Supporting Information

Discovery of Novel Azetidine Amides as Potent Small Molecule STAT3 Inhibitors

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Running Title: **Novel Azetidine-based STAT3 Inhibitors**

Keywords: STAT3, Azetidine, Small Molecule Inhibitors, Breast Cancer

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[§]These authors contributed equally.

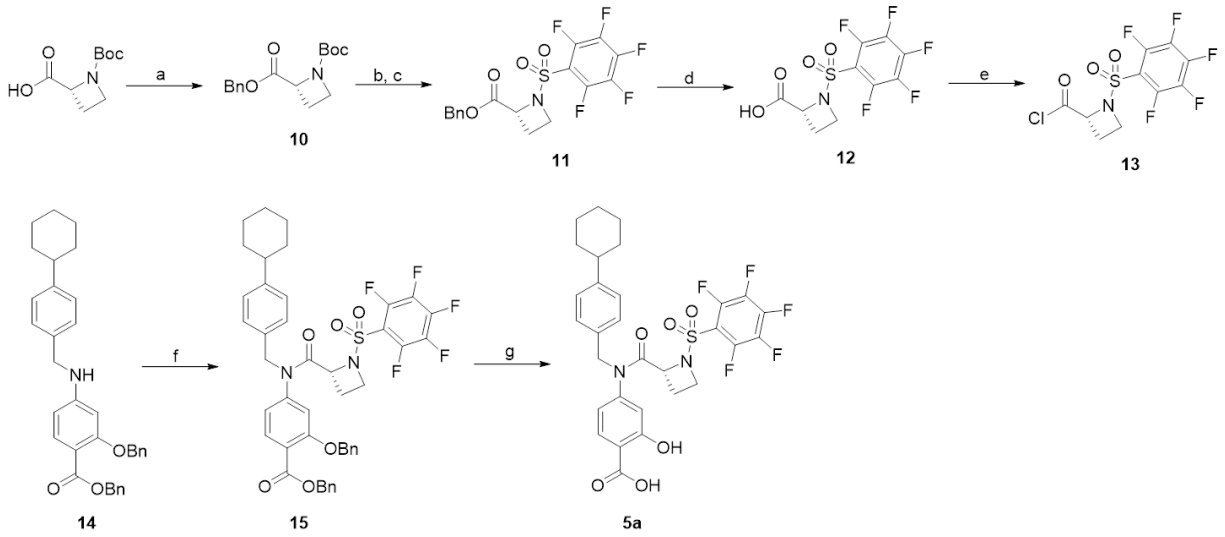
Contents:

Supplementary Results and Discussion:

Previously reported analogs (Fig. S1) showed relatively improved inhibitory potency in our STAT3 DNA-binding activity/electrophoretic mobility shift assay (EMSA), with IC_{50} of 1.80 ± 0.94 and 2.4 ± 0.2 μM for compounds **1** and **3**, respectively [1].

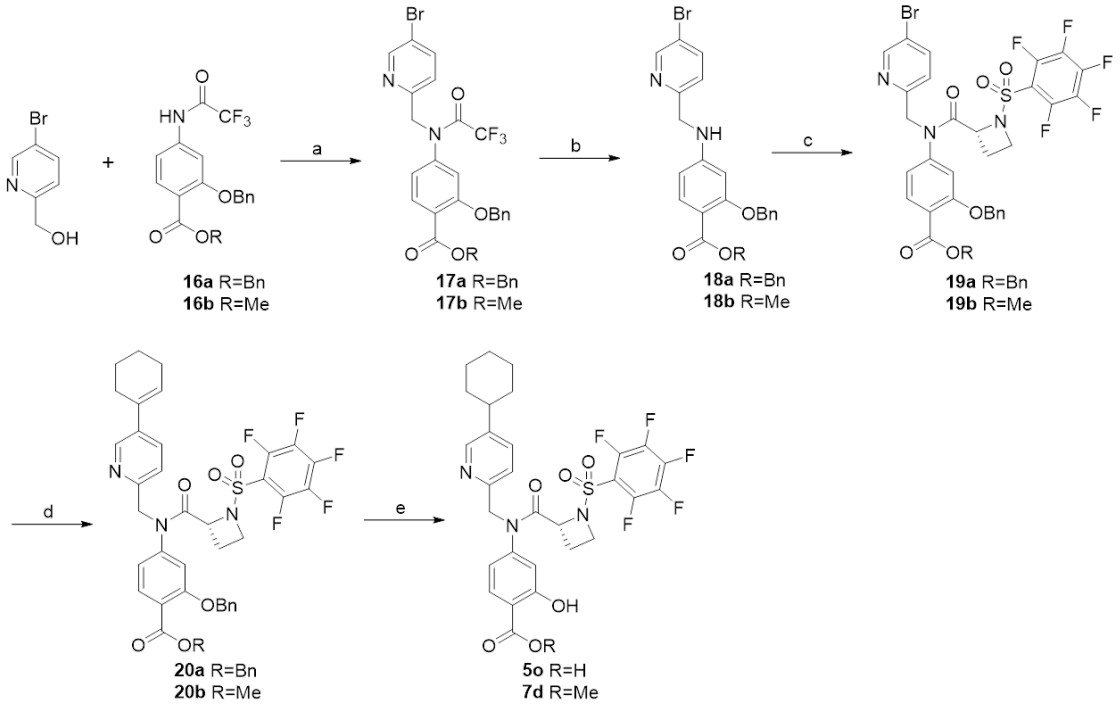
Chemistry

The general preparation of the benzoic acid and salicylic acid analogs is illustrated by the synthesis of (*R*)-4-(*N*-(4-cyclohexylbenzyl)-1-((perfluorophenyl)sulfonyl)azetidine-2-carboxamido)-2-hydroxybenzoic acid **5a** and is illustrated in Scheme 1. Synthesis of acid chloride **13** began with commercially available (*R*)-1-(*tert*-butoxycarbonyl)azetidine-2-carboxylic acid. Esterification of the acid using potassium carbonate and benzyl bromide provided the corresponding benzyl ester. Deprotection of the amine followed by sulfonamide formation with pentafluorobenzenesulfonyl choride provided ester intermediate **11**. Hydrogenolysis of the benzyl ester provided acid **12** in 73% overall yield, which was cleanly converted to the acid chloride **13** using oxalyl chloride and catalytic DMF. Pre-treatment of aniline **14** [2] with methylmagnesium bromide to form the corresponding magnesium amide salt followed by its reaction with excess acid chloride **13** provided protected anilide intermediate **15** in 70% yield. Both *O*-benzyl-protecting groups could be cleanly removed by catalytic hydrogenolysis at atmospheric pressure to afford the final product, salicylic acid **5a**. The *S*-enantiomer (**5b**) was also prepared. Before the final hydrogenolysis step, normal-phase chiral HPLC was used to determine the enantiomeric purity of intermediate **15** which was greater than 95%. The sodium salt (**5d**) was prepared by treating **5a** with sub-stoichiometric amounts of sodium bicarbonate in 1:1:1 THF: methanol: water.



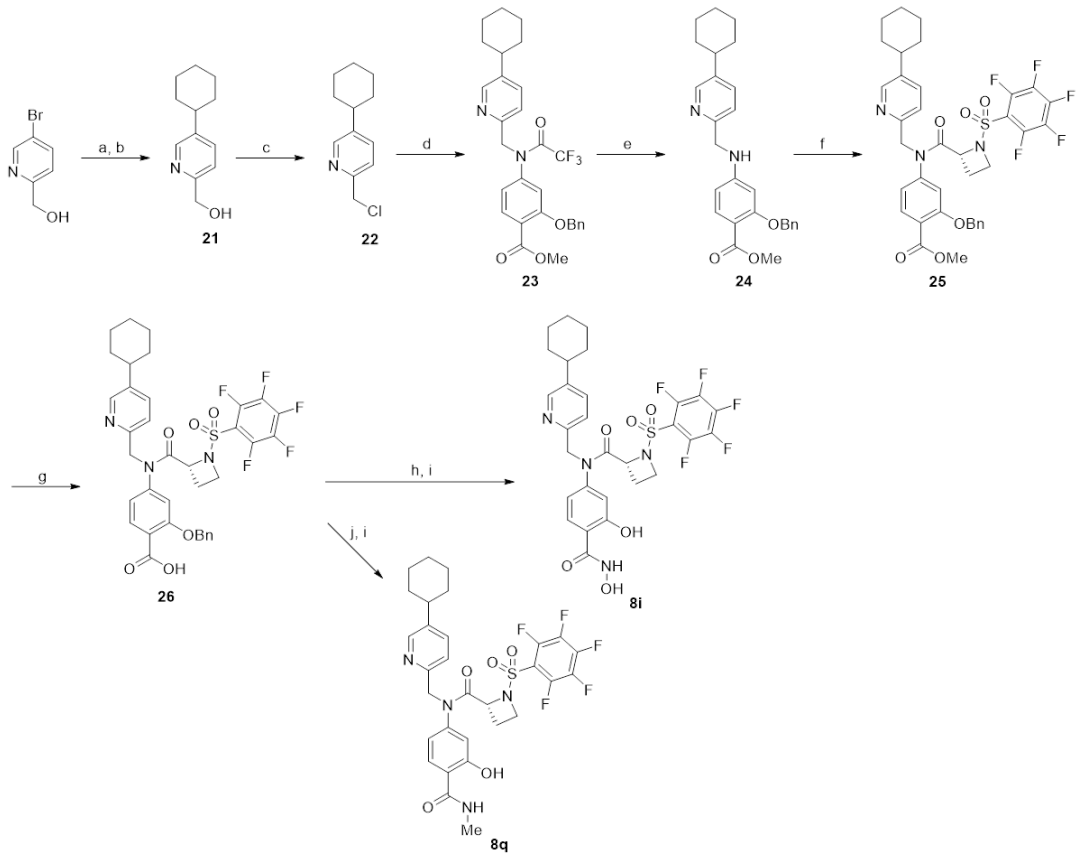
Scheme 1. Reagents and conditions: a) BnBr (0.95 eq), K_2CO_3 (1.1 eq), DMF, rt, 14 h, 97%; b) 1:5 TFA:DCM, 0 °C, rt, 14 h; c) DIPEA (3.0 eq), perfluorobenzenesulfonyl chloride (1.3 eq), DCM, rt, 5.5 h, 75%; d) H_2, 20% $Pd(OH)_2$/C, EtOAc/MeOH, rt, 2 h, 100%; e) oxalyl chloride, DMF (cat.), DCM, 3.5 h, 99%; f) MeMgBr (1.2 – 2.5 eq), THF, 0 °C, 5 min, then **13**, rt, 7 h, 70%; g) H_2, 20% $Pd(OH)_2$/C, EtOAc/MeOH, rt, 1 h, 99%

Similarly, analogs **5e**-**5t** (Table 1) and **6a**-**6l** (Table 2) were prepared from the corresponding anilines, an example of which is illustrated in Scheme 2 in the preparation of **5o and 7d**. Alkylation of benzyl 2-(benzyloxy)-4-(2,2,2-trifluoroacetamido)benzoate (**16a**) with 5-bromo-2-(bromomethyl)pyridine provided the protected anilide **17a**, which on deprotection with potassium carbonate in methanol/THF provided aniline **18a** in 74% overall yield. Treatment of the aniline with excess methylmagnesium bromide followed by coupling with acid chloride **13** afforded the desired anilide **19a** in 55% yield. A Suzuki reaction with 2-(cyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane using palladium acetate and S-Phos gave cyclohexenylpyridylmethyl intermediate, **20a** in 88% yield. Catalytic hydrogenation resulted in saturation of the cyclohexenyl double bond and concurrent hydrogenolysis of the benzyl protecting groups to provide analog **5o**. The methyl ester analogs (Table 3) were prepared in a similar manner as illustrated in Scheme 2 with the synthesis of **7d**.



Scheme 2. Reagents and conditions: a) K_2CO_3, CH_3CN, 60 ^{0}C; b) K_2CO_3, MeOH, THF, 74% 2 steps; c) *i*. MeMgBr (1.2 – 2.5 eq), THF, 0 °C, 5 min, *ii*. **13** (1.5 eq), rt, 55%; d) 2-(cyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.8 eq), K_3PO_4 (2 eq), $Pd(OAc)_2$, (0.05 eq), SPhos (0.1 eq), dioxane, 40 °C, 88%; e) H_2, 10% Pd/C, MeOH/EtOAc.

Amides and hydroxamic acid analogs (Table 4) were prepared in a similar manner as illustrated in the preparation of amide **8q** and hydroxamic acid **8i** (Scheme 3). Building block **22**, 2-(chloromethyl)-5-cyclohexylpyridine, was prepared from (5-bromopyridin-2-yl)methanol by a cross-coupling reaction with 1-cyclohexene-1-yl-boronic acid followed by hydrogenation of the cyclohexenyl double bond to provide alcohol **21**, which was converted to the chloride **22** by reaction with excess thionyl chloride in 94% overall yield. Alkylation of methyl 2-(benzyloxy)-4-(2,2,2-trifluoroacetamido)benzoate **16b** with chloride **22** in acetonitrile with potassium carbonate and catalytic sodium iodide provided trifluoroacetamide **23** in **50% yield.** Deprotection under mild conditions using potassium carbonate in methanol/THF provided aniline **24** which was coupled with the azetidine acid chloride **13** to afford anilide **25** in 85% yield. Mild and selective hydrolysis conditions using trimethyltin hydroxide [3] provided acid **26** in 61% yield.

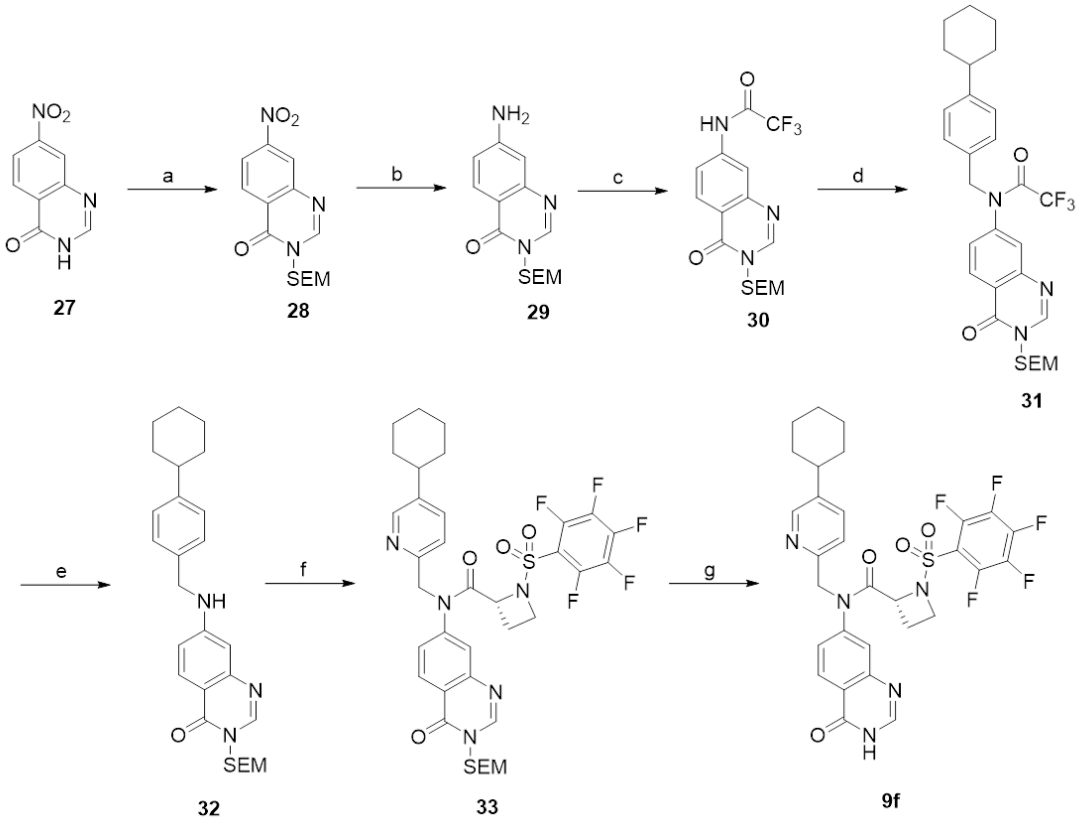


Scheme 3. Reagents and conditions: a) 1-cyclohexene-1-yl-boronic acid (1.5 eq), K_3PO_4 (2 eq), H_2O (2 eq), $Pd(OAc)_2$ (0.05 eq), SPhos (0.1 eq), THF, 40 °C, 24 h, 95%; b) H_2, 10% PtO_2, MeOH/EtOAc, 4 h, 99%; c) $SOCl_2$ (1.5 eq), DCM, rt, 3 h, 100%; d) **16b**, K_2CO_3, MeCN, NaI (cat.), 60 °C, 50%; e) K_2CO_3, MeOH, THF; f) *i*. MeMgBr (1.2 – 2.5 eq), THF, 0 °C, 5 min, *ii*. **13** (1.5 eq), rt, 85%; g) Me_3SnOH (10 eq), DCE, 85 °C, 77 h, 61%; h) *i*. HATU (1.1 eq), DIPEA (2.0 eq), DCM, rt, 75 min, *ii*. $H_2NOBn.HCl$ (1.1.eq), 5.5 h, 68%; i) H_2, 10% Pd/C, MeOH/EtOAc; j) HATU, (1.1 eq), DIPEA (1.9 eq), DCM, rt, 75 min, *ii*. $MeNH_2.HCl$ (1.1 eq), 14 h, 91%.

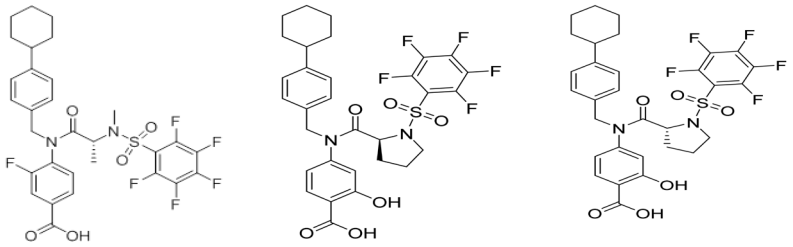
HATU mediated coupling with O-benzylhydroxylamine hydrochloride followed by hydrogenolysis of the benzyl protecting groups yielded hydroxamic acid **8i**. Similar coupling with methylamine hydrochloride followed by hydrogenolysis gave the methyl amide **8q**.

The synthesis of the benzo-fused *N*-heterocycle analog quinazolinone **9f** started from 7-nitroquinazolin-4(*3H*)-one **27** which was protected with SEM-Cl using KHMDS as the base in DMF to provide **28** in 70% yield. Iron mediated reduction of the nitro group to the aniline followed by protection with TFAA provided intermediate **30** in 95% yield for two steps. Alkylation of trifluoroacetamide **30** with chloride **22** in acetonitrile with potassium carbonate and catalytic sodium iodide provided intermediate **31** in 62% yield. Mild hydrolysis of the trifluoroacetyl group using potassium carbonate and methanol in THF provided the

desired deprotected aniline **32** in 88% yield. Deprotonation of aniline **32** with methylmagnesium bromide**,** and subsequent coupling with the azetidine acid chloride **13** gave 86% yield of anilide **33** which upon TFA mediated deprotection of the SEM group provided the final product **9f** in 84% yield.



Scheme 4. Reagents and conditions: a) *i*. KHMDS (1.2 eq), DMF, 0 °C; *ii*. SEM-Cl (1.2 eq), rt, 3 h, 70%; b) Fe(0) (42 At eq), 2:1 EtOH/H2O, NH_4Cl (10eq), 66 °C, 16 h; c) TFAA (1.1 eq), Py (2.2 eq), DCM, rt, 1.5 h, 95% two steps; d) **22** (1.4 eq), K_2CO_3 (2 eq), NaI (0.2 eq), MeCN, 65 °C, 16 h, 62%; e) K_2CO_3 (2.5 eq), MeOH/THF, rt, 2 h, 88%; f) *i*. MeMgBr (1.2-2.5 eq), THF, 10 min, 0 °C; *ii*. **13**, (1.5 eq), rt, 1 h, 86%; g) 1:1 TFA/DCM, rt, 2h, 84%.



1 **2** **3**

Fig. S1. Early Leads. Progression from a proline linker **3** [1] into other cyclic amino acid linkers (Fig. S2) led us to an exciting discovery. Although changing the 5-membered proline analog, **3**, to the corresponding 6-membered pipicolic acid analog, **4** (Fig. S2), decreased potency, changing to the 4-membered azetidine-2-carboxylic analog, **5a** (Fig. S2), gave over a four-fold boost in potency *in vitro* against STAT3 DNA-binding activity (Fig. 1A, EMSA IC_{50} 0.55 ± 0.01 μM for **5a**).

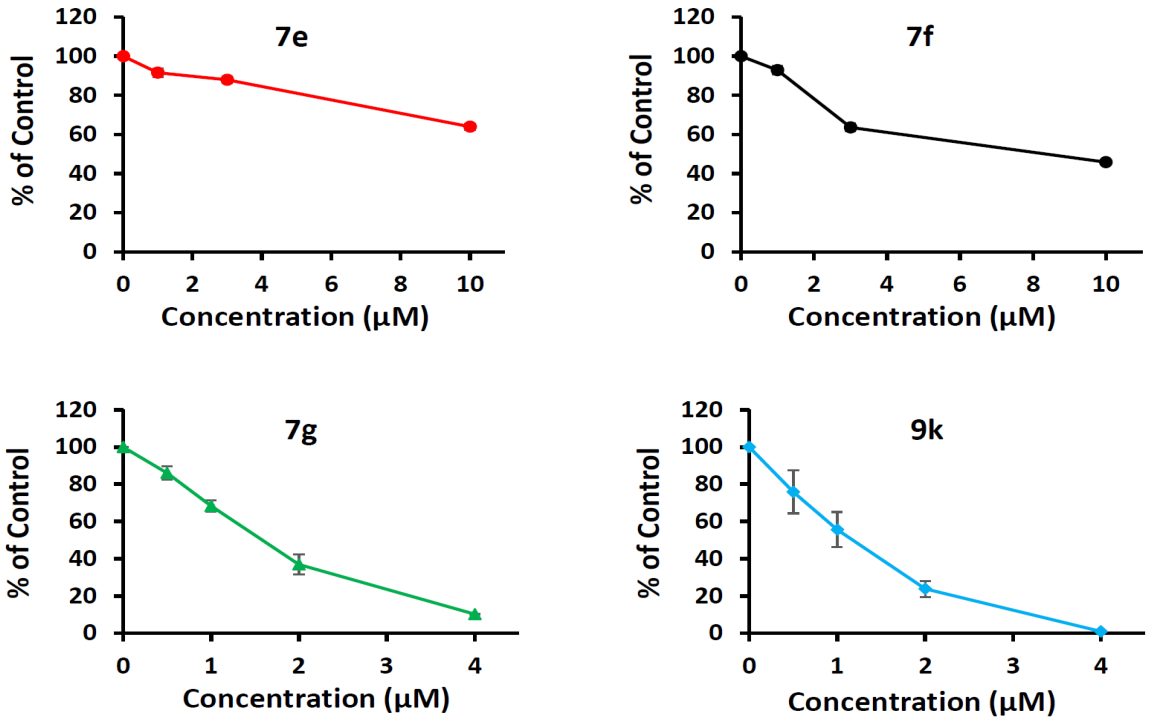


Fig. S2. Dose-response curves for the cell-free EMSA analysis for the most active compounds. Nuclear extracts from NIH3T3/v-Src fibroblasts of equal total protein containing activated STAT3 were pre-incubated with increasing concentrations of the designated compounds for 30 min at room temperature prior to incubating with the radiolabeled hSIE probe that binds STAT3 and performing EMSA analysis; bands corresponding to STAT3:DNA complexes in gel were quantified using ImageJ and represented as percent of control, and plotted against the concentration of compounds, from which IC_{50} values were determined. Control lanes (0) represent nuclear extracts pre-treated with 10% DMSO. Data representative mean +/- SD for 2 replicates.

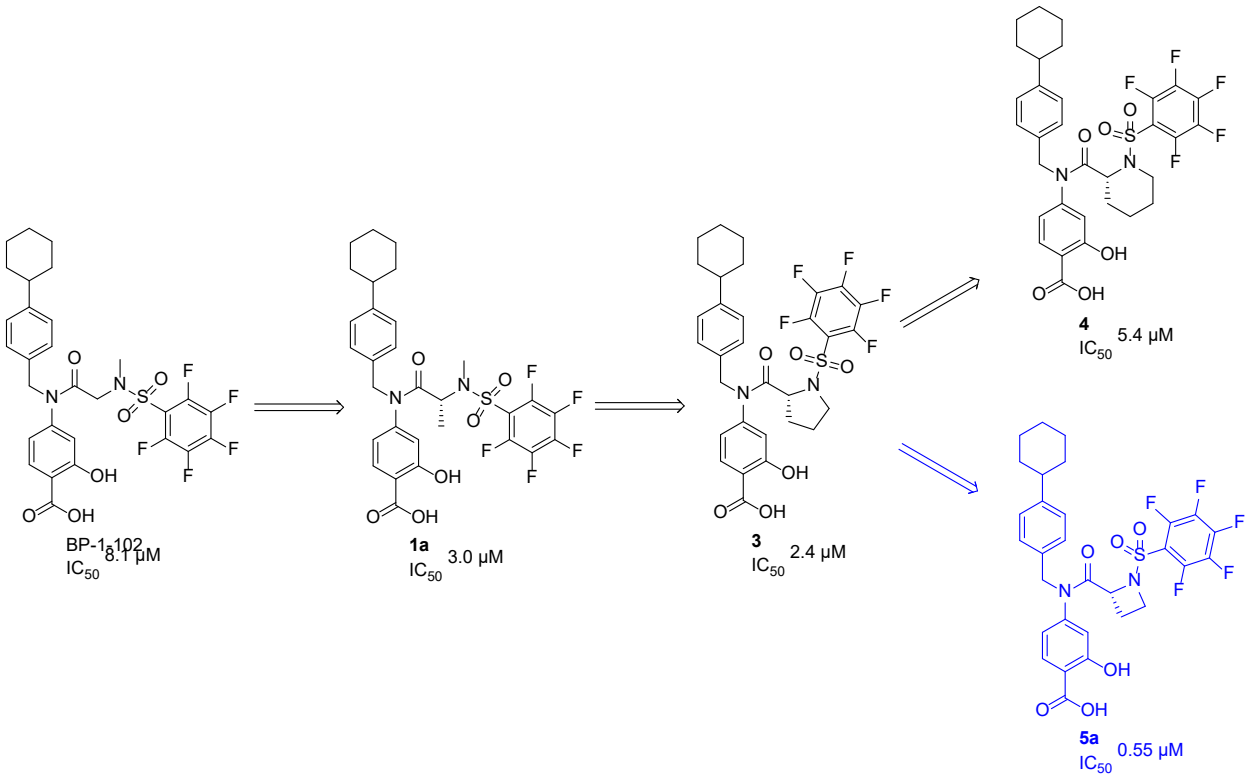


Fig. S3. Progression to Azetidine Lead Molecule 5a

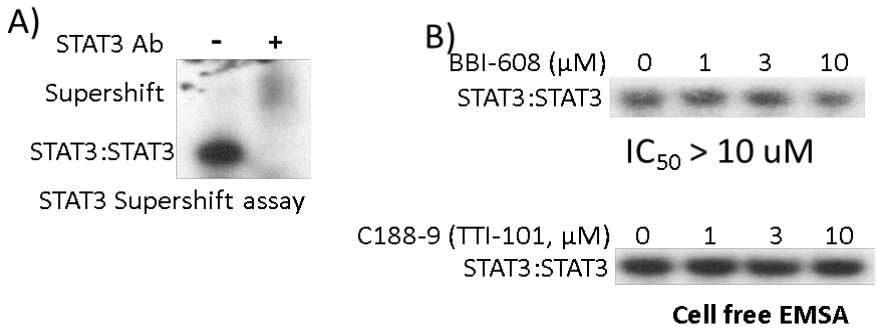
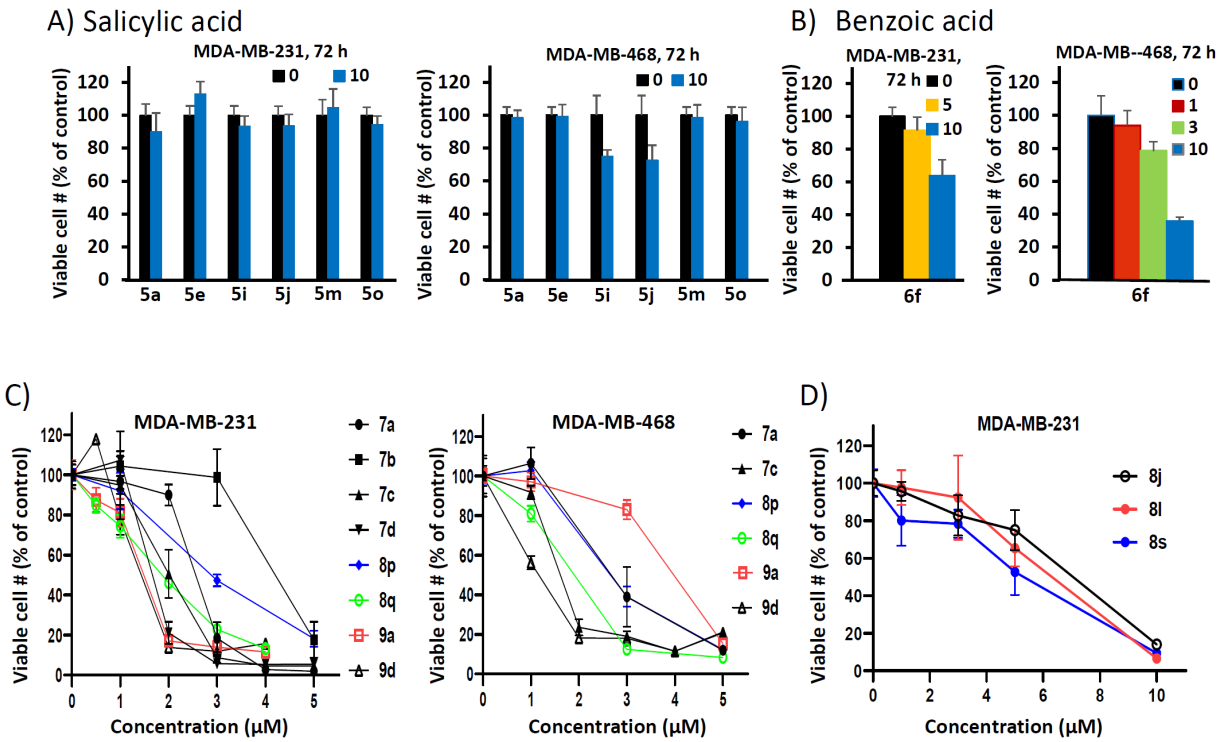


Fig. S4. STAT3 DNA-binding activity *in vitro*/EMSA with supershift analysis and the effects of C-188-9. Nuclear extracts from tumor cells of equal total protein containing activated STAT3 were pre-incubated with (A) the anti-STAT3 antibody, C-20, or (B) increasing concentration of compound BBI-608 or C-188-9 prior to incubating with the radiolabeled hSIE probe that binds STAT3 and performing EMSA

analysis; bands corresponding to STAT3:DNA complexes in gel were quantified using ImageJ and represented as percent of control, and plotted against the concentration of compounds, from which IC_{50} values were determined. Positions of STAT3:DNA complexes in gel are labeled; control lanes (0) represent nuclear extracts pre-treated with 10% DMSO. Data are representative of 2 independent determinations.



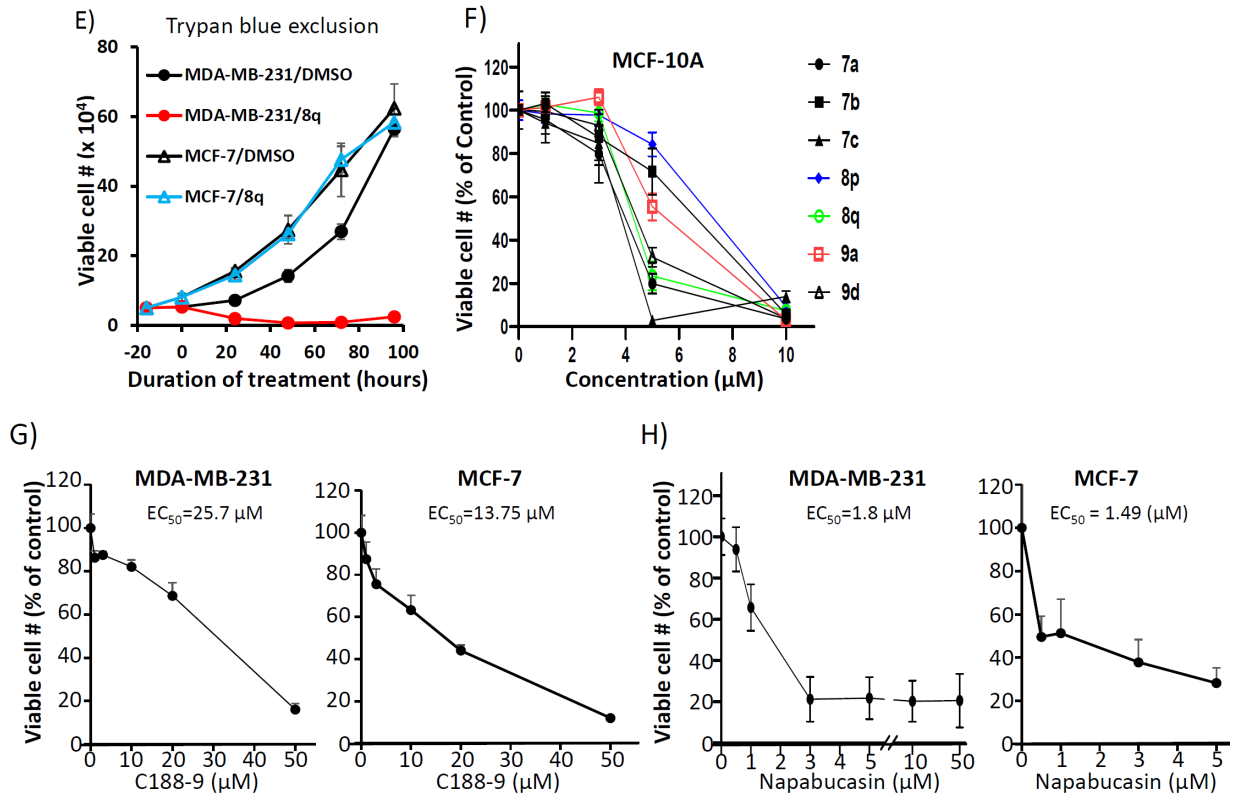


Fig. S5. *In vitro* cell viability and growth studies for effects of active azetidine analogs. (A-D, F) Human breast cancer MDA-MB-231 and MDA-MB-468 cells harboring aberrantly-active STAT3, and the normal breast epithelial MCF-10A cells that do not and growing in 96-well culture were treated once with 0-10 μM of the indicated compounds. Cells were harvested after 72 h and subjected to CyQuant cell proliferation assay for the number of viable cells, which are plotted as % number of viable cells against concentration from which EC_{50} values were derived; (E) MDA-MB-231 and MCF-7 cells growing in 6-well culture were treated with 2 μM **8q** and at every 24 h, cells were harvested and the viable cells were counted by trypan blue exclusion/phase-contrast microscopy and plotted against treatment duration; and (G, H) human breast cancer MDA-MB-231 or MCF-7 cells were treated with 0-50 μM C188-9 or 0-20 μM napabucasin (BBI-608) for 72 h and subjected to CyQuant assay for viable cells, which are plotted as % number of viable cells against concentration from which EC_{50} values were derived. Values are mean ± SEM of two-three studies each in three replicates.

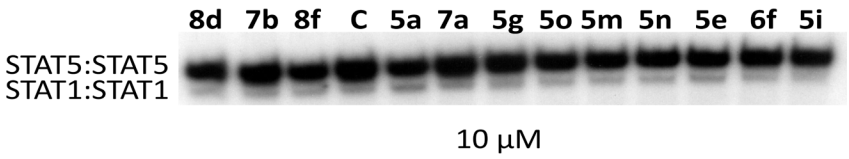


Fig. S6. Effect of new analogs on STAT1 or STAT5 DNA-binding activity *in vitro*. Nuclear extracts of equal total protein prepared from epidermal growth factor–stimulated NIH3T3/EGFR fibroblasts containing activated STAT1 and STAT5 were pre-incubated with 10 μM of the designated compounds for 30 min at room temperature prior to incubating with the radiolabeled MGFe probe that binds STAT1 and STAT5 and performing EMSA analysis. Positions of STAT:DNA complexes in gel are labeled; control lanes (C) represents nuclear extract pre-treated with 10% DMSO. Data are representative of 2 independent determinations.

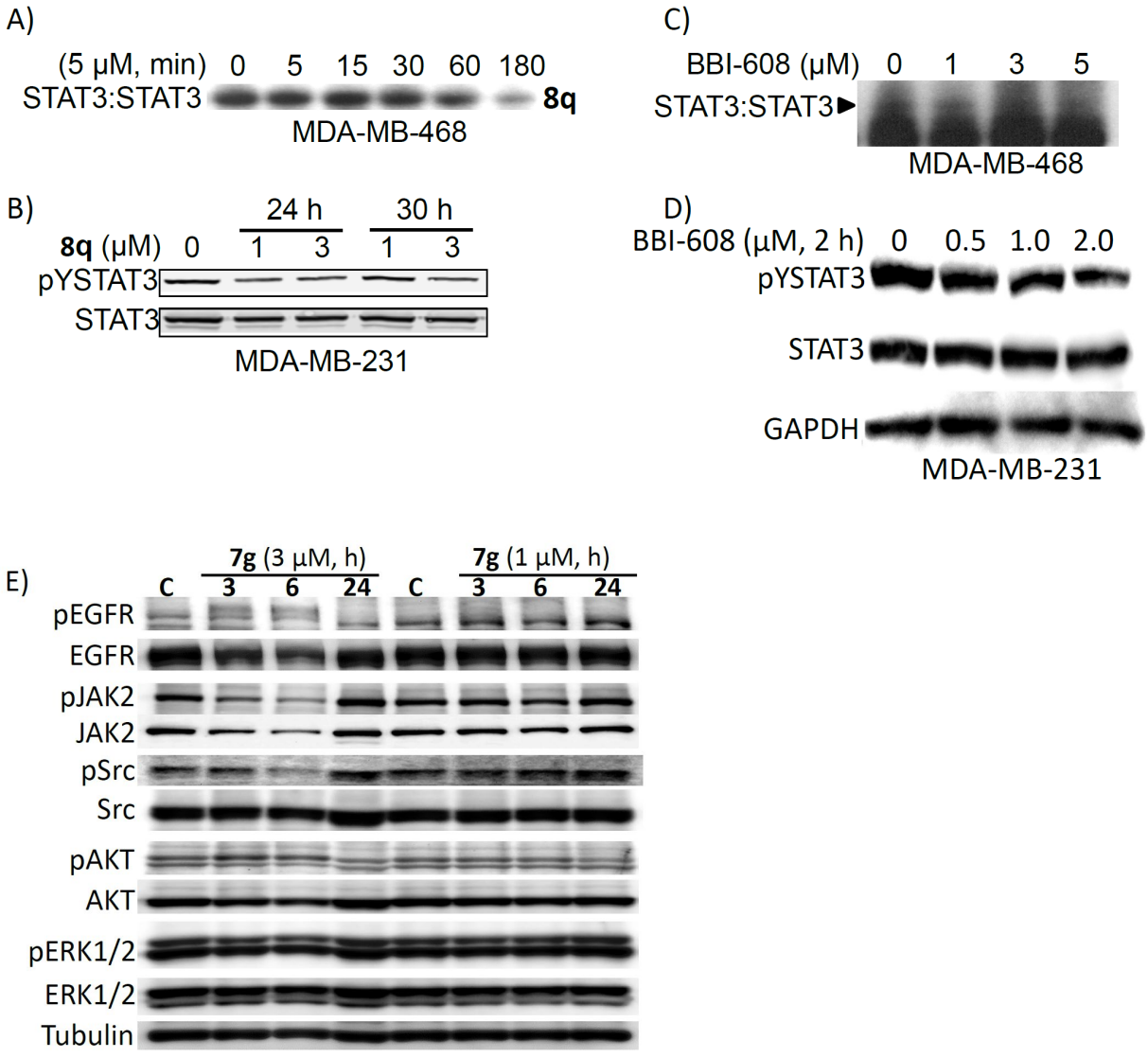


Fig. S7. Inhibition of constitutive STAT3 phosphorylation and DNA-binding activity tumor cells. Human breast cancer cells were treated with different concentrations of the designated compounds for different times and analyzed for STAT3 activation. (A, C) Nuclear extracts of equal total protein prepared from MDA-MB-468 cells untreated (DMSO, 0) or treated with (A) 5 μM **8q** for 1-3 h or (C) 1-5 μM BBI-608 for 3 h were incubated with the hSIE probe that binds STAT3 and subjected to EMSA analysis for STAT3 DNA-binding activity; and (B, D, E) Immunoblotting analysis of whole-cell lysates of equal total protein prepared from MDA-MB-231 cells untreated (DMSO, 0) or (B) treated with 1 or 3 μM of **8q** for 24 or 30 h, (D) 0.5-2 μM BBI-608 for 2 h, or (E) 1 or 3 μM **7g** for 3-24 h probing for pY705STAT3, STAT3,

pEGFR, EGFR, pSrc, Src, pJAK2, JAK2, pAKT, AKT, pERK1/2, ERK1/2, GAPDH, or Tubulin. Positions of STAT3:DNA complex or proteins in gel are shown; control (0) lane represents whole-cell lysates or nuclear extracts prepared from 0.05% DMSO-treated cells. Data are representative of 2 independent determinations.

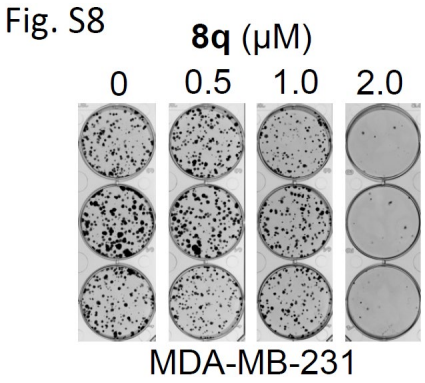


Fig. S8. Colony survival assay and the effects of STAT3 inhibitor. Human breast cancer MDA-MB-231 cells were seeded as single-cell culture and treated once with 0-2 μM **8q** and allowed to culture until large colonies were visible, which were stained with crystal violet and imaged. Data are representative of 2 independent determinations.

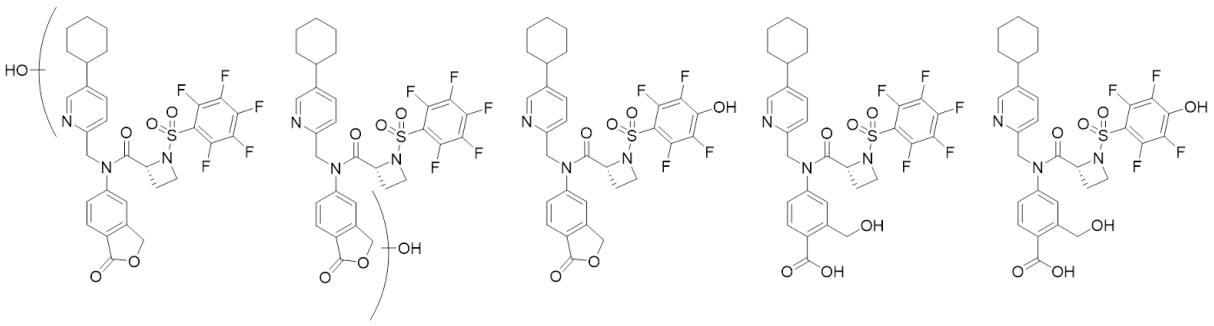


Fig. S9. Human HLM MetID study of 7g. Structures of additional metabolites apart from the parent compound.

Table S1. EMSA IC_{50} and cell viability EC_{50} values for select esters and heterocyclics.

	EMSA	MDA-MB-231	MDA-MB-468	MCF-10A	MCF-7
7a	>4	2.5	2.7	7.0	>1.0
7b	>4	4.4	n.d	6.0	nd
7c	1.1	2.1	1.7	3.6	3.5
7d	1.0	1.8	nd	nd	4.0
8p	0.7	2.8	2.6	6.7	4.6
8q	0.8	1.7	1.6	4.5	3.8
9a	1.9	1.4	3.8	5.0	6.2
9d	1.8	1.4	1.0	4.4	4.5
9i	0.6	2.0	nd	nd	nd
9j	1.1	2.0	nd	nd	nd

nd, not determined

Table S2. Aqueous Solubility of Selected Compounds.

Compound	SGF[1] (µg/mL)	SIF[2] (µg/mL)
7g	**116**	**200**
8p	**107**	**117**
8q	**115**	**131**
9f	**104**	**123**

Notes: 1. SGF: Simulated Gastric Fluid. 2. SIF: Simulated Intestinal Fluid

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Author Contributions: §CB-P and PY contributed equally.

Conflicts of interest: JT is a co-founder of Novella, LLC, which has licensed STAT3 IP. The remaining authors have no competing interests.

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Abbreviations: STAT, signal transducer and activator of transcription; EMSA, electrophoretic mobility shift assay; PARP, poly (ADP-ribose) polymerase; VEGF, Vascular endothelial growth factor; GAPDH, glyceraldehyde 3-phosphate dehydrogenase.

References

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2. Lopez-Tapia, F.; Brotherton-Pleiss, C.; Yue, P.; Murakami, H.; Costa Araujo, A. C.; Reis dos Santos, B.; Ichinotsubo, E.; Rabkin, A.; Shah, R.; Lantz, M.; Chen, S.; Tius, M. A.; Turkson, J., Linker variation and structure-activity relationship analyses of car-boxylic acid-based small molecule STAT3 inhibitors. *ACS Med Chem Lett* **2018,** *9*, 250-255.
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Compound 5a

Qualitative Analysis Report

Data Filename	CBP-5-106r.d	**Sample Name**	CBP-5-106 final
Sample Type	Sample	**Position**	Vial 43
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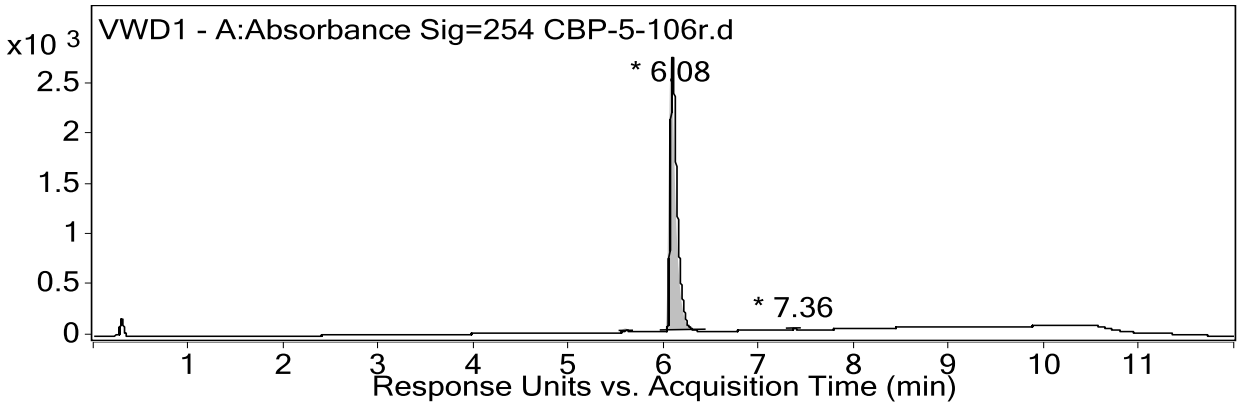
IRM Calibration Status	Not Applicable	**DA Method**	102315.m
Comment			

User Chromatograms



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2	5.96	6.08	6.45	2718.45	13654.53	100
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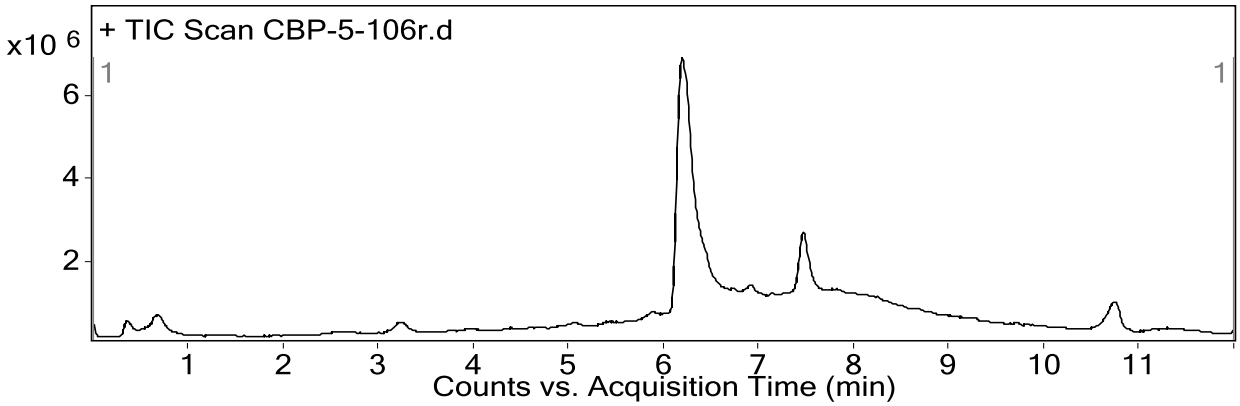
Fragmentor Voltage 165 **Collision Energy** 0 **Ionization Mode** ESI



User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
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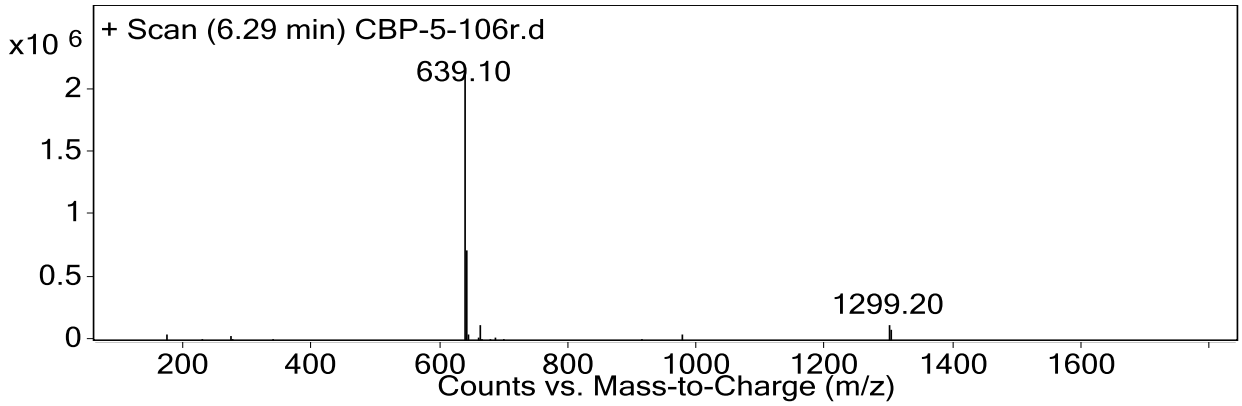

Peak List

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661.1		118830
1299.2		129054

--- End Of Report ---

Compound 5o

Qualitative Analysis Report

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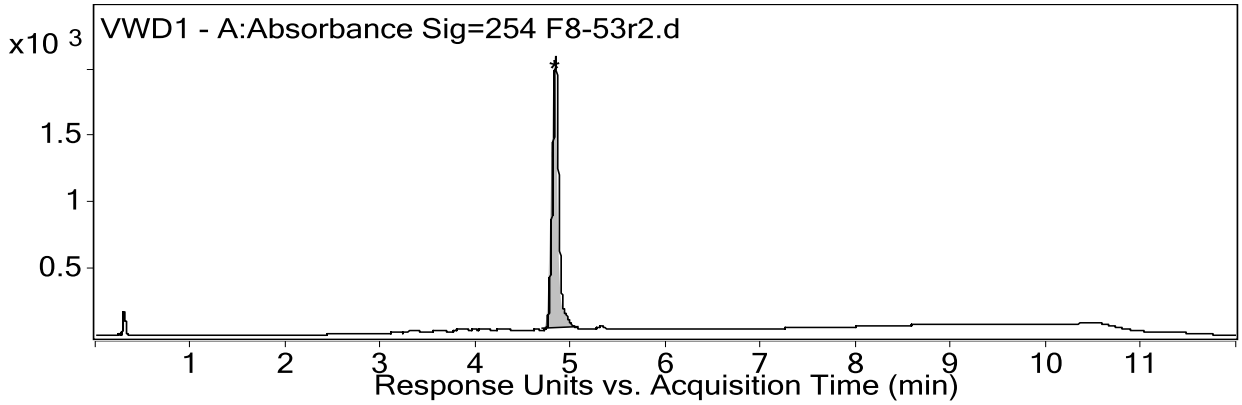
Comment

User Chromatograms



Integration Peak List

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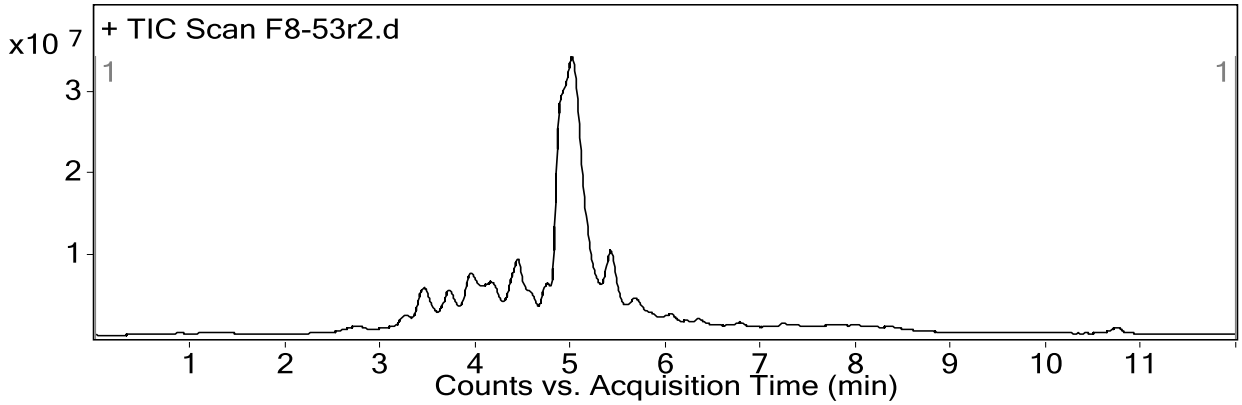
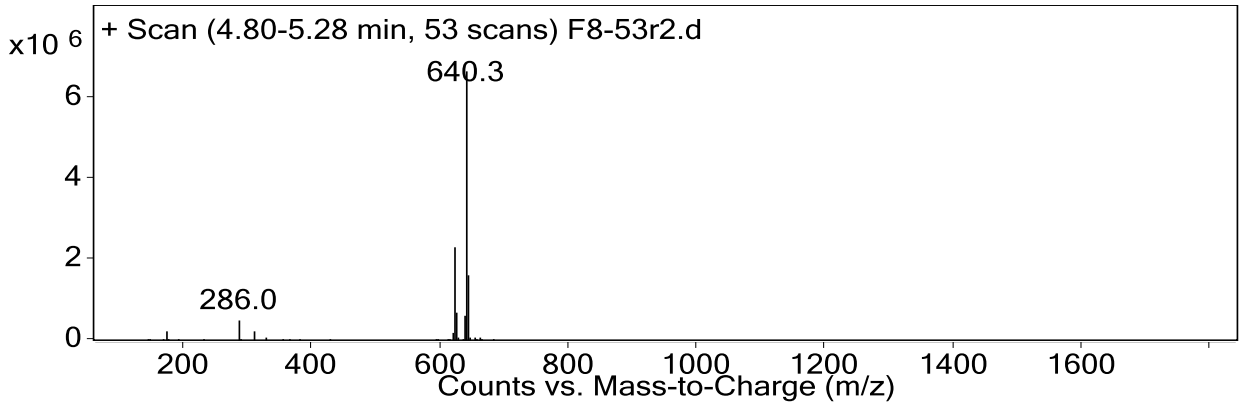
1	4.7	4.83	5.09	2062.62	9941.13	100

Fragmentor Voltage 165 **Collision Energy** 0 **Ionization Mode** ESI



User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
165	0	Esi



Peak List

m/z	z	Abund
286		485073
622.1	1	2326993
623.2	1	679020
638.1		628643
640.3	1	6667776
641.2	1	4494485
642.2	1	1626888

--- End Of Report ---

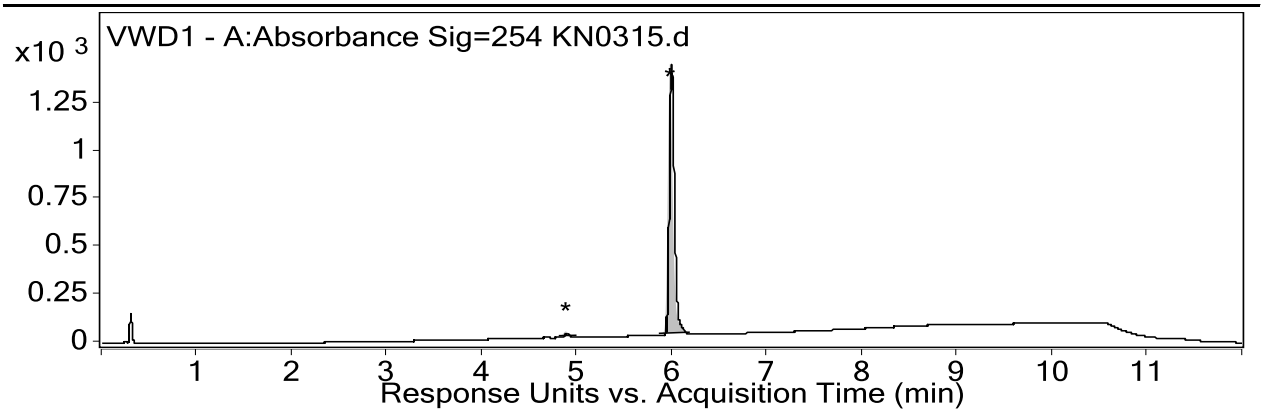
Compound 7e

Qualitative Analysis Report

Data Filename	KN0315.d	**Sample Name**	KN0315-1
Sample Type	Sample	**Position**	Vial 32
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI+20-100%_12min.m	**Acquired Time**	6/2/2017 12:35:50 PM
IRM Calibration Status	Not Applicable	**DA Method**	ChromPeakSurvey-Default.m

Comment

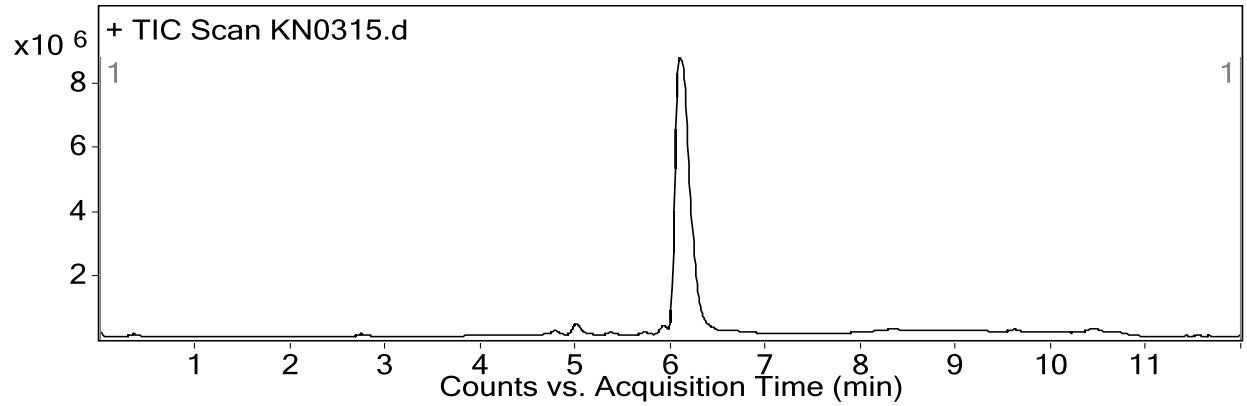
User Chromatograms



Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	4.82	4.89	5	20.66	72.41	1.37
2	5.87	5.99	6.2	1409.56	5271.02	100

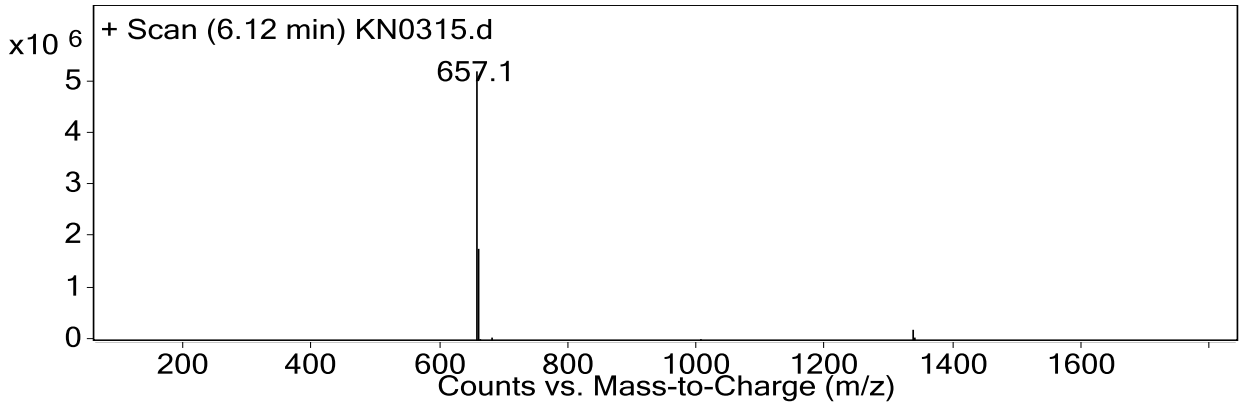
Fragmentor Voltage 165 **Collision Energy** 0 **Ionization Mode** ESI



User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
165	0	Esi

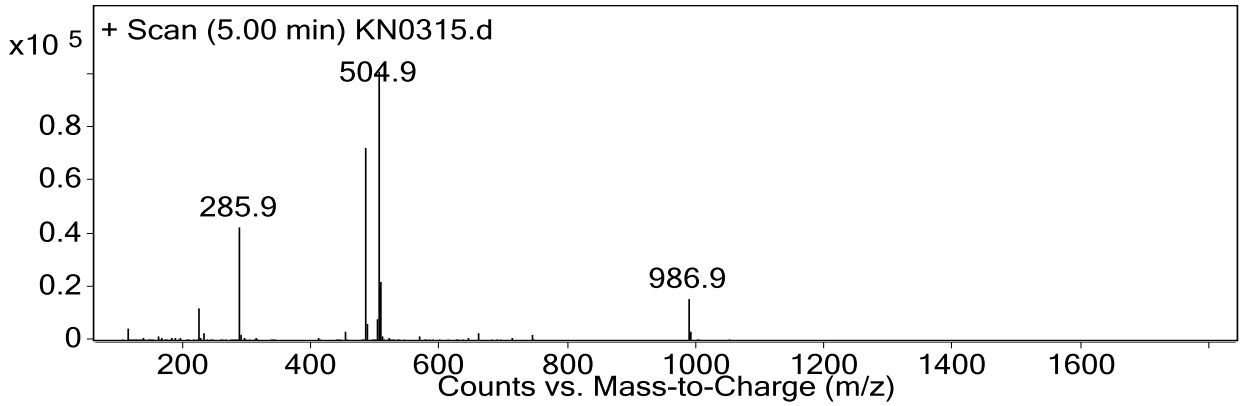
Qualitative Analysis Report



Peak List

m/z	z	Abund
657.1	1	5208514
658	1	1777412
659.1	1	533623

Fragmentor Voltage 165 **Collision Energy** 0 **Ionization Mode** Esi



Peak List

m/z	z	Abund
223.9		12022
285.9		42870
482.9	1	72229
484	1	15691
502		8362
504.9	1	101257
505.9	1	22249
506.9	1	7429
986.9	1	15750
987.9	1	6478

--- End Of Report ---

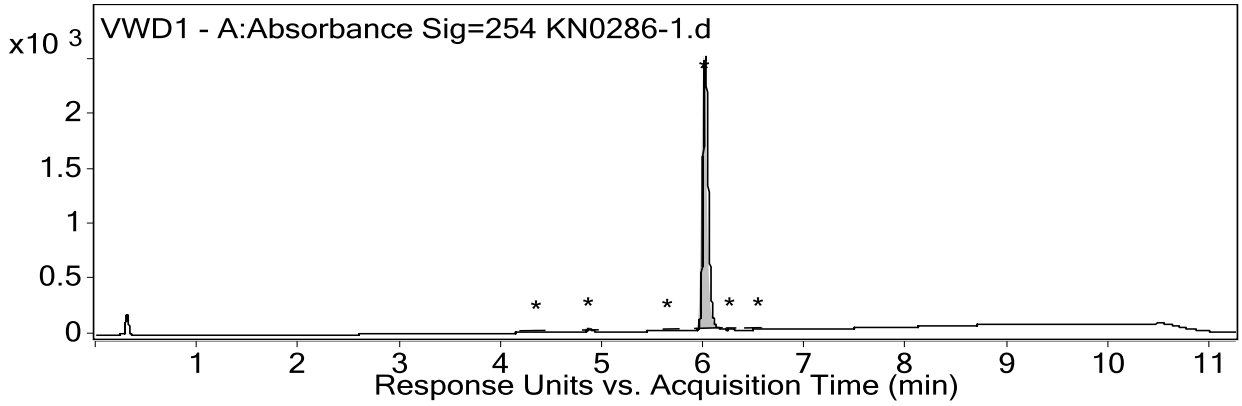
Compound 7f

Qualitative Analysis Report

Data Filename	KN0286-1.d	**Sample Name**	KN0286-1
Sample Type	Sample	**Position**	Vial 41
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI+20-100%_12min.m	**Acquired Time**	5/16/2017 2:32:17 PM
IRM Calibration Status	Not Applicable	**DA Method**	ChromPeakSurvey-Default.m

Comment

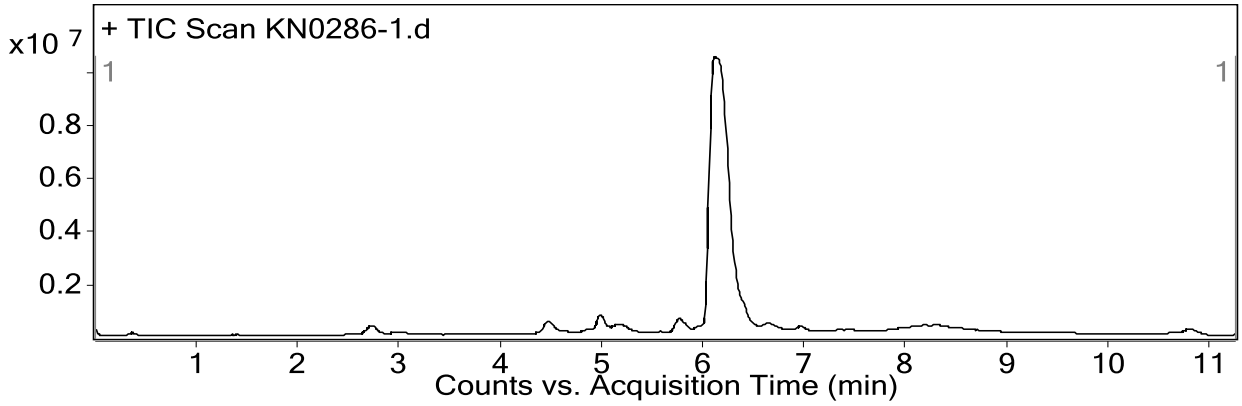
User Chromatograms



Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	4.19	4.35	4.45	6.47	32.87	0.36
2	4.81	4.87	4.97	27.8	99.57	1.08
3	5.61	5.65	5.77	2.7	11.34	0.12
4	5.92	6.01	6.2	2488.03	9229.93	100
5	6.23	6.27	6.33	4.38	14.57	0.16
6	6.41	6.55	6.59	1.1	5.94	0.06

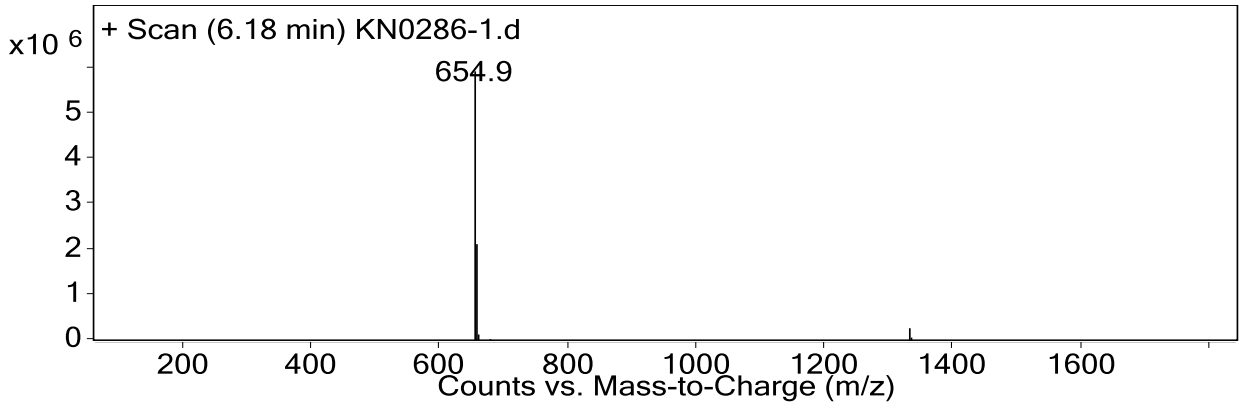
Fragmentor Voltage 165 **Collision Energy** 0 **Ionization Mode** ESI



User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
165	0	Esi

Qualitative Analysis Report



Peak List

m/z	z	Abund
654.9	1	5934357
655.9	1	2107982
656.9	1	658473

--- End Of Report ---

Compound 7g

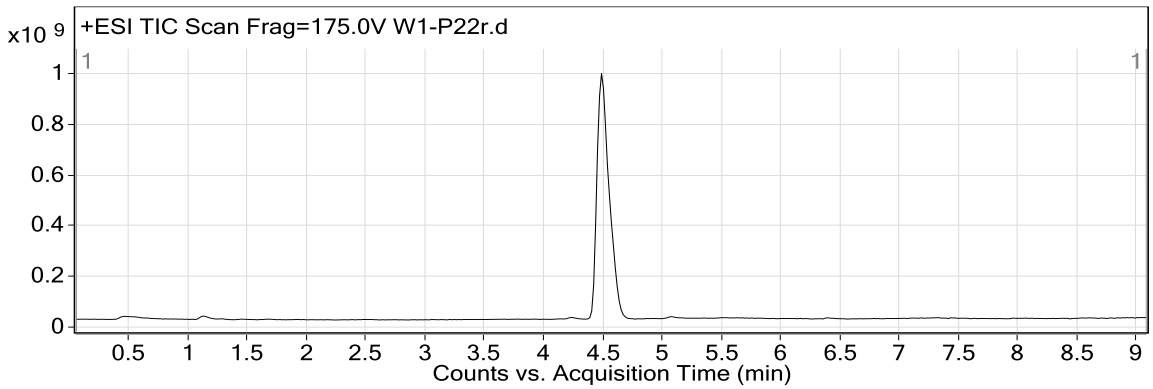
Qualitative Analysis Report

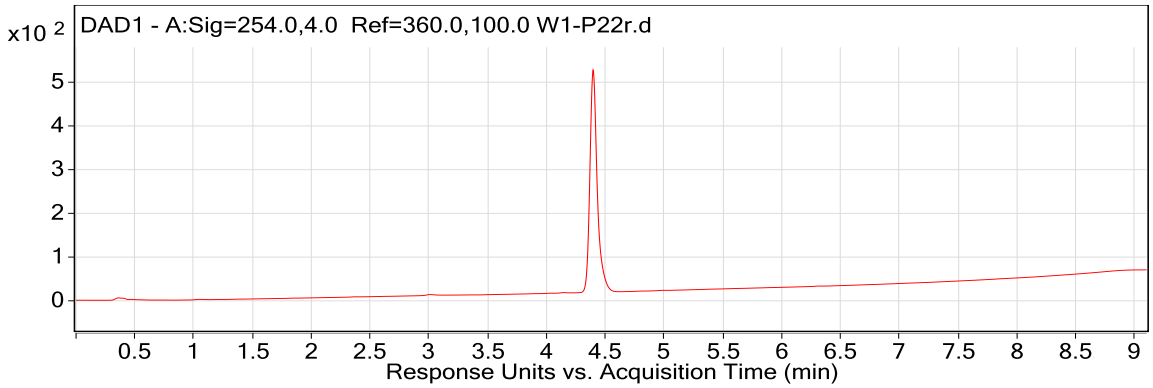
Data Filename	W1-P22r.d	**Sample Name**	W1-P22
Sample Type	Sample	**Position**	P1-E3
Instrument Name	Instrument 1	**User Name**	
Acq Method	40_90_fo_rpurity.m	**Acquired Time**	7/12/2017 3:44:14 PM
IRM Calibration Status	Success	**DA Method**	Default.m
Comment			

Sample Group		**Info.**	
Stream Name	LC 1	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.06.01 (B6157)

User Chromatograms

Fragmentor Voltage 175 **Collision Energy** 0 **Ionization Mode** ESI

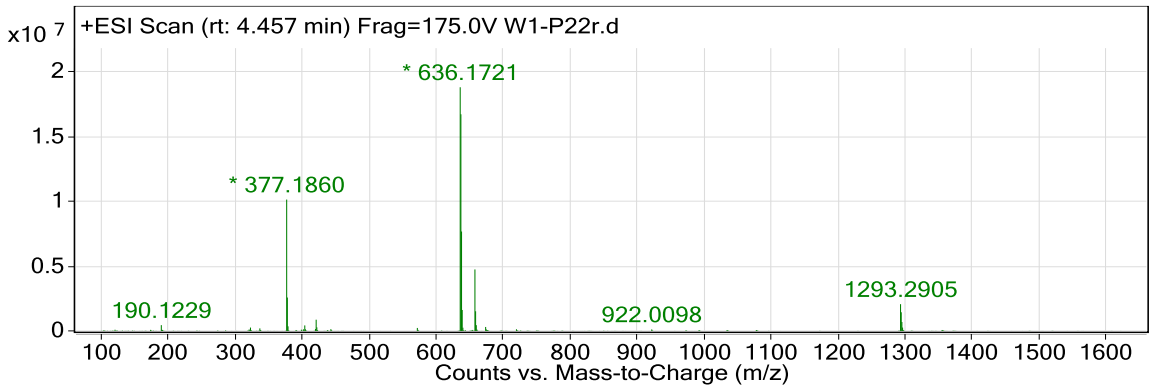




User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
175	0	ESI

Qualitative Analysis Report



Peak List

m/z	z	Abund
377.186	1	10151458
378.1885	1	2578313.5
636.1721		18834186
637.1651	1	16744369
638.1614	1	7681100.5
639.1613	1	1616957.38
658.1398	1	4749792
659.143	1	1516258.38
1293.2905	1	2065600.88
1294.2934	1	1440491

--- End Of Report ---

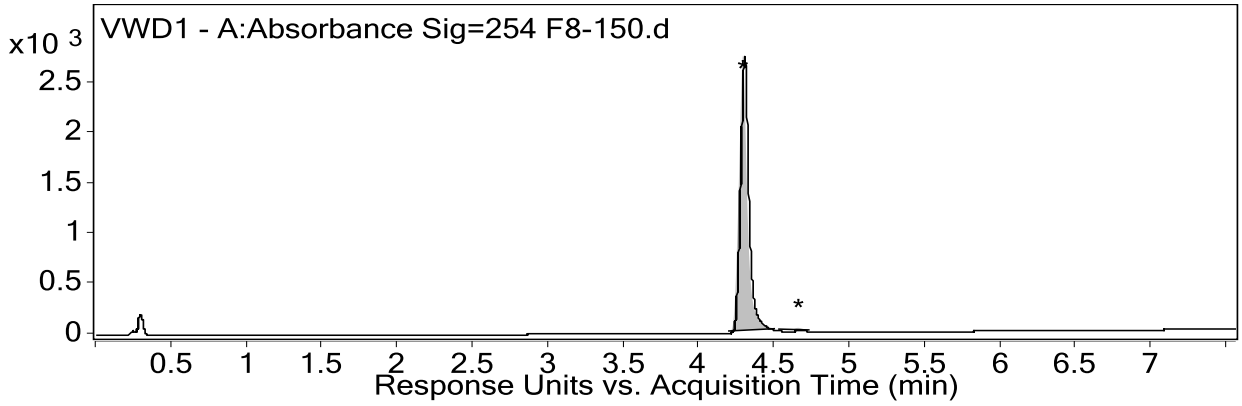
Compound 8i

Qualitative Analysis Report

Data Filename	F8-150.d	**Sample Name**	F8-150
Sample Type	Sample	**Position**	Vial 2
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI+20-100%_12min.m	**Acquired Time**	4/28/2017 4:03:42 PM
IRM Calibration Status	Not Applicable	**DA Method**	ChromPeakSurvey-Default.m

Comment

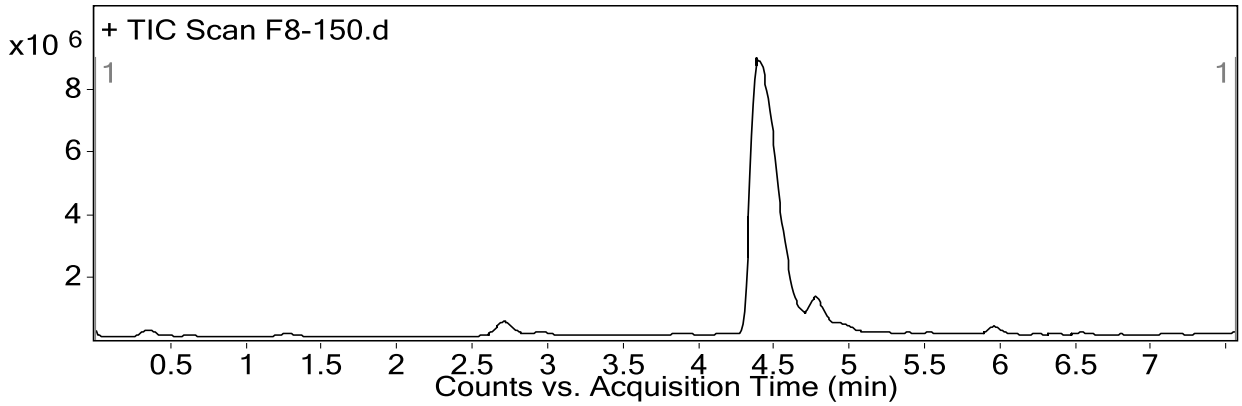
User Chromatograms



Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	4.2	4.3	4.51	2731.45	10790.87	100
2	4.53	4.66	4.74	17.57	40.2	0.37

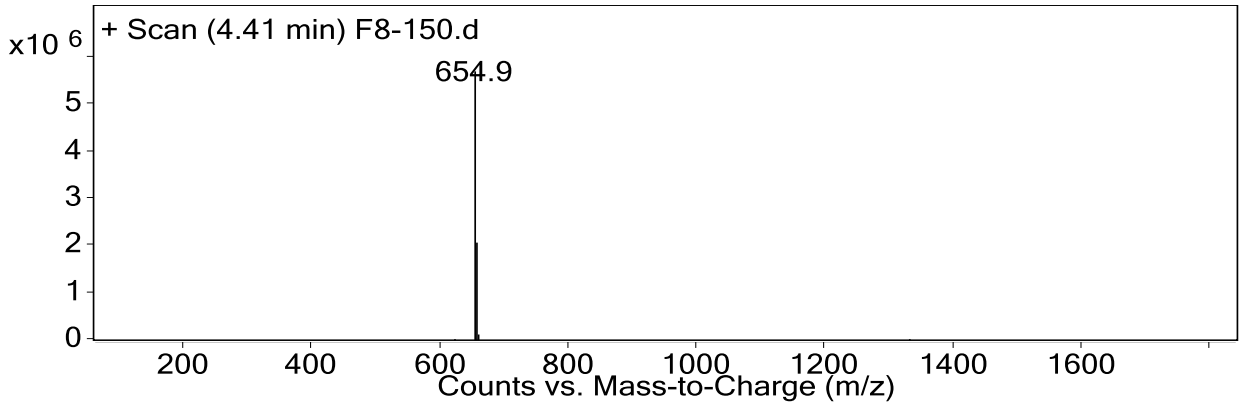
Fragmentor Voltage 165 **Collision Energy** 0 **Ionization Mode** ESI



User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
165	0	Esi

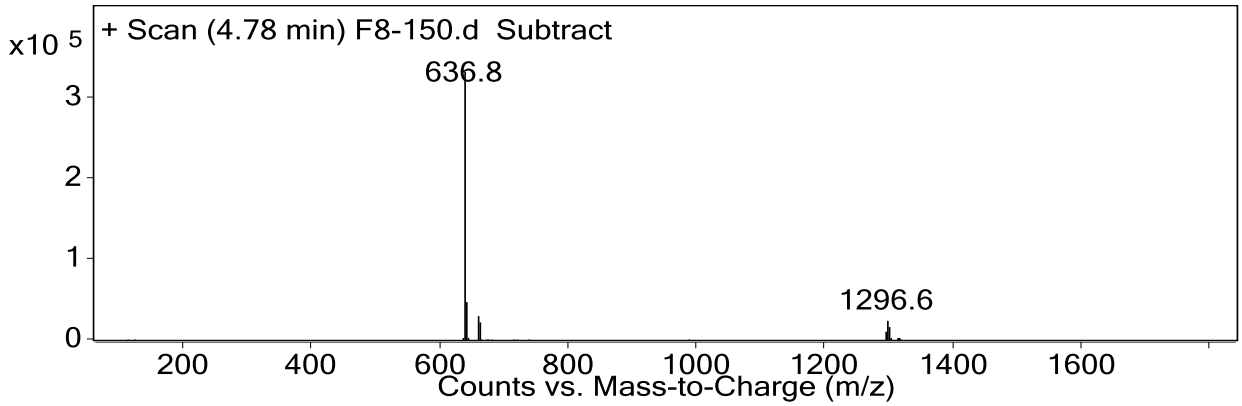
Qualitative Analysis Report



Peak List

m/z	z	Abund
654.9	1	5718987
655.9	1	2063765
656.9	1	644758

Fragmentor Voltage	Collision Energy	Ionization Mode
165	0	Esi



Peak List

m/z	z	Abund
636.8	1	334151
637.9	1	107533
638.9	1	151934
639.9	1	47706
658.8		31781
660.9		23787
1296.6		25878
1298.6		17953

--- End Of Report ---

Compound 9k

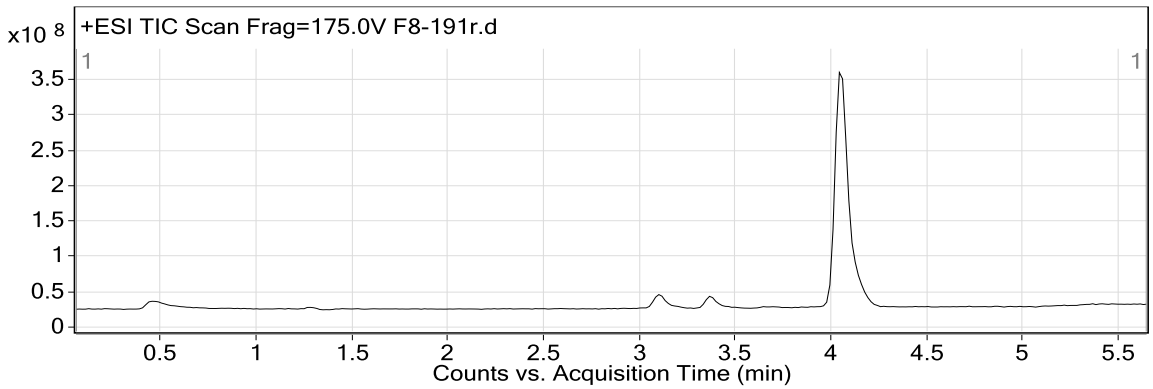
Qualitative Analysis Report

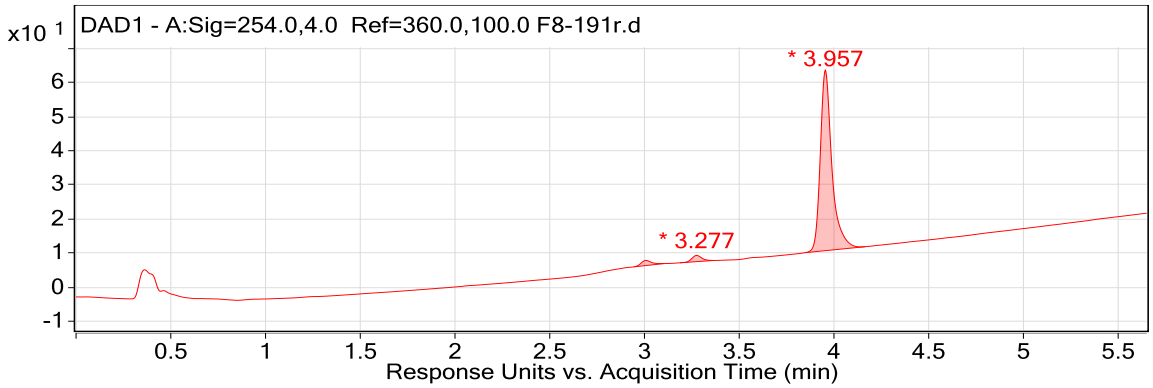
Data Filename	F8-191r.d	**Sample Name**	F8-191
Sample Type	Sample	**Position**	P1-E2
Instrument Name	Instrument 1	**User Name**	
Acq Method	40_90_fo_rpurity.m	**Acquired Time**	7/27/2017 11:51:24 AM
IRM Calibration Status	Success	**DA Method**	Default.m
Comment			

Sample Group		**Info.**	
Stream Name	LC 1	**Acquisition SW Version**	6200 series TOF/6500 series Q-TOF B.06.01 (B6157)

User Chromatograms

Fragmentor Voltage 175 **Collision Energy** 0 **Ionization Mode** ESI





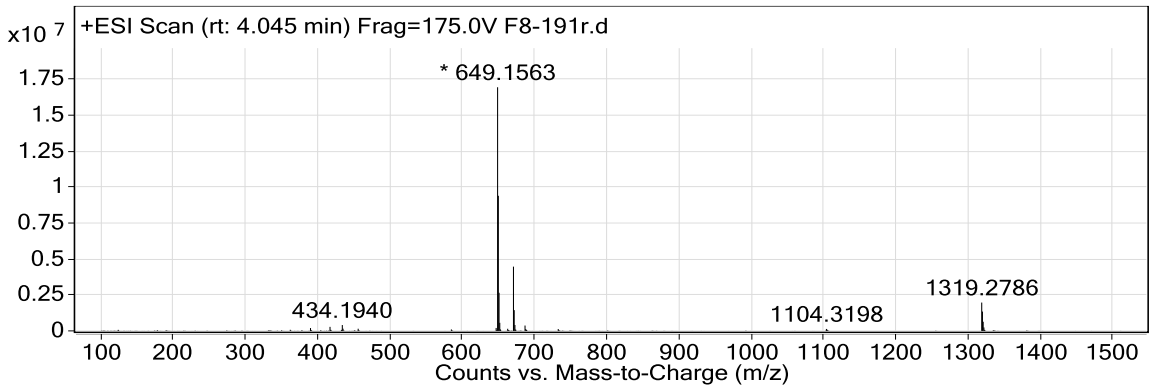
Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	2.947	3.01	3.107	1.5	5.8	2.56
2	3.19	3.277	3.367	1.82	6.71	2.97
3	3.85	3.957	4.167	52.91	225.96	100

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
175	0	ESI

Qualitative Analysis Report



Peak List

m/z	z	Abund
649.1563	1	16941758
650.1557	1	9394780
651.1547	1	2651068
652.1563	1	562220.06
671.1338	1	4467956.5
672.1368	1	1442381.25
673.1373	1	409655.94
1319.2786	1	1970475.13
1320.282	1	1342992.63
1321.2843	1	635530.19

--- End Of Report ---

Compound	SMILES	EMSA IC50 (μM)
1	OC(C1=CC=C(N(C([C@@H](C)N(C)S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)=O)CC3=CC=C(C4CCCCC4)C=C3)C(F)=C1)=O	1.80 ± 0.94
2	OC(C1=C(O)C=C(N(C([C@H]2N(S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)CCC2)=O)CC4=CC=C(C5CCCCC5)C=C4)C=C1)=O	7.2±3.4
3	OC(C1=C(O)C=C(N(C([C@H]2CCCN2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=C4)C=C1)=O	2.4±0.4
4	OC(C1=C(O)C=C(N(C([C@@H]2N(S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)CCCC2)=O)CC4=CC=C(C5CCCCC5)C=C4)C=C1)=O	5.4±1.6
5a	OC(C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=C4)C=C1)=O	0.55±0.01
5b	OC(C1=C(O)C=C(N(C([C@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=C4)C=C1)=O	2.22±0.49
5c	OC(C1=C(O)C=C(N(C(C2CN(S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)C2)=O)CC4=CC=C(C5CCCCC5)C=C4)C=C1)=O	>>2
5d	O=C(O[Na])C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=C4)C=C1	0.58±0.06
5e	OC(C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCC5)C=C4)C=C1)=O	0.71±0.11
5f	OC(C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C(C)(C)C)C=C4)C=C1)=O	2.17± 0.30
5g	OC(C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCOCC5)C=C4)C=C1)=O	1.09±0.13
5h	OC(C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCOCC5)C=C4)C=C1)=O	1.50±0.01
5i	OC(C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=C4)C(F)=C1)=O	0.66±0.07
5j	O=C(O[Na])C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=C4)C(F)=C1	0.56±0.07
5k	OC(C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C(C)C)C=C4)C(F)=C1)=O	1.28±0.16
5l	OC(C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCOCC5)C=C4)C(F)=C1)=O	0.81±0.16
5m	OC(C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)N=C4)C=C1)=O	0.66±0.16
5n	OC(C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CN=C(C5CCOCC5)C=C4)C=C1)=O	0.90±0.14
5o	OC(C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=N4)C=C1)=O	0.38±0.02
5p	OC(C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CN=C(C5CCCCC5)C=N4)C=C1)=O	0.46±0.05
5q	OC(C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=NC=C(C5CCCCC5)C=N4)C=C1)=O	0.46±0.05
5r	OC(C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)N=N4)C=C1)=O	0.70±0.03
5s	OC(C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCC5)C=N4)C=C1)=O	0.63±0.07
5t	O=C(O)C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CN=C(C5CCCC5)C=N4)C=C1	0.78±0.06
6a	OC(C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=C4)C=C1)=O	3.04±0.14
6b	OC(C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCOCC5)C=C4)C=C1)=O	3.94±0.43
6c	O=C(O)C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=N4)C=C1	1.09 ± 0.30
6d	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=C3)C5=NC(C(O)=O)=CO5	> 5
6e	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=C3)C5=CC=C(C6=NN=NN6)C=C5	1.36±0.10
6f	OC(C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=C4)C(F)=C1)=O	1.08±0.20
6g	OC(C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C(C)(C)C)C=C4)C(F)=C1)=O	3.55±0.10
6h	OC(C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=N4)C(F)=C1)=O	0.76±0.11
6i	OC(C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=N4)C=C1F)=O	0.86±0.11
6j	O=C(O)C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCC5)C=N4)C(F)=C1	1.18±0.19
6k	OC(C1=NC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=N4)C=C1)=O	> 2
6l	O=C(O)C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CN=C(C5CCCCC5)C=N4)C(F)=C1	1.72±0.04

7a	O=C(OC)C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=C4)C=C1	> 4
7b	O=C(OC)C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=C4)C(F)=C1	> 4
7c	O=C(OC)C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)N=C4)C=C1	1.05
7d	O=C(OC)C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=N4)C=C1	0.99
7e	O=C(OC)C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CN=C(C5CCCCC5)C=N4)C(F)=C1	> 10
7f	O=C(OC)C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CN=C(C5CCCCC5)C=N4)C=C1	7.4
7g	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=N3)C5=CC6=C(C(OC6)=O)C=C5	1.79
8a	O=C(NO)C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=C4)C=C1	2.51±0.23
8b	O=C(NO)C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCC5)C=C4)C=C1	2.25±0.72
8c	O=C(NO)C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCOCC5)C=C4)C=C1	2.92±0.60
8d	O=C(NO)C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=C4)C=C1	1.32± 0.36
8e	O=C(NO)C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCOCC5)C=C4)C=C1	2.07±0.115
8f	O=C(NO)C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=C4)C(F)=C1	1.75±0.19
8g	O=C(NO)C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C(C)(C)C)C=C4)C(F)=C1	3.96± 0.06
8h	O=C(NO)C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCOCC5)C=C4)C(F)=C1	2.11±0.24
8i	O=C(NO)C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=N4)C=C1	0.34±0.02
8j	O=C(NOC)C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=N4)C=C1	0.51±0.02
8k	O=C(NOC)C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=N4)C(F)=C1	1.96±0.15
8l	O=C(NO)C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=N4)C(F)=C1	0.89±0.18
8m	O=C(NO)C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCC5)C=N4)C(F)=C1	1.94±0.16
8n	NC(C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=N4)C(F)=C1)=O	> 2
8o	O=C(NC)C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=N4)C(F)=C1	1.91±0.03
8p	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=N3)C5=CC(O)=C(C(N)=O)C=C5	0.66±0.17
8q	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=N3)C5=CC(O)=C(C(NC)=O)C=C5	0.77±0.15
8r	O=C(N(C)C)C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CC=C(C5CCCCC5)C=N4)C=C1	1.72±0.21
8s	O=C(NO)C1=C(O)C=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CN=C(C5CCCCC5)C=N4)C=C1	0.53±0.05
8t	O=C(NO)C1=CC=C(N(C([C@@H](CC2)N2S(C3=C(F)C(F)=C(F)C(F)=C3F)(=O)=O)=O)CC4=CN=C(C5CCCCC5)C=N4)C(F)=C1	> 2
8u	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CN=C(C4CCCCC4)C=N3)C5=CC(O)=C(C(NC)=O)C=C5	1.90±0.02
9a	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=C3)C5=CC6=C(C(NC=C6)=O)C=C5	1.87±0.17
9b	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=N3)C5=CC6=C(C(NC=C6)=O)C=C5	0.79
9c	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=N3)C5=CC6=C(C(N(C)C=C6)=O)C=C5	0.93
9d	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=C3)C5=CC6=C(C(NN=C6)=O)C=C5	1.80±0.15
9e	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CN=C(C4CCCCC4)C=N3)C5=CC6=C(C(NN=C6)=O)C=C5	2.45±0.02
9f	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=N3)C5=CC6=C(C(NC=N6)=O)C=C5	0.98 ± 0.054
9g	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=N3)C5=CC6=C(C(N(C)C=N6)=O)C=C5	1.12
9h	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CN=C(C4CCCCC4)C=N3)C5=CC6=C(C(NC=N6)=O)C=C5	1.47±0.15
9i	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=N3)C5=CC6=C(C(NC6)=O)C=C5	0.64±0.12

9j	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=N3)C5=CC6=C(C(NC6)=O)C=C5F	1.09±0.15
9k	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=N3)C5=CC6=C(C(NC6=O)=O)C=C5	1.18±0.42
9l	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=C3)C5=CC6=C(C=NN6)C=C5F	1.90±0.37
9m	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=C3)C5=C(F)C6=C(C=NN6)C=C5	2.96±0.12
9n	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=N3)C5=CC6=C(C=NN6)C=C5F	1.80±0.09
9o	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CN=C(C4CCCCC4)C=N3)C5=CC6=C(C=NN6)C=C5F	1.42±0.10
9p	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=C3)C5=CC6=C(N=CN6)C=C5	2.35±0.55
9q	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CC=C(C4CCCCC4)C=N3)C5=CC6=C(N=NN6)C=C5	0.61±0.04
9r	O=C([C@@H](CC1)N1S(C2=C(F)C(F)=C(F)C(F)=C2F)(=O)=O)N(CC3=CN=C(C4CCCCC4)C=N3)C5=CC6=C(N=NN6)C=C5	0.63±0.01