In Silico Molecular Docking Studies of Novel Substituted Benzene Sulfonamido-N-hydroxybenzamide Derivatives as Potent Histone Deacetylase (HDAC) Inhibitors for the Treatment of Breast Cancer

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Abstract

Breast cancer is one of the leading causes of cancer-related mortality worldwide. Epigenetic misregulation, particularly through histone deacetylases (HDACs), plays a central role in its onset and progression. This study focuses on the design and in silico molecular docking of benzene sulfonamido-N-hydroxybenzamide derivatives as potential HDAC inhibitors. Approximately 22 designed molecules were subjected to molecular docking using the Schrödinger GLIDE XP protocol. Among them, five compounds exhibited favorable binding scores with Glide G-scores ranging from –4.054 to –4.609, suggesting moderate but promising binding affinity. Interaction analysis revealed that the sulfonamide and hydroxamate functionalities contribute significantly to hydrogen bonding, hydrophobic contacts, and potential Zn2+ chelation within the HDAC active site. This research highlights the potential of these derivatives as scaffolds for further development and provides a foundation for future in vitro validation.

Keywords: Histone deacetylases; benzene sulfonamido-N-hydroxybenzamide derivatives; Breast cancer; molecular docking; in silico screening

Introduction

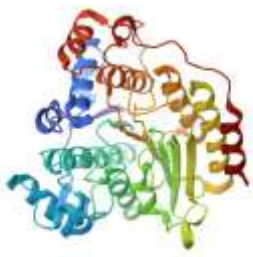
Breast cancer is the most frequently diagnosed cancer in women worldwide, accounting for nearly 25.8% of new cancer cases in 2020. It arises due to uncontrolled proliferation of mammary epithelial cells, with tumorigenesis being driven by both genetic and epigenetic alterations. Epigenetics, defined as heritable changes in gene expression without alteration in DNA sequence, plays a crucial role in cancer progression. Histone acetylation and deacetylation are critical epigenetic mechanisms that regulate gene transcription. Dysregulated histone deacetylase (HDAC) activity results in transcriptional repression of tumor suppressor genes, thereby contributing to oncogenesis.

Histone deacetylases are Zn-dependent enzymes classified into four classes, with Class I and II being directly implicated in cancer. HDAC inhibitors (HDACi) have thus emerged as promising anticancer agents, with FDA-approved examples including Vorinostat, Romidepsin, and Belinostat. Despite these advances, therapeutic efficacy against breast cancer remains limited, largely due to selectivity challenges and side effects. Hence, discovery of novel scaffolds with improved binding affinity and selectivity is warranted.

Sulfonamide moieties have gained attention in medicinal chemistry as bioisosteres of carboxylic acids, offering advantages in metabolic stability, permeability, and reduced toxicity. Several sulfonamide derivatives have demonstrated diverse pharmacological activities, including anticancer effects. In this context, benzene sulfonamido-N-hydroxybenzamide derivatives are rationally designed as potential HDAC inhibitors. The N-hydroxybenzamide group serves as a zinc-binding group (ZBG), while the sulfonamide contributes additional hydrogen bonding and structural stability.

Materials and Methods

Protein Preparation: The X-ray crystal structure of HDAC was retrieved from the RCSB Protein Data Bank (PDB). The protein was refined using Schrödinger Maestro protein preparation wizard, removing water molecules and adding missing hydrogens. Partial charges were assigned using the OPLS-AA force field.



Ligand Preparation: Approximately 22 benzene sulfonamido-N-hydroxybenzamide derivatives were designed and optimized in Maestro 9.3. Conformational energy minimization was carried out using OPLS-AA.

Docking Protocol: Molecular docking was performed using the GLIDE XP (extra precision) docking module. The docking score (Glide G-score) incorporates hydrogen bonding, hydrophobic contacts, van der Waals forces, and penalties for buried polar groups. An additional scoring function, E-model, was also used to assess pose quality.

Results

Molecular docking yielded docking scores for all 22 derivatives. The Glide G-scores ranged from –3.0 to –4.6, with five compounds emerging as top candidates. The top 5 compounds demonstrated stable interactions in the HDAC active site. Detailed interaction analysis indicated potential Zn2+ coordination, hydrogen bonding with active site residues, and hydrophobic stabilization within the binding pocket.

Top 5 Compounds with Docking Scores

Compound ID	Docking score
Compound 2	-4.609
Compound 18	-4.518
Compound 21	-4.296
Compound 8	-4.251
Compound 22	-4.054

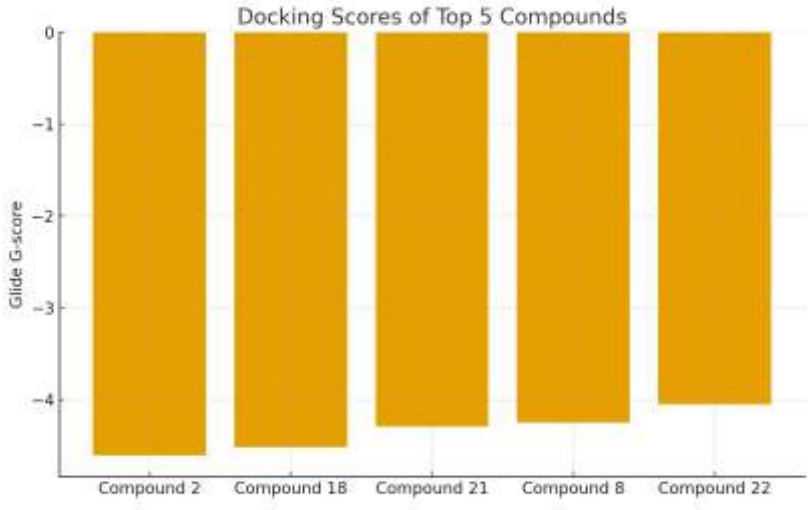


Figure 1 presents a graphical comparison of docking scores for Benzene sulfonamido-N-hydroxybenzamide analogues in HDAC active site.

Discussion

The docking results revealed that Compound 2 was the most promising derivative with a Glide G-score of –4.609 and an E-model score of –41.324, suggesting stable binding within the HDAC pocket. Compound 18 followed closely with a Glide G-score of –4.518. Detailed inspection of binding interactions revealed that both compounds engaged in critical hydrogen bonding with active site residues and showed potential coordination with the catalytic Zn2+ ion. The hydroxamate moiety of the designed molecules is primarily responsible for metal chelation, while the sulfonamide group enhances hydrogen bonding and contributes to structural stability.

Other compounds, including Compound 21, 8, and 22, demonstrated moderate binding scores in the range of –4.0 to –4.3. Although not as favorable as Compounds 2 and 18, they still exhibited productive interactions within the active site. The remaining derivatives scored lower, reflecting weaker interactions or less favorable orientations in the binding pocket. Nevertheless, their inclusion provides useful structure–activity relationship (SAR) insights for future scaffold optimization.

Conclusion

This study demonstrates that benzene sulfonamido-N-hydroxybenzamide derivatives possess potential as novel HDAC inhibitors. Among the designed derivatives, Compounds 2 and 18 exhibited the most favorable docking profiles, highlighting them as lead candidates. The incorporation of sulfonamide and hydroxamate moieties facilitated hydrogen bonding and Zn2+ chelation, which are essential for HDAC inhibition. Future work will focus on molecular dynamics simulations, synthesis of lead candidates, and in vitro assays to validate their anticancer potential.

References

1. Gelato, K.A., Adler, D., Haendler. Targeting epigenetic regulators for cancer therapy. Expert Opin. Ther. Targets 20 (7) (2016) 783–799.
2. Bates, S.E. Epigenetic therapies. N Engl J Med. 383 (7) (2020).
3. de Lera, A.R., Ganesan, A. Two-hit wonders: multitargeting epigenetic agents. Curr. Opin. Chem. Biol. 57 (2020) 135–154.
4. WHO. Breast cancer (2024). https://www.who.int/breast_cancer
5. Bertrand, P. Inside HDAC with HDAC inhibitors. Eur J Med Chem. (2010).
6. Guerriero, J.L. et al. Class IIa HDAC inhibition reduces breast tumours. Nature 543 (2017) 428–432.
7. Deng, X., Wan, Y., Chen, H., Tang, Z. Aryl sulfonamide derivatives as anti-cancer agents. Eur J Med Chem. (2021).