Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information For:

An Empirical Study of Amide–Heteroarene π-Stacking Interactions Using Reversible Inhibitors of a Bacterial Serine Hydrolase

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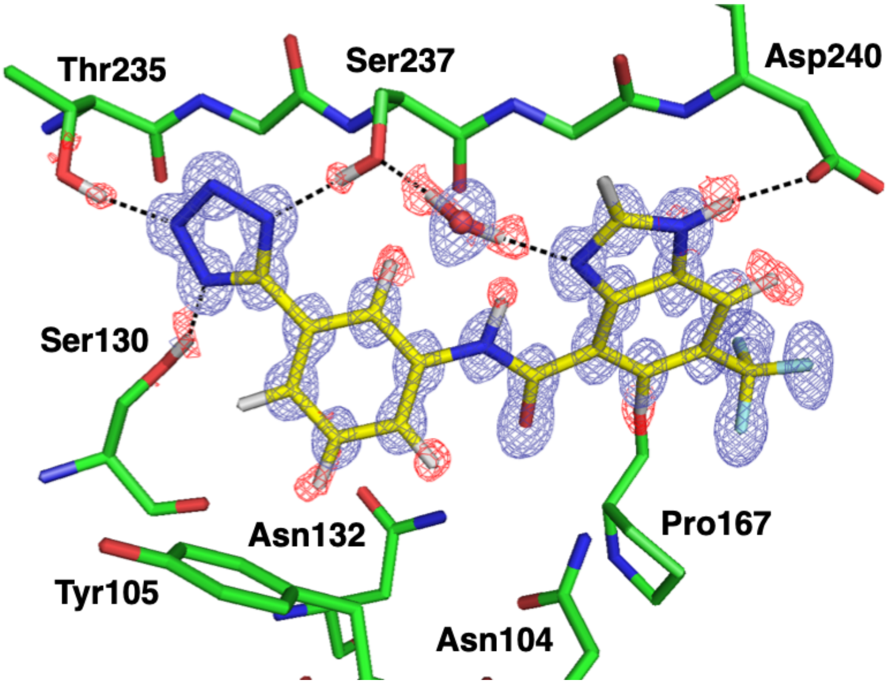
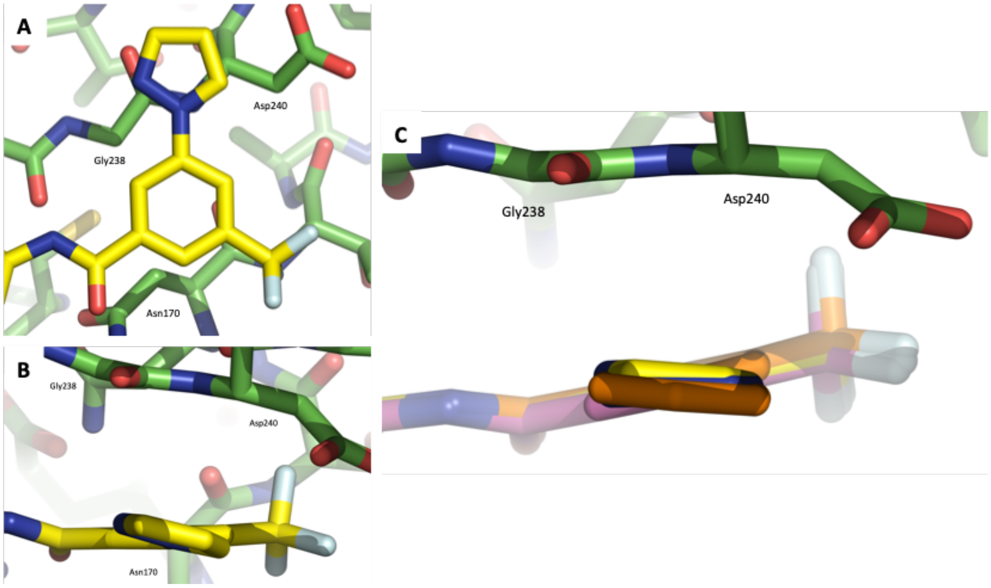
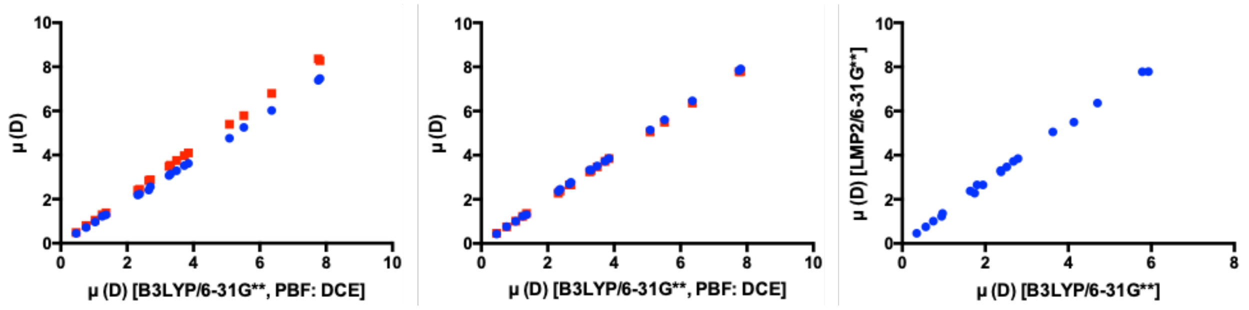


Supplementary Figure 1. Compound **1** in complex with CTX-M-14 at 0.89Å. 2Fo-Fc (blue): 1.5 σ; Fo-Fc (red): 2.5 σ (H-omit). Compound previously reported in references 16 and 17 of the main text; PDB: 4UA7.



Supplementary Figure 2. Front (A) and top (B) view of compound **14** with CTX-M-14. C) Superimposed top view of **3**, **14**, and **20** with CTX-M-14.

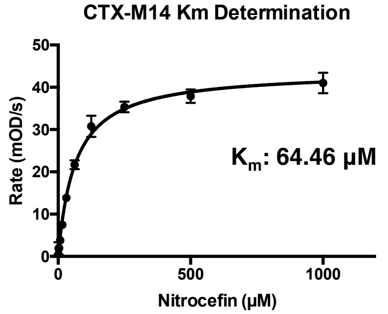


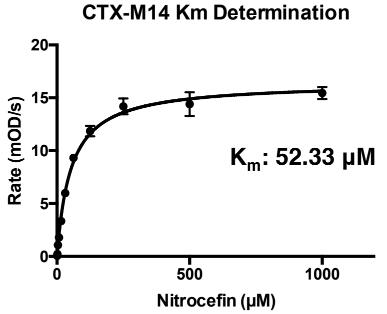
Supplementary Figure 3. Comparison of calculated dipoles between solvents and models. A) B3LYP/6-31G**, PBF: DCE (10.65 ε) vs. PBF: H_2O (blue, 80.37 ε) and PBF: $CHCl_3$ (red, 4.806 ε). B) B3LYP/6-31G**, PBF: DCE vs. M06-2X/6-31G**, PBF: DCE (blue) and B3LYP-D3/6-31G**, PBF: DCE (red). C) B3LYP/6-31G**, gas phase vs. LMP2/6-31G**, gas phase.

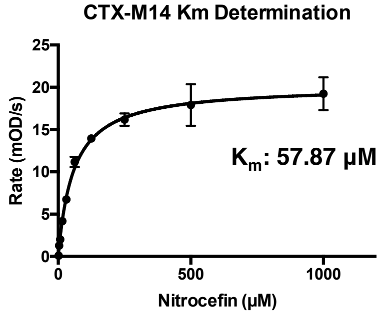
Biochemical Data

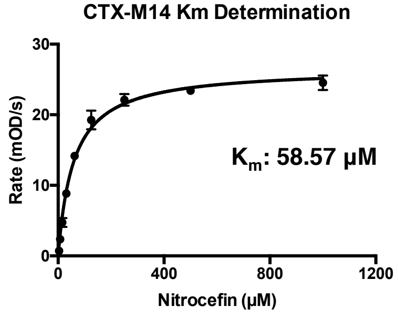
Each curve is a replicate generated from a technical triplicate. Compounds were tested up to 2.5 mM or 500 uM for CTX-M-14 and CTX-M-27, respectively (as solubility allowed).

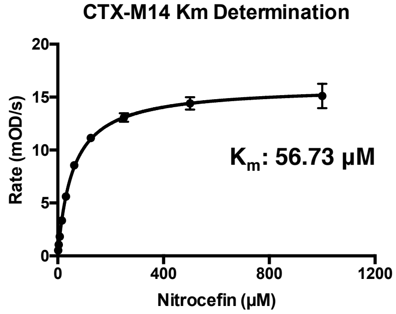
K_m Measurements:

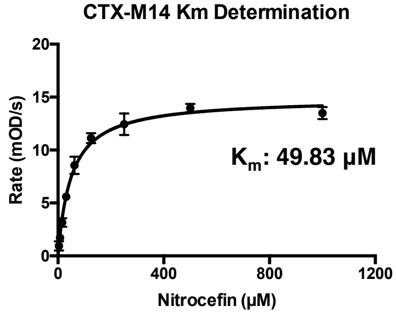




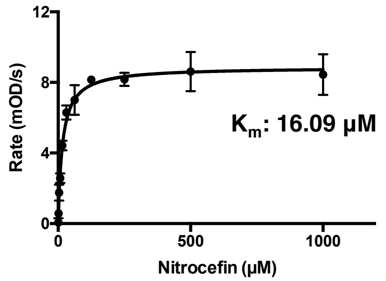








CTX-M27 Km Determination



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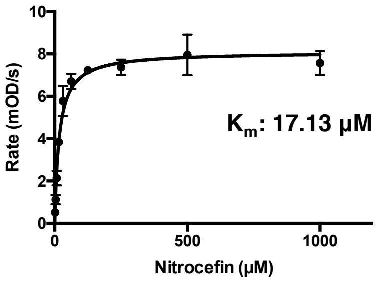

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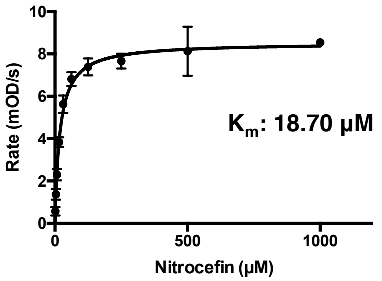

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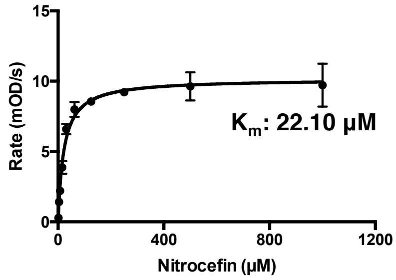

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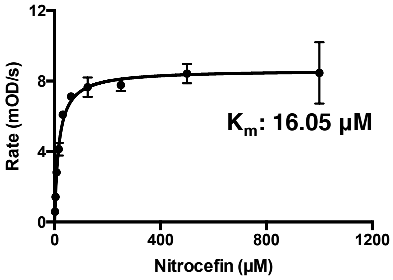

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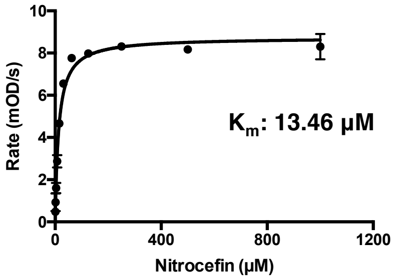

CTX-M-14 Biochemical Data:

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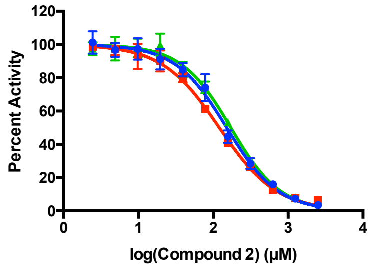

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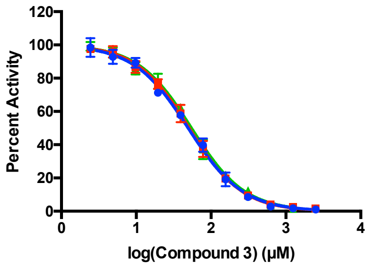

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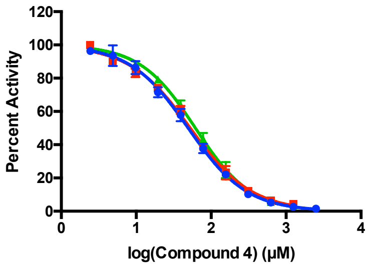

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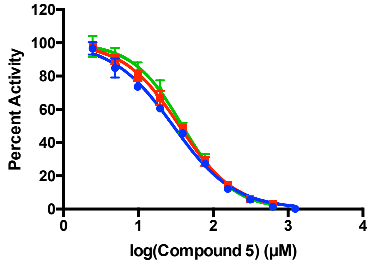

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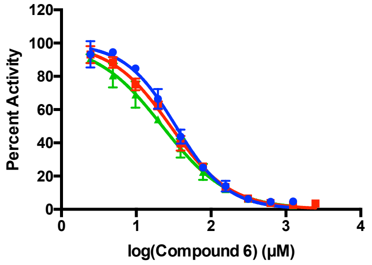

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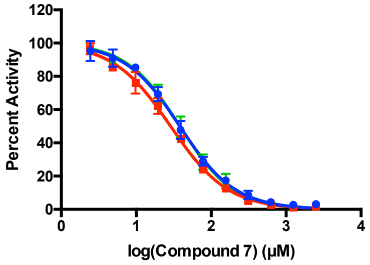

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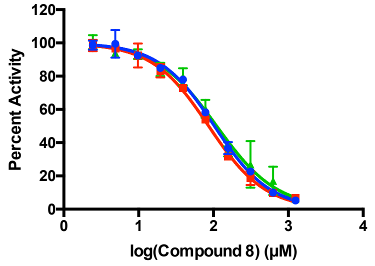

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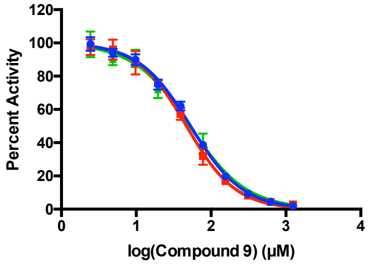

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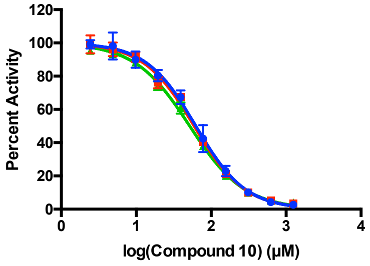

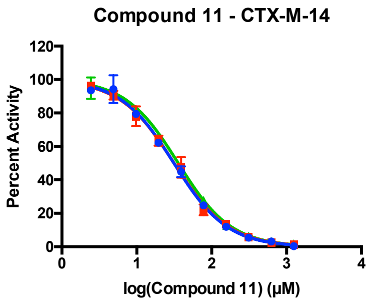
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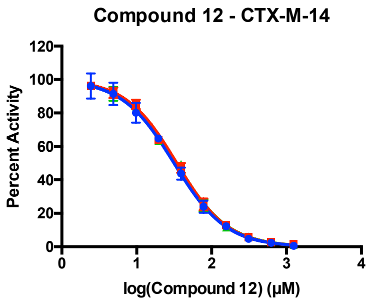
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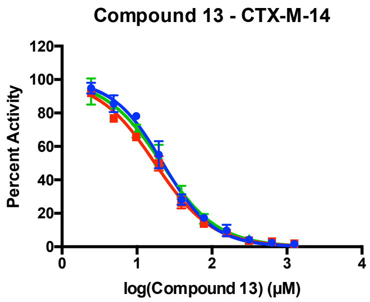
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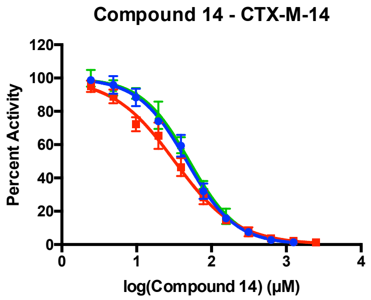
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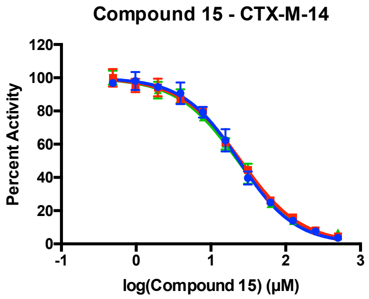
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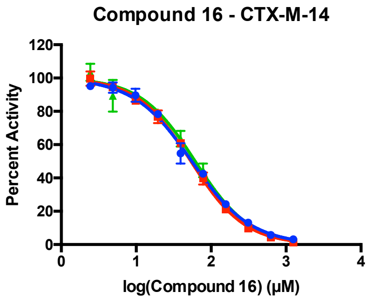
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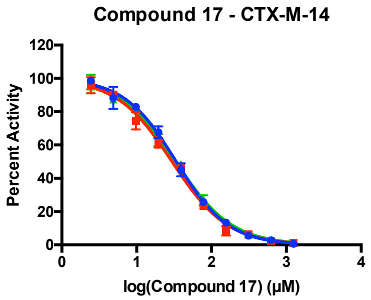
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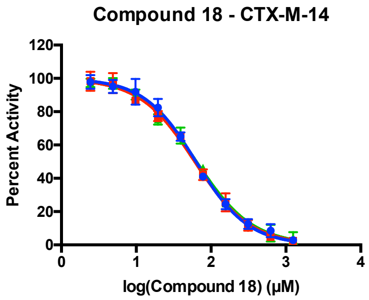
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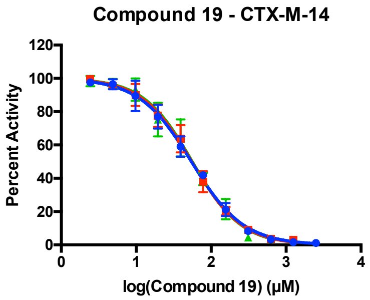
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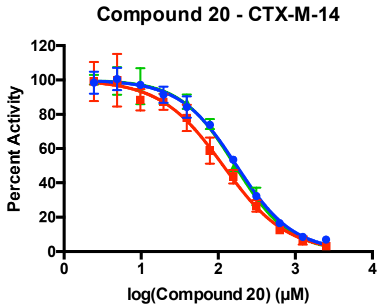
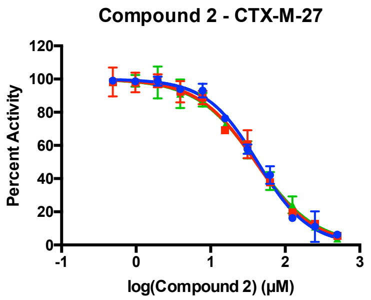

Compound 20 - CTX-M-14

CTX-M-27 Biochemical Data: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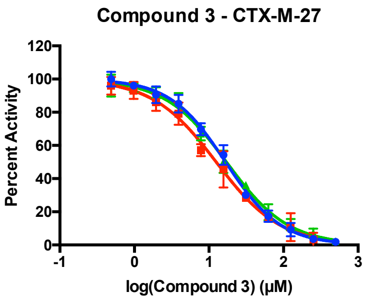
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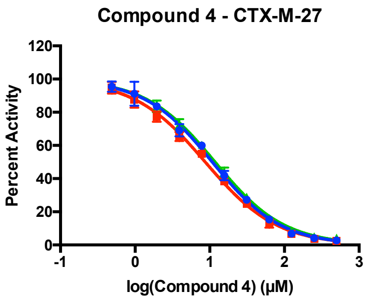
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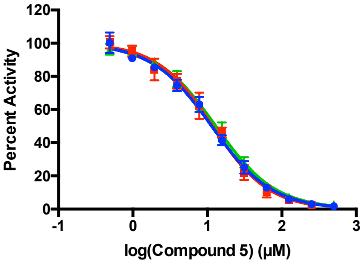
Compound 5 - CTX-M-27



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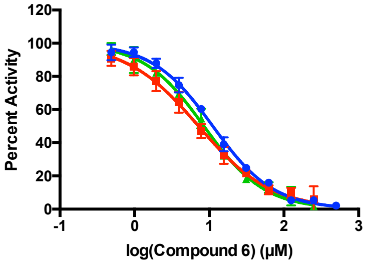

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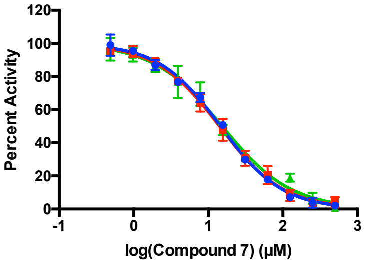

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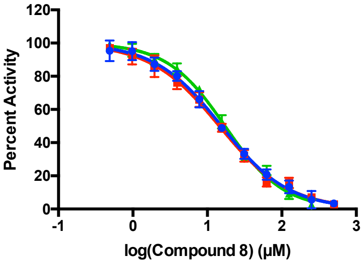

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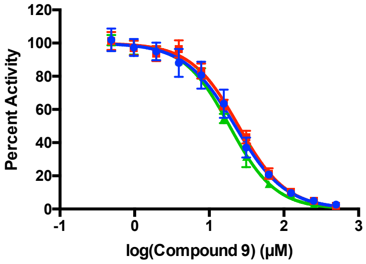

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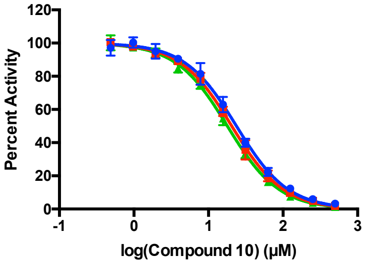

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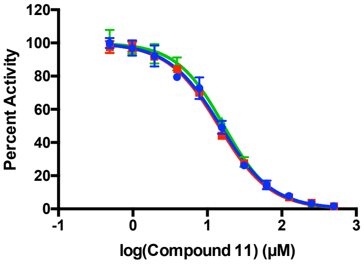

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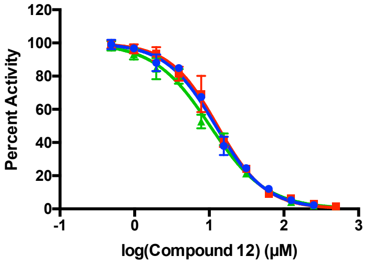

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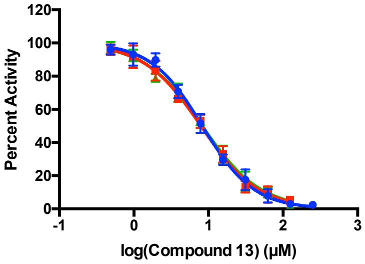

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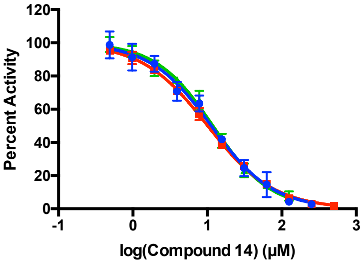

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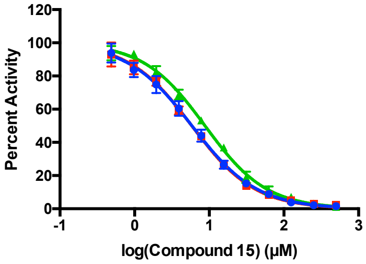

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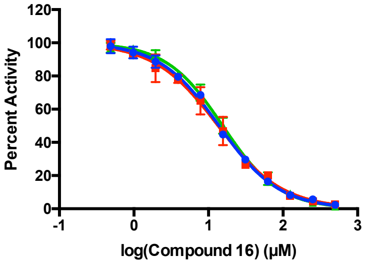

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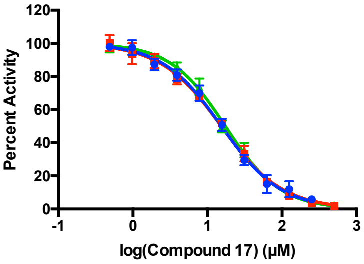

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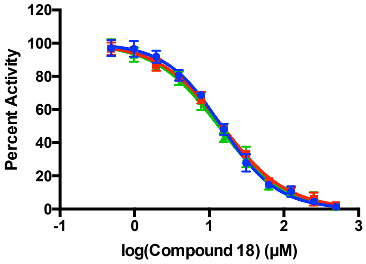

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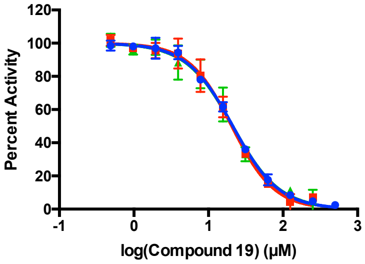
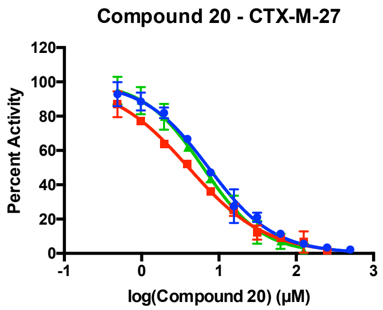
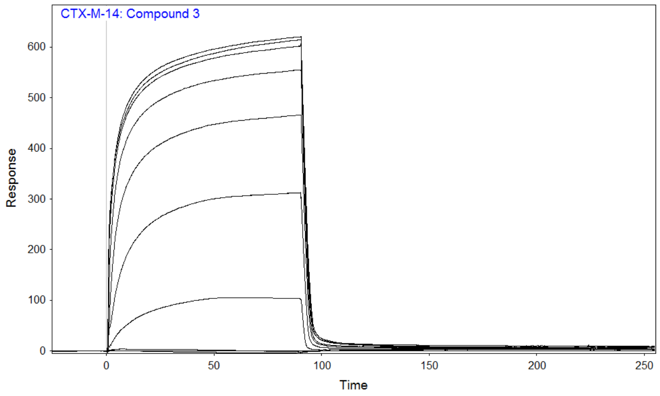


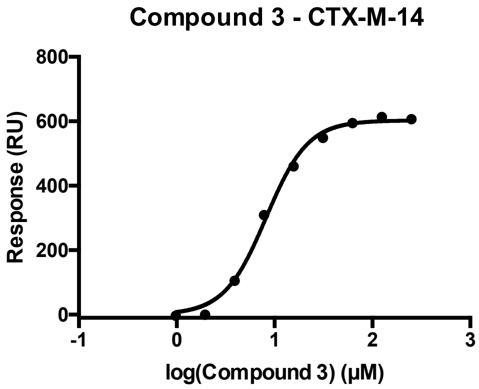


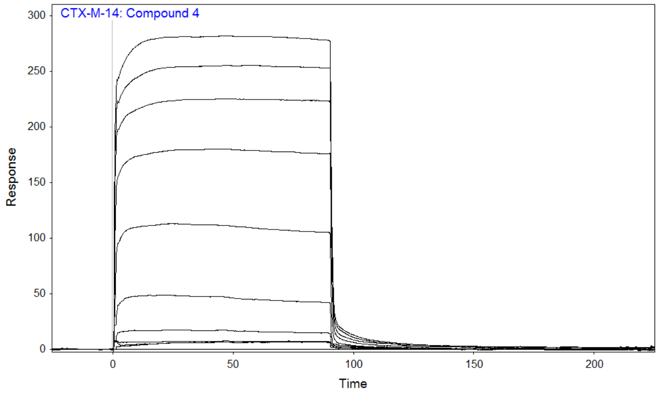
SPR Data

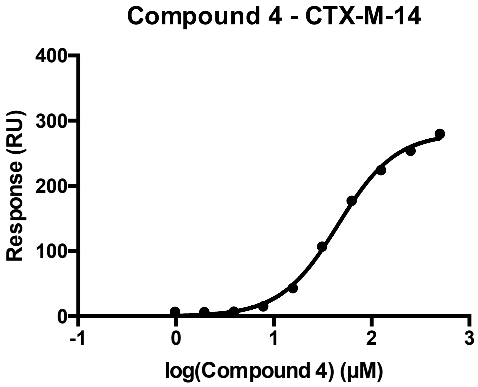
Compounds were tested in 10-point dose response with two internal blanks up to 500 uM and 50 μM for CTX-M-14 and CTX-M-27, respectively (as solubility allowed). All compounds were tested in quadruplicate for CTX-M-14 and in duplicate for CTX-M-27. K_d was measured at equilibrium binding between 65-85s.

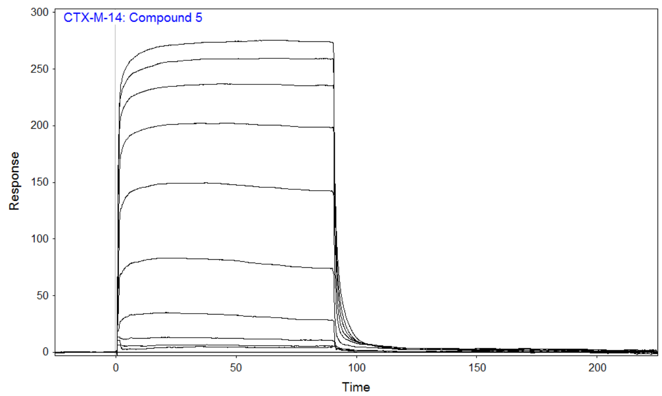
Representative sensograms for CTX-M-14:

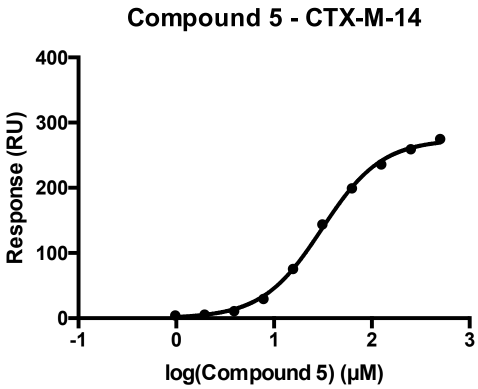


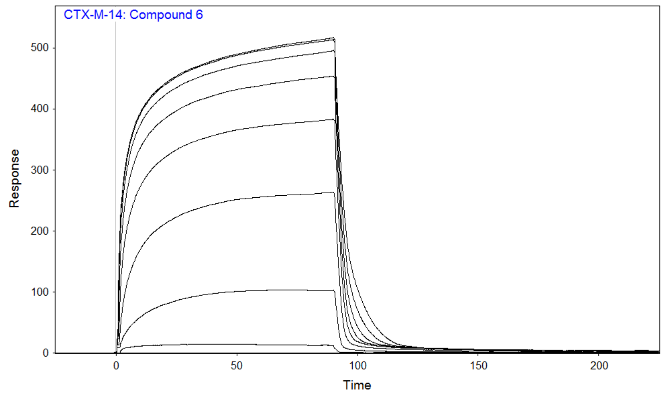


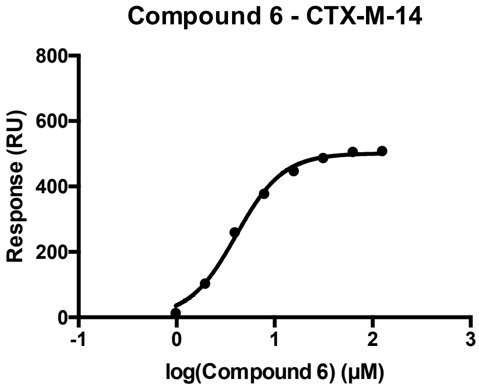


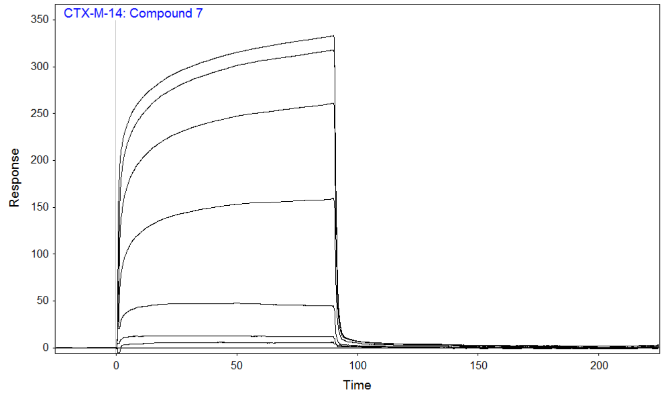


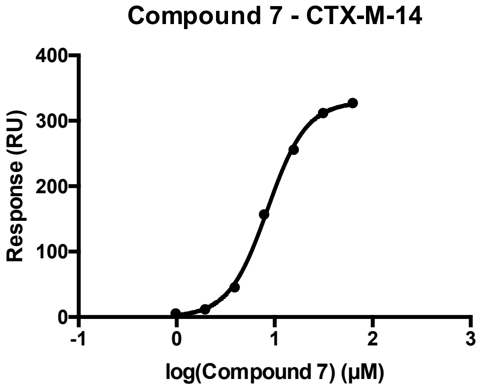

CTX-M-14: Compound 5
Response
Time
300
250
200
150
100
50
0
0
50
100
150
200

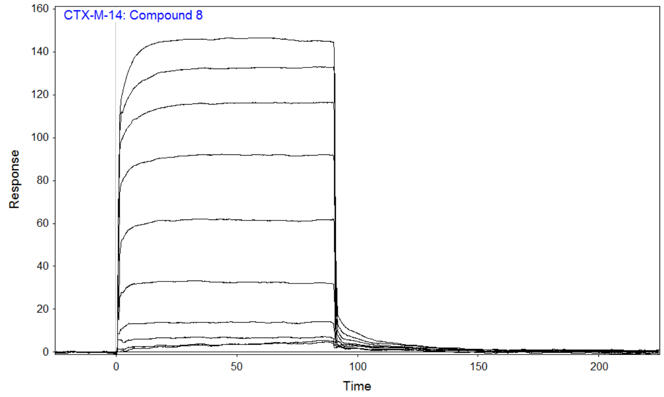

Compound 5 - CTX-M-14
Response (RU)
log(Compound 5) (µM)
400
300
200
100
0
-1
0
1
2
3

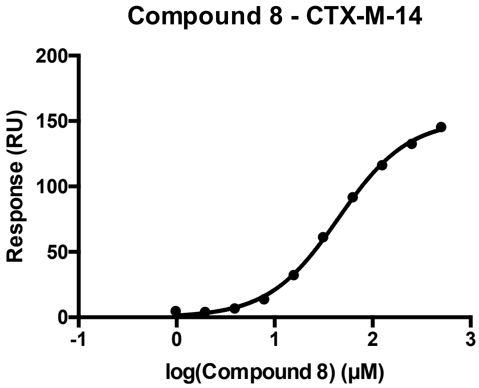

CTX-M-14: Compound 6
Response
Time
500
400
300
200
100
0
0
50
100
150
200

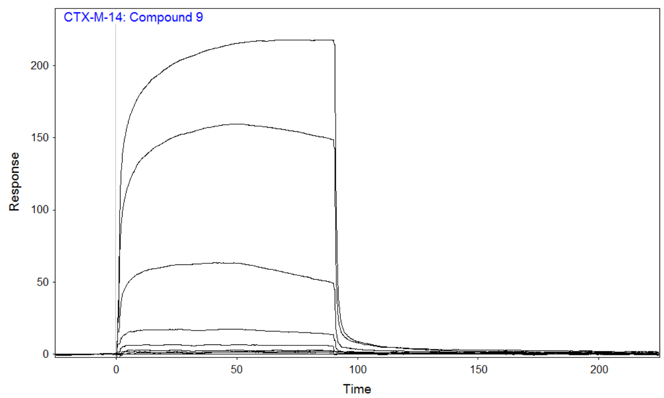

Compound 6 - CTX-M-14
Response (RU)
log(Compound 6) (µM)
800
600
400
200
0
-1
0
1
2
3

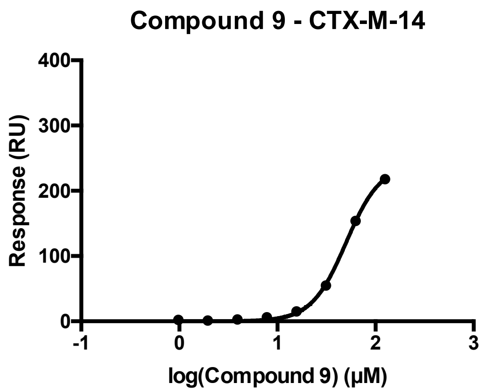

CTX-M-14: Compound 7
Response
Time
350
300
250
200
150
100
50
0
0
50
100
150
200

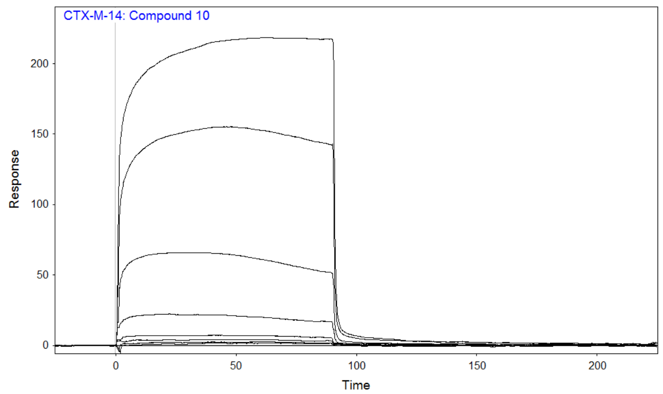

Compound 7 - CTX-M-14
Response (RU)
log(Compound 7) (µM)
400
300
200
100
0
-1
0
1
2
3

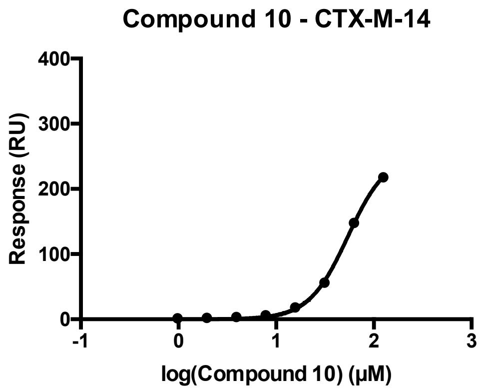

CTX-M-14: Compound 8
Response
Time
160
140
120
100
80
60
40
20
0
0
50
100
150
200

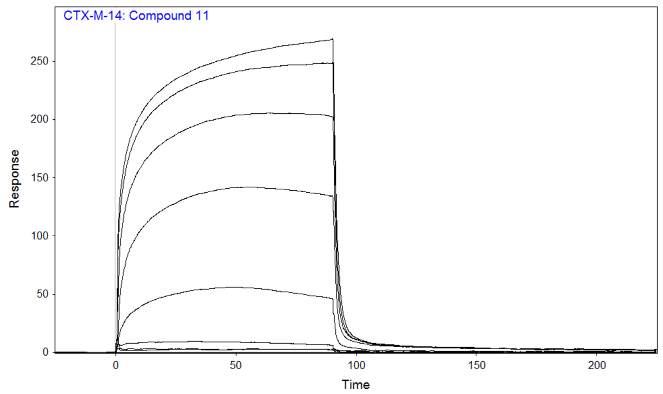

Compound 8 - CTX-M-14
Response (RU)
log(Compound 8) (µM)
200
150
100
50
0
-1
0
1
2
3

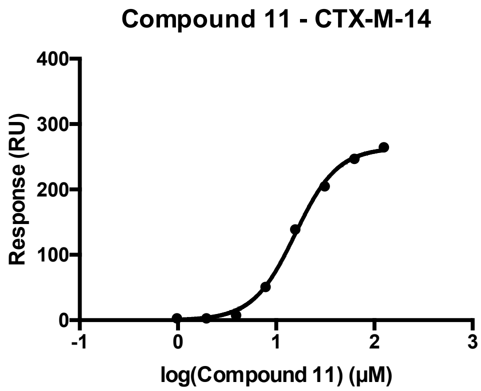

CTX-M-14: Compound 9
Response
0
50
100
150
200
0
50
100
150
200
Time

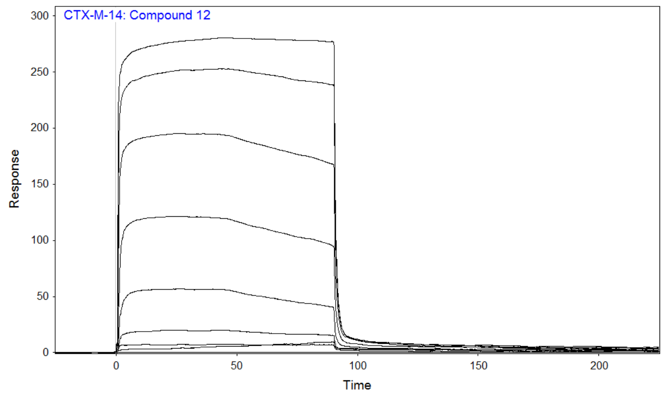

Compound 9 - CTX-M-14
Response (RU)
0
100
200
300
400
-1
0
1
2
3
log(Compound 9) (μM)

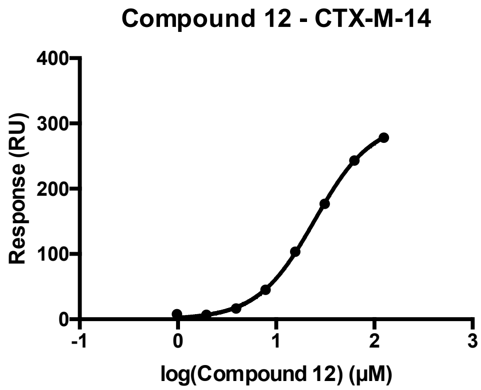

CTX-M-14: Compound 10
Response
0
50
100
150
200
0
50
100
150
200
Time

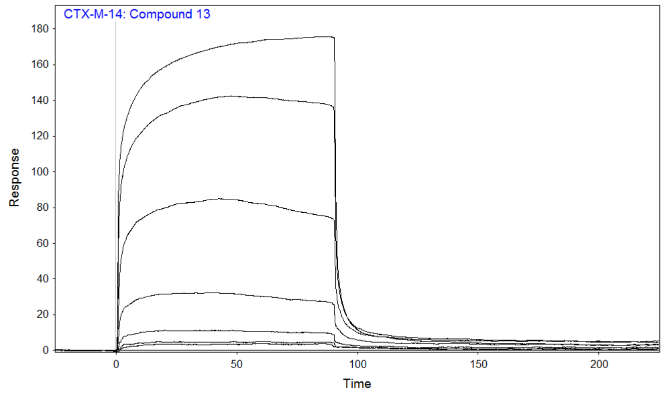

Compound 10 - CTX-M-14
Response (RU)
0
100
200
300
400
-1
0
1
2
3
log(Compound 10) (μM)

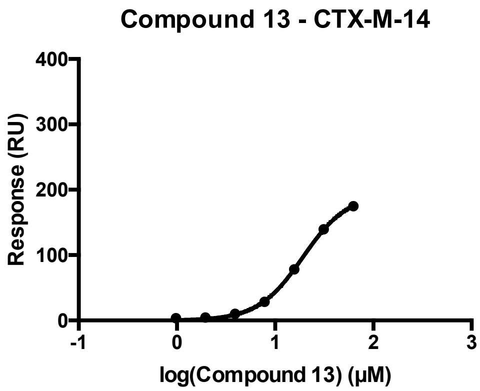

CTX-M-14: Compound 11
Response
0
50
100
150
200
250
0
50
100
150
200
Time

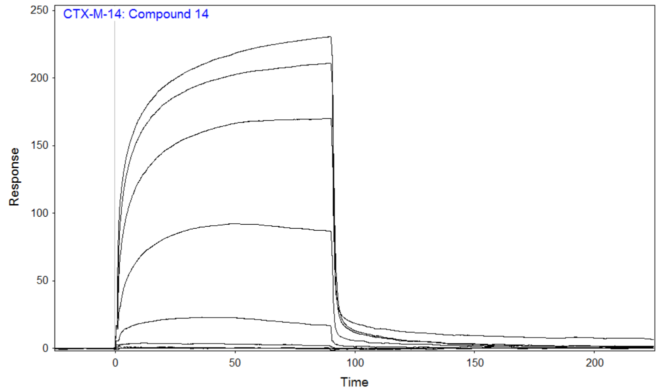

Compound 11 - CTX-M-14
Response (RU)
0
100
200
300
400
-1
0
1
2
3
log(Compound 11) (μM)

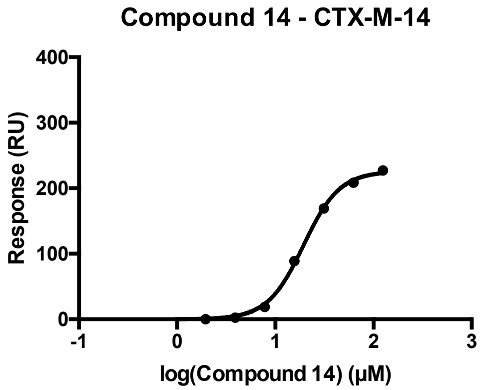

CTX-M-14: Compound 12
Response
0
50
100
150
200
250
300
0
50
100
150
200
Time

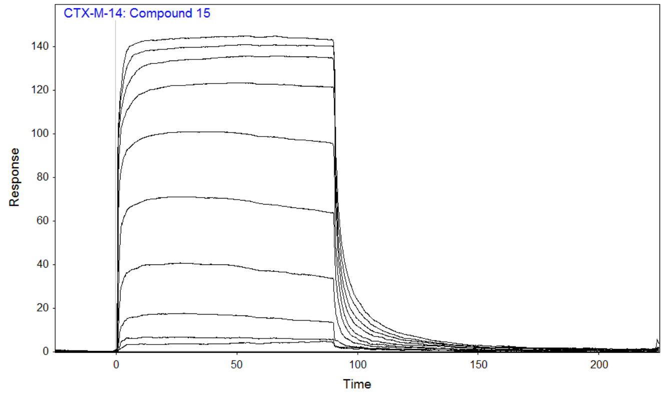

Compound 12 - CTX-M-14
Response (RU)
0
100
200
300
400
-1
0
1
2
3
log(Compound 12) (μM)

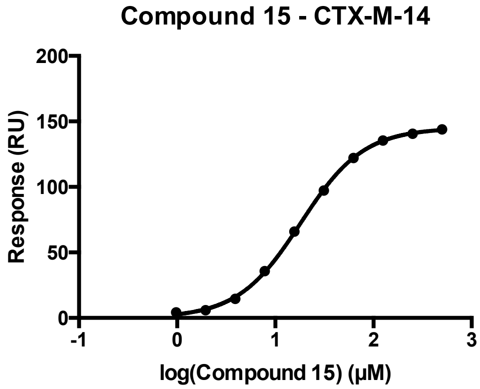

CTX-M-14: Compound 13
Response
180
160
140
120
100
80
60
40
20
0
0
50
100
150
200
Time

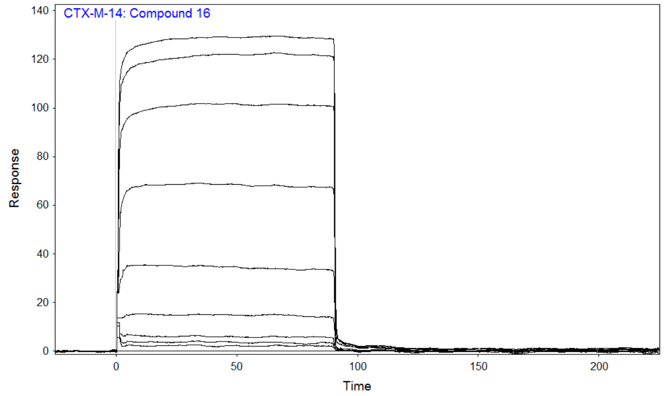

Compound 13 - CTX-M-14
Response (RU)
400
300
200
100
0
-1
0
1
2
3
log(Compound 13) (μM)

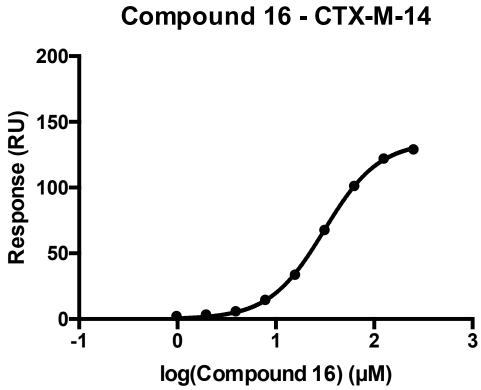

CTX-M-14: Compound 14
Response
250
200
150
100
50
0
0
50
100
150
200
Time

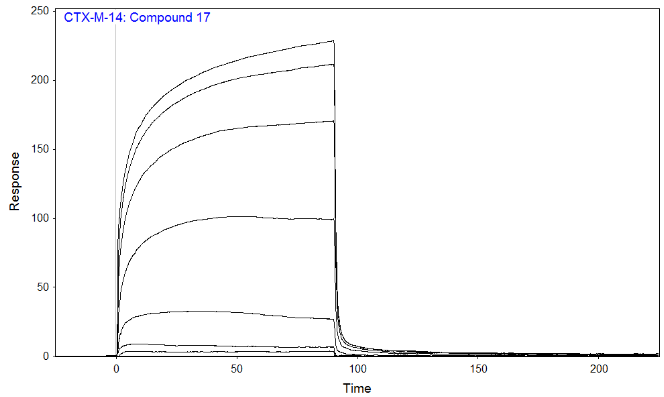

Compound 14 - CTX-M-14
Response (RU)
400
300
200
100
0
-1
0
1
2
3
log(Compound 14) (μM)

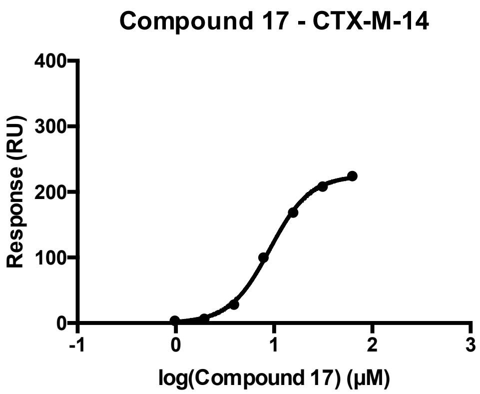

CTX-M-15: Compound 15
Response
140
120
100
80
60
40
20
0
0
50
100
150
200
Time

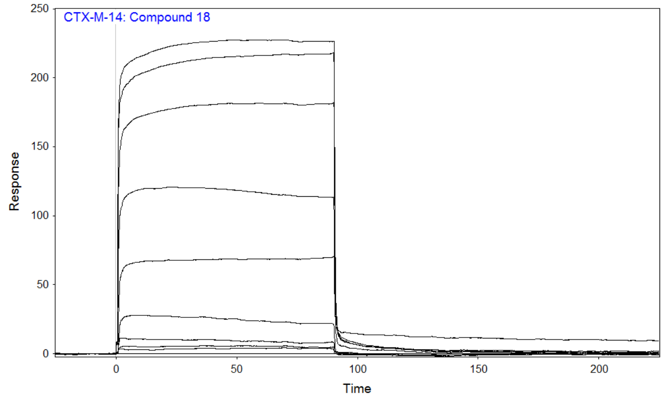

Compound 15 - CTX-M-14
Response (RU)
200
150
100
50
0
-1
0
1
2
3
log(Compound 15) (μM)

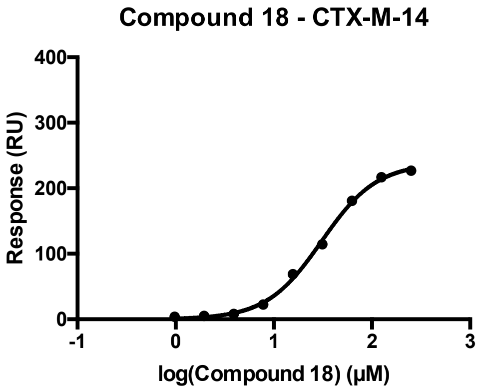

CTX-M-14: Compound 16
Response
140
120
100
80
60
40
20
0
0
50
100
150
200
Time

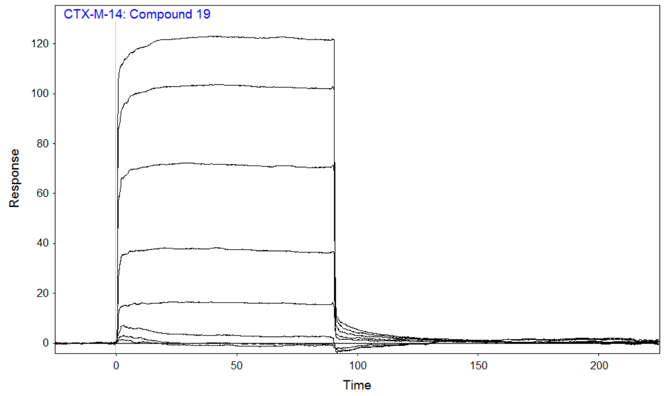

Compound 16 - CTX-M-14
Response (RU)
200
150
100
50
0
-1
0
1
2
3
log(Compound 16) (μM)

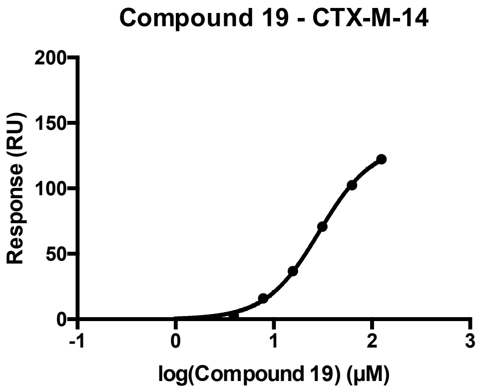

CTX-M-14: Compound 17
Response
250
200
150
100
50
0
0
50
100
150
200
Time

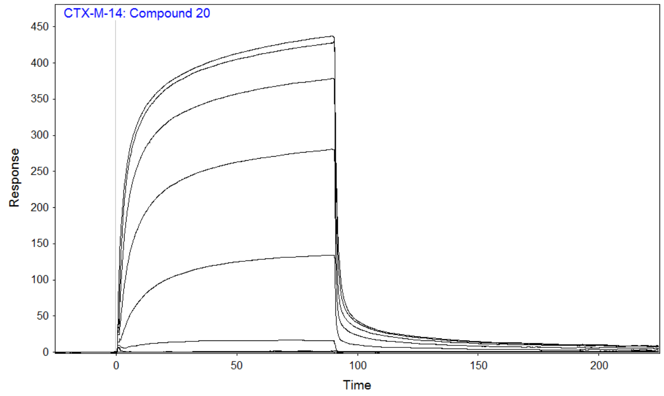

Compound 17 - CTX-M-14
Response (RU)
400
300
200
100
0
-1
0
1
2
3
log(Compound 17) (μM)

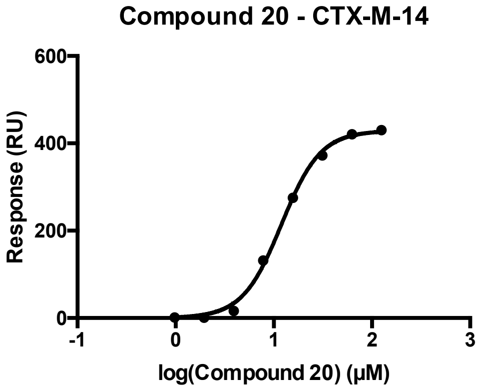

CTX-M-14: Compound 18
Response
250
200
150
100
50
0
0
50
100
150
200
Time


Compound 18 - CTX-M-14
Response (RU)
400
300
200
100
0
-1
0
1
2
3
log(Compound 18) (μM)

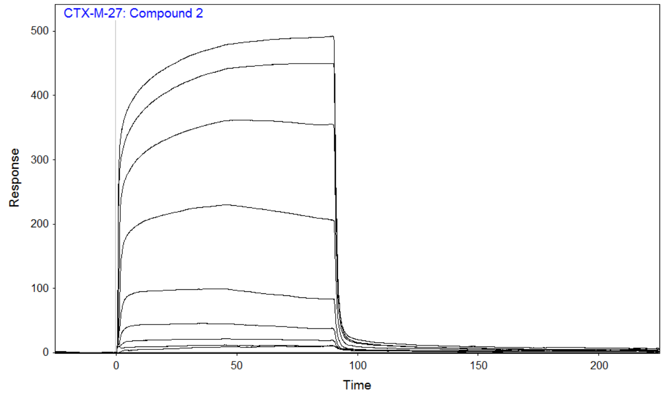

CTX-M-14: Compound 19
Response
120
100
80
60
40
20
0
0
50
100
150
200
Time

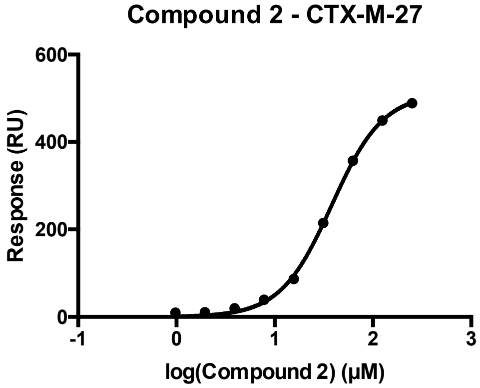

Compound 19 - CTX-M-14
Response (RU)
200
150
100
50
0
-1
0
1
2
3
log(Compound 19) (μM)

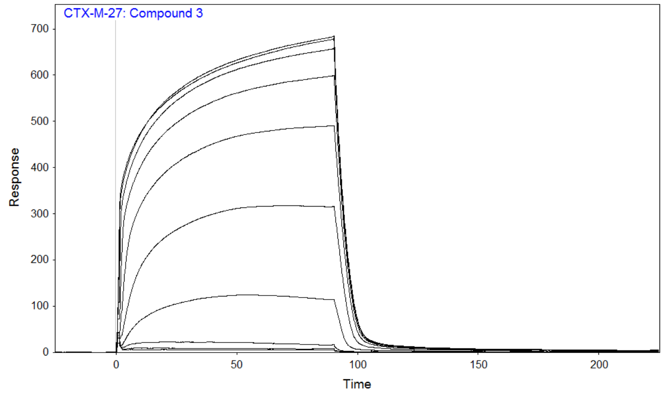

CTX-M-14: Compound 20
Response
450
400
350
300
250
200
150
100
50
0
0
50
100
150
200
Time

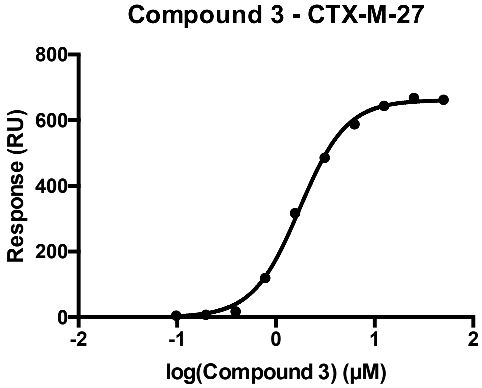

Compound 20 - CTX-M-14
Response (RU)
600
400
200
0
-1
0
1
2
3
log(Compound 20) (μM)

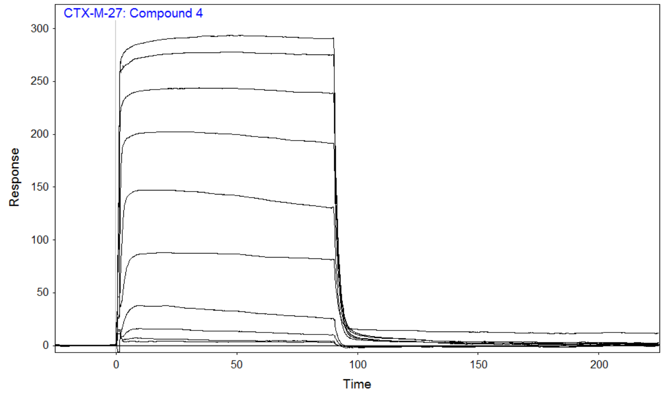
Representative sensograms for CTX-M-27:

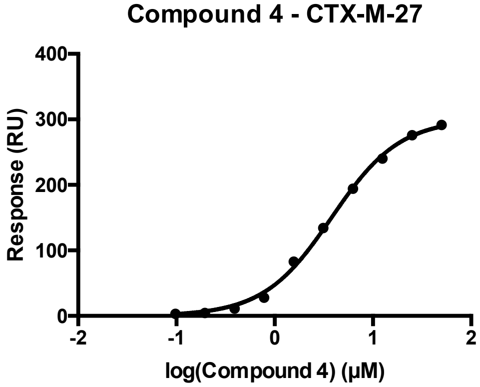


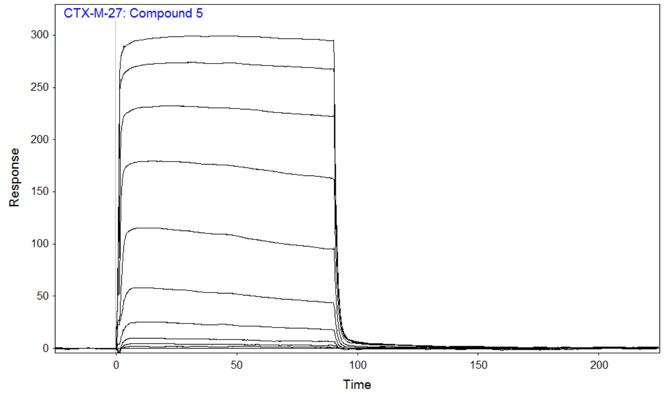


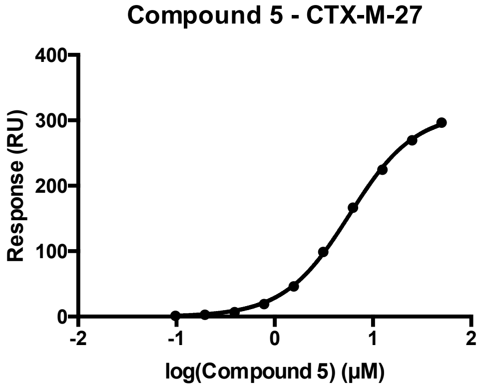


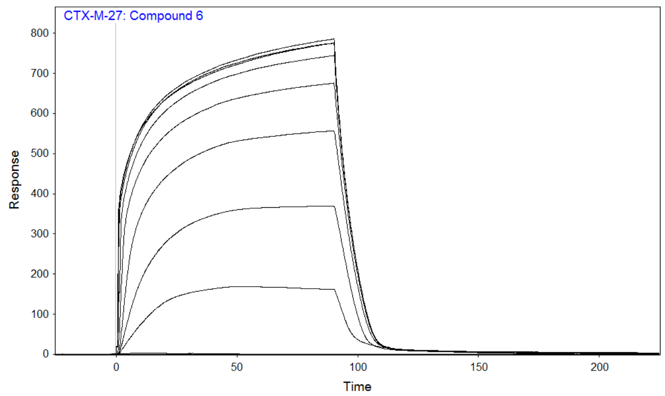


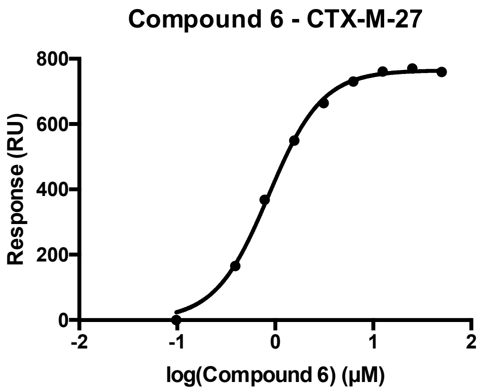


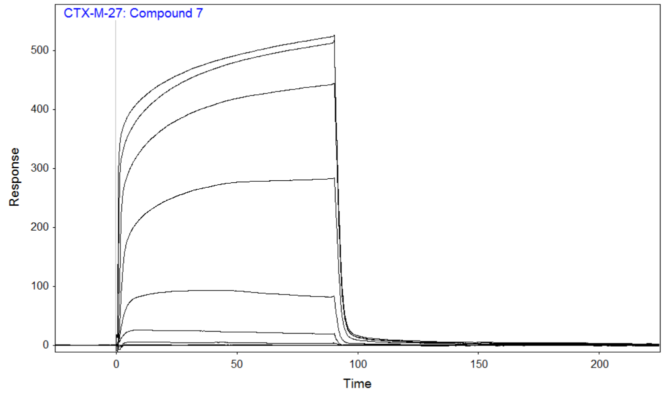


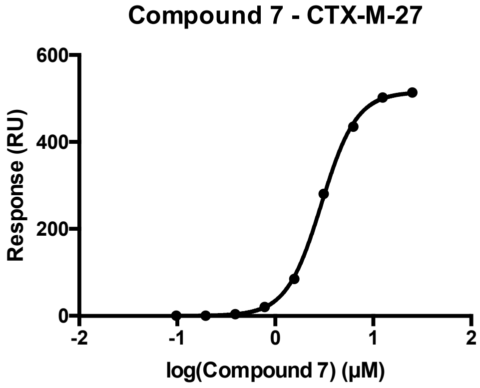


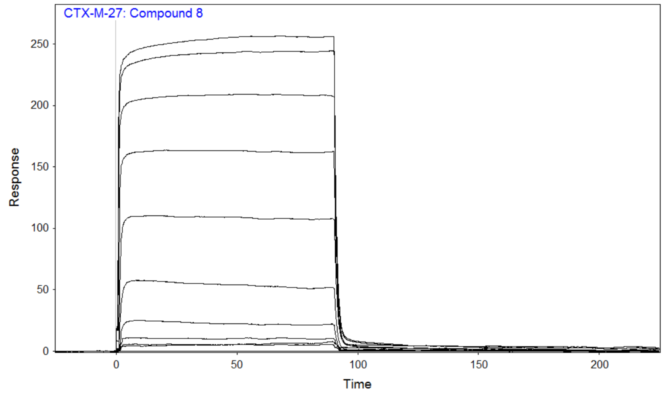


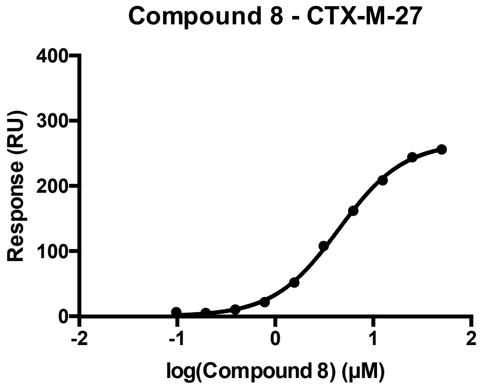

CTX-M-27: Compound 6

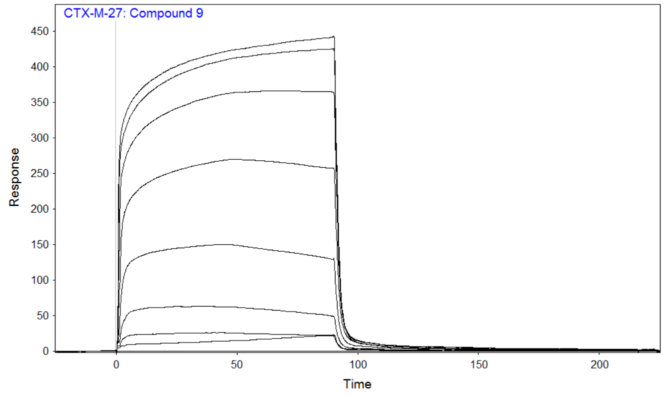

Compound 6 - CTX-M-27

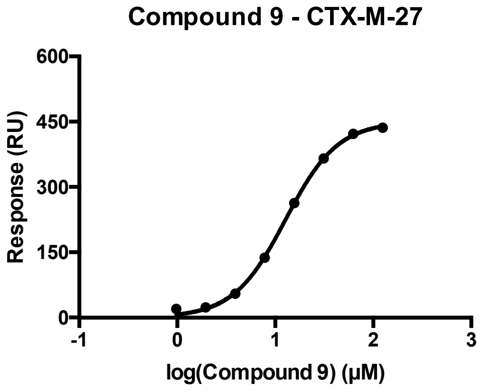

CTX-M-27: Compound 7

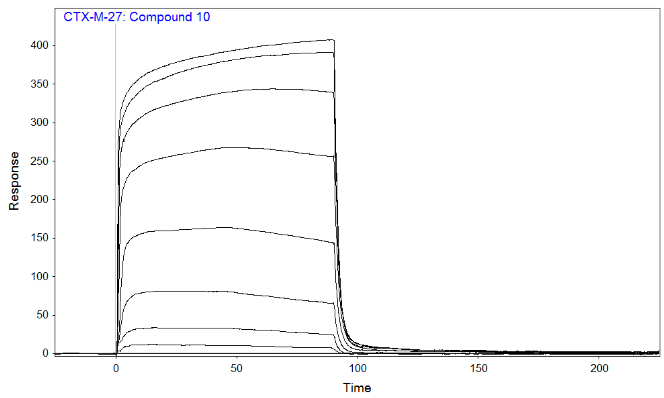

Compound 7 - CTX-M-27

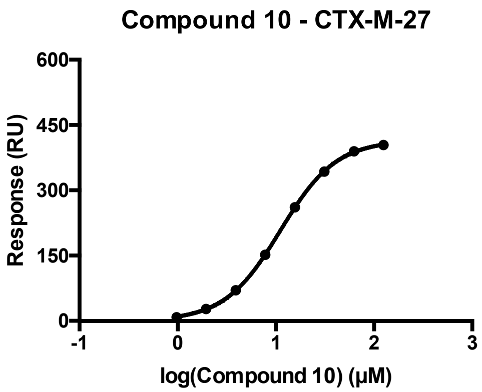

CTX-M-27: Compound 8

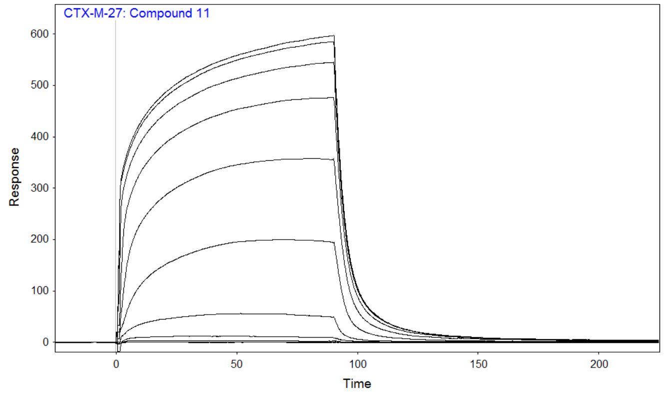

Compound 8 - CTX-M-27

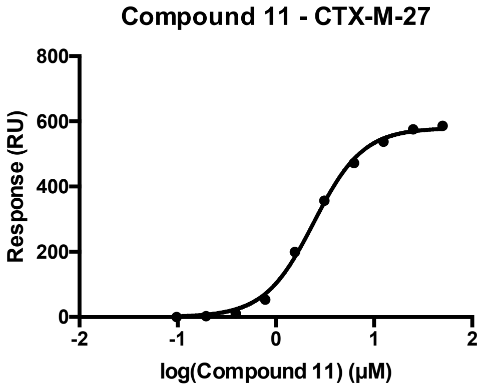

CTX-M-27: Compound 9

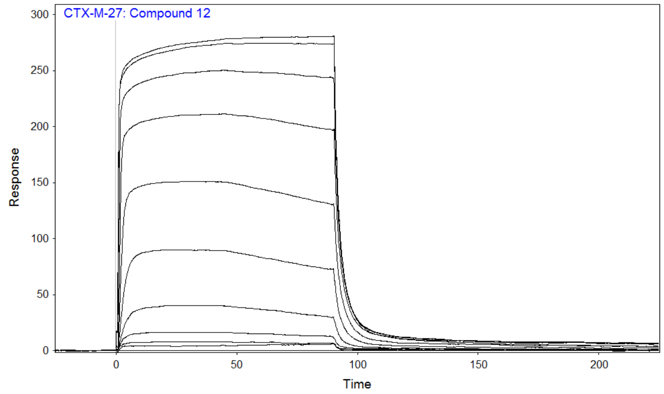

Compound 9 - CTX-M-27

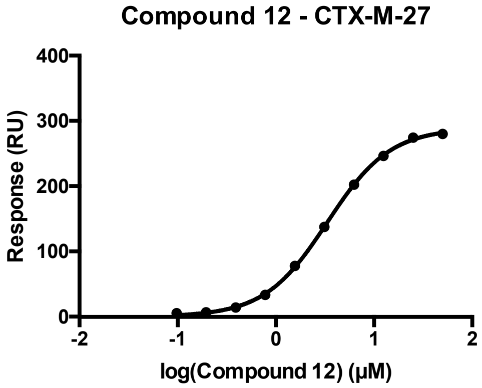

CTX-M-27: Compound 10
Response
400
350
300
250
200
150
100
50
0
0
50
100
150
200
Time

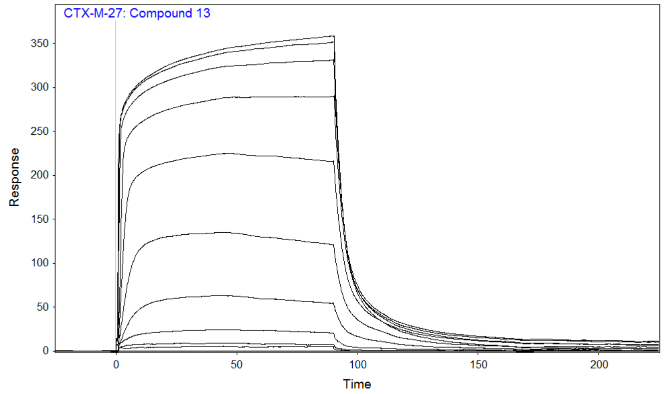

Compound 10 - CTX-M-27
Response (RU)
600
450
300
150
0
-1
0
1
2
3
log(Compound 10) (µM)

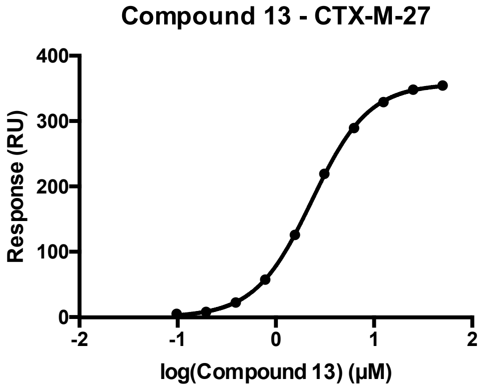

CTX-M-27: Compound 11
Response
600
500
400
300
200
100
0
0
50
100
150
200
Time

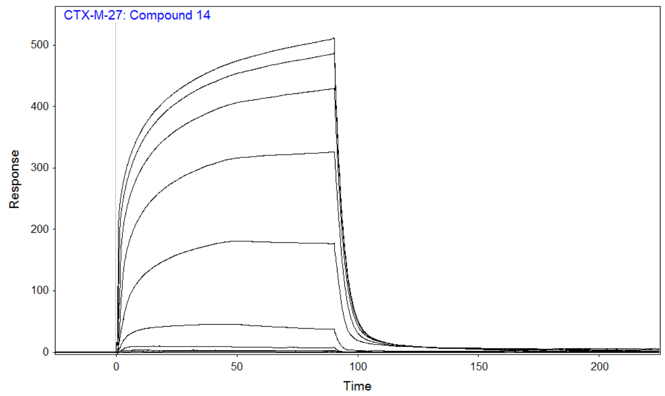

Compound 11 - CTX-M-27
Response (RU)
800
600
400
200
0
-2
-1
0
1
2
log(Compound 11) (µM)

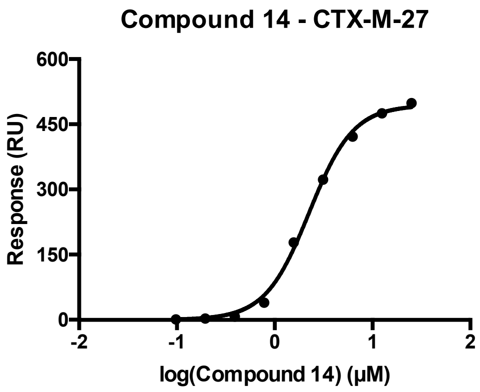

CTX-M-27: Compound 12
Response
300
250
200
150
100
50
0
0
50
100
150
200
Time

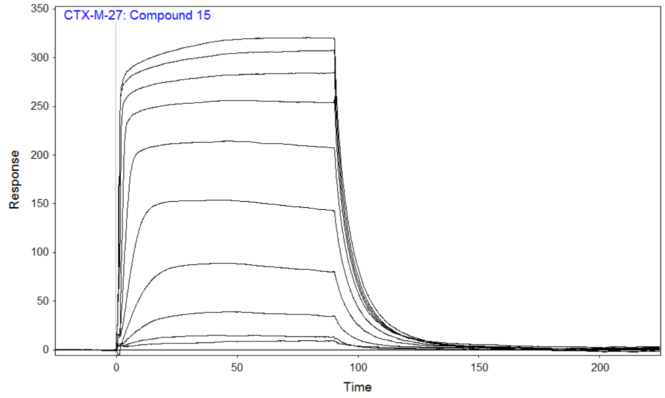

Compound 12 - CTX-M-27
Response (RU)
400
300
200
100
0
-2
-1
0
1
2
log(Compound 12) (µM)

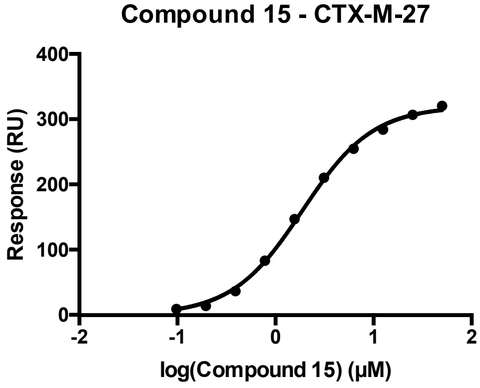

CTX-M-27: Compound 13
Response
350
300
250
200
150
100
50
0
0
50
100
150
200
Time

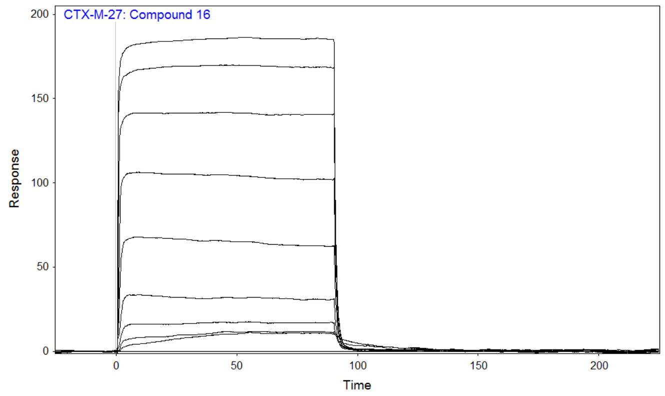

Compound 13 - CTX-M-27
Response (RU)
400
300
200
100
0
-2
-1
0
1
2
log(Compound 13) (µM)

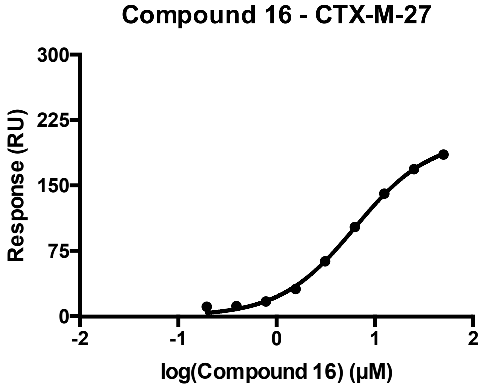

CTX-M-27: Compound 14
Response
500
400
300
200
100
0
0
50
100
150
200
Time

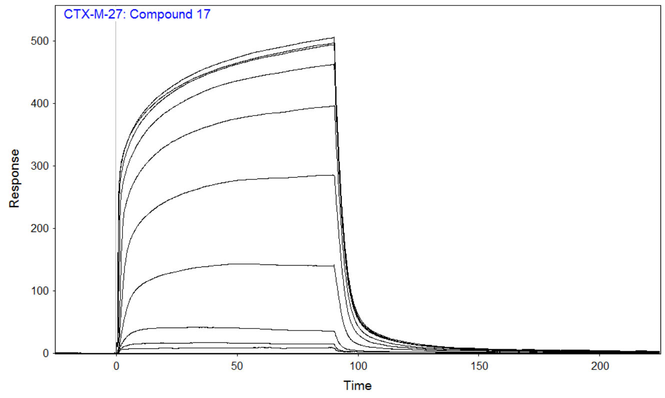

Compound 14 - CTX-M-27
Response (RU)
600
450
300
150
0
-2
-1
0
1
2
log(Compound 14) (μM)

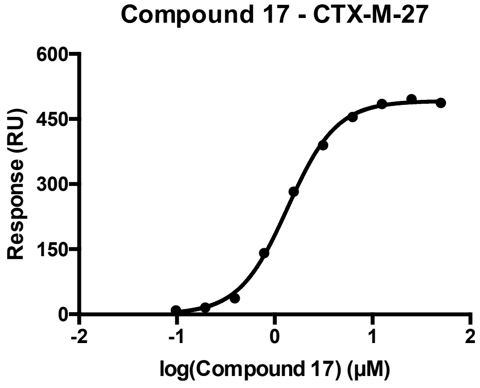

CTX-M-27: Compound 15
Response
350
300
250
200
150
100
50
0
0
50
100
150
200
Time

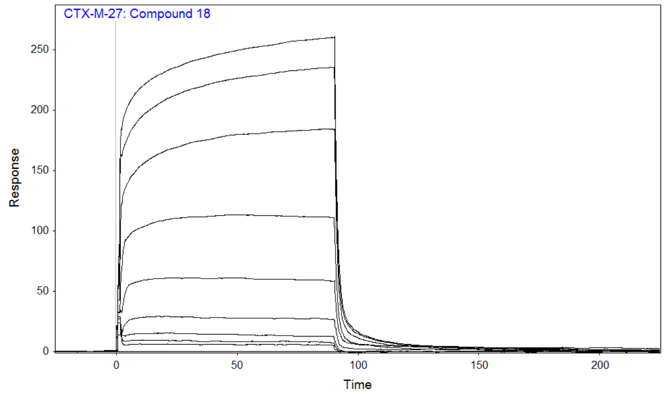

Compound 15 - CTX-M-27
Response (RU)
400
300
200
100
0
-2
-1
0
1
2
log(Compound 15) (μM)

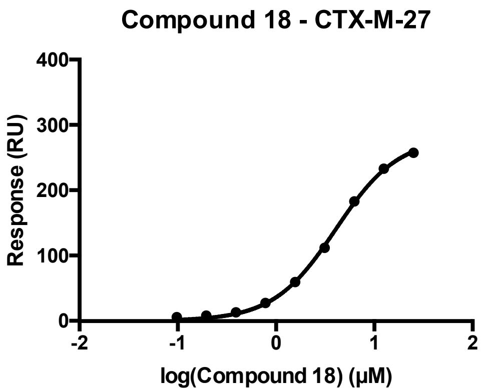

CTX-M-27: Compound 16
Response
200
150
100
50
0
0
50
100
150
200
Time

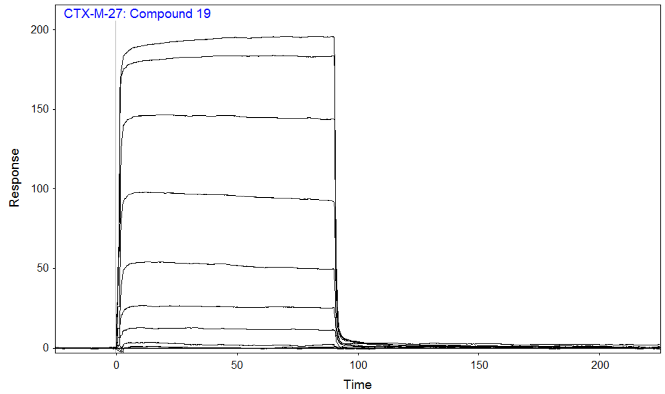

Compound 16 - CTX-M-27
Response (RU)
300
225
150
75
0
-2
-1
0
1
2
log(Compound 16) (μM)

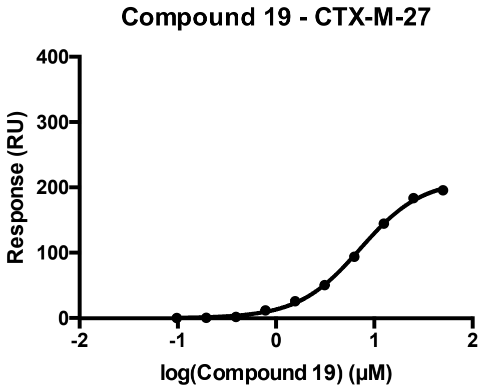

CTX-M-27: Compound 17
Response
500
400
300
200
100
0
0
50
100
150
200
Time

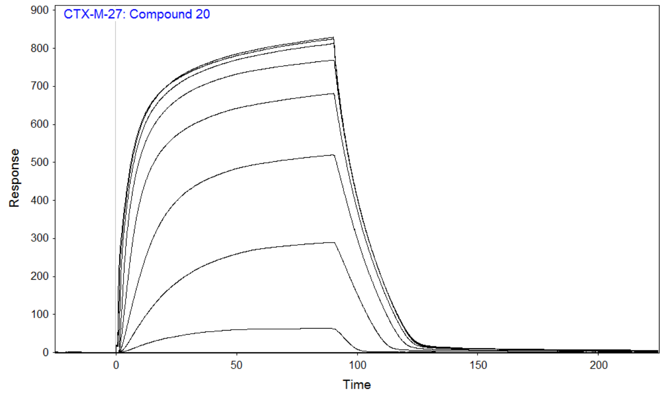

Compound 17 - CTX-M-27
Response (RU)
600
450
300
150
0
-2
-1
0
1
2
log(Compound 17) (μM)

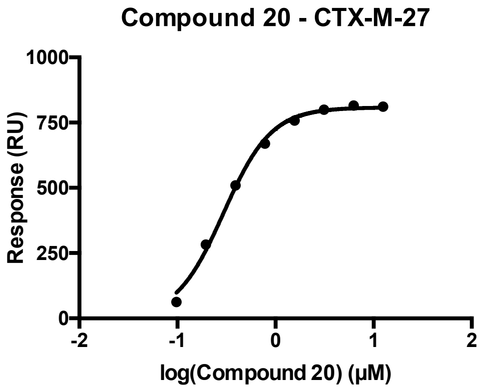

CTX-M-27: Compound 18
Response
250
200
150
100
50
0
0
50
100
150
200
Time


Compound 18 - CTX-M-27
Response (RU)
400
300
200
100
0
-2
-1
0
1
2
log(Compound 18) (μM)


CTX-M-27: Compound 19
Response
200
150
100
50
0
0
50
100
150
200
Time


Compound 19 - CTX-M-27
Response (RU)
400
300
200
100
0
-2
-1
0
1
2
log(Compound 19) (μM)


CTX-M-27: Compound 20
Response
900
800
700
600
500
400
300
200
100
0
0
50
100
150
200
Time


Compound 20 - CTX-M-27
Response (RU)
1000
750
500
250
0
-2
-1
0
1
2
log(Compound 20) (μM)

Crystallographic Data

Supplementary Table 1. X-ray Data Collection and Refinement Statistics

Data Collection

Structure (PDB ID)	6OOF	6OOE	6OOJ	6OOH	6OOK
Space Group	P 1 21 1	P 1 21 1	P 1 21 1	P 1 21 1	P 1 21 1
Cell Dimensions					
a, b, c (Å)	45.161	45.323	45.096	45.129	45.003
	107.211	107.482	106.929	107.157	106.725
	47.884	48.057	47.83	47.92	47.736
α, β, γ (°)	90	90	90	90	90
	101.656	101.715	101.611	101.906	101.73
	90	90	90	90	90
Resolution (Å)	35.3 - 1.236	30 - 1.26	25.71 - 1.4	29.92 - 1.499	25.27 - 1.4
No. Reflections	111033	107 923	86936	70775	82095
R_{merge} (%)	10.3	10.6	5.0	6.6	2.7
I / *óI*	22.36(2.15)	25.16(2.69)	26.52(3.9)	16.81(2.8)	44.04(8.02)
Completeness (%)	87.8	89.2	99.9	99.4	94.8
Redundancy	4.2(3.9)	5.7(5.8)	3.7(2.9)	3.2(2.8)	3.6(2.9)

Refinement

Resolution (Å)	35.3 - 1.236	30 - 1.26	25.71 - 1.4	29.92 - 1.499	25.27 - 1.4
R_{work}/R_{free} (%)	17.20/20.13	14.5/16.95	14.53/16.29	14.43/17.14	12.03/15.39
No. Heavy Atoms					
Protein	4988	4206	4121	4131	4136
Ligand/Ion	116	116	145	145	125
Water	691	729	738	787	697
***B*-Factors (Å^2)**					
Protein	14.00	12.10	15.84	15.14	15.72
Ligand/Ion	16.12	14.73	18.57	18.37	29.83
Water	26.43	25.92	29.59	27.74	29.02
Ramanchandran Plot					
Most Favored Region(%)	97.3	97.7	97.7	97.9	97.9
Additionally Allowed (%)	2.32	1.93	1.93	1.73	1.74
Generously Allowed (%)	0.39	0.39	0.39	0.39	0.39

[*] Values in parentheses represent highest resolution shells

Dipole Calculations

Dipoles were calculated with a methyl at the point of attachment; structures were optimized with B3LYP/6-31G** prior to dipole calculation.

B3LYP/6-31G**; PBF: DCE (10.65 ε)

Compound	Gas Phase Energy	Solution Phase Energy	Solvation Energy (kcal/mol)	HOMO	LUMO	QM Dipole (D)	QM Dipole X (D)	QM Dipole Y (D)	QM Dipole Z (D)
2	-271.578488	-271.58247	-2.499131	-0.240232	-0.002133	0.463176	-0.285068	-0.36506	0
3	-287.616296	-287.624158	-4.932937	-0.25393	-0.026293	2.651741	2.623243	-0.387716	0
4	-287.613682	-287.621816	-5.104312	-0.253439	-0.024655	3.309159	1.229136	3.072419	0
5	-287.614708	-287.623465	-5.495336	-0.262352	-0.024947	3.727299	-1.913623	-3.198563	0
6	-303.655234	-303.666316	-6.954164	-0.257676	-0.04309	2.377625	1.099734	2.108005	0
7	-303.655009	-303.666395	-7.145241	-0.262914	-0.043459	3.493428	1.07138	3.325084	0
8	-303.651512	-303.662934	-7.167572	-0.262527	-0.045594	3.844931	-1.995047	3.286835	0
9	-592.330722	-592.335014	-2.693378	-0.227616	-0.010871	1.034642	0.665349	-0.792335	-0.000768
10	-592.329452	-592.333807	-2.732275	-0.230464	-0.012426	1.363993	-0.104598	-1.359976	0.000603
11	-269.353086	-269.357967	-3.062408	-0.217858	0.016877	0.763495	0.425025	-0.634254	0.00001
12	-269.347484	-269.352356	-3.057625	-0.221196	0.014465	1.244542	-0.097378	-1.240726	0.000847
13	-249.495923	-249.504932	-5.653324	-0.20191	0.04379	2.321089	-0.426593	2.28155	0.001166
14	-265.522355	-265.532677	-6.4773	-0.244642	0.015965	3.266098	1.68403	-2.798471	-0.000869
15	-265.529696	-265.542853	-8.256297	-0.246401	0.017209	2.701276	2.409078	1.22198	0.000098
16	-265.535403	-265.549161	-8.632925	-0.228099	0.025706	5.520107	-1.256347	-5.375237	0.000983
17	-265.548463	-265.563967	-9.728804	-0.221107	0.031191	5.083593	-4.764769	1.771959	0.007474
18	-281.544963	-281.560477	-9.735667	-0.264789	-0.01048	6.360991	2.105532	-6.002412	0.000069
19	-297.573052	-297.591624	-11.654125	-0.304945	-0.026451	7.815559	0.845976	7.769638	0
20	-297.583578	-297.6046	-13.191199	-0.300764	-0.023761	7.766349	7.333139	2.557586	0

B3LYP/6-31G**; PBF: H_2O (80.37 ε)

Compound	Gas Phase Energy	Solution Phase Energy	Solvation Energy (kcal/mol)	HOMO	LUMO	QM Dipole (D)	QM Dipole X (D)	QM Dipole Y (D)	QM Dipole Z (D)
2	-271.578452	-271.581714	-2.046934	-0.239484	-0.00143	0.44862	-0.278004	-0.3521	0
3	-287.616222	-287.622584	-3.991815	-0.253299	-0.025335	2.414631	2.385242	-0.375586	0
4	-287.613617	-287.620324	-4.208525	-0.252981	-0.023801	3.133705	1.137203	2.920082	0
5	-287.614634	-287.621834	-4.518118	-0.261632	-0.023975	3.516843	-1.807647	-3.016719	0
6	-303.655093	-303.664322	-5.791053	-0.255578	-0.042322	2.231569	1.033354	1.977898	0
7	-303.654888	-303.66437	-5.949808	-0.260599	-0.042648	3.289413	0.981849	3.13946	0
8	-303.651395	-303.66086	-5.939002	-0.260244	-0.044793	3.621407	-1.879782	3.095321	0
9	-592.330647	-592.334221	-2.242323	-0.226654	-0.009866	0.963784	0.588012	-0.763624	-0.000018
10	-592.329344	-592.33299	-2.288027	-0.229424	-0.011389	1.291218	-0.092571	-1.287895	-0.000954
11	-269.353019	-269.357124	-2.575602	-0.217087	0.017587	0.715456	0.400727	-0.592702	-0.000246
12	-269.34739	-269.352191	-3.01288	-0.220349	0.014368	1.218788	-0.088761	-1.215551	0.000546
13	-249.495807	-249.503211	-4.646594	-0.200576	0.044627	2.186178	-0.391365	2.150862	0.001224
14	-265.522241	-265.530827	-5.387862	-0.24328	0.017347	3.06943	1.536605	-2.657112	-0.000978
15	-265.529418	-265.540434	-6.912604	-0.244663	0.018496	2.559449	2.267994	1.186162	0.000329
16	-265.535249	-265.546636	-7.145288	-0.226629	0.026859	5.250173	-1.205787	-5.109833	0.000633
17	-265.548258	-265.560962	-7.971984	-0.219736	0.031883	4.76464	-4.462819	1.668834	0.005931
18	-281.544782	-281.557569	-8.023798	-0.263267	-0.008382	6.019743	-1.947741	5.695929	0
19	-297.572866	-297.588371	-9.729789	-0.301057	-0.024633	7.474376	0.847945	7.426122	0
20	-297.5832	-297.600634	-10.939654	-0.299287	-0.022213	7.383831	6.948783	2.497072	0

B3LYP/6-31G**; PBF: $CHCl_3$ (4.806 ε)

Compound	Gas Phase Energy	Solution Phase Energy	Solvation Energy (kcal/mol)	HOMO	LUMO	QM Dipole (D)	QM Dipole X (D)	QM Dipole Y (D)	QM Dipole Z (D)
2	-271.578452	-271.578534	-0.051712	-0.240829	-0.002739	0.48856	-0.300036	-0.385577	0
3	-287.616222	-287.621639	-3.399163	-0.255681	-0.028817	2.842759	2.809459	-0.43384	0
4	-287.613617	-287.619234	-3.524996	-0.254987	-0.027062	3.534241	1.29068	3.290138	0
5	-287.614634	-287.620832	-3.889164	-0.264011	-0.027126	3.974551	-2.03931	-3.41149	0
6	-303.655093	-303.663985	-5.579627	-0.264041	-0.047122	2.44517	1.136897	2.164791	0
7	-303.654888	-303.6647	-6.156897	-0.269557	-0.047199	3.755247	1.174285	3.566922	0
8	-303.651395	-303.661228	-6.170466	-0.268779	-0.049059	4.092602	-2.135383	3.491351	0
9	-592.330647	-592.331157	-0.320023	-0.228298	-0.011627	1.044568	0.645105	-0.82156	0.000932
10	-592.329344	-592.329858	-0.322362	-0.231187	-0.013194	1.379518	-0.09718	-1.376091	0.000775
11	-269.353019	-269.352458	0.352449	-0.218771	0.015738	0.802421	0.467163	-0.65241	-0.000225
12	-269.34739	-269.346688	0.440413	-0.222276	0.013178	1.296883	-0.091947	-1.293619	0.000312
13	-249.495807	-249.501927	-3.840296	-0.20204	0.043967	2.403203	-0.434937	2.363516	0.002206
14	-265.522241	-265.53082	-5.383658	-0.247448	0.012345	3.484909	1.927776	-2.903146	-0.003404
15	-265.529418	-265.541846	-7.798577	-0.248477	0.014121	2.880142	2.612758	1.211904	-0.001133
16	-265.535249	-265.547646	-7.779101	-0.230055	0.023664	5.787087	-1.285639	-5.642474	-0.0005
17	-265.548258	-265.563499	-9.564275	-0.222501	0.02984	5.398173	-5.038694	1.936953	0.006607
18	-281.544782	-281.559717	-9.371439	-0.270039	-0.016725	6.79725	-2.322442	6.388182	0
19	-297.572866	-297.591159	-11.479392	-0.314829	-0.033862	8.279873	0.906028	8.230153	0
20	-297.5832	-297.606237	-14.455879	-0.306172	-0.02977	8.366223	7.912965	2.716371	0

M06-2X/6-31G**; PBF: DCE (10.65 ε)

Compound	Gas Phase Energy	Solution Phase Energy	Solvation Energy (kcal/mol)	HOMO	LUMO	QM Dipole (D)	QM Dipole X (D)	QM Dipole Y (D)	QM Dipole Z (D)
2	-271.442768	-271.447608	-3.036903	-0.292104	0.032375	0.432983	-0.270257	-0.338284	0
3	-287.479704	-287.488451	-5.488838	-0.305341	0.010172	2.693945	2.669744	-0.36029	0
4	-287.477151	-287.486049	-5.58377	-0.304821	0.01217	3.325684	1.266235	3.075195	0
5	-287.478142	-287.487715	-6.007428	-0.314898	0.01127	3.731682	-1.914788	-3.202973	0
6	-303.518445	-303.53042	-7.514676	-0.323877	-0.004964	2.452971	1.138653	2.17268	0
7	-303.518217	-303.530406	-7.648937	-0.328906	-0.005923	3.513279	1.11233	3.332544	0
8	-303.514755	-303.52687	-7.602285	-0.326966	-0.00753	3.852266	-1.998159	3.293526	0
9	-592.199498	-592.204572	-3.184479	-0.279741	0.025431	1.006035	0.654288	-0.764208	-0.000739
10	-592.198112	-592.203298	-3.254658	-0.282648	0.024006	1.307978	-0.098133	-1.304291	0.000691
11	-269.231198	-269.236944	-3.605648	-0.269791	0.058325	0.764255	0.447519	-0.619527	-0.000053
12	-269.2255	-269.23125	-3.607936	-0.273627	0.056013	1.236591	-0.08754	-1.233488	0.000887
13	-249.377746	-249.387944	-6.399138	-0.253976	0.085194	2.3648	-0.424663	2.326358	0.001263
14	-265.402102	-265.413447	-7.119553	-0.298399	0.059076	3.327758	1.717168	-2.850492	-0.000942
15	-265.408965	-265.423429	-9.076523	-0.300771	0.05996	2.770402	2.474451	1.245879	0.000179
16	-265.41715	-265.432012	-9.326421	-0.281143	0.069265	5.606389	-1.283138	-5.457578	0.000982
17	-265.430052	-265.44682	-10.521879	-0.273885	0.074125	5.149403	-4.821765	1.807453	0.007536
18	-281.422654	-281.438995	-10.25389	-0.318599	0.03554	6.463688	-2.120071	6.106108	0
19	-297.449575	-297.468754	-12.035135	-0.370799	0.022432	7.914928	0.869632	7.867009	0
20	-297.459801	-297.481551	-13.648337	-0.357342	0.025114	7.833508	7.413467	2.530681	0

B3LYP-D3/6-31G**; PBF: DCE (10.65 ε)

Compound	Gas Phase Energy	Solution Phase Energy	Solvation Energy (kcal/mol)	HOMO	LUMO	QM Dipole (D)	QM Dipole X (D)	QM Dipole Y (D)	QM Dipole Z (D)
2	-271.586283	-271.590317	-2.531579	-0.240484	-0.002368	0.460872	-0.28335	-0.363478	0
3	-287.623258	-287.631235	-5.005546	-0.254	-0.026448	2.653929	2.625399	-0.3881	0
4	-287.620856	-287.629059	-5.147537	-0.253428	-0.024674	3.301769	1.224918	3.066147	0
5	-287.621888	-287.630728	-5.547271	-0.262344	-0.024969	3.720652	-1.909846	-3.193077	0
6	-303.661245	-303.672505	-7.065548	-0.258114	-0.043193	2.378039	1.099844	2.108415	0
7	-303.661277	-303.672723	-7.182538	-0.262396	-0.043493	3.47384	1.062114	3.307488	0
8	-303.657945	-303.669523	-7.26515	-0.262922	-0.045637	3.845258	-1.995072	3.287202	0
9	-592.336615	-592.34097	-2.732324	-0.227609	-0.010826	1.009217	0.638246	-0.781768	-0.000738
10	-592.335265	-592.339726	-2.799249	-0.230406	-0.012386	1.364935	-0.105954	-1.360816	0.000601
11	-269.358227	-269.363164	-3.097821	-0.217786	0.016959	0.750408	0.414392	-0.625612	-0.000029
12	-269.352698	-269.357654	-3.109574	-0.221117	0.01455	1.227594	-0.098625	-1.223626	0.000815
13	-249.50171	-249.51078	-5.69162	-0.201869	0.043741	2.279418	-0.414338	2.241443	0.001174
14	-265.527471	-265.537828	-6.499675	-0.244664	0.016147	3.249848	1.667978	-2.78915	-0.00086
15	-265.534464	-265.547799	-8.367494	-0.246286	0.017235	2.65305	2.361626	1.208883	0.000157
16	-265.540644	-265.554512	-8.702104	-0.228082	0.02573	5.498556	-1.254802	-5.353465	0.000953
17	-265.553358	-265.568995	-9.812129	-0.221088	0.031158	5.05346	-4.737936	1.757659	0.007338
18	-281.549329	-281.565063	-9.872712	-0.264785	-0.010604	6.364264	-2.109336	6.004544	0
19	-297.576723	-297.595385	-11.71033	-0.304661	-0.026359	7.787776	0.847453	7.74153	0
20	-297.586912	-297.608356	-13.456348	-0.300768	-0.023764	7.777045	7.344791	2.556654	0

B3LYP/6-31G**; gas phase

Compound	Gas Phase Energy	Solution Phase Energy	Solvation Energy (kcal/mol)	HOMO	LUMO	QM Dipole (D)	QM Dipole X (D)	QM Dipole Y (D)	QM Dipole Z (D)
2	-271.578452	-271.590317	-2.531579	-0.235541	0.002387	0.350155	-0.216006	-0.27559	0
3	-287.616222	-287.631235	-5.005546	-0.247809	-0.020994	1.803148	1.779325	-0.292143	0
4	-287.613617	-287.629059	-5.147537	-0.248305	-0.01909	2.369615	0.837358	2.216733	0
5	-287.614634	-287.630728	-5.547271	-0.249441	-0.019466	2.678329	-1.376729	-2.297404	0
6	-303.655093	-303.672505	-7.065548	-0.24486	-0.038586	1.636696	0.765002	1.446909	0
7	-303.654888	-303.672723	-7.182538	-0.249001	-0.038582	2.516365	0.699957	2.417055	0
8	-303.651395	-303.669523	-7.26515	-0.248332	-0.040486	2.78933	-1.449873	2.382904	0
9	-592.330647	-592.34097	-2.732324	-0.222568	-0.005639	0.74899	0.421677	-0.619011	-0.000133
10	-592.329344	-592.339726	-2.799249	-0.225458	-0.00733	0.970368	-0.084307	-0.966698	-0.000455
11	-269.353019	-269.363164	-3.097821	-0.213146	0.021886	0.566741	0.305094	-0.477612	-0.000307
12	-269.34739	-269.357654	-3.109574	-0.217191	0.018931	0.94826	-0.079153	-0.944951	0.000181
13	-249.495807	-249.51078	-5.69162	-0.195236	0.04802	1.744903	-0.29823	1.719228	0.001119
14	-265.522241	-265.537828	-6.499675	-0.236191	0.023951	2.379334	1.07995	-2.120126	-0.000401
15	-265.529418	-265.547799	-8.367494	-0.236305	0.023972	1.942908	1.694168	0.951151	0.000847
16	-265.535249	-265.554512	-8.702104	-0.220244	0.031237	4.134794	-0.965472	-4.020495	0.00027
17	-265.548258	-265.568995	-9.812129	-0.214502	0.034837	3.62858	-3.40388	1.257053	0.0031
18	-281.544782	-281.565063	-9.872712	-0.256426	-0.000158	4.703161	-1.40877	4.487214	0
19	-297.572866	-297.595385	-11.71033	-0.282679	-0.01712	5.932309	0.747572	5.885017	0
20	-297.5832	-297.608356	-13.456348	-0.283974	-0.015807	5.78498	5.413476	2.039676	0

LMP2/6-31G**; gas phase

Compound	Gas Phase Energy	Solution Phase Energy	Solvation Energy (kcal/mol)	HOMO	LUMO	QM Dipole (D)	QM Dipole X (D)	QM Dipole Y (D)	QM Dipole Z (D)
2	-270.660593	-271.590317	-2.531579	-0.316801	0.143843	0.460872	-0.28335	-0.363478	0
3	-286.67968	-287.631235	-5.005546	-0.331147	0.122068	2.653929	2.625399	-0.3881	0
4	-286.678839	-287.629059	-5.147537	-0.330547	0.125119	3.301769	1.224918	3.066147	0
5	-286.679482	-287.630728	-5.547271	-0.340129	0.124353	3.720652	-1.909846	-3.193077	0
6	-302.704589	-303.672505	-7.065548	-0.360591	0.108706	2.378039	1.099844	2.108415	0
7	-302.702124	-303.672723	-7.182538	-0.366447	0.107929	3.47384	1.062114	3.307488	0
8	-302.70012	-303.669523	-7.26515	-0.35725	0.1059	3.845258	-1.995072	3.287202	0
9	-591.120704	-592.34097	-2.732324	-0.311406	0.132776	1.009217	0.638246	-0.781768	-0.000738
10	-591.119356	-592.339726	-2.799249	-0.315113	0.129543	1.364935	-0.105954	-1.360816	0.000601
11	-268.511014	-269.363164	-3.097821	-0.301147	0.170253	0.750408	0.414392	-0.625612	-0.000029
12	-268.505703	-269.357654	-3.109574	-0.30605	0.166146	1.227594	-0.098625	-1.223626	0.000815
13	-248.684136	-249.51078	-5.69162	-0.281473	0.195672	2.279418	-0.414338	2.241443	0.001174
14	-264.696015	-265.537828	-6.499675	-0.332034	0.173594	3.249848	1.667978	-2.78915	-0.00086
15	-264.702661	-265.547799	-8.367494	-0.333524	0.172465	2.65305	2.361626	1.208883	0.000157
16	-264.708941	-265.554512	-8.702104	-0.308957	0.183902	5.498556	-1.254802	-5.353465	0.000953
17	-264.721616	-265.568995	-9.812129	-0.303034	0.187446	5.05346	-4.737936	1.757659	0.007338
18	-280.703001	-281.565063	-9.872712	-0.350306	0.152408	6.364264	-2.109336	6.004544	0
19	-296.715009	-297.595385	-11.71033	-0.40561	0.14152	7.787776	0.847453	7.74153	0
20	-296.724616	-297.608356	-13.456348	-0.39568	0.142856	7.777045	7.344791	2.556654	0

Synthetic Procedures

General Procedures: Reactions were magnetically stirred. Air and/or moisture sensitive reactions were carried out under an argon atmosphere in oven-dried glassware using anhydrous solvents from commercial suppliers. Air and/or moisture sensitive reagents were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. All anhydrous solvents used were purchased from Sigma-Aldrich and used without further purification. Solvents to be employed in flash column chromatography and reaction work-up procedures were purchased from either Sigma-Aldrich or Fisher Scientific. All other reagents were obtained commercially and used without further purification, unless otherwise stated. Reactions were monitored using LCMS and thin layer chromatography (TLC) performed on 0.25-mm EMD pre-coated glass-backed silica gel 60 F-254 plates. Compounds were visualized under UV light or through staining with permanganate, bromocresol green, or magic, when appropriate. Reaction products and chromatography fractions were concentrated by rotary evaporation at 30-35 °C at 20 Torr, then Hi-Vac at 0.5 Torr overnight, unless otherwise indicated.

Instrumentation: NMR spectra were recorded on a Bruker AvanceIII HD 400 MHz spectrometer (with 5 mm BBFO Z-gradient Smart Probe) calibrated to $CH(D)Cl_3$ as an internal reference (7.26 and 77.00 ppm for ^1H and ^{13}C NMR spectra, respectively). Data for ^1H NMR spectra are reported in terms of chemical shift (δ, ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ, ppm), with multiplicity and coupling constants in the case of C–F coupling. The following abbreviations are used to denote the multiplicities: s = singlet; d = doublet; dd = doublet of doublets; dt = doublet of triplets; dq = doublet of quartets; ddd = doublet of doublet of doublets; t = triplet; td = triplet of doublets; tt = triplet of triplets; q = quartet; qd = quartet of doublets; quin = quintet; sex = sextet; m = multiplet. LCMS and compound purity were determined using a Waters Micromass ZQ 4000, equipped with a Waters 2795 Separation Module, Waters 2996 Photodiode Array Detector, and a Waters 2424 ELSD. Separations were carried out with an XBridge BEH C18, 5µm, 4.6 x 20 mm column, at ambient temperature (unregulated), using a mobile phase of water-methanol containing a constant 0.1% formic acid. HPLC was performed on a Waters 2535 Separation Module with a Waters 2998 Photodiode Array Detector. Separations were carried out with an XBridge BEH C18, 5µm, 19 x 50 mm column, at ambient temperature (unregulated), using a mobile phase of water-methanol containing a constant 0.05% formic acid. Column chromatography was carried out using a Biotage SP1 flash chromatography system with silica gel cartridges from Silicycle.

General Procedure A: A 20 mL vial is charged with the appropriate carboxylic acid (1.0 equiv), commercially available 3-(1*H*-tetrazol-5-yl)aniline (1.1 equiv), DMF, *N,N*-diisopropylethylamine (2.1 equiv), and HATU (1.1 equiv). The reaction mixture is stirred for 18h or until judged complete by LCMS. The crude reaction mixture is directly purified by reverse phase HPLC (water/MeOH/0.05% formic acid) to afford the desired product.

General Procedure B: A 20 mL vial is charged with the appropriate carboxylic acid (1.0 equiv), DMF, and *N,N*-diisopropylethylamine (1.0 equiv). HATU (1.05 equiv) is then added, and the reaction mixture is allowed to stir for 20 minutes. Commercially available 3-(1*H*-tetrazol-5-yl)aniline (1.1 equiv) and *N,N*-diisopropylethylamine (1.1 equiv) are subsequently added, and the reaction is stirred at room temperature for 24 h or until judged complete by LCMS. The crude reaction mixture is directly purified by reverse phase HPLC (water/MeOH/0.05% formic acid) to afford the desired product.

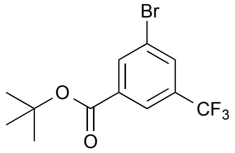
General Procedure C: A 20 mL vial is charged with the appropriate t-butyl ester (1.0 equiv), fitted with a septa, and purged with Ar. The vial is then charged with dry 4M HCl in dioxanes (4 mL), and the reaction is stirred at room temperature for 18-72h or until judged complete by LCMS. The reaction mixture is then concentrated and dried under hivac overnight, affording the desired semi-crude product.

General Procedure D: A 3 mL vial with cap is purged with Ar and charged with the appropriate halide (1.0 equiv), bis(pinacoloto)diboron (1.1 equiv), potassium acetate (2.0 equiv), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.02 equiv.), and dry tetrahydrofuran (1 mL). The reaction mixture is purged with Ar, sealed, and heated at 80 °C for 18h. The reaction mixture is then cooled to rt and charged with a solution of potassium carbonate (2.0 equiv) in water (620 ul), the second halide (1.2 equiv), and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.02 equiv). The reaction mixture is purged with Ar, sealed, and vigorously stirred at 80 °C for 18h.

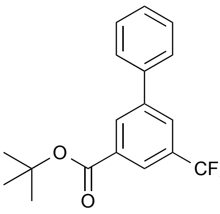
The crude reaction mixture is then transferred to a sep funnel with ~ 75 mL EtOAc and ~10 mL water. ~ 50 mL sat. $NaHCO_3$ is added, the layers separated, and the organic layer further washed with ~ 40 mL water and brine. The organic layer is dried over $MgSO_4$, concentrated, and purified on a silica column with EtOAc:hexanes to afford the desired product.

General Procedure E: S1 (1 equiv) and an aqueous K_2CO_3 solution (1M, 1.25 equiv) were added to 0.5 mL of 1,4 dioxane. Argon was bubbled through the resulting solution to remove oxygen before the boronic acid (1.2 equiv) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.05 equiv) were added. The reaction was then warmed to 80 °C and stirred until complete by LCMS (18–24h). The reaction mixture was allowed to cool to rt, diluted with MeOH, and filtered through celite. The filtrate was concentrated and purified as noted.

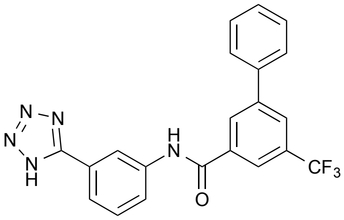
General Procedure F: Aryl t-butyl ester (1 equiv) was suspended in 1:1 TFA/CH_2Cl_2 and stirred until complete by either TLC or LCMS (3-18 h). Solvent was removed in vacuo and the resulting crude acid was used without further purification. The newly generated acid (1.0 equiv), triethylamine (3.0 equiv), and 3-(1*H*-tetrazol-5-yl)aniline (1.2 equiv) were suspended in 0.5 mL DMF and placed under argon. HATU (1.5 equiv) was added and the reaction was stirred until complete by LCMS (18-24h). The reaction was then diluted with DMF and purified by reverse phase HPLC (water/MeOH/0.05% formic acid) to afford the desired product.



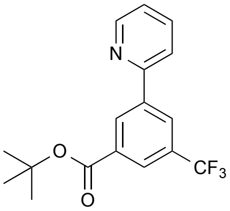
tert-butyl 3-bromo-5-(trifluoromethyl)benzoate (S1). Commercially available 3-bromo-5-trifluoromethylbenzoic acid (5.000 g, 18.6 mmol, 1.0 equiv) was dissolved in dry dichloromethane (50 ml). *N*,*N*-dimethylformamide (400 ul, 5.2 mmol, 0.3 equiv) was added; oxalyl chloride (2.000 ml, 23.3 mmol, 1.3 equiv.) was subsequently added dropwise. The reaction mixture was allowed to stir at rt for 4h. The solvent was then removed under reduced pressure, and the residue was azeotroped with toluene twice. The remaining residue was diluted with dry tetrahydrofuran (65 mL) and cooled to 0 °C. Lithium tert-butoxide (2.976 g, 37.2 mmol, 2.0 equiv) was added in bulk to the reaction mixture; the reaction mixture was allowed to slowly warm to rt over 18h. ~ 100 mL water was then added, and the reaction mixture was extracted with 2 x 100 mL EtOAc. The organics were washed with ~ 50 mL 0.1 N HCl, water, and brine, then dried over $MgSO_4$. Purified on a silica column with 0-5% EtOAc:hexanes. **S1** (4.589, 76%) obtained as a colorless, crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (s, 1H), 8.18 (s, 1H), 7.93 (s, 1H), 1.63 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.01, 135.72, 134.67, 132.49 (q, J = 33.5 Hz), 132.00 (q, J = 3.7 Hz), 125.02 (q, J = 3.7 Hz), 122.71, 122.83 (q, J = 272.9 Hz), 82.78, 28.08; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -62.89 (s, 3F); did not ionize by ESI.



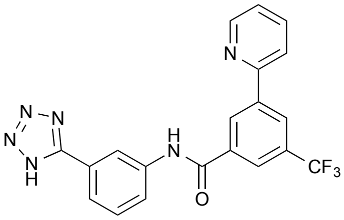
tert-butyl 5-(trifluoromethyl)-[1,1'-biphenyl]-3-carboxylate (S2). **S1** was reacted with commercially available phenylboronic acid according to general procedure E. Crude product was filtered through a silica gel plug; the plug was washed with hexanes and the product eluted with ethyl acetate. **S2** (46 mg, 65%) obtained as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.42 (s, 1H), 8.24, (s, 1H), 8.01 (s, 1H), 7.64 - 7.67 (m, 2H), 7.50 - 7.54 (m, 2H), 7.43 - 7.47 (m, 1 H), 1.67 (s, 9H); did not ionize by ESI.



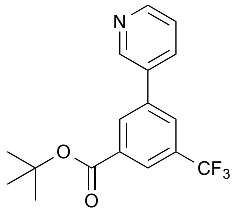
N-(3-(1*H*-tetrazol-5-yl)phenyl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carboxamide (2). **S2** (46.0 mg, 0.173 mmol, 1.0 equiv) was reacted according to general procedure F. **2** (28.8 mg, 50% over two steps) was obtained as a white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ = 10.16 (br s, 1H), 8.69 (s, 1H), 8.61 (s, 1H), 8.35 (s, 1H), 8.19 (s, 1H), 8.07 (br d, *J* = 8.04 Hz, 1H), 7.93 (br d, *J* = 7.67 Hz, 1H), 7.86 (br d, *J* = 7.43 Hz, 2H), 7.54 - 7.65 (m, 3H), 7.46 - 7.53 (m, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ = 164.22, 156.83, 142.57, 139.97, 138.60, 136.75, 131.07 (q, *J* = 32.28 Hz), 129.79, 129.69, 129.19, 128.59, 127.29, 126.21 - 126.47 (m), 125.84, 123.18 - 123.40 (m), 122.60, 118.78; ^{19}F NMR (376 MHz, acetone-d_6) δ = -63.03 (s, 3F); HRMS (ESI) calculated for $C_{21}H_{13}F_3N_5O$ $[M - H]^-$ m/z 408.1078, found 408.1070.



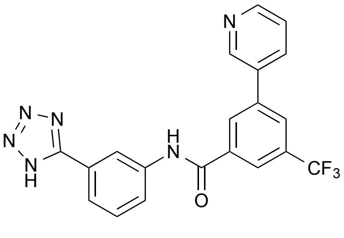
tert-butyl 3-(pyridin-2-yl)-5-(trifluoromethyl)benzoate (S3). **S1** (65.0 mg, 0.20 mmol, 1 equiv) was reacted with commercially available 2-bromopyridine according to general procedure D, except 5 mol% catalyst was used. Instead of a workup, the reaction mixture was allowed to cool to room temperature, diluted with MeOH, and filtered through celite. The filtrate was concentrated and purified via silica gel with EtOAc:hexanes. **S3** (18.0 mg, 26%) obtained as a clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.72 - 8.80 (m, 2H), 8.50 - 8.55 (m, 1H), 8.29 (s, 1H), 7.83 - 7.89 (m, 2H), 7.31 - 7.38 (m, 1H), 1.66 (s, 9H); LRMS (ESI) calculated for $C_{17}H_{17}F_3NO_2$ $[M + H]^+$ m/z 324.11, found 324.02.



N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(pyridin-2-yl)-5-(trifluoromethyl)benzamide (3). **S3** (18.0 mg, 0.056 mmol, 1.0 equiv) was reacted according to general procedure F. **3** (16.4 mg, 78% over two steps) obtained as a white solid. ^{1}H NMR (400 MHz, acetone-d$_6$) δ = 10.31 (br s, 1H), 9.05 (s, 1H), 8.77 (dd, *J* = 4.75, 0.73 Hz, 1H), 8.75 (s, 1H), 8.71 (s, 1H), 8.44 (s, 1H), 8.26 (d, *J* = 7.91 Hz, 1H), 8.17 (br d, *J* = 8.16 Hz, 1H), 7.95 - 8.01 (m, 2H), 7.57 (t, *J* = 7.97 Hz, 1H), 7.46 (ddd, *J* = 7.52, 4.78, 0.73 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d$_6$) δ = 164.09, 154.21, 149.91, 140.80, 139.95, 137.42, 136.69, 130.93 (d, *J* = 32.28 Hz), 129.62, 129.10, 126.11 (br d, *J* = 3.67 Hz), 124.78 (br d, *J* = 3.67 Hz), 123.59, 122.52, 122.07, 120.87, 118.94; ^{19}F NMR (376 MHz, acetone-d$_6$) δ = -63.12 (s, 3F); HRMS (ESI) calculated for $C_{20}H_{12}F_3N_6O$ [M - H]$^-$ m/z 409.1030, found 409.1022.

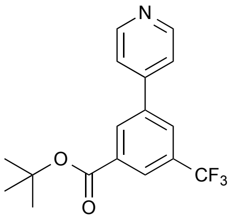


tert-butyl 3-(pyridin-3-yl)-5-(trifluoromethyl)benzoate (S4). **S1** was reacted with commercially available pyridin-3-ylboronic acid according to general procedure E. Crude product was purified via silica gel with EtOAc:hexanes. **S4** (26 mg, 40%) obtained as a colorless liquid. ^{1}H NMR (400 MHz, CDCl$_3$) δ = 8.89 - 8.94 (m, 1H), 8.70 (br d, *J* = 4.14 Hz, 1H), 8.40 (s, 1H), 8.28 (s, 1H), 7.99 (s, 1H), 7.93 - 7.97 (m, 1H), 7.46 (dd, *J* = 7.91, 4.87 Hz, 1H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 164.03, 149.56, 148.20, 139.04, 134.60, 133.86, 131.86 (q, *J* = 30.08 Hz), 131.26, 127.35 - 127.54 (m), 125.62 - 125.95 (m), 123.82, 82.49, 28.14; ^{19}F NMR (376 MHz, CDCl$_3$) δ = -62.68 (s, 3F); LRMS (ESI) calculated for $C_{17}H_{17}F_3NO_2$ [M + H]$^+$ m/z 324.11, found 324.02.

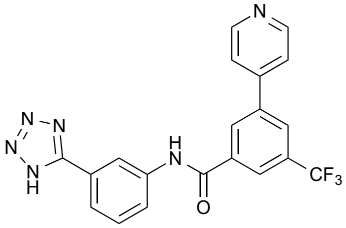


N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(pyridin-3-yl)-5-(trifluoromethyl)benzamide (4). **S4** (34 mg, 0.105 mmol, 1.0 equiv) was reacted according to general procedure F. **4** (25 mg, 58% over two steps) obtained as a white solid. ^{1}H NMR (400 MHz, pyridine-d$_5$) δ = 11.72 (s, 1H), 9.27 (br s, 1H), 9.07 - 9.22 (m, 3H), 9.04 (br s, 1H), 8.76 (br d, *J* = 4.75 Hz, 1H), 8.70 (s, 2H), 8.64 (s, 1H), 8.21 (br dd, *J* = 6.15, 1.03 Hz, 2H), 8.12 (s, 1H), 7.85 (br dd, *J* = 7.85, 1.28 Hz, 1H), 7.33

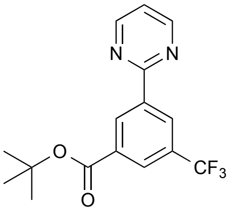
(br dd, J = 7.85, 4.81 Hz, 1H); ^{13}C NMR (100 MHz, pyridine-d_5) δ = 165.24, 149.76, 148.58, 140.59, 139.35, 137.59, 134.48, 134.16, 131.07 (d, J = 32.28 Hz), 130.48, 129.99, 127.61, 126.56 (br d, J = 3.67 Hz), 124.48 (br d, J = 4.40 Hz), 123.82, 123.13, 122.85, 119.87; ^{19}F NMR (376 MHz, pyridine-d_5) δ = -62.03 (s, 3F); HRMS (ESI) calculated for $C_{20}H_{12}F_3N_6O$ $[M - H]^-$ m/z 409.1030, found 409.1023.



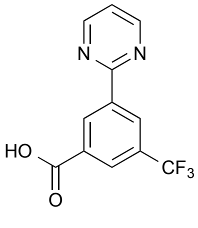
tert-butyl 3-(pyridin-4-yl)-5-(trifluoromethyl)benzoate (S5). S1 was reacted with commercially available pyridin-4-ylboronic acid according to general procedure E. Crude product was purified via HPLC using water/MeOH/0.05% formic acid. **S5** (34 mg, 54%) obtained as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.79 (br s, 2H), 8.45 (s, 1H), 8.31 (s, 1H), 8.04 (s, 1H), 7.59 (br s, 2H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.90, 150.61, 146.09, 139.42, 133.95, 131.92 (d, J = 33.01 Hz), 131.15, 127.35 (br d, J = 3.67 Hz), 126.61 (q, J = 3.67 Hz), 82.60, 28.14; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -62.70 (s, 3F); LRMS (ESI) calculated for $C_{17}H_{17}F_3NO_2$ $[M + H]^+$ m/z 324.11, found 324.09.



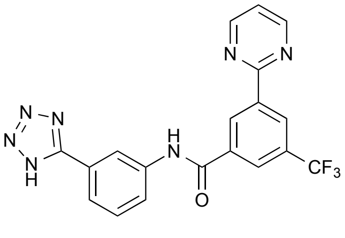
N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(pyridin-4-yl)-5-(trifluoromethyl)benzamide (5). S5 (19.4 mg, 0.060 mmol, 1.0 equiv) was reacted according to general procedure F. **5** (19 mg, 77% over two steps) obtained as a white solid. ^{1}H NMR (400 MHz, pyridine-d_5) δ = 11.74 (s, 1H), 9.26 (br d, J = 1.46 Hz, 1H), 8.77 - 8.83 (m, 2H), 8.70 (s, 3H), 8.66 (s, 1H), 8.17 - 8.23 (m, 2H), 8.15 (s, 1H), 7.56 - 7.61 (m, 1H), 7.46 - 7.52 (m, 2H); ^{13}C NMR (100 MHz, pyridine-d_5) δ = 165.10, 150.80, 145.43, 140.57, 139.53, 137.64, 131.12 (d, J = 33.01 Hz), 130.42, 130.03, 127.47, 126.53 (br d, J = 3.67 Hz), 125.17 - 125.70 (m), 123.16, 121.69, 119.87; ^{19}F NMR (376 MHz, pyridine-d_5) δ = -62.07 (s, 3F); HRMS (ESI) calculated for $C_{20}H_{12}F_3N_6O$ $[M - H]^-$ m/z 409.1030, found 409.1023.



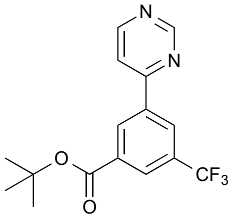
tert-butyl 3-(pyrimidin-2-yl)-5-(trifluoromethyl)benzoate (S6). **S1** (100 mg, 0.308 mmol, 1.0 equiv) was reacted with commercially available 2-bromopyrimidine according to general procedure D. **S6** (75.2 mg, 75%) obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.23 (br s, 1H), 8.90 (br s, 1H), 8.86 (d, *J* = 4.9 Hz, 2H), 8.35 (s, 1H), 7.28 (t, *J* = 4.9 Hz, 1H), 1.69 - 1.63 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.23, 162.64, 157.44, 138.87, 133.48, 132.12, 131.33 (q, *J* = 33.0 Hz), 128.58 (q, *J* = 3.7 Hz), 128.13 (q, *J* = 4.2 Hz), 123.77 (q, *J* = 272.9 Hz), 120.03, 82.17, 28.14; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -62.66 (s, 3F); LRMS (ESI) calculated for $C_{16}H_{16}F_3N_2O_2$ $[M + H]^+$ m/z 325.11, found 324.94.



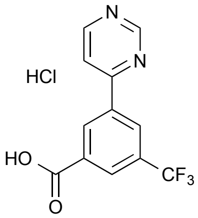
3-(pyrimidin-2-yl)-5-(trifluoromethyl)benzoic acid (S7). **S6** (75.2 mg, 0.232 mmol, 1.0 equiv) was reacted according to general procedure C (24h). Semi-crude **S7** (65.6 mg, 106%) obtained as a white solid. ^{1}H NMR (400 MHz, CD_3OD, drops $CDCl_3$) δ = 9.20 (br s, 1H), 8.90 (d, *J* = 4.9 Hz, 2H), 8.83 (br s, 1H), 8.34 (br s, 1H), 7.46 (t, *J* = 5.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD, drops $CDCl_3$) δ = 166.42, 161.55, 157.62, 138.31, 132.48, 132.26, 131.21 (q, *J* = 33.0 Hz), 128.38 (q, *J* = 3.7 Hz), 128.11 (q, *J* = 3.7 Hz), 120.49, 123.67 (q, *J* = 272.2 Hz); ^{19}F NMR (376 MHz, CD_3OD, drops $CDCl_3$) δ = -63.99 (s, 3F); LRMS (ESI) calculated for $C_{12}H_6F_3N_2O_2$ $[M - H]^-$ m/z 267.05, found 267.06.



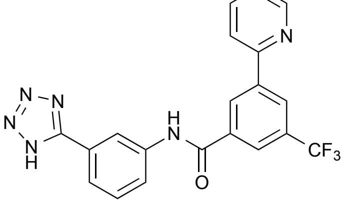
N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(pyrimidin-2-yl)-5-(trifluoromethyl)benzamide (6). **S7** (65.6 mg, 0.245 mmol, 1.0 equiv) was reacted with 3-(1*H*-tetrazol-5-yl)aniline in 3 mL DMF according to general procedure B. **6** (65.4 mg, 65%) obtained as a white solid. ^{1}H NMR (400 MHz, CD_3OD, drops $CDCl_3$) δ = 9.18 (br s, 1H), 8.84 (d, *J* = 4.9 Hz, 2H), 8.83 (br s, 1H), 8.35 (t, *J* = 1.7 Hz, 1H), 8.32 (br s, 1H), 7.91 (br dd, *J* = 1.2, 8.3 Hz, 1H), 7.74 (br d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 4.9 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD, drops $CDCl_3$) δ = 166.65, 163.18, 158.59, 157.50, 140.31, 139.95, 137.21, 132.38 (q, *J* = 30.1 Hz), 131.34, 130.75, 128.59 (d, *J* = 3.7 Hz), 127.37 (q, *J* = 3.7 Hz), 126.03, 124.49, 124.01, 124.72 (q, *J* = 272.2 Hz), 121.38, 120.32; ^{19}F NMR (376 MHz, CD_3OD, drops $CDCl_3$) δ = -63.57 (s, 3F); HRMS (ESI) calculated for $C_{19}H_{11}F_3N_7O$ $[M - H]^-$ m/z 410.0983, found 410.0974.



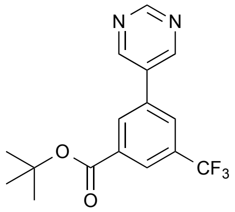
tert-butyl 3-(pyrimidin-4-yl)-5-(trifluoromethyl)benzoate (S8). **S1** (100 mg, 0.308 mmol, 1.0 equiv) was reacted with commercially available 4-chloropyrimidine hydrochloride according to general procedure D, except potassium carbonate (136 mg, 0.984 mmol, 3.2 equiv) and water (992 ul) were used in the second step. **S8** (84.5 mg, 85%) obtained as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ = 9.31 (br d, *J* = 1.4 Hz, 1H), 8.84 (d, *J* = 5.4 Hz, 1H), 8.80 (br s, 1H), 8.57 (br s, 1H), 8.33 (br s, 1H), 7.81 (dd, *J* = 1.5, 5.4 Hz, 1H), 1.63 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 163.71, 161.41, 159.24, 158.03, 137.67, 133.77, 131.82 (q, *J* = 33.0 Hz), 130.86, 128.32 (q, *J* = 3.9 Hz), 127.56 (q, *J* = 3.7 Hz), 123.43 (q, *J* = 272.9 Hz), 117.03, 82.53, 28.03; ^{19}F NMR (376 MHz, CDCl$_3$) δ = -62.78 (s, 3F); LRMS (ESI) calculated for $C_{16}H_{16}F_3N_2O_2$ [M + H]$^+$ m/z 325.11, found 325.01.



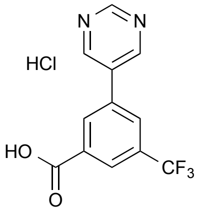
3-(pyrimidin-4-yl)-5-(trifluoromethyl)benzoic acid hydrochloride (S9). **S8** (84.5 mg, 0.261 mmol, 1.0 equiv) was reacted according to general procedure C (24h). Semi-crude **S9** (80.8 mg, 102%) obtained as a white solid. ^{1}H NMR (400 MHz, CD$_3$OD) δ = 9.60 (br s, 1H), 9.20 (d, *J* = 6.1 Hz, 1H), 9.16 (br s, 1H), 8.86 (br s, 1H), 8.67 (dd, *J* = 1.0, 6.1 Hz, 1H), 8.50 (br s, 1H); ^{13}C NMR (100 MHz, CD$_3$OD) δ = 166.81, 165.56, 153.72, 152.18, 136.13, 133.41, 132.52, 131.91 (q, *J* = 33.0 Hz), 129.89 (q, *J* = 4.2 Hz), 128.70 (q, *J* = 3.9 Hz), 123.43 (q, *J* = 272.2 Hz), 118.72; ^{19}F NMR (376 MHz, CD$_3$OD) δ = -64.35 (s, 3F); LRMS (ESI) calculated for $C_{12}H_6F_3N_2O_2$ [M - H]$^-$ m/z 267.05, found 267.06.



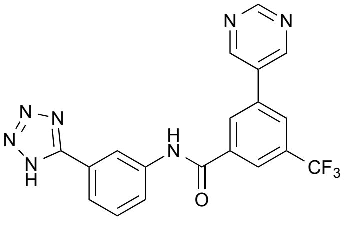
N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(pyrimidin-4-yl)-5-(trifluoromethyl)benzamide (7). **S9** (80.8 mg, 0.265 mmol, 1.0 equiv) was reacted with 3-(1*H*-tetrazol-5-yl)aniline in 3 mL DMF according to general procedure B, except 2 equiv *N,N*-diisopropylethylamine (93 uL) was used in the first step. **7** (68.8 mg, 63%) obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 10.84 (s, 1H), 9.36 (d, *J* = 1.0 Hz, 1H), 9.07 (br s, 1H), 9.00 (d, *J* = 5.4 Hz, 1H), 8.73 (s, 1H), 8.58 (s, 1H), 8.50 (s, 1H), 8.37 (dd, *J* = 1.2, 5.4 Hz, 1H), 8.03 (dd, *J* = 1.1, 8.2 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ = 163.76, 160.33, 158.90, 158.70, 155.77, 139.63, 137.60, 136.49, 130.21, 129.90, 130.22 (q, *J* = 33.0 Hz), 126.70 (br q, *J* = 3.7 Hz), 126.40 (br q, *J* = 3.7 Hz), 124.93, 122.96, 122.48, 123.72 (q, *J* = 272.9 Hz), 118.91, 117.95; ^{19}F NMR (376 MHz, DMSO-d$_6$) δ = -61.16 (s, 3F); HRMS (ESI) calculated for $C_{19}H_{11}F_3N_7O$ [M - H]$^-$ m/z 410.0983, found 410.0975.



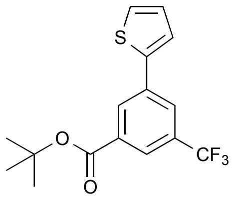
tert-butyl 3-(pyrimidin-5-yl)-5-(trifluoromethyl)benzoate (S10). S1 (100 mg, 0.308 mmol, 1.0 equiv) was reacted with commercially available 5-bromopyrimidine according to general procedure D. **S10** (74.3 mg, 75%) obtained as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ = 9.26 (s, 1H), 9.00 (s, 2H), 8.37 (br s, 1H), 8.30 (br s, 1H), 7.96 (br s, 1H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 163.55, 158.37, 154.96, 135.53, 134.21, 132.40, 132.16 (q, *J* = 33.0 Hz), 131.06, 127.18 (q, *J* = 3.7 Hz), 126.53 (q, *J* = 4.2 Hz), 123.32 (q, *J* = 272.9 Hz), 82.67, 28.02; ^{19}F NMR (376 MHz, CDCl$_3$) δ = -62.77 (s, 3F); LRMS (ESI) calculated for $C_{16}H_{16}F_3N_2O_2$ [M + H]$^+$ m/z 325.11, found 325.09.



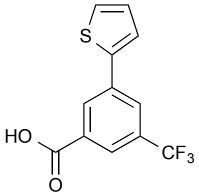
3-(pyrimidin-5-yl)-5-(trifluoromethyl)benzoic acid hydrochloride (S11). S10 (74.3 mg, 0.229 mmol, 1.0 equiv) was reacted according to general procedure C (48h). Semi-crude **S11** (70.1 mg, 100%) obtained as a white solid. ^{1}H NMR (400 MHz, CD$_3$OD, drops CDCl$_3$) δ = 9.36 (s, 1H), 9.28 (s, 2H), 8.56 (s, 1H), 8.19 (s, 1H), 7.98 (s, 1H); ^{19}F NMR (376 MHz, CD$_3$OD, drops CDCl$_3$) δ = -63.56 (s, 3F); LRMS (ESI) calculated for $C_{12}H_6F_3N_2O_2$ [M - H]$^-$ m/z 267.05, found 266.99.



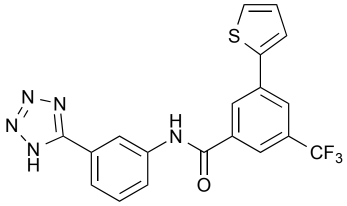
N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(pyrimidin-5-yl)-5-(trifluoromethyl)benzamide (8). S11 (70.1 mg, 0.230 mmol, 1.0 equiv) was reacted with 3-(1*H*-tetrazol-5-yl)aniline in 2.5 mL DMF according to general procedure B, except 2 eq *N,N*-diisopropylethylamine (80.2 uL) was used in the first step. **8** (16.5 mg, 17%) obtained as a white solid. ^{1}H NMR (400 MHz, $CD_3OD/CD_3CN/CDCl_3$) δ = 10.60 (s, 1H), 10.55 (br s, 2H), 9.91 (br s, 1H), 9.88 - 9.84 (m, 1H), 9.75 (br s, 1H), 9.61 (br s, 1H), 9.29 (br d, *J* = 8.3 Hz, 1H), 9.17 (br d, *J* = 7.8 Hz, 1H), 8.99 - 8.92 (m, 1H); ^{13}C NMR (100 MHz, $CD_3OD/CD_3CN/CDCl_3$) δ = 166.15, 159.15, 157.98, 156.69, 140.71, 138.28, 137.25, 133.85, 133.01 (q, *J* = 33.0 Hz), 131.22, 128.23 (br q, *J* = 3.7 Hz), 126.86, 126.21 (br q, *J* = 4.4 Hz), 124.51, 124.33, 120.54; ^{19}F NMR (376 MHz, $CD_3OD/CD_3CN/CDCl_3$) δ = -62.05 (s, 3F); HRMS (ESI) calculated for $C_{19}H_{11}F_3N_7O$ [M - H]$^-$ m/z 410.0983, found 410.0976.



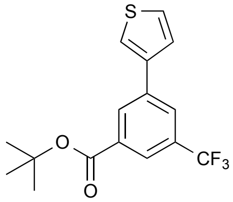
tert-butyl 3-(thiophen-2-yl)-5-(trifluoromethyl)benzoate (S12). A 3 mL vial with cap was purged with Ar and charged with **S1** (100 mg, 0.308 mmol, 1.0 equiv), thiophene-2-boronic acid (98 mg, 0.769 mmol, 2.5 equiv), cesium carbonate (251 mg, 0.769 mmol, 2.5 equiv), tetrakis(triphenylphosphine)palladium(0) (21 mg, 0.018 mmol, 0.06 equiv), and dry 1,2-dimethoxyethane (2.5 mL). The reaction mixture was purged again, sealed, and heated at 80 °C for 18h. The crude reaction mixture was transferred to a sep funnel with ~ 75 mL EtOAc and ~ 5 mL water. ~ 50 mL sat. $NaHCO_3$ was added, the layers separated, and the organic layer washed with ~ 50 mL water and brine. The EtOAc was dried over $MgSO_4$ and concentrated. Purified on a silica column with 0-15% EtOAc:hexanes. **S12** (70.7 mg, 70%) obtained as a glassy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.39 (br s, 1H), 8.13 (br s, 1H), 7.97 (br s, 1H), 7.43 (dd, *J* = 1.0, 3.7 Hz, 1H), 7.38 (dd, *J* = 1.2, 5.1 Hz, 1H), 7.13 (dd, *J* = 3.7, 5.1 Hz, 1H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.09, 141.67, 135.55, 133.55, 131.51 (q, *J* = 33.0 Hz), 129.71, 128.33, 126.35, 125.88 (q, *J* = 3.7 Hz), 124.68, 124.71 (q, *J* = 3.7 Hz), 123.61 (q, *J* = 272.9 Hz), 82.23, 28.08; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -62.77 (s, 3F); did not ionize by ESI.



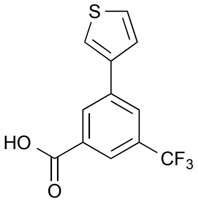
3-(thiophen-2-yl)-5-(trifluoromethyl)benzoic acid (S13). S12 (70.7 mg, 0.215 mmol, 1.0 equiv) was reacted according to general procedure C (48h). Semi-crude **S13** (59.6 mg, 102%) obtained as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.36 (s, 1H), 8.09 (s, 1H), 7.99 (br s, 1H), 7.48 (dd, *J* = 1.2, 3.7 Hz, 1H), 7.45 (dd, *J* = 1.0, 5.1 Hz, 1H), 7.10 (dd, *J* = 3.7, 5.1 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ = 166.29, 140.95, 135.90, 132.61, 131.32 (q, *J* = 33.0 Hz), 129.42, 128.23, 126.35, 125.29 (q, *J* = 3.7 Hz), 124.82, 124.23 (q, *J* = 3.7 Hz), 123.66 (q, *J* = 271.7 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ = -64.35 (s, 3F); LRMS (ESI) calculated for $C_{12}H_6F_3O_2S$ [M - H]$^-$ m/z 271.01, found 270.93.



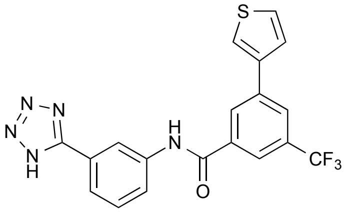
N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(thiophen-2-yl)-5-(trifluoromethyl)benzamide (9). S13 (59.6 mg, 0.219 mmol, 1.0 equiv) was reacted with 3-(1*H*-tetrazol-5-yl)aniline in 2.5 mL DMF according to general procedure B. **9** (60.9 mg, 67%) obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 10.77 (s, 1H), 8.57 (t, *J* = 1.7 Hz, 1H), 8.50 (s, 1H), 8.24 (s, 1H), 8.18 (s, 1H), 8.01 (dd, *J* = 1.2, 8.3 Hz, 1H), 7.83 (dd, *J* = 1.0, 3.7 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.71 (dd, *J* = 1.1, 5.0 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.23 (dd, *J* = 3.7, 4.9 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ = 163.83, 156.04, 140.62, 139.56, 136.45, 135.31, 130.25 (d, *J* = 32.3 Hz), 129.73, 128.81, 128.34, 127.60, 126.11, 125.34, 124.40 (br d, *J* = 4.4 Hz), 122.95 (d, *J* = 4.4 Hz), 122.78, 122.40, 123.69 (d, *J* = 272.9 Hz), 118.91; ^{19}F NMR (376 MHz, DMSO-d$_6$) δ = -61.16 (s, 3F); HRMS (ESI) calculated for $C_{19}H_{11}F_3N_5OS$ [M - H]$^-$ m/z 414.0642, found 414.0634.



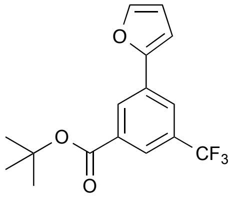
tert-butyl 3-(thiophen-3-yl)-5-(trifluoromethyl)benzoate (S14). A 3 mL vial with cap was purged with Ar and charged with **S1** (100 mg, 0.308 mmol, 1.0 equiv), thiophene-3-boronic acid (98 mg, 0.769 mmol, 2.5 equiv), cesium carbonate (251 mg, 0.769 mmol, 2.5 equiv), tetrakis(triphenylphosphine)palladium(0) (21 mg, 0.018 mmol, 0.06 equiv), and dry 1,2-dimethoxyethane (2.5 mL). The reaction mixture was purged again, sealed, and heated at 80 °C for 18h. The crude reaction mixture was transferred to a sep funnel with ~ 75 mL EtOAc and ~ 5 mL water. ~ 50 mL sat. $NaHCO_3$ was added, the layers separated, and the organic layer washed with ~ 50 mL water and brine. The EtOAc was dried over $MgSO_4$ and concentrated under reduced pressure. Purified on a silica column with 0-15% EtOAc:hexanes. **S14** (90.1 mg, 89%) obtained as a glassy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.39 (br s, 1H), 8.16 (br s, 1H), 7.98 (br s, 1H), 7.59 (dd, *J* = 1.8, 2.6 Hz, 1H), 7.45 (d, *J* = 1.2 Hz, 1H), 7.44 (s, 1H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.28, 139.96, 136.83, 133.40, 131.36 (q, *J* = 32.5 Hz), 130.35, 127.03, 126.55 (q, *J* = 3.7 Hz), 125.96, 124.56 (q, *J* = 3.7 Hz), 123.73 (q, *J* = 272.9 Hz), 122.02, 82.11, 28.09; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -62.67 (s, 3F); did not ionize by ESI.



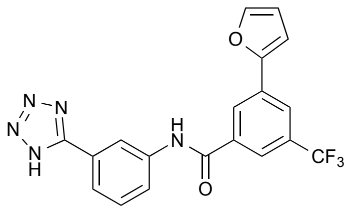
3-(thiophen-3-yl)-5-(trifluoromethyl)benzoic acid (S15). S14 (90.1 mg, 0.274 mmol, 1.0 equiv) was reacted according to general procedure C (48h). Semi-crude **S15** (79.3 mg, 106%) obtained as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.41 (t, *J* = 1.3 Hz, 1H), 8.12 - 8.10 (m, 1H), 8.05 - 8.02 (m, 1H), 7.74 (dd, *J* = 1.5, 2.9 Hz, 1H), 7.50 - 7.48 (m, 1H), 7.46 - 7.43 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ = 168.34, 141.13, 138.91, 134.07, 132.87 (q, *J* = 33.0 Hz), 131.90, 128.59, 127.96 (q, *J* = 3.7 Hz), 127.14, 125.78 (q, *J* = 4.2 Hz), 123.89, 125.54 (q, *J* = 271.7 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ = -64.16 (s, 3F); LRMS (ESI) calculated for $C_{12}H_6F_3O_2S$ $[M - H]^-$ m/z 271.01, found 270.93.



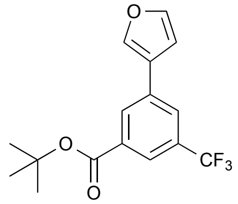
N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(thiophen-3-yl)-5-(trifluoromethyl)benzamide (10). S15 (79.3 mg, 0.291 mmol, 1.0 equiv) was reacted with 3-(1*H*-tetrazol-5-yl)aniline in 2.5 mL DMF according to general procedure B. **10** (97.3 mg, 80%) obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.74 (s, 1H), 8.61 (s, 1H), 8.58 (t, *J* = 1.7 Hz, 1H), 8.28 (s, 1H), 8.23 (dd, *J* = 1.3, 2.8 Hz, 1H), 8.21 (s, 1H), 8.04 - 8.00 (m, 1H), 7.83 - 7.78 (m, 2H), 7.76 - 7.72 (m, 1H), 7.62 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 164.16, 155.92, 139.64, 139.15, 136.56, 136.23, 130.10 (q, *J* = 31.5 Hz), 129.77, 129.00, 127.73, 126.33, 125.36 (d, *J* = 3.2 Hz), 125.10, 123.49, 122.85, 122.71 (d, *J* = 3.7 Hz), 123.86 (d, *J* = 272.9 Hz), 122.37, 118.88; ^{19}F NMR (376 MHz, DMSO-d_6) δ = -60.21 (s, 3F); HRMS (ESI) calculated for $C_{19}H_{11}F_3N_5OS$ $[M - H]^-$ m/z 414.0642, found 414.0635.



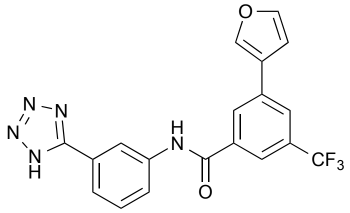
tert-butyl 3-(furan-2-yl)-5-(trifluoromethyl)benzoate (S16). S1 was reacted with commercially available furan-2-ylboronic acid according to general procedure E. Crude product was filtered through a silica gel plug; the plug was washed with hexanes and the product was eluted with CH_2Cl_2. **S16** (31 mg, 50%) obtained as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.41 - 8.46 (m, 1H), 8.29 (s, 1H), 8.02 (s, 1H), 7.65 (dd, *J* = 5.66, 3.35 Hz, 1H), 7.48 (dd, *J* = 5.78, 3.23 Hz, 1H), 1.67 (s, 9H); did not ionize by ESI.



N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(furan-2-yl)-5-(trifluoromethyl)benzamide (11). S16 (28.3 mg, 0.091 mmol, 1.0 equiv) was reacted according to general procedure F. **11** (21 mg, 58% over two steps) obtained as a white solid. ^{1}H NMR (400 MHz, pyridine-d$_5$) δ = 11.71 (br s, 1H), 10.56 (br s, 2H), 9.24 (br s, 1H), 8.35 (br s, 1H), 8.08 - 8.21 (m, 3H), 7.66 (br s, 1H), 6.96 (br d, *J* = 1.83 Hz, 1H), 6.54 (br s, 1H); ^{13}C NMR (100 MHz, pyridine-d$_5$) δ = 166.77, 153.04, 145.23, 142.14, 138.84, 133.62, 132.38 (br d, *J* = 31.54 Hz), 131.53, 128.61, 128.12, 124.25, 121.40, 113.94, 109.59; ^{19}F NMR (376 MHz, pyridine-d$_5$) δ = -62.3 (s, 3F); HRMS (ESI) calculated for $C_{19}H_{11}F_3N_5O_2$ [M - H]$^-$ m/z 398.0870, found 398.0865.

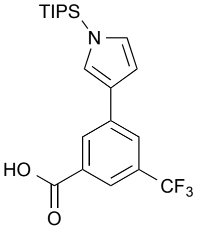


tert-butyl 3-(furan-3-yl)-5-(trifluoromethyl)benzoate (S17). S1 was reacted with commercially available furan-3-ylboronic acid according to general procedure E. Crude product was purified via silica gel with hexanes:CH_2Cl_2. **S17** (50.3 mg, 77%) obtained as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.27 - 8.29 (m, 1H), 8.12 (s, 1H), 7.86 (d, *J* = 0.85 Hz, 2H), 7.54 (t, *J* = 1.70 Hz, 1H), 6.78 (dd, *J* = 1.70, 0.73 Hz, 1H), 1.65 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.31, 144.28, 139.47, 133.73, 133.43, 131.42 (q, *J* = 32.52 Hz), 129.78, 125.73 - 126.14 (m), 124.79, 124.49 (q, *J* = 3.67 Hz), 108.56, 82.19, 28.11; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -62.79 (s, 3F); did not ionize by ESI.

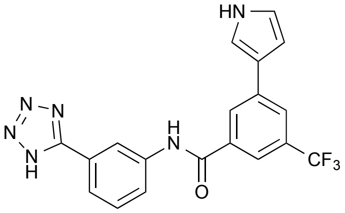


N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(furan-3-yl)-5-(trifluoromethyl)benzamide (12). S17 (30.5 mg, 0.098 mmol, 1.0 equiv) was reacted according to general procedure F. **12** (39 mg, 50% over two steps) obtained as a white solid. ^{1}H NMR (400 MHz, pyridine-d$_5$) δ = 11.82 - 12.21 (m, 2H), 11.65 - 11.75 (m, 1H), 9.22 - 9.33 (m, 1H), 8.59 - 8.69 (m, 1H), 8.37 - 8.46 (m, 1H), 8.10 - 8.32 (m, 4H), 7.70 - 7.80 (m, 1H), 7.15 - 7.35 (m, 2H), 6.92 - 7.03 (m, 1H); ^{13}C NMR (100 MHz, pyridine-d$_5$) δ = 165.47, 144.69, 140.66, 137.37, 134.23, 131.04, 130.72, 130.02, 129.17, 128.91, 128.42, 127.11, 125.54 (br d, *J* = 3.67 Hz), 125.13 (br d, *J* = 3.67 Hz), 124.93, 119.86, 108.79;

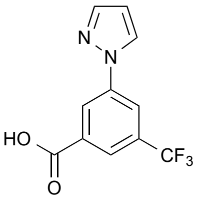
^{19}F NMR (376 MHz, pyridine-d$_5$) δ = -62.17 (s, 3F); HRMS (ESI) calculated for $C_{19}H_{11}F_3N_5O_2$ [M - H]$^-$ m/z 398.0870, found 398.0863.



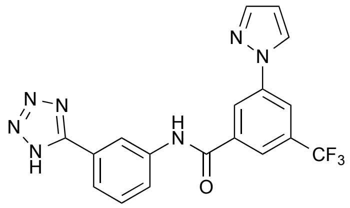
3-(trifluoromethyl)-5-(1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)benzoic acid (S18). Commercially available 3-bromo-5-(trifluoromethyl)benzoic acid (54 mg, 0.20 mmol, 1 equiv) was reacted with commercially available (1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)boronic acid according to general procedure E. Crude product was loaded onto a plug of C18-silica; the plug was washed with water and the product eluted with MeOH. Crude **S18** was used without further purification. LRMS (ESI) calculated for $C_{21}H_{27}F_3NO_2Si$ [M - H]$^-$ m/z 410.18, found 410.2.



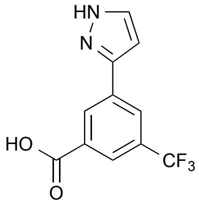
N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(1*H*-pyrrol-3-yl)-5-(trifluoromethyl)benzamide (13). Crude **S18** was taken up in 1.0 mL of a 1M tetrabutylammonium fluoride solution in THF. The reaction was stirred until complete by TLC (ca. 2 hr), then concentrated. The resulting crude 3-(1*H*-pyrrol-3-yl)-5-(trifluoromethyl)benzoic acid was reacted according to general procedure F. **13** (12 mg, 15% over three steps) obtained as a white solid. ^{1}H NMR (400 MHz, pyridine-d$_5$) δ = 12.17 - 12.39 (m, 1H), 11.57 - 11.72 (m, 1H), 9.23 (br s, 1H), 8.14 - 8.42 (m, 5H), 6.75 - 6.91 (m, 2H); ^{19}F NMR (376 MHz, pyridine-d$_5$) δ = -62.11 (s, 3F); HRMS (ESI) calculated for $C_{19}H_{12}F_3N_6O$ [M - H]$^-$ m/z 397.1030, found 397.1023.



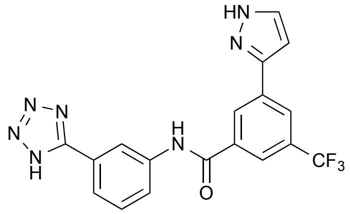
3-(1*H*-pyrazol-1-yl)-5-(trifluoromethyl)benzoic acid (S19). Commercially available 3-bromo-5-(trifluoromethyl)benzoic acid (54 mg, 0.20 mmol, 1 equiv), K_2CO_3 (155 mg, 1.1 mmol, 5.6 equiv), and *N*,*N*-dimethylglycine hydrochloride (45 mg, 0.3 mmol, 1.6 equiv) were suspended in 0.5 mL of dry DMSO. Argon was bubbled through the resulting solution to remove oxygen before copper(I) iodide (30 mg, 0.2 mmol, 0.8 equiv) and pyrazole (18 mg, 0.3 mmol, 1.3 equiv) were added to the reaction mixture. The reaction was then warmed to 100 °C and stirred for 18h. The reaction mixture was allowed to cool to room temperature, diluted with MeOH, and filtered through celite. Crude **S19** was used without further purification. LRMS (ESI) calculated for $C_{11}H_6F_3N_2O_2$ [M - H]$^-$ m/z 255.05, found 254.97.



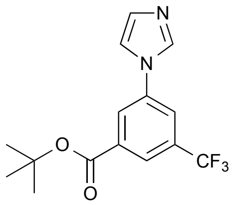
N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(1*H*-pyrazol-1-yl)-5-(trifluoromethyl)benzamide (14). Crude **S19** was reacted according to general procedure F. **14** (17 mg, 21% over two steps) obtained as a white solid. ^{1}H NMR (400 MHz, pyridine-d$_5$) δ = 11.76 (br d, *J* = 13.15 Hz, 1H), 9.23 (br d, *J* = 12.90 Hz, 1H), 8.91 (br d, *J* = 13.27 Hz, 1H), 8.50 - 8.57 (m, 1H), 8.27 - 8.45 (m, 3H), 8.09 - 8.24 (m, 3H), 7.91 (br d, *J* = 13.76 Hz, 1H), 6.57 (br d, *J* = 12.66 Hz, 1H); ^{13}C NMR (100 MHz, pyridine-d$_5$) δ = 164.87, 142.05, 140.95, 140.51, 138.19, 131.34 (d, *J* = 33.01 Hz), 130.00, 127.86, 127.38, 123.20, 121.84 - 122.04 (m), 121.49, 119.91, 117.97 (d, *J* = 2.93 Hz), 108.81; ^{19}F NMR (376 MHz, pyridine-d$_5$) δ = -62.33 (s, 3F); HRMS (ESI) calculated for $C_{18}H_{11}F_3N_7O$ [M - H]$^-$ m/z 398.0983, found 398.0976.



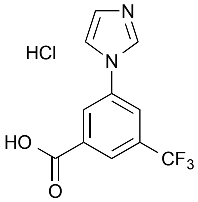
3-(1*H*-pyrazol-3-yl)-5-(trifluoromethyl)benzoic acid (S20). Commercially available 3-bromo-5-(trifluoromethyl)benzoic acid (54 mg, 0.20 mmol, 1 equiv) was reacted with commercially available (1*H*-pyrazol-3-yl)boronic acid according to general procedure E. Crude product was loaded onto a plug of C18-silica; the plug was washed with water and the product eluted with MeOH. Crude **S20** was used without further purification. LRMS (ESI) calculated for $C_{11}H_6F_3N_2O_2$ [M - H]$^-$ m/z 255.05, found 254.97.



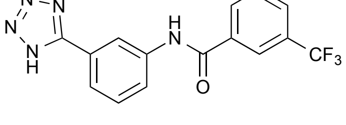
N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(1*H*-pyrazol-5-yl)-5-(trifluoromethyl)benzamide (15). Crude **S20** was reacted according to general procedure F. **15** (1.4 mg, 1.8% over two steps) obtained as a white solid. ^{1}H NMR (400 MHz, acetone-d$_6$) δ = 8.63 (br d, *J* = 15.22 Hz, 2H), 8.33 (br s, 2H), 8.18 (s, 2H), 8.07 - 8.12 (m, 1H), 7.94 (br d, *J* = 7.79 Hz, 1H), 7.58 (t, *J* = 7.97 Hz, 1H); ^{19}F NMR (376 MHz, acetone-d$_6$) δ = -63.14 (s, 3F); HRMS (ESI) calculated for $C_{18}H_{11}F_3N_7O$ [M - H]$^-$ m/z 398.0983, found 398.0977.



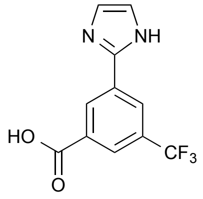
tert-butyl 3-(1*H*-imidazol-1-yl)-5-(trifluoromethyl)benzoate (S21). A 3 mL vial with cap was purged with Ar and charged with **S1** (100 mg, 0.308 mmol, 1.0 equiv), imidazole (27 mg, 0.400 mmol, 1.3 equiv), potassium carbonate (238 mg, 1.72 mmol, 5.6 equiv), copper(I) iodide (47 mg, 0.246 mmol, 0.8 equiv), and *N,N*-dimethylglycine hydrochloride (69 mg, 0.492 mmol, 1.6 equiv). The vial was purged with Ar; dry dimethyl sulfoxide (1.5 ml) was then added, and the vial was sealed and heated at 120 °C for 18h. The crude reaction mixture was transferred to a sep funnel with ~ 75 mL EtOAc and ~10 mL water. ~ 50 mL sat. $NaHCO_3$ was added, the layers separated, and the organic layer washed with ~ 40 mL water and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purified on a silica column with 0-60% EtOAc:hexanes. **S21** (34.7 mg, 36%) obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20 (s, 1H), 8.19 (br d, *J* = 1.9 Hz, 1H), 7.94 (s, 1H), 7.79 (br s, 1H), 7.36 (t, *J* = 1.3 Hz, 1H), 7.26 (br s, 1H), 1.63 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.08, 137.94, 135.47, 135.02, 132.70 (q, *J* = 33.5 Hz), 131.30, 125.16, 124.85 (q, *J* = 3.7 Hz), 121.51 (q, *J* = 3.7 Hz), 122.97 (q, *J* = 272.9 Hz), 117.97, 83.02, 28.02; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -62.84 (s, 3F); LRMS (ESI) calculated for $C_{15}H_{16}F_3N_2O_2$ $[M + H]^+$ m/z 313.11, found 313.01.



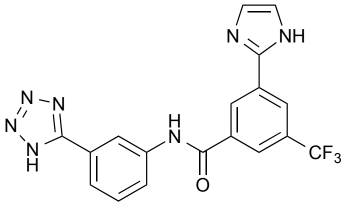
3-(1*H*-imidazol-1-yl)-5-(trifluoromethyl)benzoic acid hydrochloride (S22). **S21** (34.7 mg, 0.111 mmol, 1.0 equiv) was reacted according to general procedure C (24h). Semi-crude **S22** (33.8 mg, 104%) obtained as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 9.70 (s, 1H), 8.62 (s, 1H), 8.46 (s, 1H), 8.41 (s, 1H), 8.25 (s, 1H), 7.84 (br s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ = 164.90, 136.16, 135.26, 134.52, 132.63 (q, *J* = 34.2 Hz), 127.16 (q, *J* = 3.7 Hz), 127.04, 123.63 (q, *J* = 3.7 Hz), 122.98 (d, *J* = 272.2 Hz), 121.59, 120.90; ^{19}F NMR (376 MHz, CD_3OD) δ = -64.15 (s, 3F); LRMS (ESI) calculated for $C_{11}H_6F_3N_2O_2$ $[M - H]^-$ m/z 255.05, found 255.06.



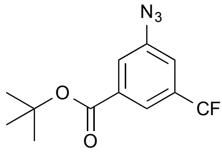
N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(1*H*-imidazol-1-yl)-5-(trifluoromethyl)benzamide (16). **S22** (33.8 mg, 0.115 mmol, 1.0 equiv) was reacted with 3-(1*H*-tetrazol-5-yl)aniline in 2 mL DMF according to general procedure B, except 2 eq *N,N*-diisopropylethylamine (40 uL) was used in the first step. **16** (30.2 mg, 66%) obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.77 (s, 1H), 8.55 (s, 3H), 8.32 (s, 1H), 8.26 (s, 1H), 8.03 (s, 1H), 8.00 (dd, *J* = 1.2, 8.3 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.20 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 163.91, 156.70, 139.94, 138.21, 137.84, 136.59 (br s), 131.36 (d, *J* = 32.3 Hz), 130.83, 130.31, 126.17, 123.83, 123.03, 122.96, 122.93 - 122.78 (m), 123.91 (d, *J* = 272.9 Hz), 120.46 - 120.30 (m), 119.25, 118.77; ^{19}F NMR (376 MHz, DMSO-d_6) δ = -61.02 (s, 3F); HRMS (ESI) calculated for $C_{18}H_{11}F_3N_7O$ [M - H]$^-$ m/z 398.0983, found 398.0976.



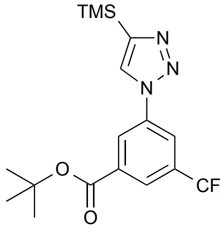
3-(1*H*-imidazol-2-yl)-5-(trifluoromethyl)benzoic acid (S23). A 3 mL vial with cap/septa was purged with Ar and charged with imidazole (22 mg, 0.323 mmol, 1.0 equiv), palladium(II) acetate (4 mg, 0.016 mmol, 0.05 equiv), copper(I) iodide (123 mg, 0.646 mmol, 2.0 equiv), and **S1** (210 mg, 0.646 mmol, 2.0 equiv). The vial was purged with Ar and charged with 1.62 mL degassed DMF (Ar bubbling for 30 min). The vial was sealed and heated at 140 °C for 48h. After cooling to rt, the reaction mixture was filtered through a nylon 0.2 um syringe filter and purified by reverse phase HPLC (water/MeOH/0.05% formic acid) to afford the desired product. **S23** (15.9 mg, 19%) obtained as a light blue solid. ^{1}H NMR (400 MHz, CD_3OD, drops $CDCl_3$) δ = 8.80 (br s, 1H), 8.40 (br s, 1H), 8.27 (br s, 1H), 7.33 (br s, 2H); ^{19}F NMR (376 MHz, CD_3OD, drops $CDCl_3$) δ = -64.29 (s, 3F); LRMS (ESI) calculated for $C_{11}H_6F_3N_2O_2$ [M - H]$^-$ m/z 255.05, found 255.11.



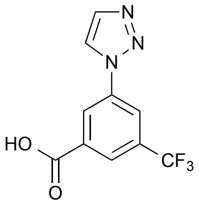
N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(1*H*-imidazol-2-yl)-5-(trifluoromethyl)benzamide (17). **S23** (15.9 mg, 0.062 mmol, 1.0 equiv) was reacted with 3-(1*H*-tetrazol-5-yl)aniline in 2.5 mL DMF according to general procedure A, except 3 eq *N,N*-diisopropylethylamine (32 uL) was used. **17** (14.1 mg, 57%) obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.73 (br s, 1H), 8.85 (br s, 1H), 8.48 (br s, 2H), 8.29 (s, 1H), 7.92 (br d, *J* = 7.8 Hz, 1H), 7.82 (br s, 1H), 7.48 (br s, 1H), 7.27 (br s, 2H); ^{19}F NMR (376 MHz, DMSO-d_6) δ = -61.20 (s, 3F); HRMS (ESI) calculated for $C_{18}H_{11}F_3N_7O$ [M - H]$^-$ m/z 398.0983, found 398.0979.



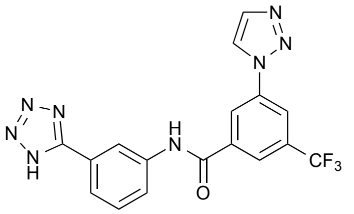
tert-butyl 3-azido-5-(trifluoromethyl)benzoate (S24). A 3 mL vial with cap was purged with Ar and charged with **S1** (125 mg, 0.384 mmol, 1.0 equiv), sodium azide (50 mg, 0.769 mmol, 2.0 equiv), copper(I) iodide (7.3 mg, 0.038 mmol, 0.1 equiv), sodium ascorbate (3.8 mg, 0.019 mmol, 0.05 equiv), and *N,N'*-dimethyethylenediamine (6.2 ul, 0.058 mmol, 0.15 equiv). Ethanol (1.28 ml) and water (550 ul) were then added; the vial was purged with Ar, sealed, and heated at 80 °C for 3h. The crude reaction mixture was then transferred to a sep funnel with ~ 75 mL EtOAc and ~ 30 mL water. The aqueous layer was basified by the addition of ~ 20 mL sat. $NaHCO_3$; the layers were separated, and the organic layer was further extracted with ~ 50 mL water and brine. The organic layer was dried over $MgSO_4$ and concentrated to an oil. Purified on a silica column with 0-10% EtOAc:hexanes. Product containing fractions were combined and carefully rotovapped. (**Note:** Product is moderately volatile) **S24** (93.7 mg, 85%) obtained as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 (s, 1H), 7.83 (br s, 1H), 7.38 (br s, 1H), 1.62 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.44, 141.48, 134.72, 132.49 (q, *J* = 33.5 Hz), 122.83, 122.47 (q, *J* = 4.2 Hz), 119.51 (q, *J* = 3.7 Hz), 123.15 (q, *J* = 272.9 Hz), 82.62, 28.04; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -63.00 (s, 3F); did not ionize by ESI.



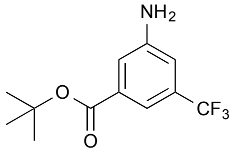
tert-butyl 3-(trifluoromethyl)-5-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)benzoate (S25). A 3 mL vial was charged with **S24** (93.7 mg, 0.326 mmol, 1.0 equiv), ethynyltrimethylsilane (1.153 mL, 8.16 mmol, 25.0 equiv), copper(I) Iodide (186 mg, 0.979 mmol, 3.0 equiv), and *N,N*-diisopropylethylamine (511 ul, 2.94 mmol, 9.0 equiv). 1.76 mL dry THF was then added, and the vial was sealed and heated at 80 °C overnight. The crude reaction mixture was filtered, and the filtrand was washed with ~ 50 mL cold THF. The filtrate was concentrated under reduced pressure, affording crude **S25** (168.4 mg, 134%) as a light brown solid. LRMS (ESI) calculated for $C_{17}H_{22}F_3N_3O_2Si$ $[M + H]^+$ m/z 386.14, found 386.01.



3-(1*H*-1,2,3-triazol-1-yl)-5-(trifluoromethyl)benzoic acid (S26). Crude **S25** (168.4 mg) was reacted according to general procedure C (32h), except after the t-butyl was removed by LCMS, 4 mL water was added, and the reaction mixture was heated at 40 °C for an additional 16h. The reaction mixture was then transferred to a sep funnel with ~ 75 mL EtOAc and ~ 30 mL water. The aqueous layer was basified by the addition of ~ 30 mL sat. $NaHCO_3$; the layers were separated, and the aqueous layer was acidified to pH 1 with concentrated HCl. The aqueous layer was further extracted with 3 x 50 mL EtOAc. The new organic layers were combined, dried over $MgSO_4$, and concentrated. Semi-crude **S26** (36.8 mg, 44% over two steps) obtained as a white solid. ^1H NMR (400 MHz, CD_3OD, drops $CDCl_3$) δ = 8.73 (s, 1H), 8.70 (s, 1H), 8.42 (s, 1H), 8.33 (s, 1H), 7.93 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD, drops $CDCl_3$) δ = 166.89, 139.35, 137.41, 133.91 (q, J = 33.7 Hz), 127.38 (q, J = 3.7 Hz), 125.87, 124.68, 124.19, 122.31 (q, J = 3.7 Hz), 124.69 (q, J = 272.2 Hz); ^{19}F NMR (376 MHz, CD_3OD, drops $CDCl_3$) δ = -64.16 (s, 3F); LRMS (ESI) calculated for $C_{10}H_5F_3N_3O_2$ $[M - H]^-$ m/z 256.04, found 256.05.

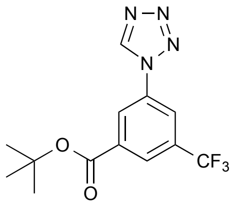


N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(1*H*-1,2,3-triazol-1-yl)-5-(trifluoromethyl)benzamide (18). S26 (36.8 mg, 0.143 mmol, 1.0 equiv) was reacted with 3-(1*H*-tetrazol-5-yl)aniline in 2.5 mL DMF according to general procedure B. **18** (28.0 mg, 49%) obtained as a white solid. ^1H NMR (400 MHz, DMSO-d_6, drops EtOAc) δ = 10.85 (s, 1H), 9.12 (s, 1H), 8.88 (s, 1H), 8.53 (s, 2H), 8.45 (s, 1H), 8.08 (s, 1H), 7.97 (br d, J = 7.5 Hz, 1H), 7.81 (br s, 1H), 7.56 (br t, J = 6.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, drops EtOAc) δ = 163.03, 156.04, 139.26, 137.48, 137.39, 134.92, 130.81 (q, J = 33.8 Hz), 129.55, 127.54 (br), 124.10 (br d, J = 2.9 Hz), 123.92, 123.28, 122.42 (br d, J = 2.9 Hz), 123.34 (d, J = 272.9 Hz), 121.76, 119.63 (br d, J = 2.2 Hz), 118.71 (br); ^{19}F NMR (376 MHz, DMSO-d_6, drops EtOAc) δ = -61.14 (s, 3F); HRMS (ESI) calculated for $C_{17}H_{10}F_3N_8O$ $[M - H]^-$ m/z 399.0935, found 399.0928.

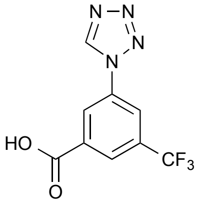


tert-butyl 3-amino-5-(trifluoromethyl)benzoate (S27). S1 (250 mg, 0.769 mmol, 1.0 equiv), copper(I) iodide (29 mg, 0.154 mmol, 0.2 equiv), potassium carbonate (319 mg, 2.31 mmol, 3.0 equiv), and trans-4-hydroxy-L-proline (40 mg, 0.308 mmol, 0.4 equiv) were added to a teflon screw capped vial. dimethyl sulfoxide (3 mL) and 30.0% ammonium hydroxide (1.500 ml, 13.5 mmol, 17.6 equiv) were added, and the reaction mixture was sealed and heated at 70 °C for 18h (**Note:** The solution began to degass upon addition of NH_4OH – seal the vessel quickly). The reaction mixture was transferred to a sep funnel with ~ 75 mL water and ~ 40 mL EtOAc. The layers were separated, and the aqueous layer was further extracted with 2 x 40 mL EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated to give colorless oil. Purified on a silica column with 0-15% EtOAc:hexanes. **S27** (46.5 mg, 23%) obtained as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.58 (s, 1H), 7.44 (s, 1H), 7.02 (s, 1H), 1.59 (s, 9H); ^{13}C NMR

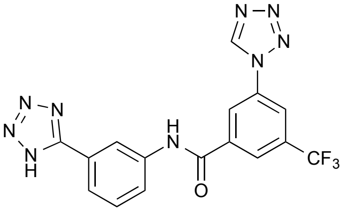
(100 MHz, $CDCl_3$) δ = 164.68, 146.90, 133.83, 131.69 (q, *J* = 32.3 Hz), 123.78 (q, *J* = 272.2 Hz), 118.53, 115.87 (q, *J* = 4.4 Hz), 114.68 (q, *J* = 4.2 Hz), 81.69, 28.07; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -62.97 (s, 3F); LRMS (ESI) calculated for $C_{12}H_{15}F_3NO_2$ $[M + H]^+$ m/z 262.10, found 261.97.



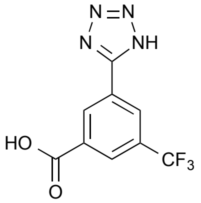
tert-butyl 3-(1*H*-tetrazol-1-yl)-5-(trifluoromethyl)benzoate (S28). A 3 mL vial was charged with **S27** (46.5 mg, 0.178 mmol, 1.0 equiv). The vial was backfilled with Ar and charged with triethyl orthoformate (148 ul, 0.890 mmol, 5.0 equiv), sodium azide (58 mg, 0.890 mmol, 5.0 equiv), and glacial acetic acid (1 mL). The reaction mixture was sealed and heated at 100 °C for 3h, then transferred to a sep funnel with ~ 75 mL water and ~ 40 mL EtOAc. The layers were separated, and the aqueous layer was further extracted with 2 x 40 mL EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated to give colorless oil. Purified on silica gel with 0-15% EtOAc:hexanes. **S28** (33.4 mg, 60%) obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.22 (s, 1H), 8.49 (br s, 1H), 8.37 (s, 1H), 8.23 (s, 1H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.49, 140.57, 135.48, 134.38, 133.21 (q, *J* = 34.0 Hz), 127.35 (q, *J* = 3.7 Hz), 124.74, 121.66 (q, *J* = 3.7 Hz), 122.66 (q, *J* = 273.4 Hz), 83.61, 28.01; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -62.92 (s, 3F); LRMS (ESI) calculated for $C_{13}H_{14}F_3N_4O_2$ $[M + H]^+$ m/z 315.10, found 315.06.



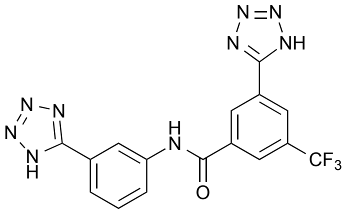
3-(1*H*-tetrazol-1-yl)-5-(trifluoromethyl)benzoic acid (S29). S28 (33.4 mg, 0.106 mmol, 1.0 equiv) was reacted according to general procedure C (48h). Semi-crude **S29** (30.0 mg, 109%) obtained as an off-white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 9.98 (s, 1H), 8.74 (s, 1H), 8.48 (s, 1H), 8.40 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ = 166.54, 143.46, 136.67, 135.85, 133.96 (q, *J* = 34.2 Hz), 128.10 (q, *J* = 3.7 Hz), 126.66, 123.14 (q, *J* = 3.2 Hz), 124.59 (q, *J* = 272.2 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ = -64.39 (s, 3F); LRMS (ESI) calculated for $C_9H_4F_3N_4O_2$ $[M - H]^-$ m/z 257.04, found 257.04.



N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(1*H*-tetrazol-1-yl)-5-(trifluoromethyl)benzamide (19). S29 (30.0 mg, 0.116 mmol, 1.0 equiv) was reacted with 3-(1*H*-tetrazol-5-yl)aniline in 2 mL DMF according to general procedure B. **21** (22.1 mg, 47%) obtained as a white solid. ^{1}H NMR (400 MHz, CD_3OD, drops CD_3CN) δ = 9.52 (s, 1H), 8.53 (s, 1H), 8.34 (s, 1H), 8.29 (s, 1H), 8.23 (s, 1H), 7.75 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD, drops CD_3CN) δ = 164.82, 157.96, 143.39, 140.43, 139.27, 136.29, 133.36 (q, *J* = 33.7 Hz), 131.17, 127.04, 126.57 (q, *J* = 3.4 Hz), 125.43, 124.35, 124.24, 124.52 (d, *J* = 272.2 Hz), 122.40 (q, *J* = 3.7 Hz), 120.32; ^{19}F NMR (CD_3OD, drops CD_3CN) δ = -62.20 (s, 3F); HRMS (ESI) calculated for $C_{16}H_9F_3N_9O$ $[M - H]^-$ m/z 400.0888, found 400.0881.



3-(1*H*-tetrazol-5-yl)-5-(trifluoromethyl)benzoic acid (S30). A 15 mL sealed tube was backfilled with argon and charged with commercially available 3-cyano-5-(trifluoromethyl)benzoic acid (100 mg, 0.465 mmol, 1.0 equiv), sodium azide (91 mg, 1.40 mmol, 3.0 equiv), and ammonium chloride (81 mg, 1.63 mmol, 3.5 equiv). 4 mL DMF was then used to wash the walls/seal area; the tube was flushed with Ar, sealed, and stirred at 100 °C for 18h. The crude reaction mixture was transferred to a sep funnel with ~ 75 mL H_2O and EtOAc, and the aqueous layer was adjusted to pH 1 with conc. HCl. The layers were separated, and the aqueous layer was further extracted with 2 x 30 mL EtOAc. The organics were combined, dried over $MgSO_4$, and concentrated, giving brown oil. Dried on hivac overnight. The remaining residue was rotovaped with 2 x 10 mL portions of toluene and dried under hivac again, yielding semi-crude **S30** (129.7 mg, 108%) as a brown solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.80 (s, 1H), 8.46 (s, 1H), 8.30 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ = 167.01, 158.00, 134.66, 133.11 (q, *J* = 33.0 Hz), 132.41, 129.29 (br d, *J* = 3.7 Hz), 128.49 (br d, *J* = 3.7 Hz), 128.33, 124.83 (q, *J* = 272.2 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ = -64.41 (s, 3F); LRMS (ESI) calculated for $C_9H_4F_3N_4O_2$ $[M - H]^-$ m/z 257.04, found 257.04.



N-(3-(1*H*-tetrazol-5-yl)phenyl)-3-(1*H*-tetrazol-5-yl)-5-(trifluoromethyl)benzamide (20). S30 (130 mg, 0.502 mmol, 1.0 equiv) was reacted with 3-(1*H*-tetrazol-5-yl)aniline in 3 mL DMF according to general procedure A. **22** (122.7 mg, 61%) obtained as a light tan solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.82 (s, 1H), 8.45 (br s, 1H), 8.44 (t, *J* = 1.8 Hz, 1H), 8.35 (s, 1H), 7.82 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.72 - 7.67 (m, 1H), 7.48 (t, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ = 166.17, 158.70, 157.72, 140.86, 138.41, 133.14 (q, *J* = 33.0 Hz), 131.12, 131.01, 128.91, 127.75 - 127.47 (m), 126.25, 124.87, 124.34, 125.02 (d, *J* = 272.2 Hz), 120.71; ^{19}F NMR (376 MHz, CD_3OD) δ = -64.25 (s, 3F); HRMS (ESI) calculated for $C_{16}H_9F_3N_9O$ [M - H]$^-$ m/z 400.0888, found 400.0882.

HRMS Spectra

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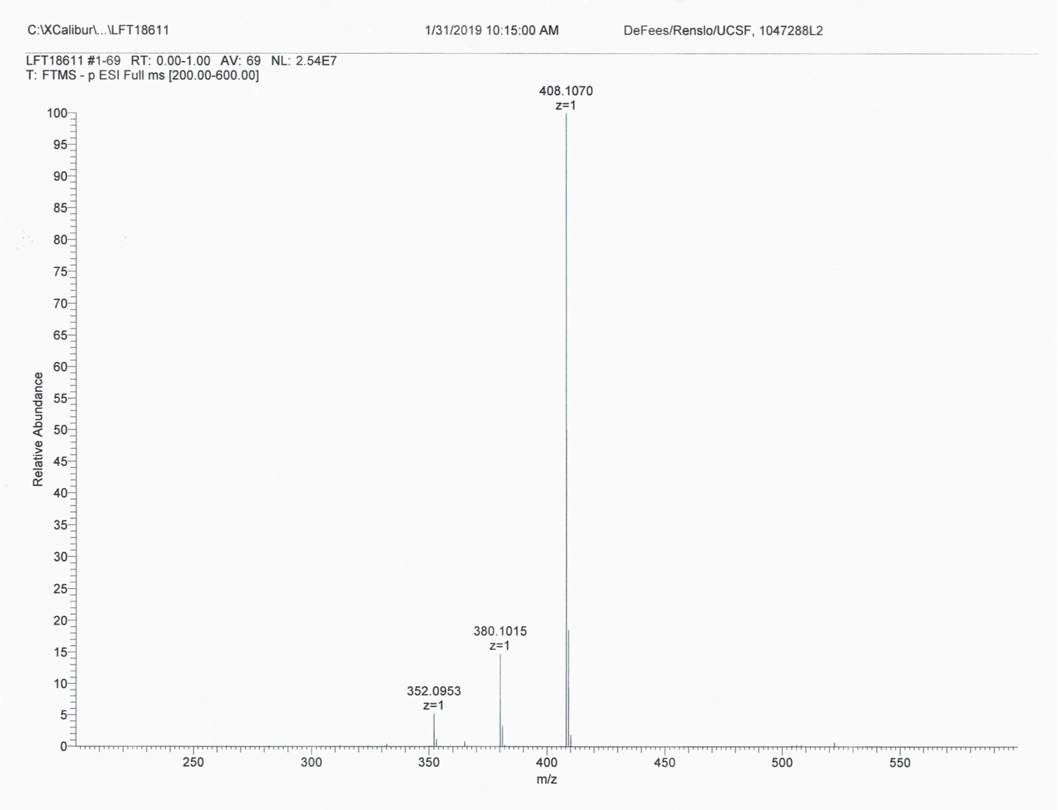

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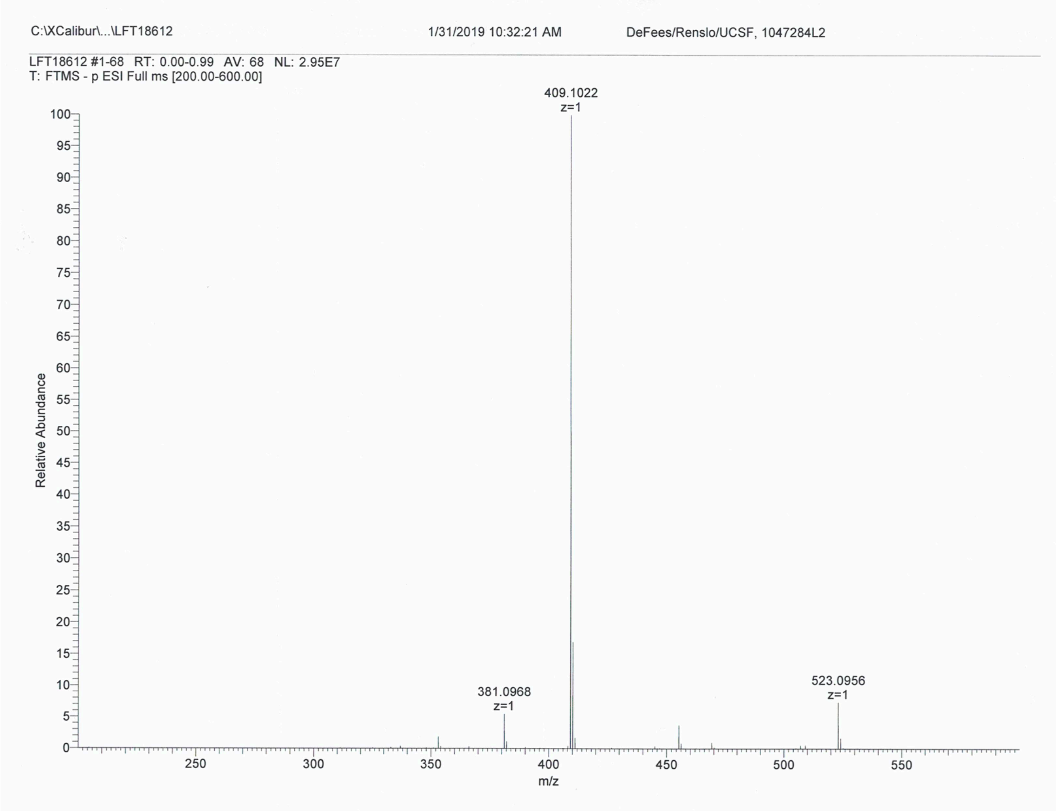

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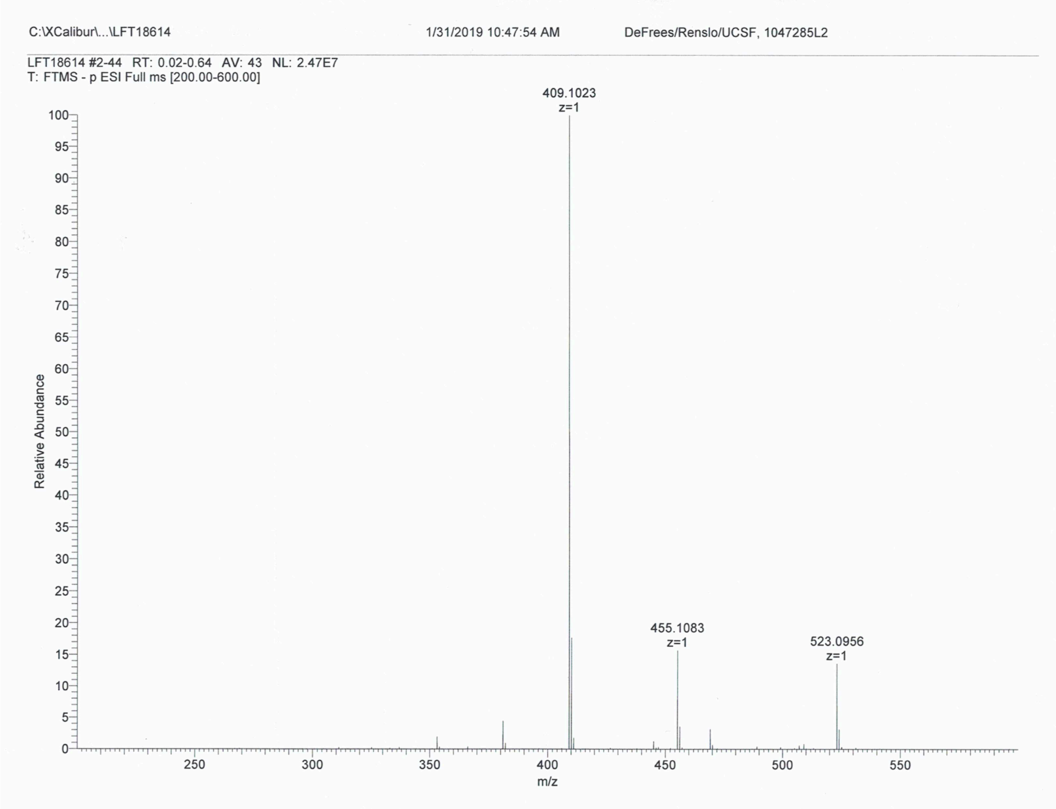

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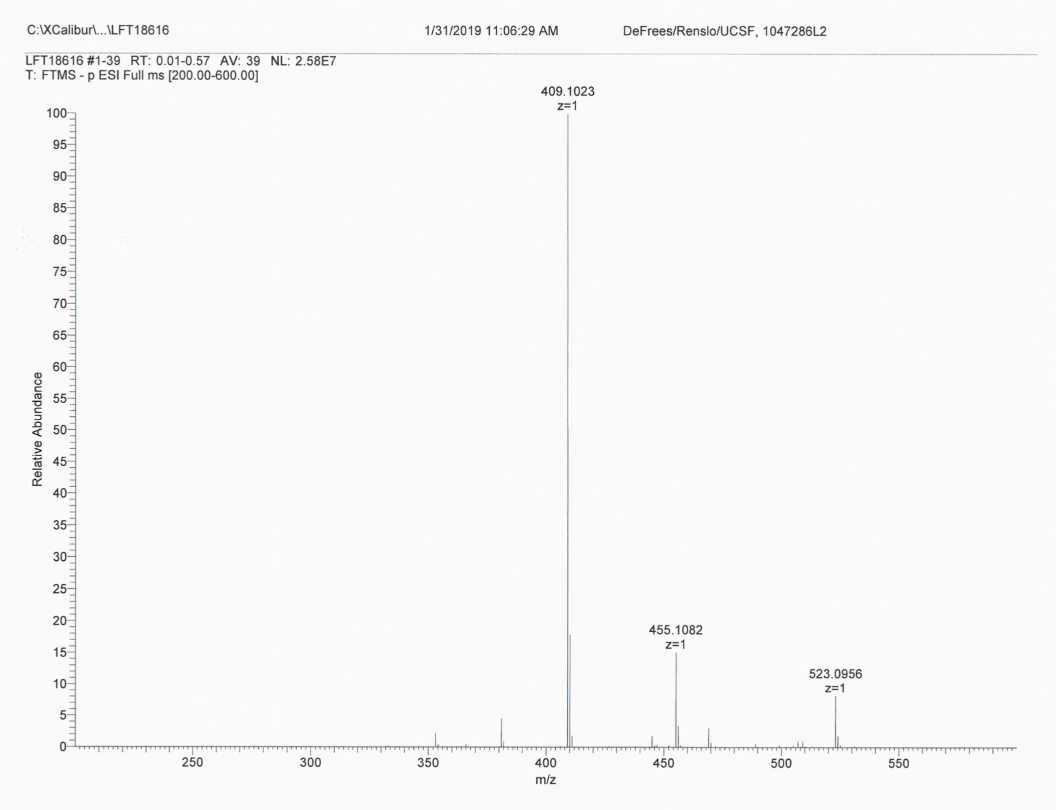

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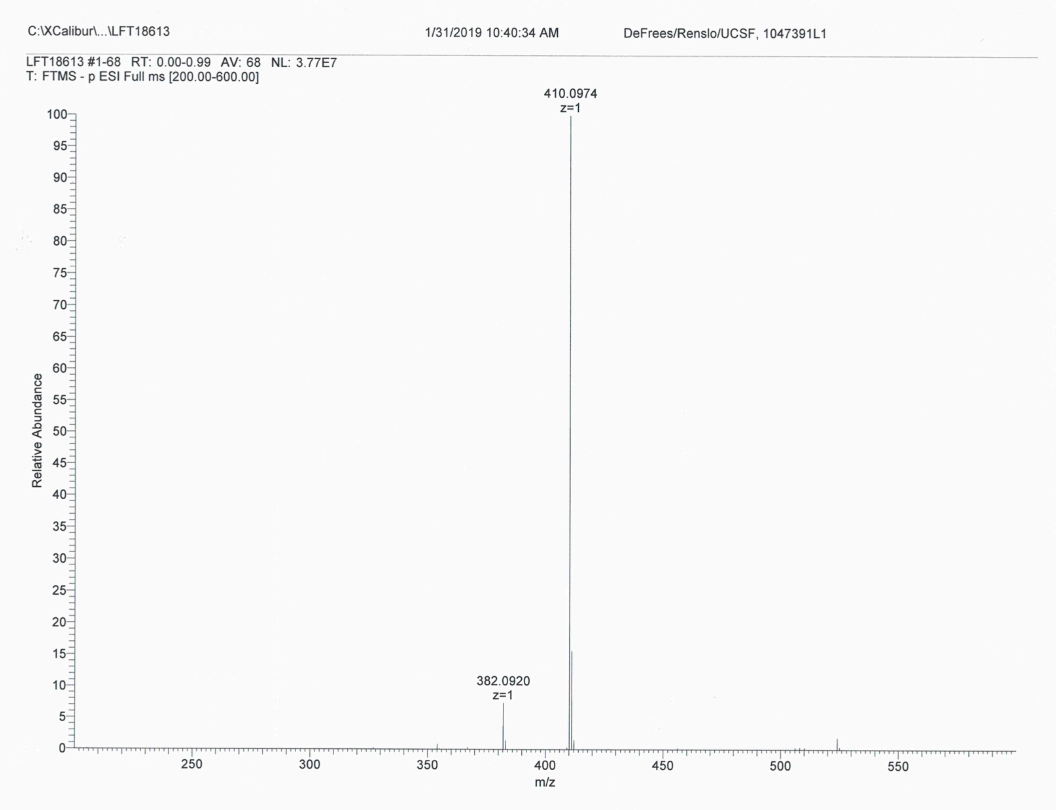
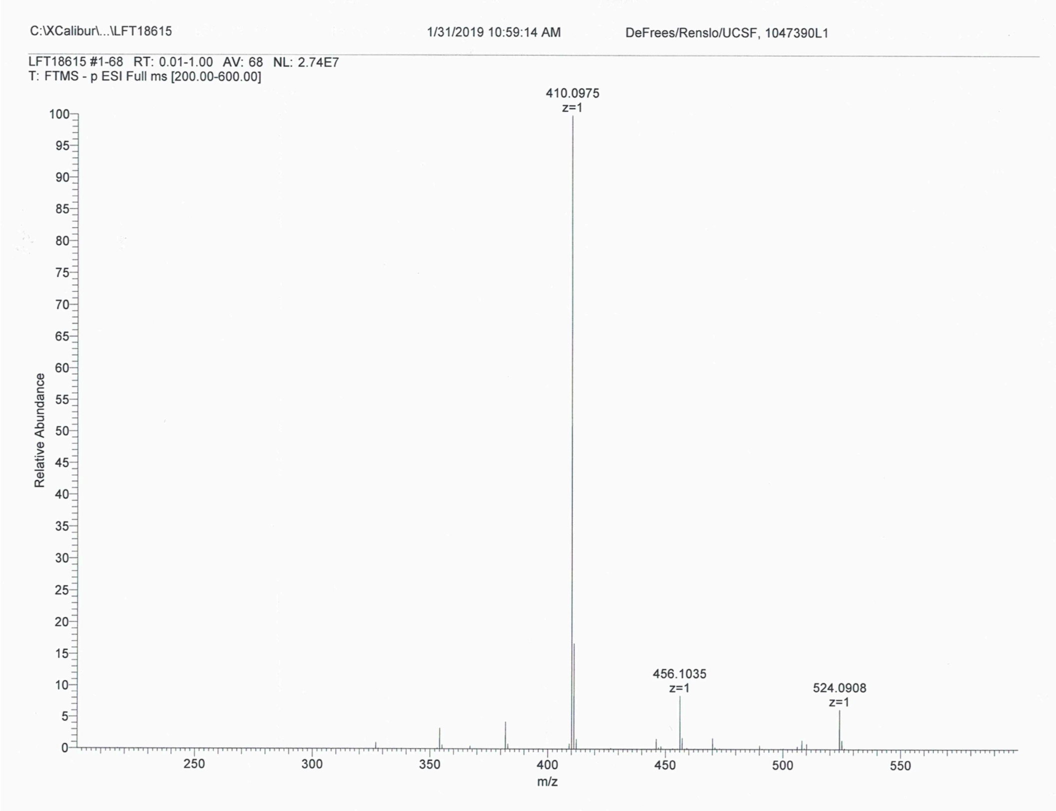


Compound 7:



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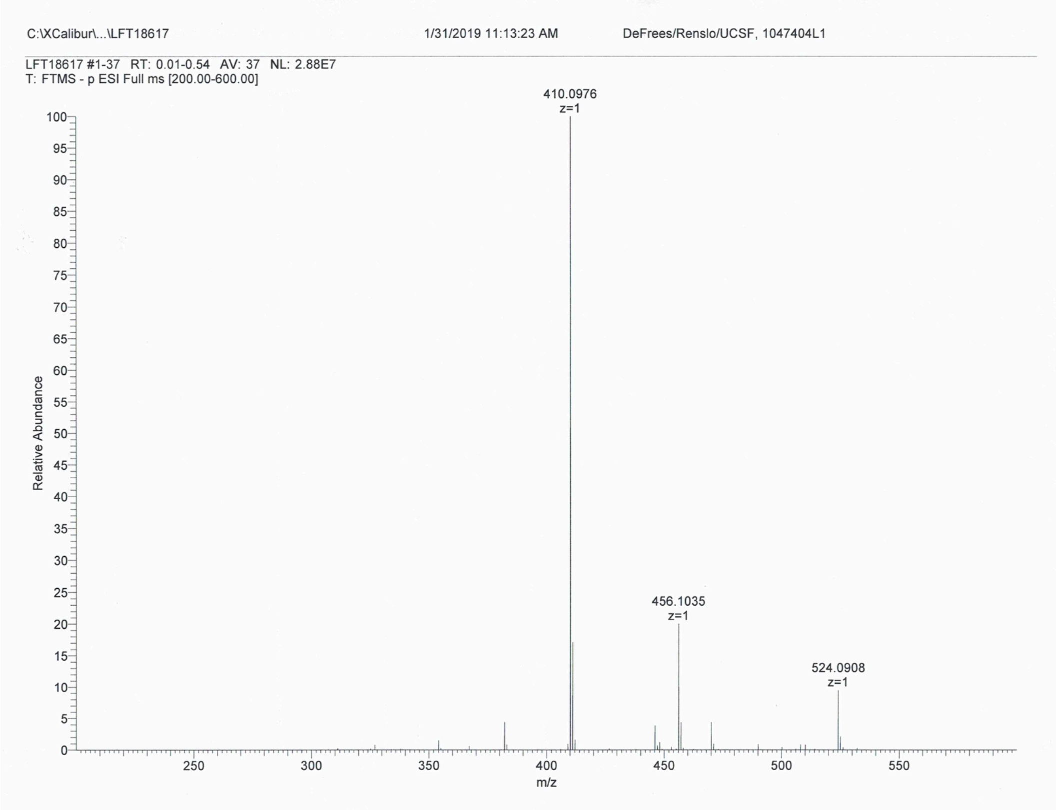

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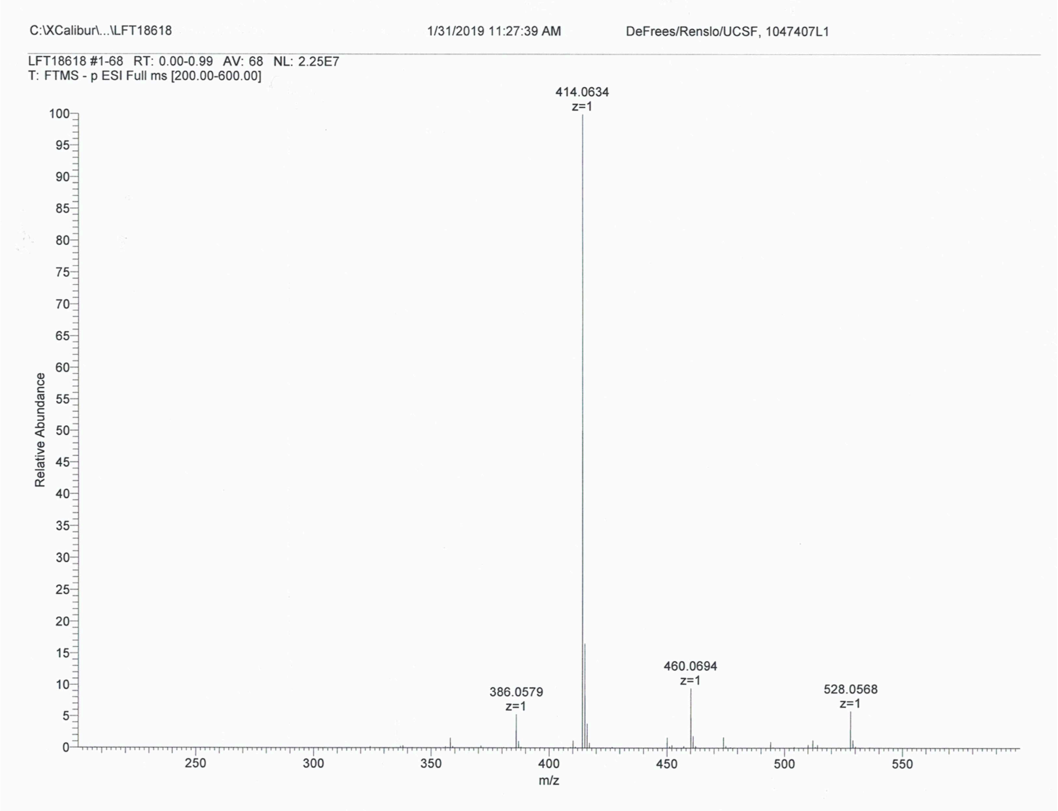

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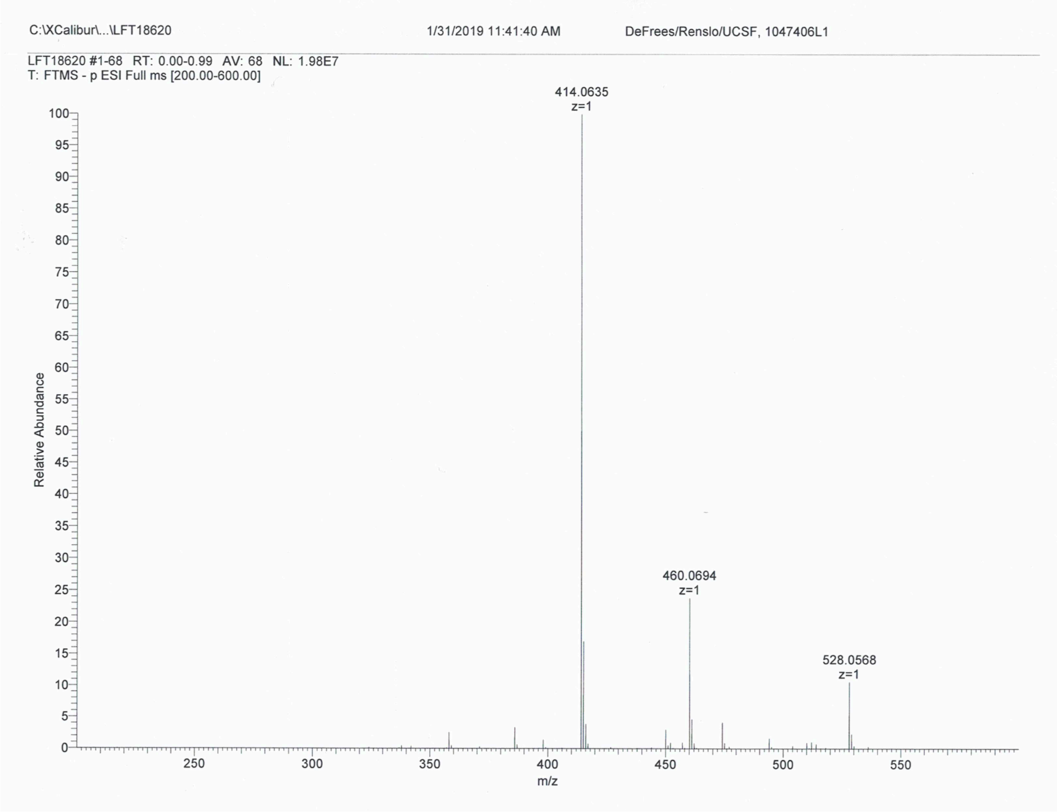

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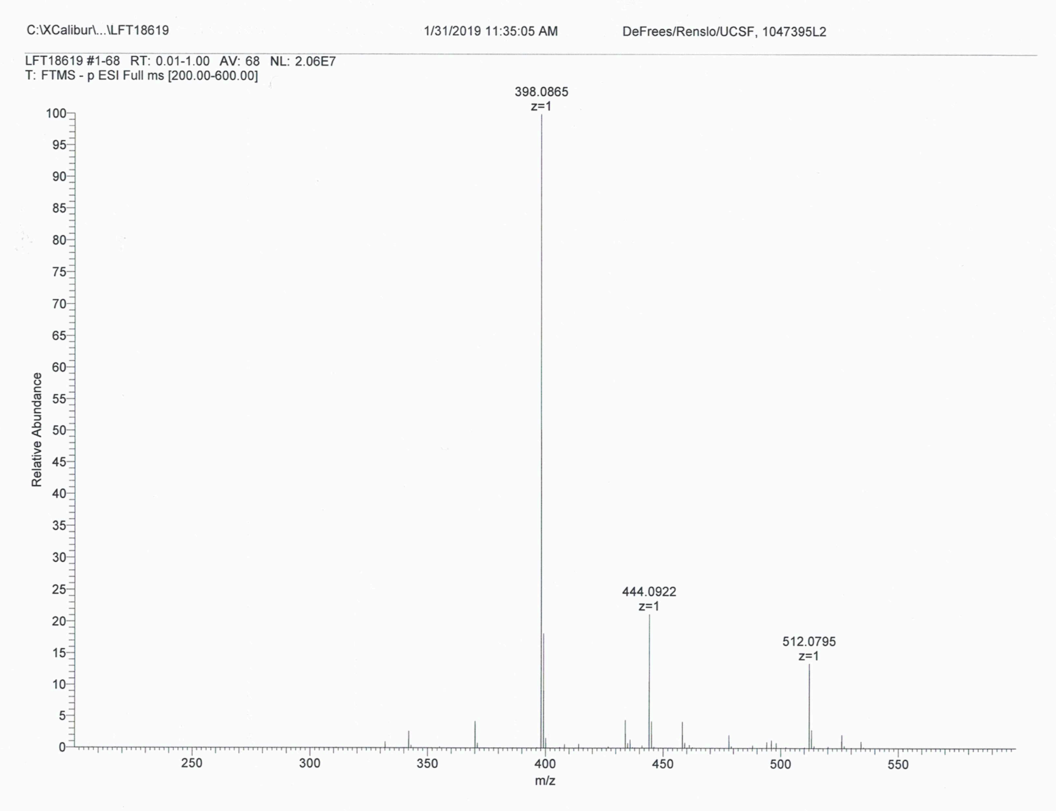

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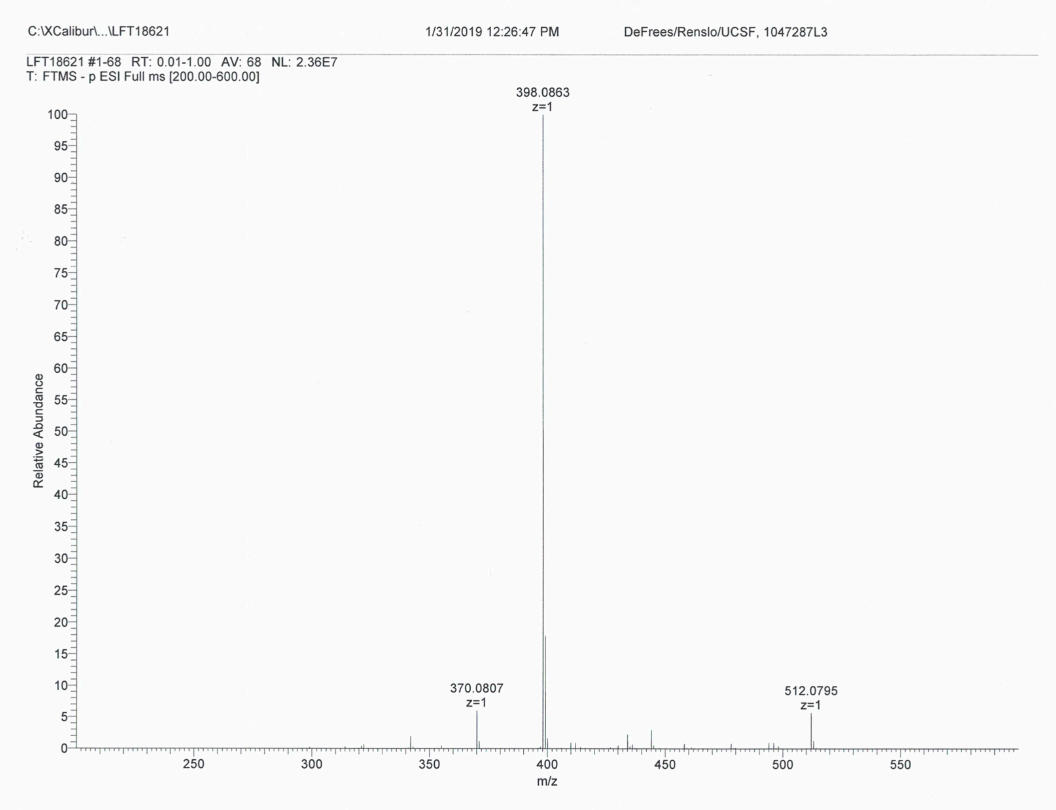

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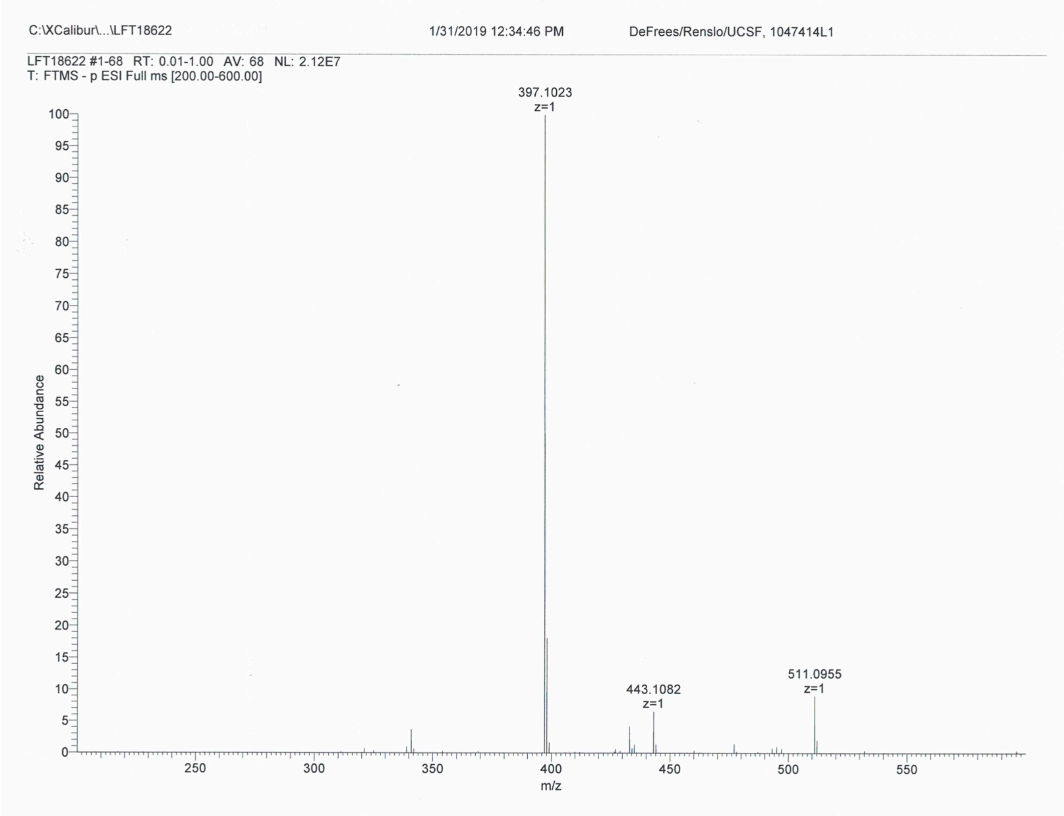

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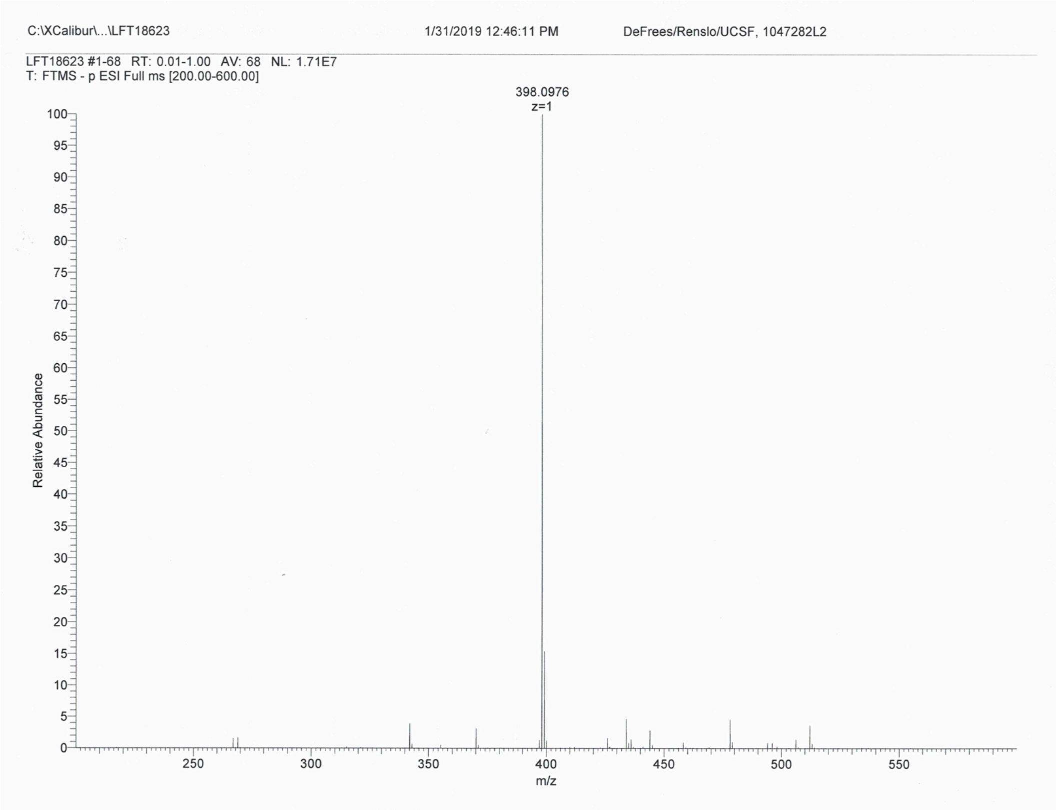

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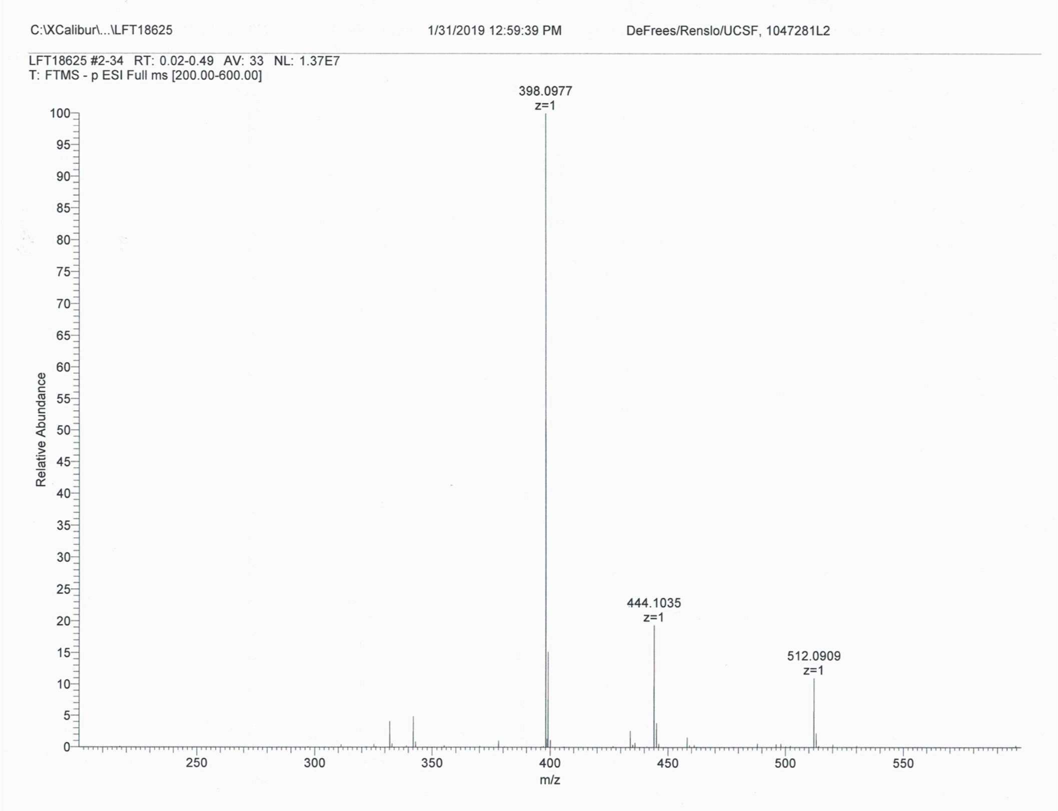

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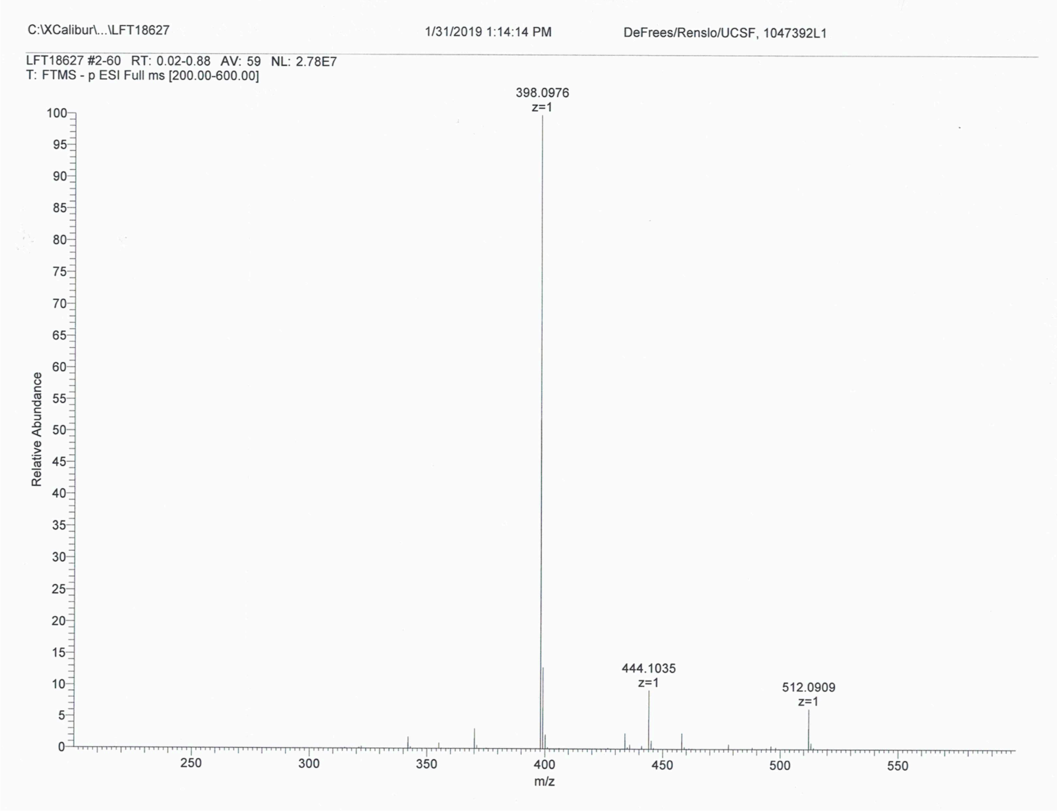

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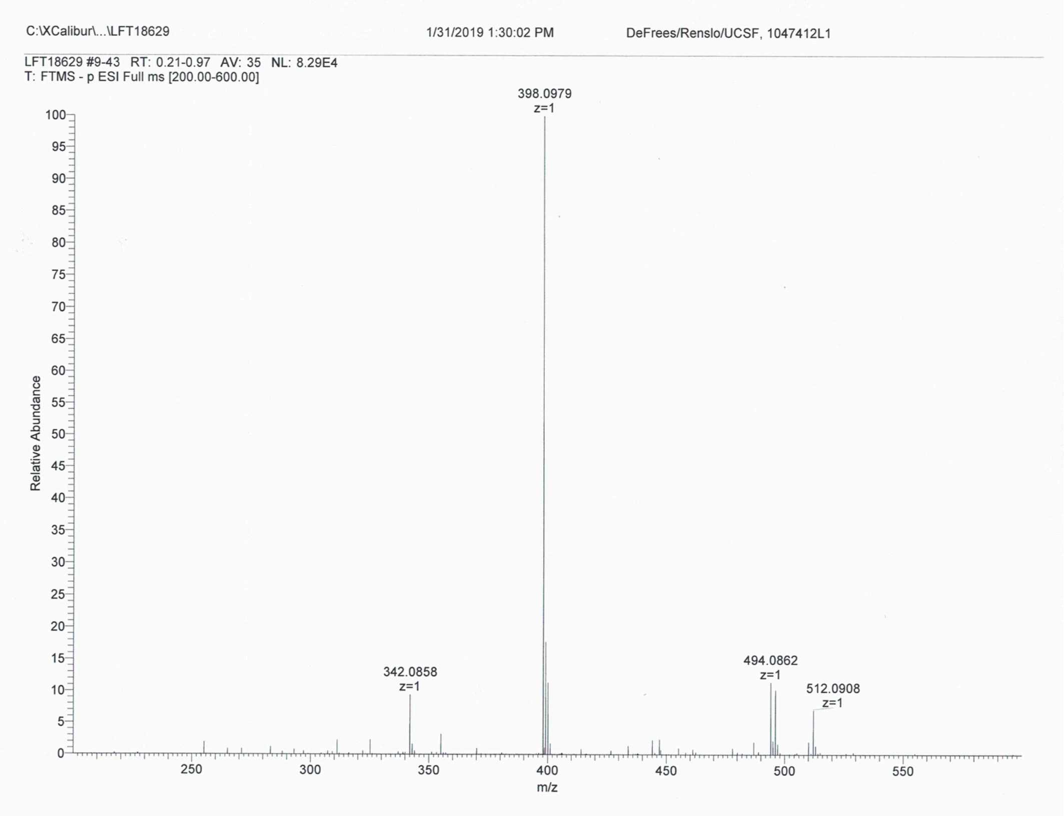

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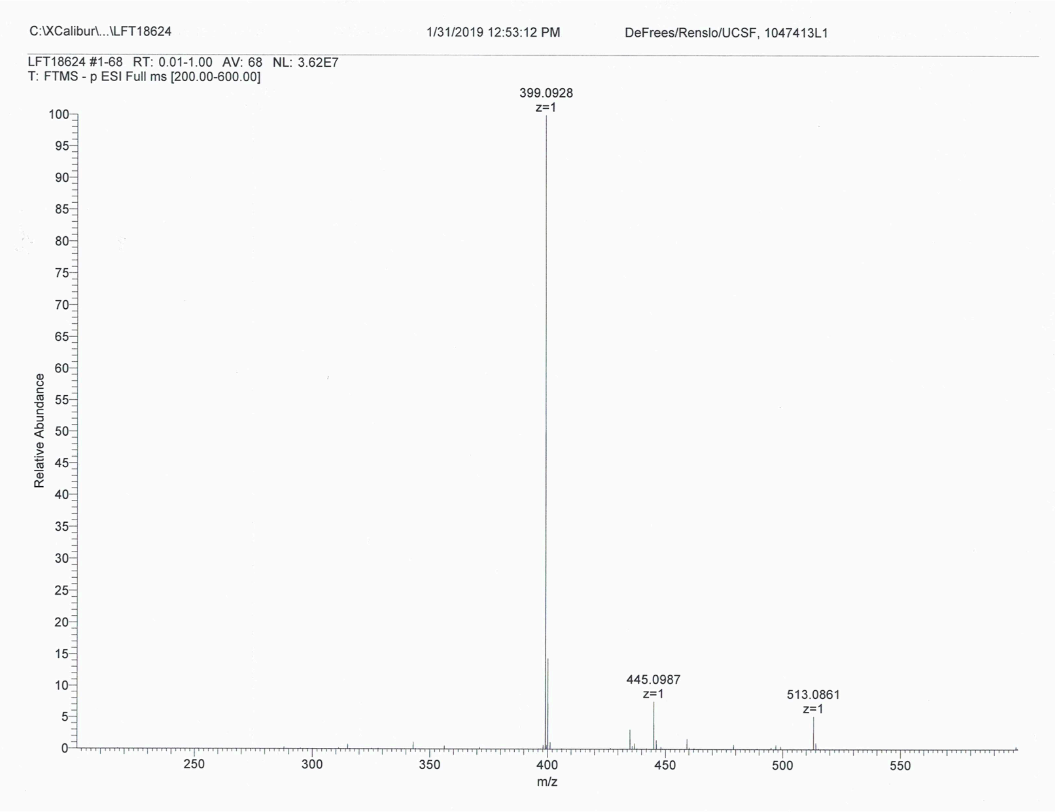

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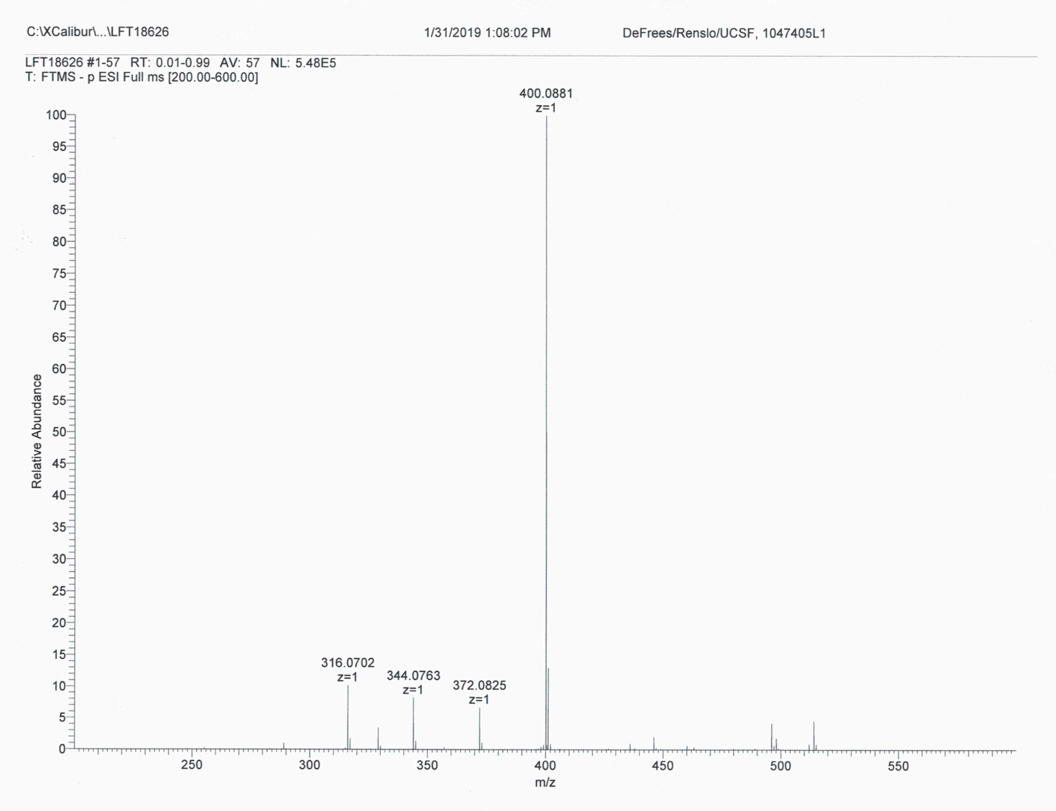

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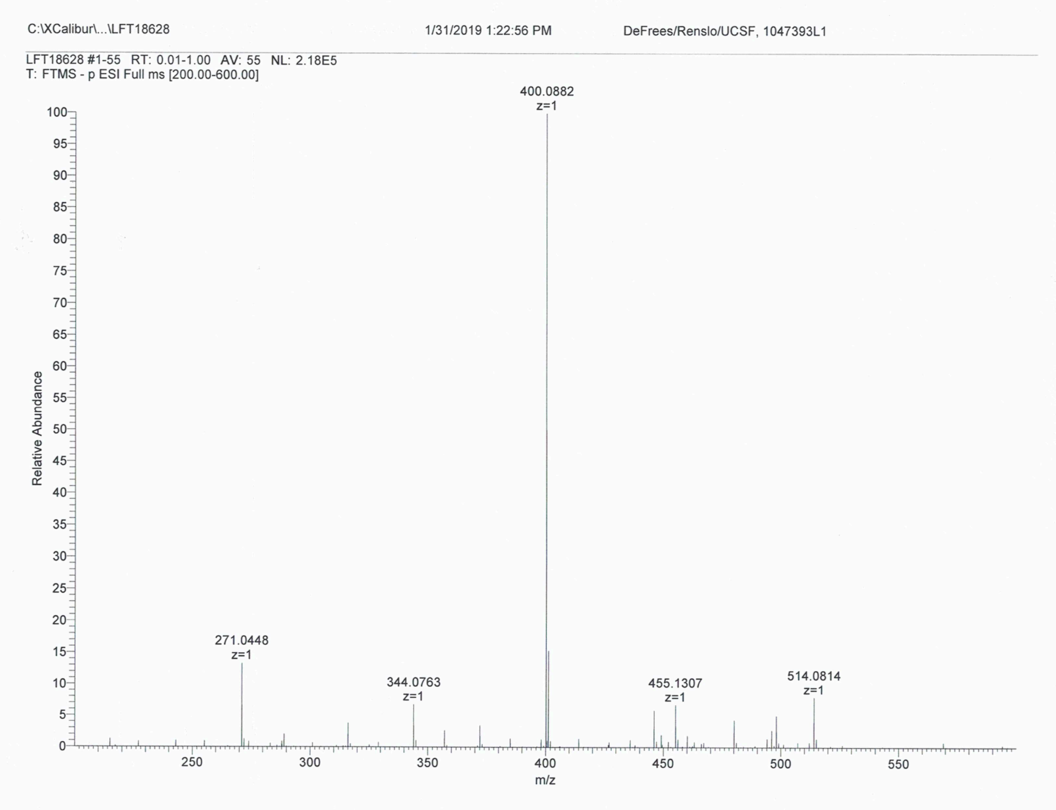
Compound 20:



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