Tropical Journal of Pharmaceutical Research July 2024; 23 (7): 1069-1076
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v23i7.4

Original Research Article

Molecular docking, ADMET, molecular dynamic simulation, synthesis, and preliminary antiproliferative study of 1,2,4-thiadiazole derivatives as possible histone deacetylase inhibitors

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Sent for review: 15 April 2024 *Revised accepted: 9 July 2024*

Abstract

Purpose: *To develop new histone deacetylase (HDAC) inhibitors with thiadiazole moiety as a zinc-binding group.*
Methods: *Maestro software was utilized to design new HDAC inhibitors. The organic synthesis of compounds* ***VIa-VIc*** *was started with the Williamson reaction between benzylic halide derivatives and methyl 4-hydroxybenzoate to form ethers* ***IIIa-IIIb****. The resultant ethers were subjected to ester hydrolysis, followed by an amide reaction with 1,2,4-thiadiazol-5-amine to produce the final compound* ***VIa-VIc****. The structures of synthesized compounds were characterized using NMR and FTIR spectroscopic techniques. Anti-proliferative activity on colon cancer cells (HRT) was evaluated using MTT assay.*
Results: *Docking study revealed that compounds* ***VIa-VIc*** *had in silico binding affinity for HDAC enzymes, while MTT assay showed that the* IC_{50} *values of* ***VIa*** *and* ***VIc*** *(1.00 and 1.44 µM, respectively) were comparable to* IC_{50} *of 3.00 µM for the reference compound, vorinostat used in this study.*
Conclusion: *New potential HDAC inhibitors with a thiadiazole moiety as a possible zinc-binding group have been successfully designed, synthesized and characterized. Results from preliminary cytotoxicity evaluation were highly promising. These findings may be useful for developing novel therapeutic agents.*

Keywords: *Histone deacetylase, Molecular docking, Vorinostat, Thiadiazole*

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INTRODUCTION

Histone deacetylase (HDAC) enzymes remove acetyl groups from lysine residues, thereby restoring the positive charge on the side chain [1]. The abundant presence of the unbound ϵ-amino group of lysine makes for robust binding between histones and negatively charged DNA. Moreover, hypoacetylation impedes the processes of angiogenesis, migration, invasion, and cell adhesion, thereby ultimately initiating and advancing the development of malignancies [2]. Mammalian tissues contain eighteen distinct HDAC isoforms, constituting members of the major classes I–IV. Histone deacetylases 1-3 and 8 (HDAC 1-3 and 8) belong to class I, while

the isoforms 4–7, 9, and 10 belong to class II, and isoform 11 represents class IV [3]. The catalytic site of each of these three classes is dependent on zinc ions [4]. The inhibition of HDAC enzymes is a promising strategy for the treatment of cancer. Indeed, several HDAC inhibitors such as Vorinostat, Romidepsin, Panobinostat, and Belinostat, have been approved for clinical use [5].

A typical HDAC inhibitor consists of three functional domains: a zinc-binding group (ZBG), a linker, and a cap group (CG). The ZBG forms coordination bonds with the zinc ion located within the enzyme active site [6]. The primary approach to inhibition of HDAC is through chelation of zinc ions [7]. Three HDAC inhibitors commonly used in clinical practice contain hydroxamate moiety as a ZBG. Hydroxamates exhibit significant toxicity and possess unfavourable pharmacokinetic properties [8]. Therefore, this work was aimed at discovering new HDAC inhibitors involving a novel ZBG.

EXPERIMENTAL

Materials and equipment

The starting materials were obtained from suppliers (Merck, Sigma Aldrich, Liyan and Macklin) and were utilized without further purification. The solvents used were dried using 3 Å molecular sieves. Macherey-Nagel TLC plates were used for monitoring reactions, while FTIR spectroscopy was conducted using the Shimadzu IRAffinity-1 Spectrometer (Shimadzu, Japan). Moreover, 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectroscopy were conducted using a Bruker Avance III spectrometer.

Molecular docking studies

Docking investigation was performed using Glide program from Schrodinger's modeling suite version 13. 0135. The HDAC2 (4LXZ), HDAC8 (1T69) and HDAC6 (5EDU) were obtained from the protein data bank website [8-10]. The proteins were prepared utilizing the protein preparation workflow within Maestro software. The receptor grid was generated to establish the boundary box in the dimensions of 12 Å x 12 Å x 12 Å. The ligand structures were drawn using the 2D Sketcher within Maestro program, in addition to utilizing LigPrep in Maestro suite. The energy for the prepared ligands was minimized using force field OPLS_2005 [10]. The prepared ligands were docked into the prepared HDAC enzymes using Glide software in standard precision (SP) [11].

ADMET study

The ligands were subjected to structure-based prediction of pharmacokinetic properties to assess their drug-likeness. This was performed in the fast mode using QIKProp tool within Maestro software, and the option "Identify the five most similar drug molecules" was also used [12].

Molecular dynamic simulation

Compounds with satisfactory *in silico* grades were utilized in molecular dynamics (MD) studies using Desmond tool within Maestro software version 2.0 (13). The MD simulation system was constructed using system builder wizard incorporating the SPC water model. The system was limited within the orthorhombic periodic box in the dimension of 10 Å using the OPLS_2005 force field. Neutral pH environment was accomplished by the addition of counter ions (Na^+ and Cl^-). The MD simulations were conducted for 50 nanoseconds (nano sec), with data recorded every 50 picoseconds. The simulations were carried out at 300 Kelvin and 1 bar.

Chemical synthesis

General method for the synthesis of methyl 4-(benzyloxy) benzoate derivatives (IIIa-IIIc)

Into a round bottom flask were added methyl 4-hydroxybenzoate (I) (0.76 g, 7.5 mmol, 1.5 equivalent); K_2CO_3 (0.69 g, 5 mmol, 1 equivalent), and 15 mL of solvent (DMSO). The mixture was stirred at 50 ^{o}C for 100 min. Then, the derivatives of benzylic halides (IIa-IIc) (5 mmol, 1 equivalent) were separately added and stirred for 5 h. At the end of the reactions, crude products were washed with distilled water and then recrystallized with ethanol to obtain pure products (IIIa-IIIc) with reaction yields of 80 – 90 % [14].

Methyl 4-((4-methyl-benzyl) oxy) benzoate (IIIa): melting point (M. pt.): 93 - 95 ^{o}C; FTIR bands: 2951 and 2843 for aromatic C-H str., 1708 for (ester C=O str.), and 1246 and 999.13 for ether C-O str. bands); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 7.7 Hz, 2H), 7.20 (d, *J* = 7.6 Hz, 2H), 7.11 (d, *J* = 8.7 Hz, 2H), 5.13 (s, 2H), 2.30 (s, 3H), 3.81 (s, 3H).

Methyl 4-((3-nitrobenzyl) oxy) benzoate (**IIIb):** M.pt. 135 - 137 ^{o}C. FT-IR bands: 3109, 2962 for aromatic C-H str., 1705 for ester C=O str., 1516/1346 for nitro N-O str. bands, and

1257/1107 for ether C-O str. bands. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.21 (d, *J* = 8.3 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 3H), 7.72 (t, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 3.81 (s, 3H), 5.36 (s, 2H).

Methyl 4-((1,1'-biphenyl)-4-ylmethoxy) benzoate (IIIc): M.pt. 122 - 125 ^{o}C. FTIR bands: 3032, 2881 for aromatic C-H str.; 1708 for ester C=O str., and 1111 and 1002 for ether C-O str. bands. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 – 6.98 (m, 13H), 5.25 (s, 2H), 3.82 (s, 3H).

General method for the synthesis of 4-(benzyloxy)benzoic acid derivatives (IVa-IVc)

The mixture of IIIa-IIIc (5 mmol, 1 equivalent) and sodium hydroxide (1.2 g, 10 % aqueous solution, 30 mmol, 6 equivalent) was separately mixed with a 1:1 solvent mixture of methanol and tetrahydrofuran (4 mL/mmol), followed by stirring at laboratory temp. for 16 h. The residues produced were rinsed in 3 N hydrochloric acid (HCl) and filtered to obtain grey powder products (**IVa**-**IVc**) at yields of 90 - 95 % [15].

4-((4-methyl-benzyl) oxy) benzoic acid (IVa). M.pt. range: 195 - 200 ^{o}C, with FT-IR bands 2877 (for acid O-H str.) and 1674 (for acid C=O str.).

4-((3-nitro-benzyl) oxy) benzoic acid (**IVb**). M.pt. range: 230 - 233 ^{o}C, with FT-IR bands 2866 (for acid O-H str.), 1674 (for acid C=O str.), and 1523/1354 (for nitro N-O str.).

4-((1,1'-diphenyl)-4-ylmethoxy) benzoate (IVc). M.pt. range: 128 - 130 ^{o}C, with FT-IR bands 3032 for acid O-H str. and 1670 for acid C=O str.

Method used for preparation of final compounds (VIa-**VIc)**

Into a round-bottom flask were separately added **IVa**-**IVc** (5 mmol, 1 equivalent), followed by EDC (1 g, 5.5 mmol, 1.1 equivalent); DIPEA (3.22 g, 10 mmol, 5 equivalent); HOBT (0.06 g, 0.5 mmol, 0.5 equivalent), and DCM (0.015L). All mixtures were vortexed for 1 h, after which 1,2,4-thiadiazol-5-amine **V** (0.5 g, 5 mmol, 1 equivalent) and DMAP (0.67 g, 5.5 mmol, 1.1 equivalent) were added, followed by 18-h stirring at laboratory temperature. All products were washed in 5 % HCl and 10 % $NaHCO_3$ and the resultant residues were subjected to column chromatography using neutralized silica gel in a mobile phase of ethyl acetate: hexane, to obtain the products **VIa**-**VIc** with purity of 40 – 45 % [16].

4-((4-Methylbenzyl)oxy)-*N*-(1,2,4-thiadiazol-5-yl)benzamide (VIa): White powder, M.pt. range: 210 - 213 ^{o}C, with FT-IR bands 3140 for amide N-H str. and 1654 for amide C=O str. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.35 (s, 1H), 8.54 (s, 1H), 8.20 – 8.12 (m, 2H), 7.36 (d, J = 7.8 Hz, 2H), 7.24 – 7.14 (m, 4H), 5.17 (s, 2H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d6): δ 176.36, 166.16, 162.88, 158.98, 137.82, 133.82, 131.14, 129.52, 128.42, 123.21, 115.39, 69.96 and 21.25.

4-((3-Nitrobenzyl)oxy)-*N*-(1,2,4-thiadiazol-5-yl)benzamide (VIb): Yellow powder, M.pt: 235 - 237 ^{o}C. FT-IR: 3143 for amide N-H str., and 1654 for amide C=O str. ^{1}H NMR (400 MHz, DMSO-d6): δ 13.36 (s, 1H), 8.53 (s, 1H), 8.35 (t, J = 2.0 Hz, 1H), 8.35 – 7.72 (m, 6H), 7.28 – 7.19 (m, 2H), 5.39 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d6): δ 176.34, 166.12, 162.42, 158.98, 148.32, 139.26, 134.66, 131.22, 123.41, 122.66, 115.42, 68.71.

4-((1,1'-Biphenyl)-4-ylmethoxy)-N-(1,2,4-thiadiazol-5-yl)benzamide (VIc): White powder, M.pt: 208 - 210 ^{o}C. FT-IR: 3143 for amide N-H str., 1662 for amide C=O str. ^{1}H NMR (400 MHz, DMSO-d6): δ 13.37 (s, 1H), 8.54 (s, 1H), 8.18 (d, J = 8.5 Hz, 2H), 7.70 – 7.23 (m, 11H), 5.29 (s, 2H). ^{13}C NMR (101 MHz, DMSO): δ 176.43, 166.21, 162.83, 158.99, 140.39, 140.20, 136.07, 131.18, 129.44, 128.94, 128.04, 127.30, 127.17, 123.37, 115.42, 69.73.

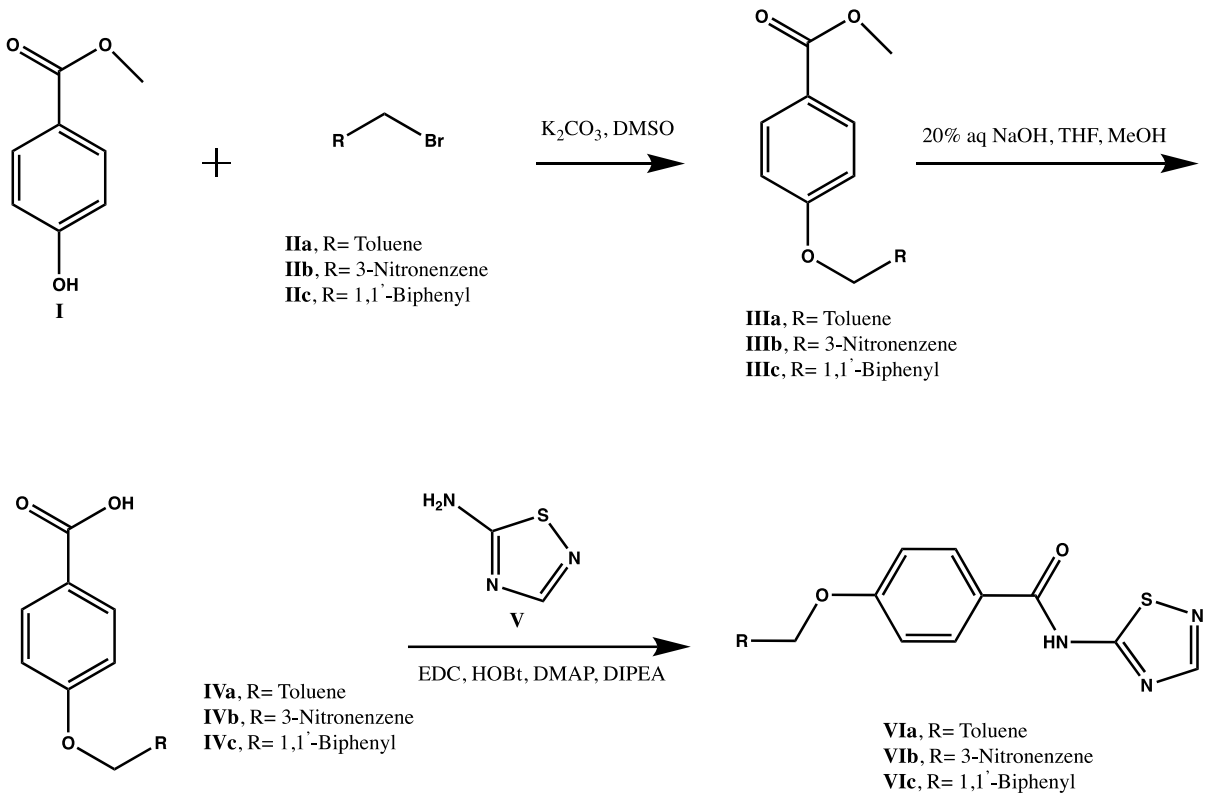
Anti-proliferative properties of compounds VIa–VIc

The MTT assay for cell viability was utilized to assess anti-proliferative activity. Compounds **VIa**–**VIc** and positive control (Vorinostat) were incubated with colon cancer cells at specified concentrations of 10, 5, 2.5, 1.25 and 0.62 µg/mL. Cell viability was assessed after incubation with the compounds for three days. Cells were mixed with MTT solution (2 mg/mL) and incubated at 37 ^{o}C for 2 h. Then, MTT medium was aspirated off and replaced with DMSO to solubilize the resultant formazan crystals. The absorbance of formazan solution was read in a microplate reader at 570 nm [5].

RESULTS

Molecular docking

The docking score of **VIa**-**VIc** and the reference SAHA on various HDAC isoforms in (Table 1) and the two-dimensional (2D) interactions of compound **VIa** with HDAC8 are in Figure 1.



Scheme 1: Chemical synthesis for final compounds

Table 1: Docking scores of ligands

Code	Docking score (kcal/mol)		
	HDAC2	HDAC6	HDAC8
Vorinostat	-5.613	-5.107	-4.642
VIa	-8.434	-7.169	-9.233
VIb	-8.830	-7.502	-9.072
VIc	-8.784	-5.133	-8.677

Table 2: Expected ADMET data for the final compounds (**V1a** – **V1c**)

Code	Rule of 5	Rule of 3	Human absorption	CNS
Vorinostat	0	0	69	-2
VIa	0	0	100	0
VIb	0	0	84	-2
VIc	0	1	100	-1

The criteria for Rule of five are as follows: molecular weight (MW) must be less than 500; logarithm of P (QPlogPo/w) must be < 5; donorHB must be ≤ 5, and population of accptHB must be ≤ 10. Compounds that satisfy these criteria are classified as drug-like. #metab‡: number of probable metabolic reactions. In the rule of three, QPlogS value is less than -5.7, QP PCaco value is greater than 22 nm/s, and the concentration of metabolites is less than 7. Compounds that have fewer violations of these principles are more likely to be safe when taken orally. The range of 0 to 5 is CNS-anticipated central nervous system activity measured on a scale ranging from -2 (inactive) to +2 (active)

Drug-likeness properties

To evaluate the drug-like molecule properties, several parameters might be virtually evaluated, including *the rule of five*, *the rule of three,* oral bioavailability and central nervous system (CNS) penetration is shown in Table 2.

Molecular dynamics simulation

Molecular dynamics (MD) investigation simulations have become a well-established technique for effectively understanding macromolecular ligand-receptor bindings. Therefore, the highest-scoring ligands with the most significant drug-like properties were subjected to MD simulations to understand the evolution of receptor binding ability over time (Figure 2).

Anti-proliferative activity

The *in vitro* MTT assay of the synthesized compounds against colon cancer cell line (HRT-18) the IC_{50} (Table 3).

Table 3: IC_{50} µM of compound **VIa** and **VIc**

Code	IC_{50} µM
Vorinostat	3.00
VIa	1.00
VIc	1.44

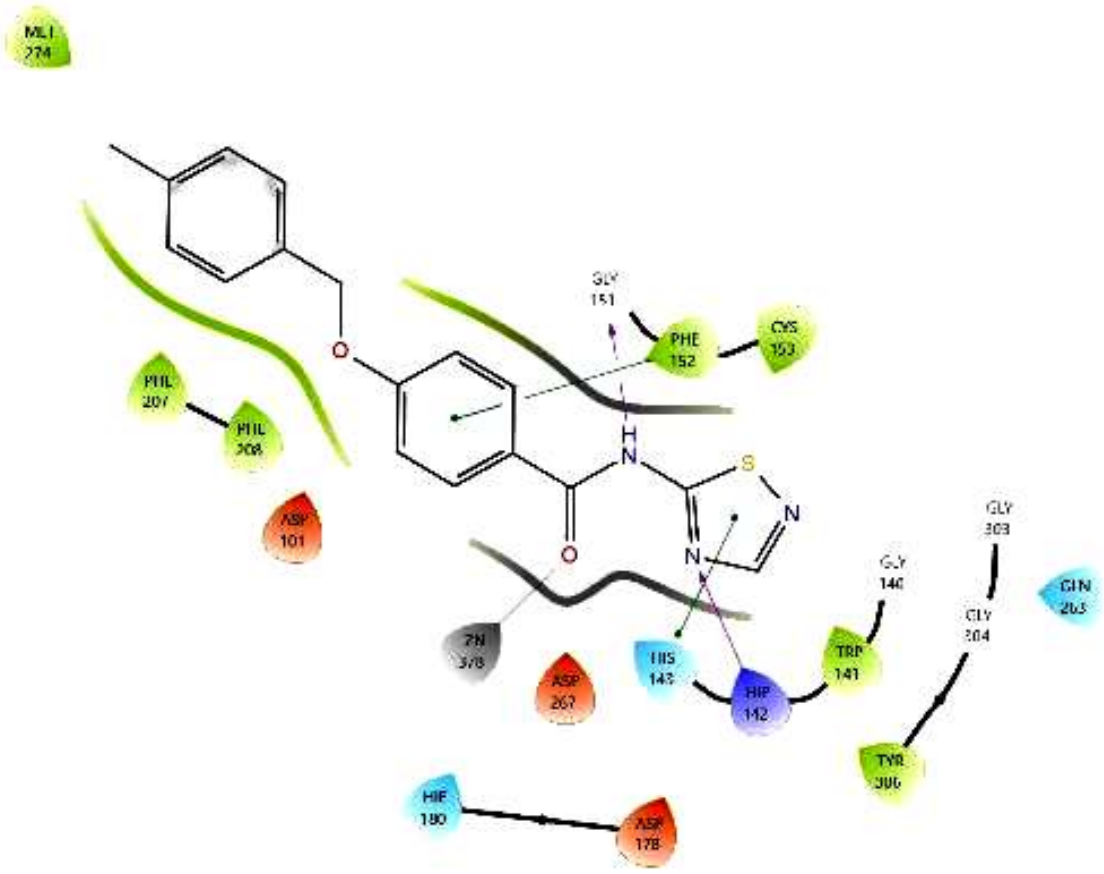


Figure 1: The two-dimensional (2D) interactions of compound **VIa** with HDAC8

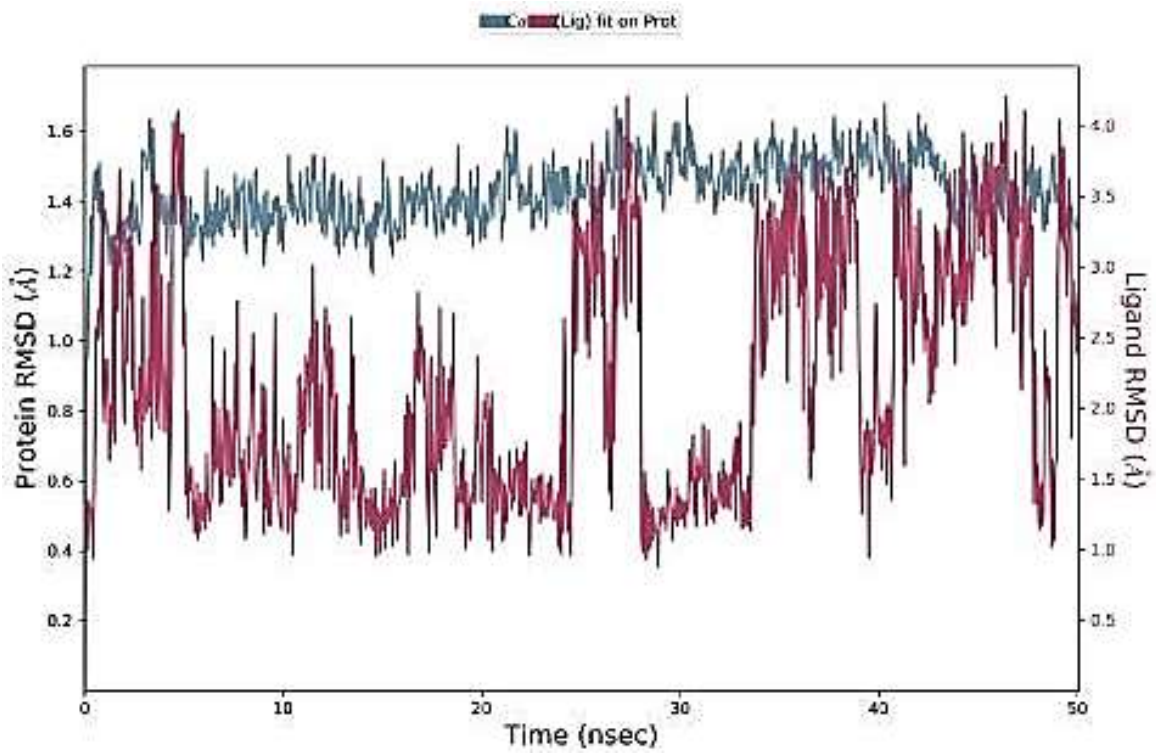


Figure 2: RMSD for **VIa**-HDAC8 complex

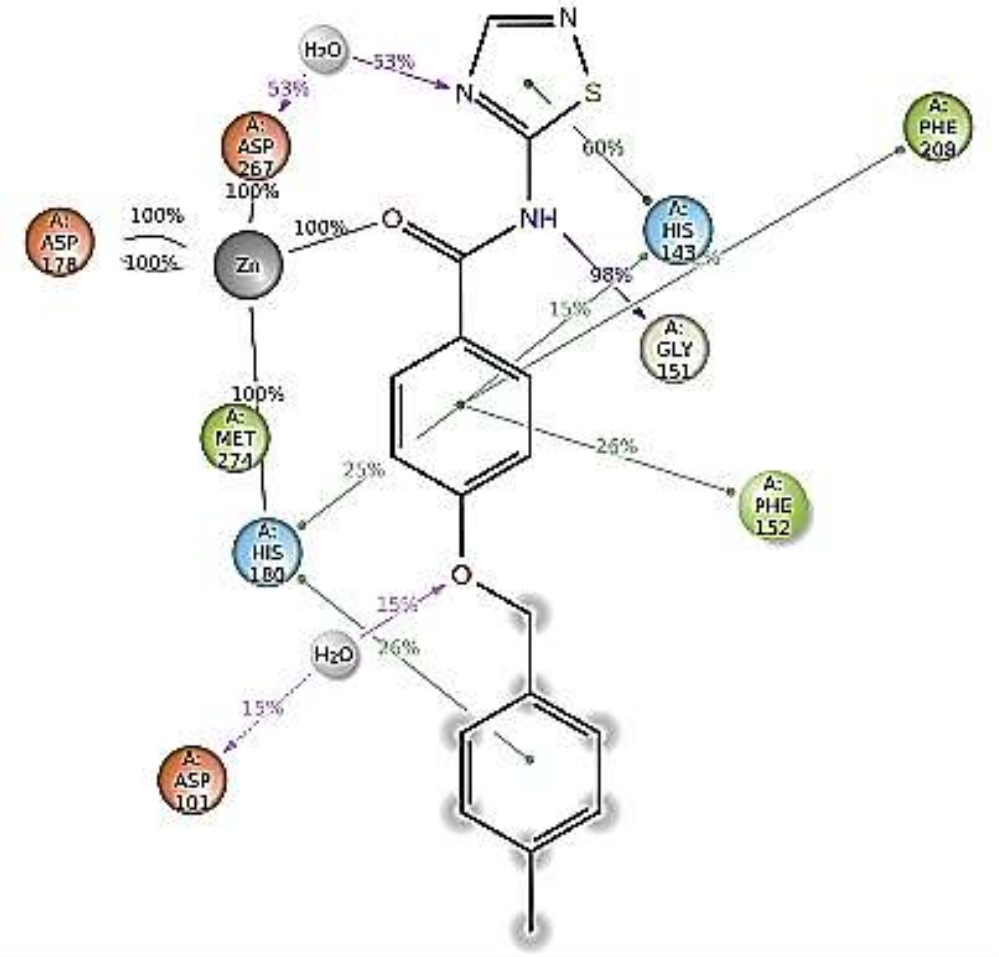


Figure 3: Two-dimensional interaction of compound **VIa** with HDAC8

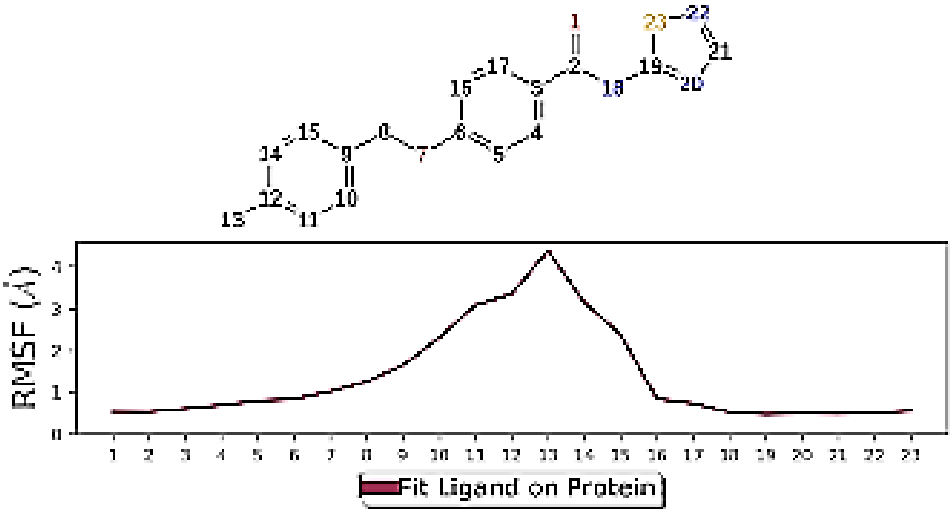


Figure 4: Ligand RMSF for the interaction of compound **VIa** with HDAC8

DISCUSSION

The docking scores for compounds **VIa**-**VIc** on various HDAC isoforms were generally higher than those for Vorinostat [2]. The ligand-receptor interaction showed acceptable fitness of compounds **VIa**-**VIc** into HDACs through the formation of zinc monodentate chelation and multiple interactions with several residues within the active site. More specifically, the amide carbonyl group of compounds **VIa** coordinated with zinc ion in the active site of HDAC8. In

addition, *π-π* stacking interaction was noticed between the thiadiazole ring of compound **VIa** and the linker benzene ring to HDAC8 HIS143 and PHE152 residues. Two hydrogen bonds were observed between thiadiazole N4 of compound **VIa** and HIP142 residue and between compound **VIa** amide N-H and GLY151 residue. Additional hydrophobic interactions with compound **VIa** cap group were observed to probe the molecule outside HDAC8 rim [6].

It is crucial to develop compounds with favourable physicochemical characteristics. Compounds that are categorized as drug-like molecules must conform to specific criteria such as *the rule of five* and *the rule of three*. Oral bioavailability is desirable as it prevents expensive delays in late-stage preclinical and clinical research. The proposed compounds **VIa**-**VIc** showed favourable pharmacokinetic features, as all compounds demonstrated compliance with both the *Rule of 5* and the *Rule of 3*. Compounds **VIa** and **VIc** exhibited complete absorption in humans, whereas compound **VIb** demonstrated 84 % absorption, while Vorinostat showed 69 % absorption. Additionally, all compounds exhibited low central nervous system (CNS) penetration. The stability of the interaction between compound **VIa** and HDAC8 was assessed using a molecular dynamics (MD) simulation analysis. The Root Mean Square Deviation (RMSD) of the ligand and protein was less than 2.5 Å throughout the simulation, thereby indicating a stable ligand-protein interaction [15].

Furthermore, compound **VIa** exhibited a permanent coordination contact with the zinc ion [16]. The thiadiazole ring demonstrated a 60 % π-π stacking interaction with HIS143, while the NH of the amide moiety formed 98 % hydrogen bond interaction with GLY151. Three weak π-π stacking interactions were noticed between the linker benzene moiety in probabilities of 15 % with HIS143, 26 % with PHE152, and 25 % with HIS180. The compound toluene cap group of **VIa** formed 26 % π–π stacking with HIS180 residue. The Ligand Root Mean Square Fluctuation (L-RMSF) provides valuable insights into the stability of the ligand atoms during the simulation period. The thiadiazole ring, amide linkage, and linker benzene moiety of compound **VIa** were in firm interaction with HDAC8 [15].

The synthesis of chemicals **VIa-VIc** was launched with the Williamson reaction of benzylic bromide derivatives **IIa**-**IIc** with methyl 4-hydroxybenzoate **I** to produce ethers **IIIa-IIIc**. Then, the ester groups of compounds **IIIa-IIIc** were hydrolyzed with NaOH to liberate acids **IVa-IVc**. The final compounds **VIa-VIc** were synthesized via the amide reaction of compounds **IVa-IVc** with 1,2,4-thiadiazol-5-amine in a reaction mediated by the couplers DMAP, EDC, HOBT, and DIPEA. The resulting molecules were purified using column chromatography and characterized using NMR and FT-IR spectroscopy.

The preliminary findings from MTT assay showed that at a concentration of 10 µg/mL, compounds **VIa** and **VIc** significantly reduced growth of the colon cancer cells (HRT). The dose-response assay of the effects of compounds **VIa**, **VIc**, and Vorinostat on HRT cells demonstrated that compounds **VIa** and **VIc** had activities comparable to those of Vorinostat, with IC_{50} values of 1.00 and 1.44 µM, respectively, while the IC_{50} of Vorinostat was 3.00 µM [16].

CONCLUSION

Novel HDAC inhibitors incorporating thiadiazole moiety as a potential ZBG have been developed. The synthesis of the final compounds **VIa**-**VIc** have been successfully accomplished. Assessments conducted on the virtual pharmacokinetic properties and molecular dynamics simulation for compounds **VIa**-**VIc** indicate adequate virtual physicochemical properties. The final compounds show highly promising cytotoxicity at low micromolar IC_{50} values that are comparable to the activity of FDA-approved Vorinostat. Therefore, these preliminary findings may provide an opportunity for creating novel HADC inhibitors.

DECLARATIONS

Acknowledgements

The authors would like to thank the College of Pharmacy, University of Baghdad for her support. The project was partially supported by the College of Pharmacy, University of Baghdad.

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Study design: Rusul Mohammed Hasan Ali and Ayad A Al-Hamashi; data collection: Rusul Mohammed Hasan Ali; analysis and interpretation of results: Rusul Mohammed Hasan Ali and Ayad A Al-Hamashi.; draft manuscript preparation: Rusul Mohammed Hasan Ali; manuscript editing Ayad A Al-Hamashi.

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