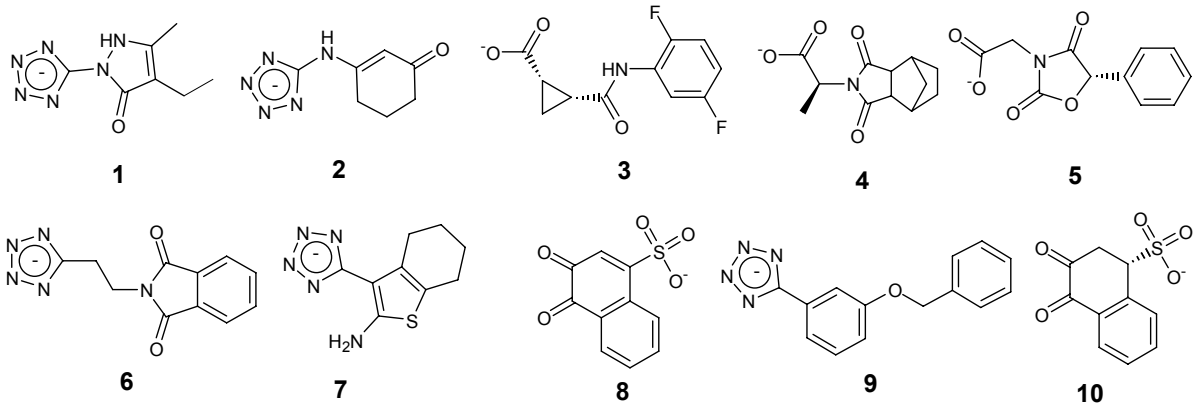
Supplementary Material

Molecular docking and ligand specificity in fragment-based inhibitor discovery

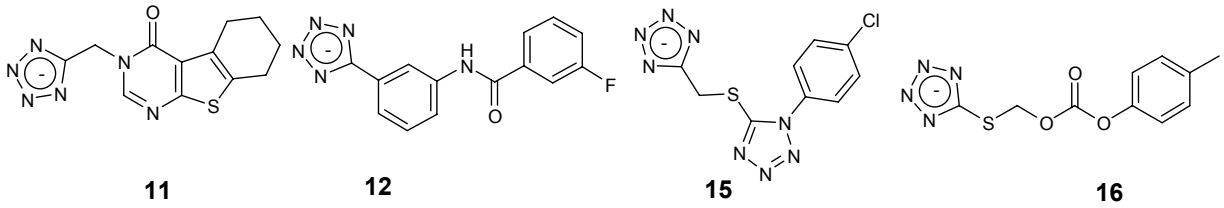
Chen & Shoichet

Nature Chemical Biology: doi:10.1038/nchembio.155

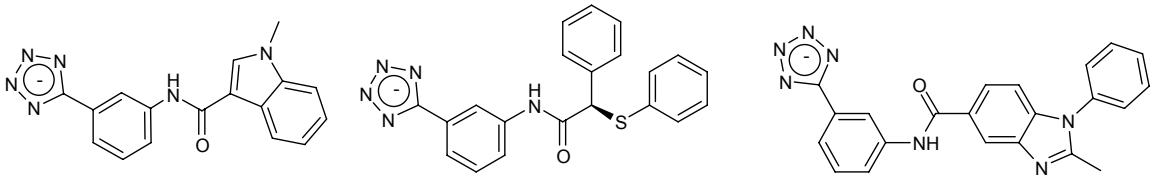


1 **2** **3** **4** **5**

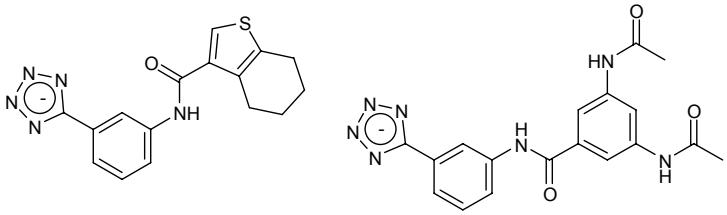
6 **7** **8** **9** **10** **(a)**



11 **12** **15** **16** **(b)**



13 **14** **17**



18 **19** **(c)**

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Figure S1 Inhibitors identified against CTX-M. K_i values were determined for compounds **1-4**, **6**, **11**, **12**, **13** and **14**, the first seven of which were also crystallized. (a) Fragment inhibitors identified by molecular docking. All had IC_{50} ~mM. Compounds **1**, **4**, **5** were also previously identified as inhibitors against AmpC. (b) Lead-like tetrazole compounds selected by molecular docking. Their Ki values ranged from mM to sub-mM with the best at 21 μM (compound **12**). (c) Analogs of the most potent tetrazole inhibitor from docking, identified by similarity search. All inhibited CTX-M at 250 μM and the best has Ki at 10 μM (compound **13**).

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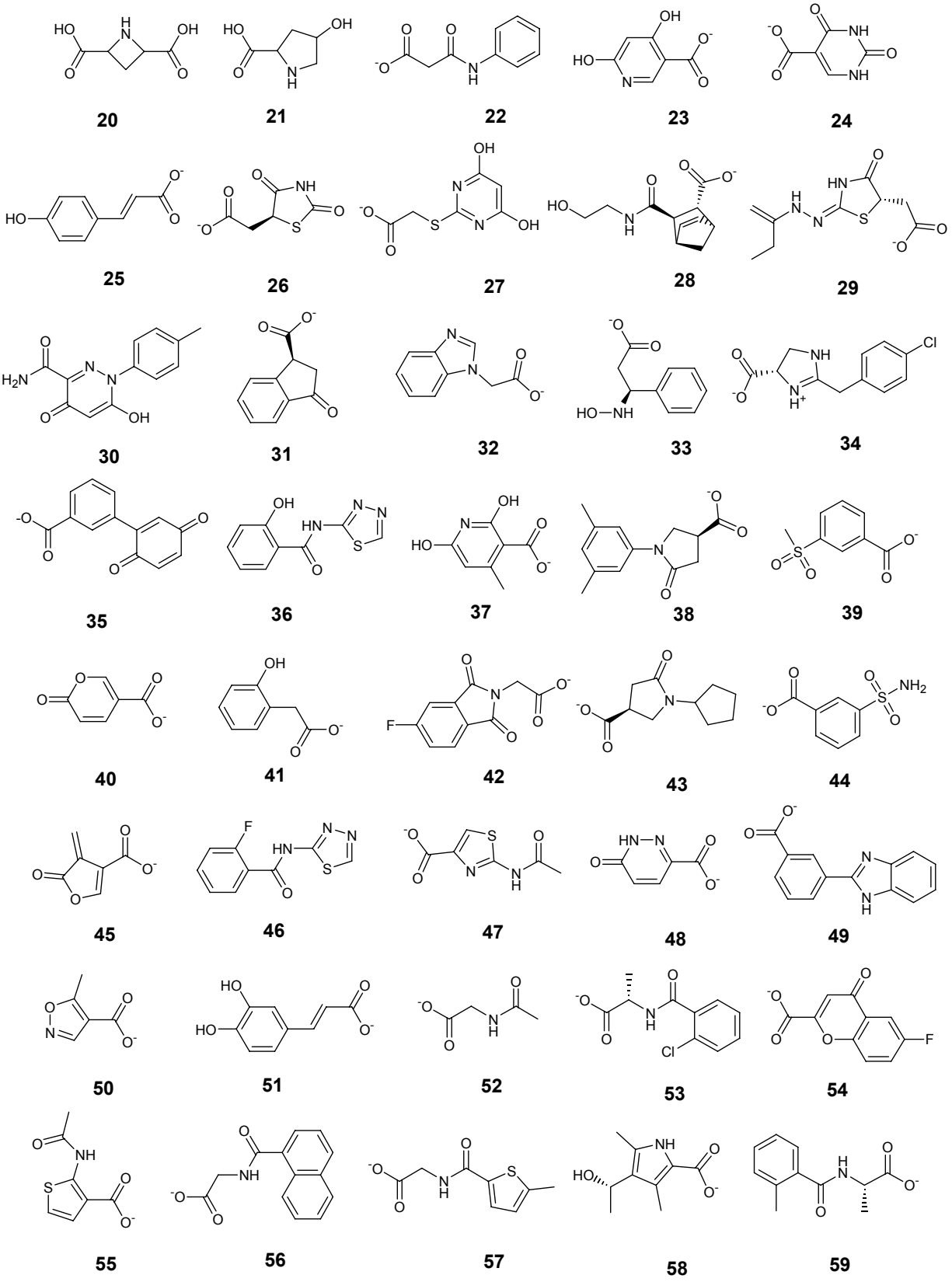

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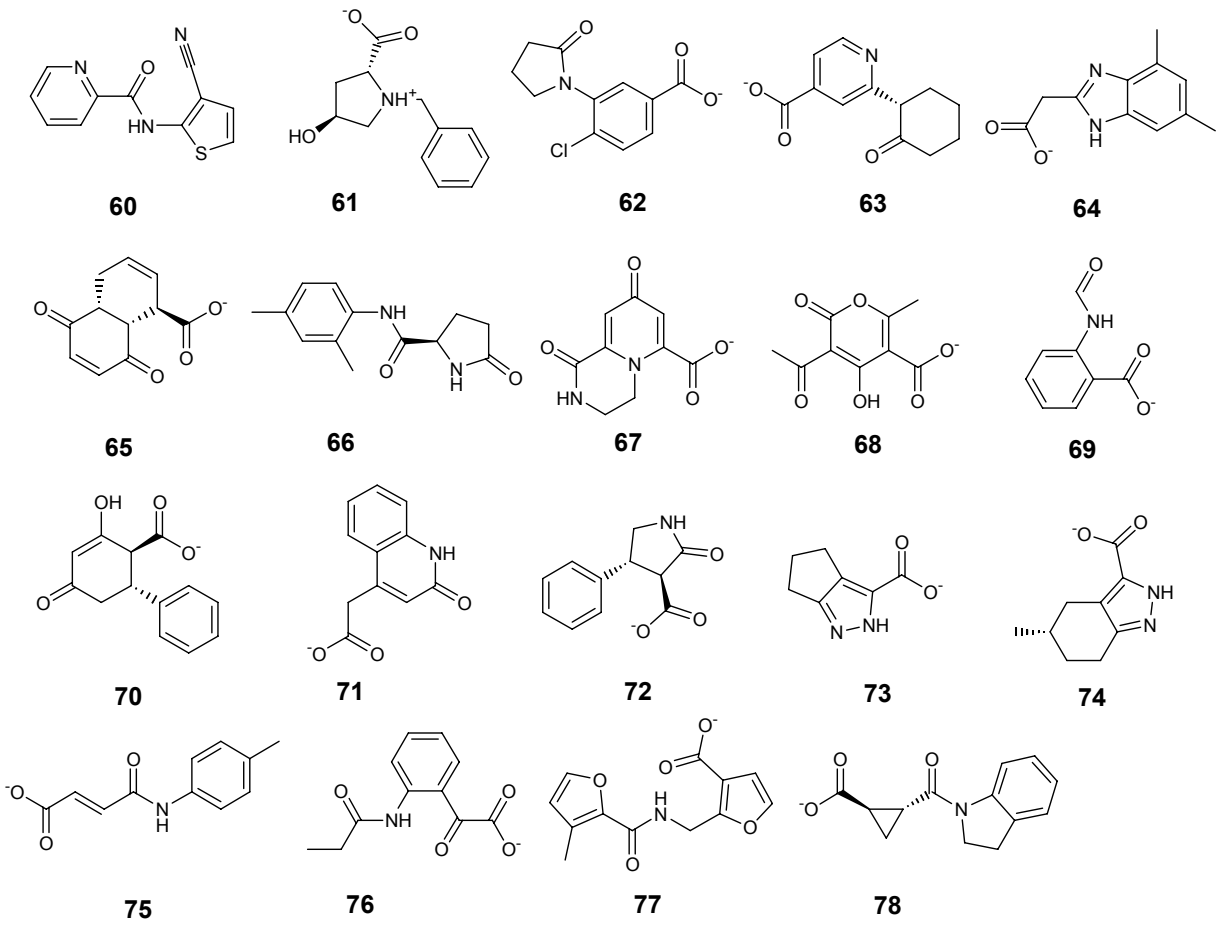

Figure S2 Non-binding fragments selected by docking. These compounds did not inhibit CTX-M when tested at up to 5 mM concentrations, or as their solubility allowed.

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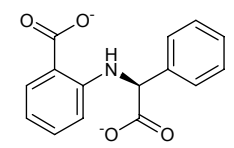

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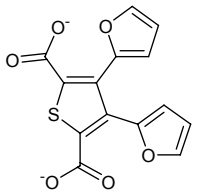

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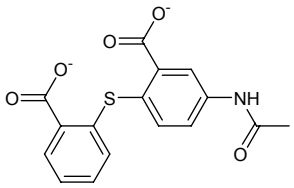

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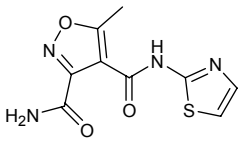

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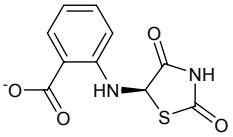

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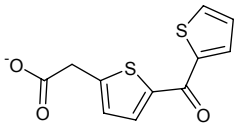

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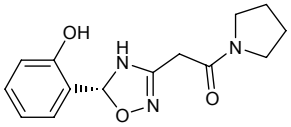

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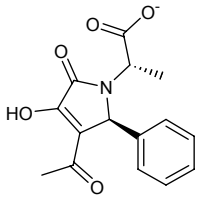

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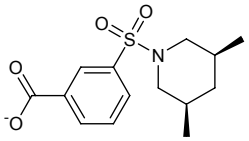

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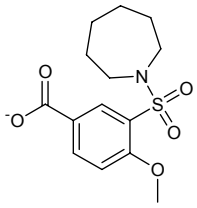

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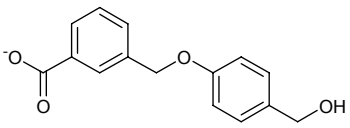

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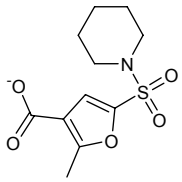

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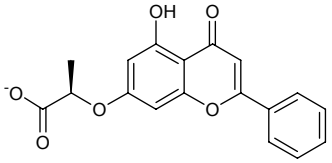

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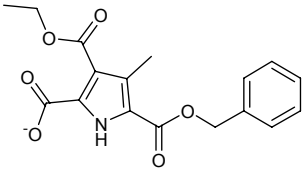

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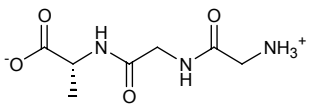

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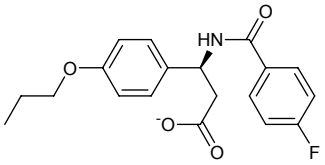

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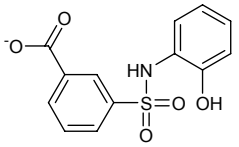

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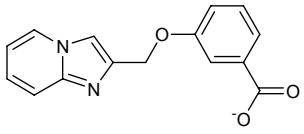

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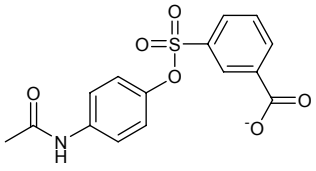

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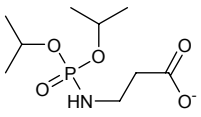

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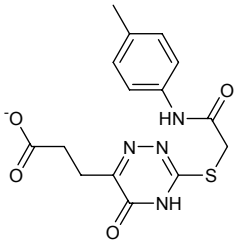

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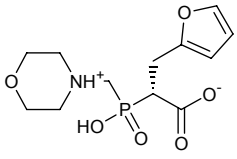

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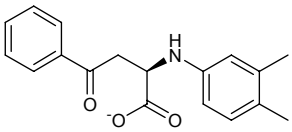

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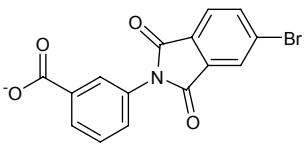

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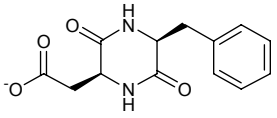

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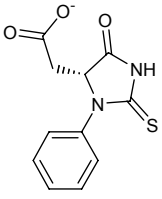

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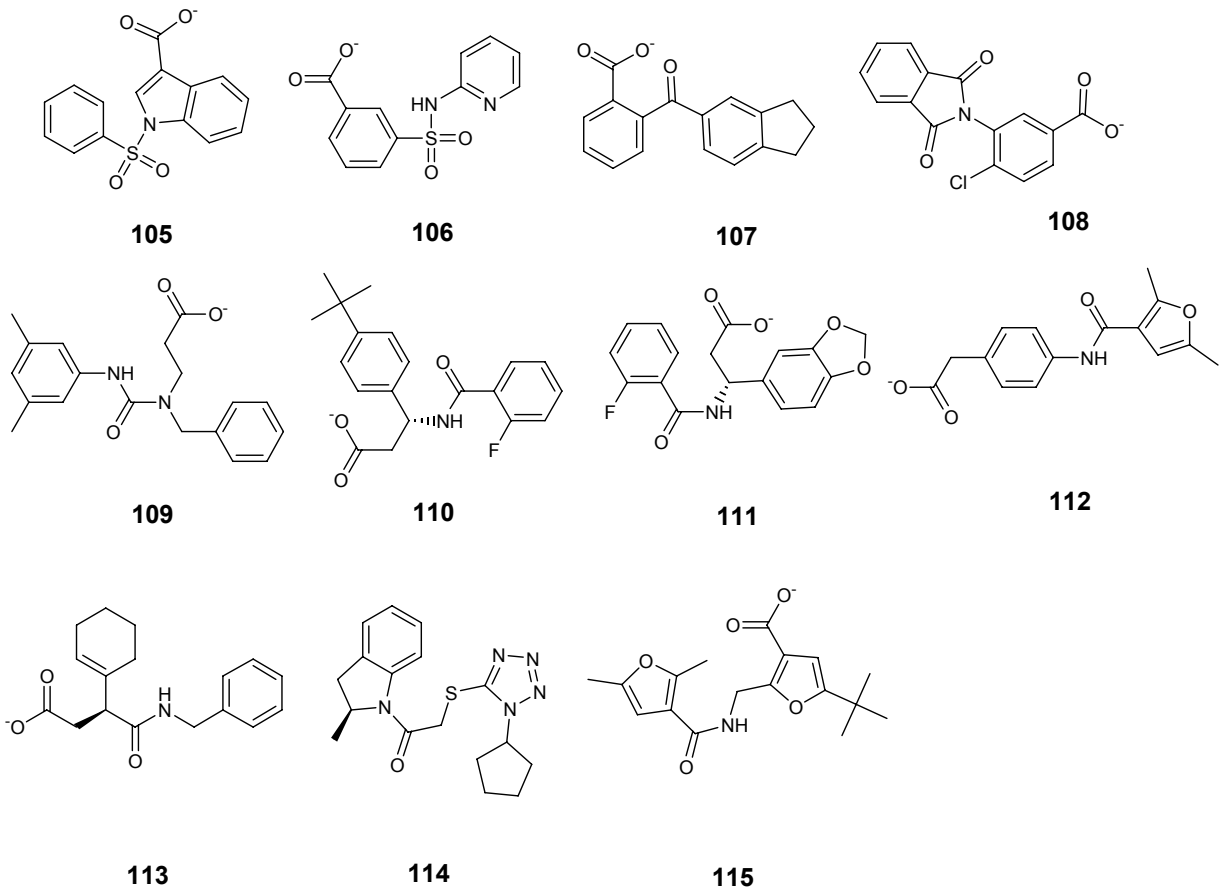

Figure S3 Non-binding lead-like compounds selected by docking. These compounds did not inhibit CTX-M when tested at up to 5 mM concentrations, or as their solubility allowed.

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Table S1 Fragment database compounds most similar to ligands

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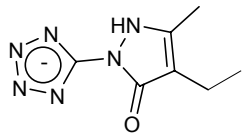
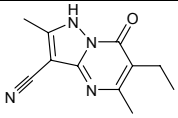
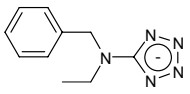
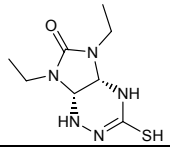
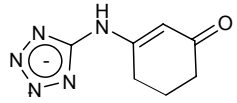
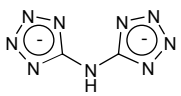
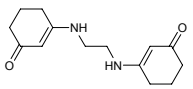
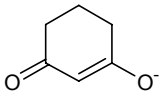
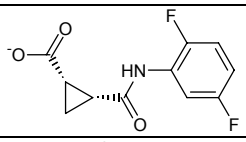
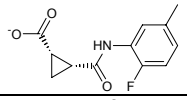
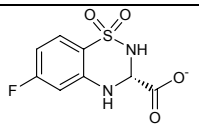
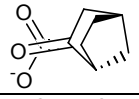
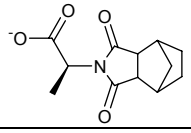
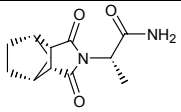
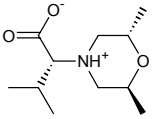
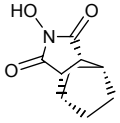
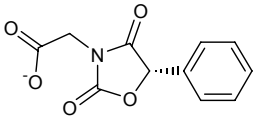
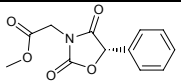
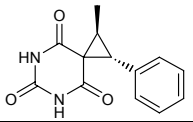
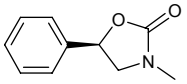
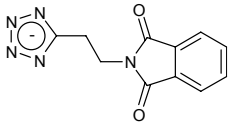
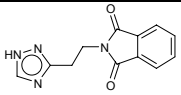
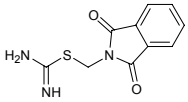
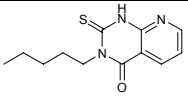
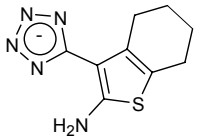
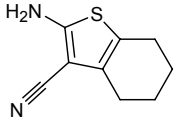
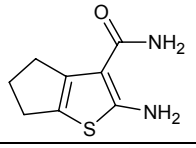
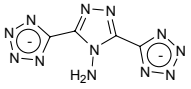
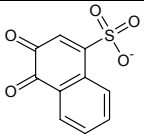
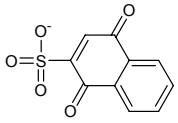
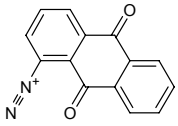
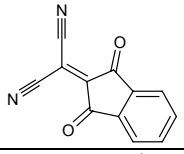
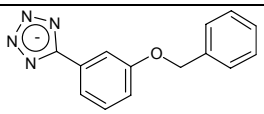
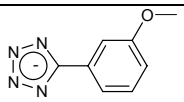
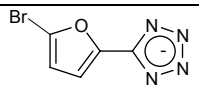
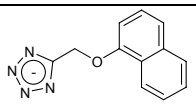
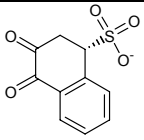
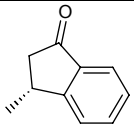
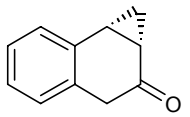
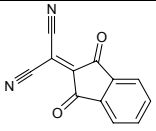
1			0.3878		0.3125		0.2449
2			0.4688		0.4324		0.3243
3			0.7500		0.3077		0.2889
4			0.7273		0.2857		0.4545
5			0.6829		0.2708		0.3636
6			0.4872		0.3571		0.2745
7			0.4250		0.3571		0.3250
8			0.7037		0.2973		0.3636
9			0.6250		0.2979		0.3600
10			0.4167		0.3077		0.3158

a. Latest fragment subset of ZINC database, 317,000 compounds.
b. The compounds that are the centers of the 2500 clusters from the fragment database.
c. The compounds randomly chosen from the 2500 clusters (one from each cluster).
d. Tanimoto similarity score between the ligand and the compound using ECFP-4 fingerprint.

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Table S2 Crystallographic statistics

Compound #	1	2	3	4	6	11	12
Data collection							
Space group	$P2_1$	$P2_1$	$P322_1$	$P2_1$	$P2_1$	$P2_1$	$P2_1$
Cell dimensions							
a, b, c (Å)	45.154 106.877 47.703	45.211 107.256 47.512	41.803 41.803 230.542	45.279 106.765 47.777	45.110 107.098 47.477	45.141 106.886 47.445	45.265 107.243 47.727
α, β, γ (°)	90.000 101.906 90.000	90.000 101.678 90.000	90.000 90.000 120.000	90.000 101.74 90.000	90.000 101.660 90.000	90.000 101.628 90.000	90.000 99.932 90.000
Resolution (Å)	50.0-1.31 (1.36-1.31)*	50.0 – 1.50 (1.55-1.50)	50.0 – 1.80 (1.86-1.80)	50-1.70 (1.76-1.70)	50.0-1.31 (1.36-1.31)	50.0-1.31 (1.36-1.31)	50.0 – 1.41 (1.46-1.41)
R_{merge} (%)	5.1 (21.2)	4.6 (34.5)	5.6 (57.1)	7.7 (34.1)	5.1 (27.1)	4.7 (24.9)	4.4 (30.0)
$I / \sigma I$	11.3(2.9)	15.0 (2.0)	20.7 (2.0)	10.8 (2.4)	20.6 (4.0)	22.6 (5.1)	16.7 (2.6)
Completeness(%)	91.6 (96.7)	98.3 (93.5)	99.7 (98.5)	98.6 (87.1)	99.4 (98.3)	99.9 (99.9)	98.6 (94.0)
Redundancy	1.8 (1.7)	2.5 (2.0)	7.4 (5.9)	3.5 (2.9)	3.9 (3.7)	3.9 (3.6)	2.5 (2.2)
Refinement							
Resolution (Å)	50.0-1.31 (1.36-1.31)	50.0-1.50 (1.55-1.50)	50.0-1.80 (1.86-1.80)	50.0-1.70 (1.76-1.70)	50.0-1.31 (1.36-1.31)	50.0-1.31 (1.36-1.31)	50.0-1.41 (1.46-1.41)
No. reflections	96597 (10197)	69190 (6567)	22803 (2167)	48236 (4241)	104717(10346)	106059(10591)	84588 (8057)
R_{work}/R_{free}	16.1 / 18.8	15.1/ 18.8	20.8 / 24.5	16.8 / 20.3	15.2 / 18.2	15.5 (18.0)	15.5 / 18.2
No. atoms							
Protein	4057	3989	1997	3952	4064	4051	3996
Ligand/ion	40	54	51	107	83	102	134
Water	613	576	157	356	677	652	607
B-factors (Å^2)							
Protein	11.39	16.90	24.25	14.71	11.96	11.14	14.52
Ligand/ion	23.68	22.50	35.41	27.33	20.83	16.73	25.36
Water	23.25	30.95	33.12	23.13	26.33	24.65	30.11
r.m.s. deviations							
bond lengths (Å)	0.007	0.008	0.017	0.012	0.006	0.006	0.007
bond angles (°)	1.385	1.277	1.697	1.668	1.393	1.325	1.164

* Values in parenthesis represent highest resolution shells.

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