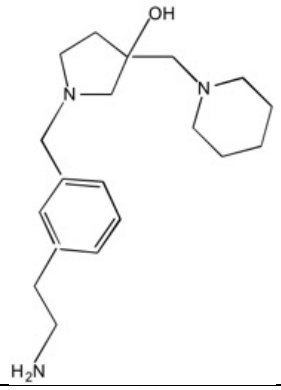
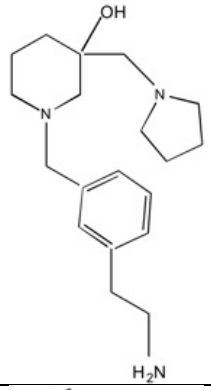
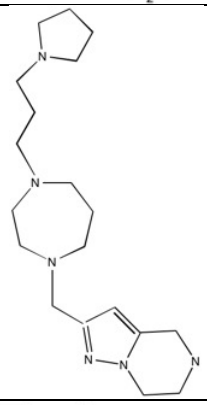
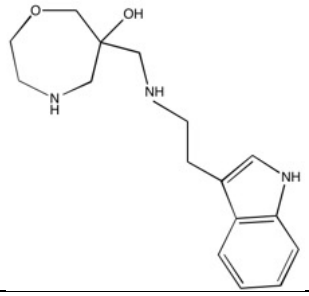
Electronic Supplementary Material (ESI) for MedChemComm.

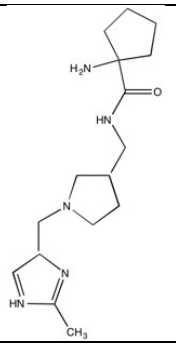
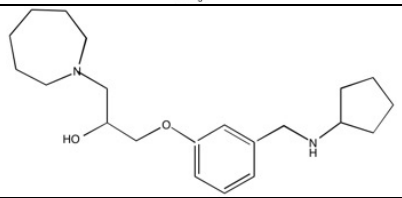
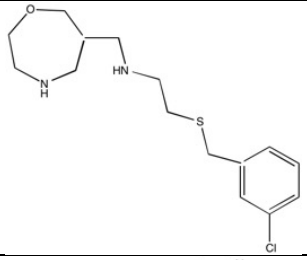
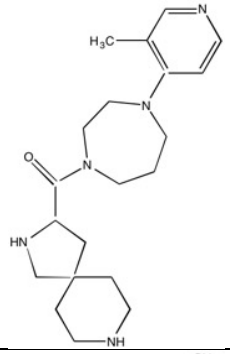
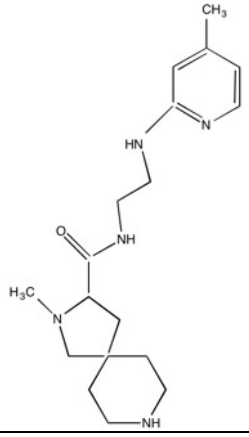
Supplementary Information

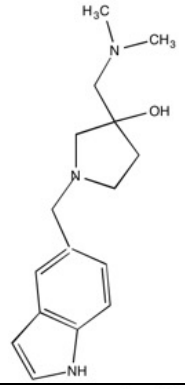
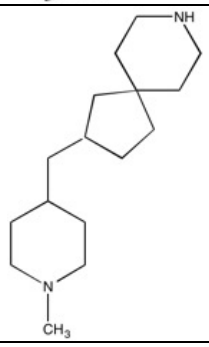
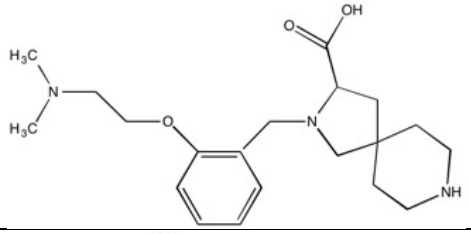
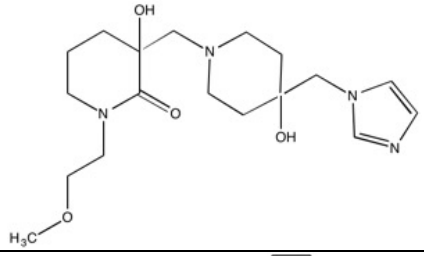
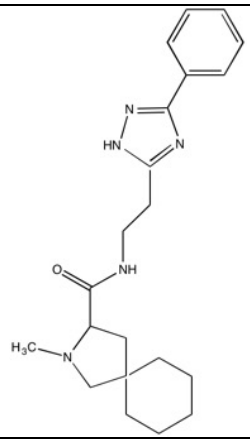
Identification of an Inhibitor of the Aminoglycoside 6'-*N*-Acetyltransferase type Ib [AAC(6')-Ib] by Glide Molecular Docking

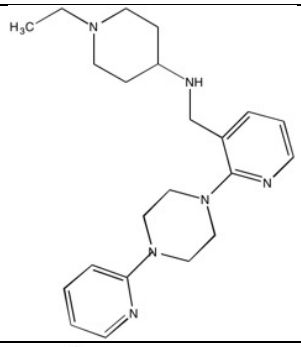
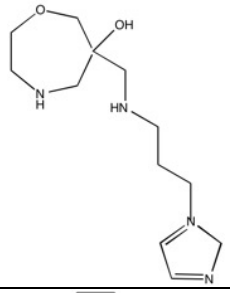
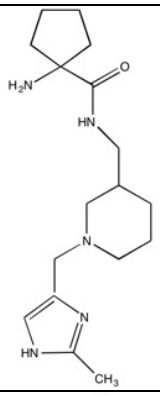
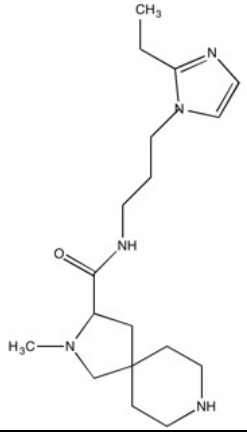
Kevin Chiem, Saumya Jani, Brooke Fuentes, David L. Lin, Madeline E. Rasche, and Marcelo E. Tolmasky*

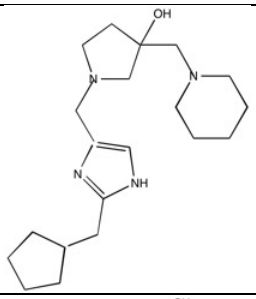
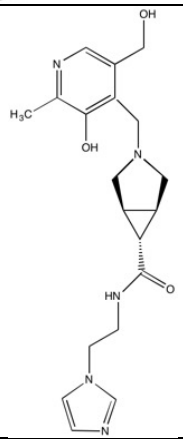
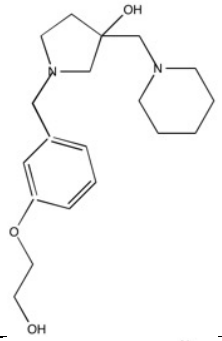
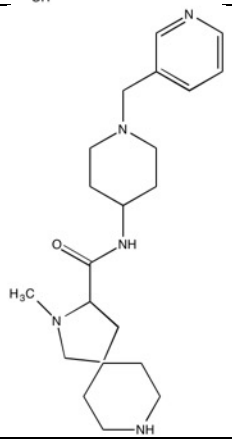
Table S1. Compounds tested as inhibitors of AAC(6')-Ib

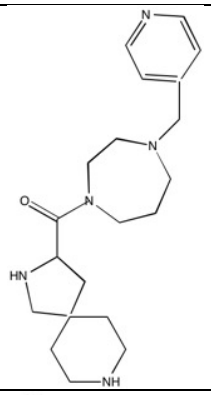
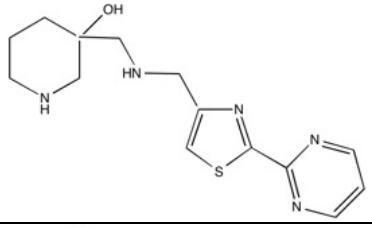
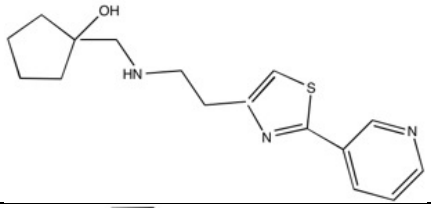
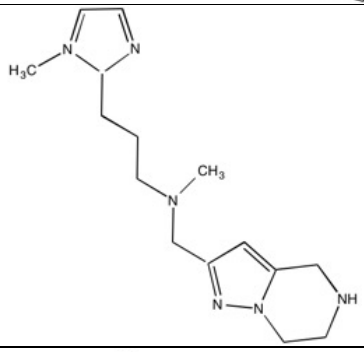
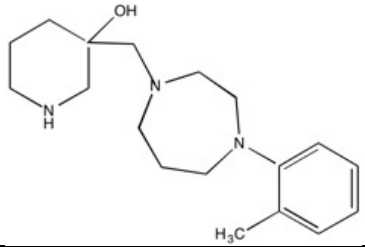
ChemBridge ID[1]	Structure	Percent Inhibition of Acetylation Reaction[2]
22896979 Compound **1**		100.0 ± 1.73
93879050		59.68 ± 1.35
30329891		53.27 ± 5.86
94589519		48.47 ± 1.06

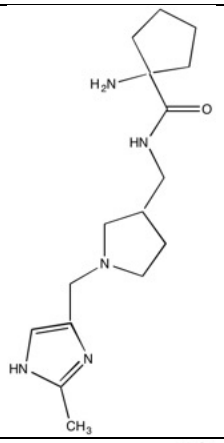
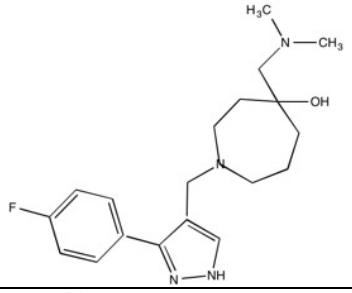
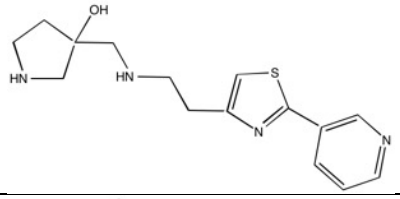
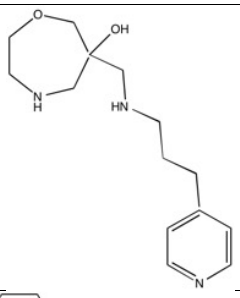
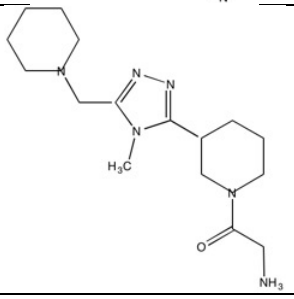
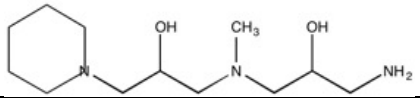
90848357		41.98 ± 2.58
91616357		40.18 ± 3.98
80407791		39.33 ± 2.46
59279450		38.68 ± 2.86
61069326		37.90 ± 6.95

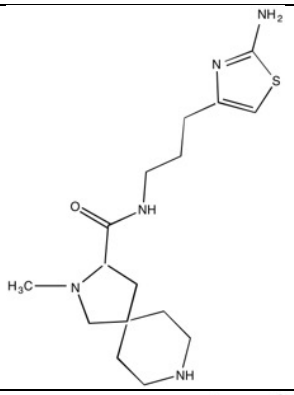
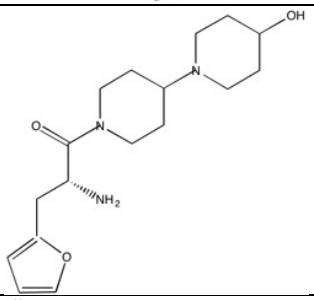
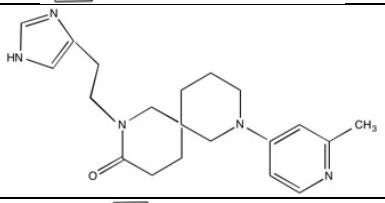
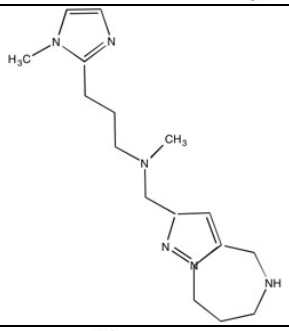
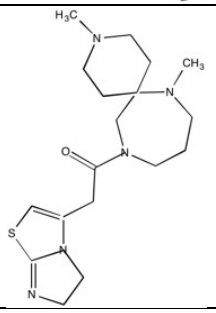
20695937		37.07 ± 1.89
99389828		31.47 ± 1.81
20754978		27.65 ± 0.73
57652128		27.45 ± 2.68
71823596		25.89 ± 2.45

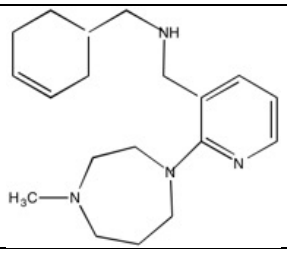
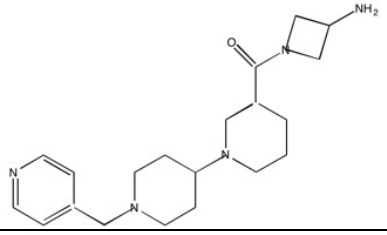
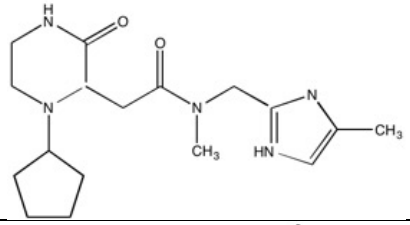
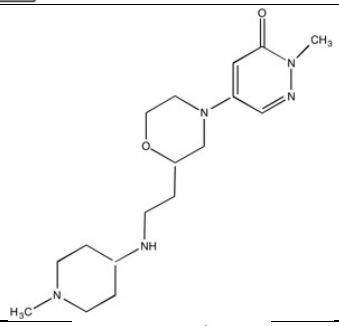
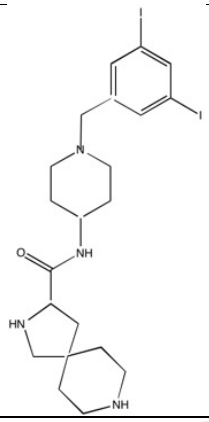
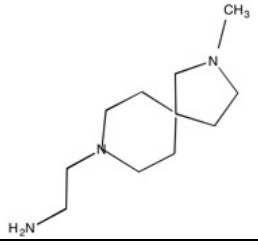
52928134		25.53 ± 0.67
88103368		25.26 ± 1.43
85613854		24.00 ± 2.84
60814121		21.07 ± 1.76

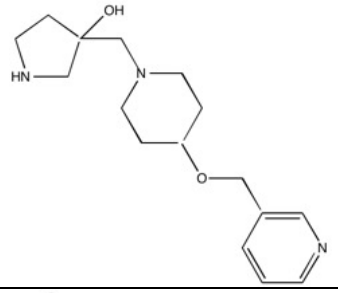
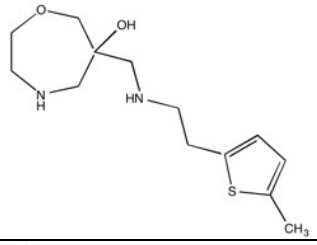
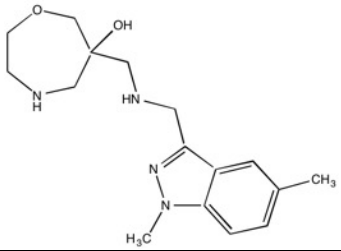
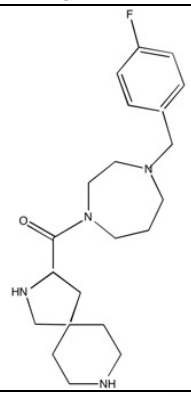
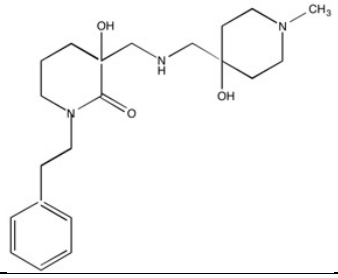
83925201		20.74 ± 0.55
56116028		20.60 ± 3.04
40816753		17.96 ± 1.71
15619196		17.35 ± 2.52

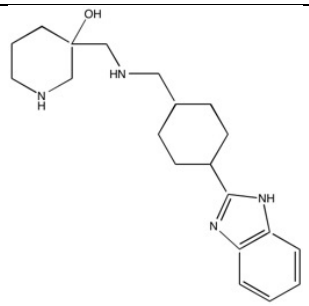
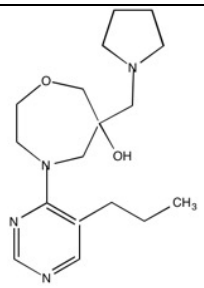
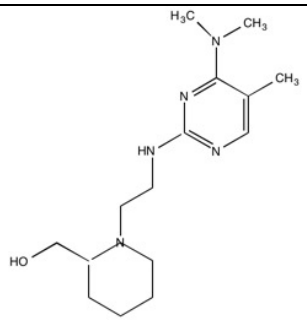
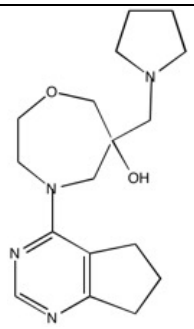
68367909		16.97 ± 1.9
98693459		16.84 ± 0.58
44543373		16.58 ± 1.85
73081811		15.56 ± 2.63
83823695		14.83 ± 1.55

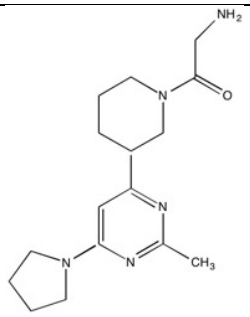
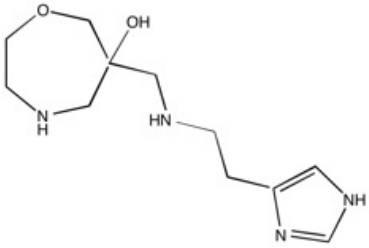
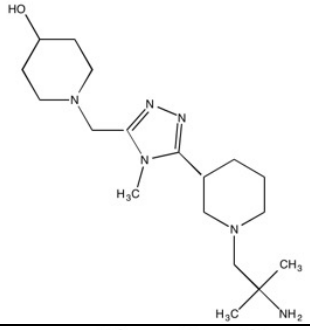
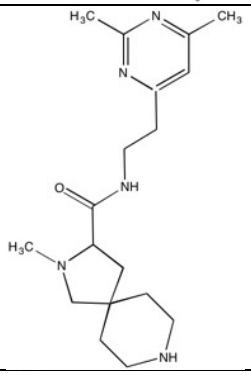
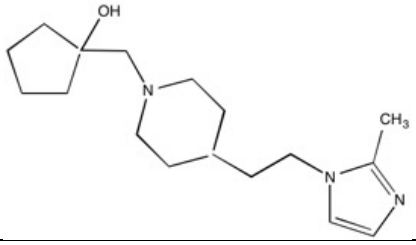
90848357		14.58 ± 2.22
83753367		14.41 ± 4.90
44543373		13.15 ± 1.88
57810593		13.15 ± 1.8
40375225		13.03 ± 1.89
5182367		11.62 ± 2.38

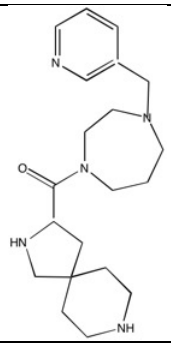
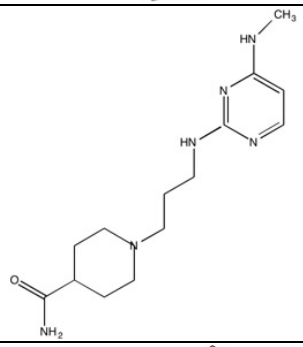
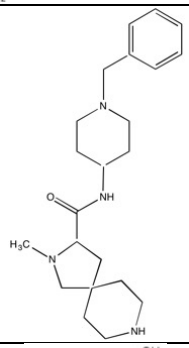
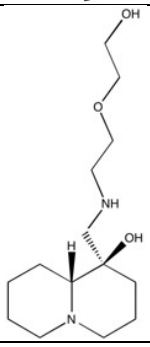
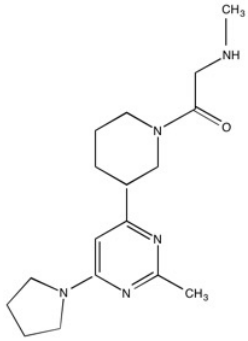
29912354		11.57 ± 2.33
46016366		11.44 ± 2.04
94559063		11.35 ± 2.92
26465522		10.56 ± 2.84
21841095		9.07 ± 3.67

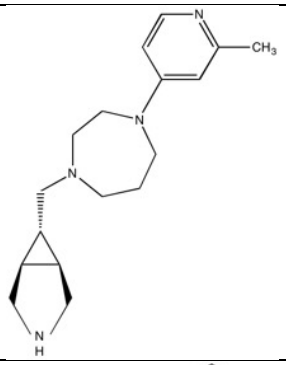
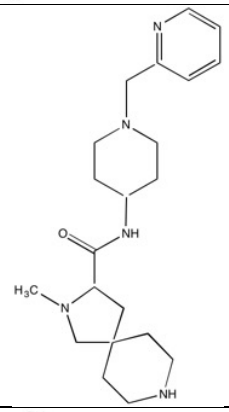
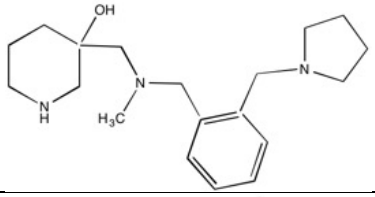
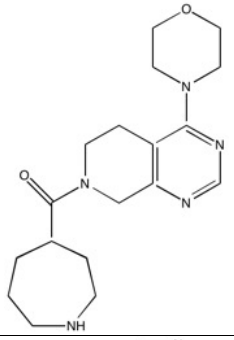
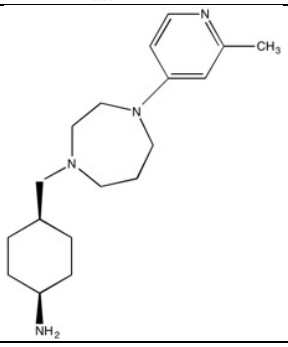
13504400		8.95 ± 9.44
34704411		8.43 ± 1.39
30260789		7.92 ± 0.56
23298740		7.55 ± 0.91
13596131		7.27 ± 1.71
97289196		6.66 ± 2.57

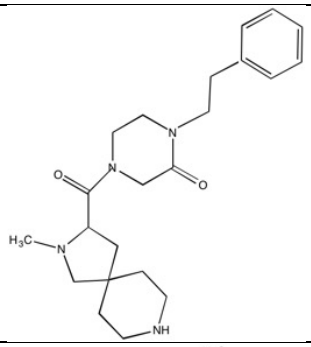
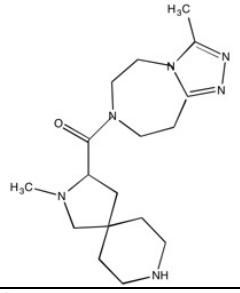
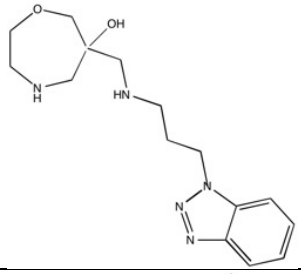
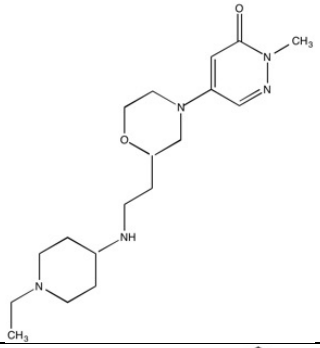
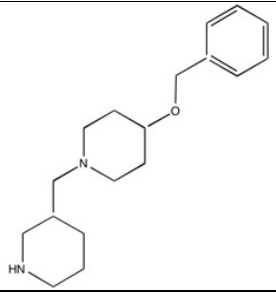
28907079		6.42 ± 1.50
98119603		5.43 ± 2.18
29374672		4.86 ± 1.84
80706220		2.88 ± 8.04
75327975		2.05 ± 2.23

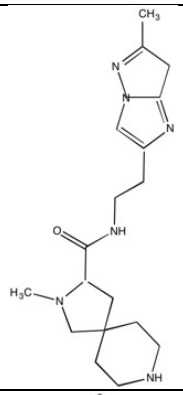
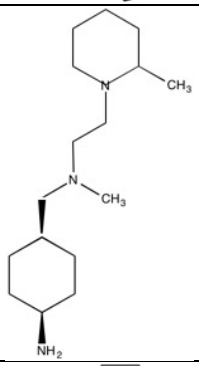
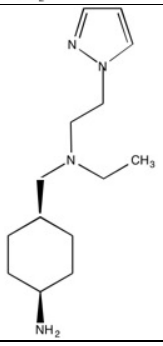
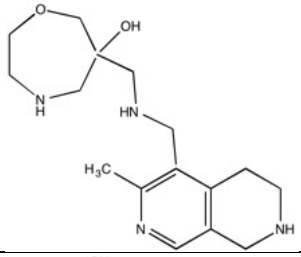
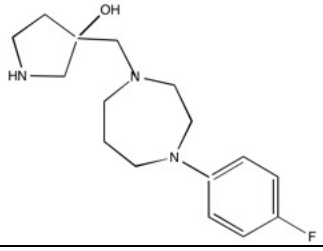
21332802		1.69 ± 3.00
96600577		1.38 ± 1.41
23199679		0.98 ± 1.98
55859094		0.78 ± 3.06

56259057		0.74 ± 2.29
86130383		0.55 ± 4.00
98321509		0.54 ± 1.70
79606218		0.28 ± 4.22
30328021		0.18 ± 3.62

37121052		0.04 ± 5.75
86144845		0.00 ± 4.58
28440084		0.00 ± 4.31
45784601		0.00 ± 1.25
73942197		0.00 ± 3.25

15596574		0.00 ± 6.82
48828171		0.00 ± 6.88
83388228		0.00 ± 0.59
62708991		0.00 ± 7.11
70246546		0.00 ± 3.88

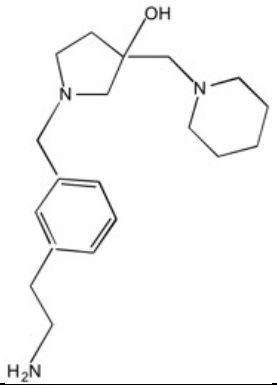
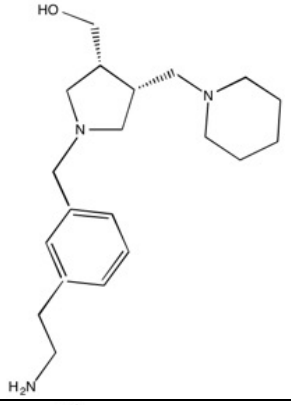
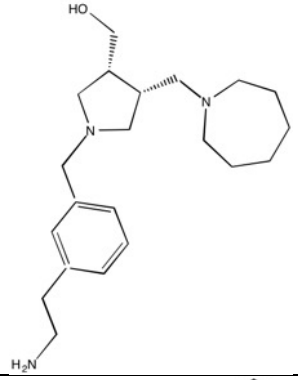
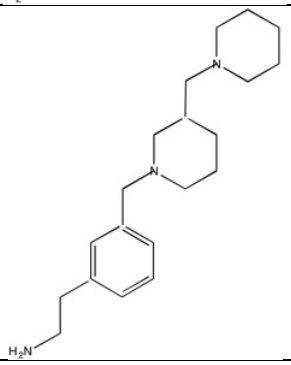
24594899		0.00 ± 6.27
31426510		0.00 ± 1.12
15871409		0.00 ± 3.35
54229610		0.00 ± 5.81
86817668		0.00 ± 4.09

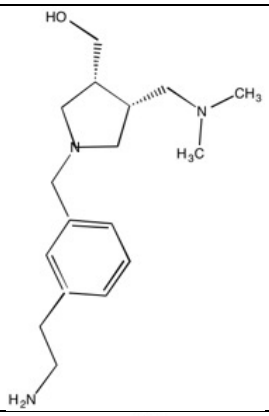
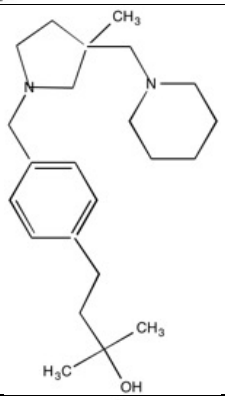
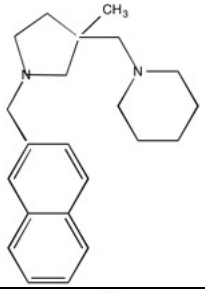
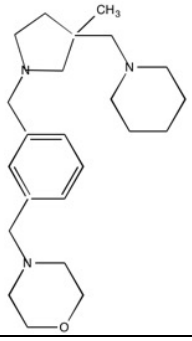
28982681		0.00 ± 4.64
52459795		0.00 ± 1.23
19263094		0.00 ± 4.83
70239608		0.00 ± 3.84
24752274		0.00 ± 5.95

[1]Numbering from ChemBridge Corporation.

[2]The percent inhibition is the decrease in the rate of acetylation when the enzymatic activity was determined in the presence of 150 μM acetyl CoA, 18 μM kanamycin A, and 500 μM compound.

Table S2. Analogs (80% similarity to compound 1) tested as inhibitors of AAC(6')-Ib

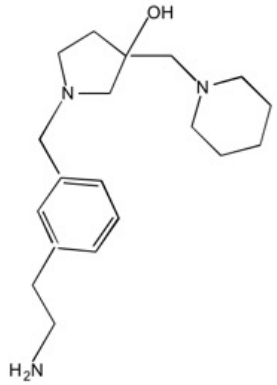
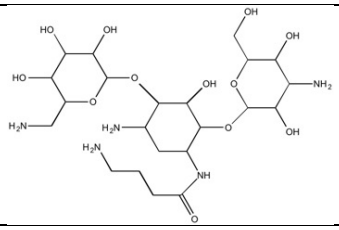
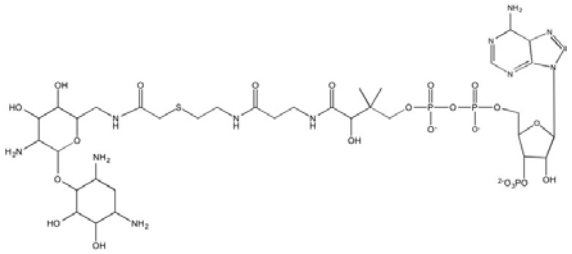
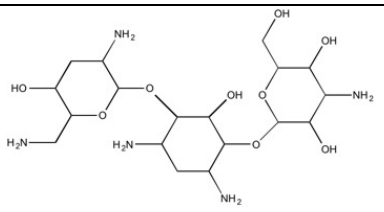
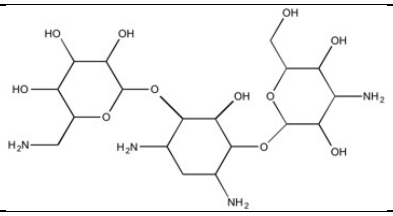
ChemBridge ID[1]	Structure	Percent Inhibition[3]
22896979 Compound **1**		100.0 ± 1.73
26834434		54.48 ± 1.53
65562247		54.04 ± 3.25
86601631		50.23 ± 0.23

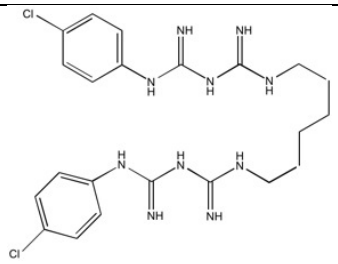
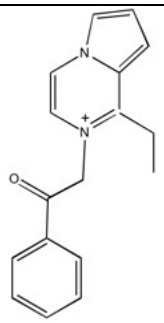
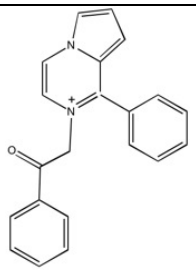
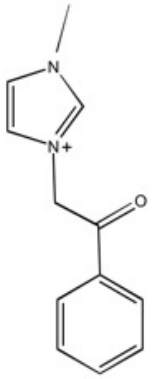
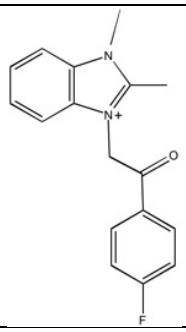
40006174		34.52 ± 1.92
53766828		27.80 ± 4.94
42328479		17.87 ± 1.95
41901671		15.47 ± 1.52

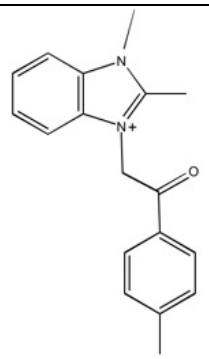
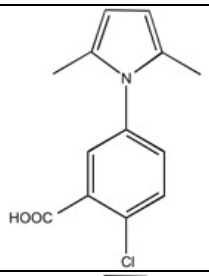
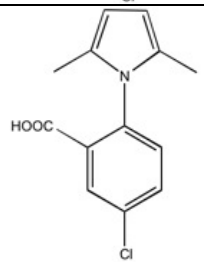
[1]Numbering from ChemBridge Corporation.

[2]The percent inhibition is the decrease in the rate of acetylation when the enzymatic activity was determined in the presence of 150 μM acetyl CoA, 18 μM kanamycin A, and 500 μM compound.

Table S3. Extra precision Glide docking of selected previously described inhibitors of aminoglycoside acetyltransferases

Compound	Structure	Glide XP GScore[1]
Compound **1**		-11.29
Amikacin		-15.51
Aminoglycoside-coenzyme A Bisubstrate[1]		-13.70
Tobramycin		-12.50
Kanamycin A		-12.47

Chlorhexidine[2]		-10.98
Compound 5[2]		-7.98
Compound 4[2]		-7.83
Compound 14[2]		-7.38
Compound 15[2]		-6.93

Compound 16[2]		-6.12
Compound 28[2]		-3.13
Compound 27[2]		-2.97

Compounds are ordered by decreasing binding affinity with the exception of compound **1** which is shown at the top.
Compounds are named as in the original articles.

References

1. F. Gao, X. Yan, T. Shakya, O. M. Baettig, S. Ait-Mohand-Brunet, A. M. Berghuis, G. D. Wright and K. Auclair, *J. Med. Chem.*, 2006, **49**, 5273-5281.
2. K. D. Green, W. Chen and S. Garneau-Tsodikova, *ChemMedChem*, 2012, **7**, 73-77.