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Design, Molecular Docking, and Pharmacokinetic Evaluation of 4-Aminoantipyrine Derivatives as Potential Anticancer Compounds Targeting Histone Deacetylase-2 (HDAC-2)

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ABSTRACT

Objective: Histone deacetylase-2 (HDAC-2) has emerged as an important molecular target in cancer therapy because of its role in gene silencing, regulation of the cell cycle, and resistance to apoptosis in several cancer types. In the present study, a series of novel 4-aminoantipyrine-based derivatives incorporating semicarbazide, thiosemicarbazide, and hydroxylamine pharmacophoric groups were rationally designed and evaluated for their potential HDAC-2 inhibitory activity using in silico approaches.

Methods: The binding affinity of the newly designed compounds toward the HDAC-2 enzyme and their interactions within the catalytic pocket were investigated using molecular docking analysis. The three-dimensional structure of HDAC-2 (PDB ID: 4LXZ) was obtained from the RCSB Protein Data Bank and prepared for docking studies.

Results: Docking indicated that ligand stability within the enzyme active site was mainly achieved through coordination with the catalytic zinc ion, in addition to hydrogen bonding and hydrophobic interactions with essential amino acid residues located in the HDAC-2 catalytic domain. The reference inhibitor vorinostat (SAHA) was used as a standard compound and produced a docking score of −5.445 kcal/mol. Among the designed compounds, Compound Ia exhibited the most favorable binding energy with a calculated ΔG of −9.711 kcal/mol. In addition, Compound IIe and Compound Ib demonstrated promising docking scores of −8.285 and −8.147 kcal/mol, respectively.

Conclusions: Pharmacokinetic properties were predicted using the QikProp module, revealing that most designed compounds exhibited acceptable drug-likeness according to Lipinski's Rule of Five. These computational findings suggest that the designed derivatives may represent promising candidates as HDAC-2 inhibitors with potential anticancer activity.

Keywords: semicarbazide derivative, 4-aminoantipyrine, HDAC-2 inhibitors, anticancer, thiosemicarbazide derivative.

INTRODUCTION

Cancer is a huge challenge for public health right now. In 2022 alone, there were around 20 million new cases worldwide, and close to 10 million people died from it. The numbers keep climbing, and experts expect them to get even higher in the years ahead [1]. In spite of advances in therapy, including surgery, conventional

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chemotherapy, and biological therapy, the clinical management of various types of cancer is inadequate because of therapeutic resistance, toxicity, and heterogeneity of tumors [2]. Therefore, there is an urgent unmet need to identify and develop new anticancer drugs that are more effective and have better therapeutic indices [3].

Aberrant epigenetic regulation is now increasingly recognized as one of the major hallmarks of cancer, leading to aberrant patterns of gene expression that result in the initiation, progression, and metastasis of tumors [4]. Among the enzymes that have been implicated in the regulation of epigenetics in cancer, histone deacetylases (HDACs), on the other hand, hold a position of preeminence [5]. HDACs are known to remove acetyl groups from the lysine residues of histones, thereby inducing chromatin compaction and transcriptional repression of tumor suppressor genes [6]. There are 18 members of the HDAC protein family, divided into four classes on the basis of structural and functional considerations [7]. Class I HDACs, such as HDAC-1, HDAC-2, and HDAC-3, are invariably found to be overexpressed in a variety of human cancers, and these are known to influence tumor cell proliferation, differentiation, and apoptosis. HDAC-2, a class I HDAC, has emerged as a promising target for cancer therapy owing to its overexpression in colorectal, gastric, cervical, and lung cancers, among others. Researchers have dug into the 3D structure of HDAC-2 and found something interesting: the enzyme uses a zinc ion right at its active site, which surrounded by key amino acids like Tyr308, His145, His146, Asp181, and Tyr29 in a hydrophobic channel [8]. This zinc-based catalytic setup there's a unique pocket in the enzyme when drug developers can target using zinc-binding groups like hydroxamic acid or benzamide.

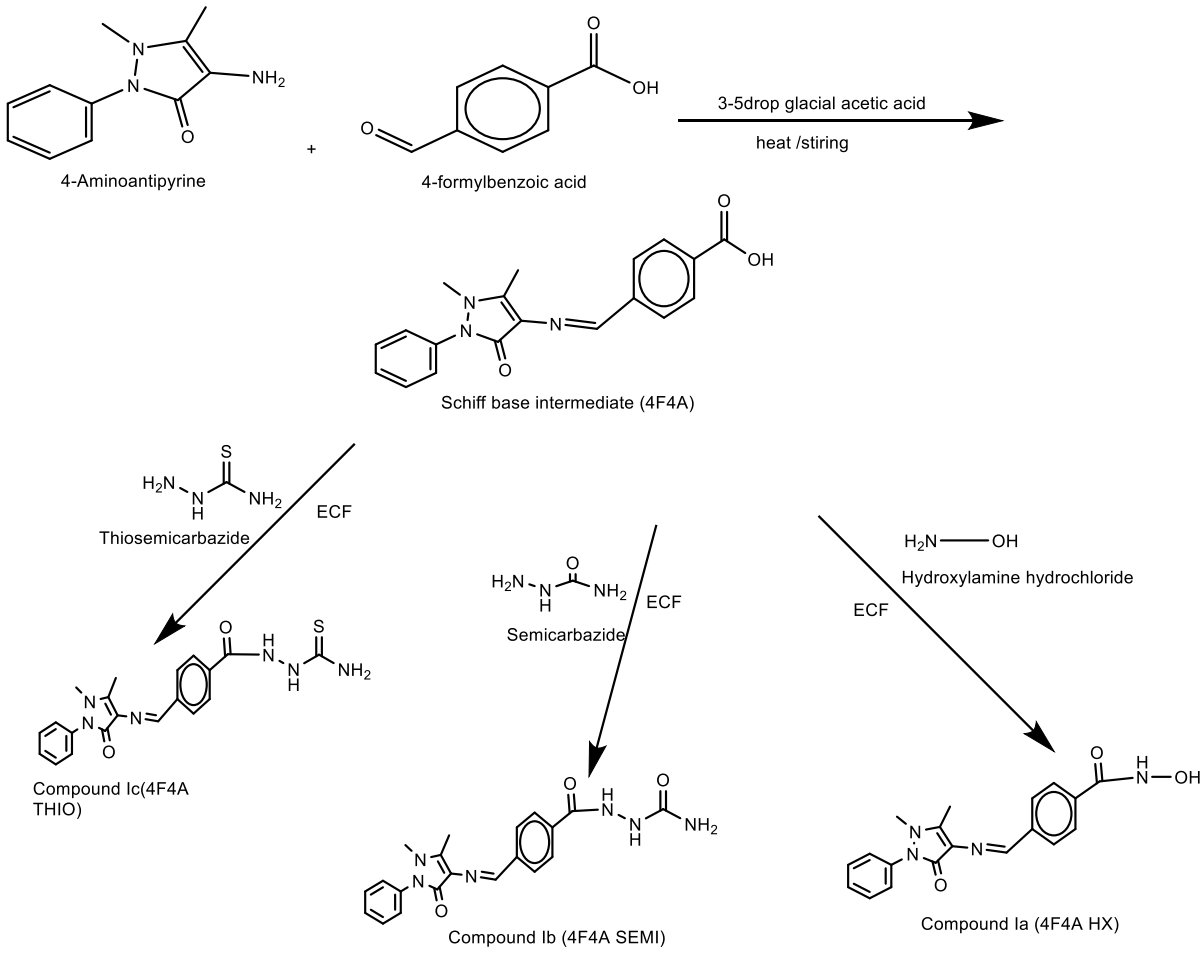
HDAC inhibition isn't just a lab idea—it's already proved itself in cancer therapy. Several small-molecule HDAC inhibitors have made it to the clinic, including vorinostat, romidepsin, belinostat, and Panobinostat [9]. It's the go-to compound for studying structure-activity relationships and running computational models of HDAC inhibition [10]. Nevertheless, the effectiveness of these HDAC inhibitors is often limited by their side effects and anticancer selectivity, which has led to ongoing efforts to develop more effective and selective HDAC inhibitors [11].

4-Aminoantipyrine (4-AAP) is a pyrazolone-based core that is recognized for its analgesic, anti-inflammatory, and antipyretic properties. In recent years, this core has gained more attention as a privileged template for the development of bioactive heterocyclic compounds [12]. The amino functional group of this core is used to anchor a variety of functional groups, such as semicarbazide derivative, thiosemicarbazide derivative, and hydrazones, which are used to develop hybrids of zinc-chelating groups and the inherent biological activity of the pyrazolone core [13]. Recent studies have shown that 4-AAP derivatives possess considerable anticancer activity against different cancer cells, confirming the utility of this structure in cancer therapy [14].

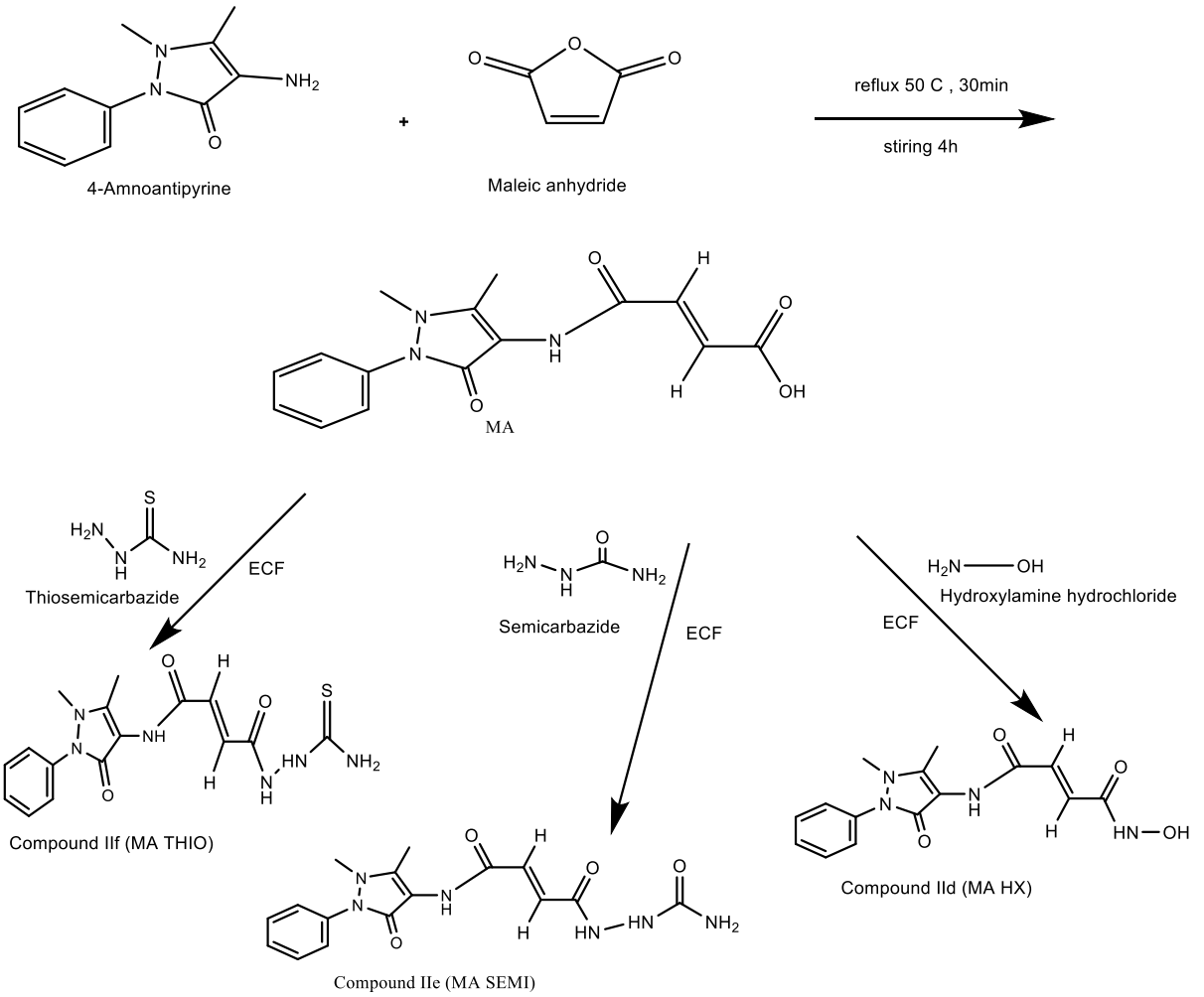
Molecular docking has emerged as an essential computer-aided tool in drug design studies that predicts the binding model and affinity of ligands to the active site of enzymes before their synthesis [15].

The current drug design study used this tool to design a set of novels 4-aminoantipyrine derivatives with different semicarbazide derivative, thiosemicarbazide derivative, and hydroxylamine functional groups [16]. These compounds were designed based on structural information from the pharmacophore model of HDAC-2 inhibitors [17]. These compounds were then subjected to molecular docking studies using the crystal structure of HDAC-2 in complex with a known inhibitor (vorinostat) (PDB ID: 4LXZ). Finally, the pharmacokinetics of these compounds were predicted using ADME prediction tools such as QikProp [18].

The results were analyzed in accordance with established structure-activity relationship studies on HDAC inhibitors to derive structure-activity relationships.



Scheme1. A suggested scheme for the synthesis of compound Ia, compound Ib , and compound Ic.



Scheme2. A suggested scheme for the synthesis of compound IId, compound IIe , and compound IIf.

MATERIALS AND METHODS

Protein Preparation

The protein-ligand complex structure of histone deacetylase-2 (HDAC-2) bound to vorinostat was downloaded from the RCSB Protein Data Bank (PDB ID: 4LXZ; https://www.rcsb.org) [19]. Before the calculation of the protein-ligand interactions via the process of molecular docking, the downloaded protein structure was extensively prepared using the Protein Preparation Wizard tool embedded in the Maestro suite of the Schrödinger suite of molecular modeling tools (Release 2025) [20, 21]. This process included the correction of inconsistencies in the protein structure that are generally present in protein-ligand complex structures obtained from X-ray crystallography. Hydrogens were added to the protein structure; bond orders were corrected to correspond to the valency of the atoms to which the bond was formed; and the protonation state of ionizable residues was corrected to correspond to physiological conditions (pH 7.4). Water molecules were removed if they were beyond 5 Å from the ligand. After protein structure preparation, a restrained energy minimization was carried out on the protein structure to eliminate any steric clashes. This was done using the OPLS4 force field and an RMSD convergence of 0.30 Å for the heavy atoms[22].

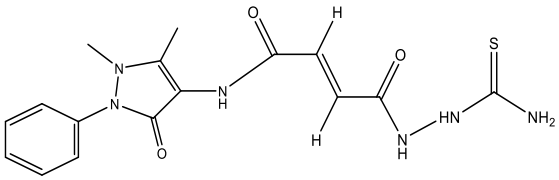
Ligand Preparation

The designed 4-aminoantipyrine analogs were created using a two-dimensional representation of the molecule using the 2D molecular editor tool provided inside the Maestro environment. Three-dimensional coordinates were generated for the compounds using the LigPrep tool provided by the Schrödinger molecular modeling package. Additionally, the protonation states were also generated at a physiological pH (7.2 ± 0.2), and low-energy conformers were also generated using the LigPrep tool. Geometry optimization was performed on all the ligand molecules using the OPLS4 force field with default computational settings. The 3D coordinates were

checked for chemical accuracy before proceeding with the docking studies. The reference inhibitor SAHA was also prepared using the same protocol for a comparative analysis [23].

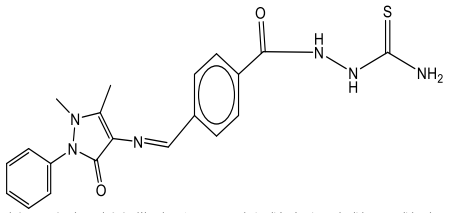
Receptor Grid Generation

Receptor grid generation for the molecular docking studies was carried out using the Glide tool provided by the Schrödinger Maestro molecular modeling package. For the molecular docking studies, the binding site was created by setting the grid center at the spatial coordinates of the co-crystalized ligand (vorinostat) placed at the catalytic site of HDAC-2. The centroid was automatically placed by the program at the geometric center of the ligand. The default grid box size was also applied for the docking studies to ensure the active site and the surrounding amino acid residues were fully covered.



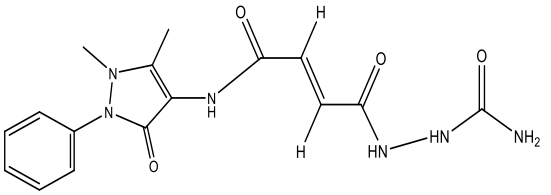
(*E*)-4-(2-carbamothioylhydrazineyl)-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-4-oxobut-2-enamide

Compound Ic (4FAA Thio)



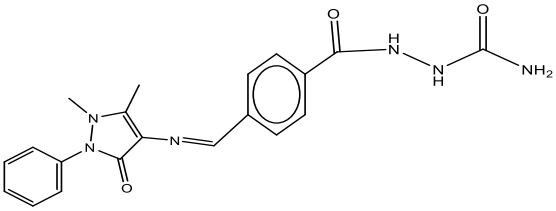
2-(4-(((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)imino)methyl)benzoyl)hydrazine-1-carbothioamide

Compound IIe (MA Semi)



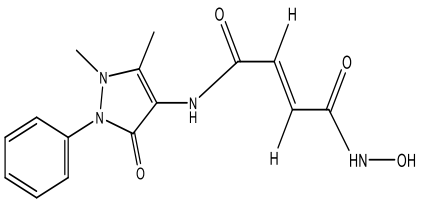
(*E*)-2-(4-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)amino)-4-oxobut-2-enoyl)hydrazine-1-carboxamide

Compound Ib (4FAA Semi)



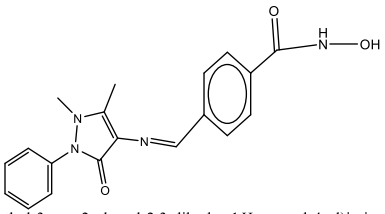
2-(4-(((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)imino)methyl)benzoyl)hydrazine-1-carboxamide

Compound IIf (MA Thio)



N^1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-N^4-hydroxyfumaramide

Compound Ia (4FAA HX)



4-(((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)imino)methyl)-*N*-hydroxybenzamide

Compound IId (MA HX)

Figure 1. Structure of proposed derivatives.

Molecular Docking Studies

Molecular docking studies were carried out using the Standard Precision (SP) and Extra Precision (XP) modes of the Glide tool provided by the Schrödinger Maestro molecular modeling package. The 4-aminoantipyrine analogs were docked into the catalytic site of HDAC-2 (PDB ID: 4LXZ) along with the standard inhibitor SAHA. The LigPrep-optimized ligand structures were utilized as inputs for all docking calculations. The GlideScore function was also employed for ranking the affinities of the ligands and the identification of the optimal docked poses. The docking protocol was validated by redocking the co-crystallized ligand (SAHA) into the binding pocket. The pose was then superimposed on the experimental binding pose. The interaction analysis of the top-ranked docking poses was conducted using the 2D Interaction Diagram tools provided by Maestro. This made it possible to map out how zinc coordinates, where hydrogen bonds form, and how hydrophobic interactions lock in with the active site residues.

ADME Pharmacokinetic Prediction

Pharmacokinetic and physicochemical properties were predicted using the QikProp tool provided by the Schrödinger Maestro molecular modeling platform. This tool is based on a validated approach using Quantitative Structure-Property Relationship (QSPR) models. The tool was utilized for the prediction of a wide range of ADME properties. The parameters evaluated include: molecular dipole moment, the number of hydrogen bond donors and acceptors, the logarithm of the octanol/water partition coefficient (QPlog o/w), the number of likely metabolic reactions (#metab), compliance with Jorgensen's Rule of Three, compliance with Lipinski's Rule of Five, and predicted percentage human oral absorption [18]. These parameters were collectively interpreted to evaluate the drug likeness and the oral bioavailability potential of each compound. For each parameter, I stuck to the acceptable ranges set by QikProp and followed standard medicinal chemistry guidelines [19].

RESULTS AND DISCUSSION

Docking Validation

The reliability of the molecular docking methodology was initially proven through redocking of the co-crystallized ligand, vorinostat, also known as SAHA, into the HDAC-2 catalytic site. This docking was done to confirm the appropriateness of the docking methodology for the evaluation of the binding behavior of the designed derivatives. This was proven to be correct, as the predicted binding orientation of the SAHA molecule, with the hydroxamic acid moiety binding to the zinc metal center of the HDAC enzyme in a bidentate fashion, correlated well with previously established crystallographic data and docking validations [8, 10].

Molecular Docking Results

The predicted binding affinities of all investigated compounds, expressed as GlideScore docking values, are compiled in Table 1. As expected, the reference compound SAHA, a known HDAC-2 inhibitor and a clinically used drug, revealed a docking score of -5.445 kcal/mol. In contrast, the designed 4-aminoantipyrine derivatives showed a wide range of binding affinities, from -4.764 to -9.711 kcal/mol, with the majority of the compounds revealing predicted binding energies that are higher than that of SAHA.

Table 1. HDAC-2 docking scores of the designed 4-aminoantipyrine derivatives and the reference compound SAHA.

Compound	HDAC-2 Docking Score (kcal/mol)
SAHA (Reference)	−5.445
Compound Ia	−9.711
Compound IIe	−8.285
Compound Ib	−8.147
Compound IIf	−5.499
Compound IId	−5.155
Compound Ic	−4.764

Compound Ia , 4-Aminoantipyrine derivative, showed the best docking scores among all tested compounds, with a ΔG of -9.711 kcal/mol. This compound showed an increase of around 4.3 kcal/mol over SAHA. Thus, the hydroxylamine pharmacophore, when combined with the 4-formylbenzoic acid–derived phenyl moiety, appears to achieve an optimal balance for both zinc coordination and geometric complementarity within the HDAC-2 catalytic channel. The aromatic ring and para-carboxyl group may enhance binding through hydrophobic contacts and potential hydrogen-bonding interactions with residues lining the active site, thereby improving overall binding stability. in addition to exerting electronic effects to augment the zinc-chelating capability of the hydroxylamine warhead [8].

Compound IIe and Compound Ib, 4-Aminoantipyrine derivative, showed good docking scores of -8.285 and -8.147 kcal/mol. This has been well studied and proven to be potent zinc-chelating agents with strong anticancer activities. This is due to the capacity of the semicarbazide pharmacophore to participate in hydrogen bonding with metalloenzyme active sites [13]. The docking scores for Compound IIe and Compound Ib were pretty close, which shows the aldehyde-derived substituent only moderately affects binding energy in this group of compounds.

Compound IIf and Compound IId had docking scores of -5.499 and -5.155 kcal/mol, right in line with the reference compound SAHA. That suggests the compounds, thiosemicarbazide derivative and hydroxylamine analogs, have a basic level of HDAC-2 inhibitory activity. However, Compound Ic showed the lowest docking score at -4.764 kcal/mol among all the designed compounds. This suggests that the thiosemicarbazide derivative warhead may indicate that this compound does not interact optimally with the HDAC-2 active site. It looks like the warhead's size doesn't quite fit the catalytic channel, or maybe the sulfur atom isn't lining up with the zinc ion like it should [15].

Molecular Interaction Analysis

When visualizing and analyzing the top docking poses, a clearer picture of the key molecular interactions that stabilize the ligand inside the HDAC-2 catalytic site. As described in Figure 2, the binding of high-affinity ligands, such as Compound Ia, was mediated by three types of molecular interactions: (i) direct zinc ion coordination by the zinc-binding groups of the hydroxamic acids and semicarbazide derivative; (ii) hydrogen bonding to the HDAC-2 catalytic site residues His145, His146, Tyr308, and Asp181; and (iii) hydrophobic interaction with the HDAC-2 hydrophobic tube.

Metal ion coordination, described by coordinate bonds between the zinc ion and the zinc-binding groups of the inhibitors, was a common feature of all high-affinity ligand poses. This interaction was critical for HDAC inhibitory activity. In fact, zinc ion coordination by hydroxamic acids and their bioisosteres was shown to displace the water molecule necessary for HDAC enzymatic activity, thereby inhibiting HDAC enzymatic function. The maintenance of this interaction in the docked poses of Compound Ia, Compound IIe, and Compound Ib strongly supports the predicted efficacy of these inhibitors.

Hydrogen bonding between the functional groups of the ligand and the key active site residue side chains, such as His145, His146, and Tyr308, has previously been identified as a critical factor for the binding affinity of HDAC inhibitors, based on a number of crystallographic and simulation studies [8, 10]. The hydrogen bonding patterns observed for the docked binding modes of the highest-ranking compounds were also consistent with the previously identified patterns, supporting the biological relevance of the binding modes predicted by the docking studies.

The hydrophobic interactions between the aryl and heteroaryl groups of the 4-aminoantipyrine core structure and the hydrophobic amino acid side chains Phe155, Phe210, and Leu276 of the binding channel are expected to significantly contribute to the higher binding affinity of the 4-aminoantipyrine + 4-formylbenzoic acid -containing derivatives. The addition of the 4-formylbenzoic acid-derived phenyl moiety enhanced hydrophobic interactions within the binding pocket; found to result in the optimal van der Waals interactions within the hydrophobic binding pocket, based on the reported SAR studies of HDAC inhibitors [11,14].

Structure-Activity Relationships

Collectively, the docking studies provide initial observations for the designed compound series. For example, the following trends were noted: (i) the hydroxylamine warhead, when paired with 4F4A, provided the highest binding affinity, indicating the optimal geometry for zinc coordination and complementarity of the active sites; (ii) semicarbazide derivatives (SEMI) were generally more potent than the thiosemicarbazide derivative (THIO) for both the 4F4A and the maleic anhydride- derived (MA series) substitution patterns; (iii) the 4F4A series did not uniformly demonstrate higher binding affinity compared to the methyl-substituted series, indicating that the pharmacophore warhead played a more dominant role in binding affinity compared to the influence of the aldehyde-derived warhead for the compound series; (iv) the thiosemicarbazide derivative warhead generally provided lower docking scores compared to the hydroxylamine and semicarbazide derivative warheads, suggesting that the larger sulfur atom may impart a steric or electronic penalty for the zinc binding pocket.

ADME Pharmacokinetic Prediction

The pharmacokinetic and physicochemical parameters of the proposed compounds and the reference drug SAHA, which were calculated and predicted using the QikProp module and are given in Table 2, are indicative of a theoretical estimation of the drug-like and bioavailability potential of each compound according to medicinal chemistry principles.

Table 2. Predicted ADME pharmacokinetic properties of the designed 4-aminoantipyrine derivatives and SAHA.

Comp.	Dipole	Donor HB	Accpt HB	QPlog o/w	#metab	RO3	RO5	% Oral Abs.
SAHA	11.558	3.000	6.700	0.747	3	0	0	70.477
Compound IIf	11.271	3.500	10.000	1.059	2	0	0	65.124
Compound Ic	14.800	3.250	9.250	2.518	2	1	0	79.844
Compound Ib	4.488	2.500	8.000	1.624	2	1	0	59.671
Compound Ia	14.190	2.000	9.200	1.621	1	0	0	76.518
Compound IIe	5.302	2.750	8.750	0.124	2	1	0	43.920

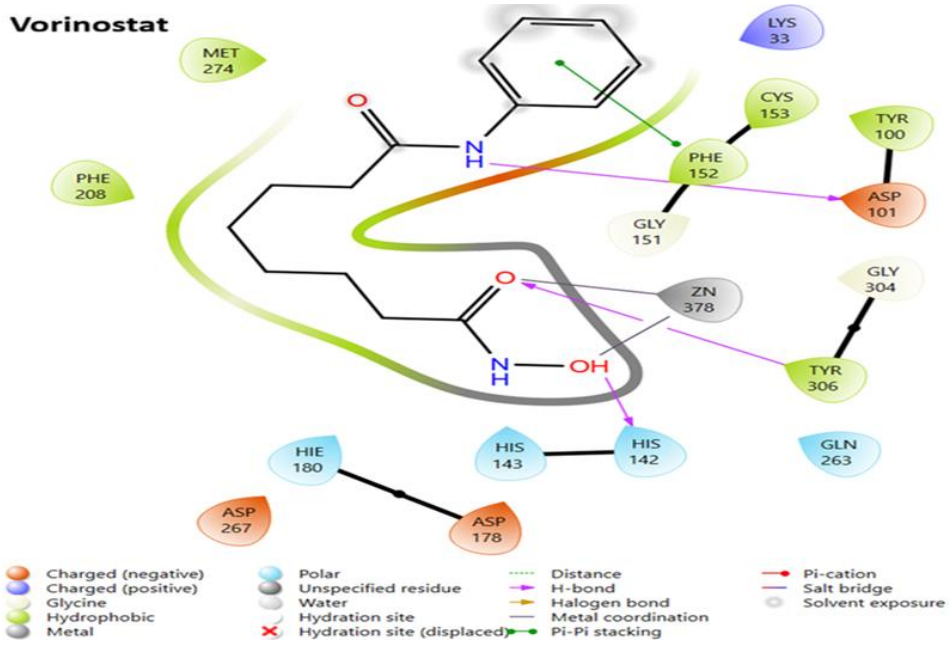
Recommended QikProp ranges: Dipole 1.0–12.5 D; HB Donors 0–6; HB Acceptors 2–20; QPlog o/w −2 to 6.5; #metab 1–8; RO3: violations 0; RO5: violations ≤4; % Human Oral Absorption >80% high, <25% low.

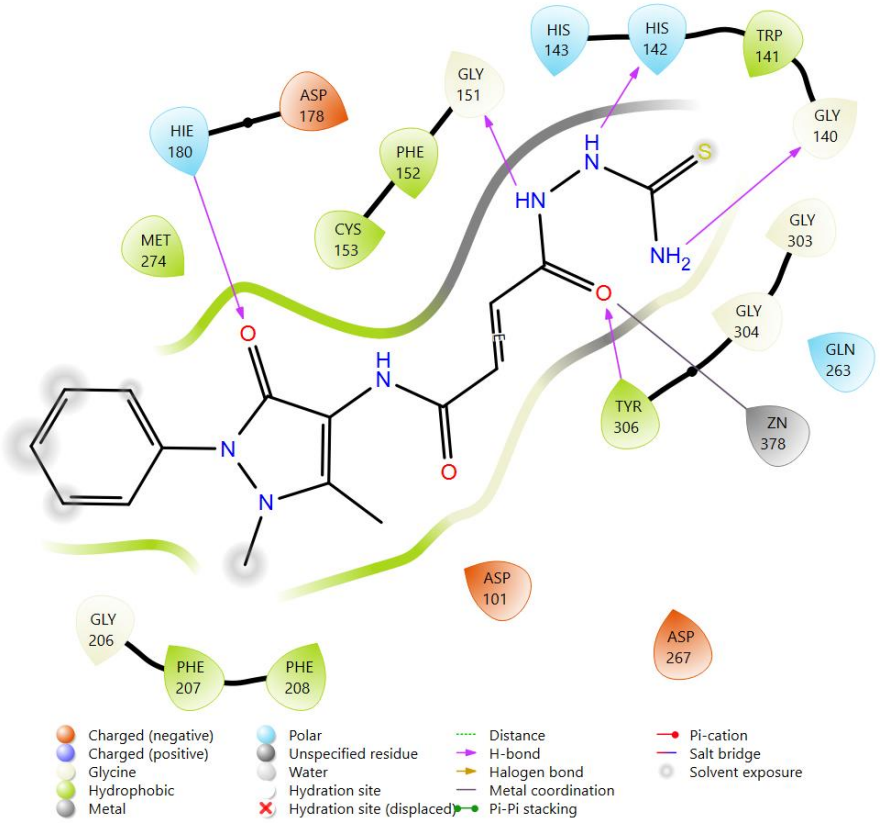
The designed compounds were also tested in compliance with the rule of Five (RO5) by Lipinski. The bioavailability of orally administered drugs is a property that is linked to a molecular weight ≤ 500 Da, a cLogP ≤ 5, a number of hydrogen bond donors ≤ 5, and a number of hydrogen bonds acceptors ≤ 10 [19]. The synthetic compounds developed were discovered to be Lipinski RO5 compliant with no or a few violations. This correlates with the moderate size of the molecule of 4-aminoantipyrine core, as well as the simple pharmacophoric groups employed in the designing process [12, 13] . When looking at hydrogen bonding, the compounds struck the correct numbers of both donors and acceptors as QikProp would. In the case of donors, the counts were between 2.000 in Compound Ia and 3.500 in Compound IIf. In terms of acceptors, they increased to 10.000 in compound IIf after being at 6.700 at SAHA. The increase in acceptor number in Compound IIf and Compound Ic due to the additional nitrogen and sulfur in the thio semicarbazide derivative moiety. The QPlog o/w is essentially the logarithm of the partition coefficient of octanol and water which is used to determine the permeability of the membrane and the lipophilic nature of a compound. To achieve a desired effect when the compound is not administered orally, a QPlog o/w of between -2.0 and 6.5 should be obtained. Our entire design remained in this range, with 0.124 as the highest value in the case of compound IIe and 2.518 in the case of compound Ic. Therefore the compounds possess the desired lipophilicity.

The predicted human oral absorption values were also inconsistent in the compound set. Compound Ic possessed the highest predicted oral absorption (79.844%), followed by compound Ia (76.518%) and SAHA (70.477%). Compounds IIe and IId possessed lower predicted oral absorption values at 43.920%, which may indicate limitations in oral bioavailability that could be addressed through structural optimization. Finally, the predicted metabolic reactions (#metab) ranged from 1 to 3 for the entire set of compounds, which is consistent with drug compounds.

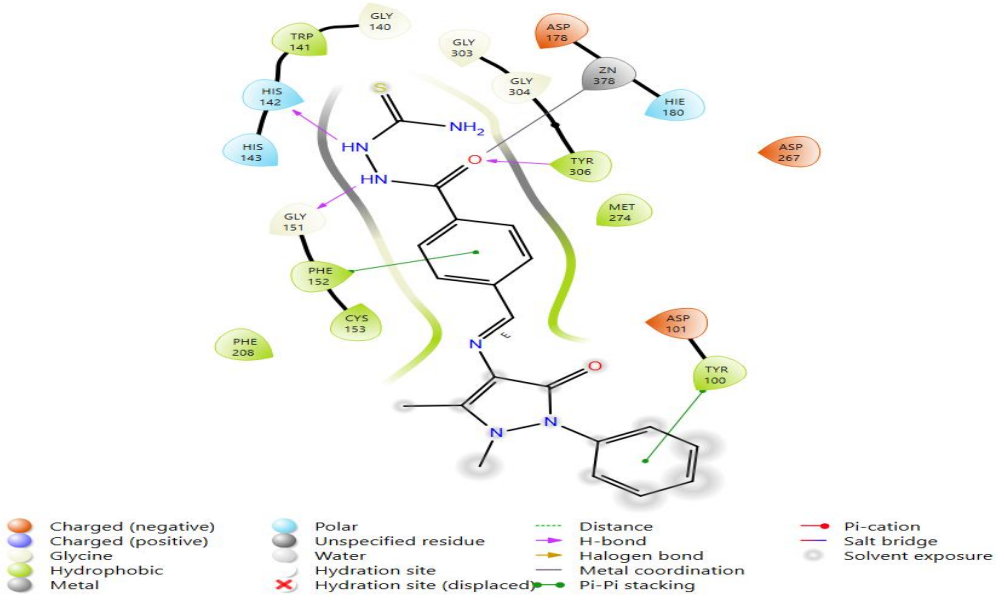
The molecular dipole moments of the designed compounds were also inconsistent and ranged from 4.488 D (Compound Ib) to 14.800 D (Compound Ic). Elevated dipole moments in thiosemicarbazide derivative analogs could be due to electronic asymmetry caused by the presence of a polarizable C=S bond, which may affect solubility and membrane permeability characteristics [16].

From the results obtained for the ADME profiling, it can be concluded that the vast majority of the designed 4-aminoantipyrine derivatives have acceptable characteristics for a drug, which makes them suitable for further development as leads for additional synthetic and biological studies. Compound Ia, which has the best docking score and favorable ADME characteristics, including 76.518% oral absorption and one metabolic reaction, is of particular interest for further development.

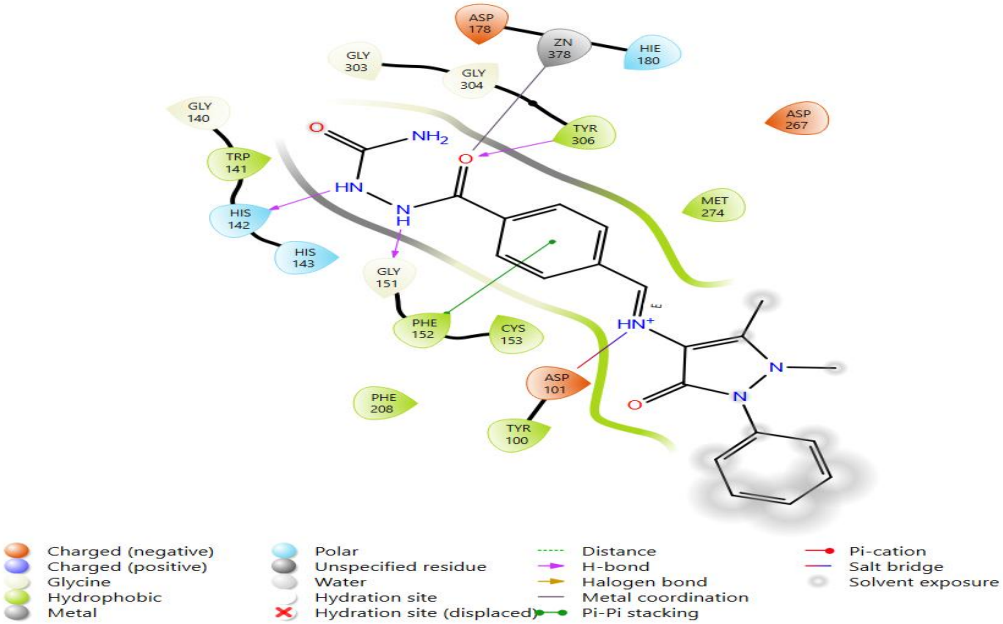




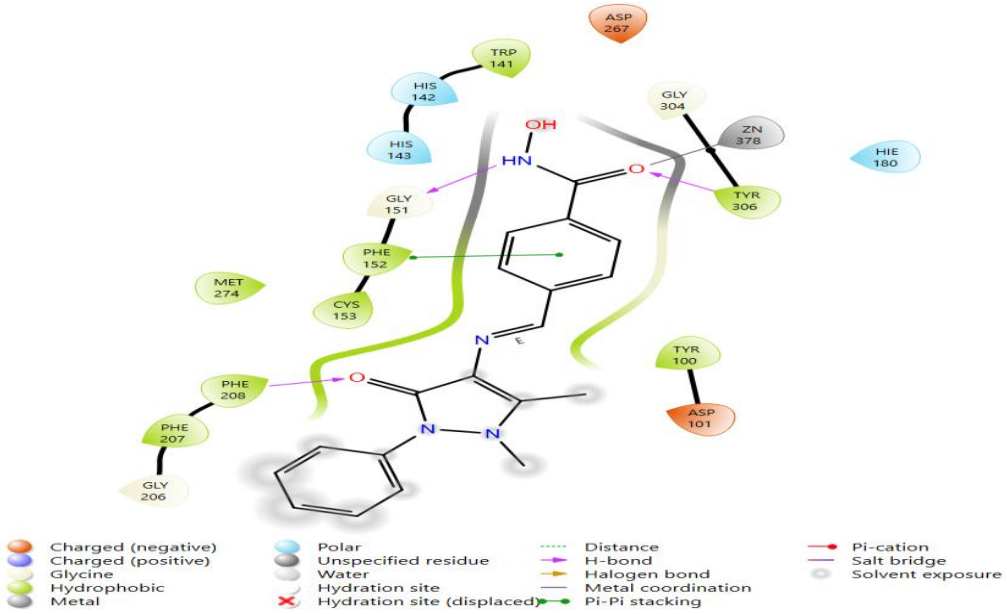
Compound IIf



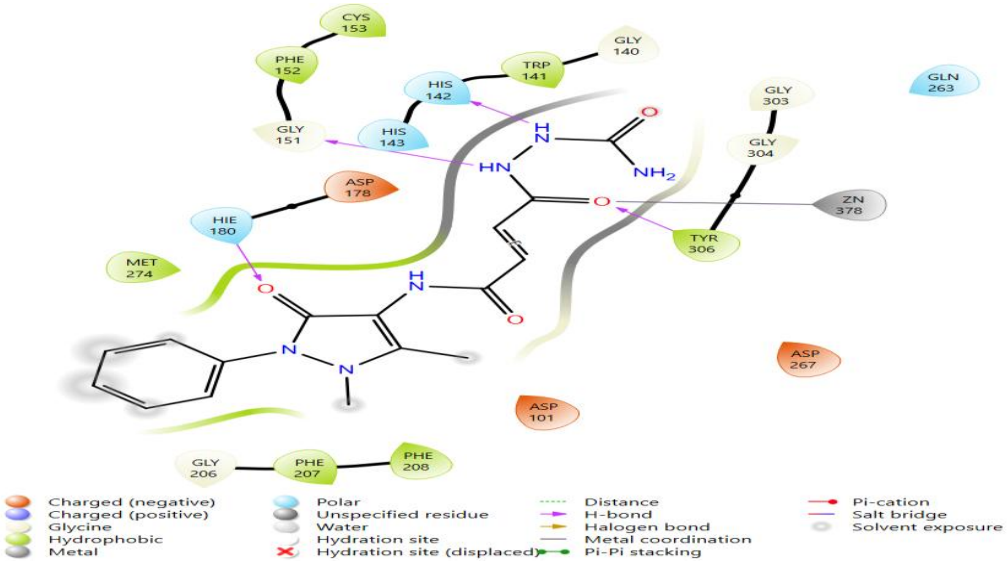
Compound Ic



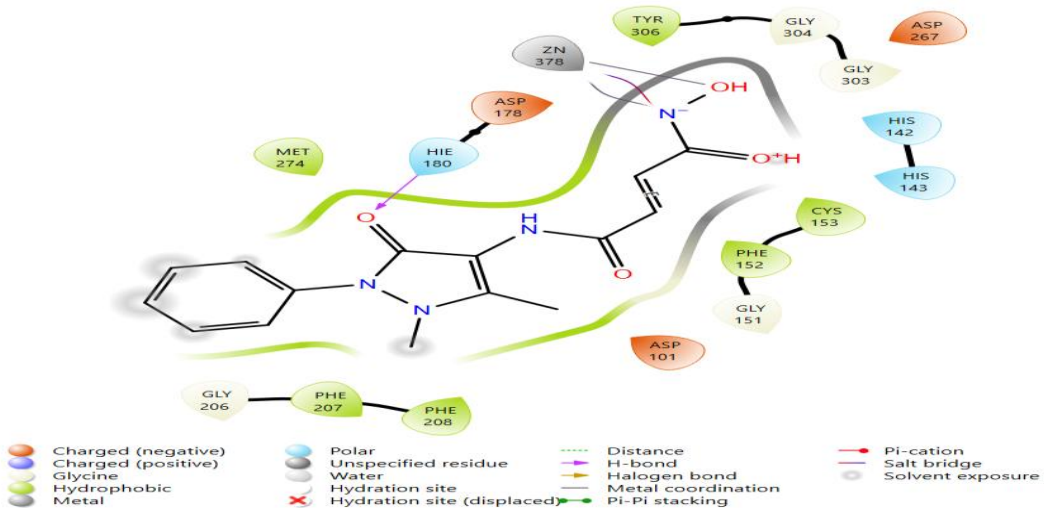
Compound Ib



Compound Ia



Compound IIe



Compound IId

Figure 2: The investigated compound (and SAHA) docked in the HDAC enzyme.

CONCLUSION

The computational strategy adopted in this research, which involves the concurrent application of structure-based molecular docking and pharmacokinetics profiling, enables a multi-dimensional evaluation of the drug potential of the designed 4AA-based HDAC-2 inhibitors. The observation that certain compounds in this series exhibit good binding affinity in addition to drug-like characteristics supports the rationale for their evaluation. The marked increase in predicted binding affinity for Compound Ia compared to the reference SAHA ($\Delta\Delta G \approx -4.3$ kcal/mol) is intriguing and should be understood in the context of the structural elements that have led to this observation. Indeed, the hydroxylamine pharmacophore has been established as a potent zinc-chelating bioisostere of the hydroxamic acid functional group that is known to bind to the Zn^{2+} ion in the active site via a bidentate coordination mode. From a broader medicinal chemistry point of view, the 4-aminoantipyrine core structure may have some inherent advantages for HDAC inhibitors. The pyrazolone ring system imparts conformational rigidity to the attached zinc-binding warhead, pre-orienting the binding moiety for effective binding to the active site. In addition, the presence of the phenyl ring can potentially interact with the aromatic amino acid residues at the outer rim of the HDAC-2 binding channel through π-stacking and CH-π interactions. These computational findings suggest that the designed derivatives may represent promising candidates as HDAC-2 inhibitors with potential anticancer activity. However, the predictions obtained must be validated through the synthesis and biological activity of the compounds, in addition to hydrogen bonding and hydrophobic interactions with essential residues. Furthermore, ADMET analysis and Lipinski's rule of five confirmed that these compounds possess favorable pharmacokinetic properties and drug-likeness. These findings highlight the potential of these derivatives as promising candidates for further development as effective anticancer agents.

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CONFLICTS OF INTEREST

No conflict of interest

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ETHICS STATEMENTS

Not applicable

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تصميم، ودراسة الإرساء الجزيئي، وتقييم الحركية الدوائية لمشتقات 4-أمينو أنتيبيرين كمركبات محتملة مضادة للسرطان تستهدف إنزيم "هستون دي أسيتيلاز-2(HDAC-2) "

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الخلاصة

الهدف: يُعد إنزيم "هستون دي أسيتيلاز-2 (HDAC-2) "هدفاً جزيئياً واعداً في علاج السرطان، نظراً لدوره في إسكات الجينات، والتحكم في دورة الخلية، والهروب من الموت الخلوي المبرمج في أنواع مختلفة من السرطانات. في الدراسة الحالية، تم تصميم سلسلة من المركبات الجديدة القائمة على هيكل "4-أمينو أنتيبيرين" مع مجموعات "فارماكوفور" من السيمي كاربازون، والثيوسيمي كاربازون، والهيدروكسيلامين بشكل عقلاني، واستقصاء قدرتها على تثبيط إنزيم HDAC-2 باستخدام تقنيات الحاسوب.(in silico)

الطرائق: تم تحليل تقارب المركبات المصنعة حديثاً لإنزيم HDAC-2 وتفاعلها مع الموقع الحفزي للإنزيم باستخدام تقنيات الإرساء الجزيئي (Molecular Docking).

النتائج: تم الحصول على بنية إنزيم HDAC-2 المعرف الرقمي 4 (LXZمن بنك بيانات البروتينات .(RCSB) واستُخدم المركب القياسي "فورينوستات (SAHA) "لحساب درجات الإرساء، حيث سجل قيمة -5.445 كيلو كالوري/مول.

ضمن هذه السلسلة من المركبات، أظهر المركب **4F4A HX**أفضل طاقة ارتباط محسوبة $\Delta G = -9.711$ كيلو كالوري/مول). وبالمثل، سجلت المركبات **MA SEMI**و **4F4A SEMI**درجات إرساء جيدة بلغت -8.285 و -8.147 كيلو كالوري/مول على التوالي. ومن خلال التفاعلات، لوحظ أن استقرار الارتباط في الموقع النشط للإنزيم قد تحقق من خلال التنسيق مع أيون الزنك، والروابط الهيدروجينية، والتفاعلات الكارهة للماء مع الثمالات الحفزية الحرجة للإنزيم.

الاستنتاجات: تم إجراء ملف الحركية الدوائية للمركبات باستخدام وحدة(QikProp) ، والتي أكدت أن غالبية المركبات المصممة أظهرت خصائص جيدة "تشبه العقاقير (drug-likeness) "وفقاً لتوقعات "قاعدة ليبينسكي الخماسية". تشير نتائج هذه الدراسة الحسابية إلى أن الإمكانات العلاجية لهذه المركبات كمثبطات لإنزيم HDAC-2 هي إمكانات كبيرة وذات أهمية.

الكلمات المفتاحية: -4أمينو أنتيبيرين، مثبطاتHDAC-2 ، مضاد للسرطان، مشتقات سيمي كاربازايد، مشتقات ثيوسيمي كاربازايد.