SUPPORTING INFORMATION

Discovery and optimization of 2*H*-1λ^2-pyridin-2-one inhibitors of mutant isocitrate dehydrogenase 1 for the treatment of cancer

Jason M. Rohde[a,g], Surendra Karavadhi[a,], Rajan Pragani[a], Li Liu[a], Yuhong Fang[a], Weihe Zhang[b], Andrew McIver[b], Hongchao Zheng[b], Qingyang Liu[b], Mindy I. Davis[a], Daniel J. Urban[a], Tobie D. Lee[a], Dorian M. Cheff[a], Melinda Hollingshead[c], Mark J. Henderson[a], Natalia J. Martinez[a], Kyle R. Brimacombe[a], Adam Yasgar[a], Wei Zhao[a], Carleen Klumpp-Thomas[a], Sam Michael[a], Joseph Covey[d], William J. Moore[e], Gordon M. Stott[e], Zhuyin Li[a], Anton Simeonov[a], Ajit Jadhav[a], Stephen Frye[b], Matthew D. Hall[a*], Min Shen[a*], Xiaodong Wang[b*], Samarjit Patnaik[a*], Matthew B. Boxer[a,f]

[a]National Center for Advancing Translational Sciences, National Institutes of Health, 9800 Medical Center Drive, Rockville, MD, 20850, USA

[b]Center for Integrative Chemical Biology and Drug Discovery, Division for Chemical Biology and Medicinal Chemistry, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC 27514

[c]Biological Testing Branch, Developmental therapeutics Program, National Cancer Institute, Frederick, MD 21702

[d]Developmental Therapeutics Program Division of Cancer Treatment and Diagnosis, National Cancer Institute, Rockville, MD 20850

[e]NExT Program Support, Applied/Developmental Research Directorate, Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, Maryland, 21702

[f]Current address: Veralox Therapeutics Inc., 4539 Metropolitan Ct., Frederick, MD 21704

[g]Current address: Walter Reed Army Institute of Research, 503 Robert Grant Avenue, Silver Spring, MD 20910

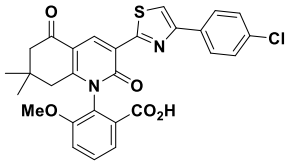
*To whom correspondence should be addressed
Matthew D. Hall, Min Shen, Samarjit Patnaik: 9800 Medical Center Dr., Rockville, MD 20850, Email: matthew.hall@nih.gov, shenmin@mail.nih.gov, samarjit.patnaik@nih.gov
Xiaodong Wang: 3204 Marsico Hall, 125 Mason Farm Rd, Chapel Hill, NC 27599-7363, Email: xiaodonw@unc.edu

Keywords:
mIDH1 ,inhibitor, 2-hydroxyglutarate

Table of Contents **page**

S1. QC and ^{1}H NMR of representative analogs

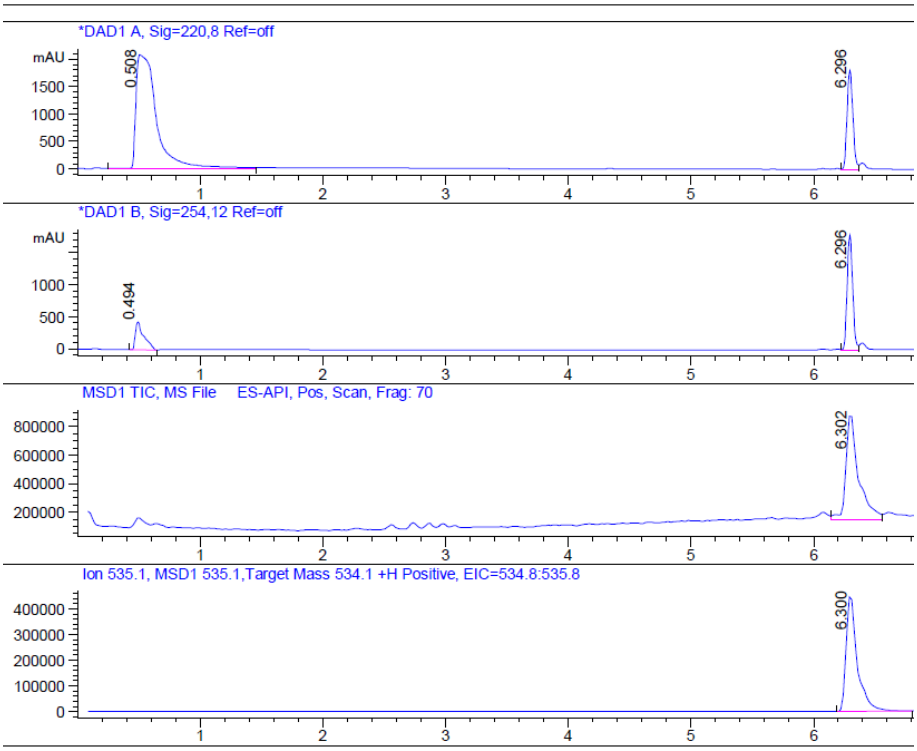
2-(3-(4-(4-Chlorophenyl)thiazol-2-yl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)-3-methoxybenzoic acid (**59**):



59

Chemical Formula: $C_{28}H_{23}ClN_2O_5S$
Exact Mass: 534.10

```
Method Info : Standard Gradient 4% to 100% Acetonitrile (0.05% TFA) over 7 mi
              Luna C18 3 micron 3 x 75mm
```

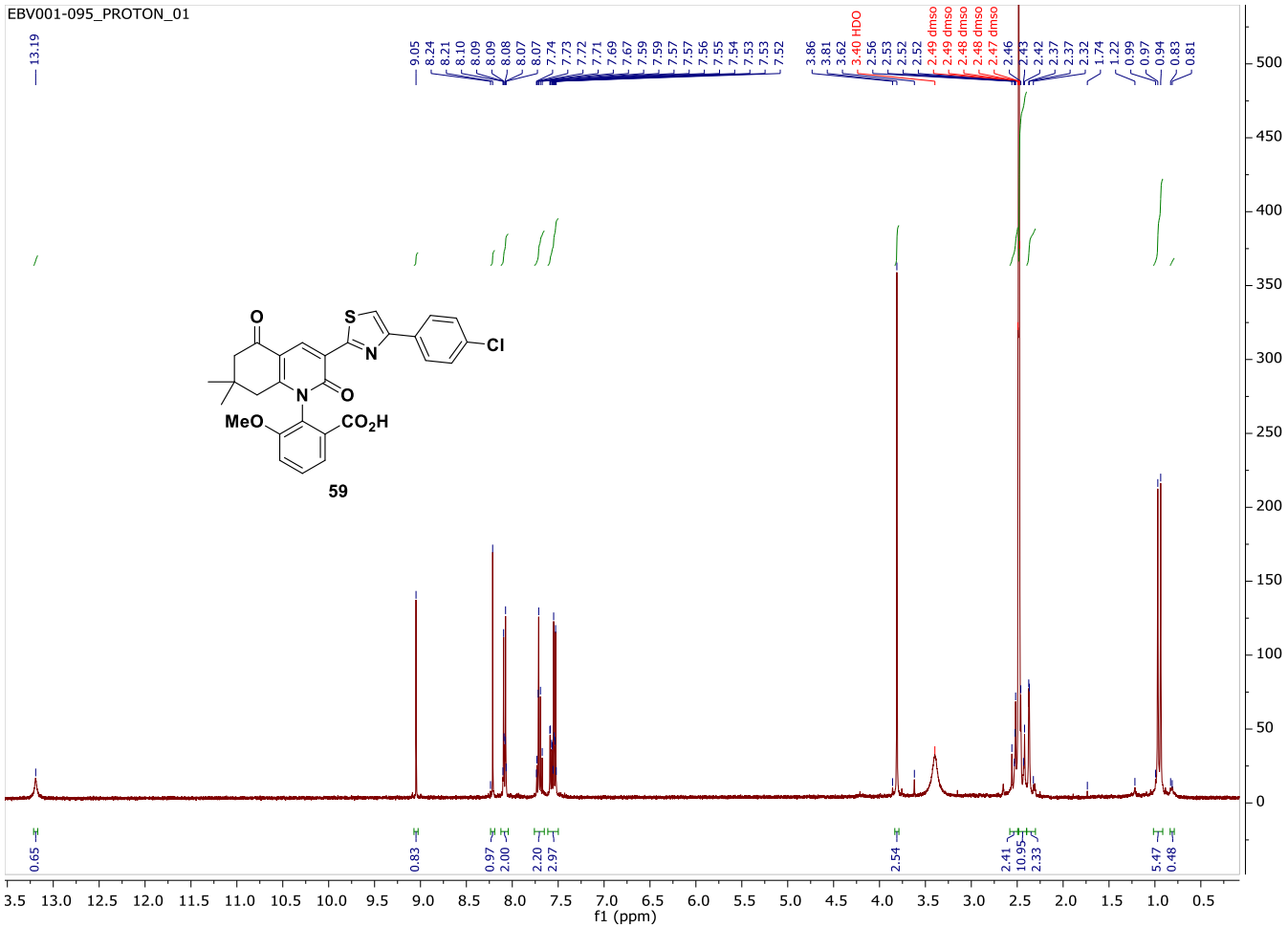


Integration Results for DAD1 A, Sig=220,8 Ref=off

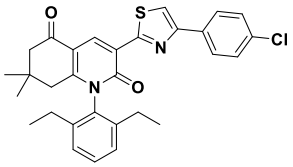
RetTim	Width	Area	Height	Area%	MS(+)
0.51	0.15	24789.49	2081.57	80.80	317
6.30	0.05	5890.87	1803.96	19.20	535

Integration Results for DAD1 B, Sig=254,12 Ref=off

RetTim	Width	Area	Height	Area%	MS(+)
0.49	0.07	2118.98	441.56	27.35	317
6.30	0.05	5628.41	1798.31	72.65	535

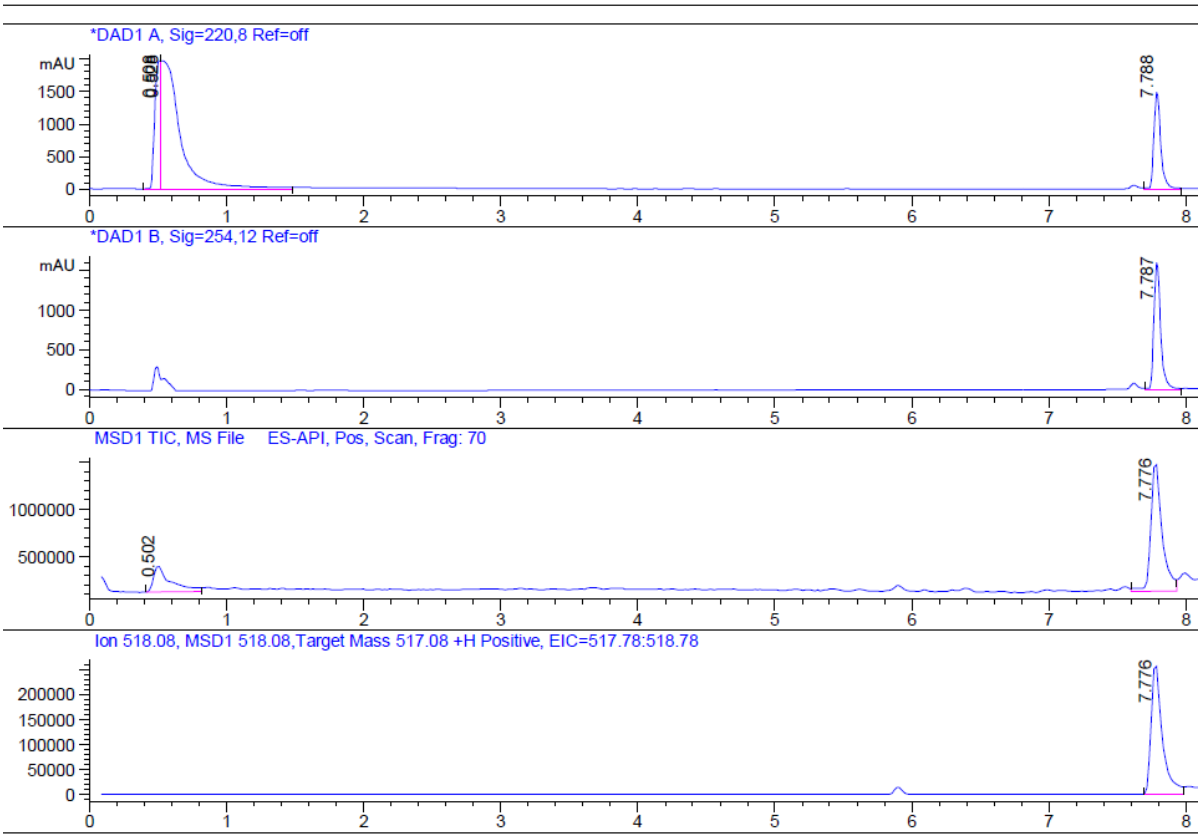

EBV001-095_PROTON_01
59
f1 (ppm)

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (**66**):



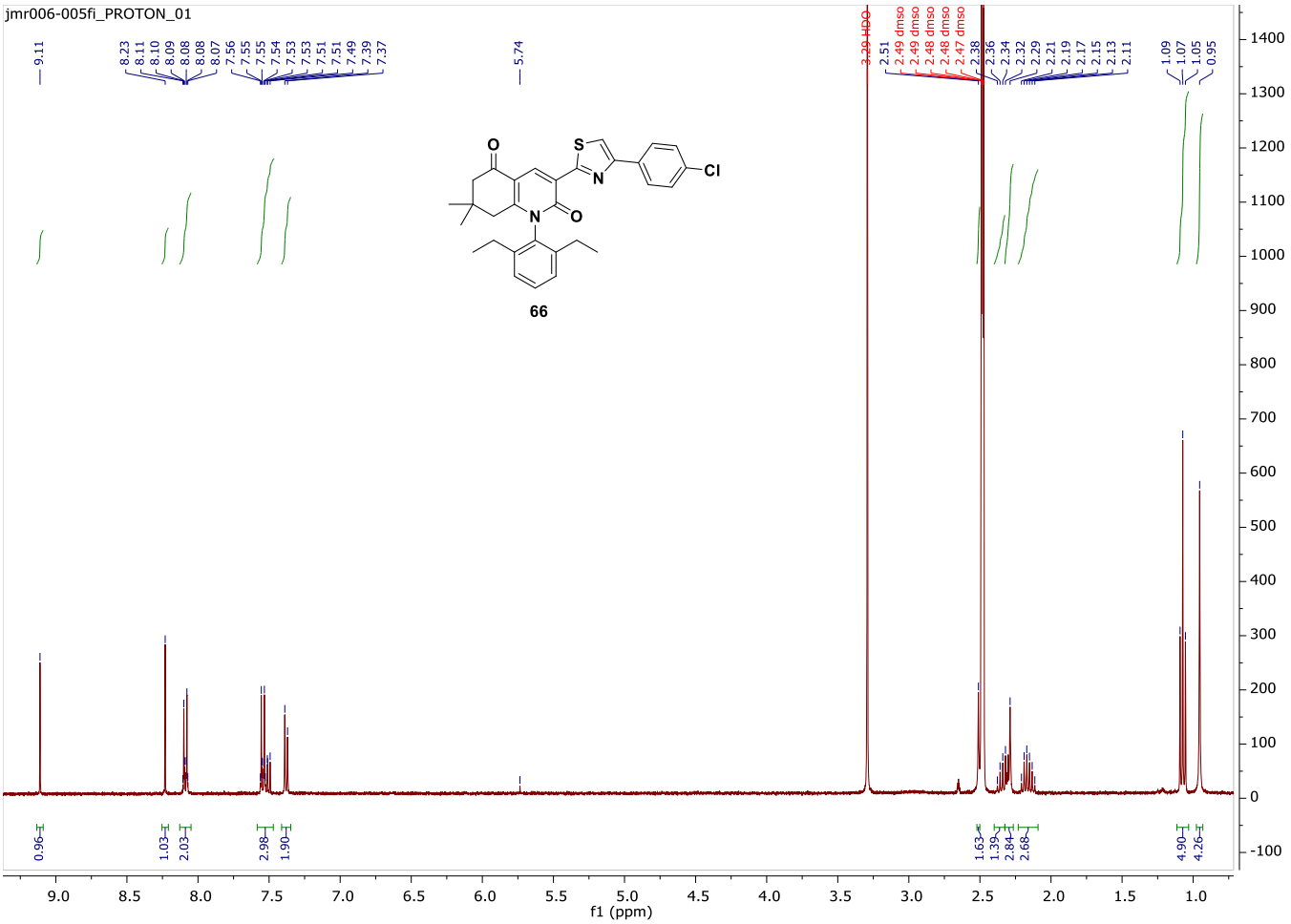
66
Chemical Formula: $C_{30}H_{29}ClN_2O_2S$
Exact Mass: 516.16

Method Info : Standard Gradient 4% to 100% Acetonitrile (0.05% TFA) over 7 minutes
Luna C18 3 micron 3 x 75mm

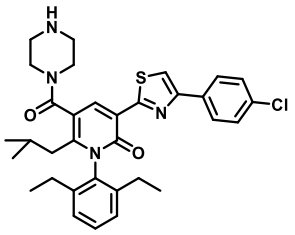


Integration Results for DAD1 A, Sig=220,8 Ref=off

RetTim	Width	Area	Height	Area%	MS(+)
0.51	0.04	5289.90	1971.53	17.47	179
0.53	0.17	19805.24	1970.02	65.41	179
7.79	0.05	5182.13	1489.39	17.12	517

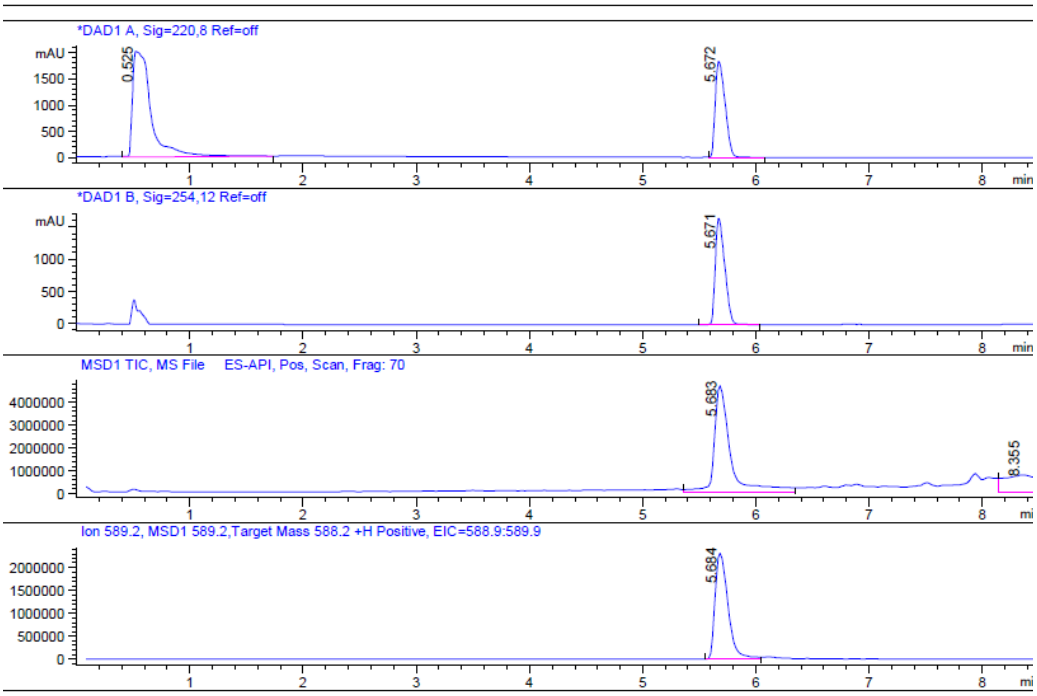

jmr006-005fi_PROTON_01
66
f1 (ppm)

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-isobutyl-5-(piperazine-1-carbonyl)pyridin-2(1H)-one (**91**):



Chemical Formula: $C_{33}H_{37}ClN_4O_2S$
Exact Mass: 588.23

Method Info : Standard Gradient 4% to 100% Acetonitrile (0.05% TFA) over 7 minutes
Luna C18 3 micron 3 x 75mm

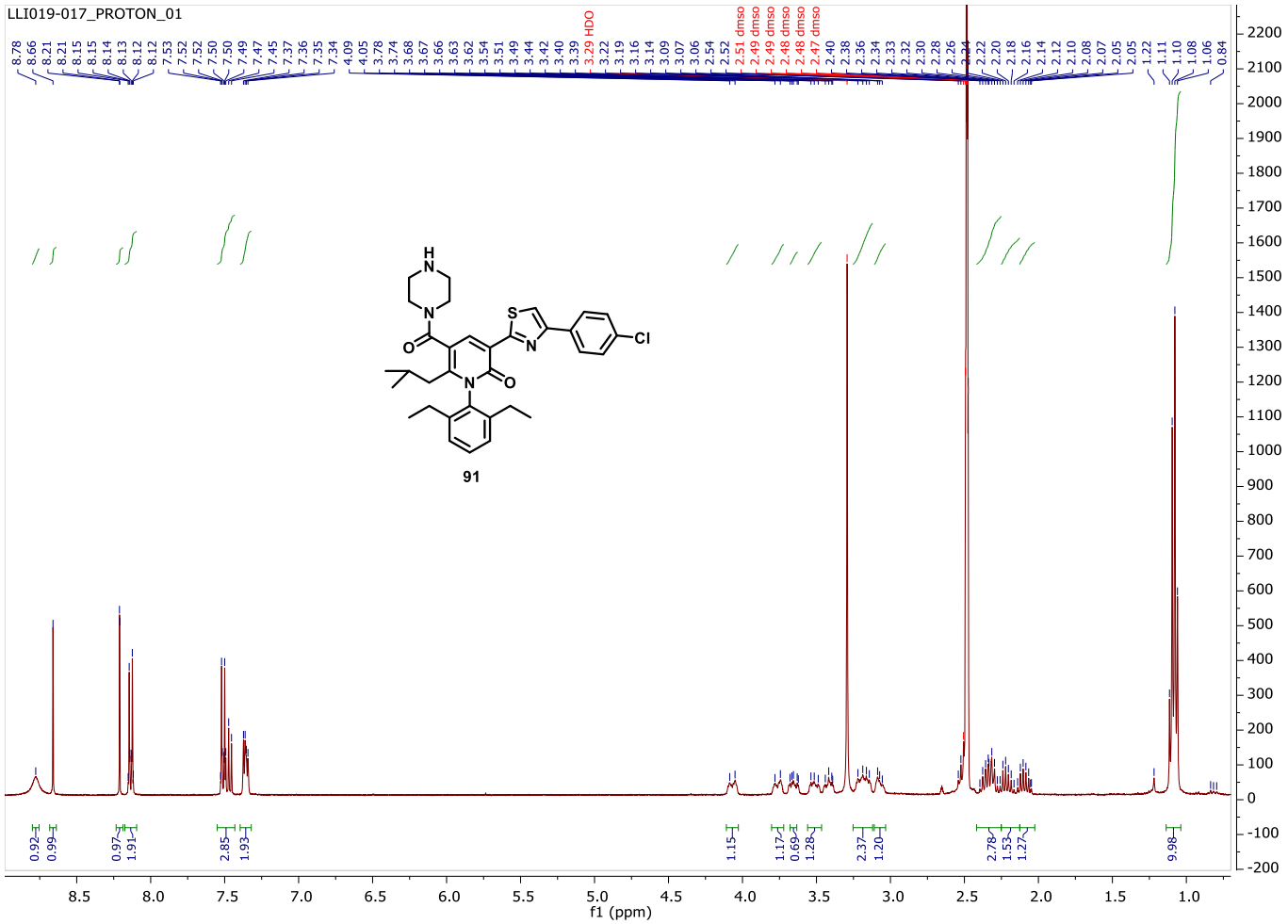


Integration Results for DAD1 A, Sig=220,8 Ref=off

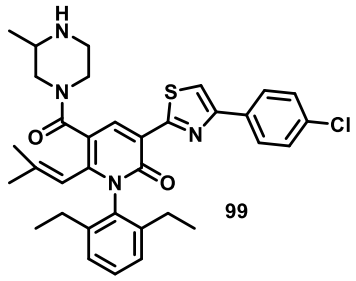
RetTim	Width	Area	Height	Area%	MS(+)
0.53	0.15	22919.35	2019.42	67.53	179
5.67	0.10	11018.99	1832.58	32.47	589

Integration Results for DAD1 B, Sig=254,12 Ref=off

RetTim	Width	Area	Height	Area%	MS(+)
5.67	0.09	9588.02	1658.08	100.00	589


LLI019-017_PROTON_01
91
f1 (ppm)

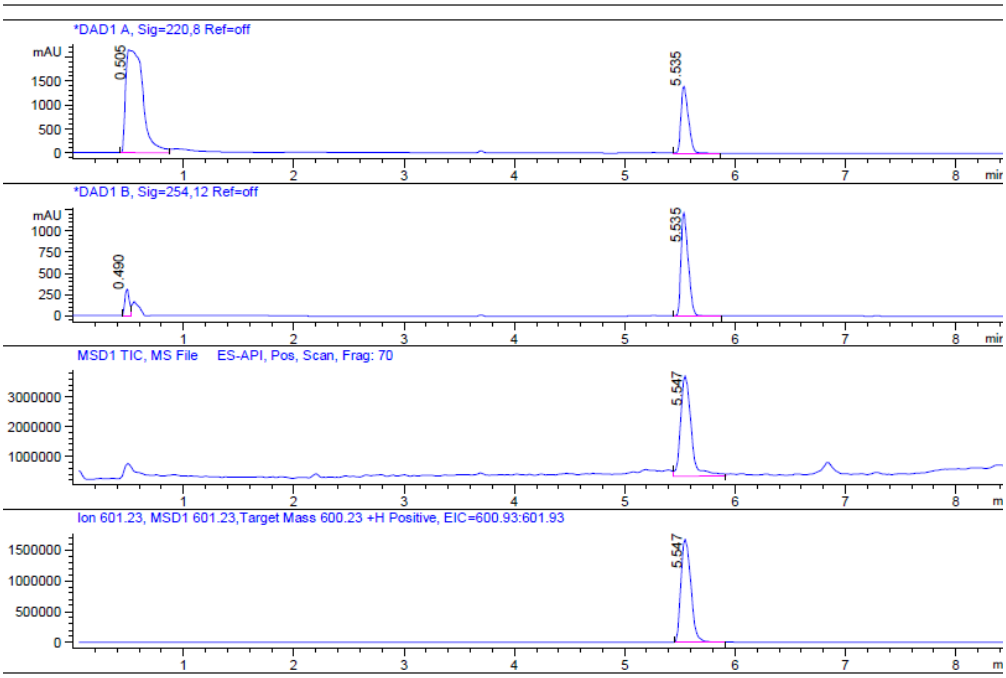
3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(3-methylpiperazine-1-carbonyl)-6-(2-methylprop-1-en-1-yl)pyridin-2(1H)-one (**99**)



99

Chemical Formula: $C_{34}H_{37}ClN_4O_2S$
Exact Mass: 600.23

Method Info : Standard Gradient 4% to 100% Acetonitrile (0.05% TFA) over 7 minutes
Luna C18 3 micron 3 x 75mm

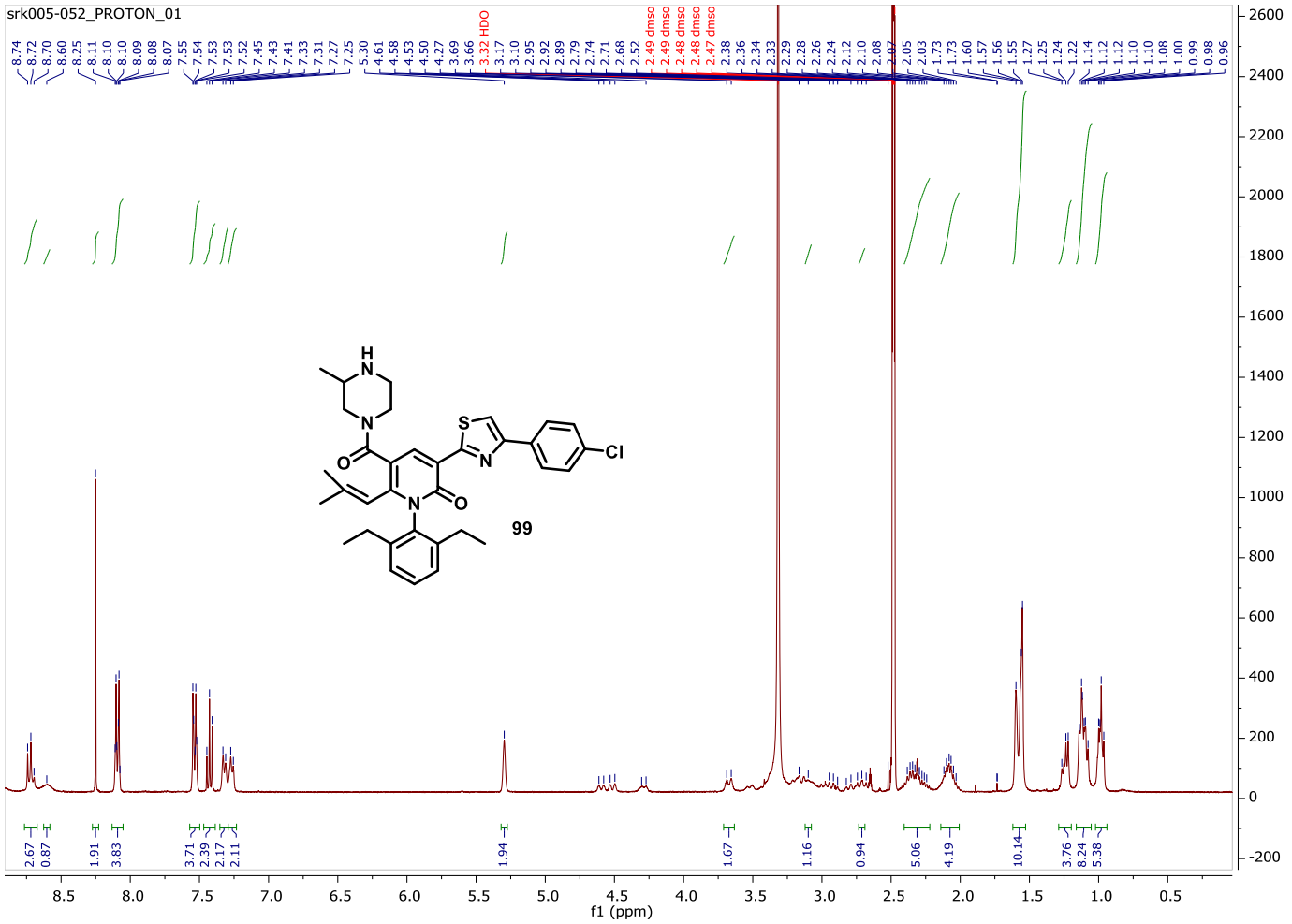


Integration Results for DAD1 A, Sig=220,8 Ref=off

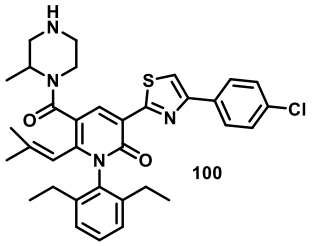
RetTim	Width	Area	Height	Area%	MS(+)
0.50	0.14	23445.16	2156.96	78.38	179
5.53	0.07	6466.48	1400.39	21.62	601

Integration Results for DAD1 B, Sig=254,12 Ref=off

RetTim	Width	Area	Height	Area%	MS(+)
0.49	0.04	861.07	313.55	13.21	179
5.53	0.07	5656.51	1223.25	86.79	601

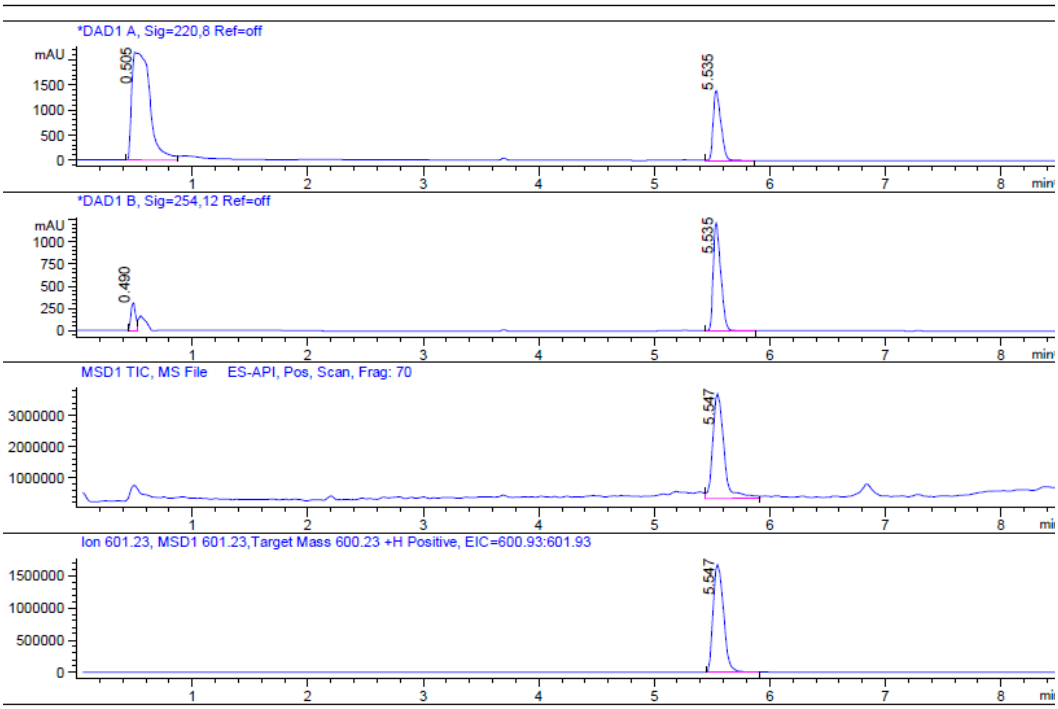

srk005-052_PROTON_01
99
f1 (ppm)

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(2-methylpiperazine-1-carbonyl)-6-(2-methylprop-1-en-1-yl)pyridin-2(1H)-one (**100**):



Chemical Formula: $C_{34}H_{37}ClN_4O_2S$
Exact Mass: 600.23

Method Info : Standard Gradient 4% to 100% Acetonitrile (0.05% TFA) over 7 minutes
Luna C18 3 micron 3 x 75mm

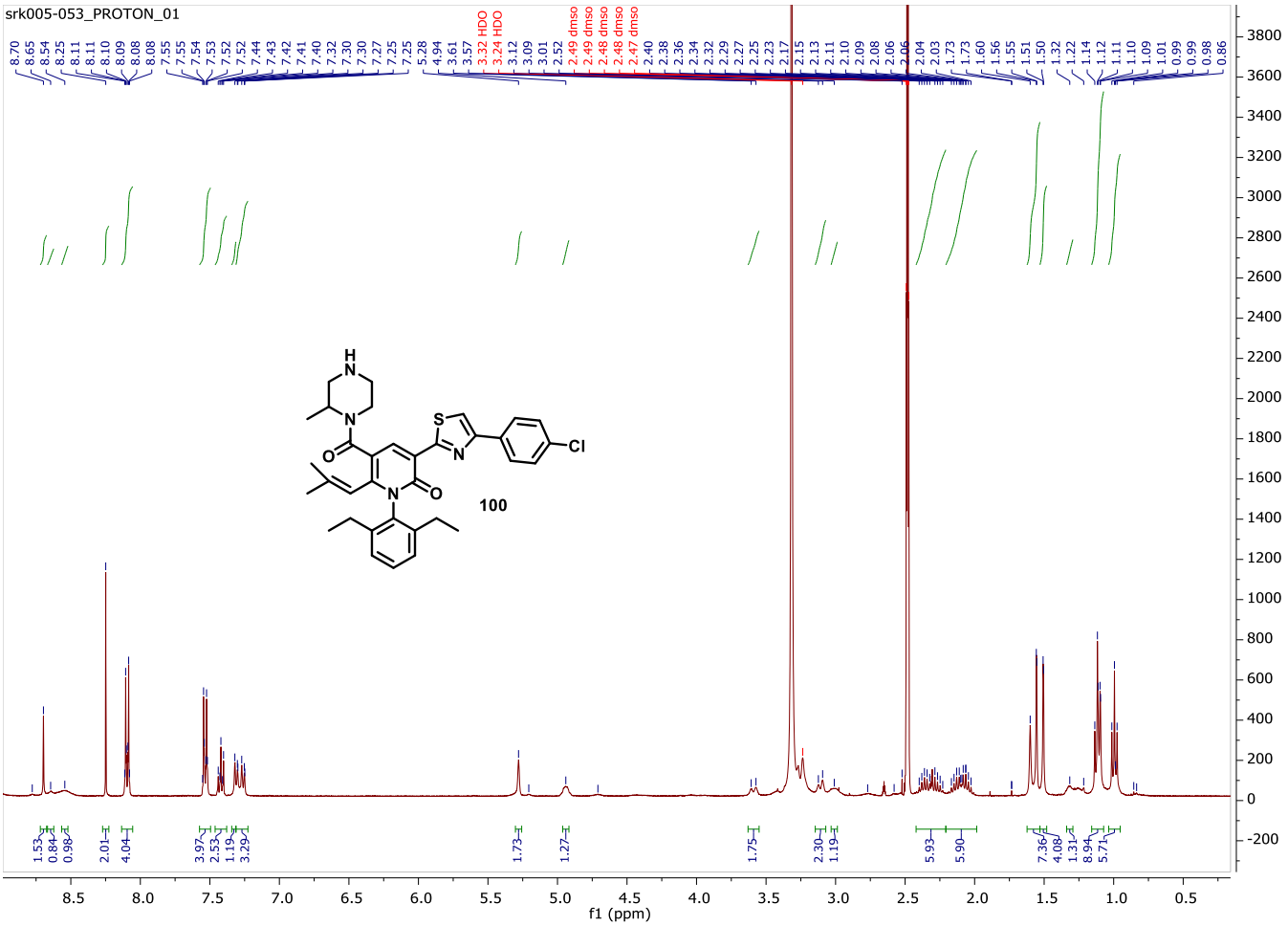


Integration Results for DAD1 A, Sig=220,8 Ref=off

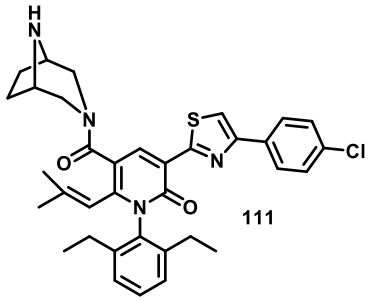
RetTim	Width	Area	Height	Area%	MS(+)
0.50	0.14	23445.16	2156.96	78.38	179
5.53	0.07	6466.48	1400.39	21.62	601

Integration Results for DAD1 B, Sig=254,12 Ref=off

RetTim	Width	Area	Height	Area%	MS(+)
0.49	0.04	861.07	313.55	13.21	179
5.53	0.07	5656.51	1223.25	86.79	601


srk005-053_PROTON_01
100
f1 (ppm)

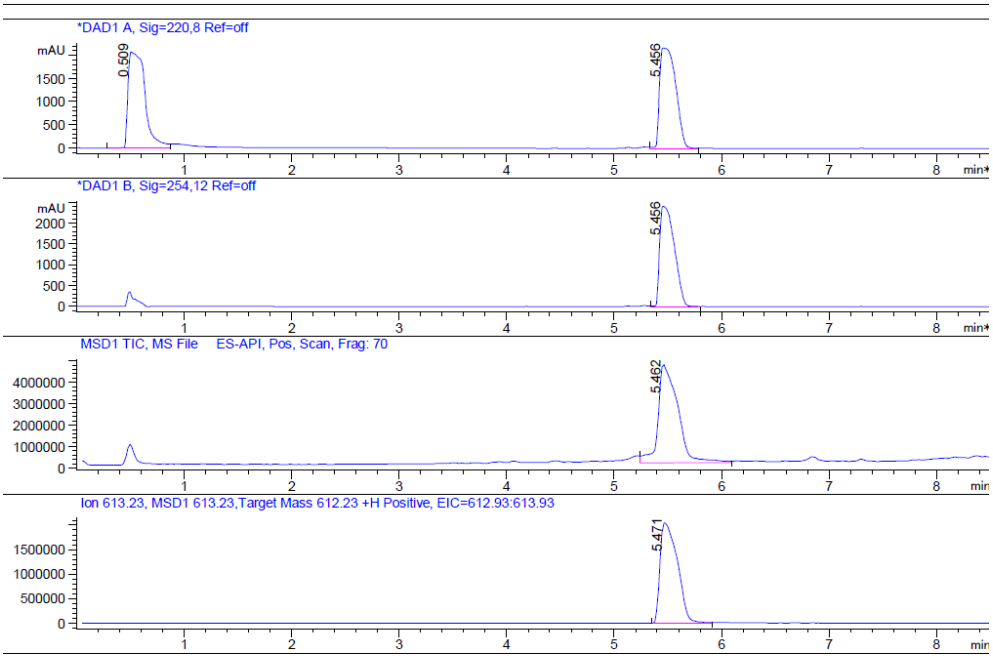
5-((1R,5S)-3,8-Diazabicyclo[3.2.1]octane-3-carbonyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methylprop-1-en-1-yl)pyridin-2(1H)-one (**111**):



111

Chemical Formula: $C_{35}H_{37}ClN_4O_2S$
Exact Mass: 612.23

Method Info : Standard Gradient 4% to 100% Acetonitrile (0.05% TFA) over 7 minutes
Luna C18 3 micron 3 x 75mm

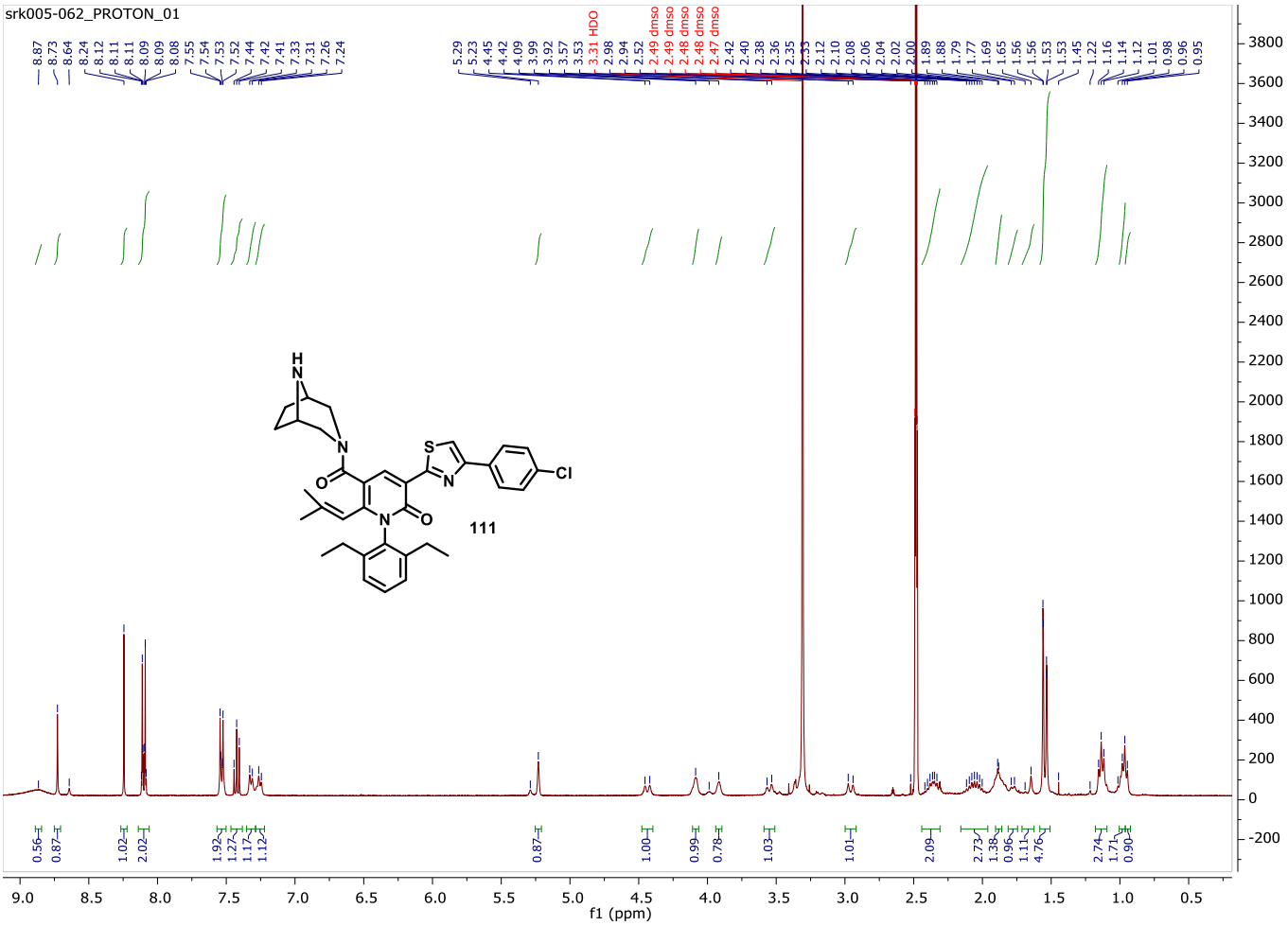


Integration Results for DAD1 A, Sig=220,8 Ref=off

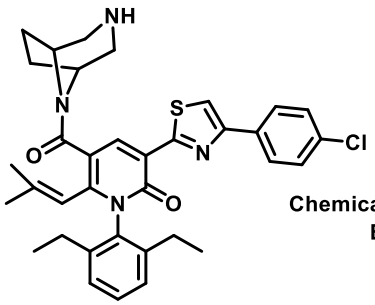
RetTim	Width	Area	Height	Area%	MS(+)
0.51	0.14	22721.78	2080.79	50.12	179
5.46	0.14	22613.84	2174.38	49.88	613

Integration Results for DAD1 B, Sig=254,12 Ref=off

RetTim	Width	Area	Height	Area%	MS(+)
5.46	0.12	22897.88	2419.07	100.00	613

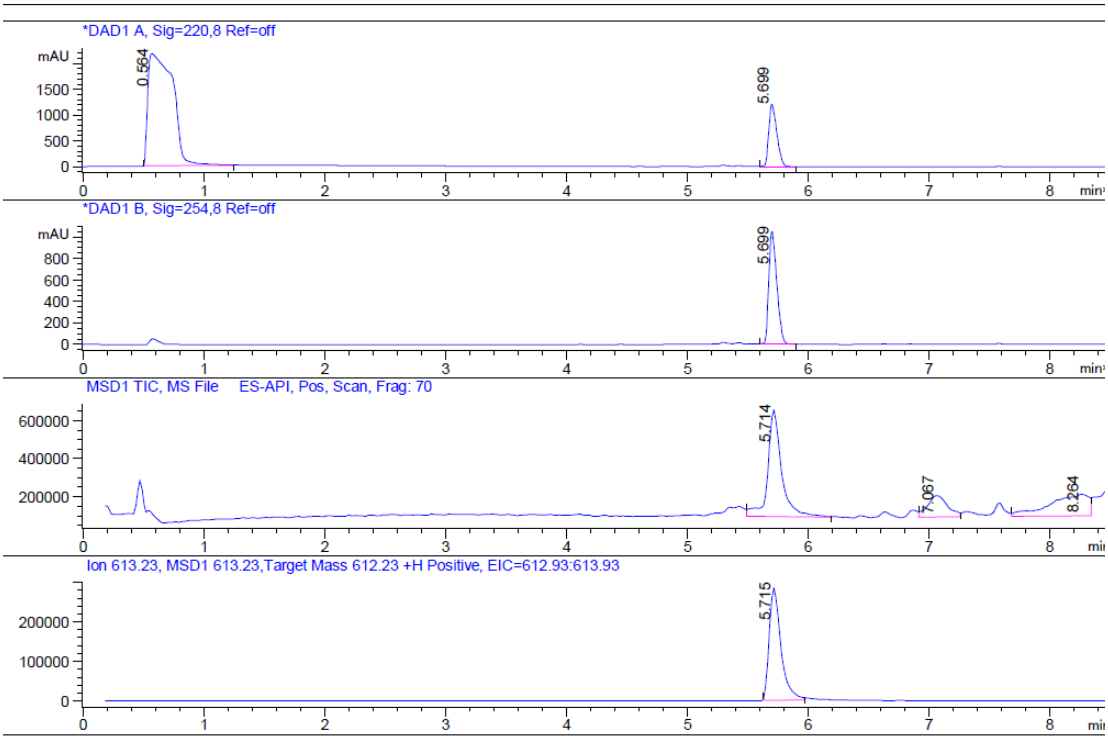

srk005-062_PROTON_01
111
f1 (ppm)

5-(3,8-Diazabicyclo[3.2.1]octane-8-carbonyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methylprop-1-en-1-yl)pyridin-2(1H)-one (**112**):



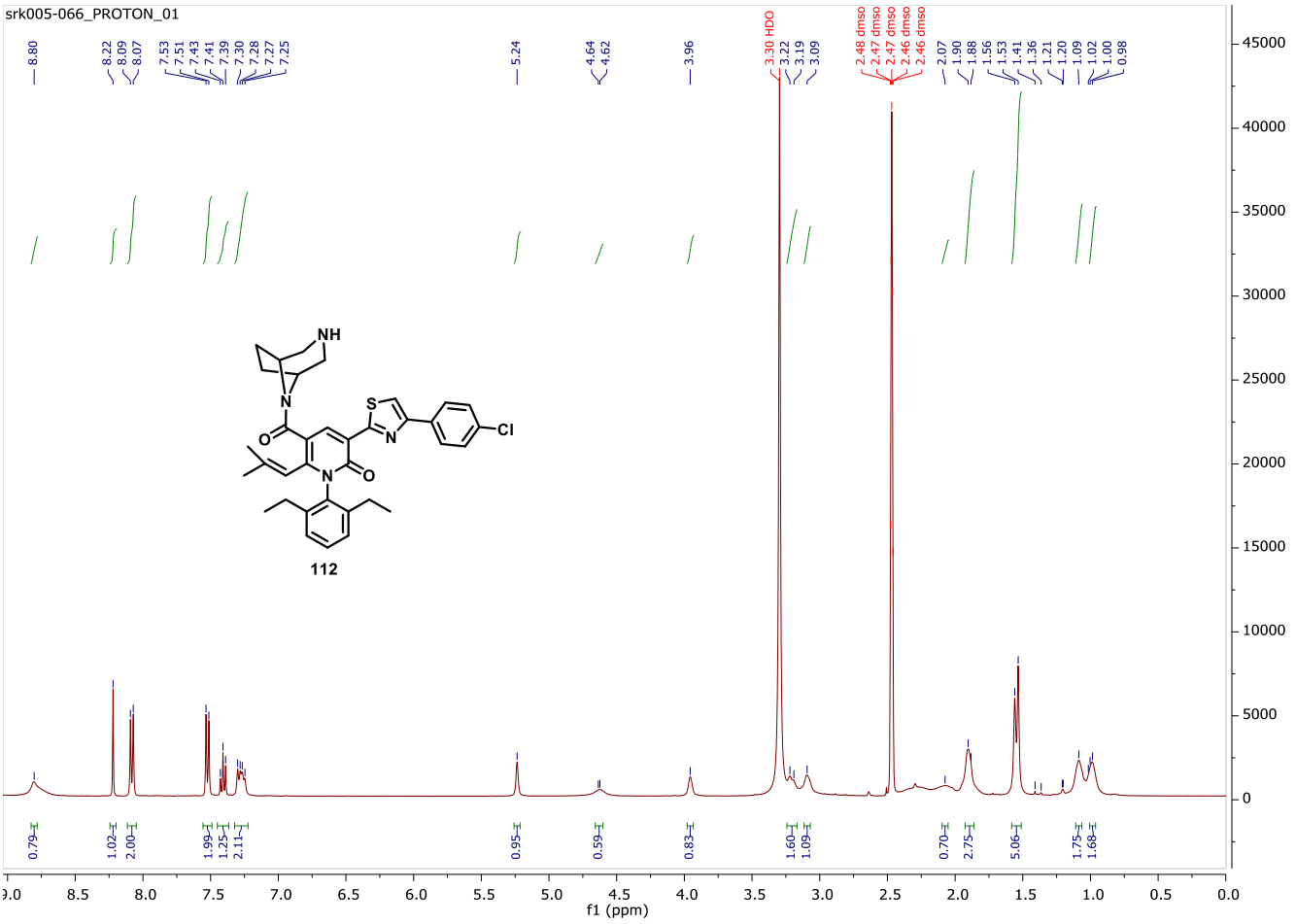
Chemical Formula: $C_{35}H_{37}ClN_4O_2S$
Exact Mass: 612.23

Method Info : Long Gradient 4% to 100% ACN over 7 minutes (0.05%TFA)
Luna C18 3.0 x 75 mm

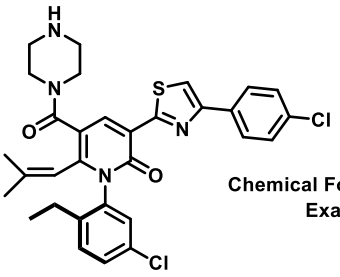


Integration Results for DAD1 A, Sig=220,8 Ref=off

RetTim	Width	Area	Height	Area%	MS(+)
0.56	0.19	30958.56	2171.89	84.66	179
5.70	0.07	5607.86	1208.39	15.34	613

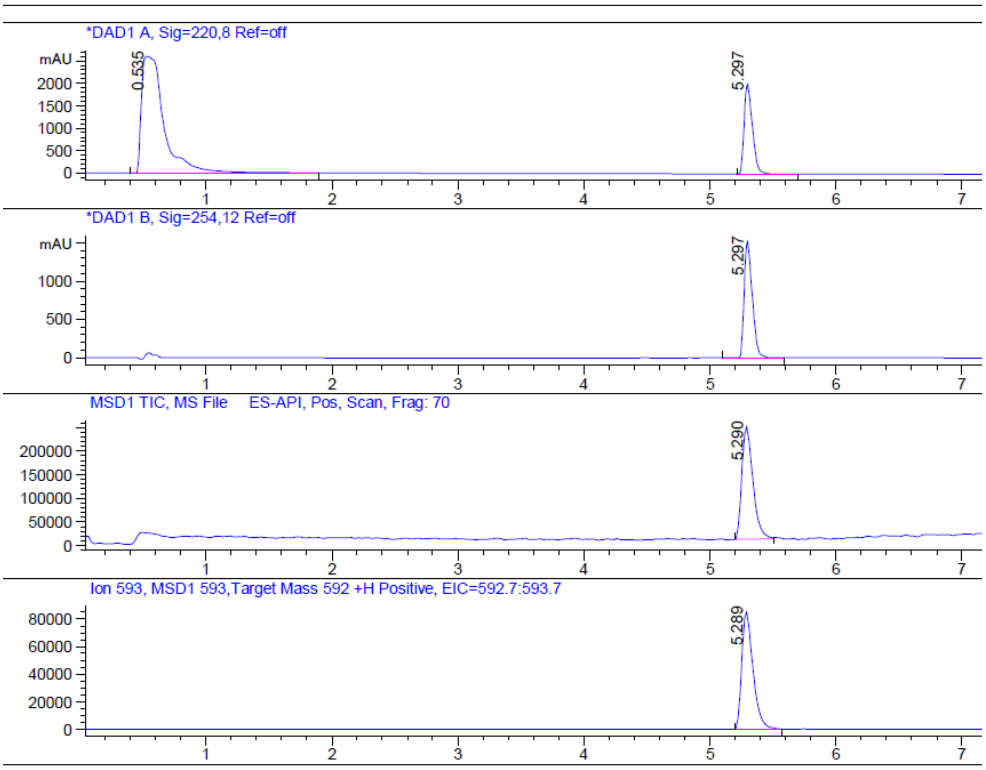

srk005-066_PROTON_01
8.80
8.22
8.09
8.07
7.53
7.51
7.43
7.41
7.39
7.30
7.28
7.27
7.25
5.24
4.64
4.62
3.96
3.30 HDO
3.22
3.19
3.09
2.48 dmso
2.47 dmso
2.47 dmso
2.46 dmso
2.46 dmso
2.07
1.90
1.88
1.56
1.53
1.41
1.36
1.21
1.20
1.09
1.02
1.00
0.98
0.79
1.02
2.00
1.99
1.25
2.11
0.95
0.59
0.83
1.60
1.09
0.70
2.75
5.06
1.75
1.68
NH
N
O
S
N
Cl
O
N
112
f1 (ppm)

1-(5-Chloro-2-ethylphenyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-6-(2-methylprop-1-en-1-yl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one (**119**):



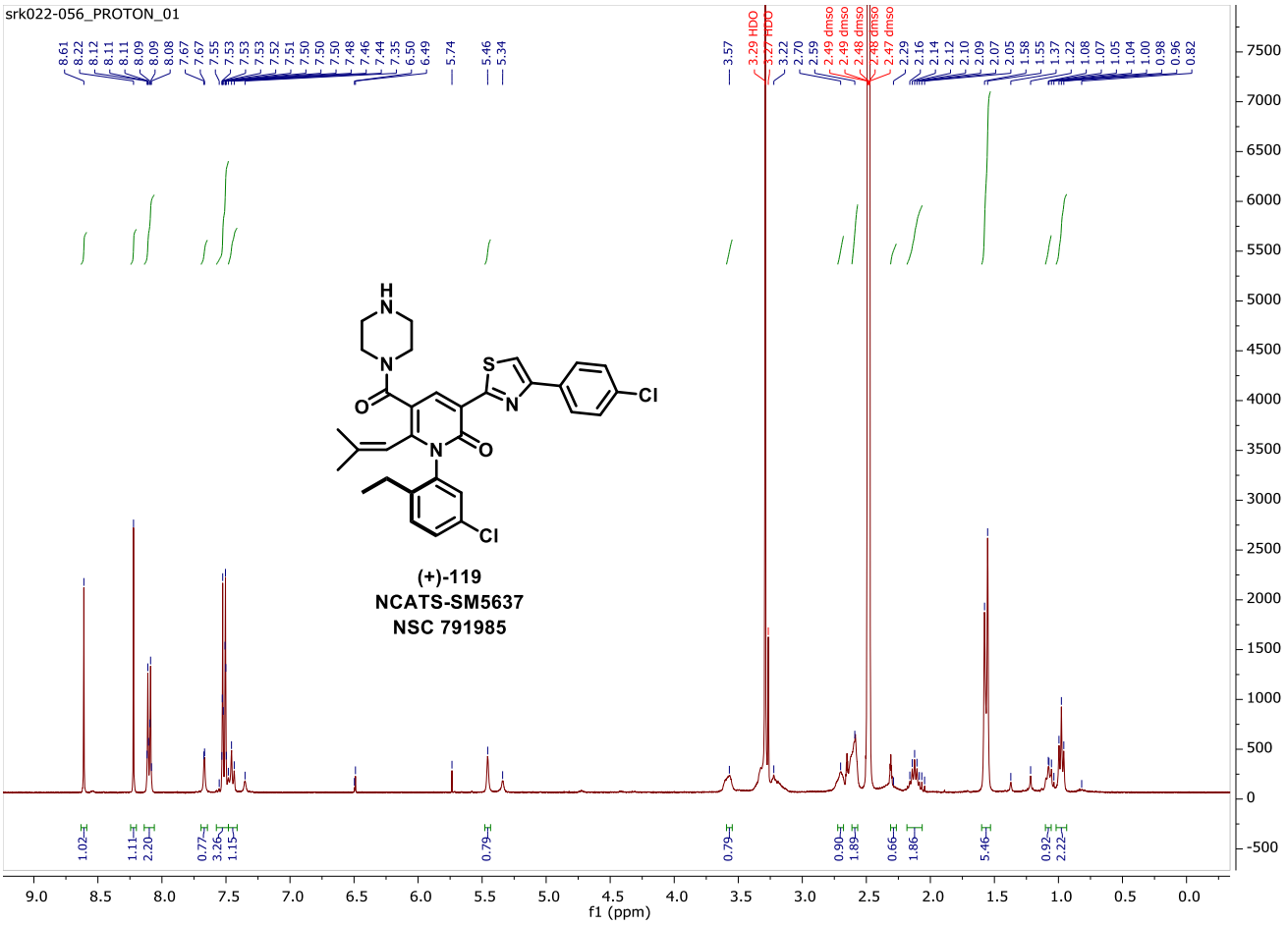
Chemical Formula: $C_{31}H_{30}Cl_2N_4O_2S$
Exact Mass: 592.15

Method Info : Long Gradient 4% to 100% Acetonitrile (0.05% TFA) over 7 minutes
Agilent Eclipse XDB-C18 3 micron 3 x 75mm



Integration Results for DAD1 A, Sig=220,8 Ref=off

RetTim	Width	Area	Height	Area%	MS(+)
0.54	0.17	32192.69	2597.78	78.15	179
5.30	0.07	9002.09	1996.44	21.85	593


srk022-056_PROTON_01
(+)-119
NCATS-SM5637
NSC 791985
f1 (ppm)

S2. Profiling data for (+)-**119**

Biochemical IC_{50}	IDH1-R132C	94 nM
	IDH1-R132H	39 nM
Cellular 2-HG inhibition	U87 (R132H)	0.4 nM
Liver micro. stability ($t_{1/2}$/min)	human	200
	rat	125
	dog	273
	mouse	78
Hepat. stability ($t_{1/2}$/min)	human	733
	rat	160
	dog	326
	mouse	152
Solubility (μM)	SGF (pH 1.2)	84
	FaSSGF (pH 1.6)	86
	FeSSIF (pH 5.0)	480
	FaSSIF (pH 6.5)	425
	SIF (pH 6.8)	17
	PBS (pH 7.4)	11
LogD	pH 1.6	3.04
	pH 5	3.28
	pH 7.4	3.48
	pH 9	3.24
PPB	human	>99%
	rat	>99%
	mouse	>99%
mouse PK	plasma AUC (h*ng/mL)	1415
PO (3 mg/kg)	plasma C_{max} (ng/mL)	119
	plasma %F	64
IV (3 mg/kg)	plasma Cl (mL/min/kg)	23
PO (30 mg/kg)	plasma AUC (h*ng/mL)	24645
	plasma C_{max} (ng/mL)	2013
	brain AUC (h*ng/g)	7138
	brain C_{max} (ng/g)	595
	plasma/brain AUC ratio	3.5
	plasma/brain C_{max} ratio	3.7

Note: There might be slight difference in the values here and the main text as these values are from different experiments and within the variability of the assays.

S3. Crystal Structure Report for **VIIb (Scheme 3)**

This was formed from **(+)-119** during crystallization. VIIb is referred as **NIH33** here**.**
Dr. Curtis Moore, UCSD Crystallography Lab, 5128 Urey Hall, 9500 Gilman Dr, La Jolla, CA 92093-0358, current email: moore.4060@osu.edu

Experimental Summary

The single crystal X-ray diffraction studies were carried out on a Bruker Kappa APEX-II CCD diffractometer equipped with Cu K_α radiation (λ = 1.5478). Crystals of the subject compound were grown from the following. Approximately 3mg of sample was dissolved in 1000µL of a dilute Ethanol/HCl solution and then filtered through silica. The solution was then vapor diffused with MTBE for 7 days and then the resultant solution was allowed to slowly evaporate for 3 days. A 0.054 x 0.031 x 0.007 mm piece of a yellow plate was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ϖ scans. Crystal-to-detector distance was 40 mm using variable exposure time (10s-30s) depending on θ with a scan width of 1.0°. Data collection was 98.7% complete to 68.00° in θ. A total of 22479 reflections were collected covering the indices, -15<=h<=15, -11<=k<=11, -13<=l<=13. 5469 reflections were found to be symmetry independent, with a R_{int} of 0.0608. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be $P2_1$. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. The absolute stereochemistry of the molecule was established by anomalous dispersion using the Parson's method with a Flack parameter of 0.000(12). Crystallographic data are summarized in Table 1.

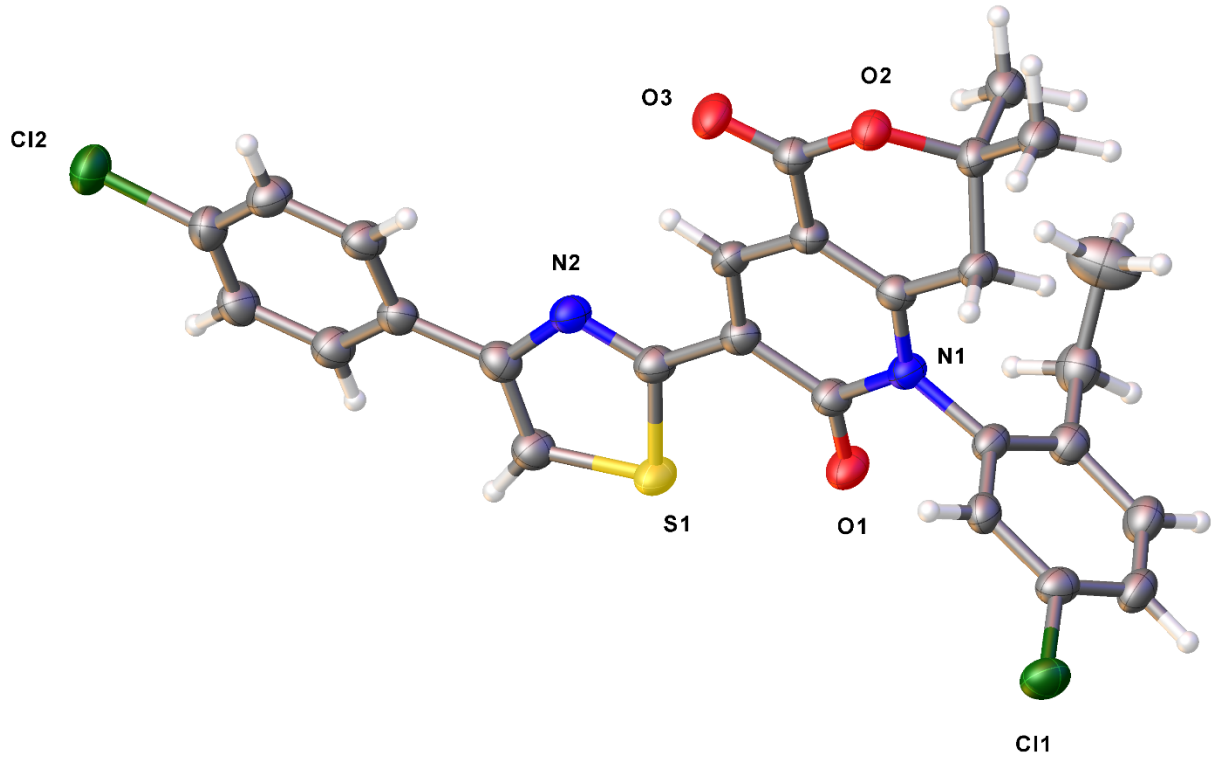


Table S1. Crystal data and structure refinement for NIH33.

Report date	2017-07-21	
Identification code	Compound 2	
Empirical formula	C32 H34 Cl2 N2 O4 S	
Molecular formula	C27 H22 Cl2 N2 O3 S, C5 H12 O	
Formula weight	613.57	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 12.5473(4) Å	α= 90°.
	b = 9.3011(3) Å	β= 95.207(2)°.
	c = 13.0174(4) Å	γ = 90°.
Volume	1512.91(8) $Å^3$	
Z	2	
Density (calculated)	1.347 Mg/m^3	
Absorption coefficient	2.897 mm^{-1}	
F(000)	644	
Crystal size	0.054 x 0.031 x 0.007 mm^3	
Crystal color, habit	Yellow Plate	
Theta range for data collection	3.409 to 68.509°.	
Index ranges	-15<=h<=15, -11<=k<=11, -13<=l<=15	
Reflections collected	22479	
Independent reflections	5469 [R(int) = 0.0608, R(sigma) = 0.0515]	
Completeness to theta = 68.000°	98.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.3201 and 0.2197	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5469 / 1 / 377	
Goodness-of-fit on F^2	1.018	
Final R indices [I>2sigma(I)]	R1 = 0.0496, wR2 = 0.1137	
R indices (all data)	R1 = 0.0609, wR2 = 0.1196	
Absolute structure parameter	0.000(12)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.463 and -0.247 $e.Å^{-3}$	

Table S2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for NIH33. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	6600(1)	2403(1)	9182(1)	43(1)
Cl(2)	2341(1)	2690(2)	-2311(1)	47(1)
S(1)	6176(1)	906(1)	3256(1)	36(1)
O(1)	7325(3)	2066(4)	4935(3)	39(1)
O(2)	6099(3)	8553(3)	5352(3)	32(1)
O(3)	5081(3)	7962(4)	3957(3)	41(1)
N(1)	7199(3)	4316(4)	5608(3)	29(1)
N(2)	5354(3)	3093(4)	2280(3)	32(1)
C(1)	6968(4)	3280(5)	4817(4)	31(1)
C(2)	6306(4)	3776(5)	3921(4)	31(1)
C(3)	5949(4)	5165(5)	3865(4)	30(1)
C(4)	6223(4)	6139(5)	4674(4)	30(1)
C(5)	6837(4)	5705(5)	5538(4)	29(1)
C(6)	7104(4)	6741(5)	6403(4)	31(1)
C(7)	7103(4)	8282(5)	5993(4)	32(1)
C(8)	5944(4)	2746(5)	3110(4)	31(1)
C(9)	5761(4)	7611(5)	4617(4)	32(1)
C(10)	8021(4)	8570(5)	5341(4)	35(1)
C(11)	7102(5)	9365(5)	6861(4)	37(1)
C(12)	7707(4)	3755(5)	6579(3)	30(1)
C(13)	7038(4)	3457(5)	7336(4)	32(1)
C(14)	7467(4)	2844(5)	8238(4)	35(1)
C(15)	8532(4)	2522(6)	8401(4)	38(1)
C(16)	9190(4)	2828(6)	7637(4)	40(1)
C(17)	8790(4)	3442(5)	6689(4)	35(1)
C(18)	9530(4)	3746(6)	5873(4)	42(1)

C(19)	9753(7)	5287(8)	5695(6)	65(2)
C(20)	5428(4)	640(5)	2109(4)	35(1)
C(21)	5059(4)	1903(6)	1697(4)	33(1)
C(22)	4359(4)	2083(5)	718(4)	33(1)
C(23)	4242(4)	980(6)	-7(4)	37(1)
C(24)	3620(5)	1149(6)	-934(4)	39(1)
C(25)	3099(4)	2437(6)	-1127(4)	37(1)
C(26)	3182(4)	3553(6)	-420(4)	38(1)
C(27)	3811(4)	3370(5)	497(4)	36(1)
O(1S)	10420(4)	2641(6)	2032(3)	58(1)
C(1S)	9155(7)	3930(9)	2854(5)	65(2)
C(2S)	9343(5)	3219(7)	1845(5)	51(1)
C(3S)	8540(7)	2032(10)	1603(6)	75(2)
C(4S)	9294(7)	4344(8)	991(5)	63(2)
C(5S)	10816(8)	1851(11)	1221(6)	76(2)

Table S3. Bond lengths [Å] and angles [°] for NIH33.

Cl(1)-C(14)	1.762(5)	C(10)-H(10C)	0.9800
Cl(2)-C(25)	1.752(5)	C(11)-H(11A)	0.9800
S(1)-C(8)	1.744(5)	C(11)-H(11B)	0.9800
S(1)-C(20)	1.708(5)	C(11)-H(11C)	0.9800
O(1)-C(1)	1.220(6)	C(12)-C(13)	1.380(8)
O(2)-C(7)	1.469(6)	C(12)-C(17)	1.385(7)
O(2)-C(9)	1.338(6)	C(13)-H(13)	0.9500
O(3)-C(9)	1.200(6)	C(13)-C(14)	1.370(7)
N(1)-C(1)	1.421(6)	C(14)-C(15)	1.368(8)
N(1)-C(5)	1.370(6)	C(15)-H(15)	0.9500
N(1)-C(12)	1.458(6)	C(15)-C(16)	1.378(8)
N(2)-C(8)	1.294(6)	C(16)-H(16)	0.9500
N(2)-C(21)	1.373(6)	C(16)-C(17)	1.410(7)
C(1)-C(2)	1.446(7)	C(17)-C(18)	1.499(8)
C(2)-C(3)	1.367(7)	C(18)-H(18A)	0.9900
C(2)-C(8)	1.467(7)	C(18)-H(18B)	0.9900
C(3)-H(3)	0.9500	C(18)-C(19)	1.483(9)
C(3)-C(4)	1.408(7)	C(19)-H(19A)	0.9800
C(4)-C(5)	1.365(7)	C(19)-H(19B)	0.9800
C(4)-C(9)	1.487(6)	C(19)-H(19C)	0.9800
C(5)-C(6)	1.496(7)	C(20)-H(20)	0.9500
C(6)-H(6A)	0.9900	C(20)-C(21)	1.355(7)
C(6)-H(6B)	0.9900	C(21)-C(22)	1.490(7)
C(6)-C(7)	1.529(6)	C(22)-C(23)	1.393(8)
C(7)-C(10)	1.514(8)	C(22)-C(27)	1.397(7)
C(7)-C(11)	1.514(7)	C(23)-H(23)	0.9500
C(10)-H(10A)	0.9800	C(23)-C(24)	1.385(8)
C(10)-H(10B)	0.9800	C(24)-H(24)	0.9500

C(24)-C(25)	1.376(8)	O(1)-C(1)-C(2)	125.1(4)
C(25)-C(26)	1.385(7)	N(1)-C(1)-C(2)	115.7(4)
C(26)-H(26)	0.9500	C(1)-C(2)-C(8)	119.4(4)
C(26)-C(27)	1.380(7)	C(3)-C(2)-C(1)	120.4(4)
C(27)-H(27)	0.9500	C(3)-C(2)-C(8)	120.0(4)
O(1S)-C(2S)	1.454(8)	C(2)-C(3)-H(3)	119.6
O(1S)-C(5S)	1.414(9)	C(2)-C(3)-C(4)	120.8(4)
C(1S)-H(1SA)	0.9800	C(4)-C(3)-H(3)	119.6
C(1S)-H(1SB)	0.9800	C(3)-C(4)-C(9)	119.2(4)
C(1S)-H(1SC)	0.9800	C(5)-C(4)-C(3)	120.5(4)
C(1S)-C(2S)	1.508(10)	C(5)-C(4)-C(9)	120.1(4)
C(2S)-C(3S)	1.508(10)	N(1)-C(5)-C(6)	120.5(4)
C(2S)-C(4S)	1.523(9)	C(4)-C(5)-N(1)	119.5(4)
C(3S)-H(3SA)	0.9800	C(4)-C(5)-C(6)	120.0(4)
C(3S)-H(3SB)	0.9800	C(5)-C(6)-H(6A)	109.6
C(3S)-H(3SC)	0.9800	C(5)-C(6)-H(6B)	109.6
C(4S)-H(4SA)	0.9800	C(5)-C(6)-C(7)	110.4(4)
C(4S)-H(4SB)	0.9800	H(6A)-C(6)-H(6B)	108.1
C(4S)-H(4SC)	0.9800	C(7)-C(6)-H(6A)	109.6
C(5S)-H(5SA)	0.9800	C(7)-C(6)-H(6B)	109.6
C(5S)-H(5SB)	0.9800	O(2)-C(7)-C(6)	109.4(4)
C(5S)-H(5SC)	0.9800	O(2)-C(7)-C(10)	108.0(4)
		O(2)-C(7)-C(11)	104.5(4)
C(20)-S(1)-C(8)	88.5(2)	C(10)-C(7)-C(6)	112.6(4)
C(9)-O(2)-C(7)	119.6(4)	C(11)-C(7)-C(6)	111.3(4)
C(1)-N(1)-C(12)	115.4(4)	C(11)-C(7)-C(10)	110.7(4)
C(5)-N(1)-C(1)	123.2(4)	N(2)-C(8)-S(1)	114.4(4)
C(5)-N(1)-C(12)	120.7(4)	N(2)-C(8)-C(2)	123.7(4)
C(8)-N(2)-C(21)	111.4(4)	C(2)-C(8)-S(1)	121.6(3)
O(1)-C(1)-N(1)	119.3(4)	O(2)-C(9)-C(4)	118.1(4)

O(3)-C(9)-O(2)	119.5(4)	C(12)-C(17)-C(18)	123.5(5)
O(3)-C(9)-C(4)	122.3(4)	C(16)-C(17)-C(18)	120.1(5)
C(7)-C(10)-H(10A)	109.5	C(17)-C(18)-H(18A)	108.4
C(7)-C(10)-H(10B)	109.5	C(17)-C(18)-H(18B)	108.4
C(7)-C(10)-H(10C)	109.5	H(18A)-C(18)-H(18B)	107.4
H(10A)-C(10)-H(10B)	109.5	C(19)-C(18)-C(17)	115.6(5)
H(10A)-C(10)-H(10C)	109.5	C(19)-C(18)-H(18A)	108.4
H(10B)-C(10)-H(10C)	109.5	C(19)-C(18)-H(18B)	108.4
C(7)-C(11)-H(11A)	109.5	C(18)-C(19)-H(19A)	109.5
C(7)-C(11)-H(11B)	109.5	C(18)-C(19)-H(19B)	109.5
C(7)-C(11)-H(11C)	109.5	C(18)-C(19)-H(19C)	109.5
H(11A)-C(11)-H(11B)	109.5	H(19A)-C(19)-H(19B)	109.5
H(11A)-C(11)-H(11C)	109.5	H(19A)-C(19)-H(19C)	109.5
H(11B)-C(11)-H(11C)	109.5	H(19B)-C(19)-H(19C)	109.5
C(13)-C(12)-N(1)	116.4(4)	S(1)-C(20)-H(20)	124.4
C(13)-C(12)-C(17)	122.6(4)	C(21)-C(20)-S(1)	111.2(4)
C(17)-C(12)-N(1)	120.8(4)	C(21)-C(20)-H(20)	124.4
C(12)-C(13)-H(13)	120.7	N(2)-C(21)-C(22)	119.3(4)
C(14)-C(13)-C(12)	118.6(5)	C(20)-C(21)-N(2)	114.5(4)
C(14)-C(13)-H(13)	120.7	C(20)-C(21)-C(22)	126.1(5)
C(13)-C(14)-Cl(1)	118.3(4)	C(23)-C(22)-C(21)	121.0(5)
C(15)-C(14)-Cl(1)	119.8(4)	C(23)-C(22)-C(27)	118.1(5)
C(15)-C(14)-C(13)	121.8(5)	C(27)-C(22)-C(21)	120.9(4)
C(14)-C(15)-H(15)	120.5	C(22)-C(23)-H(23)	119.2
C(14)-C(15)-C(16)	118.9(5)	C(24)-C(23)-C(22)	121.5(5)
C(16)-C(15)-H(15)	120.5	C(24)-C(23)-H(23)	119.2
C(15)-C(16)-H(16)	119.1	C(23)-C(24)-H(24)	120.7
C(15)-C(16)-C(17)	121.8(5)	C(25)-C(24)-C(23)	118.6(5)
C(17)-C(16)-H(16)	119.1	C(25)-C(24)-H(24)	120.7
C(12)-C(17)-C(16)	116.3(5)	C(24)-C(25)-Cl(2)	119.2(4)

C(24)-C(25)-C(26)	121.7(5)	H(4SA)-C(4S)-H(4SB)	109.5
C(26)-C(25)-Cl(2)	119.1(4)	H(4SA)-C(4S)-H(4SC)	109.5
C(25)-C(26)-H(26)	120.5	H(4SB)-C(4S)-H(4SC)	109.5
C(27)-C(26)-C(25)	119.0(5)	O(1S)-C(5S)-H(5SA)	109.5
C(27)-C(26)-H(26)	120.5	O(1S)-C(5S)-H(5SB)	109.5
C(22)-C(27)-H(27)	119.5	O(1S)-C(5S)-H(5SC)	109.5
C(26)-C(27)-C(22)	121.1(5)	H(5SA)-C(5S)-H(5SB)	109.5
C(26)-C(27)-H(27)	119.5	H(5SA)-C(5S)-H(5SC)	109.5
C(5S)-O(1S)-C(2S)	116.8(5)	H(5SB)-C(5S)-H(5SC)	109.5
H(1SA)-C(1S)-H(1SB)	109.5		
H(1SA)-C(1S)-H(1SC)	109.5		
H(1SB)-C(1S)-H(1SC)	109.5		
C(2S)-C(1S)-H(1SA)	109.5		
C(2S)-C(1S)-H(1SB)	109.5		
C(2S)-C(1S)-H(1SC)	109.5		
O(1S)-C(2S)-C(1S)	103.4(5)		
O(1S)-C(2S)-C(3S)	110.9(6)		
O(1S)-C(2S)-C(4S)	110.6(6)		
C(1S)-C(2S)-C(3S)	110.4(7)		
C(1S)-C(2S)-C(4S)	109.6(6)		
C(3S)-C(2S)-C(4S)	111.7(5)		
C(2S)-C(3S)-H(3SA)	109.5		
C(2S)-C(3S)-H(3SB)	109.5		
C(2S)-C(3S)-H(3SC)	109.5		
H(3SA)-C(3S)-H(3SB)	109.5		
H(3SA)-C(3S)-H(3SC)	109.5		
H(3SB)-C(3S)-H(3SC)	109.5		
C(2S)-C(4S)-H(4SA)	109.5		
C(2S)-C(4S)-H(4SB)	109.5		
C(2S)-C(4S)-H(4SC)	109.5		

Table S4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for NIH33. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	56(1)	40(1)	33(1)	6(1)	5(1)	-2(1)
Cl(2)	55(1)	49(1)	34(1)	0(1)	-12(1)	-3(1)
S(1)	50(1)	24(1)	32(1)	1(1)	-6(1)	1(1)
O(1)	51(2)	26(2)	38(2)	-1(1)	-10(2)	6(2)
O(2)	37(2)	25(2)	33(2)	-2(1)	-3(1)	3(1)
O(3)	47(2)	30(2)	44(2)	2(1)	-16(2)	6(2)
N(1)	36(2)	25(2)	26(2)	2(2)	-1(2)	1(2)
N(2)	41(2)	26(2)	28(2)	1(2)	0(2)	0(2)
C(1)	39(2)	24(2)	30(2)	-1(2)	0(2)	-1(2)
C(2)	36(2)	29(2)	29(2)	3(2)	2(2)	-3(2)
C(3)	35(2)	29(2)	26(2)	5(2)	-2(2)	-2(2)
C(4)	33(2)	24(2)	31(2)	3(2)	-1(2)	-2(2)
C(5)	32(2)	25(2)	30(2)	1(2)	4(2)	-2(2)
C(6)	38(2)	29(2)	24(2)	1(2)	0(2)	0(2)
C(7)	36(2)	27(2)	32(2)	0(2)	-4(2)	-1(2)
C(8)	38(2)	26(2)	30(2)	1(2)	2(2)	2(2)
C(9)	35(2)	26(2)	33(2)	2(2)	-1(2)	-1(2)
C(10)	40(3)	28(2)	36(2)	-1(2)	-4(2)	-1(2)
C(11)	46(3)	28(2)	35(3)	0(2)	-4(2)	0(2)
C(12)	40(3)	22(2)	25(2)	-1(2)	-5(2)	2(2)
C(13)	36(2)	28(2)	31(2)	-3(2)	-7(2)	-3(2)
C(14)	47(3)	26(2)	30(2)	0(2)	1(2)	-1(2)
C(15)	48(3)	34(2)	30(2)	1(2)	-9(2)	4(2)
C(16)	39(3)	38(3)	40(3)	0(2)	-6(2)	7(2)

C(17)	40(3)	30(2)	34(2)	-2(2)	-1(2)	1(2)
C(18)	39(3)	44(3)	42(3)	-3(2)	1(2)	6(2)
C(19)	72(5)	45(3)	85(5)	-6(3)	42(4)	-1(3)
C(20)	45(3)	28(3)	33(2)	-2(2)	1(2)	0(2)
C(21)	37(3)	29(2)	34(2)	-4(2)	4(2)	-2(2)
C(22)	37(2)	31(2)	31(2)	2(2)	3(2)	-4(2)
C(23)	45(3)	31(2)	34(2)	0(2)	1(2)	-1(2)
C(24)	47(3)	34(3)	35(2)	-6(2)	0(2)	-5(2)
C(25)	39(3)	39(3)	31(2)	-2(2)	-3(2)	-4(2)
C(26)	48(3)	31(2)	35(3)	2(2)	0(2)	3(2)
C(27)	46(3)	28(2)	32(2)	-1(2)	3(2)	-2(2)
O(1S)	61(2)	70(3)	39(2)	-8(2)	-4(2)	5(2)
C(1S)	73(5)	77(5)	42(3)	5(3)	-2(3)	19(4)
C(2S)	54(3)	56(4)	42(3)	4(3)	-4(3)	-4(3)
C(3S)	84(5)	82(5)	55(4)	13(4)	-16(4)	-28(4)
C(4S)	85(5)	55(4)	47(3)	1(3)	-7(3)	-6(3)
C(5S)	93(6)	87(5)	47(4)	-9(4)	6(4)	12(5)

Table S5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for NIH33.

	x	y	z	U(eq)
H(3)	5512	5478	3273	36
H(6A)	7817	6510	6751	37
H(6B)	6571	6652	6916	37
H(10A)	7994	7880	4771	52
H(10B)	8701	8466	5767	52
H(10C)	7961	9549	5064	52
H(11A)	7047	10338	6573	55
H(11B)	7767	9277	7313	55
H(11C)	6490	9181	7260	55
H(13)	6295	3671	7235	39
H(15)	8815	2095	9031	46
H(16)	9932	2621	7752	48
H(18A)	10218	3252	6065	51
H(18B)	9218	3322	5216	51
H(19A)	10357	5372	5270	98
H(19B)	9932	5767	6358	98
H(19C)	9119	5741	5338	98
H(20)	5289	-274	1800	42
H(23)	4598	91	137	44
H(24)	3554	392	-1426	47
H(26)	2812	4431	-563	46
H(27)	3873	4131	985	43
H(1SA)	9153	3199	3395	97

H(1SB)	8464	4427	2784	97
H(1SC)	9727	4626	3037	97
H(3SA)	8703	1537	971	112
H(3SB)	7819	2442	1505	112
H(3SC)	8578	1345	2176	112
H(4SA)	9786	5133	1197	95
H(4SB)	8563	4718	873	95
H(4SC)	9503	3904	356	95
H(5SA)	11561	1575	1416	113
H(5SB)	10781	2445	597	113
H(5SC)	10382	984	1086	113