Supporting Information

Discovery of Conformationally Constrained ALK2 Inhibitors

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1. SUPPLEMENTARY TABLES

Table S1. Kinase (422) Selectivity Panel

	% Enzyme Activity (relative to DMSO control) @ 1 μM compound and 10 μM ATP
Kinase	**M4K2304**
AAK1(h)	95
Abl(h)	73
Abl(m)	79
Abl (H396P) (h)	88
Abl (M351T)(h)	71
Abl (Q252H) (h)	74
Abl(T315I)(h)	109
Abl(Y253F)(h)	77
ACK1(h)	77
ACTR2(h)	54
ALK(h)	98
ALK1(h)	3
ALK2(h)	0
ALK4(h)	32
ALK6(h)	11
Arg(h)	96
AMPKα1(h)	96
AMPKα2(h)	114
A-Raf(h)	105
Arg(m)	86
ARK5(h)	91
ASK1(h)	109
Aurora-A(h)	104
Aurora-B(h)	94
Aurora-C(h)	92

Axl(h)	86
BIKe(h)	98
Blk(h)	85
Blk(m)	64
BMPR2(h)	104
Bmx(h)	107
BRK(h)	31
BrSK1(h)	104
BrSK2(h)	118
BTK(h)	107
BTK(R28H)(h)	102
B-Raf(h)	96
B-Raf(V599E)(h)	92
CaMKI(h)	113
CaMKIß(h)	106
CaMKIγ(h)	102
CaMKIIα(h)	106
CaMKIIβ(h)	106
CaMKIIγ(h)	100
CaMKIδ(h)	106
CaMKIIδ(h)	84
CaMKIV(h)	107
CaMKK1(h)	107
CaMKK2(h)	109
Cdc7/cyclinB1(h)	117
CDK1/cyclinB(h)	99
CDK2/cyclinA(h)	100
CDK2/cyclinE(h)	107
CDK3/cyclinE(h)	118
CDK4/cyclinD3(h)	125
CDK5/p25(h)	109
CDK5/p35(h)	112
CDK6/cyclinD3(h)	117
CDK7/cyclinH/MAT1(h)	115
CDK9/cyclin T1(h)	100
CDK12/cyclinK(h)	123
CDK13/cyclinK(h)	118
CDK14/cyclinY(h)	102
CDK16/cyclinY(h)	110
CDK17/cyclinY(h)	108
CDK18/cyclinY(h)	97
CDKL1(h)	108
CDKL2(h)	104
CDKL3(h)	113
CDKL4(h)	115

ChaK1(h)	107
CHK1(h)	100
CHK2(h)	111
CHK2(I157T)(h)	97
CHK2(R145W)(h)	102
CK1α(h)	95
CK1ε(h)	119
CK1γ1(h)	96
CK1γ2(h)	108
CK1γ3(h)	104
CK1δ(h)	107
CK1(y)	48
CK2(h)	110
CK2α1(h)	85
CK2α2(h)	105
CLIK1(h)	111
CLK1(h)	112
CLK2(h)	104
CLK3(h)	103
CLK4(h)	106
cKit(h)	107
cKit(D816V)(h)	87
cKit(D816H)(h)	98
cKit(V560G)(h)	92
cKit(V654A)(h)	89
CRIK(h)	97
CSK(h)	106
c-RAF(h)	101
cSRC(h)	92
DAPK1(h)	101
DAPK2(h)	108
DCAMKL1(h)	101
DCAMKL2(h)	104
DCAMKL3(h)	121
DDR1(h)	29
DDR2(h)	91
DMPK(h)	100
DRAK1(h)	107
DRAK2(h)	111
DYRK1A(h)	113
DYRK1B(h)	110
DYRK2(h)	96
DYRK3(h)	108
eEF-2K(h)	109
EGFR(h)	93

EGFR(L858R)(h)	36
EGFR(L861Q)(h)	48
EGFR(T790M)(h)	103
EGFR(T790M,L858R)(h)	106
EphA1(h)	90
EphA2(h)	103
EphA3(h)	109
EphA4(h)	103
EphA5(h)	107
EphA7(h)	113
EphA8(h)	96
EphB2(h)	92
EphB1(h)	101
EphB3(h)	93
EphB4(h)	101
ErbB2(h)	106
ErbB4(h)	112
FAK(h)	102
Fer(h)	111
Fes(h)	86
FGFR1(h)	87
FGFR1(V561M)(h)	91
FGFR2(h)	98
FGFR2(N549H)(h)	95
FGFR3(h)	93
FGFR4(h)	111
Fgr(h)	93
Flt1(h)	99
Flt3(D835Y)(h)	99
Flt3(h)	98
Flt4(h)	86
Fms(h)	105
Fms(Y969C)(h)	87
Fyn(h)	94
GCK(h)	85
GCN2(h)	104
GRK1(h)	94
GRK2(h)	92
GRK3(h)	95
GRK5(h)	108
GRK6(h)	112
GRK7(h)	102
GSK3α(h)	101
GSK3β(h)	101
Haspin(h)	103

Hck(h)	102
Hck(h) activated	101
HIPK1(h)	107
HIPK2(h)	110
HIPK3(h)	103
HIPK4(h)	116
HPK1(h)	109
HRI(h)	96
ICK(h)	113
IGF-1R(h)	93
IGF-1R(h), activated	111
IKKα(h)	120
IKKβ(h)	104
IKKε(h)	102
IR(h)	107
IR(h), activated	116
IRE1(h)	100
IRR(h)	96
IRAK1(h)	106
IRAK4(h)	97
Itk(h)	97
JAK1(h)	90
JAK2(h)	106
JAK3(h)	105
JNK1α1(h)	100
JNK2α2(h)	118
JNK3(h)	99
KDR(h)	110
LATS1(h)	118
LATS2(h)	109
Lck(h)	49
Lck(h) activated	81
LIMK1(h)	91
LIMK2(h)	109
LKB1(h)	101
LOK(h)	99
Lyn(h)	41
Lyn(m)	44
LRRK2(h)	103
LTK(h)	107
MAK(h)	109
MAPK1(h)	90
MAPK2(h)	110
MAPK2(m)	98
MAP4K3(h)	98

MAP4K4(h)	75
MAP4K5(h)	94
MAPKAP-K2(h)	108
MAPKAP-K3(h)	114
MEK1(h)	88
MEK2(h)	102
MARK1(h)	103
MARK3(h)	111
MARK4(h)	105
MEKK2(h)	103
MEKK3(h)	108
MELK(h)	99
Mer(h)	120
Met(h)	99
Met(D1246H)(h)	94
Met(D1246N)(h)	105
Met(M1268T)(h)	86
Met(Y1248C)(h)	92
Met(Y1248D)(h)	90
Met(Y1248H)(h)	86
MINK(h)	61
MKK3(h)	93
MKK4(m)	88
MKK6(h)	101
MLCK(h)	102
MLK1(h)	106
MLK2(h)	117
MLK3(h)	104
MLK4(h)	116
Mnk2(h)	100
MOK(h)	103
MRCKα(h)	108
MRCKβ(h)	109
MRCKγ(h)	102
MSK1(h)	114
MSK2(h)	115
MSSK1(h)	123
MST1(h)	97
MST2(h)	93
MST3(h)	112
MST4(h)	115
mTOR(h)	102
mTOR/FKBP12(h)	103
MuSK(h)	113
MYLK2(h)	105

MYO3B(h)	104
NDR1(h)	118
NDR2(h)	101
NEK1(h)	112
NEK2(h)	92
NEK3(h)	100
NEK4(h)	105
NEK6(h)	109
NEK7(h)	99
NEK9(h)	103
NIM1(h)	108
NEK11(h)	112
NLK(h)	94
NUAK2(h)	113
OSR1(h)	103
p70S6K(h)	102
PAK1(h)	97
PAK2(h)	101
PAK4(h)	108
PAK3(h)	105
PAK5(h)	112
PAK6(h)	111
PAR-1Bα(h)	118
PASK(h)	117
PEK(h)	109
PDGFRα(h)	94
PDGFRα(D842V)(h)	73
PDGFRα(V561D)(h)	76
PDGFRβ(h)	88
PDHK2(h)	138
PDHK4(h)	113
PDK1(h)	97
PhKγ1(h)	112
PhKγ2(h)	118
Pim-1(h)	105
Pim-2(h)	110
Pim-3(h)	103
PKA(h)	102
PKAcβ(h)	113
PKBα(h)	92
PKBβ(h)	132
PKBγ(h)	103
PKCα(h)	88
PKCβI(h)	102
PKCβII(h)	100

PKCγ(h)	100
PKCδ(h)	104
PKCε(h)	103
PKCη(h)	115
PKCι(h)	105
PKCμ(h)	107
PKCθ(h)	117
PKCζ(h)	108
PKD2(h)	100
PKD3(h)	92
PKG1α(h)	96
PKG1β(h)	107
PKR(h)	102
Plk1(h)	99
Plk3(h)	101
Plk4(h)	92
PRAK(h)	104
PRKG2(h)	110
PRK1(h)	102
PRK2(h)	112
PrKX(h)	104
PRP4(h)	99
PTK5(h)	73
Pyk2(h)	100
Ret(h)	99
Ret (V804L)(h)	108
Ret(V804M)(h)	102
RIPK1(h)	108
RIPK2(h)	27
ROCK-I(h)	98
ROCK-II(h)	104
ROCK-II(r)	92
Ron(h)	102
Ros(h)	119
Rse(h)	102
Rsk1(h)	110
Rsk1(r)	110
Rsk2(h)	101
Rsk3(h)	98
Rsk4(h)	125
SAPK2a(h)	98
SAPK2a(T106M)(h)	93
SAPK2b(h)	92
SAPK3(h)	106
SAPK4(h)	109

SBK1(h)	109
SGK(h)	118
SGK2(h)	128
SGK3(h)	108
SIK(h)	92
SIK2(h)	79
SIK3(h)	102
SLK(h)	106
Snk(h)	106
SNRK(h)	118
Src(1-530)(h)	94
Src(T341M)(h)	96
SRMS(h)	117
SRPK1(h)	98
SRPK2(h)	110
STK16(h)	108
STK25(h)	103
STK32A(h)	104
STK32B(h)	101
STK32C(h)	131
STK33(h)	111
STK39(h)	105
Syk(h)	84
TAF1L(h)	115
TAK1(h)	95
TAO1(h)	90
TAO2(h)	111
TAO3(h)	97
TBK1(h)	114
Tec(h) activated	107
TGFBR1(h)	52
TGFBR2(h)	103
Tie2 (h)	94
Tie2(R849W)(h)	98
Tie2(Y897S)(h)	102
TLK1(h)	90
TLK2(h)	104
TNIK(h)	40
TRB2(h)	108
TrkA(h)	117
TrkB(h)	92
TrkC(h)	99
TSSK1(h)	107
TSSK2(h)	99
TSSK3(h)	102

TSSK4(h)	104
TTBK1(h)	98
TTBK2(h)	104
TTK(h)	106
Txk(h)	107
TYK2(h)	103
ULK1(h)	110
ULK2(h)	102
ULK3(h)	107
VRK1(h)	113
VRK2(h)	101
Wee1(h)	95
Wee1B(h)	117
WNK1(h)	103
WNK2(h)	105
WNK3(h)	106
WNK4(h)	123
Yes(h)	64
ZAK(h)	72
ZAP-70(h)	108
ZIPK(h)	108
ATM(h)	99
ATR/ATRIP(h)	93
DNA-PK(h)	106
PI3 Kinase (p110b/p85a)(h)	94
PI3 Kinase (p120g)(h)	98
PI3 Kinase (p110d/p85a)(h)	101
PI3 Kinase (p110a/p85a)(m)	102
PI3 Kinase (p110a/p65a)(m)	89
PI3 Kinase (p110a(E545K)/p85a)(m)	108
PI3 Kinase (p110a(H1047R)/p85a)(m)	99
PI3 Kinase (p110b/p85b)(m)	90
PI3 Kinase (p110b/p85a)(m)	88
PI3 Kinase (p110d/p85a)(m)	94
PI3 Kinase (p110a(E542K)/p85a)(m)	100
PI3 Kinase (p110a/p85a)(h)	97
PI3 Kinase (p110a(E542K)/p85a)(h)	100
PI3 Kinase (p110a(H1047R)/p85a)(h)	91
PI3 Kinase (p110a(E545K)/p85a)(h)	108
PI3 Kinase (p110a/p65a)(h)	102
PI3KC2a(h)	108
PI3KC2g(h)	102
PIP4K2a(h)	106
PIP5K1a(h)	109
PIP5K1g(h)	100

Table S2. Co-crystal ALK2•M4K2304: Diffraction Data Collection and Refinement Statistics

PDB accession code	**8C7W**
Data Collection Statistics	
Radiation source	Diamond I03
Wavelength (Å)	0.976254
Space group	$P3_221$
Unit cell dimensions:	
a, b, c (Å)	66.05, 66.05, 145.93
α, β, γ (°)	90, 90, 120
Number of molecules/asymmetric unit	1
Resolution range (Å)	57.20-2.26 (2.30-2.26)
Total observations	360338 (18021)
Unique reflections	17992 (874)
Completeness (%)	100.00 (98.76)
Multiplicity	20.03 (20.62)
R_{merge}[a]	0.4368 (2.1056)
Average I/σ *(I)*	3.6 (0.54)
$CC_{1/2}$ (%)	98.83 (81.65)
Refinement and model statistics	
Ligand	M4K2304
Resolution range (Å)	57.20-2.26
Number of reflections used	17918
R_{work}[b]/R_{free}[c] (%)	20.70/23.92
Average B values (Å^2)	
All atoms	32.590
Protein atoms	32.186
Ligand	27.715
PEG	39.009
H_2O	34.440
Sulfate	52.055
Root mean square deviation from ideality	
Bond lengths (Å)	0.002
Bond angles (°)	0.567
Ramachandran analysis	
Favoured regions / Allowed regions /	98.31/1.69/0.00

Outliers (% of residues)	
Rotamer outliers (%)	0.79
Clashscore	2.32
Number of atoms	
Protein atoms	2348
Ligand	34
PEG	16
H_2O	178
Sulfate	35

[a] R_{merge}= ΣΣ|Ih,i− ⟨I⟩h|ihΣΣIh,ih/ where <I>h is the mean intensity of the symmetry-equivalent reflections.
[b] R_{work}= Σ||Fo|− |Fc||hΣ|Fo|h/,where Fo and Fc are the observed and calculated structure factor amplitudes, respectively, for reflection h.
[c] R_{free} is the R value for a subset of 5% of the reflection data, which were not included in the crystallographic refinement.

Table S3. Co-crystal ALK2•M4K2308: Diffraction Data Collection and Refinement Statistics

PDB accession code	**8C7Z**
Data Collection Statistics	
Radiation source	Diamond I03
Wavelength (Å)	0.976254
Space group	$P3_221$
Unit cell dimensions:	
a, b, c (Å)	67.28, 67.28, 140.76
α, β, γ (°)	90, 90, 120
Number of molecules/asymmetric unit	1
Resolution range (Å)	58.27-2.23 (2.27-2.23)
Total observations	380615 (19096)
Unique reflections	18645 (895)
Completeness (%)	100.0 (99.33)
Multiplicity	20.4 (21.3)
R_{merge}[a]	0.6976 (4.2176)
Average I/σ *(I)*	3.66 (0.55)
$CC_{1/2}$ (%)	98.51 (69.61)
Refinement and model statistics	
Ligand	M4K2308
Resolution range (Å)	58.27-2.23
Number of reflections used	18578
R_{work}[b]/R_{free}[c] (%)	21.36/26.13
Average B values (Å^2)	

All atoms	36.863
Protein atoms	36.394
Ligand	33.705
PEG	46.528
H_2O	38.109
Sulfate	60.188
Ammonium	26.810
Root mean square deviation from ideality	
Bond lengths (Å)	0.002
Bond angles (°)	0.46
Ramachandran analysis	
Favoured regions / Allowed regions / Outliers (% of residues)	97.61/2.39/0.00
Rotamer outliers (%)	0.40
Clashscore	4.17
Number of atoms	
Protein atoms	2345
Ligand	33
PEG	44
H_2O	166
Sulfate	25
Ammonium	1

[a] R_{merge}= ΣΣ|Ih,i− ⟨I⟩h|ihΣΣIh,iih/ where <I>h is the mean intensity of the symmetry-equivalent reflections.

[b] R_{work}= Σ||Fo|− |Fc||hΣ|Fo|h/,where Fo and Fc are the observed and calculated structure factor amplitudes, respectively, for reflection h.

[c] R_{free} is the R value for a subset of 5% of the reflection data, which were not included in the crystallographic refinement.

Table S4. *In Vivo* BBB Penetration of M4K2306

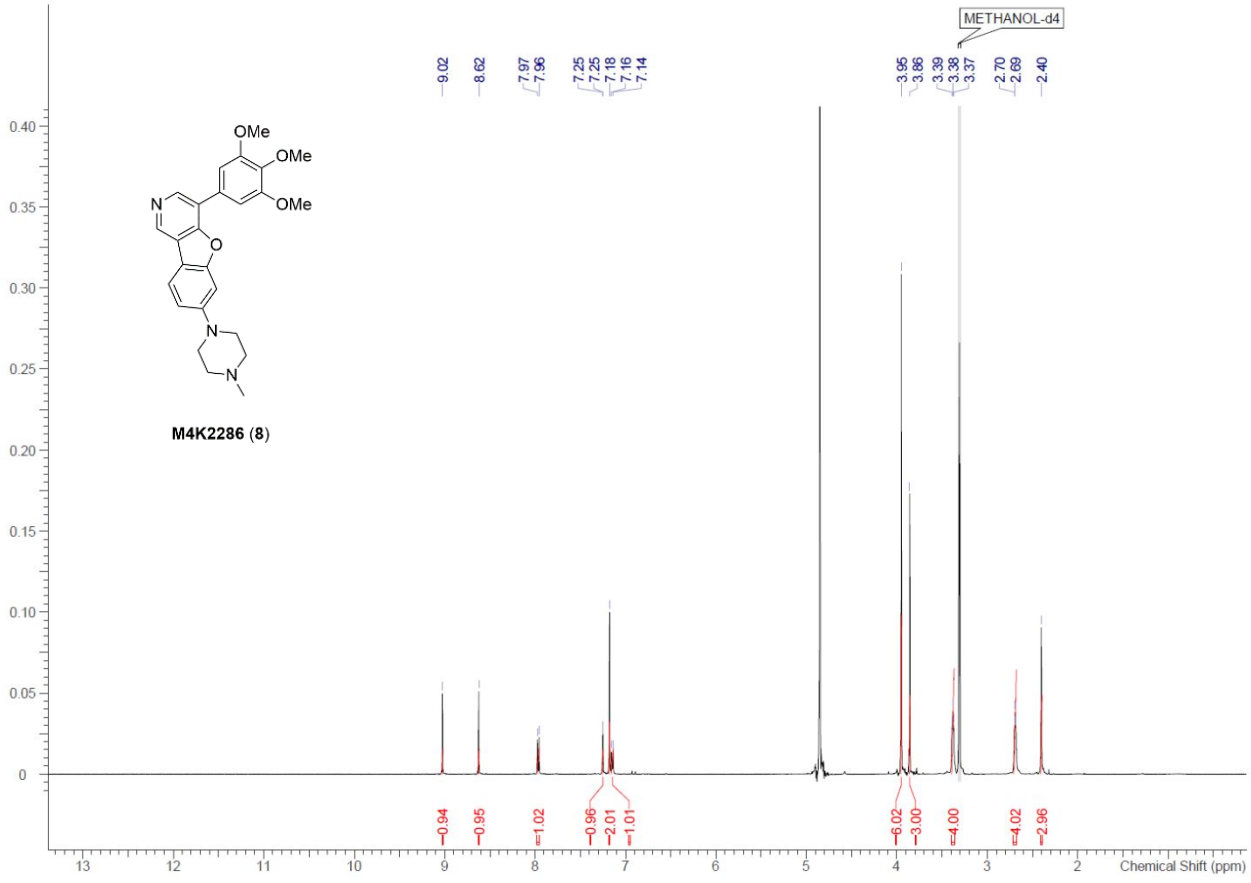
We decided to run the *in vivo* BBB penetration study of **M4K2306** a second time to ensure the exceptional B/P ratio of the compound.

Compound	C_{plasma} @ 2 h (nM)	C_{brain} @ 2 h (nM)	C_{plasma} @ 4 h (nM)	C_{brain} @ 4 h (nM)	C_{brain}/C_{plasma} @ 4 h
M4K2009	5250	2321	2683	888	0.3
M4K2306 (First run)	74	3301	40	2692	67.3

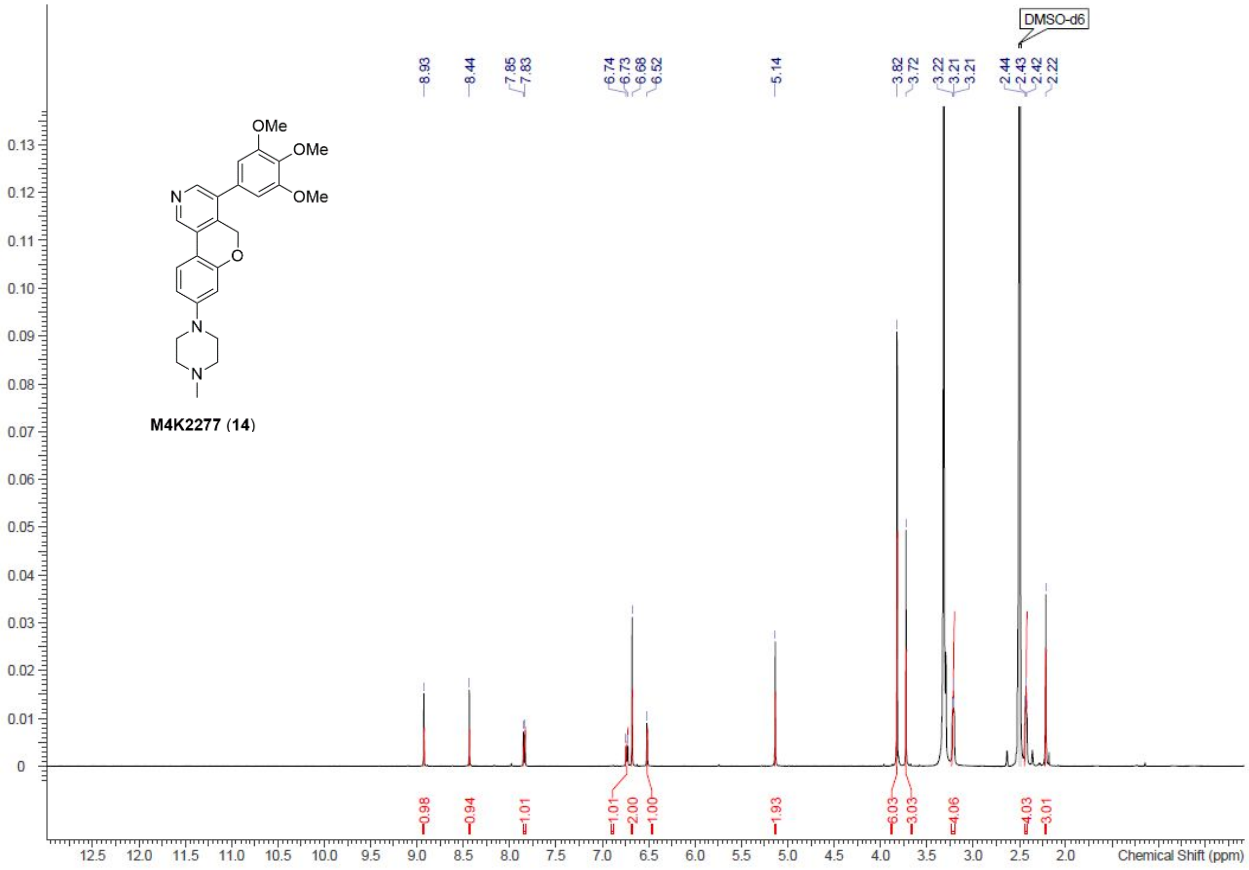
M4K2306 (Second run)	75	4966	45	3813	84.7

2. ^{1}H NMR Spectra of Final Compounds

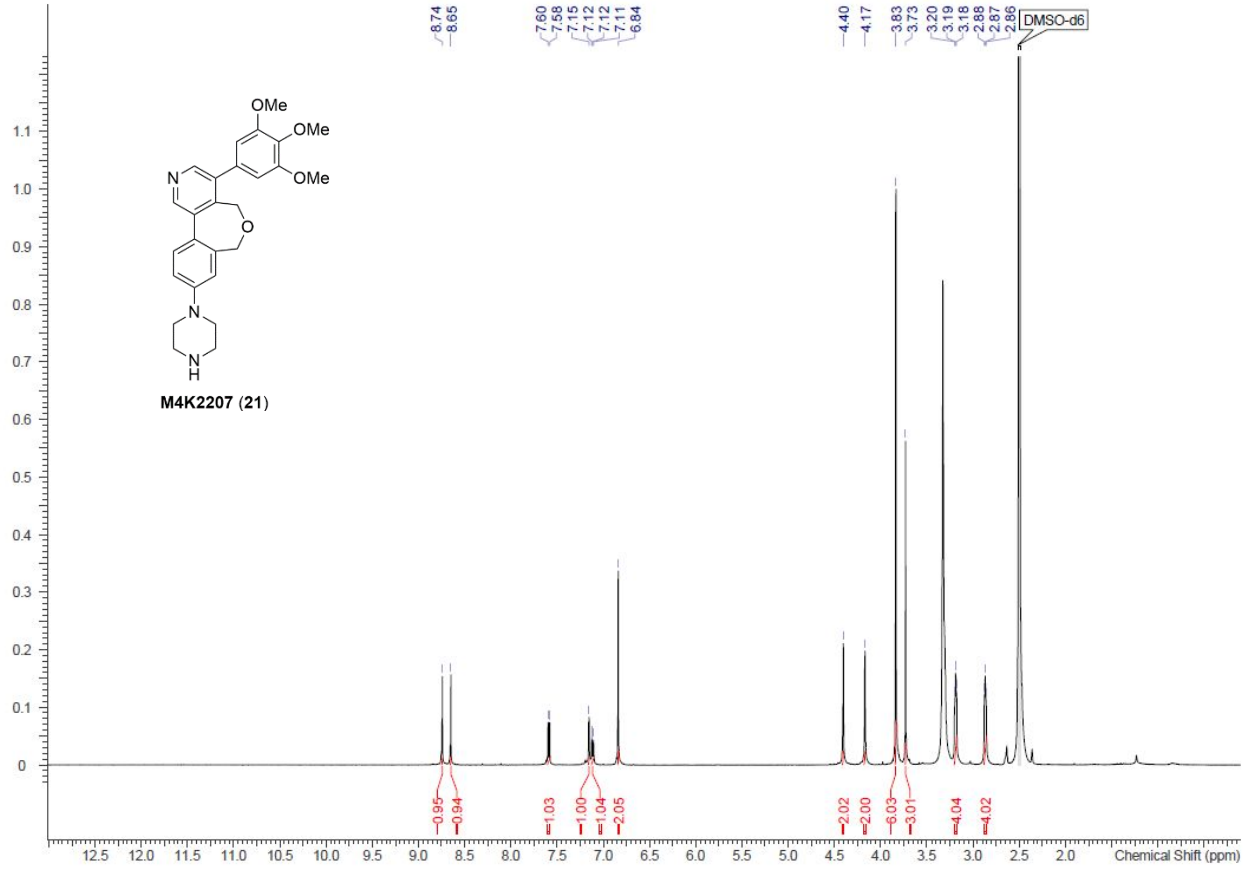
^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 9.02 (s, 1 H) 8.62 (s, 1 H) 7.97 (d, *J*=8.68 Hz, 1 H) 7.25 (d, *J*=1.83 Hz, 1 H) 7.18 (s, 2 H) 7.15 (dd, *J*=8.74, 1.90 Hz, 1 H) 3.95 (s, 6 H) 3.86 (s, 3 H) 3.40 - 3.37 (m, 4 H) 2.71 - 2.68 (m, 4 H) 2.40 (s, 3 H)



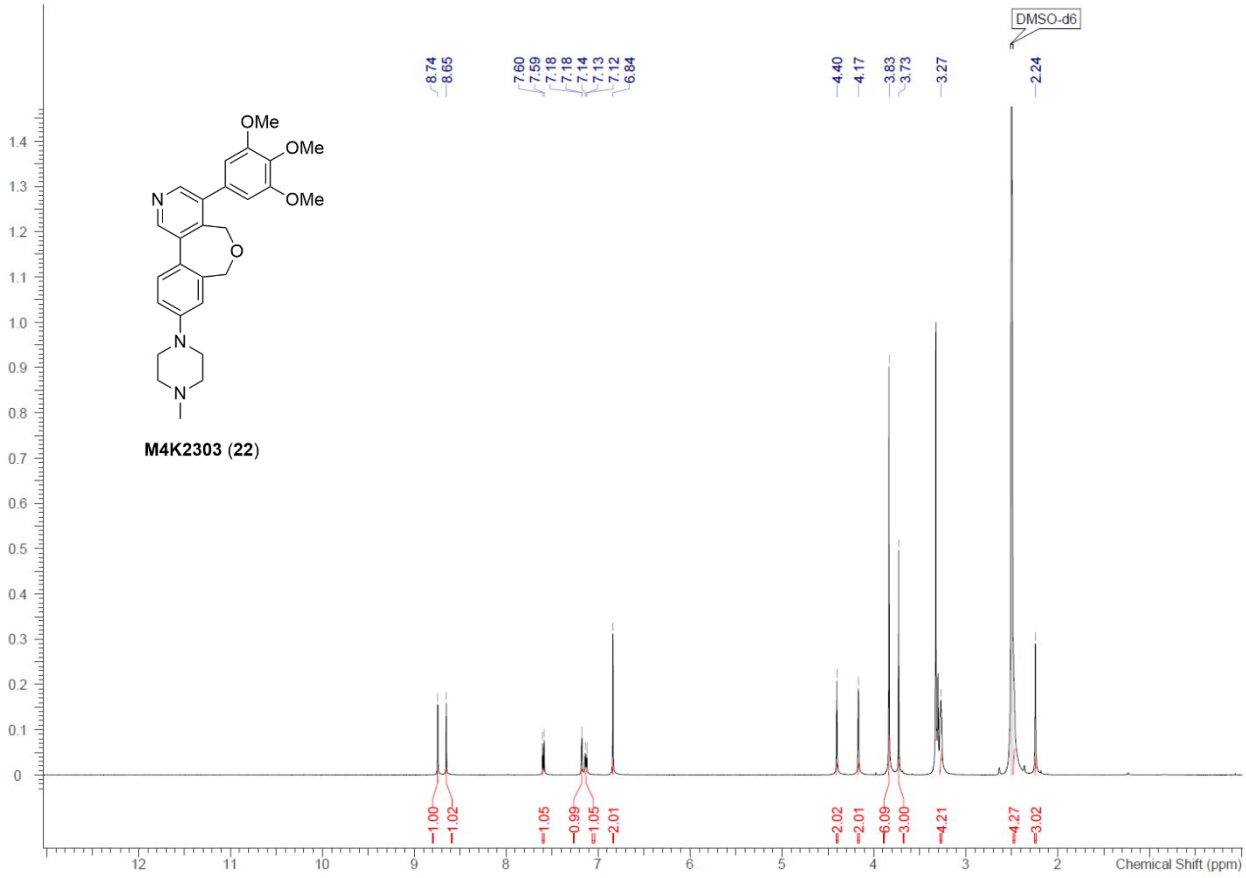
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.93 (s, 1 H) 8.44 (s, 1 H) 7.84 (d, *J*=8.68 Hz, 1 H) 6.74 (dd, *J*=8.68, 2.08 Hz, 1 H) 6.68 (s, 2 H) 6.52 (d, *J*=1.96 Hz, 1 H) 5.14 (s, 2 H) 3.82 (s, 6 H) 3.72 (s, 3 H) 3.23 - 3.20 (m, 4 H) 2.45 - 2.42 (m, 4 H) 2.22 (s, 3 H)



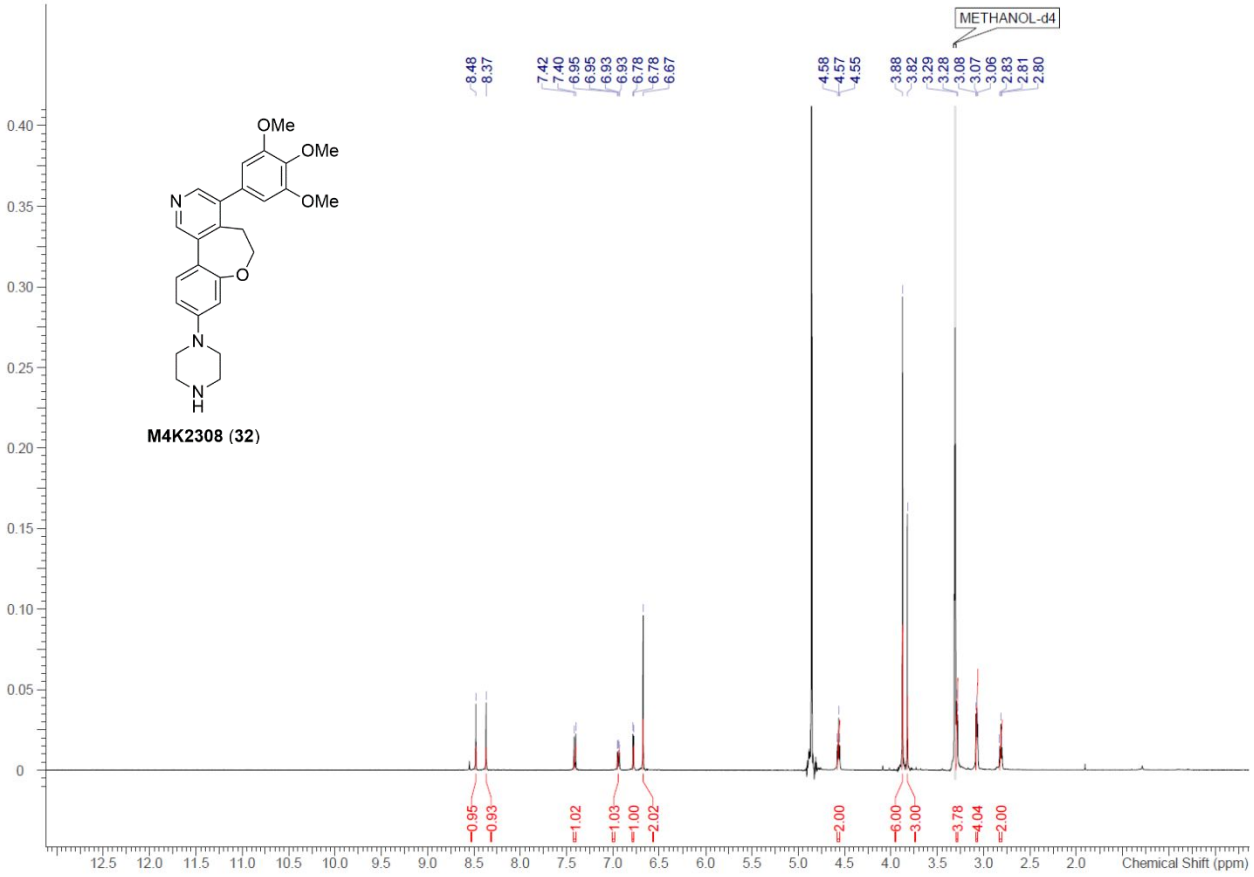
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.74 (s, 1 H) 8.65 (s, 1 H) 7.59 (d, *J*=8.56 Hz, 1 H) 7.16 (d, *J*=2.08 Hz, 1 H) 7.11 (dd, *J*=8.56, 2.20 Hz, 1 H) 6.84 (s, 2 H) 4.40 (s, 2 H) 4.17 (s, 2 H) 3.83 (s, 6 H) 3.73 (s, 3 H) 3.20 - 3.17 (m, 4 H) 2.88 - 2.85 (m, 4 H)



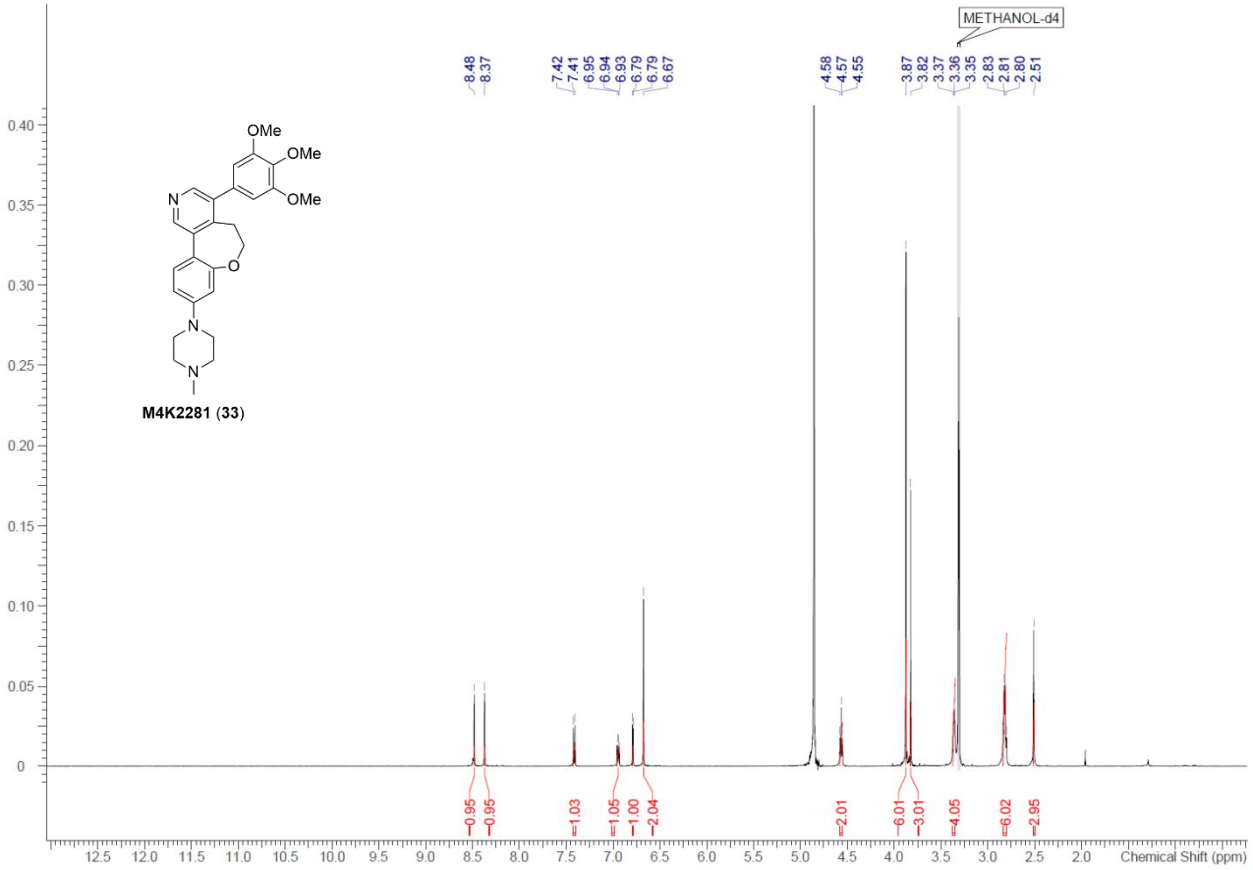
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.74 (s, 1 H) 8.65 (s, 1 H) 7.59 (d, *J*=8.44 Hz, 1 H) 7.18 (d, *J*=2.08 Hz, 1 H) 7.13 (dd, *J*=8.50, 2.14 Hz, 1 H) 6.84 (s, 2 H) 4.40 (s, 2 H) 4.17 (s, 2 H) 3.83 (s, 6 H) 3.73 (s, 3 H) 3.28 - 3.26 (m, 4 H) 2.48 - 2.47 (m, 4 H) 2.24 (s, 3 H)



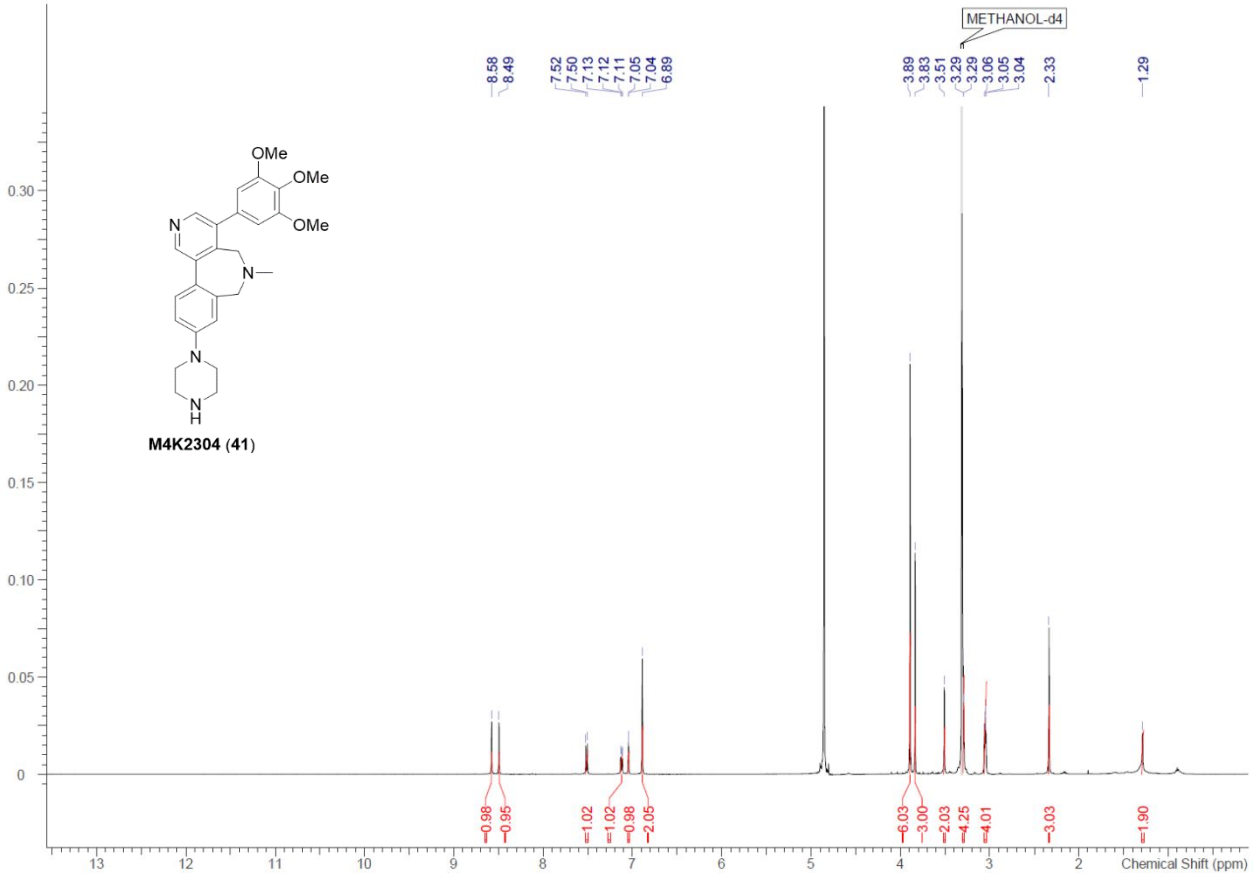
^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.48 (s, 1 H) 8.37 (s, 1 H) 7.41 (d, *J*=8.56 Hz, 1 H) 6.94 (dd, *J*=8.56, 2.45 Hz, 1 H) 6.78 (d, *J*=2.45 Hz, 1 H) 6.67 (s, 2 H) 4.57 (t, *J*=6.36 Hz, 2 H) 3.88 (s, 6 H) 3.82 (s, 3 H) 3.30 - 3.28 (m, 4 H) 3.09 - 3.06 (m, 4 H) 2.81 (t, *J*=6.30 Hz, 2 H)



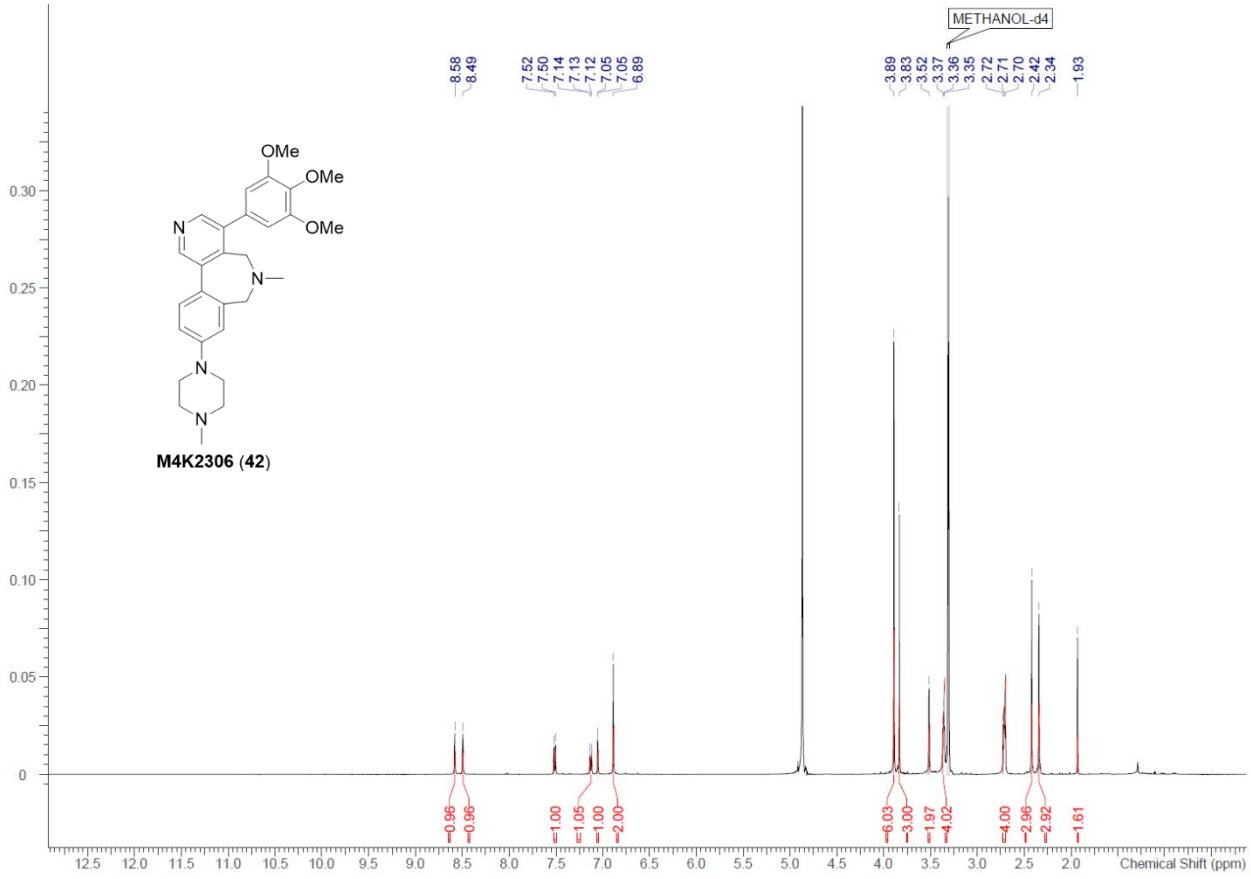
^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.48 (s, 1 H) 8.37 (s, 1 H) 7.41 (d, *J*=8.56 Hz, 1 H) 6.95 (dd, *J*=8.56, 2.57 Hz, 1 H) 6.79 (d, *J*=2.45 Hz, 1 H) 6.67 (s, 2 H) 4.57 (t, *J*=6.36 Hz, 2 H) 3.87 (s, 6 H) 3.82 (s, 3 H) 3.38 - 3.35 (m, 4 H) 2.84 - 2.80 (m, 6 H) 2.51 (s, 3 H)



^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.58 (s, 1 H) 8.49 (s, 1 H) 7.51 (d, *J*=8.44 Hz, 1 H) 7.12 (dd, *J*=8.50, 2.38 Hz, 1 H) 7.04 (d, *J*=2.32 Hz, 1 H) 6.89 (s, 2 H) 3.89 (s, 6 H) 3.83 (s, 3 H) 3.51 (s, 2 H) 3.30 - 3.29 (m, 4 H) 3.06 - 3.04 (m, 4 H) 2.33 (s, 3 H) 1.29 (s, 2 H)



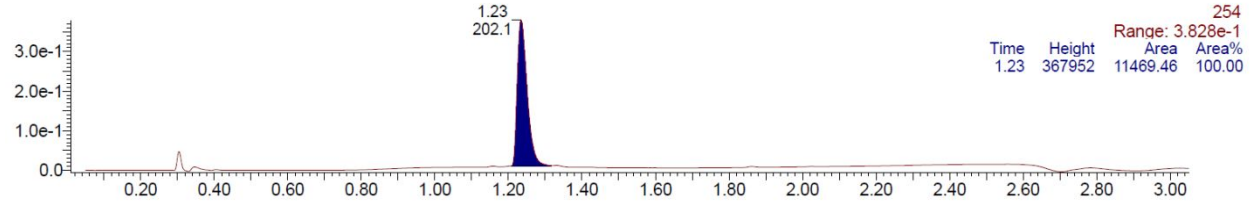
^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.58 (s, 1 H) 8.49 (s, 1 H) 7.51 (d, J=8.44 Hz, 1 H) 7.13 (dd, J=8.44, 2.45 Hz, 1 H) 7.05 (d, J=2.45 Hz, 1 H) 6.89 (s, 2 H) 3.89 (s, 6 H) 3.83 (s, 3 H) 3.52 (s, 2 H) 3.37 - 3.35 (m, 4 H) 2.73 - 2.70 (m, 4 H) 2.42 (s, 3 H) 2.34 (s, 3 H) 1.93 (s, 2 H)



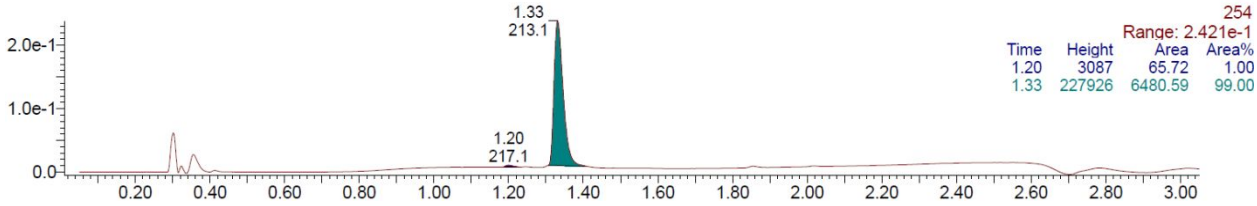
3. HPLC Traces of Final Compounds

Compound purity was determined by UV absorbance at 254 nm during tandem liquid chromatography/mass spectrometry (LCMS) using a Waters Acquity separations module. All final compounds had a purity of ≥95% as determined using this method. The column used was an Acquity UPLC HSS T3 (2.1 × 50 mm, 100 Å, 1.8 μm. part no. 186003538). Mobile phase A consisted of 0.1% formic acid in water, while mobile phase B consisted of 0.1% formic acid in acetonitrile. The gradient went from 98% to 5% mobile phase A over 1.8 min, maintained at 5% for 0.5 min, then increased to 98% over 0.2 min for a total run time of 3 min. The flow rate was 0.4 mL/min, and column temperature was maintained at 25 °C.

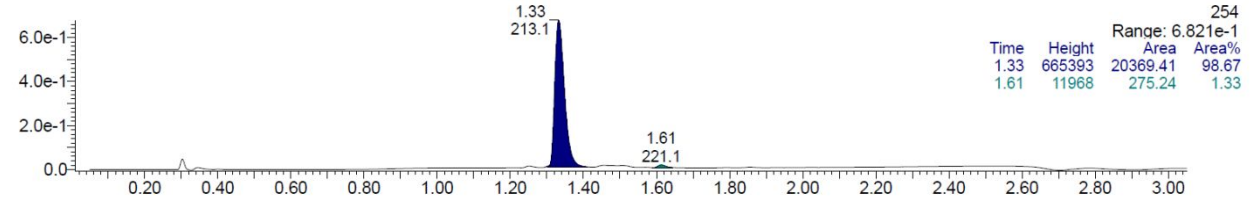
M4K2286 (8)



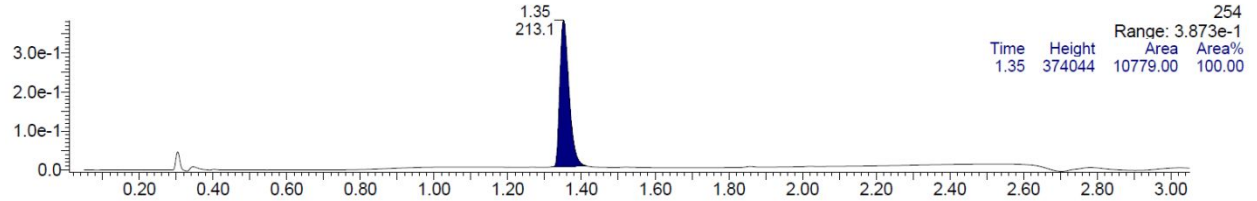
M4K2277 (14)



M4K2207 (21)



M4K2303 (22)



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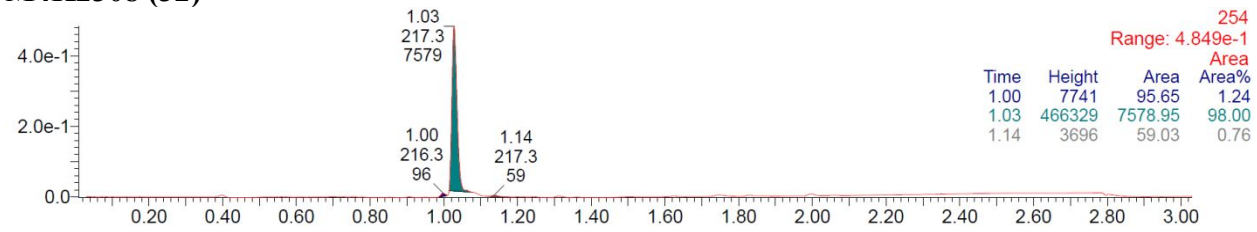
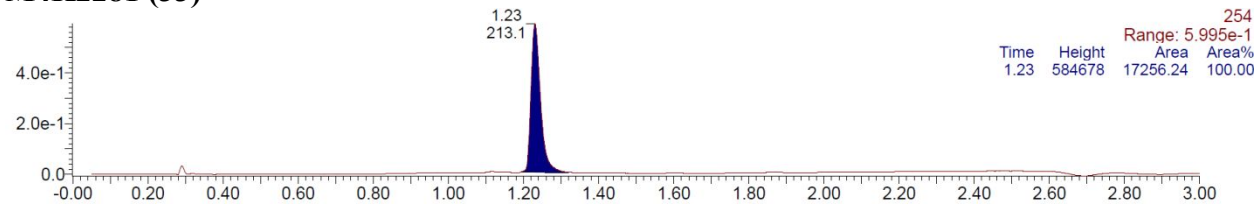
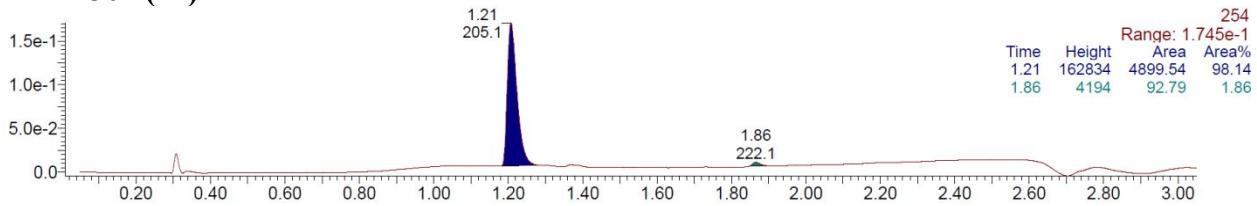


M4K2281 (33)



M4K2304 (41)



M4K2306 (42)