**Supplementary material**

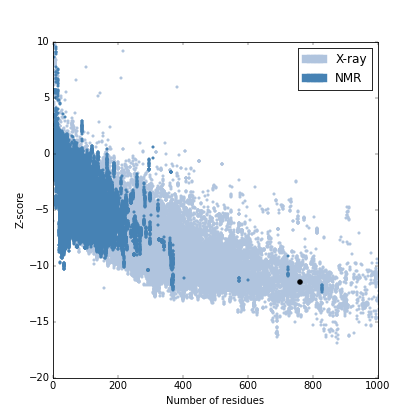
**Structural and energetic basis for the inhibitory selectivity of both catalytic domains of dimeric HDAC6**

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**Figure S1.** Structure model validation using molprobity[1](#_ENREF_1" \o "Hintze, 2016 #29).

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**Figure S2.** Structure model validation using ProSa Server[2](#_ENREF_2).



**Figure S3.** Binding poses obtained by molecular docking among DD1-, DD2-HDAC6 and the following ligands: A) 9-peptide- DD1,B) 9-peptide-DD2; C)CAY10603-DD1, D) CAY10603-DD2; E)HPOB-DD1, F) HPBO-DD2; G) Nexturastat-DD1, H) Nexturastat-DD2. Ligands are shown as blue ball and sticks, Residues as pink sticks, Zinc as green sphere.

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**Figure S4.** Binding poses obtained by molecular docking among DD1-, DD2-HDAC6 and following ligands, : A) Rocilinostat-DD1,B) Rocilinostat-DD2; C) Tubacin-DD1, D) Tubacin-DD2; E) Tubastatin-DD1, F) Tubastatin-DD2. Ligands are shown as blue ball and sticks, Residues as pink sticks, Zinc as green sphere.

**References**

1. Hintze, B. J.; Lewis, S. M.; Richardson, J. S.; Richardson, D. C., Molprobity's ultimate rotamer-library distributions for model validation. *Proteins* **2016**, 84, 1177-89.

2. Wiederstein, M.; Sippl, M. J., ProSA-web: interactive web service for the recognition of errors in three-dimensional structures of proteins. *Nucleic acids research* **2007**, 35, W407-10.