Discovery of histone deacetylase inhibitors and HIV-1 latency-reversing agents by large-scale virtual screening

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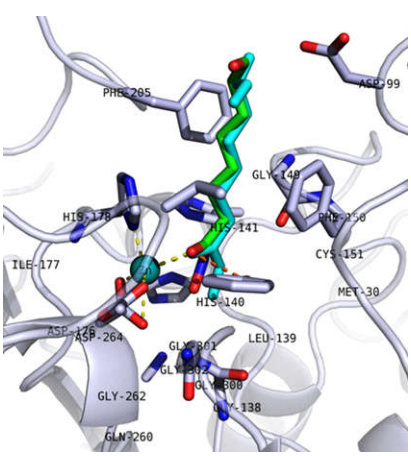
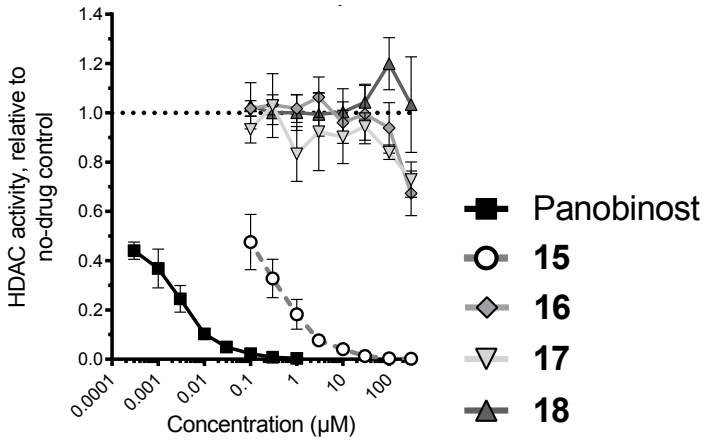
Current antiretroviral therapies used for HIV management do not target or eliminate latent viral reservoirs in humans. The experimental "shock-and-kill" therapeutic approach involves use of latency-reversal agents (LRAs) that reactivate HIV expression in reservoir-containing cells, followed by infected cell elimination through viral or host immune cytopathic effects.[1,2] Several LRAs that function as histone deacetylase (HDAC) inhibitors are reported to reverse HIV latency in cells and in clinical trials; however, none to date have consistently reduced viral reservoirs in humans, prompting a need to identify new LRAs. Toward this goal, we describe here a virtual screening (VS) approach which uses 14 reported HDAC inhibitors to probe PubChem and identifies 60 LRA candidates.





We then show that 4 screening "hits" including (*S*)-*N*-Hydroxy-4-(3-methyl-2-phenylbutanamido)benzamide (compound **15**), *N*-(4-Aminophenyl)heptanamide (16), *N*-[4-(Heptanoylamino)phenyl]heptanamide (**17**), and 4-(1,3-Dioxo-1*H*-benzo[de]isoquinolin-2(3*H*)-yl)-*N*-(2-hydroxyethyl)butanamide (**18**) inhibit HDAC activity and/or reverse HIV latency *in vitro*.[3] This proof-of-concept study demonstrates that VS-based approaches can readily identify novel HDAC inhibitors and LRAs, which in turn may help to develop new chemical leads to improve shock-and-kill-based HIV eradication efforts.

[1] R.J. Andersen, F. Ntie-Kang, I. Tietjen, *Antiviral Res*., **2018**, *158*, 63-77.
[2] E. Abner, A. Jordan, A. *Antiviral Res*., **2019**, *166*, 19-34.
[3] N.M. Archin, D.M. Margolis, *Curr. Opin. Infect. Dis*., **2014**, *27*, 29-35.