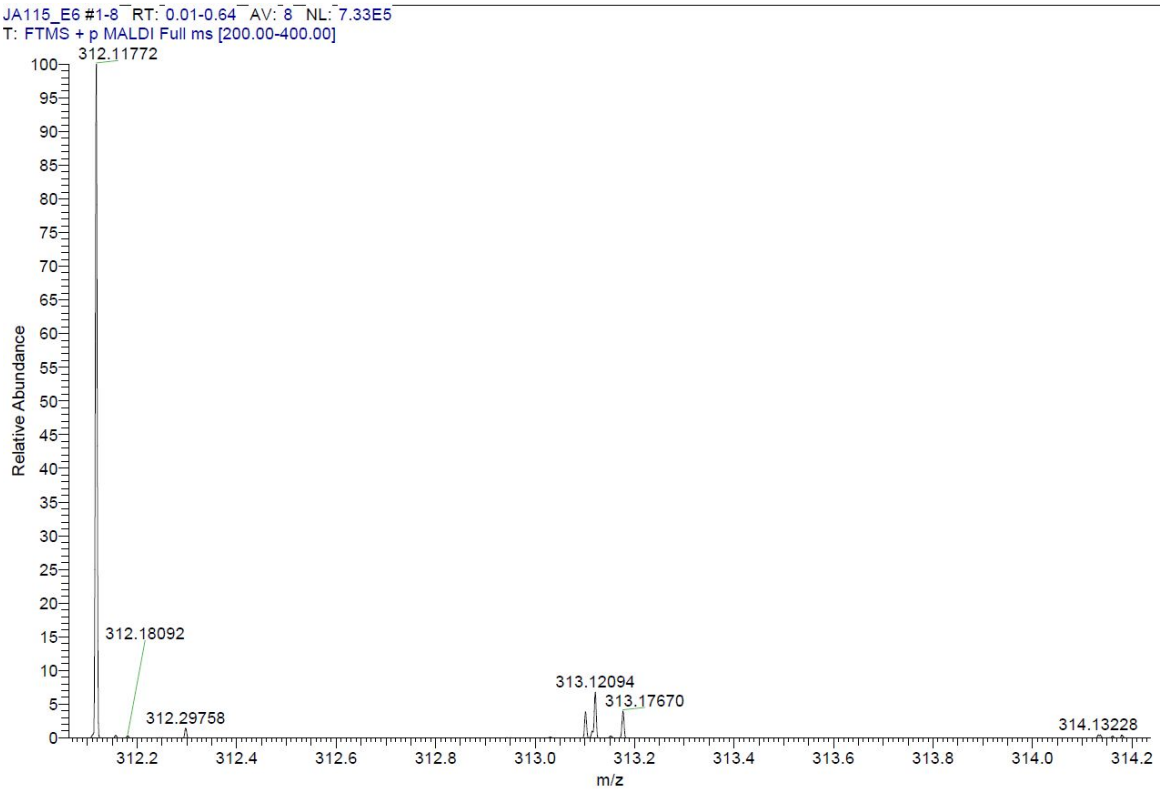
RT [min]	Type	Width [min]	Area	Height	Area%	Name
11.916	MM	0.1592	10.7461	1.1248	0.6305	
12.658	BB	0.1635	1693.7252	158.7199	99.3695	
		Sum	1704.4713			

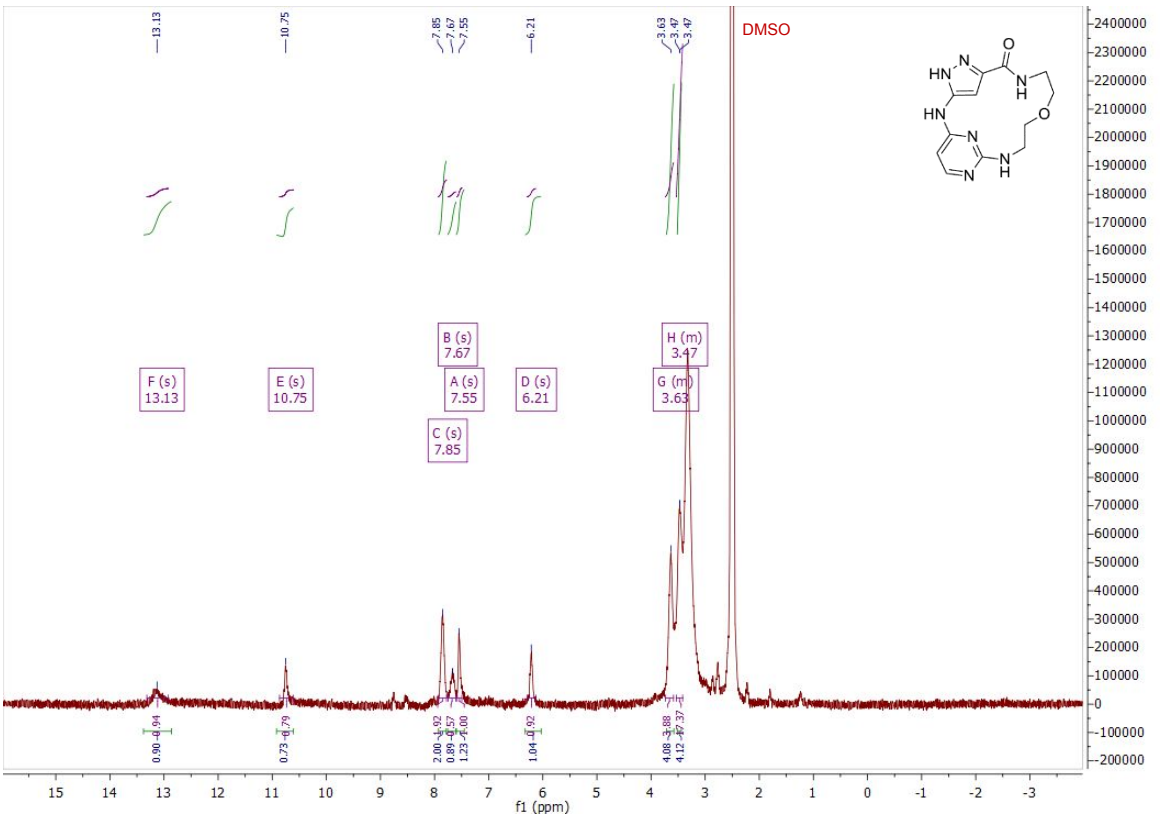
Signal: MWD1 B, Sig=280,4 Ref=off

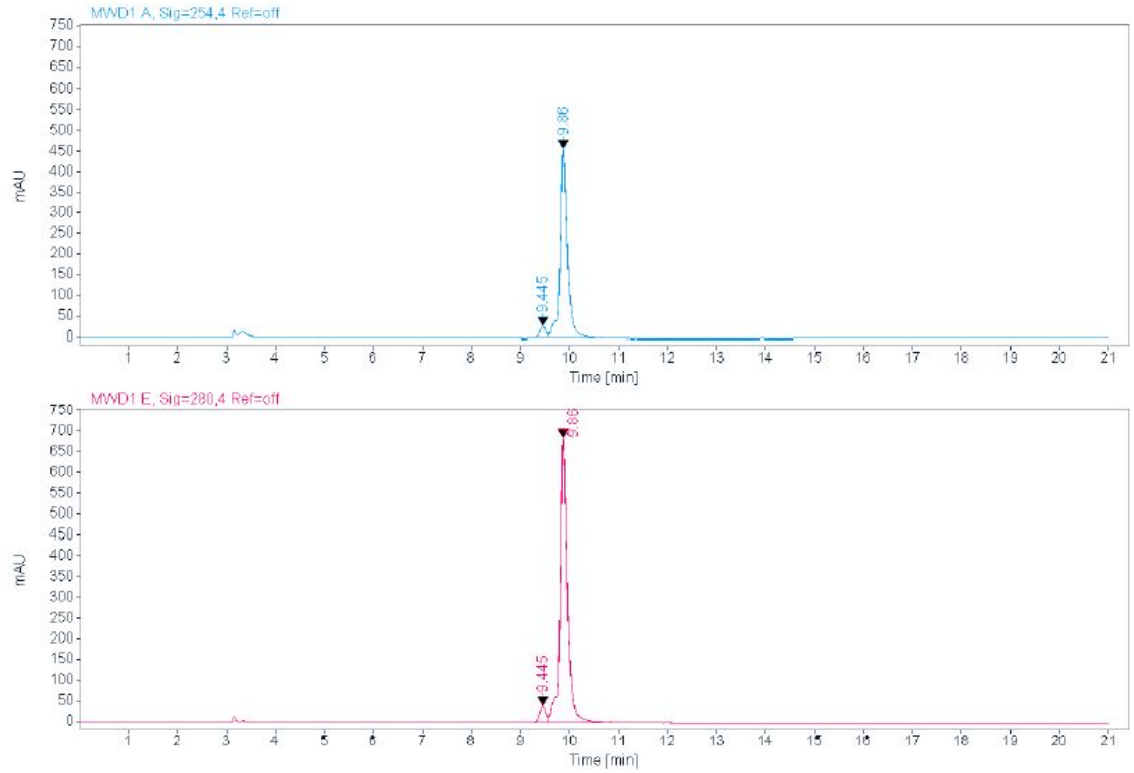
RT [min]	Type	Width [min]	Area	Height	Area%	Name
12.658	BB	0.1629	2562.1594	241.2934	100.0000	
		Sum	2562.1594			

ESI, HRMS, ^{1}H and HPLC data of compound **8d**.




JA115_E6 #1-8 RT: 0.01-0.64 AV: 8 NL: 7.33E5
T: FTMS + p MALDI Full ms [200.00-400.00]
312.11772
312.18092
312.29758
313.12094
313.17670
314.13228
Relative Abundance
m/z


DMSO
F (s) 13.13
E (s) 10.75
B (s) 7.67
A (s) 7.55
C (s) 7.85
D (s) 6.21
H (m) 3.47
G (m) 3.63
f1 (ppm)



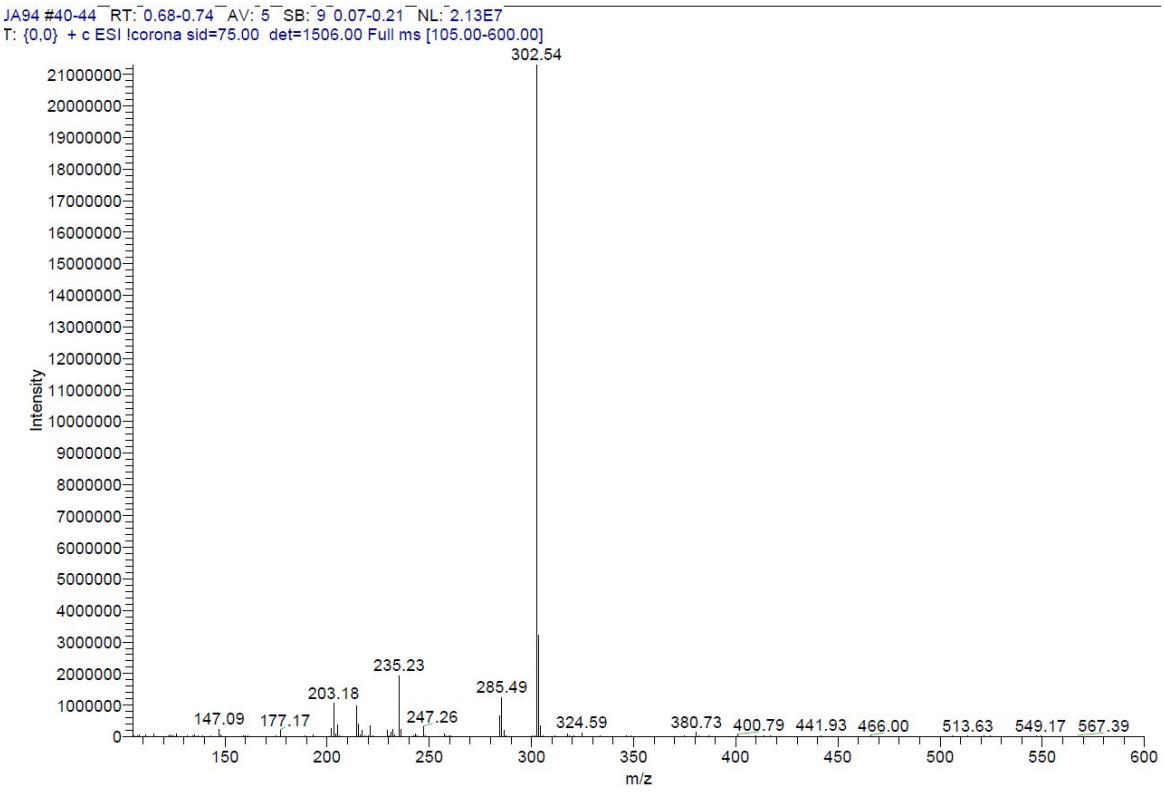
Signal: MWD1 A, Sig=254,4 Ref=off

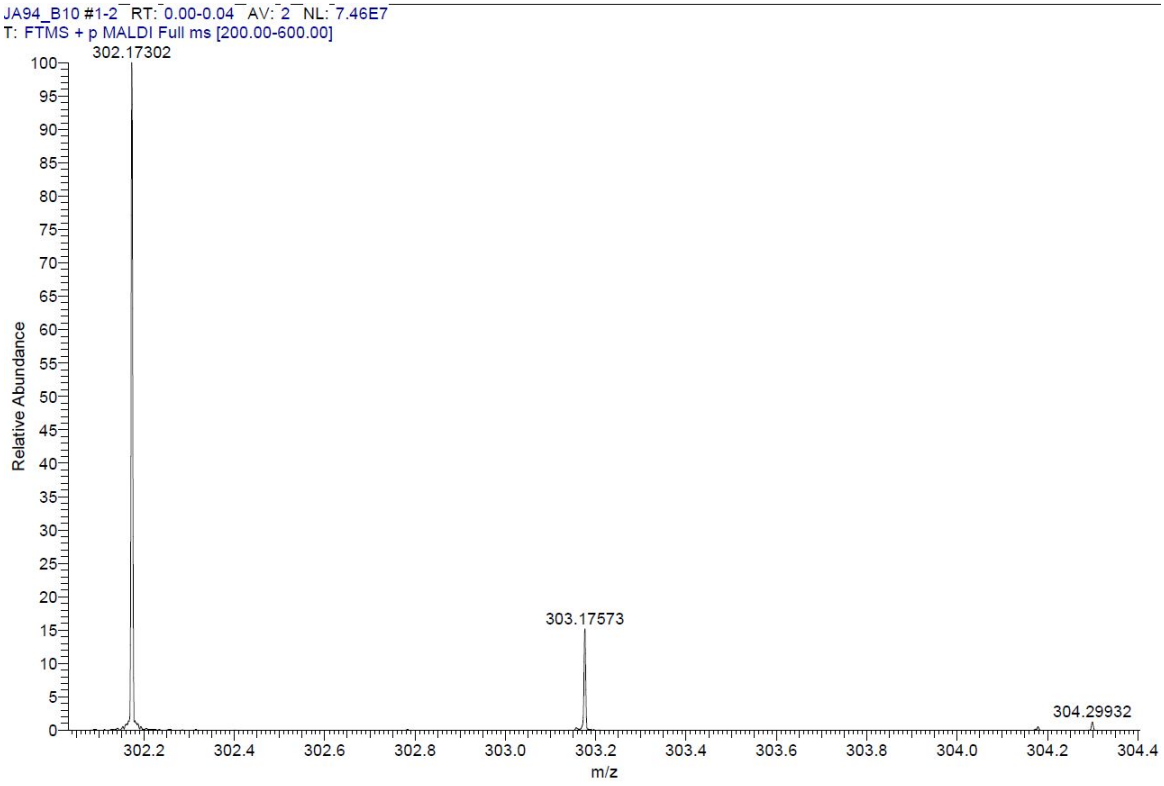
RT [min]	Type	Width [min]	Area	Height	Area%	Name
9.445	MF	0.1440	238.0683	27.5513	4.8982	
9.860	FM	0.1687	4622.2915	456.7866	95.1018	
		Sum	4860.3598			

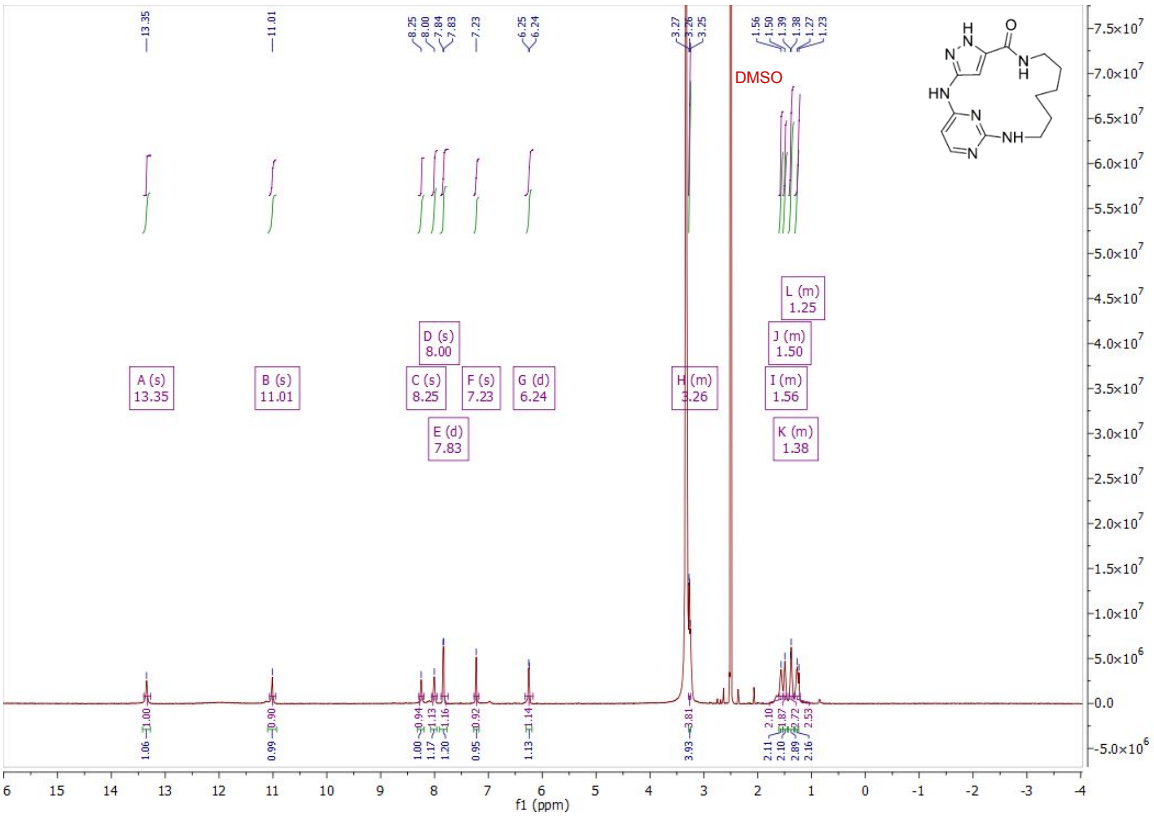
Signal: MWD1 E, Sig=280,4 Ref=off

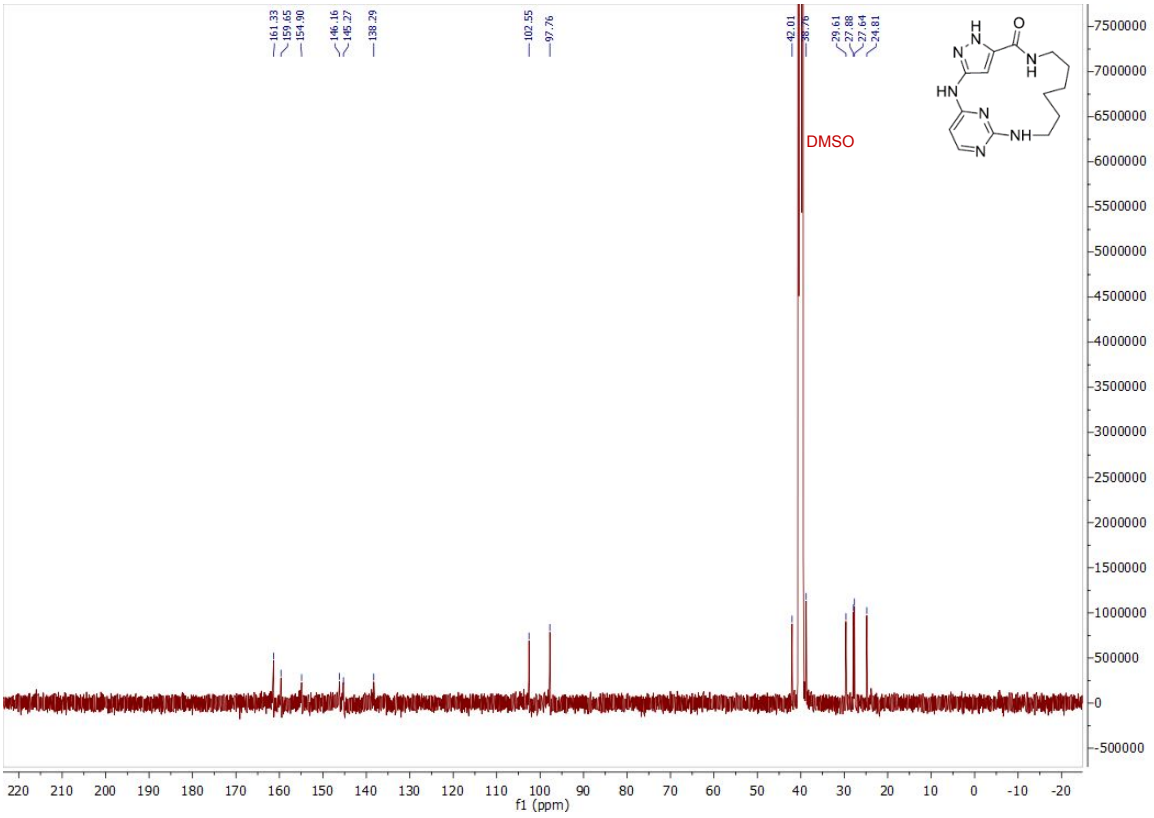
RT [min]	Type	Width [min]	Area	Height	Area%	Name
9.445	MF	0.1484	359.6102	40.3998	4.8889	
9.860	FM	0.1702	6996.0698	684.9609	95.1111	
		Sum	7355.6800			

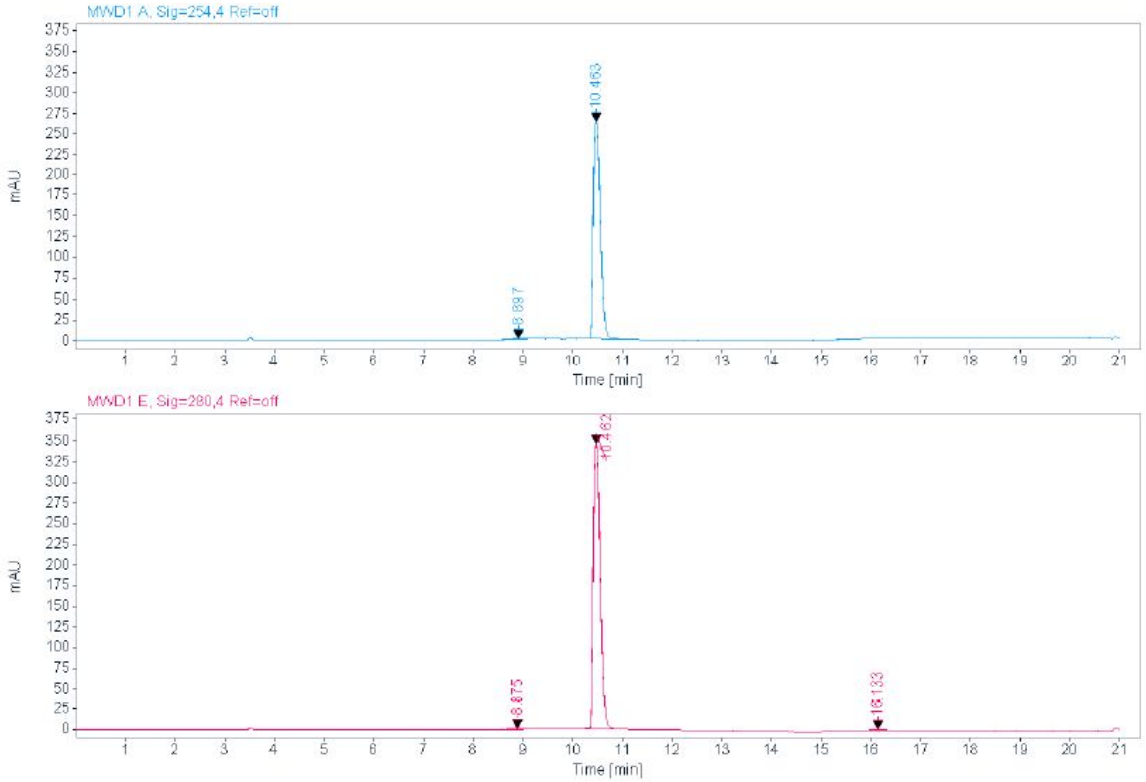
ESI, HRMS, ^{1}H, ^{13}C NMR and HPLC data of compound **8e**.






DMSO
A (s) 13.35
B (s) 11.01
C (s) 8.25
D (s) 8.00
E (d) 7.83
F (s) 7.23
G (d) 6.24
H (m) 3.26
I (m) 1.56
J (m) 1.50
K (m) 1.38
L (m) 1.25
f1 (ppm)


DMSO
f1 (ppm)



Signal: MWD1 A, Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
8.897	MM	0.5393	47.0867	1.4552	1.7937	
10.463	VV	0.1582	2578.0837	263.4731	98.2063	
		Sum	2625.1704			

Signal: MWD1 E, Sig=280,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
8.875	MM	0.5720	46.9116	1.3668	1.3633	
10.462	VB	0.1565	3344.0491	346.7501	97.1821	
16.133	MM	0.3865	50.0530	2.1585	1.4546	
		Sum	3441.0137			

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(3) Eberhardt, J.; Santos-Martins, D.; Tillack, A. F.; Forli, S. AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings. *J Chem Inf Model* **2021**, *61* (8), 3891–3898.

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(8) Adasme, M. F.; Linnemann, K. L.; Bolz, S. N.; Kaiser, F.; Salentin, S.; Haupt, V. J.; Schroeder, M. PLIP 2021: Expanding the Scope of the Protein-Ligand Interaction Profiler to DNA and RNA. *Nucleic Acids Res.* **2021**, *49* (W1), W530–W534.