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Small molecules targeting HDAC6: indirect microtubule assembly modulators.

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Abstract

Protein lysine acetylation is a fundamental post-translational modification regulating diverse cellular processes, and its dysregulation is implicated in numerous human diseases. Histone deacetylase 6 (HDAC6) is a unique cytoplasmic deacetylase that primarily targets non-histone proteins, including α-tubulin, and plays critical roles in cytoskeletal organization, intracellular transport, and protein quality control. Due to its involvement in neurodegenerative disorders, cancer, inflammatory diseases, fibrosis, and cardiovascular and metabolic dysfunction, HDAC6 has emerged as an attractive therapeutic target. However, the development of highly selective HDAC6 inhibitors remains challenging because the catalytic pocket and zinc-coordinating residues are highly conserved across HDAC isoforms. In this study, we employed a computational approach combining pharmacophore-based virtual screening, molecular docking, binding site interaction analysis, and ADMET prediction to identify novel selective inhibitors of human HDAC6. From the Enamine compound library screened using the Pharmit service, seven compounds were selected based on their predicted high affinity for HDAC6 and low affinity for other human HDAC isoforms. Docking analysis revealed that these compounds coordinate the catalytic Zn^{2+} ion via alternative monodentate neutral O-donor zinc-binding groups (carbonyl or sulfoxide oxygen) and establish key interactions with residues in the L1 and L2 pockets (Leu749, Ser568, Phe620) that determine HDAC6 isoform selectivity, as well as with catalytically essential residues His611 and Tyr782. Experimental validation in primary porcine neuron cultures confirmed the biological activity of all seven compounds, with no observed cytotoxicity toward neural stem cells. Importantly, comparative analysis with plant tubulin-associated histone deacetylases, particularly *Arabidopsis thaliana* HDA14, revealed that six compounds exhibited high predicted affinity for these plant enzymes, recapitulating the binding pattern observed for human HDAC6. These findings demonstrate the potential of human HDAC6-selective inhibitors for selective targeting of plant tubulin deacetylases and provide a structural framework for the rational design of isoform-selective inhibitors across eukaryotic lineages.

Introduction

Protein lysine acetylation is a fundamental and evolutionarily conserved post-translational modification regulating numerous aspects of cellular physiology. Initially recognized as a chromatin-associated mechanism controlling histone function and gene expression, lysine acetylation is now known to regulate thousands of non-histone proteins involved in cytoskeletal organization, intracellular trafficking, protein quality control, signal transduction, metabolism, and cellular stress responses (Chen and Zhang, 2026). Consequently, lysine deacetylases are recognized as key regulators of both nuclear and cytoplasmic acetylation networks that maintain cellular homeostasis and shape. Among the eighteen human histone deacetylases, HDAC6 exhibits distinctive structural and functional characteristics (Kaur et al., 2022). HDAC6 is predominantly localized in the cytoplasm, where it primarily deacetylates non-histone proteins that regulate diverse cellular processes (Chen and Zhang, 2026). Its distinctive domain organization, comprising two catalytic deacetylase domains and a unique C-terminal zinc-finger ubiquitin-binding (ZnF-UBP) domain, integrates lysine deacetylation with ubiquitin-dependent protein quality control, thereby coordinating cytoskeletal organization, intracellular transport, and proteostasis

(James et al., 2026). These features have established HDAC6 as an attractive therapeutic target working in tight connection with tubulin-focused acetyltransferases and responsible for a broad spectrum of disorders (Rybachuk et al., 2025; Raevsky et al., 2016).

HDAC6 deacetylates diverse proteins involved in cytoskeletal organization, intracellular signaling, and protein quality control (Jo et al., 2022; Kaur et al., 2022). Among these substrates, α-tubulin is the best-characterized substrate and the primary mediator of HDAC6-dependent regulation of microtubule functions (Liang et al., 2025). Reversible deacetylation of α-tubulin at Lys40 regulates the properties of long-lived microtubules that support efficient motor protein-dependent intracellular transport rather than solely controlling microtubule polymerization or stability (Naren et al., 2023; Rayevsky et al., 2023; Rayevsky et al., 2025). Consequently, HDAC6 regulates multiple microtubule-dependent processes, including vesicular and mitochondrial trafficking, aggresome formation, autophagic flux, and cellular adaptation to proteotoxic stress (Liang et al., 2025; Rayevsky et al., 2021). In addition, HDAC6 cooperates with components of the aggresome-autophagy pathway, thereby linking cytoskeletal dynamics to protein quality control (James et al., 2026; Bordoni et al., 2025).

Dysregulation of HDAC6 activity has profound consequences for cellular homeostasis and has been implicated in a broad spectrum of human disorders. HDAC6 contributes to disease pathogenesis by disrupting fundamental microtubule-dependent processes, including intracellular transport, autophagic degradation, mitochondrial trafficking, and protein quality control, thereby promoting pathological changes across multiple tissues (Kaur et al., 2022). Consequently, HDAC6 has emerged as an important therapeutic target in neurodegenerative disorders (James et al., 2026; Bordoni et al., 2025), where impaired axonal transport and defective clearance of protein aggregates contribute to disease progression, as well as in cancer (Chen and Zhang, 2026; Bello et al., 2025), inflammatory diseases (Liang et al., 2025), fibrosis (Tao et al., 2026), cardiovascular disorders (Ranjbarvaziri et al., 2024), and metabolic dysfunction (Guan et al., 2024).

The development of highly selective HDAC6 inhibitors remains particularly challenging because the catalytic pocket and the zinc-coordinating residues are highly conserved across zinc-dependent HDAC isoforms (Pires et al., 2025). This high degree of structural conservation is observed across diverse eukaryotic lineages, including animals, fungi, and plants (Stykhylias et al., 2024; Rayevsky et al., 2019). Likewise, α-tubulin is among the most evolutionarily conserved cytoskeletal proteins, with the Lys40 acetylation site preserved throughout eukaryotes (Rayevsky et al., 2025). Exploiting these structural features therefore represents a promising strategy for the rational design of isoform-selective HDAC6 inhibitors.

The therapeutic potential of HDAC inhibition has been recognized for more than two decades, leading to the development of numerous small-molecule inhibitors targeting zinc-dependent HDACs. Early hydroxamate-based HDAC inhibitors, including trichostatin A, vorinostat, and panobinostat, demonstrated potent antitumor activity but generally lacked isoform selectivity owing to the high conservation of the catalytic pocket among HDAC family members. Although several pan-HDAC

inhibitors have been approved primarily for the treatment of hematological malignancies, their limited isoform selectivity has driven efforts to develop more selective HDAC inhibitors, including tubacin, tubastatin A, ricolinostat (ACY-1215), citarinostat (ACY-241), and several next-generation compounds currently undergoing preclinical and clinical evaluation (Kaur et al., 2022; Chen and Zhang, 2026; James et al., 2026; Bello et al., 2025; Rajput et al., 2026). Despite substantial progress, the rational development of HDAC6 inhibitors capable of simultaneously achieving high potency, exceptional isoform selectivity, favorable pharmacokinetic properties, and clinical efficacy remains a major challenge (Liang et al., 2025). Building upon these advances, the present study reports the identification of novel potentially selective human HDAC6 and plant HDA14 inhibitors.

Materials and Methods

Annotated amino acid sequences of histone deacetylases from *A. thaliana* and *O. sativa* were retrieved from the UniProtKB database (https://www.uniprot.org/). Their completeness or partiality with respect to the catalytic histone deacetylase domain was analyzed using the SMART protein domain architecture prediction tool (https://smart.embl.de/). The availability of experimentally determined spatial structures of deacetylases was examined in the RCSB Protein Data Bank (RCSB PDB; https://www.rcsb.org/). The catalytic domains of known deacetylases were used in this work: HDAC1 (PDB ID: 4BKX), HDAC2 (PDB ID: 7KBG), HDAC3 (PDB ID: 4A69), HDAC4 (PDB ID: 2VQM), HDAC6 (PDB ID: 5EDU), HDAC7 (PDB ID: 3C0Z), and HDAC8 (PDB ID: 1T64). Missing amino acid residues in the experimentally determined structures were modeled by homology modeling. The obtained models of histone deacetylase spatial structures were additionally relaxed using molecular dynamics. Subsequently, a detailed analysis of interactions with inhibitors in the binding sites was performed. Experimental structures of human HDAC6 complexes with selective inhibitors are currently unavailable, and in publications, interactions in the binding sites are often either not analyzed at all or analyzed using spatial structures from *Danio rerio* (Porter et al., 2017).

Pharmit online service (https://pharmit.csb.pitt.edu/search.html) was used, connected to the Enamine compound library, which was the specific library to be screened. During the final system setup, the properties of the features were defined as follows: their diameters were set (R = 1), interaction vectors were adjusted according to the donors and acceptors of the target site, as well as according to the centroids of cyclic fragments of aromatic amino acids, allowing for parallel/perpendicular stacking (π-π). For cyclic interactions, the features allowed for π-π and/or hydrophobic interactions. Ultimately, the ligand docking model in the binding site was constructed based on three anchors formed by assigning hydrophobic regions, four hydrogen-bonding atoms, and one steric constraint (corresponding to a negatively charged group) in the region of the acetyl and zinc-binding site. Screening results were ranked according to their "Score." The Score threshold was defined as the minimum Score value found in the control group compounds.

Molecular docking was performed using the CCDC Gold 5.3 software package (https://www.ccdc.cam.ac.uk/), which employs a genetic algorithm for searching optimal ligand

conformations in the protein binding site. Protein structure preparation was carried out in the Hermes environment by adding hydrogen atoms. The binding site was defined as a sphere with a radius of 5 Å centered on the catalytic Zn^{2+} ion. To ensure correct ligand positioning, a constraint on coordination to the catalytic zinc ion was applied. During docking, all amino acid residues of the binding site were defined as flexible side chains, allowing for conformational mobility of their side chains during ligand interactions. Docking was performed using the following program parameters: population size – 100, selection pressure – 1.1, number of islands – 10, and 100,000 genetic operations. For each compound, 100 independent docking poses were generated, after which the results were ranked according to scoring function values. Primary evaluation of the complexes was performed using the ChemPLP scoring function, followed by rescoring using GoldScore and ChemScore functions. Complexes with the best scoring function values were selected for further analysis. Visualization of complexes and analysis of intermolecular interactions were performed using the PyMOL software package.

Results

The present work is a continuation of research aimed at identifying effectors of enzymes that regulate microtubule acetylation levels. In a previous study by our research group, using computational modeling and experimental validation, novel modulators of human αTAT1 were identified. In the present study, the main focus was on identifying selective inhibitors of human tubulin deacetylase HDAC6 and assessing their potential applicability to plant tubulin-associated histone deacetylases.

Since only one crystal structure of the HDAC6 deacetylase domain in complex with an inhibitor is currently experimentally determined – the complex with trichostatin A (PDB ID: 5EDU) – this structure was used as the structural reference for analyzing interactions in the catalytic center. In the crystal structure of the HDAC6-trichostatin A complex, the hydroxamate group interacts with the catalytic Zn^{2+} through oxygen atoms, forming characteristic bidentate coordination, which is one of the key determinants of high-affinity inhibitor binding to the enzyme. Furthermore, key interactions stabilizing the protein-ligand complex also include classical hydrogen bonds formed between the hydroxamate group of the ligand and amino acid residues His610 and Tyr782 of the histone deacetylase. The same mechanism of catalytic Zn^{2+} coordination is characteristic of other hydroxamate pan-HDACis.

It has been shown that a key feature of the HDAC6 active site is the L1 pocket, formed by the L1-loop near the entrance to the catalytic channel. Interactions of cap groups of selective inhibitors with the L1 pocket are considered one of the main determinants of their isoform selectivity toward HDAC6 (Porter et al., 2018; Osko et al., 2020). It is noted that the key amino acid residues defining this pocket in HDAC6 from *D. rerio* are His463, Pro464, Phe583, and Leu712. These amino acid residues are strictly conserved between HDAC6 from *H. sapiens* (Porter et al., 2018). Thus, these amino acid residues forming the L1 pocket correspond to His500, Pro501, Phe620, and Leu749 in HDAC6 from *H. sapiens*. Additionally, evidence indicates that Ser568, localized in the L2 pocket formed by the L2 loop, may also play a role in HDAC6 selectivity (Sandrone et al., 2021).

The key interactions stabilizing the protein-ligand complexes were classical hydrogen bonds formed between amino acid residue Tyr782 and the linker or chelating group of the ligand. Additionally, π-π stacking interactions played an important role in stabilizing the protein-ligand complexes, involving amino acid residues His611 and Phe680, which interacted with aromatic groups of the ligand (Fig. 1). These interactions were present in the HDAC6 complexes with all selected inhibitors. Furthermore, amino acid residue Phe680 could also participate in the formation of classical hydrogen bonds, while Tyr782 could be involved in π-π stacking interactions with the ligand. Other interactions important for protein-ligand complex stabilization were also present in the HDAC6 binding sites with the selected compounds, though they were not characteristic of absolutely all complexes examined.

It is also known that substitution of amino acid residue Ser531 leads to a 10-fold reduction in catalytic activity, while substitution of Tyr782 abolishes the catalytic activity of the corresponding deacetylase domain – CD2 (Hai and Christianson, 2016). It is also known that substitution of amino acid residue His611 with alanine abolished the deacetylase activity of the CD2 domain (Grozinger et al., 1999).

Based on literature data and multiple poses of reference compounds we generated a set of constraints important for the ligand binding and repeated for all studied compounds. The observed interaction map turned out to be suitable for the screening search (Pharmit) and further docking (Gold) refinement. All presented HDAC6 inhibitor compounds possess aromatic or heterocyclic cap groups localized near the entrance to the active site channel. It was established that compound Z1865409129 interacts with amino acid residue Leu749, forming a classical hydrogen bond. As already noted, Leu749 is localized in the L1 pocket of the site and is important for isoform selectivity toward HDAC6. Compound Z1277775223 also forms a hydrogen bond with an amino acid residue associated with HDAC6 selectivity, Ser568, which is localized in the L2 pocket of the binding site. Compound Z295845670 forms van der Waals interactions with Ser568. The remaining compounds form hydrophobic interactions with amino acid residues Phe620 and/or Leu749. Thus, all identified HDAC6 inhibitor compounds interact, in one way or another, with key amino acid residues of the L1 and L2 pockets responsible for ensuring isoform selectivity, located near the entrance to the binding site channel.

Analyzing the docking results, thousands of compounds were identified that had good predicted binding affinity for HDAC6 and other human histone deacetylases analyzed in this work. An additional filter for compounds was predicted weak affinity for other human histone deacetylases. Compounds obtained from such selection were also analyzed according to their physicochemical descriptor values. Ultimately, 7 compounds were selected (Fig. 1), for which experimental activity is now under investigation.

Additionally, we assessed the formation of interactions in the L1 and L2 pocket regions important for ensuring selectivity toward tubulin deacetylases between the investigated potential inhibitors and the corresponding amino acid residues of HDA14. Based on the results of structural alignment (Fig. 2), it was established that amino acid residues Leu749 of the L1 pocket and Ser568 of the L2 pocket of the active site, important for ensuring isoform selectivity toward human HDAC6, correspond to Leu333 and Pro154 in Arabidopsis HDA14. The positioning of cap groups of potential tubulin deacetylase inhibitors

in the region near the entrance to the catalytic tunnel of the active site differed somewhat for the plant deacetylase compared to the human enzyme. All examined compounds localized near amino acid residue Leu333, while no interactions with amino acid residue Pro154 of the L2 pocket were observed.

Regarding the features of the binding mechanism of the identified inhibitor compounds, two groups can be distinguished that interact with Zn^{2+} in the catalytic site of HDAC6. In contrast to hydroxamate inhibitors, in the compounds we investigated, coordination of the catalytic Zn^{2+} ion is accomplished through the oxygen of a sulfoxide or carbonyl group, demonstrating alternative modes of interaction with the HDAC6 catalytic center. Figure 6.6 shows an example of zinc coordination by the oxygen of the carbonyl group of compound Z1127124609. Compounds Z1865409129, Z402603198, and Z295845670 are characterized by the same binding mechanism, respectively. In contrast, for compounds Z1268394624, Z1175286936, and Z1277775223, zinc coordination is accomplished through the oxygen of a sulfoxide group. Both of these chelating groups are monodentate neutral O-donors.

To assess the potential for selective inhibition of plant tubulin deacetylases, HDA14 from *Arabidopsis thaliana* was selected based on experimentally confirmed involvement in tubulin deacetylation (Tran et al., 2012) and findings indicating its potential tubulin deacetylase function (Stykhylias et al., 2024; Stykhylias et al., 2026).

Comparative analysis of the binding of the identified compounds to plant histone deacetylases showed that six compounds – Z402603198, Z1127124609, Z1865409129, Z295845670, Z1175286936, and Z1277775223 – had high predicted affinity for HDA14 from *A. thaliana*, whereas their affinity for the other plant deacetylases was substantially lower (Fig. 3). For HDA14, analysis of inhibitor-protein interactions revealed a pattern that largely recapitulated the binding features observed for HDAC6, including coordination of Zn^{2+} by alternative ZBGs (zinc-binding groups), a conventional hydrogen bond between Tyr370 and the ZBG, π-π stacking interactions between Phe211 and aromatic groups of the ligands, positioning of capping groups within the L1 pocket, and interactions with the conserved Leu333 residue. An additional characteristic feature of HDA14 complexes was the formation of a conventional hydrogen bond between Gly210 and the amino group of the zinc-binding moiety in compounds containing a carbonyl ZBG.

Given the structural correspondence between Gly230 in rice HDAC10 and Gly210 in *A. thaliana* HDA14, interaction with this conserved glycine may represent a characteristic feature of plant tubulin deacetylases. At the same time, all three tubulin-associated deacetylases – human HDAC6 and *A. thaliana* HDA14 – showed positioning of inhibitor capping groups within the L1 pocket and interactions with the conserved leucine residue (Leu749, Leu333, and Leu353, respectively), suggesting that this structural region may retain a role in selective recognition of tubulin deacetylases across different evolutionary lineages.

Overall, these results indicate the potential of human HDAC6-selective inhibitors for selective inhibition of plant tubulin-associated histone deacetylases and support their further investigation as molecular tools for studying tubulin deacetylation in plants. Comparative analysis of inhibitor interactions with

tubulin-associated deacetylases of different evolutionary origins further identified both conserved and enzyme-specific interaction patterns and highlighted structural features potentially contributing to isoform-selective recognition. These findings may facilitate the rational identification and design of selective inhibitors targeting both human HDAC6 and plant tubulin-associated histone deacetylases.

For experimental verification of the computational identification results of potential HDAC6 inhibitors, a cellular study of the selected compounds was performed. Their biological activity toward HDAC6 was assessed by evaluating the effect on tubulin cytoskeleton organization in primary porcine neuron culture using confocal laser microscopy. The obtained results confirmed the biological activity of the identified compounds in the cellular model.

Analysis of physicochemical descriptors and predicted ADMET parameters showed that the identified compounds are characterized by favorable properties and, based on the comprehensive set of investigated parameters, are not inferior to, and in some parameters surpass, known HDAC6 inhibitors from the DrugBank database.

Experimental verification confirmed the biological activity of all seven selected compounds toward human HDAC6, thereby validating the effectiveness of the applied computational screening approach.

None of the test compounds (n = 6) exhibited toxic effects on neural stem cells (NSCs) under the specified culture conditions. Upon addition of the test compounds to the NSC culture, signs of cellular differentiation (into neurons) were observed; however, in most cases, the NSCs retained their primary proliferative property. No significant effect on the formation of primary adherent neurospheres was detected.

Discussion

Summarizing the results obtained in this section, it can be concluded that the conducted study consistently confirmed the feasibility of using human HDAC6 as a reference model for identifying selective inhibitors of plant tubulin-associated histone deacetylases. It was shown that, despite certain structural differences in the active sites, the catalytic domains of human and plant histone deacetylases are characterized by a high degree of conservation, which explains the ability of known human pan-HDACis to also inhibit plant histone deacetylases. At the same time, the results of comparative analysis of structures, binding sites, and ligand sets obtained from molecular docking suggest that *A. thaliana* HDA14 is closer to human HDAC6 than human HDAC10. These results provide additional support for our hypothesis regarding the possible tubulin deacetylase function of rice HDAC10 and justify the use of *A. thaliana* HDA14 as the primary plant model when assessing the selectivity of inhibitors developed for human HDAC6.

Based on the developed approach, which combined molecular docking, binding site interaction analysis, physicochemical and ADMET parameter evaluation, and experimental verification, seven novel human HDAC6 inhibitors were identified. For all compounds, a common interaction mechanism was

established, including coordination of the catalytic Zn^{2+} by alternative monodentate neutral O-donor zinc-binding groups, formation of a characteristic set of classical hydrogen bonds and π-π stacking interactions, as well as interaction with amino acid residues of the L1 and L2 pockets that determine HDAC6 isoform selectivity.

Comparative analysis of the binding of experimentally active compounds to plant histone deacetylases showed that six of the seven inhibitors are characterized by high predicted affinity specifically for *A. thaliana* HDA14, whereas their affinity for other plant histone deacetylases was significantly lower. For HDA14, an interaction pattern was established that largely recapitulates the binding mechanism characteristic of human HDAC6, including coordination of Zn^{2+} by alternative zinc-binding groups, formation of a classical hydrogen bond between Tyr370 and the chelating group of the ligand, π-π stacking interactions between Phe211 and aromatic groups of the ligand, localization of cap groups within the L1 pocket region, and interaction with the conserved Leu333 residue. It is worth noting that the aforementioned amino acid residues participating in the formation of key interactions stabilizing the ligand position in all HDAC6 complexes with the identified inhibitors are also critically important for ensuring deacetylase activity. These include His611 and Tyr782, amino acid substitutions in which completely abolish the deacetylase activity of the CD2 domain of HDAC6. Thus, the identified inhibitor compounds block the ability of HDAC6 to interact with its specific deacetylation substrates, which include tubulin. An additional characteristic feature of interactions in the HDA14 binding site was the formation, for compounds with a carbonyl zinc-binding group, of a classical hydrogen bond between Gly210 and the amino group of the zinc-binding fragment of the ligand.

The obtained results indicate the promise of applying selective human HDAC6 inhibitors for selective inhibition of plant tubulin-associated histone deacetylases and open possibilities for their further use as molecular tools for studying tubulin deacetylation processes in plants. Furthermore, the conducted analysis of inhibitor interactions in the binding sites of tubulin-associated histone deacetylases of different evolutionary origins allowed the identification of common and specific interaction patterns, as well as the establishment of key structural determinants responsible for ensuring isoform selectivity of these enzymes. The identified patterns are important for the rational discovery and design of new selective inhibitors of both human tubulin deacetylase HDAC6 and plant tubulin-associated histone deacetylases.

Declarations

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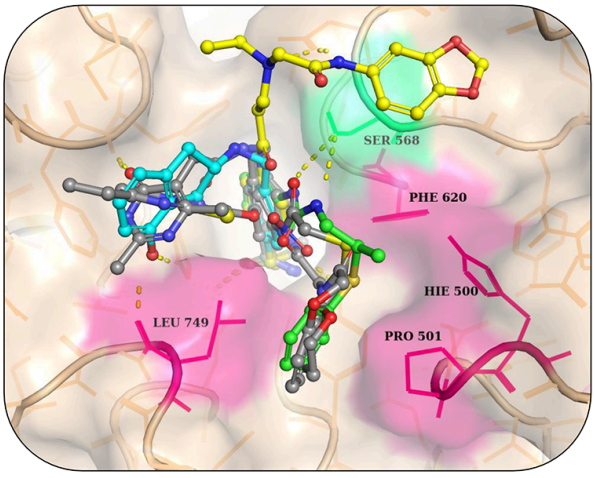
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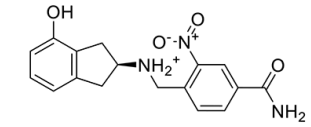
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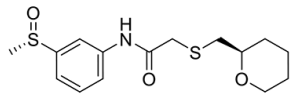
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Figures

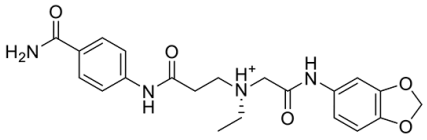




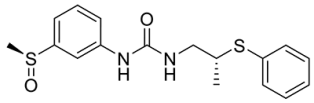
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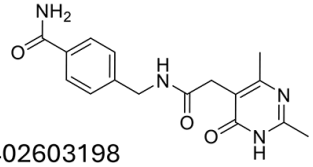
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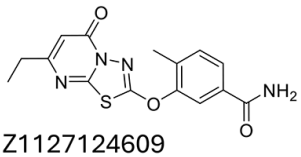
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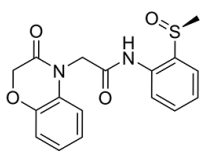


Z402603198



Z1127124609

Molecule	log Kp	MW	FSP3	RTB	TPSA	XLOGP3	Log S	HBA	HBD
Z402603198	-8.76	314.34	0.25	6	117.94	-0.76	-1.30	4	3
Z1127124609	-6.72	330.36	0.20	4	127.82	2.24	-3.52	5	1
Z1175286936	-7.11	327.46	0.53	7	99.91	1.67	-2.67	3	1
Z295845670	-8.08	412.44	0.29	11	122.99	1.03	-2.62	6	3
Z1268394624	-7.24	344.38	0.18	5	94.92	1.64	-3.05	4	1
Z1277775223	-6.52	348.48	0.24	8	102.71	2.69	-3.55	2	2



Z1268394624

Figure 1

Position of the investigated inhibitors in the catalytic tunnel and L1 and L2 pockets of the human HDAC6 binding site. Key amino acid residues that play a role in ensuring isoform selectivity toward HDAC6 are localized in the L1 (pink) and L2 (green) pockets located near the entrance to the catalytic tunnel of the active site. Compounds Z1865409129, Z1277775223, and Z295845670 are highlighted in blue, green, and yellow, respectively. The remaining compounds are colored gray.

```
HDA14_AT      ----TATVE---DIANVHDKAY----VFG--LEKAMDEASDSGLIFIEGSGPTYATSTTFQDS 165
HDAC10_OS     QDFQPA---SLDDIALVH----SRSYI--TGLEKAMSRASDEGLIFIEGTGPTYATQTTFQEC 185
HDAC6_HS      ---RPA---TEAELLTCH----SAEYV--GHLRATEKMKTRELHRESSNFDSIYICPSTFACA 579
                 ..*   ........*    .....  ..*                        ...**...

HDA14_AT      LIAAGAGMALVDSVIAASRNSVDPPIGFALIRPPGHHAVPK-GPMGFCVFGNVAIAARHAQ-- 225
HDAC10_OS     LLSAGAGITLVDSVVAASKLGPKPPLGFALVRPPGHHAVP-EGPMGFCVFGNIAVAARYAQNQ 248
HDAC6_HS      QLATGAACRLVEAVLSGEVLN-----GAAVVRPPGHHAEQ-DAACGFCFFNSVAVAARHAQ-- 634
              ....**...**..*..          *.*..*******.. ....***.*...*.***.**

HDA14_AT      DAHVLDPLANLQFTTATY-----------------YSLAKDIKRLAKEVCGGRCVFFLEGGYN 371
HDAC10_OS     DAHALDPLAGLQFTTGTFYMLAARIREVAAELCGG-----------------RCVFFLEGGYN 391
HDAC6_HS      DAARGDPLGGCQVSPEGY-----------------AHLTHLLMGLAS----GRIILILEGGYN 783
              **...***...*......                  ........        .*....******
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Figure 2

Structural alignment of human, Arabidopsis, and rice deacetylases associated and putatively associated with tubulin deacetylase activity. Conserved amino acid residues important for stabilizing complexes with inhibitors and ensuring isoform selectivity are highlighted in color.

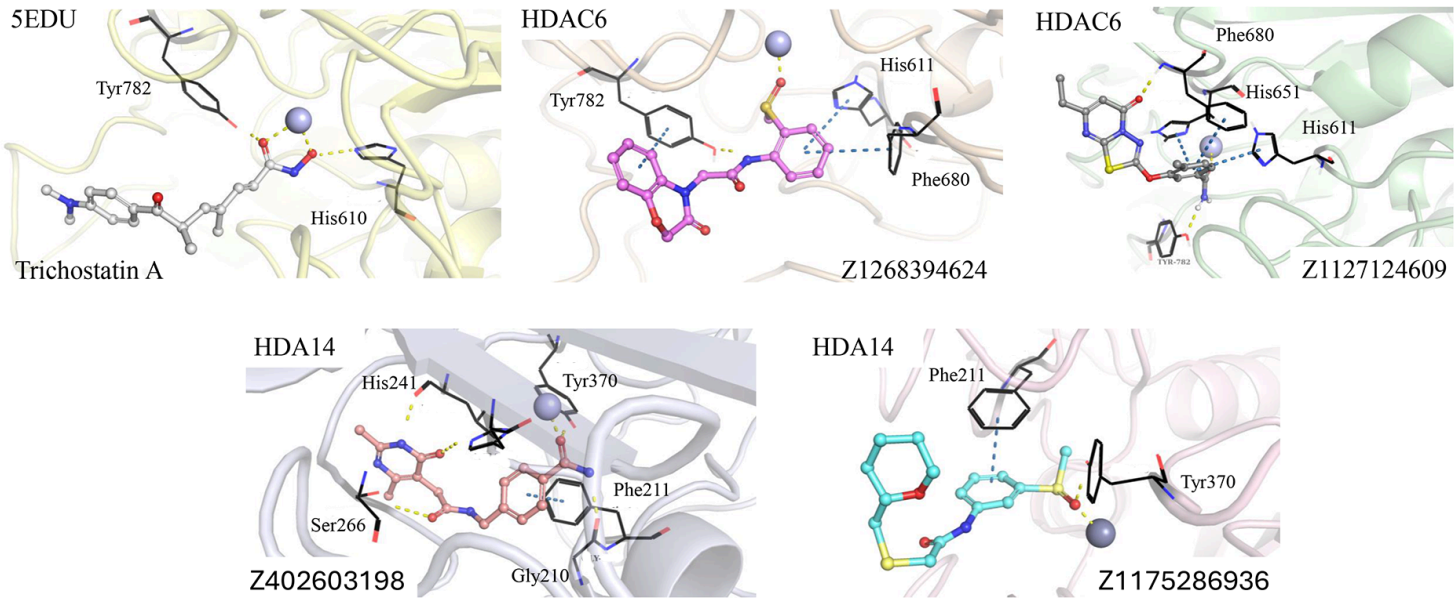


Figure 3

Comparative representation of the binding modes for the identified compounds in human and plant histone deacetylases.