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Design, Synthesis, and Preliminary Antiproliferative Evaluation of 1,2,4-Thiadiazole Derivatives as Possible Histone Deacetylase Inhibitors

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Abstract

Histone deacetylase (HDAC) enzymes are involved in a wide range of clinical situations, encompassing cancer. Most o the current clinically used HDAC inhibitors are containing hydroxamate moiety as a zinc-binding group (ZBG). The poor selectivity and undesired pharmacokinetic characteristics of hydroxamate inhibitors prompted the exploration of new HDAC inhibitors. Therefore, the objective of this work is to design new HDAC inhibitors incorporating thiadiazole moiety as a ZBG. This study involved the design and virtual analysis of a series of thiadiazole derivatives using Maestro software. Compounds with accepted docking score which include compound **6a** [4- (benzyloxy)-N-(1,2,4-thiadiazol-5-yl)benzamide] -8.953 kcal/mol, compound **6b** [4-(naphthalen-1-ylmethoxy)-N-(1,2,4-thiadiazol-5- yl)benzamide] -9.290 kcal/mol, and compound **6c** [4-((4-methoxybenzyl)oxy)benzoic acid] -8.57 kcal/mol while the FDA approved vorinostat has a docking score -5.613 kcal/mol against HDAC 2 (4LXZ). Compounds **6a-c** were subjected to the organic synthesis applying traditional chemical reactions. The synthesis was commenced with **3a-c** formation using Williamson reaction by reacting benzylic halogen derivatives **2a-c** with methyl 4-hydroxybenzoate, then the intermediates underwent ester hydrolysis to produce 4-(benzyloxy)benzoic acid derivatives **4a-c** and then reacted with 1,2,4-thiadiazol-5- amine to produce **6a-c** using 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) as coupling reagent. The intermediates and final products were characterized by FT-IR, MS and NMR spectroscopy. The cytotoxic effect was assessed using the MTT cell viability assay indicate that the IC_{50} of **6b** is 0.66 µM while the IC_{50} of vorinostat is 1.48 µM.

Keywords:Histone Deacetylase, Molecular Docking, Vorinostat.

Introduction

Epigenetics refers to the changes in DNA expression without modification of its sequence[(1)]. Many types of disease are related to the uncontrolled epigenetic modifications, including cancer[(2,3)]. Cancer is a leading cause of death, and this has led many researchers and pharmaceutical companies to focus their research on creating novel pharmaceutical interventions capable of halting cancer progression[(4,5)]. The relation between cancer disease and uncontrolled epigenetic modification is well document[(6)]. There are many types of epigenetic modifications, including chromatin remodelling, DNA methylation, and histone modification[(7)]. Histone acetylation is a dynamic process that controlled by two enzymes, histone acetylase (HAT) and histone deacetylase (HDAC)[(8)]. The elevated level of the deacetylated lysine ϵ-amino group enables a strong connection between histones and DNA's negative charge. Furthermore, hypoacetylation hinders angiogenesis, migration, invasion, and cell adhesion, eventually initiating and advancing malignancies. Cancer is generally characterized by a decreased acetylation of histones[(5)]. Design HDAC enzyme inhibitors are a promising approach for treating cancer[(9)]. The ideal HDAC inhibitors consist of three crucial structural components: a zinc-binding group (ZBG), a linker, and a cap group[(10)]. Vorinostat, romidepsin, panobinostat, and belinostat are HDAC inhibitors that have been licensed by the FDA for the treatment of cancer. Most of the approved HDAC inhibitors contain hydroxamate groups as ZBG. Hydroxamates are characterized with unfavourable selectivity and poor pharmacokinetic properties[(2)]. Thiadiazole ring is a significant structure with wide-ranging biological effects. Thiadiazole is an excellent bioisostere for several bioactive pharmacophores. The presence of sulphur atom in thiadiazole improve its lipophilicity and enhance cellular membranes penetration. Acetazolamide and methazolamide are thiadiazole-containing drugs that act as diuretics by inhibiting carbonic anhydrase. Furthermore, the first-generation cephalosporins cefazedone and the beta-adrenergic receptor blocker timolol timolol are also containing thiadiazole[(11)].

The objective of this work is to design, synthesis, and preliminary antiproliferative activity evaluation of new thiadiazole derivatives as possible HDAC inhibitors.

Materials and Methods

Molecular docking

The docking study was carried out employing Glide software from Schrodinger's modeling suite version 13.0135. The crystal structure of human HDAC2 (4LXZ), HDAC8 (6HSK), and HDAC6 (5EDU) was downloaded from the protein data bank (PDB) as a biological unit[12-14]. Then the proteins were prepared using the protein preparation workflow embedded in Maestro software which was preprocessed the protein to assign bond order, replace hydrogen, using Prime to fill missing loops, generate het states (with Epike) at pH 7.4, and minimize using force field OPLS_2005. The water molecules farther than 3 Å from ligands were deleted[15]. The grid for protein was generated by the co-crystallized ligand as the central reference point to establish the boundary box. The boundary box used had dimensions of (12 Å * 12 Å * 12 Å). Designed ligands were sketched using 2D Sketcher within the Maestro program. Ligand structures were optimized by LigPrep in Maestro suite using force field OPLS_2005 and generate possible states at target pH 7, desalt, and generate tautomers[16]. The prepared ligands were docked on the protein grid using standard precision, and written out at most 5 poses per ligand[17,18]. The docking poses of all compounds were ranked based on their docking scoring function, and visualized using the Maestro v 13.0.135 interface (Schrodinger, New York, NY, 2021).

ADME Study

The ligands underwent structure-based prediction of ADME properties to evaluate the drug-likeness of the designed compounds using the QIKProp application within Maestro software using fast mode and the option "Identify the 5 most similar drug molecules" also activated[19].

Molecular dynamic simulation

The top-ranked compound underwent molecular dynamic (MD) simulation study implicating Desmond application within Maestro software version 2.0[20]. The system was built with an SPC water model in an orthorhombic periodic box of dimension 10 Å with OPLS_2005 force field, and then neutralized with counter ions (Na+ and Cl) at neutral pH. MD simulations were run for 50 ns, recording interval 50 ps, the approximate number of frames 1000, elapsed 0, energy 1.2 at a constant temperature of 300 K, and pressure 1 bar.

Materials and equipment

Starting materials and reagents were purchased from commercial suppliers (Sigma Aldrich, Liyan, *Macklin*, LOBA Chemie PVT, and Merck), and used without further purification. The solvents employed were dehydrated using 3 Å molecular sieves. The thin-layer chromatography (TLC) 20*20 cm silica gel 60 F254 sheet manufactured by Macherey-Nagel was used for reaction monitoring. The detection of the compounds on TLC plates was accomplished using ultraviolet (UV) light with a wavelength of 254 nm. FTIR spectroscopy was conducted using the Shimadzu IRAffinity-1 spectrometer, manufactured by Shimadzu in Japan. The ^{1}H-NMR and ^{13}C-NMR analyses were performed at frequencies of 400 MHz and 100 MHz, respectively, using a Bruker Avance III 400 MHz spectrometer. The NMR solvent used was *d6*-DMSO. The mass spectrum was conducted using AB SCIEX Triple Quad 4500 manufactured in Germany.

Organic synthesis

General procedure for the synthesis of methyl 4-(benzyloxy) benzoate derivative

The mixture of methyl 4-hydroxybenzoate **1** (0.76 g, 7.5 mmol, 1.5 eq.) and K_2CO_3 (0.69 g, 5 mmol, 1 eq.) in 15 mL DMSO were stirred at 50 °C for 100 min, then added variant benzyl halide derivatives (**2a**-**2c**) (5 mmol, 1 eq.) separately. The reaction was monitored by TLC (ethyl acetate: hexane 1:1). The resulting residue was worked up by washing with distilled water, and then recrystallized with ethanol to obtain (80-90)% white powder as pure products **3a**-**3c**[21, 22].

Methyl 4-(benzyloxy) benzoate (3a): M.P. 90-93 °C. FTIR 2954, 2885 (aromatic C-H str.), 1708 (ester C=O str.), 1242, 1010 (ether C-O str. bands). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, *J* = 8.8 Hz, 2H), 7.70 – 7.25 (m, 5H), 7.13 (d, *J* = 8.8 Hz, 2H), 5.19 (s, 2H), 3.81 (s, 3H).

Methyl 4-(naphthalen-1-ylmethoxy) benzoate (3b): M.P. 83-86 °C. FT-IR 3047, 3016 (aromatic C-H str.), 1708 (ester C=O str.), 1238, 1002 (ether C-O str. bands). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, *J* = 9.2 Hz, 1H), 8.03 – 7.97 (m, 2H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 7.0 Hz, 1H), 7.64 – 7.49 (m, 3H), 7.23 (d, *J* = 8.8 Hz, 2H), 5.65 (s, 2H), 3.82 (s, 3H).

Methyl 4-((4-methoxybenzyl)oxy) benzoate (3c) M.P. 102-105 °C. FT-IR 2951, 2920 (aromatic C-H str.), 1712 (ester C=O str.), 1242, 1029 (ether C-O str. bands). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.2 Hz, 2H), 5.09 (s, 2H), 3.81 (s, 3H), 3.76 (s, 3H).

General procedure for the preparation of 4-(benzyloxy)benzoic acid derivatives

To a round bottom flask added **3a-3c** (5 mmole, 1eq.)**,** sodium hydroxide solution (1.2 g, 10% aqueous solution, 30 mmol, 6 eq.), 1:1 mixture of methanol and tetrahydrofuran (4 mL/mmol). The reaction was stirred at room temperature for 16 hours. The completion reaction was monitored by TLC (ethyl acetate: hexane 1:1). The mixture was concentrated and washed with 3N HCl, then filtrated to obtain (90-95)% grey powder as pure products **4a-4c**[22,23].

4-(benzyloxy)benzoic acid (4a) M.P. 190-192 ºC. FT-IR 2661 (acid O-H str.), 1670 (acid C=O str.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.70 (s, 1H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.51 – 7.32 (m, 5H), 7.11 (d, *J* = 8.8 Hz, 2H), 5.18 (s, 2H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 167.46, 162.40, 136.98, 131.83, 128.96, 128.48, 128.29, 123.63, 115.06, 69.90.

4-(naphthalen-1-ylmethoxy)benzoic acid (**4b**) M.P. 248-250 ºC. FT-IR 2661 (acid O-H str.), 1670 (acid C=O str.) .

4-((4-methoxybenzyl)oxy)benzoic acid (4c) M.P. 260-265 ºC. FT-IR 2935(acid O-H str.), 1674 (acid C=O str.).

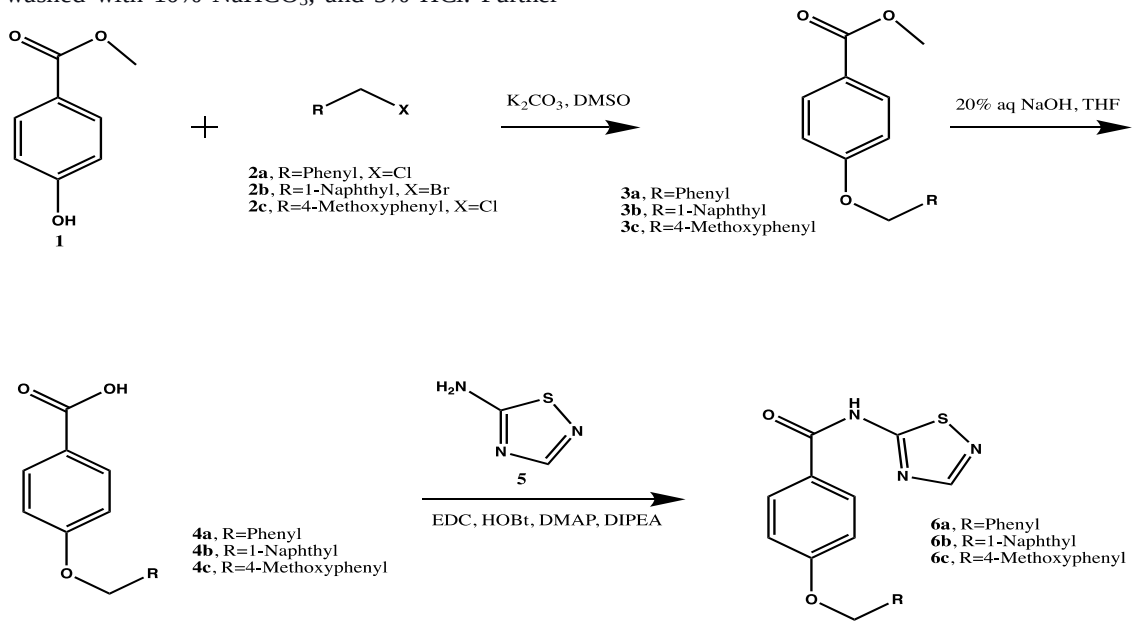
General procedure for the preparation of final compounds

A mixture of **4a-4c** (5 mmol, 1eq.) and EDC (1g, 5.5 mmol, 1.1 eq.), and HOBT (0.06 g, 0.5 mmol, 0.5 eq.), and DIPEA (3.22 g, 10 mmol, 5 eq.) were dissolved in 15 mL DCM and stirred at room temperature for 1 hr. The reaction was monitored with TLC (ethyl acetate: hexane 1:1) until the disappearance of acid,. Then add 1,2,4-thiadiazol-5-amine (**5**) (0.5 g, 5 mmol ,1 eq.) and DMAP (0.67 g, 5.5 mmol, 1.1 eq.) and the reaction stirred for 18 hr at room temperature. The resultant residue was washed with 10% $NaHCO_3$, and 5% HCl. Further purification was performed via column chromatography on neutralized silica gel using (ethyl acetate: hexane) as eluent to afford (40-45)% pure powder **6a-6c**[4].

4-(benzyloxy)-N-(1,2,4-thiadiazol-5-yl) benzamide(6a). White powder, M.P. 203-205 ºC. FT-IR 3136 (amide N-H str.), 1654 (amide C=O str.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.41 (s, 1H), 8.59 (s, 1H), 8.22 (d, *J* = 8.8 Hz, 2H), 7.70 – 7.32 (m, 5H), 7.25 (d, *J* = 8.8 Hz, 2H), 5.28 (s, 2H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 176.36, 166.16, 162.85, 159.00, 136.87, 131.16, 128.99, 128.54, 128.33, 123.29, 115.40, 70.05. MS (ESI): calcd for $C_{16}H_{14}N_3O_2S$ $[M + H]^+$ 312.08; found 312.20.

4-(naphthalen-1-ylmethoxy)-N-(1,2,4-thiadiazol -5- yl)benzamide (**6b**). White powder, M.P. 2014-216 ºC. FT-IR. 3136 (amide N-H str.), 1654 (amide C=O str.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.37 (s, 1H), 8.55 (s, 1H), 8.21 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 7.2 Hz, 1H), 8.03 – 7.93 (m, 2H), 7.72 (d, *J* = 7.0 Hz, 1H), 7.65 – 7.51 (m, 3H), 7.30 (d, *J* = 8.8 Hz, 2H), 5.69 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 176.40, 166.21, 162.94, 158.98, 133.77, 132.36, 131.56, 131.20, 129.38, 129.00, 127.33, 127.03, 126.53, 125.87, 124.32, 123.42, 115.48, 68.66. MS (ESI): calcd for $C_{20}H_{16}N_3O_2S$ $[M + H]^+$ 362.43; found 362.0.

4-((4-methoxybenzyl)oxy)benzoic acid (6c). Pink powder, M.P. 208-210 ºC., FT-IR 3140 (amide N-H str.), 1654 (amide C=O str.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.36 (s, 1H), 8.54 (s, 1H), 8.16 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.9 Hz, 2H), 7.18 (d, *J* = 8.9 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 5.14 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 176.36, 166.16, 162.93, 159.62, 158.99, 131.13, 130.21, 128.69, 123.13, 115.38, 114.34, 69.86, 55.57. MS (ESI): calcd for $C_{17}H_{16}N_3O_3S$ $[M + H]^+$ 342.39; found 342.20.



Scheme 1. The chemical synthesis for final compounds.

Antiproliferative activity study

The antiproliferative *activity* was measured using the MTT cell viability assay in 96-well plates. The cell lines were seeded at a density of 1 × 104 cells per well. After 24 hours of generating a fully saturated layer of cells, the cells were separately exposed to compounds **6a**–**6c** and vorinostat at specified concentrations.(10, 5, 2.5, 1.25, 0.625 µg/mL). After 72 hours of exposure, cell viability was assessed by withdrawing the culture medium, by applying 28 µL of a 2 mg/mL MTT solution and maintaining a temperature of 37°C for a duration of 2 hr, the experiment is conducted. Following the removal of the MTT solution, the crystals in the wells were dissolved with 100 µL of DMSO and then incubated at 37°C for 15 minutes with agitation. The absorbency was measured using a microplate reader at 620 nm (test wavelength), and the assay was conducted in triplicate. The cytotoxicity percentage, which represents the rate of inhibition in cell growth, was calculated using the following equation: The proliferation rate (PR) is determined by the formula B/A*100, where A represents the average optical density of untreated wells, B represents the optical density of treated wells[24].

Results and Discussion

Molecular docking study

The molecular docking data provided information about the binding energies of ligands to receptors, as indicated by the diverse G-Scores. The general pharmacophores of HDAC inhibitors consist of a ZBG, a linker, and a cap group[9]. In this work, a new ZBG of 1,2,4-thiadiazole ring was developed, in addition to the benzene group containing linker and variant benzylic cap group derivatives. The virtual results indicated that the amide connection between the thiadiazole ring and the linker benzene ring has improved the affinity for proteins compared to other linkages, such as imine or aliphatic chains. This is due to the coordination of the carbonyl group to zinc in the amide linkage. The cap maximizes the HDAC inhibitors' efficacy and selectivity[25]. The docking score of compounds **6a**-**6c** were higher than vorinostat, which might be related to the multiple interactions between thiadizole ring, the linker phenyl moiety, and the cap group with different amino acids in the protein (Figure 1). The docking score for the most biologically active compound **6b** is fitting well in the binding groove of HDAC2 enzyme, and is relatively higher than vorinostat and other compounds (Table 1). The derivatives of the cap group demonstrate that compound **6b** has a higher affinity, which might be attributed to its larger size and hydrophobic interaction. The two dimensional interaction of **6b** with HDAC2 indicated the metal coordination between zinc ion and carbonyl of amide linkage. A hydrogen bonding is formed between the amide linkage N-H and GLY154. The thiadiazole ring is forming a π–π stacking with HIS146. The linker benzene moiety is also forming a π–π stacking with PHE155. Finally, additional a π–π stacking is noticed between naphthalene moiety of the cap group and TYR209 (Figure 1).

Table 1. ligands docking score

Code	Docking score (kcal/mol)		
	HDAC2	HDAC6	HDAC8
vorinostat	-5.613	-5.107	-5.241
6a	-8.953	-7.320	-8.520
6b	-9.290	-7.688	-8.610
6c	-8.576	-6.144	-8.518

Drug-likeness properties

The predicted pharmacokinetic properties for the proposed compounds were studied using the Qikprop application within Maestro software. In comparison to vorinostat[3], all compound were adhered to the rule of five and the rule of three (Table 2). The most active compound **6b** has 100% human oral absorption, two metabolic interaction which can give long half-life, and has only 1 star which is acceptable. Compound **6b** has no CNS penetration which might reduce the CNS toxic effect.

Table 2. The predicted ADME data for the synthesized compounds.

Code	Rule of 5	Rule of 3	Human Absorption	#metab	Star	CNS
vorinostat	0	0	69	3	0	-2
6a	0	0	100	2	0	0
6b	0	0	100	2	1	0
6c	0	0	100	3	0	-1

Rule of Five Number of violations of Lipinski's rule of five. The rules are: mol_MW < 500, QPlogPo/w < 5, donorHB ≤ 5, accptHB ≤ 10. Compounds that satisfy these rules are considered drug like.
#metab‡: Number of likely metabolic reactions.The three rules are: QPlogS > -5.7, QP PCaco > 22 nm/s, Primary Metabolites < 7. Compounds with fewer (and preferably no) violations of these rules are more likely to be orally available.
#Star is the number of property or feature that placed 95% outside the desired property to make the compound more drug like , the more stars mean the compound is less drug like, the less is the better.
The value from0-5 .CNS Predicted central nervous system activity on a –2 (inactive) to +2 (active) scales
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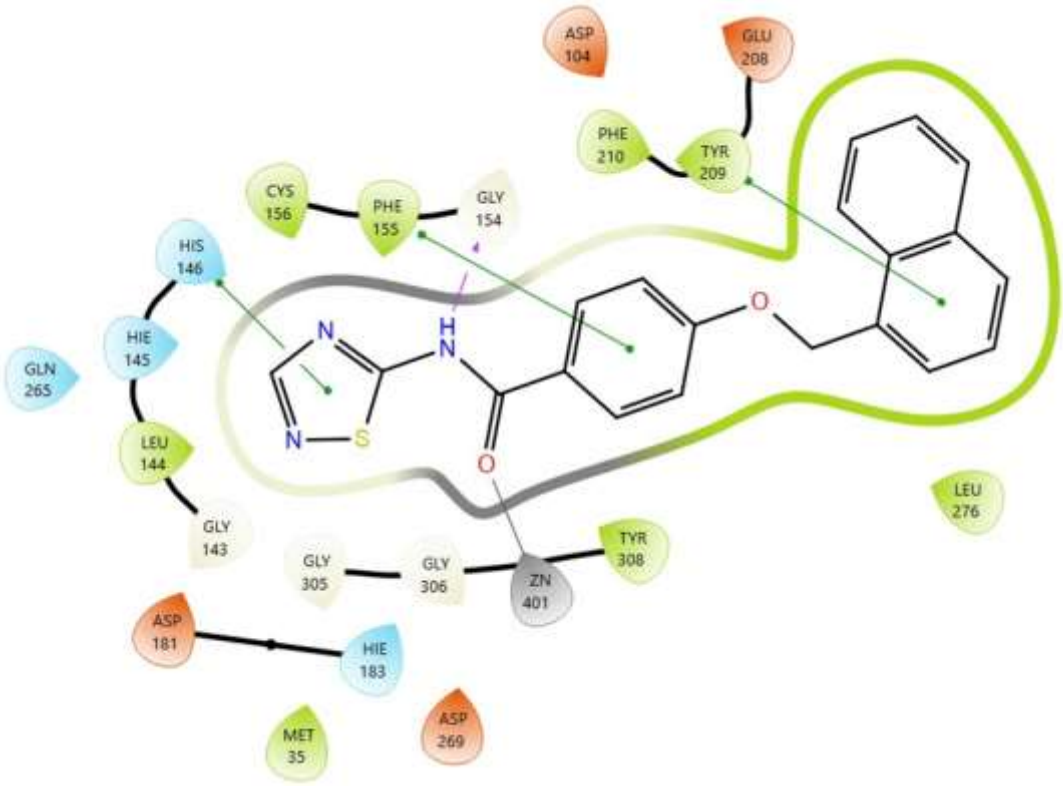

Figure 1. The two dimensional interaction of 6b with HDAC2.

Molecular dynamic simulation

A molecular dynamics (MD) simulation analysis was performed to study the binding stability between compound **6b** and HDAC2. Compound **6b** exhibit persistent 100% monodentate interaction with the zinc ion. Additionally, there are two π–π stacking between the thiadiazole ring and TYR308 and HIS146 which were stable in 42% and 68% of simulation time, respectively. As well as the hydrogen link between TYR308 and thiadiazole N4 atom was persistent in 67% of simulation time. Furthermore, there is another hydrogen bond between the NH of the amide and GLY154 which was preserved for 93% of simulation time. Finally, the π–π stacking interaction between TYR209 and naphthalene cap group was constant in 65% of the simulation time (Figure 2).

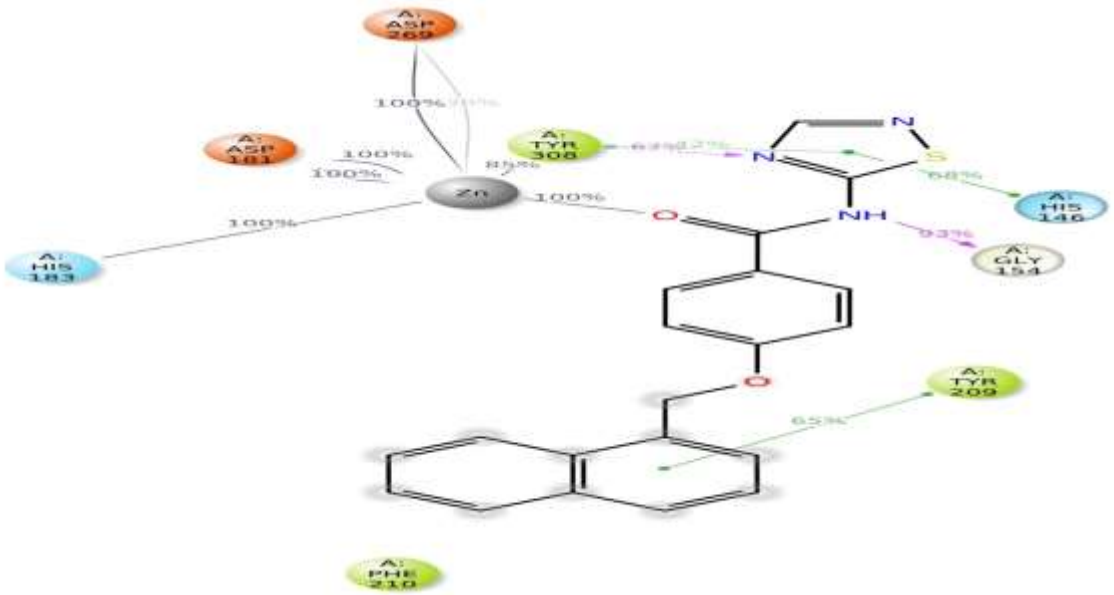

Figure 2. The two dimensional interaction for compound 6d with HDAC2.

Protein-RMSF

The root-mean-square-fluctuation (*RMSF*) is giving the information about the protein contacts with ligand for the complete simulation. Further, the overall noticed fluctuation is below 2 Å, giving enormous information about the stability of the complexes of compound **6b** with HDAC2. On other hand, the same is for complex of vorinostat and HDAC2, as the amino acid residues that interacted with vorinostat and that interact with **6b** are the same (Figure 3).

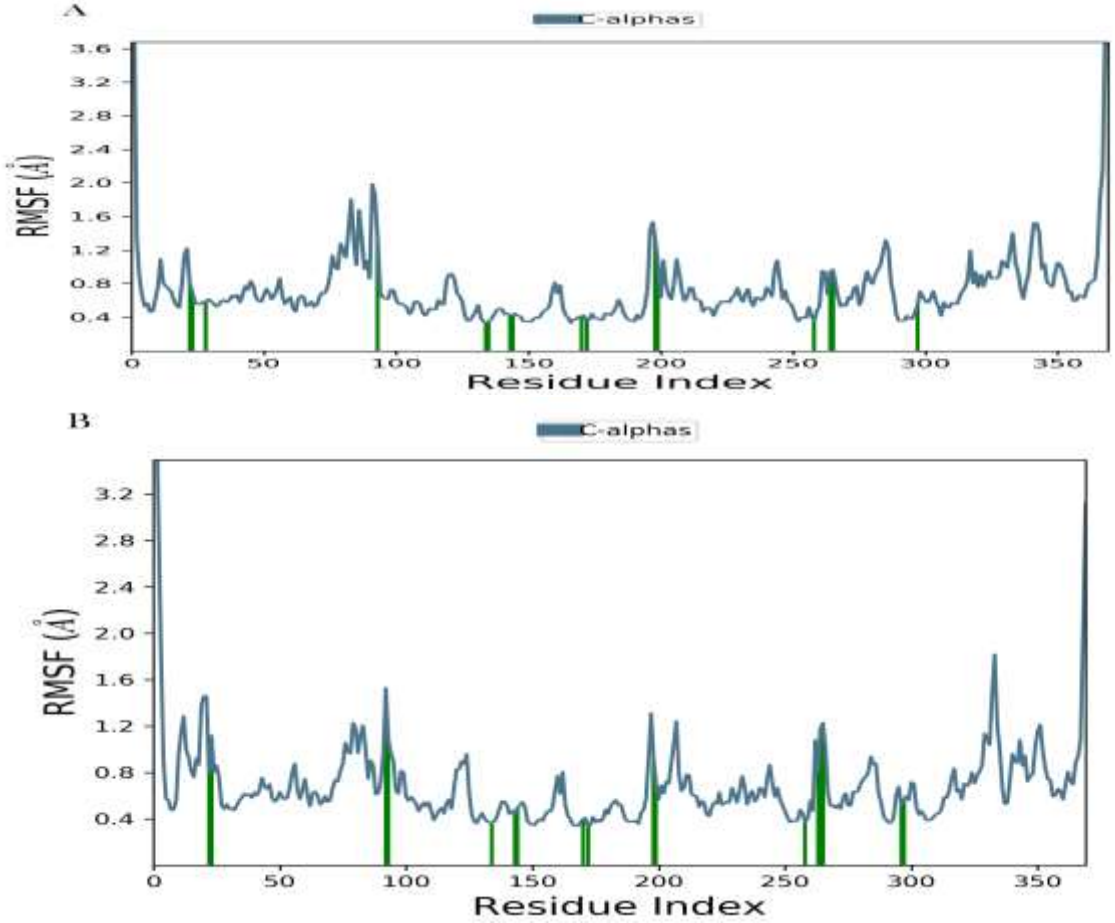

Figure 3. The P-RMSF for (A) compound 6b and (B) vorinostat, with HDAC2.

Ligand -RMSF

The Ligand Root Mean Square Fluctuation (L-RMSF) is helpful in characterizing changes in the ligand atom positions. The L-RMSF for compound **6b** indicated that the thiadiazole ring and amide linkage below 2 Å, which gives good stability to ligands, and the same for vorinostat, which is shows how tightly the ligand binds to the protein (Figure 4).

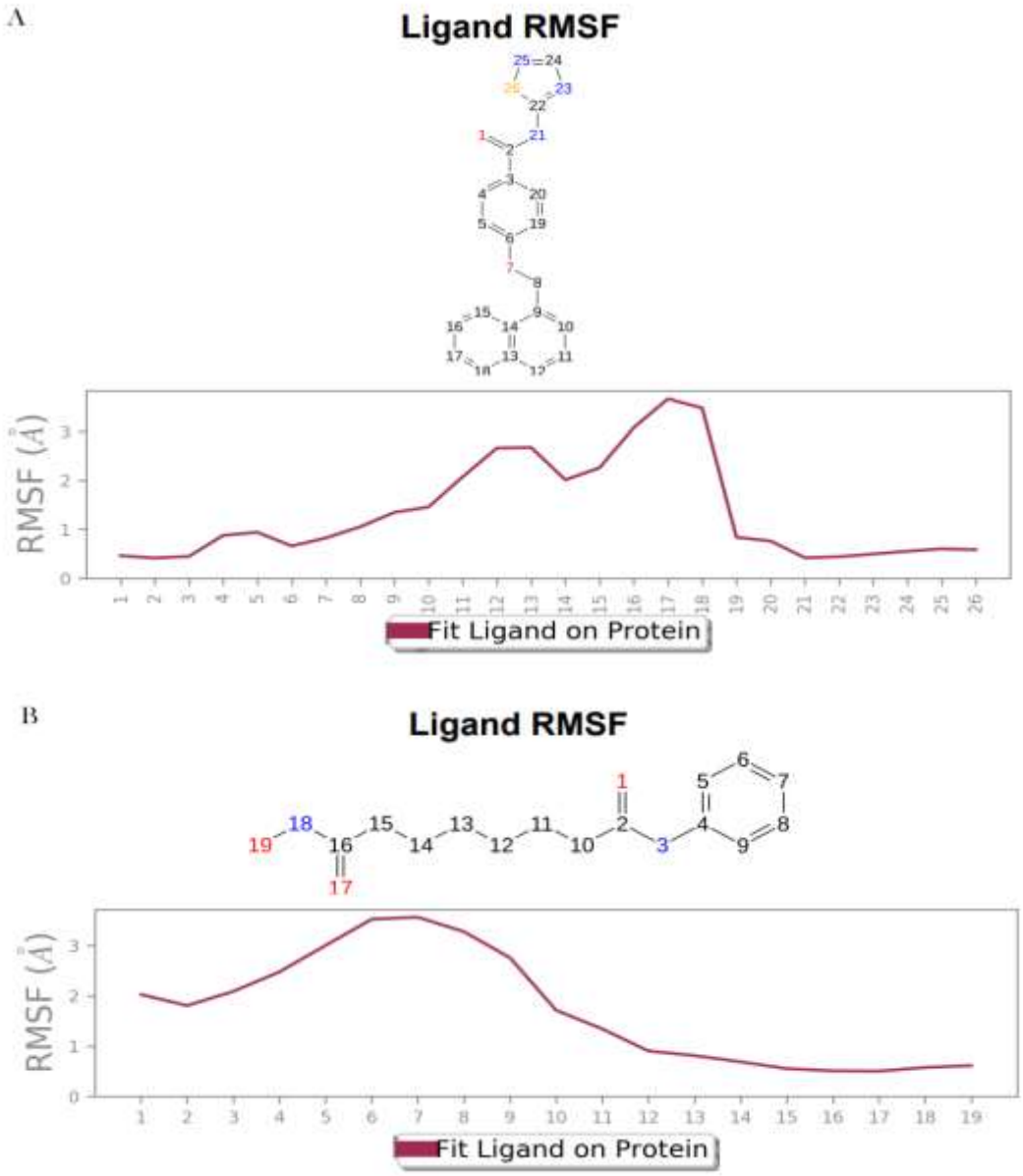

Figure 4. The L-RMSF for (A) compound 6b and (B) vorinostat, with HDAC2.

Chemical synthesis

Compounds **6a**, **6b** and **6c** are prepared by reaction of benzylic halide derivatives with methyl 4-hydroxybenzoate to produce ether (**3a-3c**) using Williamson reaction. Then, the intermediates underwent ester hydrolysis by NaOH to afford acid (**4a-4c**), which were reacted with 1,2,4-thiadiazol-5-amine to produce final amide using EDC, DMAP, HOBT and DIPEA as coupling reagents. The final products (**6a-6c**) were purified by column chromatography and characterized by NMR and FT-IR spectroscopy.

Antiproliferative activity

The initial findings from Hela cancer cell growth inhibition assay (MTT assay) indicated that the compound **6b** at concentration 10 µg/ml showed the most significant inhibition activity in contrast to **6a** and **6c**. Compound **6b** and vorinostat underwent another MTT assay at serial dilution to calculate IC_{50}. Compound **6b** has a submicromolar inhibition activity with IC_{50} 0.66 µM, which is comparable to vorinostat inhibition activity in IC_{50} 1.48 µM in the Hela cell line (Figure 5).

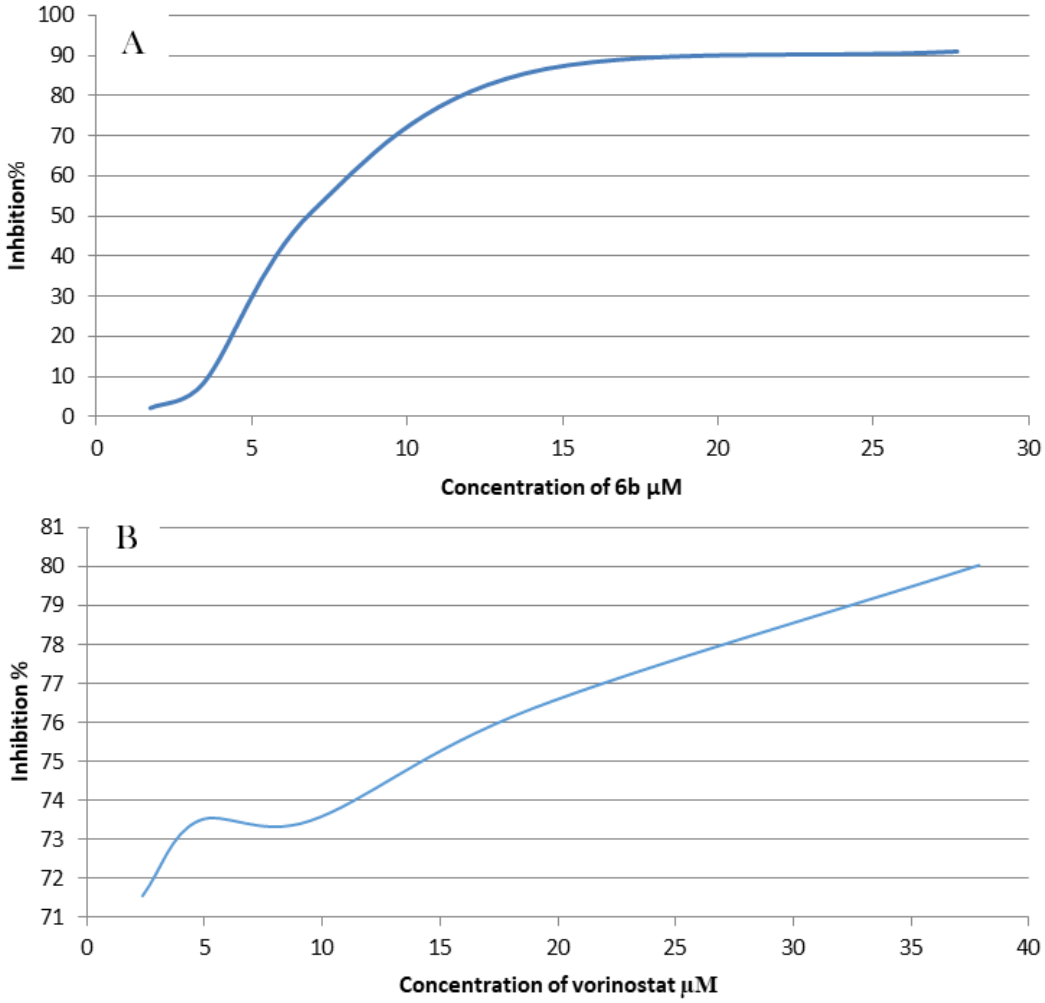

Figure 5. The IC_{50} for (a) compound 6b and (B) vorinostat, in Hela cancer cell.

Conclusion

A new potential zinc binding group of thiadiazole was introduced to provide possible HDAC inhibitors. Molecular docking studies were conducted using licensed Glide software to examine zinc chelation. The compounds bind to HDAC with high docking scores and chelate zinc ions. Compounds demonstrated acceptable pharmacokinetic characteristics through virtual ADME experiments. The intended compounds were successfully synthesized with acceptable yields using traditional organic synthesis techniques. The intermediates and final products were characterized using FTIR and NMR spectroscopy. The antiproliferative activity study showed compound **6b** involves promising preliminary Hela cancer cell inhibition activity comparable to vorinostat. The current findings are highly promising, and further SAR and biological studies are possibly carried out to validate the current data.

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Conflicts of Interest

The author declared no conflict of interest.

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Ethics Statements

We confirm as authors that our signing of this form is to guarantee that the submitted manuscript is in accordance with the ethical considerations, and we have received the ethical approval from the related institution(s) and no animal or human samples were involved in this work.

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: Ayad A. Al-Hamashi, Rusul Mohammed Hasan Ali; data collection: Rusul Mohammed Hasan Ali; analysis and interpretation of results: Ayad A. Al-Hamashi, Rusul Mohammed Hasan Ali; draft manuscript preparation: Rusul Mohammed Hasan Ali. All authors reviewed the results and approved the final version of the manuscript.

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التصميم والتصنيع والتقييم البيولوجي الأولي لمشتقات ١،٢،٤-الثياديازول كمثبطات محتملة لإنزيم هيستون دياسيتيلاز

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الخلاصة

انزيمات هيستون دياسيتيلاز (HDACs) هي فئة من البروتينات مسؤولة عن مجموعة واسعة من الحالات المرضية، بما في ذلك مرض السرطان. معظم مثبطات HDAC المستخدمة في علاج الحالات المرضية تتكون من مجموعة الهيدروكساميت. ضعف الانتقائية والخصائص الحركية الدوائية الغير مرغوب فيها للعديد من الأدوية التي تنتمي إلى مجموعة الهيدروكساميتات أدت الى اكتشاف مثبطات HDAC من غير الهيدروكساميتات ذات الانتقائية المحتملة والفعالية العالية. ولذلك، فإن الهدف من هذا العمل هو تصميم مثبطات HDAC جديدة تشتمل على شاردة الثياديازول. تضمنت هذه الدراسة التصميم والتحليل الافتراضي لسلسلة من مشتقات الثاديازول باستخدام برنامج Maestro . حيث ان المركبات ذات درجة إرساء جيدة تشمل المركب **6a** مع درجة إرساء -٨,٩٥٣ كيلو كالوري/مول والمركب **6b** مع درجة إرساء -٩,٢٩٠ سعرة حرارية/مول ومركب **6c** مع درجة إرساء -٨,٥٧ سعرة حرارية/مول في حين أن vorinostat المعتمد من إدارة الغذاء والدواء لديه درجة إرساء -٥,٦١٣ سعرة حرارية/مول مقابل (HDAC2) . وتم إخضاع المركب **6c, 6b, 6a** للتخليق العضوي باستخدام التفاعلات الكيميائية التقليدية. بدأالتخليق بتكوين الأثير باستخدام تفاعل ويليامسون عن طريق تفاعل مشتقات بروميد البنزيليك مع ميثيل-هيدروكسي بنزوات، ثم تحلل الإستر الوسيط لإنتاج حمض البنزويك ٤- (بنزيلوكسي) ثم التفاعل مع ١،٢،٤- ثيادايازول- ٥- أمين عن طريق تكوين أميد باستخدام ١-إيثيل-٣-(٣-ثنائي ميثيل أمينوبروبيل) كاربوديميد (EDC) كمساعد اقتران. تم تشخيص المنتجات الوسيطة والنهائية التحليل الطيفي بالأشعة تحت الحمراء والتحليل الطيفي بالرنين المغناطيسي النووي. تم تقييم نشاط المركبات ضد الخلايا السرطانية باستخدام تحليل MTT الذي يشير إلى أن IC50 للمركب **6b** يبلغ 0.66 ميكرولتر بينما يبلغ IC50 لـ فورينوستات 1.48 ميكرولتر.

الكلمات المفتاحية: هيستون دياسيتيلاز، الإرساء الجزيئي ، فورينوستات.

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