In-silico Prediction of Binding Affinities and Pharmacokinetic Parameters of Indoline-2-one Derivatives as Anticancer HDAC Inhibitors

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Article Info:

Received 14 Dec 2025
Revised 5 Jan 2026
Accepted 20 Jan 2026
Published 31 Mar 2026
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DOI: https://doi.org/10.32947/ajps.v26i1.13467

Abstract:

The present work explores the molecular docking and pharmacokinetic features of indoline-2-one derivatives as potential anticancer agents by targeting histone deacetylase enzyme (HDAC1) which is the crucial element in tumor progression. Docking studies on the derivatives were performed based on histone deacetylase enzyme crystal structure (PDB ID: 1C3S) comparing with reference inhibitor vorinostat to ascertain inhibitory activity.

Docking outcomes demonstrated that the fitness scores of all analogs are superior to those of vorinostat. The binding types were stabilized mainly by hydrogen bond, hydrophobic contact and coordination with the zinc ion in the active site of enzyme, showing good complementarity and certain inhibitory effect. Pharmacokinetics screening via the Swiss ADME (absorption, distribution, metabolism, and excretion) platform revealed that these compounds complied with the Lipinski's rule for drug likeness, and had favorable physicochemical properties (good lipophilicity, suitable topological polar surface area values as well as good gastrointestinal absorption). The indoline-2-one derivatives did not interact with P-glycoprotein and presented a good oral bioavailability.

These results indicate that these compounds exhibit predicted inhibitory potential toward the histone deacetylase enzyme, supported by favorable docking scores and pharmacokinetic properties and can be further optimized for anticancer drug research.

Key words: Anticancer HDAC1 inhibitors, Indoline-2-one derivatives, *In-silico* study, Molecular docking; PLP fitness, Pharmacokinetic Parameters, SwissADME.

التنبؤ الحاسوبي بقوى الارتباط والمعايير الحركية الدوائية لمشتقات الإندولين-2-ون بوصفها مثبطات لإنزيم HDAC ذات فعالية مضادة للسرطان

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الخلاصة:
يهدف هذا البحث إلى دراسة الارتباط الجزيئي وتقييم الخصائص الحركية الدوائية لمجموعة من مشتقات الإندولين-2-ون المصممة بوصفها مثبطات لإنزيم نازعة الأسيتيل من النوع الأول(HDAC1) ، الذي يُعد أحد الأهداف الإبيجينية الرئيسة المرتبطة بتطور الأورام وانتشارها. تم إجراء محاكاة الارتباط الجزيئي باستخدام البنية البلورية للإنزيم(PDB ID: 1C3S) ، إذ جرت مقارنة أنماط الارتباط للمركبات المحضّرة مع المثبط المرجعي فورينوستات بهدف تقييم فعاليتها التثبيطية. أظهرت نتائج الارتباط الجزيئي امتلاك جميع المركبات المختبرة قيم مرتفعة تفوقت فيها على القيمة المسجلة للمركب المرجعي، مع تكوينها مجموعة من التآثرات الرئيسة داخل الجيب الحفّاز، شملت الروابط الهيدروجينية، والتآثرات الكارهة للماء، إضافة إلى التناسق المباشر مع أيون الزنك التحفيزي، مما يشير إلى قدرة عالية على الاستقرار داخل الموقع الفعّال وإحداث التثبيط المطلوب.كما جرى تقييم الخصائص الحركية الدوائية للمركبات باستخدام منصة Swiss ADME، وقد بيّنت النتائج توافق المركبات مع قواعد ليبنسكي للدوائية، إضافة إلى امتلاكها خصائص فيزيائية-كيميائية ملائمة مثل قيم لمساحة السطح القطبي الطوبولوجي المقبولة، ومستويات جيدة من الامتصاص المعوي، وتوقعات تُظهر عدم كونها ركائز لناقل P-glycoprotein، فضلاً عن امتلاكها درجات مناسبة من التوافر الحيوي، مما يدعم إمكانية إعطائها عن طريق الفم.وتشير النتائج إجمالاً إلى أن مشتقات الإندولين-2-ون المدروسة تُعد مرشحات واعدة لتكون مثبطات فعالة لإنزيم نازعة الأسيتيل ، مع امتلاكها صفات دوائية مشجعة تجعلها قابلة للتطوير مستقبلاً كمركبات ذات فعالية مضادة للسرطان.

الكلمات المفتاحية: مثبطات HDAC1 المضادة للسرطان، مشتقات الإندولين-2-ون، دراسة حاسوبية *In-silico*, الارتباط الجزيئي Molecular Docking, درجة PLP للملاءمة، المعايير الحركية الدوائية، منصة SwissADME.

1. Introduction:

Cancer is a multifactorial disease characterized by growth deregulation, abnormal differentiation, invasion of normal tissues and metastasis of malignant cells [1]. Its development consists of genetic and epigenetic events implicating abnormal growth, apoptosis, DNA repair and cell cycle control [2]. Mutations in oncogenes and loss of function in tumor suppressors, among others, are known to facilitate the malignant transformation and heterogeneity of tumors [3]. Furthermore, defects in DNA methylation and histone modification are important mechanisms in the development of many cancers [4].

Deregulated epigenetics is a characteristic feature of cancer and results in chromatin compartment changes are responsible for suppression or promotion of oncogenic pathway as tumor-suppressor genes are silenced by it [5]. Histone acetylation and deacetylation, catalysed by histone acetyltransferases (HATs) and histone deacetylases (HDACs), are a key aspect of chromatin structure and transcriptional results [6]. In the normal state, HAT and HDAC activities are in balance [7]. Overexpression of HDAC disturbs equilibrium, resulting in chromatin condensation , transcriptional repression and suppression of genes controlling apoptosis, growth arrest and differentiation [8]. Therefore, HDAC disorder is related to cancer induction, development, propagation and resistance to therapy [9].

HDAC proteins represent a group of eighteen isoforms that are classified into four classes, as these prove to have different structure, catalytic mechanisms and location [10]. The classical HDACs (class I, II, and IV) are Zn^{2+} -dependent metallo-enzymes, whereas class III (sirtuins) have NAD^{+} -dependence activities [11, 12]. One of the class I members (HDAC1) is predominantly localized in the nucleus and is required for transcriptional repression, chromatin remodeling and control of genes implicated in carcinogenesis [13]. Increased HDAC1 expression contributes to the proliferation of cancer cells, inhibition of apoptosis, angiogenesis, and metastasis in different

cancers [14]. Therefore, HDAC1 is a potential target for anticancer drugs and selective inhibition of this enzyme may be a valuable strategy in cancer treatment [15].

HDAC inhibitors (HDACIs) counteract acetylation to obtain regular levels, reactivate the silenced tumour-suppressor genes and stimulate apoptosis [16]. Vorinostat, romidepsin, belinostat and panobinostat have been approved for hematological malignancies providing further support on the relevance of targeting epigenetic modulators [17]. Current HDACIs are mostly nonselective or have poor isoform-selectivity, and suffer from toxicity, bioavailability, and off-target toxicities. These efforts have driven discovery for new scaffolds and hybrids to improve potency, selectivity, and pharmacokinetic profiles toward safer and more effective cancer treatments [18].

Many therapeutic medicines rely on heterocyclic compounds for their structure [19], making them essential components in pharmaceutical science. Isatin (1H-indole-2,3-dione) is an attractive privileged heterocyclic template in medicinal chemistry because of its structural flexibility and pharmacological potentials [20]. Isatin analogs, having antibacterial, antiviral activity, anti-inflammatory, antioxidant ,neuroprotective and anticancer properties [21]. Isatin based lead molecule like sunitinib, toceranib and nintedanib are clinically used anticancer drugs which signify the importance of isatin toward drug modification [22]. Furthermore, isatin-based Schiff-base derivatives have a high degree of anticancer activity and much research was carried on their HDAC isoforms' inhibitory studies [23]. The electrophilic C-3 carbonyl of isatin, an aromatic nucleus, and the opportunity to attach various substitutions make it a privileged template for designing HDAC-targeting anticancer drugs [24].

The investigations have shown that structural modifications at the isatin C-5 position, installation of electron-withdrawing group and linkage to zinc-binding groups remarkably contribute to the HDAC inhibitory activity and selectivity [25]. These findings have prompted the development of a series of novel indoline-2-one based derivatives that engage the HDAC1 catalytic site through important molecular interactions including zinc coordination, hydrogen bonding as well as hydrophobic stabilization [26]. As a result of the advances in computational chemistry, the use of *in-silico* tools such as molecular docking methods and ADME prediction values are sensitive to assess ligand protein interactions, predict their pharmacokinetic behavior and early-stage optimization of drugs prior its chemical production [27]. Docking studies allow characterization of binding affinities and interaction medium involving the HDAC1 active site, whereas SwissADME builds rapid predictions for drug likeness, bioavailability and physicochemically properties to new chemical entities [28].

With these in mind, an integrated *in-silico* strategy is applied in the current investigation to analyze binding affinity and pharmacokinetic properties of a set of indoline-2-one based derivatives as HDAC1 inhibitors with potential anticancer activity [29]. By the molecular docking study with HDAC1 crystal structure (PDB: 1C3S) together with *in-silico* pharmacokinetic screening through Swiss ADME, this research sets out to find structurally promising derivatives having suitable interaction patterns and positive ADME properties which could promote their further development as new anticancer drug candidates [30].

2. Aim of the study:

The purpose of the present study was to develop a new series of indoline–2–one

derivative as anticancer agents against histone deacetylase-1 (HDAC1), an important epigenetic enzyme which is involved in tumor growth, progression and gene silencing. Molecular docking studies runs with the synthesized derivatives and native ligand were performed using the HDAC1 crystal structure (PDB ID: 1C3S) to evaluate binding affinities of the obtained derivatives in comparison to reference HDAC inhibitor, vorinostat) in order to identify compounds with superior interactions and increased inhibitory potential. In addition, an *in-silico* pharmacokinetic evaluation was performed using the Swiss ADME platform to assess the ADME (absorption, distribution, metabolism, and excretion) profiles and drug-likeness properties of the designed compounds. This dual computational method aims to identify promising compounds with favorable binding behavior and suitable pharmacokinetic characteristics, eventually contributing to the rational design of novel HDAC1-targeted anticancer agents.

3. Computational Method:

It is reported that isatin-based scaffolds and HDACs inhibitors have great anticancer properties based on previous literature, direct the molecular design of indoline-2-one derivatives discussed in this work. An in silico modeling study was carried out to analyze the inhibitory performance of these derivatives with HDAC1, an epigenetic enzyme known to be involved in cancer development. [31]. The docking was performed in the active site of HDAC1 to evaluate ligand compatibility, and key non-covalent interactions like hydrogen bond, hydrophobic contacts, π–π stacking and Zn^{2+} coordination were analyzed. These interactions are critical for stabilizing ligand binding and enhancing inhibitory activity [32]. In parallel, the pharmacokinetic properties of all derivatives were predicted using the Swiss ADME online platform to estimate their absorption, distribution, metabolism, and excretion (ADME) characteristics and to evaluate their drug-likeness [33].

3.1. Preparation of designed compounds:

The chemical structures of the designed indoline-2-one derivatives (5a1–6 and 5b4–9) were made using ChemDraw Professional (v.22.0.0). Energy minimization was subsequently performed using Chem3D (v.22.0.0) employing the MM2 force field to obtain the most stable three-dimensional conformations prior to docking analysis.

3.2. Molecular Docking: Preparation of the Protein Receptor:

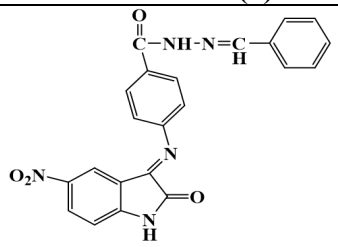
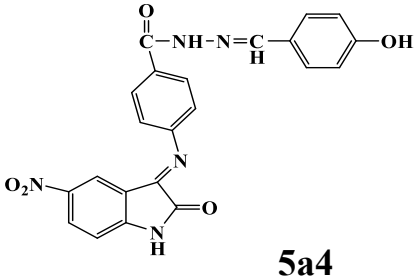
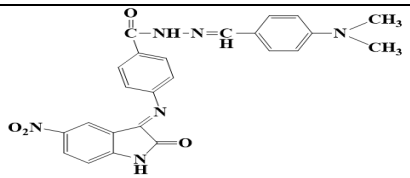
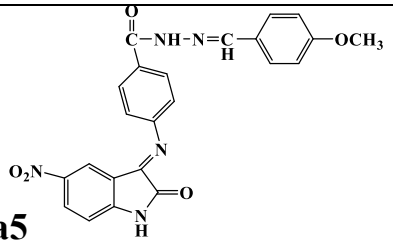
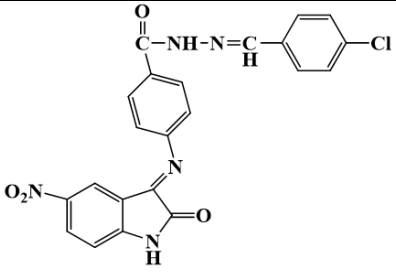
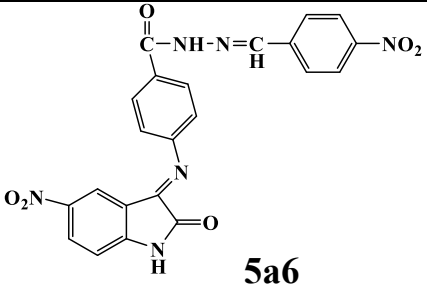
The crystal structure of histone deacetylase-1 (PDB ID: 1C3S) was retrieved from the Protein Data Bank and prepared for molecular docking using the GOLD 2022 docking suite (Cambridge Crystallographic Data Centre, CCDC). To validate the docking procedure, hydrogen was added to the protein and the active site residues were checked for tautomerism and ionization states. Non-essential chains, ligands, water molecules and cofactors were removed, while the catalytic Zn^{2+} ion coordinated by ASP168, HIS170, and ASP258 was retained, as it plays an essential role in ligand binding and HDAC inhibition. The original ligand of the protein was extracted from the active site. The active site of the protein was loaded with the reference drug (Vorinostat) and the designed compounds to generate docking process [34]. The docked compounds were assessed through their PLP fitness score as regards ligand–protein interactions. Docking poses were analyzed for interactions primarily, hydrogen bonds, hydrophobic contacts π-π stacking and coordination with Zn^{2+} ion. These interactions were filtered using the GOLD Hermes module and interaction profiles were recorded. This analysis found favorable bounding poses of designed

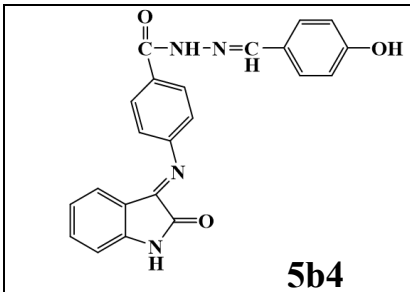
derivatives within the HDAC1 active site and revealed their possible inhibitory properties. Docking parameters and scoring functions were selected based on previously validated protocols for HDAC1 studies, and the use of vorinostat as a reference ligand served to validate the reliability of the docking procedure. [35].

3.3. ADME Prediction:

Pharmacokinetic behavior and physicochemical profiles of indoline-2-one derivatives (5a1–6 and 5b4–9) were analyzed using the Swiss ADME server designed in ChemDraw [36]. The chemical names of each compound were converted to SMILES format for the characterization of properties such as molecular weight, lipophilicity (LogP), topological polar surface area (TPSA), hydrogen-bond donors and acceptors, Solubility, rotatable bonds. Lipinski's Rule of Five and the Veber's criteria were used for evaluating drug-likeness and to estimate oral bioavailability and permeability [37].The BOILED-Egg model predicted gastrointestinal absorption, blood–brain barrier penetration and P-glycoprotein interaction [38]. Swiss ADME allows to perform fast *in-silico* pharmacokinetic profile prediction allowing to prioritize compounds with better drug-like qualities and discarding those with bad ADME properties [39].

Table (1): Structures of the designed compounds

 **5a1**	 **5a4**
 **5a2**	 **5a5**
 **5a3**	 **5a6**



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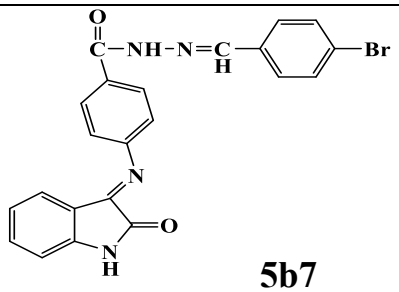

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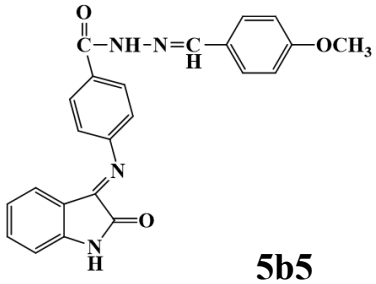

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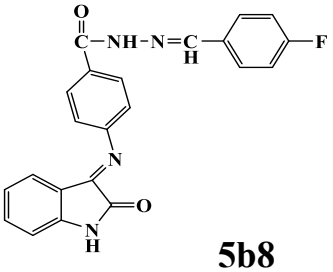

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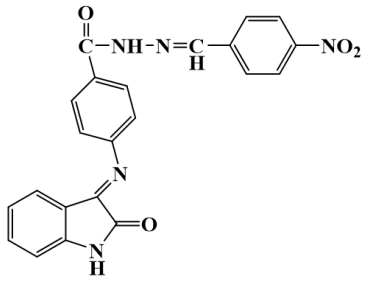

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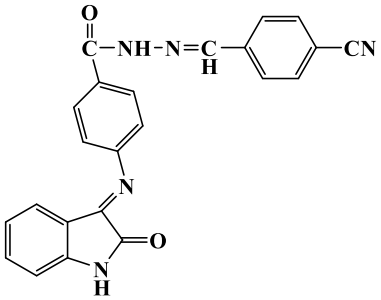

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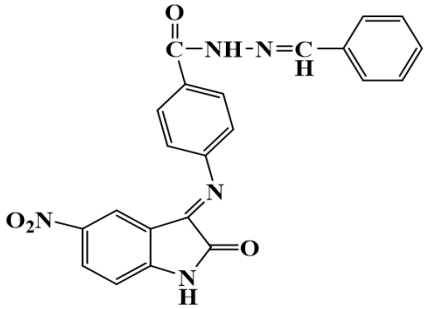
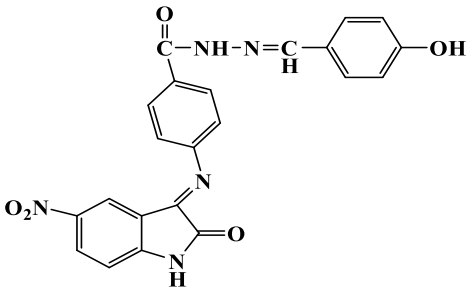


5a1



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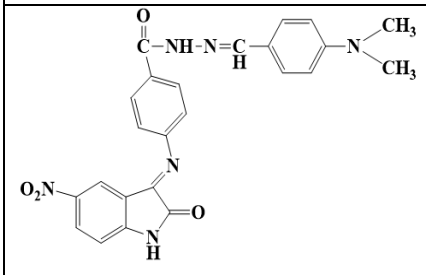

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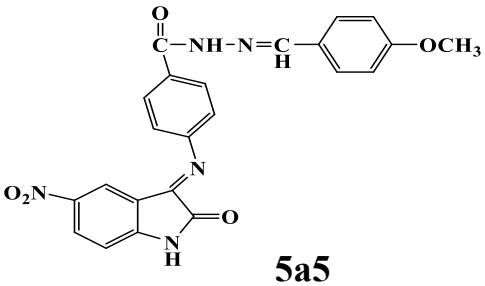

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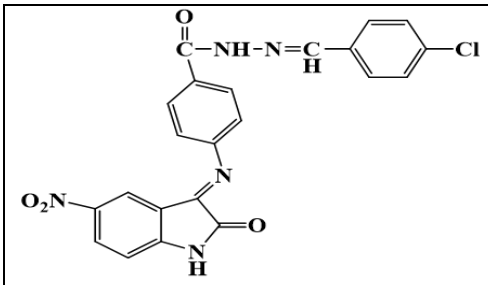

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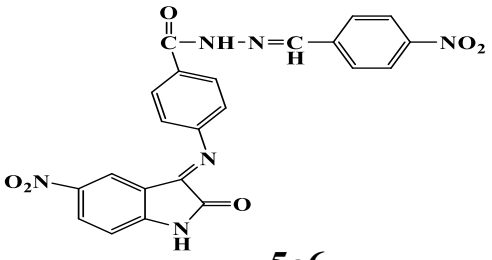

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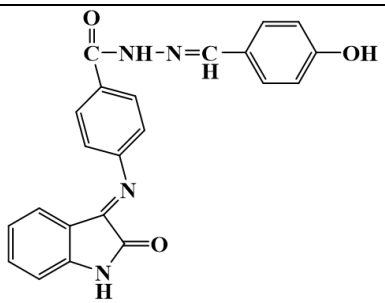

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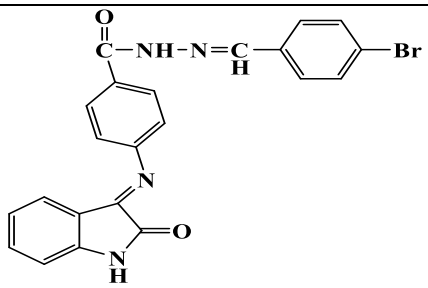

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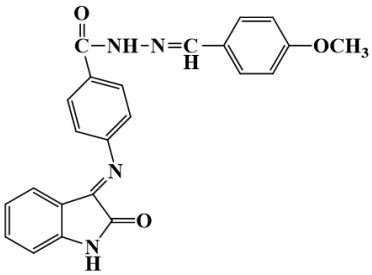

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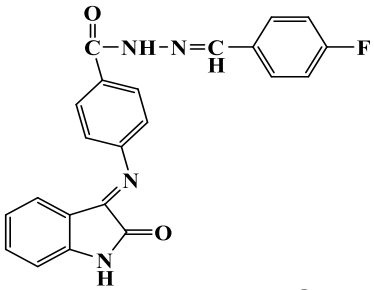

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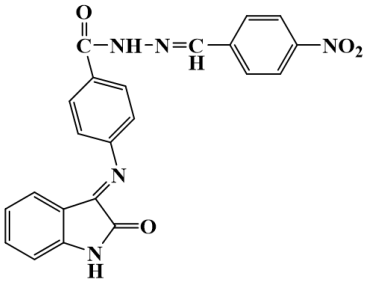

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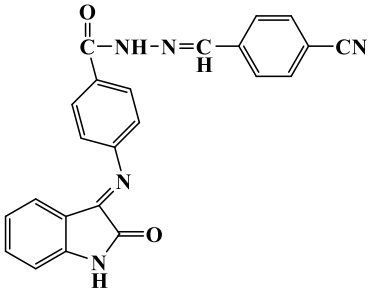

5b9

4. Result and Discussion:

The indoline-2-one analogs (5a1–6 and 5b4–9) were designed to be investigated for histone deacetylase-1 inhibitory activity as an anticancer agent. Molecular docking analyses estimate binding affinities, interaction modes and coordination of the catalytic Zn^{2+} ion in relation to vorinostat. Furthermore, the pharmacokinetic and drug-likeness profiles were analyzed by Swiss ADME server to predict ADME properties and adherence to medicinal chemistry for oral bioavailability. Docking and ADME results elucidate some of the molecular and physicochemical

properties that influence binding to HDAC1, supporting indoline-2-one derivatives as promising candidates with predicted anticancer potential.

4.1. Interpretation of molecular docking study:

The molecular docking study was carried out to predict the binding affinities and interaction patterns of the designed indoline-2-one derivatives (5a1–6 and 5b4–9) toward the active site of histone deacetylase-1 (HDAC1; PDB ID: 1C3S), which reflects the overall binding strength and complementarity between each ligand and enzyme. The docking results determine the hydrogen bonds, short contact and hydrophobic interactions between protein atoms and ligands. The high number of H-bond interactions and hydrophobic interactions increases the pharmacological activity required for substrate binding to the active site.

Overall, all compounds showed favorable binding affinities toward the HDAC1 catalytic site, with PLP fitness scores ranging from 74.57 to 88.49, exceeding the score of the reference drug vorinostat (66.19). Compounds 5a6, 5a4, 5b4, 5b7 and 5a5 scored the highest PLP fitness scores (88.49, 85.95, 84.56, 83.07 and 82.15), respectively suggesting that their binding orientation were more favorable with more strong interactions within the catalytic pocket. As summarized in Table (2), the superior docking performance of compounds 5a6, 5a4, 5b4, and 5b7 may be attributed to their enhanced hydrogen bonding, hydrophobic interactions, and effective coordination with the catalytic Zn^{2+} ion. Docking analysis confirmed the involvement of active site of Zn^{2+} ion in stabilizing ligand ion, as reflected by the observed coordination interaction with ASP168, HIS170, and ASP258acrossthe majority of docked compounds.

Most docked ligands formed a hydrogen bond with ASP168 and HIS170, these residues directly coordinating the zinc ion, thereby stabilizing the enzyme-ligand complex and enhancing their potential inhibitory potency. Additional hydrogen bonds and π–π stacking interactions were observed with aromatic and polar residues such as TYR297, PhE141, HIS132, and GLU92, as well as hydrophobic contacts with ALA127, PhE198, and LEU265 further contributed to the binding stabilization .The docking poses revealed that the isatin moiety participates predominantly in polar and hydrogen-bond interactions, whereas the benzamide fragment contributes to hydrophobic and van-der Waals interactions, improving anchoring within the enzyme pocket site. The Schiff base linkage provides structural rigidity and favorable orientation, allowing the pharmacophoric portion of isatin to align optimally toward the Zn^{2+} catalytic site. Collectively, these results suggest that the designed indoline-2-one derivatives exhibit favorable binding affinity toward HDAC1, surpassing the reference inhibitor in docking performance and displaying interaction profiles consistent with potential HDAC1 inhibition. These results support their activity as promising anticancer candidates. The PLP fitness scores and interaction patterns are presented in table (2).

Table (2): Molecular docking results against HDAC1 enzyme using GOLD software

Compounds	PLP-Fitness	Hydrogen-bond interactions	Hydrophobic interactions
5a1	80.58	PHE198 and TYR297(2)	HIS170, GLN192(2), ASP258, LEU265and TYR297(2), Bridging through Zn^{+2} with ASP168, HIS170 and ASP258
5a2	77.76	GLU92(2), GLY129, PHE141and ASP168	LEU23, ASP168(2) Bridging through Zn^{+2} with ASP168, HIS170 and ASP258
5a3	74.57	GLY129, PHE141, ASP168 and HIS170	GLU92, PHE141 and ASP168(3) Bridging through Zn^{+2} with ASP168, HIS170 and ASP258
5a4	85.95	HIS131, TYR297 and ASP168(2)	LEU23, GLY129, HIS131(3),PHE141 and ASP168(2) Bridging through Zn^{+2} with ASP168, HIS170 and ASP258
5a5	82.15	GLY294 and TYR297	TYR17(3), ALA127 and PHE141 Bridging through Zn^{+2} with ASP168, HIS170 and ASP258
5a6	88.49	HIS132, ASP168(2) and TYR297	GLU92, GLY129, HIS131, HIS 132 and ASP168(2) Bridging through Zn^{+2} with ASP168, HIS170 and ASP258
5b4	84.56	GLY128 and TYR297 (3)	ALA127 Bridging through Zn^{+2} with ASP168, HIS170 and ASP258
5b5	77.35	GLU92, GLY129 and ASP168	ASP168(2) Bridging through Zn^{+2} with ASP168, HIS170 and ASP258
5b6	77.93	ARG27,ALA127and TYR297(2)	ALA127(2), GLY128, HIS170(2) and TYR297(2) Bridging through Zn^{+2} with ASP168, HIS170 and ASP258
5b7	83.07	TYR297(2) and ALA127	ALA127 and GLY128 Bridging through Zn^{+2} with ASP168, HIS170 and ASP258
5b8	80.66	HIS170 and TYR297	ALA127, HIS170 and TYR297(2) Bridging through Zn^{+2} with ASP168, HIS170 and ASP258
5b9	77.56	ASP168, HIS170(2) and GLY295	ASP168(2)
Vorinostat	66.19	ALA127	HIS132, Bridging through Zn^{+2} with ASP168, HIS170 and ASP258

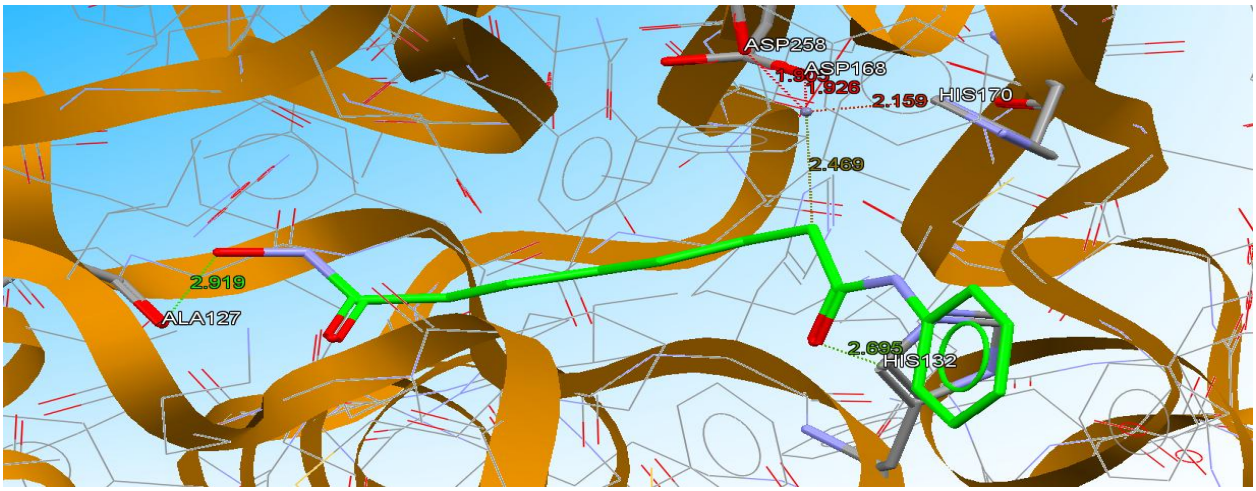

Figure (1): Three-dimensional structural representation of interactions between vorinostat and HDAC1 (PDB ID: 1C3S; 2.50 Å) generated using GOLD software

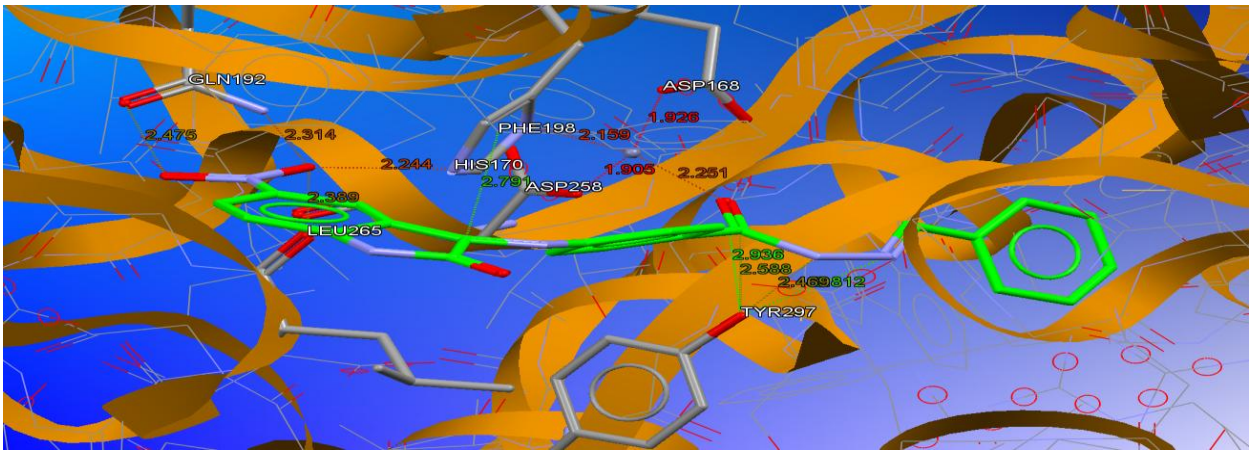

Figure (2): Three-dimensional structural representation of interactions between compound 5a1 and HDAC1 (PDB ID: 1C3S; 2.50 Å) generated using GOLD software

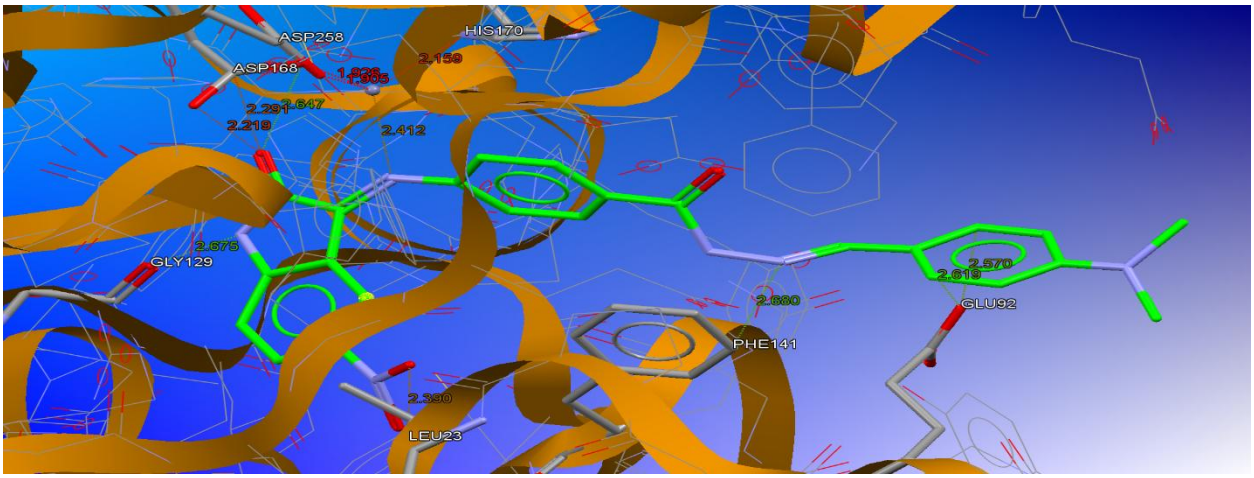

Figure (3): Three-dimensional structural representation of interactions between compound 5a2 and HDAC1 (PDB ID: 1C3S; 2.50 Å) generated using GOLD software

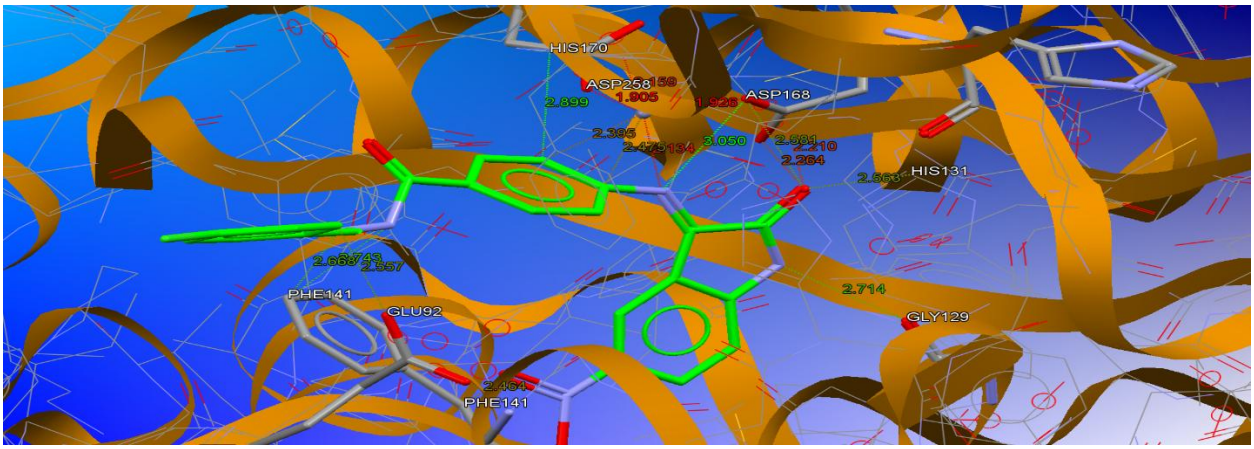

Figure (4): Three-dimensional structural representation of interactions between compound 5a3 and HDAC1 (PDB ID: 1C3S; 2.50 Å) generated using GOLD software

Figure (5): Three-dimensional structural representation of interactions between compound 5a4 and HDAC1 (PDB ID: 1C3S; 2.50 Å) generated using GOLD software.

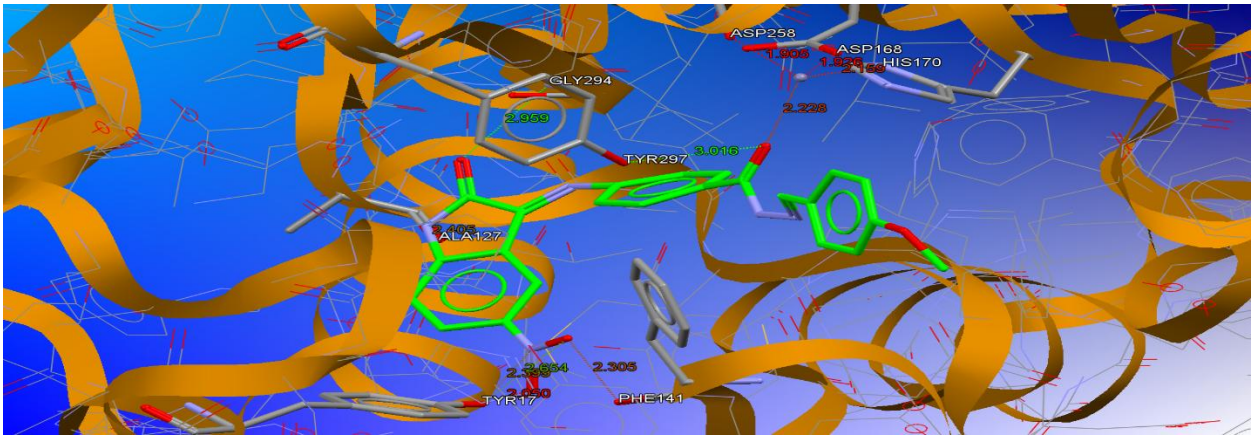

Figure (6): Three-dimensional structural representation of interactions between compound 5a5 and HDAC1 (PDB ID: 1C3S; 2.50 Å) generated using GOLD software

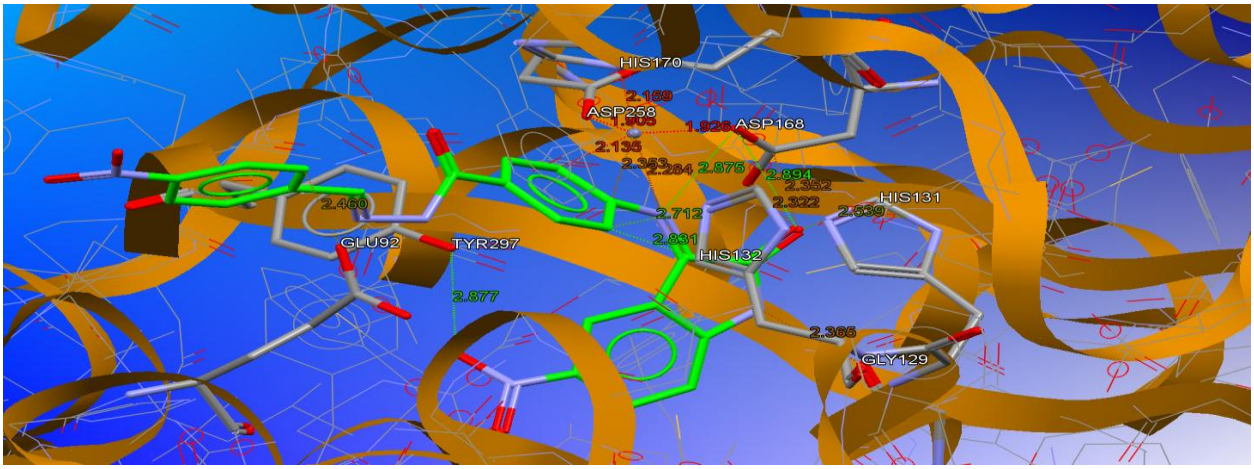

Figure (7): Three-dimensional structural representation of interactions between compound 5a6 and HDAC1 (PDB ID: 1C3S; 2.50 Å) generated using GOLD software

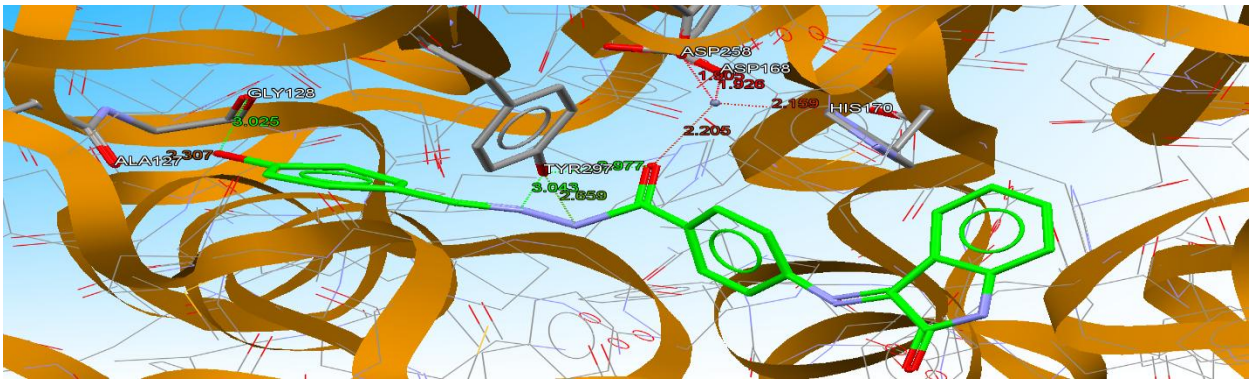

Figure (8): Three-dimensional structural representation of interactions between compound 5b4 and HDAC1 (PDB ID: 1C3S; 2.50 Å) generated using GOLD software

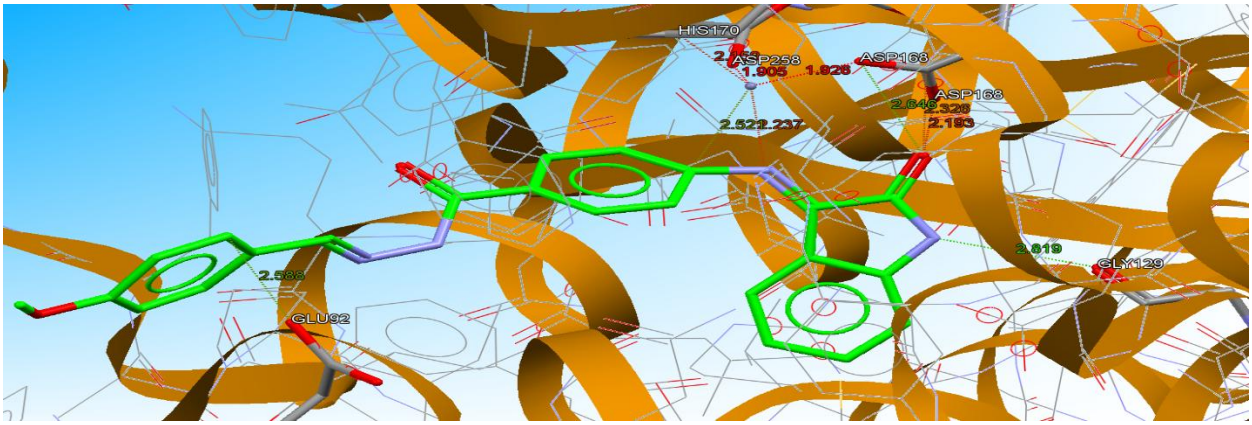

Figure (9): Three-dimensional structural representation of interactions between compound 5b5 and HDAC1 (PDB ID: 1C3S; 2.50 Å) generated using GOLD software

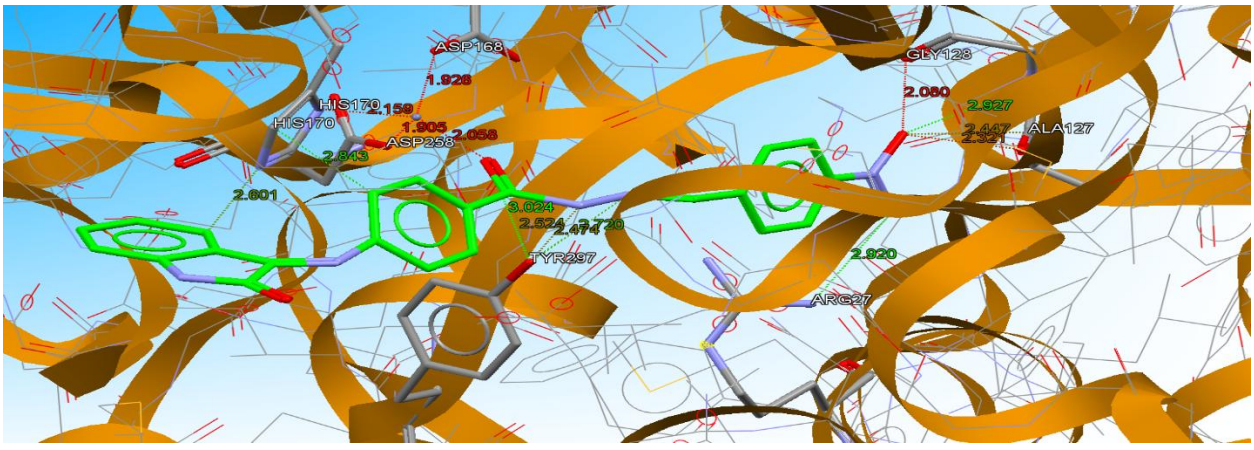

Figure (10): Three-dimensional structural representation of interactions between compound 5b6 and HDAC1 (PDB ID: 1C3S; 2.50 Å) generated using GOLD software

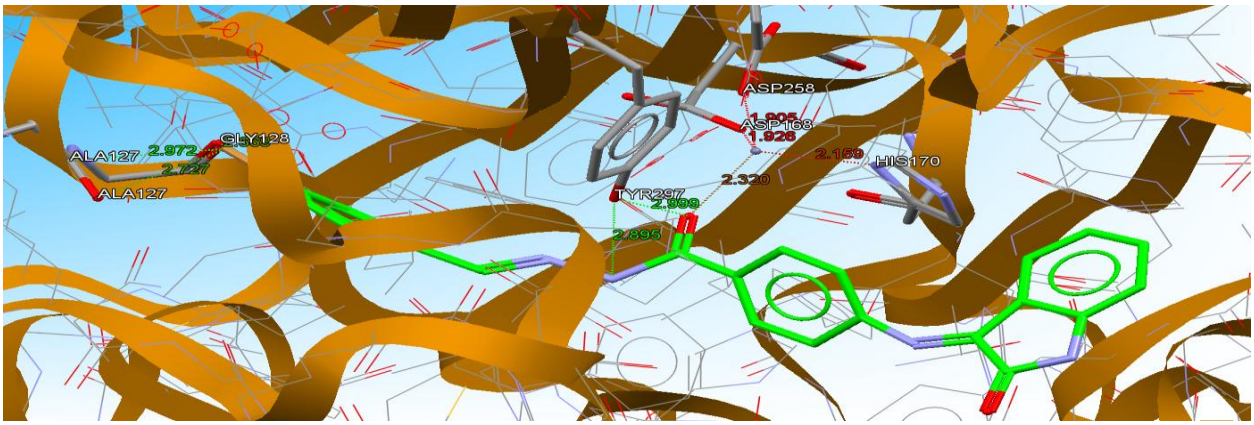

Figure (11): Three-dimensional structural representation of interactions between compound 5b7 and HDAC1 (PDB ID: 1C3S; 2.50 Å) generated using GOLD software

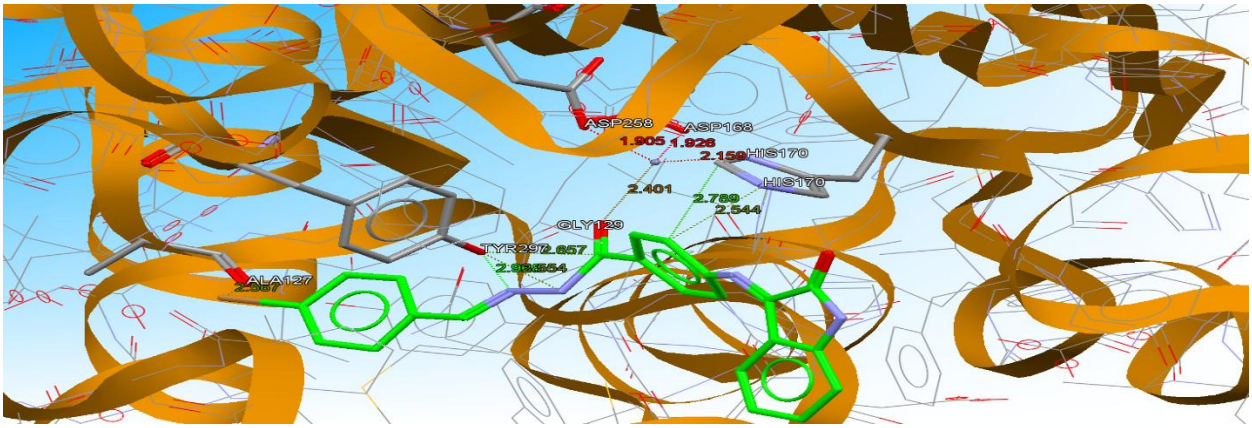

Figure (12): Three-dimensional structural representation of interactions between compound 5b8 and HDAC1 (PDB ID: 1C3S; 2.50 Å) generated using GOLD software

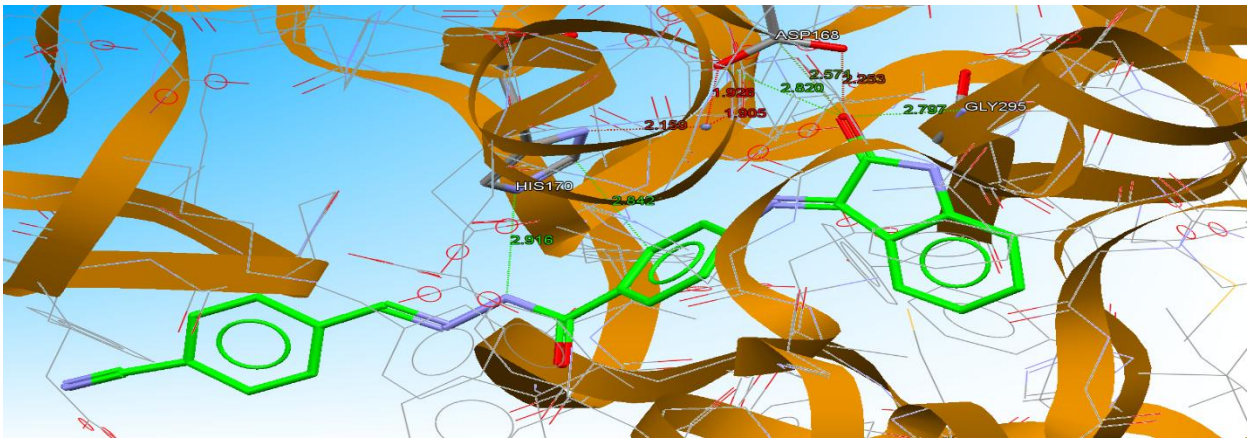

Figure (13): Three-dimensional structural representation of interactions between compound 5b9 and HDAC1 (PDB ID: 1C3S; 2.50 Å) generated using GOLD software

4.2. Interpretation of ADME study:

In-silico pharmacokinetic profiles of the developed indoline-2-one derivatives, (oral absorption, lipophilicity and polarity), drug-likeness criteria and interaction with a P-glycoprotein transporter were predicted using the Swiss ADME platform. The objective of this analysis was to find compounds with desirable physicochemical properties and pharmacokinetics to advance a more potent class of orally available HDAC1 inhibitors.

Topological polar surface area (TPSA), an important parameter for prediction of intestinal permeability, ranged from 82–175 Å² for the compounds. Developed agents having TPSA value lower than 140 Å² were found to have better chances of good gastrointestinal absorption in comparison to the compounds near or crossed this threshold. All derivatives had an oral bioavailability score of 0.55, indicating their potential to reach systemic circulation following oral administration.

The lipophilicity (LogP) values, related to the membrane permeability and solubility varied from 1.81 to 3.75, drugs with optimal log P balance between hydrophilic and lipophilic properties. All the designed compounds were in accordance with Lipinski's Rule of Five i.e., good molecular weight, LogP and number of H-bond donors and acceptors. These results indicate that the compounds in general have drug-likeness properties.

The BOILED-Egg prediction was also consistent with these results, presenting all derivatives in the white area, characterized by their high gastrointestinal absorption. Finally, all of the compounds are shown as PGP-negative (red dots), indicating that they were not substrates to p-glycoprotein. This feature increases their cell retention and could facilitate their pharmacological effect. Table (3) summarize the key physicochemical and pharmacokinetic parameters of the designed compounds. Overall, the *in-silico* ADME results demonstrate that the majority of these derivatives show promising pharmacokinetic behavior, appropriate physicochemical properties, acceptable molecular weight, LogP values within the optimal range, compline with Lipinski's Rule of Five and favorable drug-likeness profiles. These findings support their suitability as orally bioavailable anticancer candidates and justify their further biological evaluation as HDAC1 inhibitors.

Table (3): Physicochemical parameters of the final compounds

No.	Molecular Weight	Number of Rotatable bonds	Number of H-bond acceptors	Number of H-bond donors	MR	TPSA	Log P	GI Absorption
5a1	413.39	6	6	2	120.45	128.74	2.54	High
5a2	456.46	7	6	2	134.66	131.98	2.33	High
5a3	447.83	6	6	2	125.46	128.74	3.07	High
5a4	429.39	6	7	3	122.48	148.97	1.99	Low
5a5	443.42	7	7	2	126.95	137.97	2.39	Low
5a6	458.39	7	8	2	129.28	174.56	1.81	Low
5b4	384.39	5	5	3	113.66	103.15	2.76	High
5b5	398.42	6	5	2	118.12	92.15	3.14	High
5b6	413.39	6	6	2	120.45	128.74	2.43	High
5b7	447.29	5	4	2	119.33	82.92	3.75	High
5b8	386.39	5	5	2	111.59	82.92	3.45	High
5b9	393.40	5	5	2	116.35	106.71	2.93	High

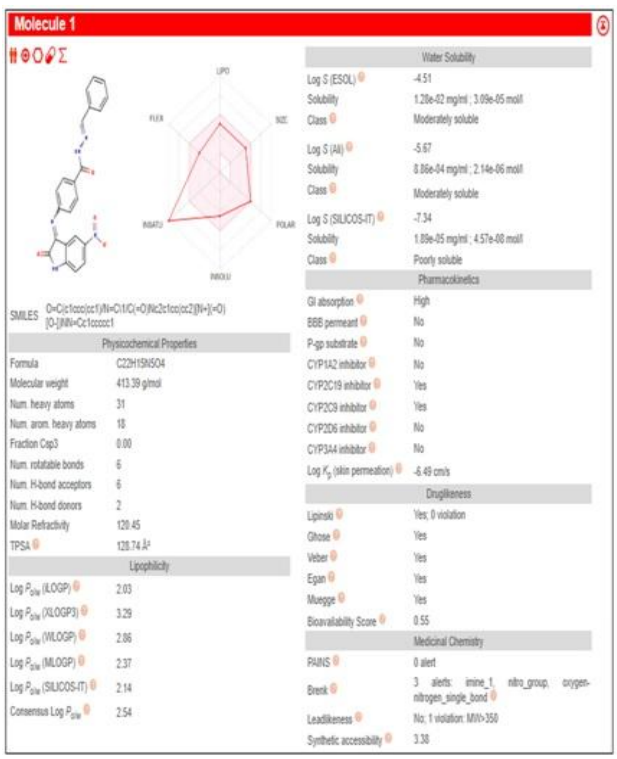

Figure (14): *In-silico* ADME parameters of compound 5a1

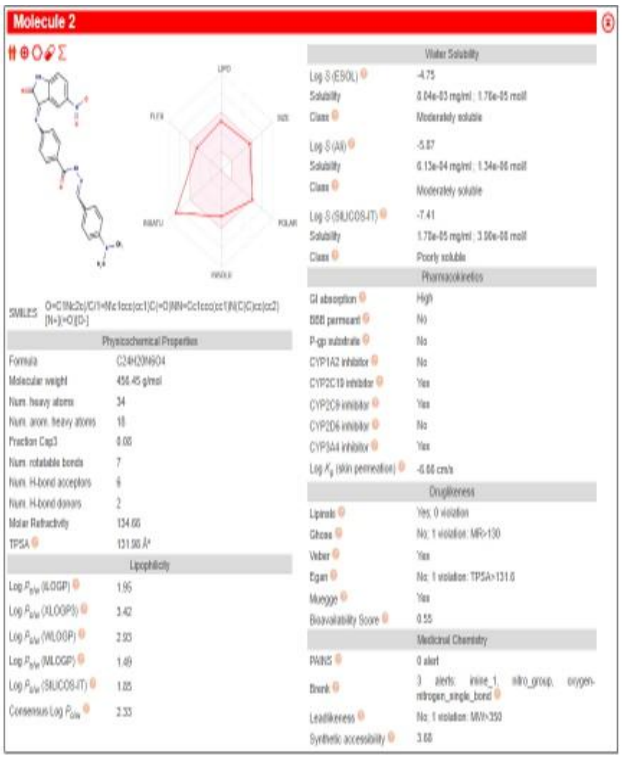

Figure (15): *In-silico* ADME parameters of compound 5a2

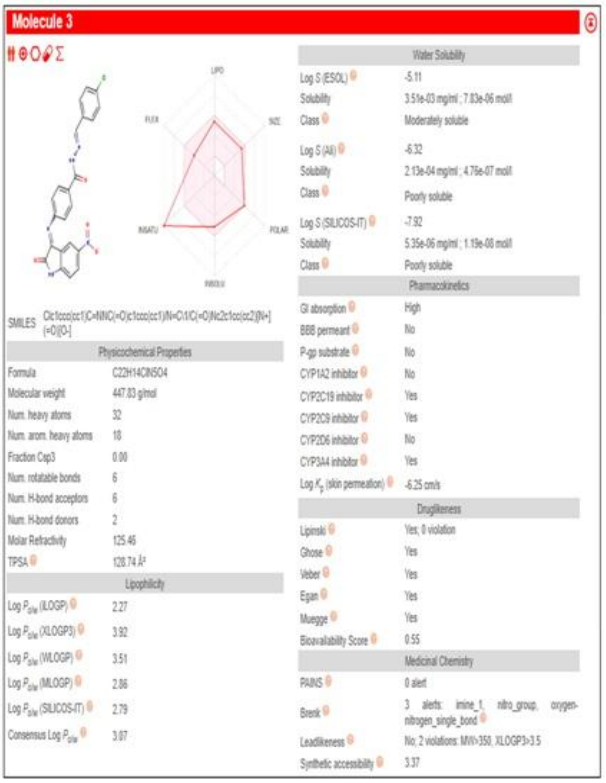

Figure (16): *In-silico* ADME parameters of compound 5a3

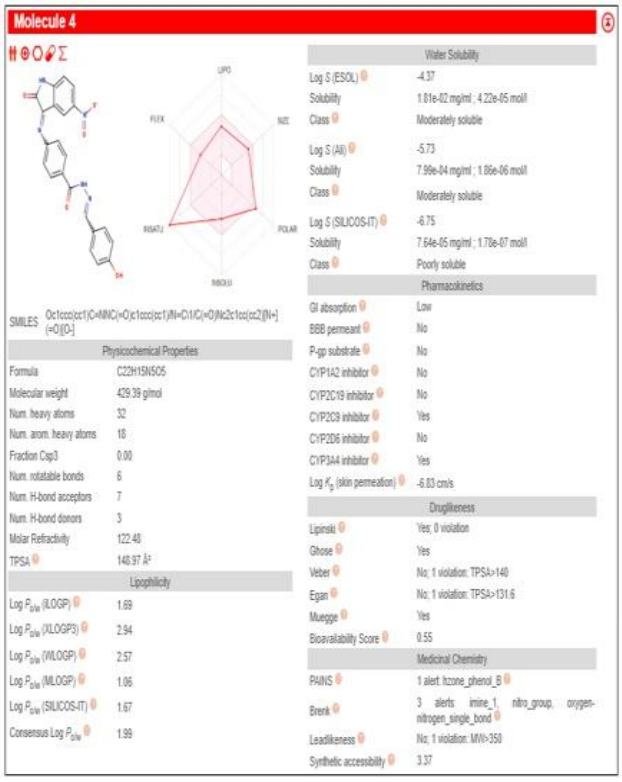

Figure (17): *In-silico* ADME parameters of compound 5a4

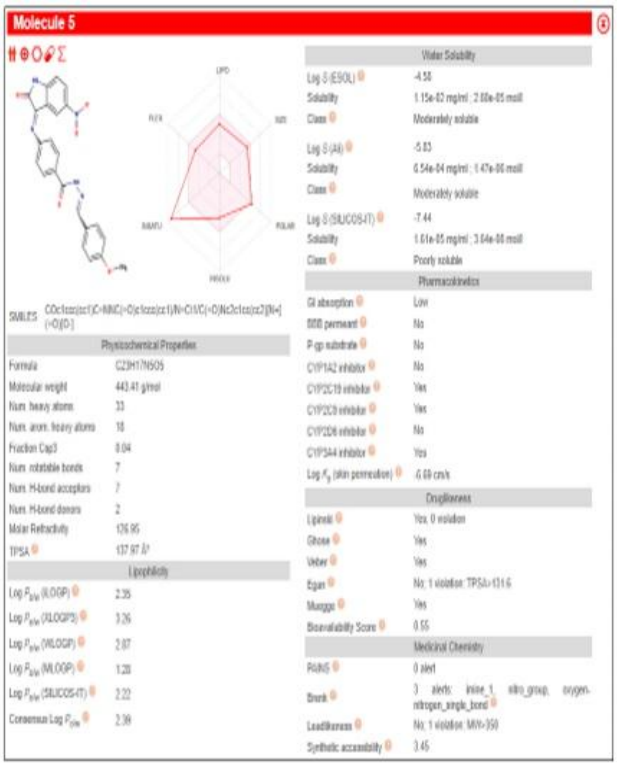

Figure (18): *In-silico* ADME parameters of compound 5a5

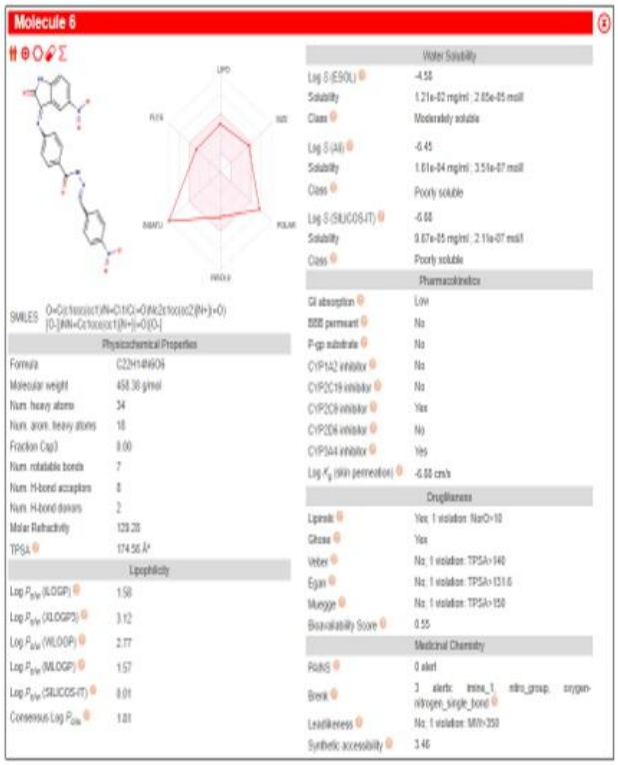

Figure (19): *In-silico* ADME parameters of compound 5a6

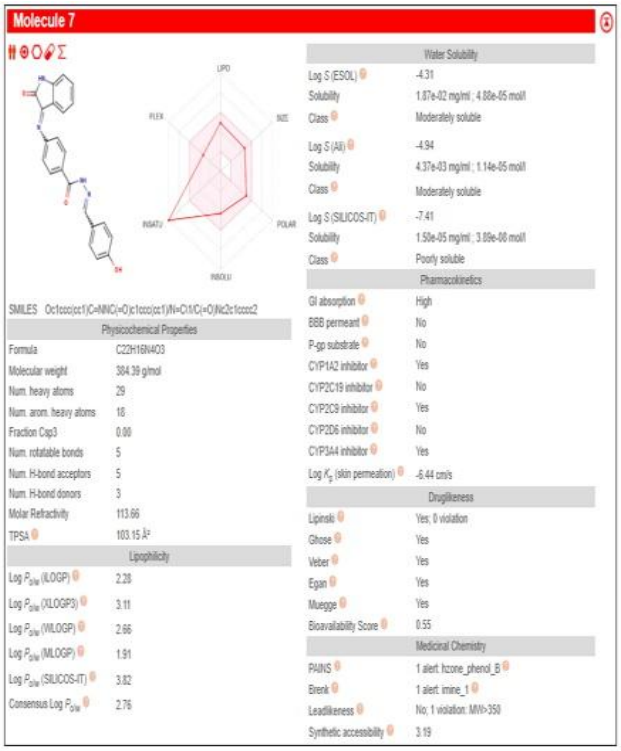

Figure (20): *In-silico* ADME parameters of compound 5b4

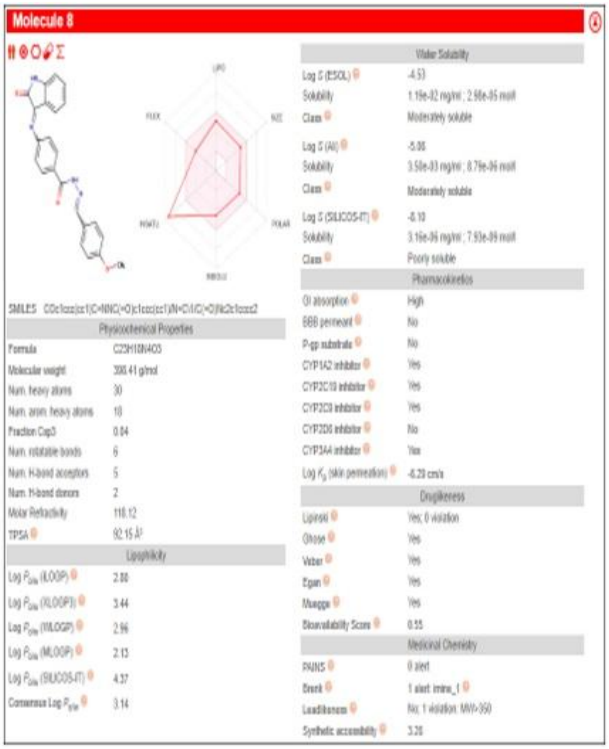

Figure (21): *In-silico* ADME parameters of compound 5b5

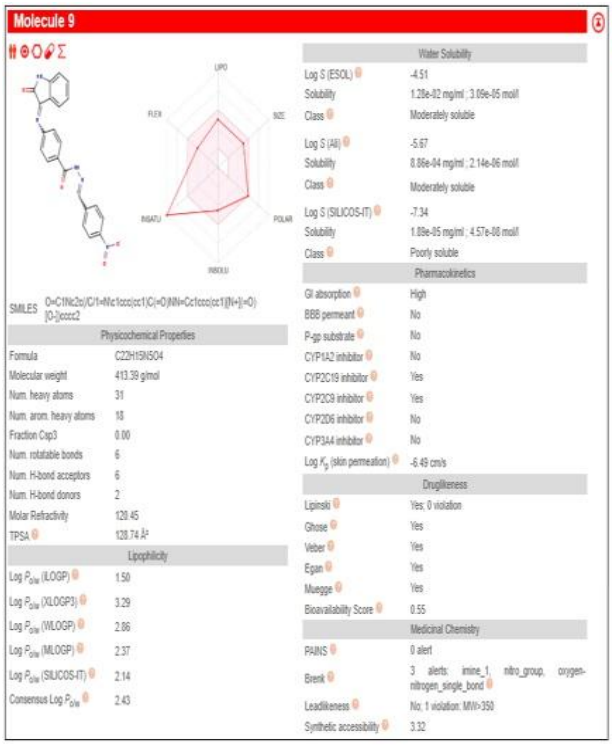

Figure (22): *In-silico* ADME parameters of compound 5b6

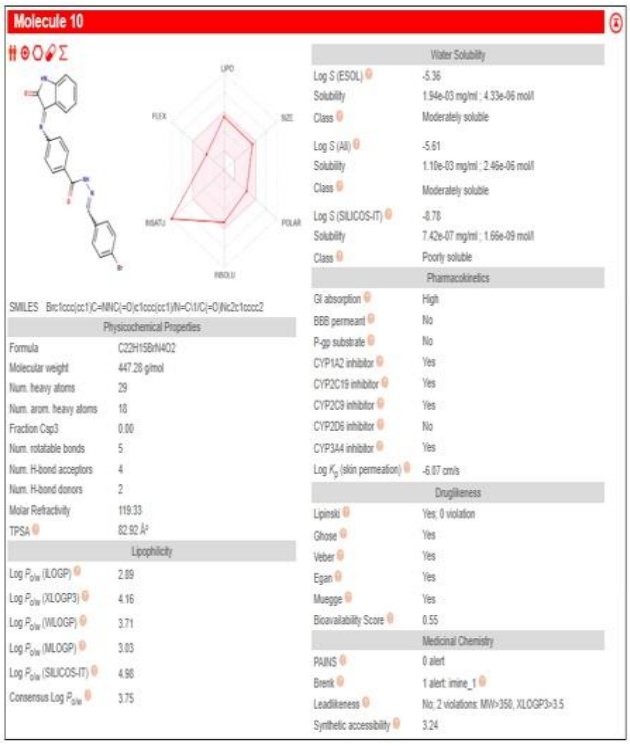

Figure (23): *In-silico* ADME parameters of compound 5b7

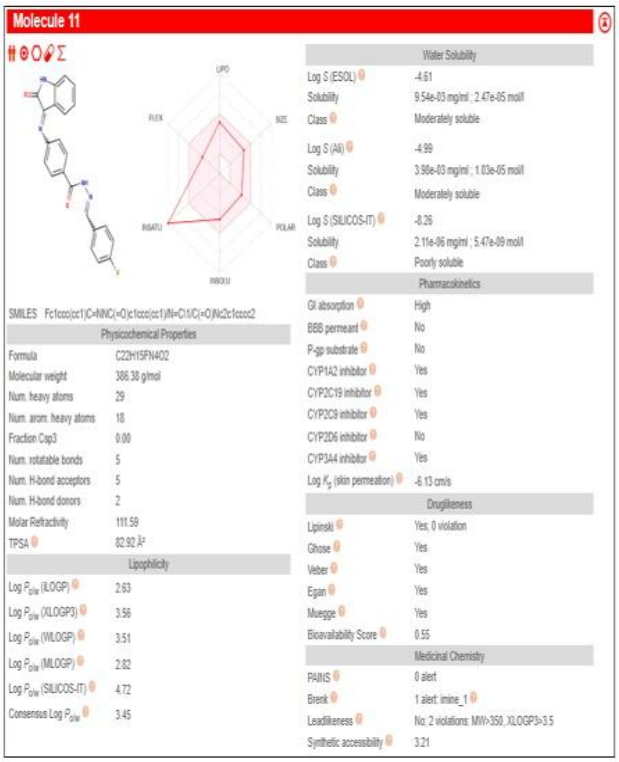

Figure (24): *In-silico* ADME parameters of compound 5b8

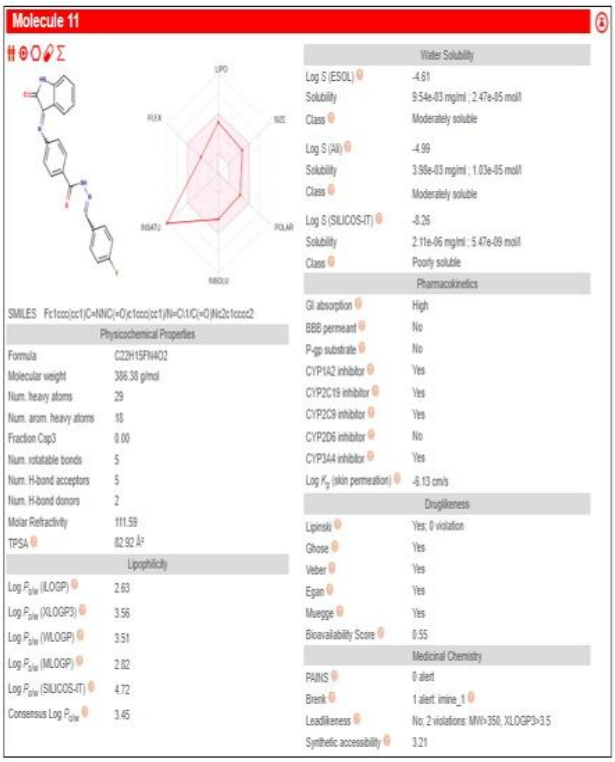

Figure (25): *In-silico* ADME parameters of compound 5b9

5. Conclusion:

The present *in-silico* study demonstrates that the designed indoline-2-one derivatives exhibit promising predicted activity as novel HDAC1 inhibitors with potential anticancer activity. Molecular docking studies revealed that all synthesized derivatives exhibited favorable PLP fitness scores, exceeding the reference inhibitor vorinostat and showing stable interactions with key catalytic residues within the HDAC1 active pocket, including ASP168, HIS170, and ASP258. The capacity of these derivatives to directly coordinate the catalytic Zn^{2+} center through extensive network of hydrogen bonds, hydrophobic interactions and pi-stacking further emphasizes their structural compatibility for HDAC1 inhibition.

Additionally, the ADME-related predictions of the compounds were all consistent with drug likeness, Lipinski's rule, acceptable log P and gut absorption, and no predicted interaction of P-glycoprotein. The BOILED-Egg profile also showed favored in vivo pharmacokinetic properties with promising oral bioavailability.

Collectively, the docking and pharmacokinetic results highlight these indoline-2-one derivatives as promising HDAC1 inhibitor candidates with potential anticancer activity.

While the present study provides valuable *in-silico* insights into the interaction of indoline-2-one derivatives with HDAC1, further experimental investigations, including *in vitro* and *in vivo* studies, are recommended to corroborate the predicted inhibitory activity and anticancer potential of the designed compounds.

6. Acknowledgements:

The authors would like to thank the Department of Pharmaceutical Chemistry, College of Pharmacy, Mustansiriyah University (www.uomustansiriyah.edu.iq), Baghdad, Iraq, for providing the facilities and support necessary to complete this work.

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