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In-Silico Profiling of New Mefenamic Acid Derivatives as HDAC 8 Inhibitors

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ABSTRACT

Vital cellular processes such as, proliferation and tumor progression were reported to be centrally controlled by histone deacetylase (HDAC) enzymes which make them an interesting therapeutic target. Recently, a new paradigm has attracted researches to combine nonsteroidal anti-inflammatory drugs (NSAIDs) with para-aminobenzoic acid (PABA) and a zinc binding group (ZBG), presenting a synergistic impact on HDAC activity and inflammatory process. In the current study, a novel series of hybrid compounds (A1-6) were designed and evaluated for their HDAC binding affinity by molecular docking technique along with conducting an in-silico ADME (absorption, distribution, metabolism, and elimination) profiling to assess their pharmacokinetic characteristics. Compound A6 displayed the highest binding energy score (-9.539 kcal/mol) with the active site of HDAC 8 enzyme compared with the reference ligand, SAHA (-4.606 kcal/mol). Its worth mentioning that compound A6 has comparable coordination to the catalytic zinc ion with SAHA along with engaging additional hydrophobic and aromatic interaction within the active site of HDAC 8 enzyme. ADME analysis predicated high gastrointestinal absorption for A2, A5, and A6, which also comply with Lipinski's rule, indicating good oral bioavailability. Conversely, A1, A3, and A4 showed moderate absorption, suitable for parenteral or localized/colon-targeted delivery, potentially advantageous for colon cancer treatment. These results highlight these hybrids' potential as HDAC inhibitors and support further synthesis and biological testing.

Keywords: HDAC inhibitors, NSAIDs, Zinc-binding groups, molecular docking, ADME

INTRODUCTION

1.1. Epigenetic Regulation and HDACs as Therapeutic Targets

Cellular function, development, and illness are largely regulated by epigenetic alterations, which are heritable shifts in gene expression that do not involve changes to the DNA sequence. Among these changes, histone acetyltransferases (HATs) and histone deacetylases (HDACs) catalyze the reversible acetylation of lysine residues on histones and non-histone proteins. HATs relax chromatin and generally increase gene expression, whereas HDACs remove acetyl groups, which promotes chromatin condensation and transcriptional suppression (1, 2)

Numerous diseases, including cancer, neurodegeneration, inflammation, and metabolic disorders, have been linked to dysregulation of HDAC activity (2). Apoptosis resistance, cell proliferation, genomic instability, and the silence of tumor suppressor genes are all facilitated by abnormal HDAC overexpression in many malignancies. As a result, HDACs are now recognized therapeutic targets for epigenetic treatment (3)

Eighteen HDAC isozymes have been identified and categorized into four classes in mammals thus far based on sequence homology to yeast protein orthologues: class I (HDAC1, 2, 3, 8), class IIa (HDAC4, 5, 7, 9), class IIb (HDAC 6, 10), and class IV (sole HDAC11) are enzymes that require zinc, while class III HDACs (sirtuins 1–7) are enzymes that require NAD+ (4, 5).

The development of HDAC inhibitors (HDACis) has advanced significantly over the past few decades. Up to this point, five HDAC inhibitors—vorinostat, romidepsin, belinostat, panobinostat, and chidamide—have been approved for clinical use, primarily in hematologic malignancies, such as multiple myeloma and cutaneous T-cell lymphoma (5, 6). However, there are still significant drawbacks, such as dose-limiting adverse effects, inadequate pharmacokinetics, and low isoform selectivity, which can result in off-target toxicities. Consequently, there is ongoing research into finding new HDAC inhibitors that compromise potency, selectivity, and advantageous ADME (absorption, distribution, metabolism, excretion) characteristics (6, 7).

1.2. Strategies in HDAC Inhibitor Design

HDAC inhibitors typically contain a three-part pharmacophore consisting of: (1) a ZBG, which chelates the catalytic Zn^{2+} ion situated in the active site of the enzyme, (2) a linker section that crosses the tubular channel formed within the enzyme's binding pocket, and (3) a cap or surface recognition domain that interacts with residues at the entrance of the binding cavity8. The common zinc-binding groups are hydroxamic acids, benzamides, thiols, and certain ketones. However, most inhibitors, especially hydroamate-containing ones, suffer from a low metabolic stability or undesirable off-target effects despite potency (8, 9). Recent advancements in anticancer drug research include hybrid and multitarget HDAC inhibitors, which combine an HDAC-inhibitory framework with other bioactive properties to boost therapeutic efficacy and overcome resistance. Another intriguing method is to repurpose or structurally modify current medications to target HDACs, to leverage their established pharmacokinetic and safety profiles for better therapeutic results. Together, these strategies provide new prospects for cancer treatments that are more effective and safer (10, 11).

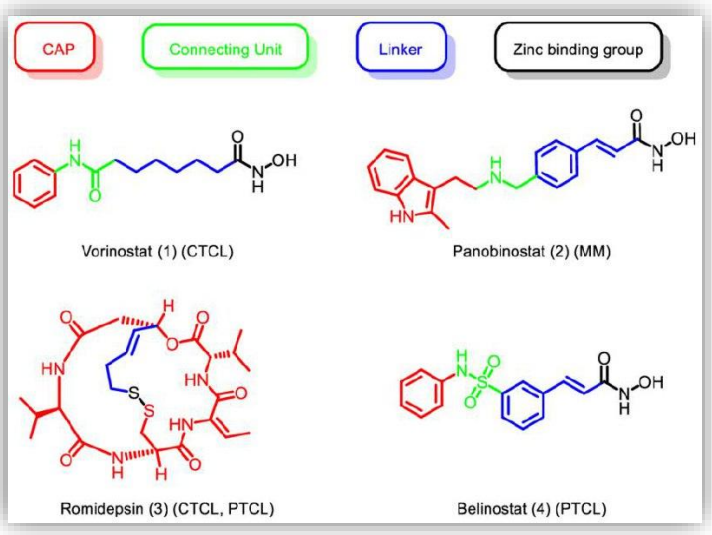


Figure 1: A general pharmacophore model of HDAC inhibitors, as well as the chemical structures and indications of FDA-approved HDACi (1-4). CTCL refers to cutaneous T-cell lymphoma, PTCL to peripheral T-cell lymphoma, and MM to multiple myeloma(12).

1.3. Mefenamic Acid and Its Derivatives as a Scaffold for Modification

Mefenamic acid is an NSAID from the anthranilic-acid (fenamate) class. It is often used to treat pain and inflammation by blocking COX. Its anthranilic framework provides chemical adaptability for alterations. Previous studies have investigated mefenamic acid derivatives to improve anti-inflammatory efficacy or diminish toxicity. In addition to its traditional application, mefenamic acid exhibits supplementary biological activities: a study demonstrated its ability to increase the sensitivity of drug-resistant cancer cell lines (e.g., HeLa and Sa3) by inhibiting the Aldo-keto reductase 1C family (AKR1C) enzymes (13-15). Due to its established pharmacological properties, synthetic availability, and structural adaptability, the design of mefenamic acid-derived compounds as selective Histone deacetylase (HDAC) inhibitors represents a promising approach for drug repositioning, potentially yielding advantageous ADME and safety profiles.

1.4. Computational Methods: Docking and ADME Evaluation

Computational approaches play an essential role in the early stages of discovering new therapeutic agents, particularly when the aim is to design inhibitors of epigenetic enzymes such as HDACs. Molecular docking enables examination of how a small molecule fits within the binding site of a given HDAC isoform and prediction of the HDAC isoform type and the interactions that may stabilize the complex (16). This technique was utilized to estimate the strength of ligand association with the amino acid residues within the active site of HDAC 8 protein and identify the main intermolecular non-covalent interactions, such as hydrogen bonds, dipole-dipole, and van der Waals interactions (17). Computational ADME profiling helps researches to predict the compound behavior in the biological system and estimating the drug-likeness of the designed molecules allowing researchers to identify potential problems such as, low bioavailability, metabolic instability especially by the effect of cytochrome P450 enzymes increasing the efficiency of transition process from initial hits to more refined lead compounds (18, 19).

1.5. Rationale and Objectives of the Present Study

Recent advances in the field of histone deacetylase (HDAC) modulation have highlighted several scientific and clinical challenges, particularly the need for improved isoform selectivity, reduced toxicity, and enhanced pharmacokinetic properties. Mefenamic acid, which possesses a rigid aromatic framework and established pharmacological activity, was adopted as a starting scaffold to explore new structural options for HDAC inhibition through computational analysis. In this context, the study focuses on examining structurally modified derivatives of mefenamic acid and on assessing their interaction profiles and predicted pharmacokinetic characteristics using established in silico techniques.

The current study aims to:

1. Design of a new Mefenamic acid-based derivative by attaching and linking small functional groups that fit important features found in typical HDAC inhibitors.

2. Use of molecular docking studies on HDAC8 to predict how these designed molecules might interact and bind with the enzyme.

3. An in-silico ADME evaluation to examine the possibility of pharmacokinetic behavior and overall drug-like nature of the compounds.

Using this in silico multistep computational methodology, we aim to identify potential mefenamic acid-based HDAC inhibitors for further pharmacological evaluation to advance epigenetic therapeutics toward safer, more effective applications.

MATERIALS AND METHODS

2.1. Enzyme Preparation

The Protein Data Bank (https://www.rcsb.org/) supplied the 3D X-ray crystallographic structure of the Histone Deacetylase 8 (HDAC8) enzyme, identified by PDB ID 169 (20) . Using the Schrödinger Suite 2025-1's Protein Preparation Wizard (including the Glide module), structural corrections were applied, including adding missing hydrogen atoms and adjusting bond orders. Disulfide bonds were formed automatically between neighboring sulfur atoms after removing water molecules more than 5 Å away from the active site. A final refinement was performed using the OPLS3e force field through complete energy minimization, with the heavy atom RMSD constrained to 0.3 Å (21).

2.2. Ligand Preparation

The studied mefenamic acid derivatives (A1–B3) were first generated with the 2D Sketcher tool and then imported into the Maestro workspace of the Schrödinger Suite. To find the lowest energy configuration, each 2D structure was converted into a 3D form and optimized. The Epik module was employed to evaluate the physiological ionization and tautomeric states at a pH of 7.2 ± 0.2. All other parameters were kept at their default values, and the OPLS3e force field was used to perform energy minimization.

2.3. Grid Generation

A receptor grid for docking was generated using the Glide workflow in the Schrödinger suite. Identification of the HDAC8 binding region was based on the coordinates of the co-crystallized ligand contained in the crystal structure (PDB ID:1T69). The grid was positioned to encompass the catalytic zinc ion together with the residues that define the enzyme's binding pocket. Standard grid-generation parameters were maintained, allowing the system to reflect the native interaction environment required for consistent docking evaluations (22).

2.4. Molecular Docking

Docking studies were carried out in standard precision (SP) mode using the Glide platform to score and evaluate how each ligand interacts with the HDAC8 active site. Affinities were determined using the GlideScore, which accounts for contributions from metal coordination, hydrophobic interactions, and hydrogen bonding (23). To better understand the binding patterns, we examined the 2D interaction maps generated with Maestro. These maps clearly showed how the ligand interacts with the catalytic zinc ion and the important amino acid residues that make up the HDAC8 binding pocket (24).

The docking poses were further examined using 2D interaction diagrams in Maestro to identify key interactions between the ligands and the active site residues of HDAC8.

2.5. ADME Prediction

The pharmacokinetic properties of the designed compounds, including gastrointestinal absorption, systemic distribution, metabolism, excretion, and drug-likeness, were assessed using the SwissADME tool. The compounds were first drawn as 2D structures and converted to SMILES for analysis. The simulation results were captured as images.

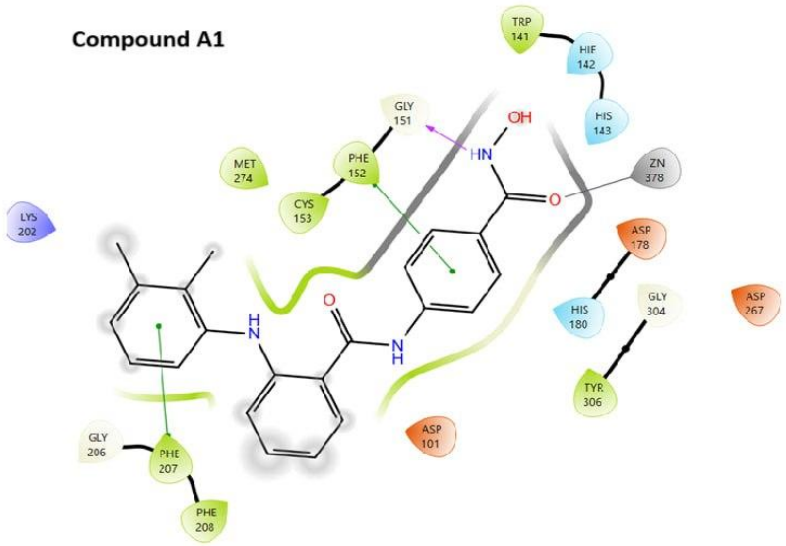
RESULTS AND DISCUSSION

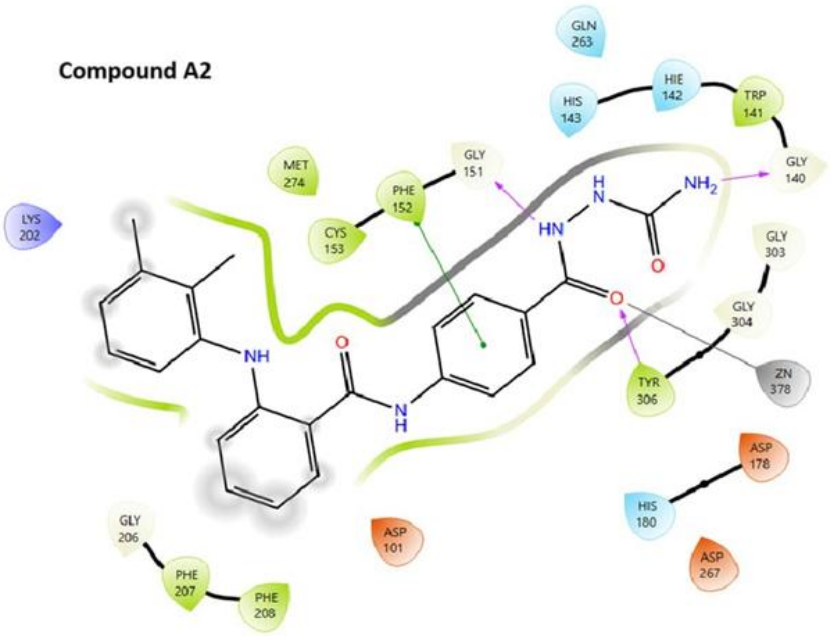
3.1.MD Study

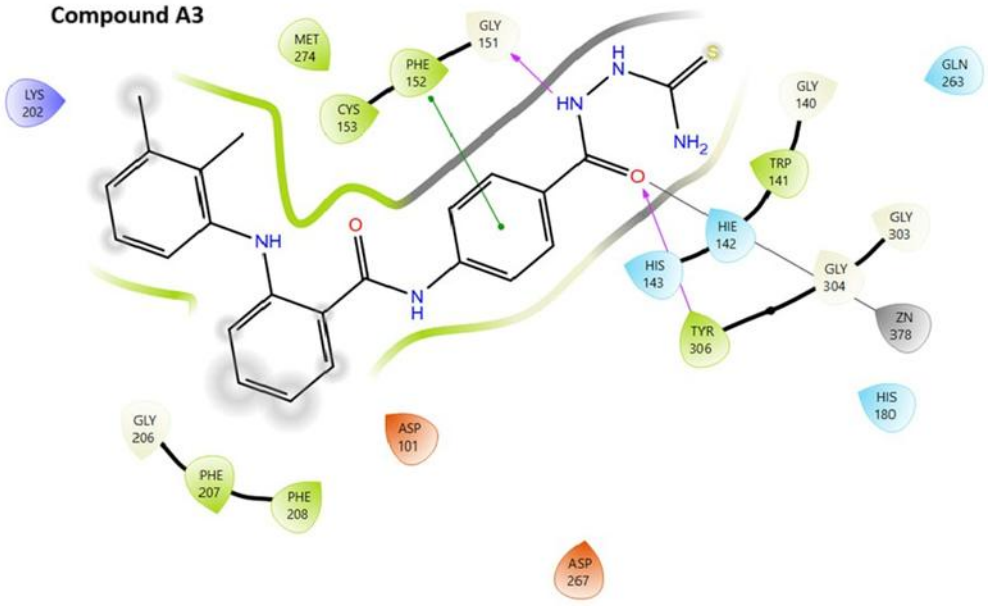
The molecular docking study was cone to see how well the suggested mefenamic acid derivatives (A1–A6) fit into the active site of the HDAC8 enzyme. It determined the energy required for each compound to bind and compared it to the energy needed for the reference inhibitor, vorinostat, to bind. Table 3-1 shows the docking scores and points out the most important amino acids involved in the ligand-receptor interactions. Figure 2 also shows how the compounds fit within the enzyme's active site.

Table 1: Table 3-1 shows the expected binding energies (kcal/mol) for mefenamic acid derivatives (A1–A6) and the reference inhibitor vorinostat at the active site of HDAC8 (PDB ID: 1T69).

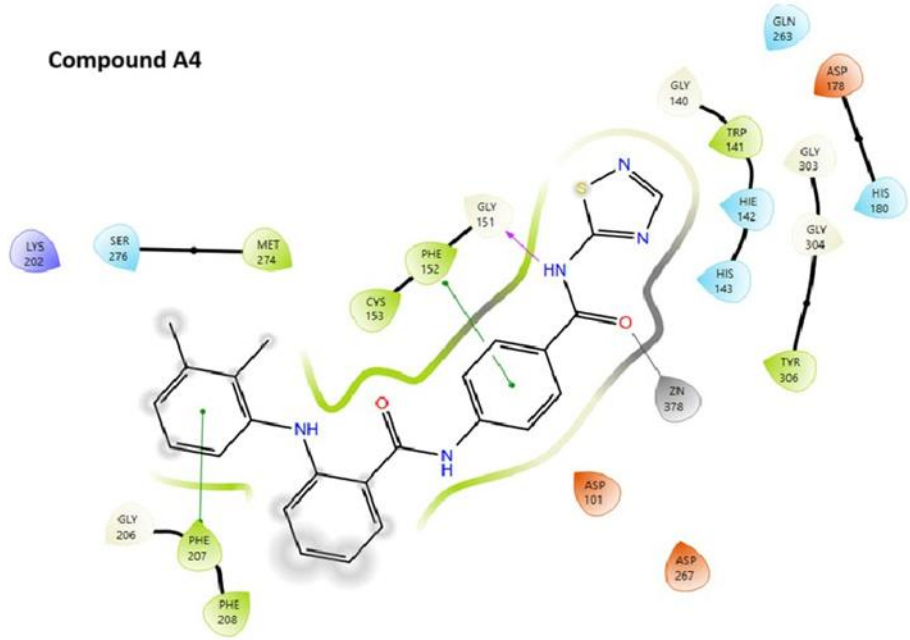
Compounds	Docking Score in Kcal/mol	Amino acid residues that play a role in ligand-receptor interaction
Compound A1	-8.432	
Compound A2	-8.911	Zn378,Gly151,Phe152,Phe207,
Compound A3	-8.957	Zn378,Gly151,Gly140,Phe152,Tyr306
Compound A4	-8.325	Zn378,Gly151,Phe152,Tyr306
Compound A5	-8.261	Zn378,Gly151,Phe152,Phe207
Compound A6	-9.539	Zn378,Gly151,Phe207,Tyr306
Vorinostat (SAHA)	-4.606	Zn378,Gly151,Gly140,Phe152



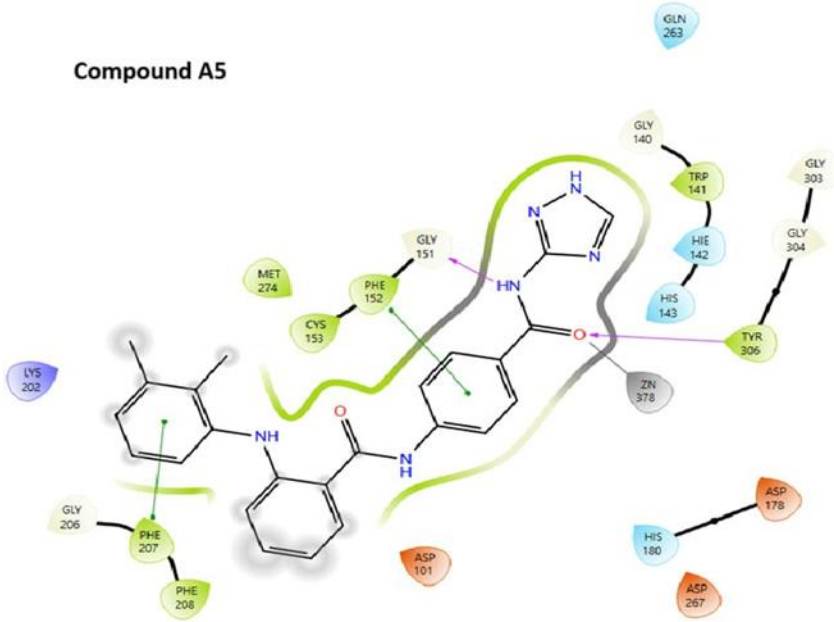

Compound A2
GLN 263
HIE 142
HIS 143
TRP 141
GLY 140
MET 274
GLY 151
PHE 152
CYS 153
LYS 202
GLY 303
GLY 304
TYR 306
ZN 378
ASP 178
HIS 180
ASP 101
ASP 267
GLY 206
PHE 207
PHE 208


Compound A3
MET 274
GLY 151
PHE 152
CYS 153
LYS 202
GLN 263
GLY 140
TRP 141
HIE 142
GLY 303
HIS 143
GLY 304
TYR 306
ZN 378
HIS 180
ASP 101
GLY 206
PHE 207
PHE 208
ASP 267

Compound A4



Compound A5



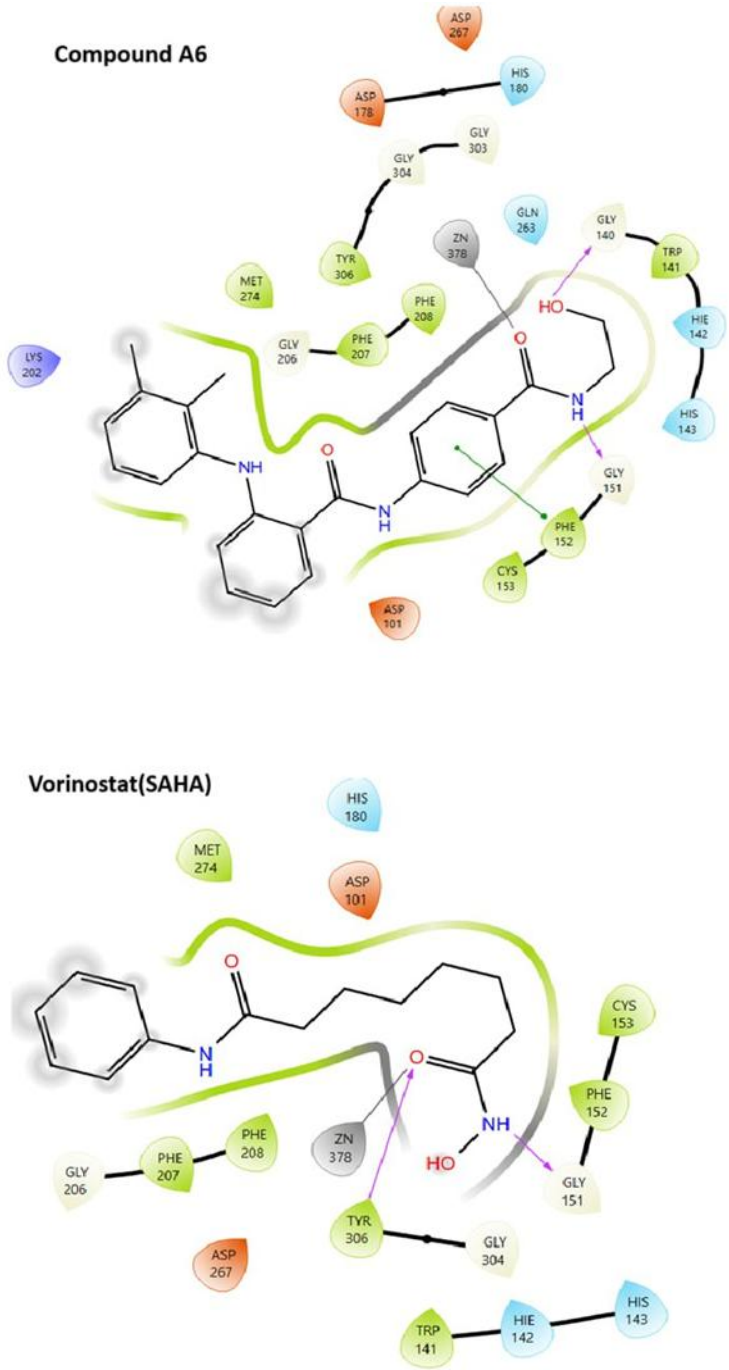


Figure 2 shows how compounds A1-A6, along with the reference inhibitor vorinostat, are positioned within the HDAC8 active site (PDB ID: 1T69).

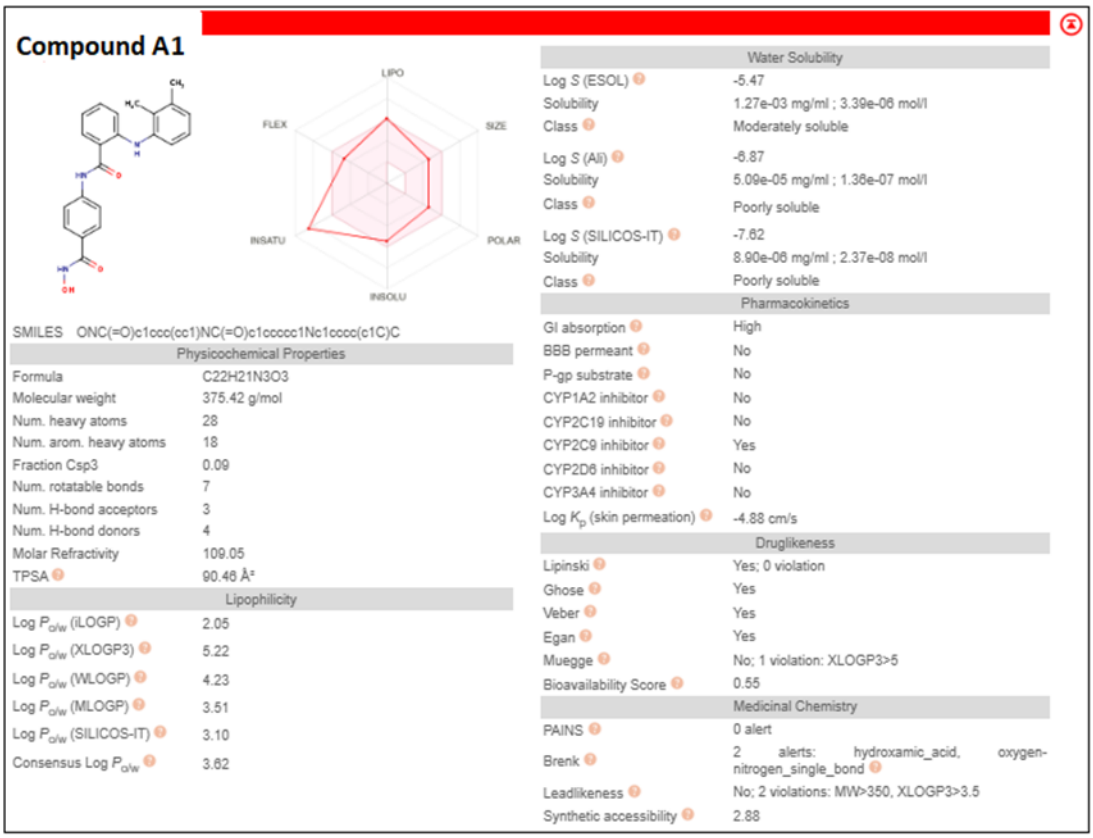
The designed derivatives displayed a marked ability to bind within the HDAC8 active site, with docking scores between -8.261 and -9.539 kcal/mol. In comparison, the reference inhibitor, vorinostat, had a much lower docking score of -4.606 kcal/mol. Compound A6 showed the highest binding energy at -9.539 kcal/mol, followed by A3 at -8.957 kcal/mol and A2 at -8.911 kcal/mol. The docking results suggest that the newly designed compounds can form more stable and energetically favorable complexes with HDAC8 than the standard inhibitor, vorinostat. The interaction study showed that all derivatives were able to coordinate with the catalytic Zn ion

(Zn378), which is a key requirement for HDAC inhibition. Addition, the compounds established several stabilizing interactions, mainly hydrogen bonds and π-π stacking with residues such as Gly151, Gly140, Phe152, Phe207, and Tyr306. These interactions help stabilize the ligand within the active pocket and maintain the proper orientation of the aromatic fragment in the catalytic tunnel. Since these interaction patterns are similar to those seen with known HDAC inhibitors, the designed molecules are expected to show inhibitory activity.

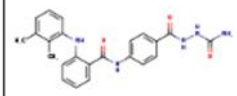
Overall, the docking results show that mefenamic acid-based derivatives have high binding affinity and preferential orientations within the HDAC8 binding pocket. Most compounds form hydrophobic, aromatic, and zinc-coordinating interactions that are required to keep the ligands stable in the catalytic channel. While some derivatives have slightly higher docking scores than others, all have structural features that suggest potential HDAC inhibitory activity.

3.2. ADME evaluation

The predicted pharmacokinetic and drug-likeness properties of the designed mefenamic acid derivatives (A1–A6) were evaluated using the SwissADME server, and the results are shown in Figure 3.



Compound A2

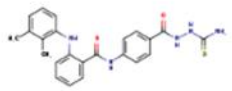


SMILES NC(=O)NNC(=O)c1ccc(cc1)NC(=O)c1ccccc1Nc1cccc(c1C)C

Physicochemical Properties	
Formula	C23H23N5O3
Molecular weight	417.46 g/mol
Num. heavy atoms	31
Num. arom. heavy atoms	18
Fraction Csp3	0.09
Num. rotatable bonds	9
Num. H-bond acceptors	3
Num. H-bond donors	5
Molar Refractivity	119.23
TPSA	125.35 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.27
Log $P_{o/w}$ (XLOGP3)	4.64
Log $P_{o/w}$ (WLOGP)	3.42
Log $P_{o/w}$ (MLOGP)	3.29
Log $P_{o/w}$ (SILICOS-IT)	2.04
Consensus Log $P_{o/w}$	3.13

Water Solubility	
Log *S* (ESOL)	-5.19
Solubility	2.71e-03 mg/ml ; 6.50e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-7.00
Solubility	4.19e-05 mg/ml ; 1.00e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-7.81
Solubility	6.51e-06 mg/ml ; 1.56e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.55 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
Synthetic accessibility	3.17

Compound A3

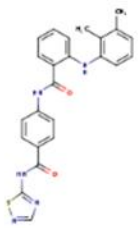


SMILES NC(=S)NNC(=O)c1ccc(cc1)NC(=O)c1ccccc1Nc1cccc(c1C)C

Physicochemical Properties	
Formula	C23H23N5O2S
Molecular weight	433.53 g/mol
Num. heavy atoms	31
Num. arom. heavy atoms	18
Fraction Csp3	0.09
Num. rotatable bonds	9
Num. H-bond acceptors	2
Num. H-bond donors	5
Molar Refractivity	126.43
TPSA	140.37 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.31
Log $P_{o/w}$ (XLOGP3)	5.24
Log $P_{o/w}$ (WLOGP)	3.59
Log $P_{o/w}$ (MLOGP)	3.26
Log $P_{o/w}$ (SILICOS-IT)	3.49
Consensus Log $P_{o/w}$	3.58

Water Solubility	
Log *S* (ESOL)	-5.66
Solubility	9.38e-04 mg/ml ; 2.16e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-7.94
Solubility	5.02e-06 mg/ml ; 1.16e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-8.00
Solubility	4.39e-06 mg/ml ; 1.01e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.22 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	No; 1 violation: TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: thiocarbonyl_group
Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
Synthetic accessibility	3.25

Compound A4

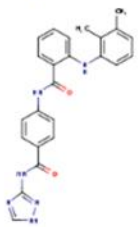


SMILES O=C(c1ccccc1Nc1cccc(c1C)C)Nc1ccc(cc1)C(=O)Nc1ncns1

Physicochemical Properties	
Formula	C24H21N5O2S
Molecular weight	443.52 g/mol
Num. heavy atoms	32
Num. arom. heavy atoms	23
Fraction Csp3	0.08
Num. rotatable bonds	8
Num. H-bond acceptors	4
Num. H-bond donors	3
Molar Refractivity	127.81
TPSA	124.25 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.71
Log $P_{o/w}$ (XLOGP3)	5.58
Log $P_{o/w}$ (WLOGP)	5.02
Log $P_{o/w}$ (MLOGP)	2.43
Log $P_{o/w}$ (SILICOS-IT)	4.65
Consensus Log $P_{o/w}$	4.08

Water Solubility	
Log *S* (ESOL)	-6.11
Solubility	3.45e-04 mg/ml ; 7.78e-07 mol/l
Class	Poorly soluble
Log *S* (All)	-7.95
Solubility	4.97e-06 mg/ml ; 1.12e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-9.18
Solubility	2.92e-07 mg/ml ; 6.59e-10 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.04 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
Synthetic accessibility	3.36

Compound A5



SMILES O=C(c1ccccc1Nc1cccc(c1C)C)Nc1ccc(cc1)C(=O)Nc1n[nH]cn1

Physicochemical Properties	
Formula	C24H22N6O2
Molecular weight	426.47 g/mol
Num. heavy atoms	32
Num. arom. heavy atoms	23
Fraction Csp3	0.08
Num. rotatable bonds	8
Num. H-bond acceptors	4
Num. H-bond donors	4
Molar Refractivity	124.29
TPSA	111.80 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.71
Log $P_{o/w}$ (XLOGP3)	4.81
Log $P_{o/w}$ (WLOGP)	4.29
Log $P_{o/w}$ (MLOGP)	2.86
Log $P_{o/w}$ (SILICOS-IT)	3.54
Consensus Log $P_{o/w}$	3.44

Water Solubility	
Log *S* (ESOL)	-5.52
Solubility	1.29e-03 mg/ml ; 3.03e-06 mol/l
Class	Moderately soluble
Log *S* (All)	-6.89
Solubility	5.49e-05 mg/ml ; 1.29e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-9.14
Solubility	3.10e-07 mg/ml ; 7.26e-10 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.49 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
Synthetic accessibility	3.17

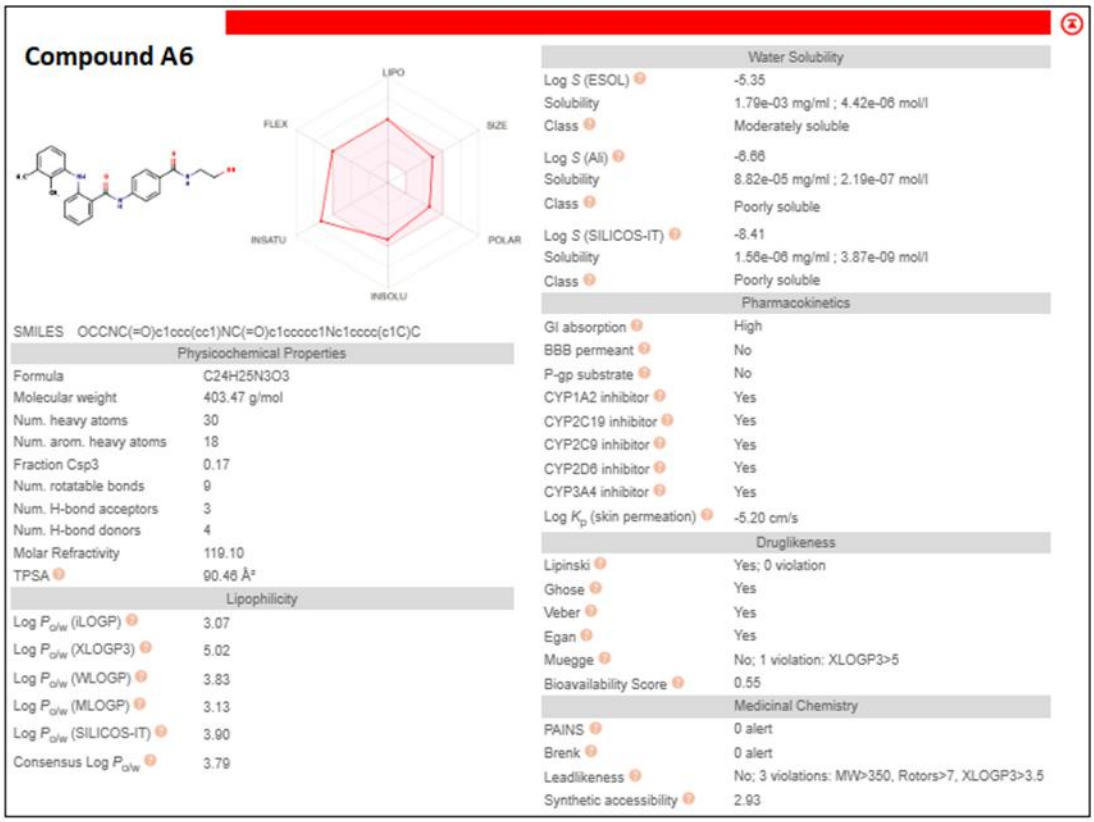


Figure 3: The expected ADME and drug-likeness features of compounds A1-A6.

The in silico ADME evaluation showed that compounds A2, A5, and A6 have high predicted gastrointestinal absorption and fully meet Lipinski's rule. This means they are likely to be well absorbed orally and have good membrane permeability. On the other hand, A1, A3, and A4 had moderate absorption profiles, suggesting that these derivatives might be better suited for parenteral (e.g., IV) administration or for localized/colon-targeted oral delivery to achieve the most therapeutic exposure.

In terms of blood-brain barrier (BBB) permeability, compounds that are predicted not to cross the BBB are less likely to cause adverse effects in the central nervous system, which may be advantageous for peripheral HDAC inhibition. Compounds that are predicted to cross the BBB, on the other hand, may have therapeutic implications in CNS-related conditions such as brain tumors or neuroinflammatory disorders, where HDAC modulation is essential.

These results were considered interesting and encouraging for future synthesis and for the in vitro and in vivo evaluation of the investigated compounds A1-6.

The predicted pharmacokinetic properties enhance the potential drug-like qualities of the designed compounds.

CONCLUSION

In this in silico study, six new mefenamic acid derivatives (A1–A6) were developed and examined to determine whether they might inhibit HDAC8. All compounds had high binding affinities, exceeding those of the reference inhibitor, vorinostat. A6 achieved the best docking score (-9.539 kcal/mol) and made a stable zinc coordination. ADME analysis showed that A2, A5, and A6 were well absorbed orally. The other compounds might be better for targeted or parenteral delivery. In general, the results show that the designed hybrids, especially A6, have properties that make them good candidates for further synthesis and biological testing as HDAC8 inhibitors. ŏTo confirm the predicted HDAC inhibitory activity of these compounds, future experimental studies on their synthesis and biological evaluation will be crucial.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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التوصيف الحاسوبي لمشتقات جديدة من حمض الميفيناميك كمثبطات لـ HDAC 8

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الخلاصة

أن العمليات الخلوية الحيوية مثل التكاثر وتقدم الورم يتم التحكم فيها بشكل مركزي بواسطة إنزيمات هيستون ديأسيتيلز (HDAC) ، مما يجعلها هدفًا علاجيًا مثيرًا للاهتمام .مؤخراً، اجتذب نموذج جديد الباحثين لدمج الأدوية غير الستيرويدية المضادة للالتهابات (NSAIDs) مع حمض البارا امينو بنزويك (PABA) ومجموعة ربط الزنك(ZBG) ، مما أظهر تأثيراً تآزرياً على نشاط إنزيمات إزالة الأسيتيل الهيستون (HDAC) وعملية الالتهاب .في الدراسة الحالية، تم تصميم سلسلة جديدة من المركبات الهجينة (A1-6) وتقييم قدرتها على الارتباط بـ HDAC باستخدام تقنية التثبيت الجزيئي، بالإضافة إلى إجراء تحليل ADME (الامتصاص، التوزيع، الأيض، والإخراج) باستخدام الحاسوب لتقييم خصائصها الدوائية . أظهر المركب A6 أعلى درجة طاقة ارتباط (-9.539 كيلو كالوري/مول) مع الموقع النشط لإنزيم HDAC 8 مقارنةً بالليغاند المرجعي، SAHA (-4.606)كيلو كالوري/مول. من الجدير بالذكر أن المركب A6 يتمتع بتنسيق مشابه لأيون الزنك مع SAHA بالإضافة إلى التفاعل الهيدروفوبي والعطري الإضافي داخل الموقع النشط لإنزيم HDAC 8. تحليل ADME توقع امتصاصًا عاليًا للجهاز الهضمي للمركبات A2 و A5وA6، والتي تتوافق أيضًا مع قاعدة ليبينسكي، مما يشير إلى توافر حيوي جيد عن طريق الفم .على العكس، أظهرت A1 و A3وA4 امتصاصًا معتدلًا، مما يجعلها مناسبة للإعطاء عن طريق الحقن أو التسليم الموضعي/المستهدف للقولون، وهو ما قد يكون مفيدًا لعلاج سرطان القولون .تُبرز هذه النتائج إمكانيات هذه الهجائن كمثبطات لـ HDAC وتدعم المزيد من التخليق والاختبار البيولوجي.

الكلمات المفتاحية: مثبطاتHDAC ، مضادات الالتهاب غير الستيرويدية، مجموعات ربط الزنك، الربط الجزيئي، ADME