Bisubstrate Inhibitors to Target Histone Acetyltransferase 1 (HAT1)

Liza Ngo, Tyler Brown, Y. George Zheng *

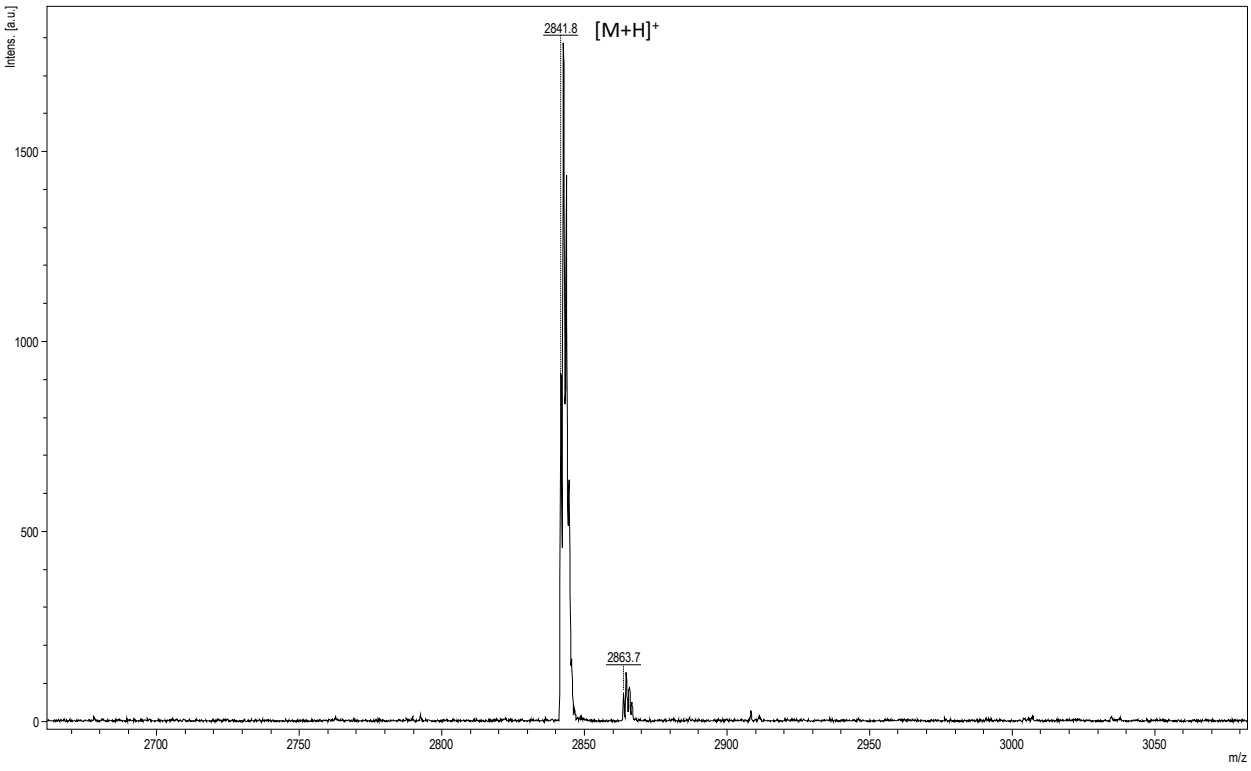
Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy, University of Georgia, Athens, Georgia, 30302, U.S.A.

* To whom correspondence should be addressed: yzheng@uga.edu.

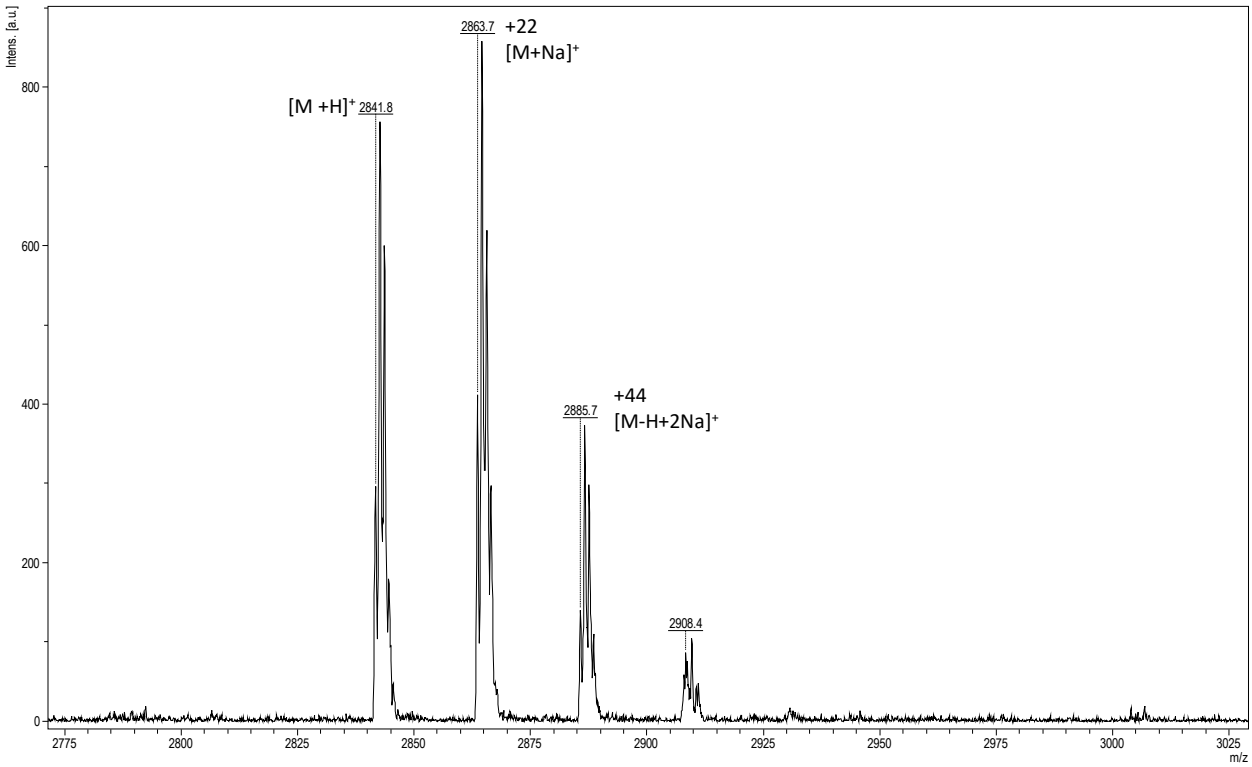
Supporting Information

Figure S1: MALDI-MS spectra of bisubstrate inhibitors. The identities of all the peptides were analyzed via matrix assisted laser desorption/ionization mass spectrometry (MALDI-MS) on the Bruker Daltonics, model Autoflex with a 0.02% error.

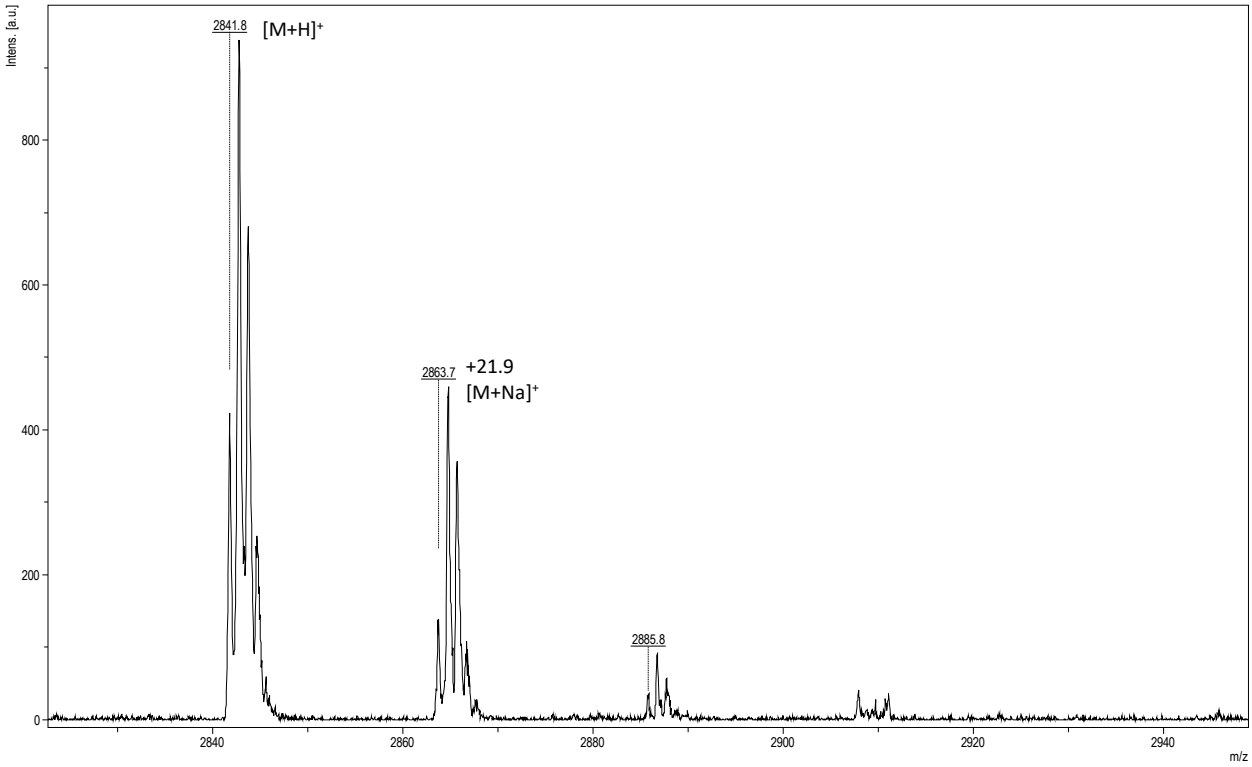
H4K5CoA



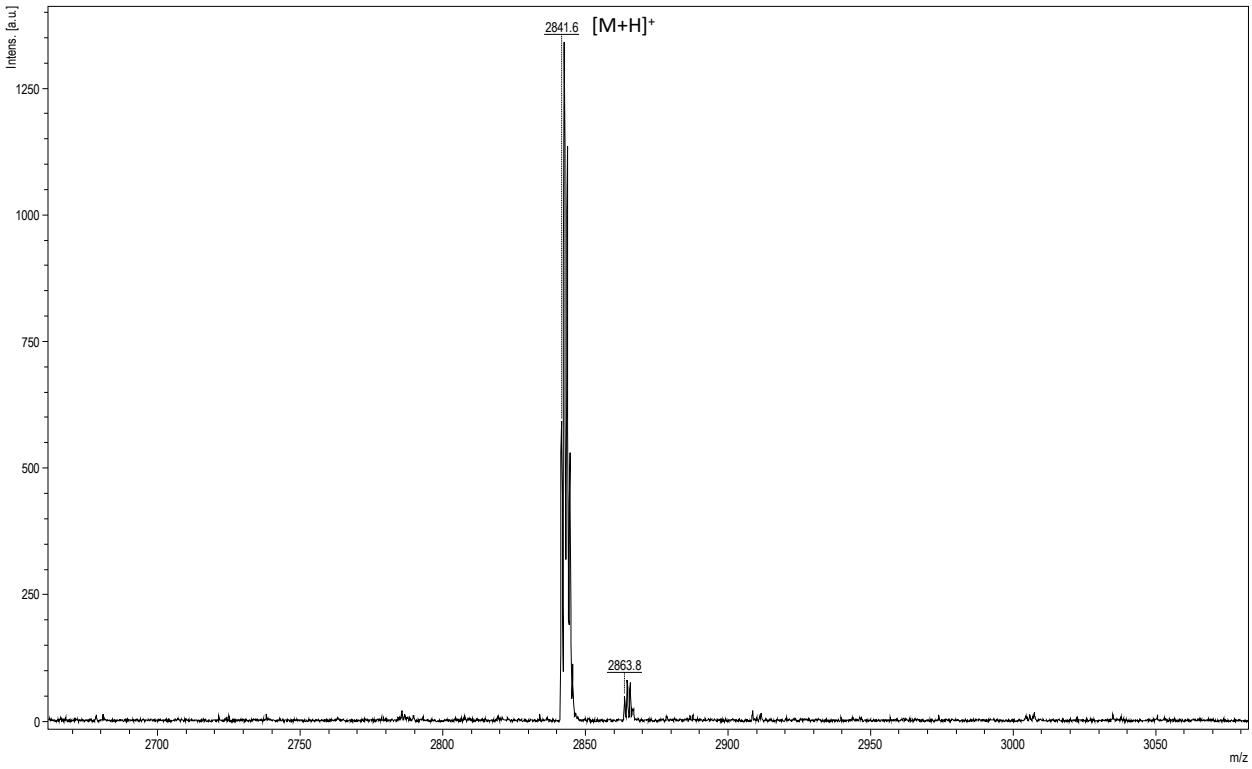
H4K8CoA


Intens. [a.u.]
800
600
400
200
0
2775
2800
2825
2850
2875
2900
2925
2950
2975
3000
3025
m/z
2863.7
+22
[M+Na]+
[M +H]+ 2841.8
2885.7
+44
[M-H+2Na]+
2908.4

H4K12CoA


Intens. [a.u.]
2841.8
[M+H]+
2863.7
+21.9
[M+Na]+
2885.8
0
200
400
600
800
2840
2860
2880
2900
2920
2940
m/z

H4K16CoA


Intens. [a.u.]
1250
1000
750
500
250
0
2841.6
[M+H]+
2863.8
2700
2750
2800
2850
2900
2950
3000
3050
m/z

Lys CoA

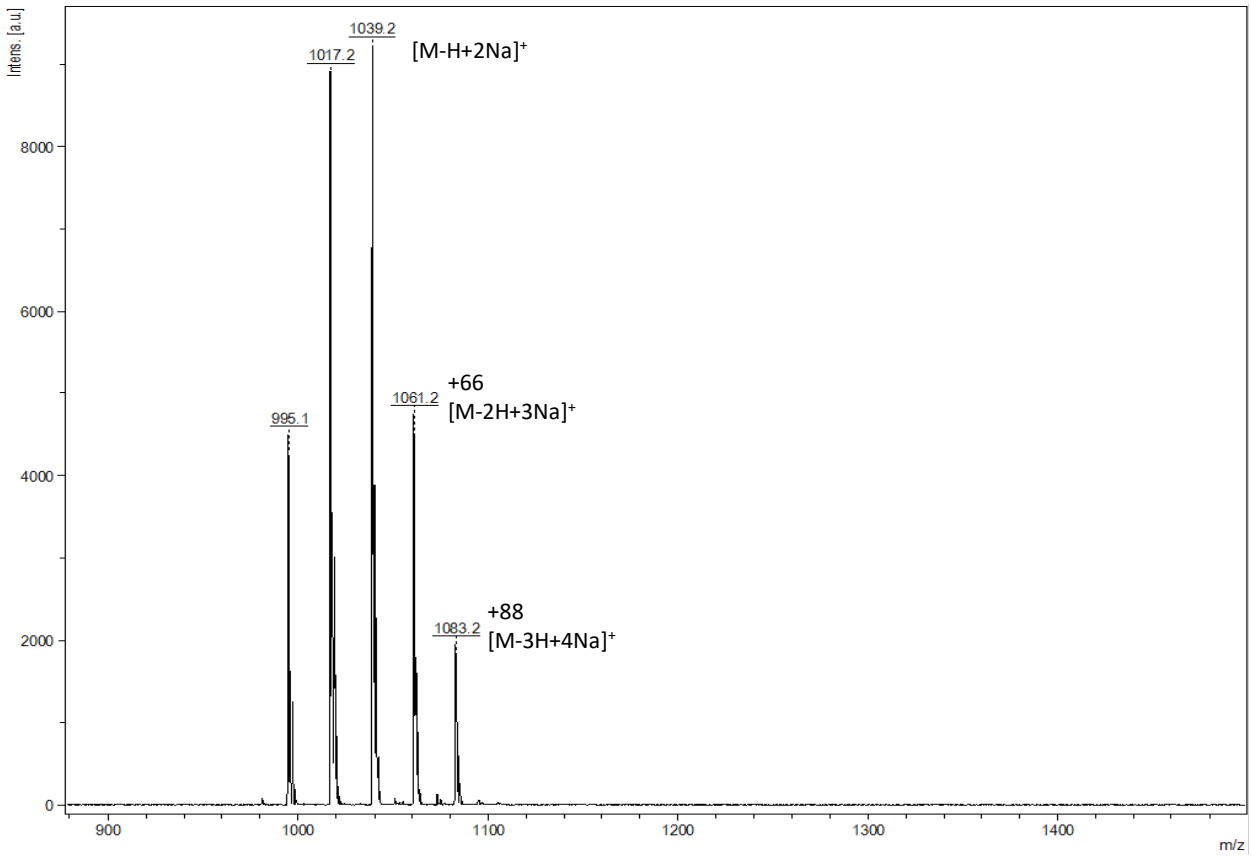
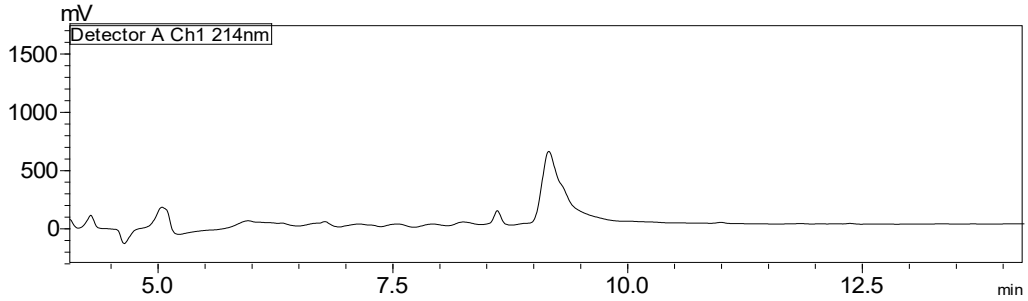
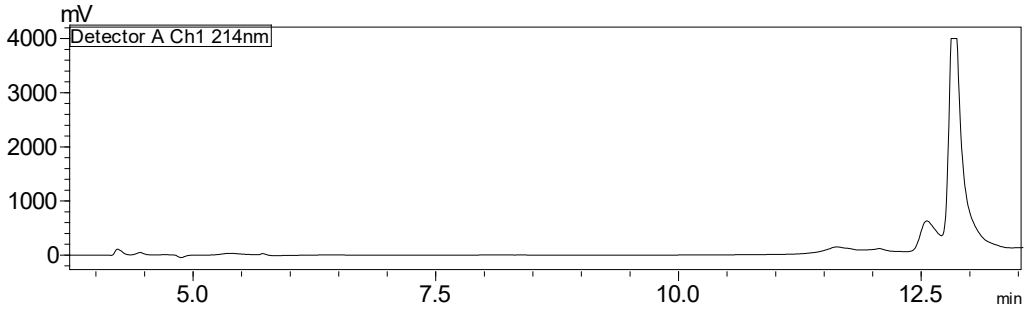

Intens. [a.u.]
8000
6000
4000
2000
0
900
1000
1100
1200
1300
1400
m/z
1039.2
1017.2
[M-H+2Na]+
995.1
1061.2
+66
[M-2H+3Na]+
1083.2
+88
[M-3H+4Na]+

Figure S2: Analytical HPLC chromatograms of each bisubstrate inhibitor. All purified peptides were run on an Aeris PEPTIDE 3.6u XB-C18 (250 x 4.6 mm) column. The samples were analyzed using a UV detector at 214nm, and the intensities of the signals were quantified to calculate the percent composition of the sample. H4K8CoA and H4K12CoA were analyzed using a gradient of 2-25% acetonitrile in water over 13 minutes. H4K5CoA and H4K16CoA were analyzed using a gradient of 2-30% acetonitrile in water over 13 minutes. LysCoA was analyzed using a gradient of 2-37% acetonitrile in water over 23 minutes. For the following traces retention times (t_R) are reported.

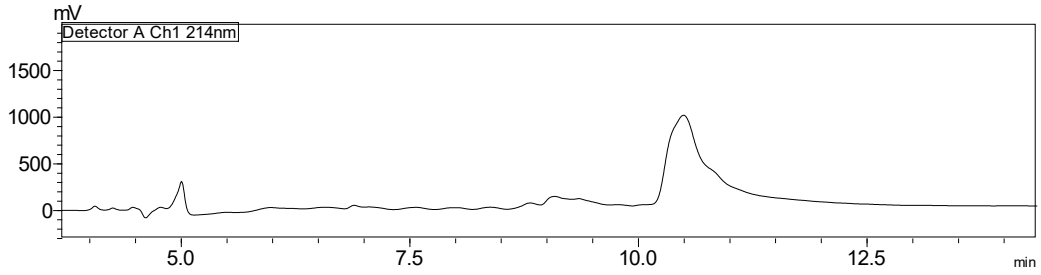
H4K5CoA. t_R: 9.1 min



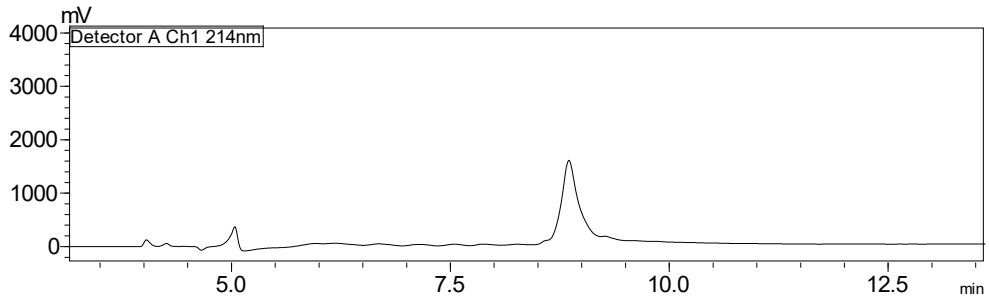
H4K8CoA. t_R: 12.9 min



H4K12CoA. t_R: 10.5 min



H4K16CoA. t_R: 8.8 min



Lys-CoA. t_R: 8.6 min

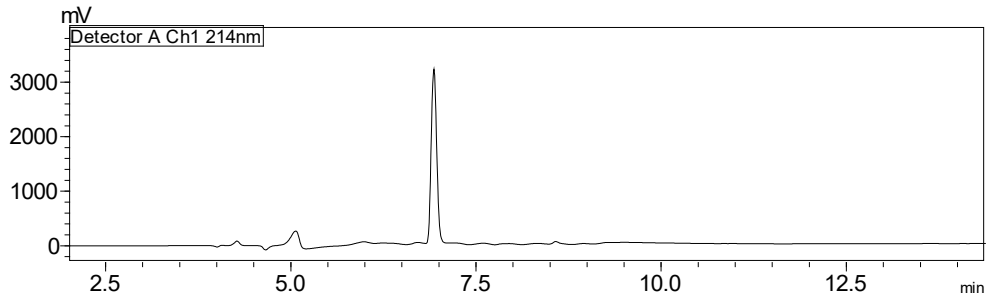
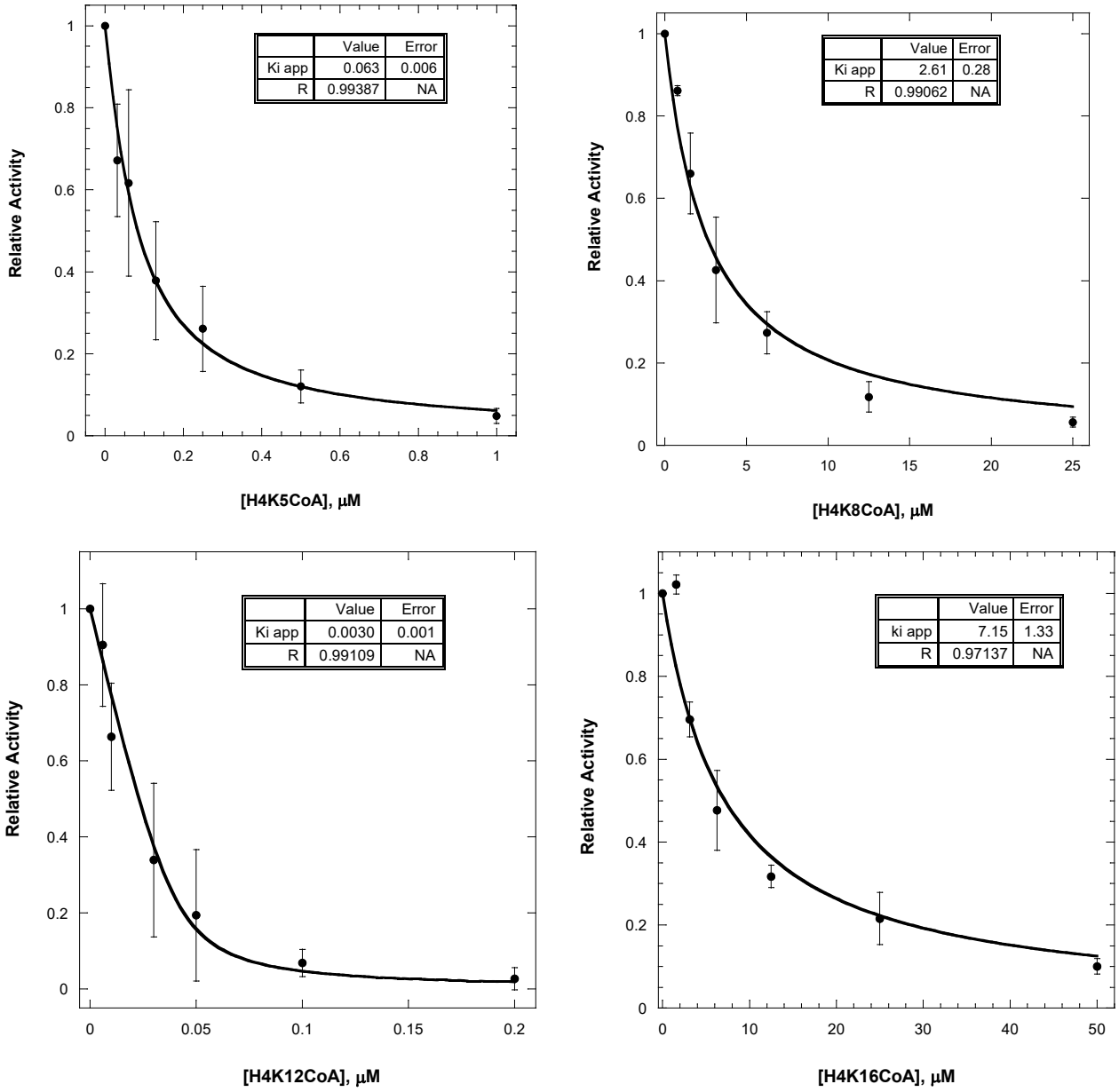
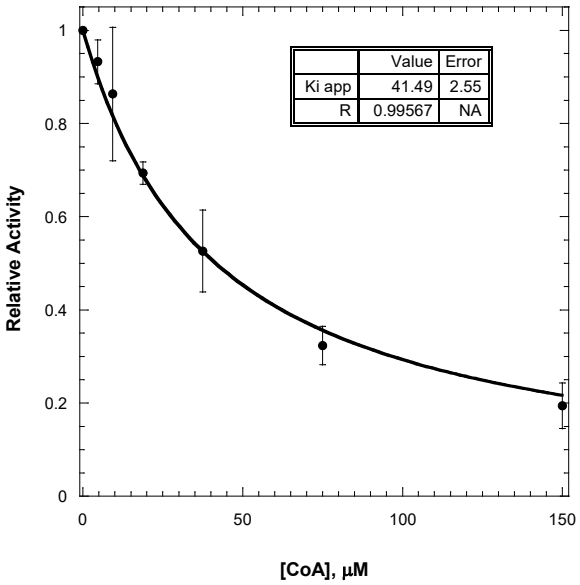
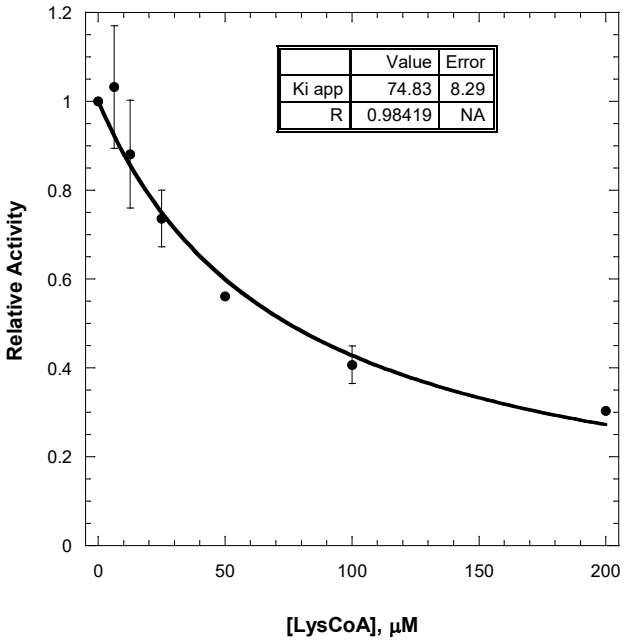


Figure S3: Fitting data to Morrison equation to obtain K_i^{app} values of each compounds tested with HAT1. The SPA was used to measure the potency of each inhibitor against HAT1. Reactions containing 40 nM HAT1, 2.5 µM H4-20 BTN, and 1 µM [^{3}H]AcCoA were incubated at 30°C for 20 min.




Value Error
Ki app 41.49 2.55
R 0.99567 NA
Relative Activity
[CoA], µM


Value Error
Ki app 74.83 8.29
R 0.98419 NA
Relative Activity
[LysCoA], µM