

Original Research Article

Prediction of pharmacokinetics and molecular docking of new 1,2,3,4-tetrahydropyrimidine derivatives linked to carbonylhydrazide by aromatic and heteroaromatic linkers

Ameer H Alwash^{1*}, Sumia Samer Tayeh², Massara Nazar Ahmed³, Shaymaa Alshimary⁴

¹Department of Pharmaceutical Chemistry, College of Pharmacy, Al-Bayan University, ²Pharmacy College, Al-ESRAA University, ³Department of Pharmacy, Al-Hikma University College, ⁴Department of Pharmacy, AL Nukhba University College, Baghdad, Iraq

*For correspondence: **Email:** ameer.hussein@albayan.edu.iq

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Abstract

Purpose: To predict pharmacokinetic parameters and molecular docking of a new series of 1,2,3,4-tetrahydropyrimidine derivatives linked to a carbonylhydrazide moiety through different aromatic and heteroaromatic linkers (Compounds I-X)

Methods: The pharmacokinetic parameters (absorption, distribution, metabolism, excretion) were predicted using *in silico* studies. The binding complementarity, pose, and affinity to the active site of HDAC8 were investigated using molecular docking, which showed the effect of different linkers on the active site of the enzyme and the potential activity of the compounds.

Results: The ADME analysis revealed that the compounds may be beneficial for targeting colon diseases such as colon cancer without significant systemic or central side effects, along with a lower incidence of multidrug resistance. Furthermore, compounds III, IV, VI, VII, and IX demonstrated acceptable properties according to Ghose parameter and compounds (I-X) have acceptable medicinal chemistry characteristics according to PAINS parameters. All designed compounds (I-X) show comparable interaction with amino acid residues in the active site of HDAC8 enzyme with the reference ligand (SAHA), along with higher binding energies than SAHA (-5.54 kcal/mol).

Conclusion: This study demonstrates the potential of 1,2,3,4-tetrahydropyrimidine-carbonylhydrazide hybrids as promising scaffolds for the design of selective HDAC8 inhibitors and provides valuable insights for further structural optimization and synthesis.

Keywords: ADME, Carbonylhydrazide, Colon cancer, HDAC8 inhibitors, 1,2,3,4-Tetrahydropyrimidine, Molecular docking

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INTRODUCTION

Histone deacetylases (HDACs) are interesting Zn²⁺-dependent enzymes in proteomics that participate in many post-translational protein modifications, which play pivotal role in various cellular processes such as gene silencing and expression, cytoskeletal dynamics, cellular

growth and proliferation. Histone deacetylases (HDACs) catalyze the deacetylation of histone and non-histone proteins, thereby shifting toward a more compressed form of chromatin structure and affecting the gene transcription process. Currently, there are 18 known HDAC isoforms, classified as 1-18, which differ in many aspects, including cellular localization, structure, function,

and expression patterns. Histone deacetylase 8 (HDAC8) is regarded as a distinctive member of the HDAC family because its gene is located on the X chromosome. It possesses a flexible, accessible active site that facilitates the development of selective inhibitors that operate independently. It also uniquely targets a wide range of non-histone substrates, including SMC3 and p53, in addition to histones, which affects various aspects of cellular homeostasis. Thus, dysregulation of HDAC8 is associated with multiple cancers, neurodegenerative conditions, and inflammatory disorders. As a result, HDAC8 has gained considerable attention as a therapeutic target, and selective inhibition may provide effective disease modulation while minimizing the off-target adverse effects commonly associated with pan-HDAC inhibitors [1,2].

The scaffold (1,2,3,4-tetrahydropyrimidine) is a privileged heterocycle with a wide range of biological activities, such as anti-inflammatory, anti-cancer, and antimicrobial properties. Its structural versatility allows for modification to interact favorably with biological targets. Carbohydrazide moieties, on the other hand, are useful in drug design because they enhance binding in enzyme active sites, particularly metalloproteins like HDACs, form hydrogen bonds, and chelate metal ions like Zn^{2+} . Affinity and selectivity are modulated by adjusting electronic, steric, and conformational properties using aromatic and heteroaromatic linkers between pharmacophoric units. Computational tools like molecular docking (MD) and absorption, distribution, metabolism, and excretion (ADME) prediction are now useful in early stages of lead identification and optimization in drug discovery. The fate of molecules *in vivo* is referred to as ADME. Before any expensive synthesis or *in vitro* testing, *in silico* ADME prediction allows quick evaluation of drug-likeness, metabolic stability, possible toxicity, and other pharmacokinetics (PK) characteristics [3]. Key descriptors include lipophilicity (Log P), solubility, molecular weight, topological polar surface area (TPSA), number of hydrogen bond donors and acceptors, rotatable bonds, and compliance with the rule of five-type criteria. More recent models also predict parameters like blood-brain barrier penetration (if applicable), CYP450 inhibition, and Caco-2 permeability, frequently using machine learning to increase prediction accuracy [4]. Molecular docking enhances ADME prediction by forecasting the binding orientation and estimating binding affinity using scoring functions. Successful inhibition of HDAC8 typically necessitates hydrogen bonding with catalytic

residues, coordination to the active-site Zn^{2+} , and accommodation of the ligand's 'cap' moiety in the enzyme's rim or recognition site. Selectivity and ligand binding also depend on the hydrophobic tunnel and substrate-binding channel. Molecular docking sheds light on structure-activity relationships (SAR), assisting in determining which residues are essential, which linkers or substituents enhance binding interactions, and how changes impact binding orientation [5,6]. Recent structural biology has provided high-resolution X-ray crystal structures of HDAC8 bound to selective inhibitors (e.g., phenylhydroxamate inhibitors), which reveal unusual zinc coordination modes and conformational flexibility in the active site. These structures provide reliable templates for docking studies [7]. Also, recent research has combined molecular docking studies with *in vitro* evaluation, showing that changes in cap groups, linker types, or substituent patterns on inhibitor scaffolds (including fluorinated cap groups, heterocyclic cores, etc.) significantly affect both binding energy and cell-based efficacy against cancer cell lines [8].

In this study, a series of aromatic and heteroaromatic moieties was introduced as linkers for conjugating the 1,2,3,4-tetrahydropyrimidine scaffold to carbohydrazide, which acts as a zinc-binding group (ZBG), to design new derivatives with potential binding with Zn^{+2} and the other crucial residues in the active site of HDAC8. The pharmacokinetics and drug-likeness characteristics of the designed compounds were evaluated by *in silico* ADME profiling. Also, the mechanism of binding, residue complementarity, poses, and affinity were investigated using molecular docking. This study seeks to obtain promising lead molecules that combine strong interaction potentials and good profiles by comparing predicted ADME properties with docking results. This will serve as a foundation for additional optimization and experimental validation.

EXPERIMENTAL

Pharmacokinetics (ADME) prediction

This study was performed using the SwissADME web tool. The chemical structures of compounds (I–X) were drawn using the Marvin JS editor, converted into SMILES notation, and subsequently submitted for analysis by selecting the run option. Afterwards, the outcomes were recorded as images.

Molecular docking study

Preparation of the protein

X-ray crystallography of HDAC8 protein was retrieved from the Protein Data Bank (PDB) website (<https://www.rcsb.org>, PDB ID:1T69). The file was uploaded to the Schrodinger software (Maestro suite 2025-1, Glide module). The protein was prepared using the Protein Preparation Panel. All options were kept as default, and the 'run' option was selected. The grid was established using the Receptor Grid Generation panel, during which the reference ligand in the active site of the enzyme (vorinostat, also known as SAHA) was selected manually. Finally, the grid file was saved.

Ligands' preparation

Chemical structures of compounds (I-X), including the reference ligand (SAHA), were sketched by the 2D sketcher panel and saved to the workspace. These ligands were prepared for docking by LigPrep panel, in which all options were kept as default except for the choosing option add metal binding states), and thereafter submitted for analysis by selecting the 'run' option.

Ligands docking

Files of the grid and prepared ligands were uploaded from their destination, and the docking

process was conducted. At the end, docking scores in kcal/mol and 2D ligand-amino acid residue interactions were recorded as images.

RESULTS

Pharmacokinetics (ADME) study

The Swiss ADME wizard was utilized to evaluate the pharmacokinetics and drug-likeness characteristics of the compounds (I-X) (Figures 1 to 10).

Molecular docking study

Schrodinger software (Maestro suite 2025-1, Glide module) was used to conduct a molecular docking study. The 2D visualization outcomes of this study showed ligand poses (Compounds I-X and reference ligand, SAHA) along with the mode of binding and amino acid residues involved in the ligand-receptor binding within the active site of HDAC8 enzyme (PDB ID: 1T69). Docking scores (which represent the binding energies) in kcal/mol and amino acid residues involved in the ligand-receptor interaction within the active site of the enzyme are presented in Table 1. The red color represents residues that are in common with the reference ligand (SAHA) interacting with the active site of HDAC8 enzyme (Figure 11 and Figure 12).

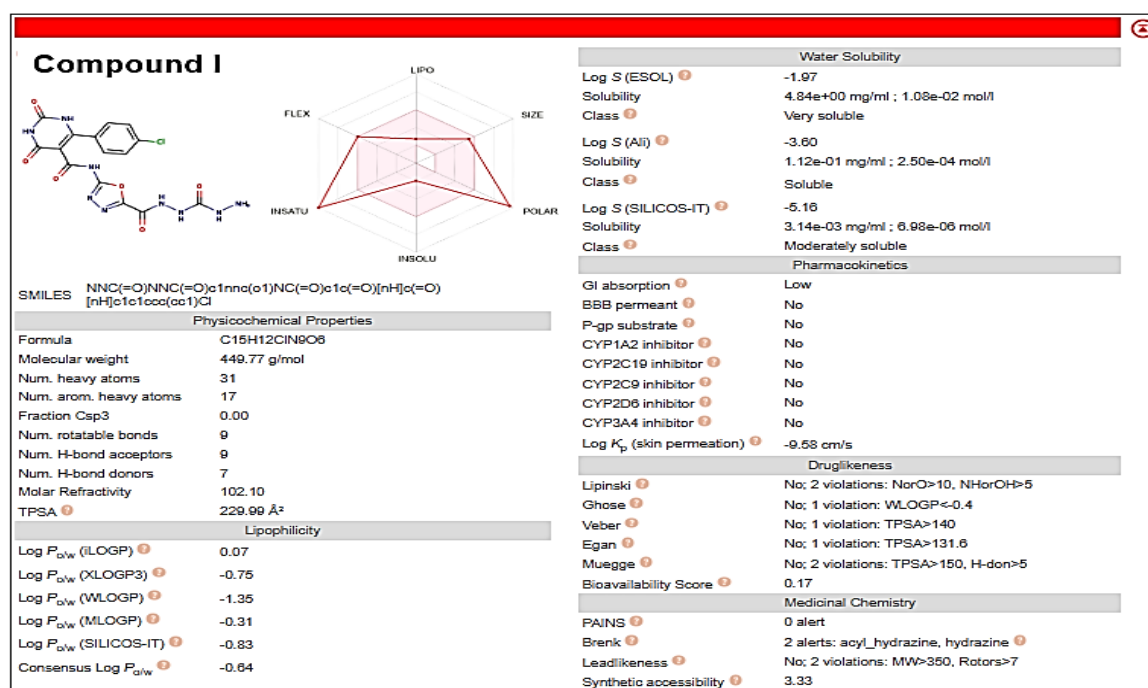


Figure 1: SwissADME prediction for the PK and drug-likeness characteristics of compound I

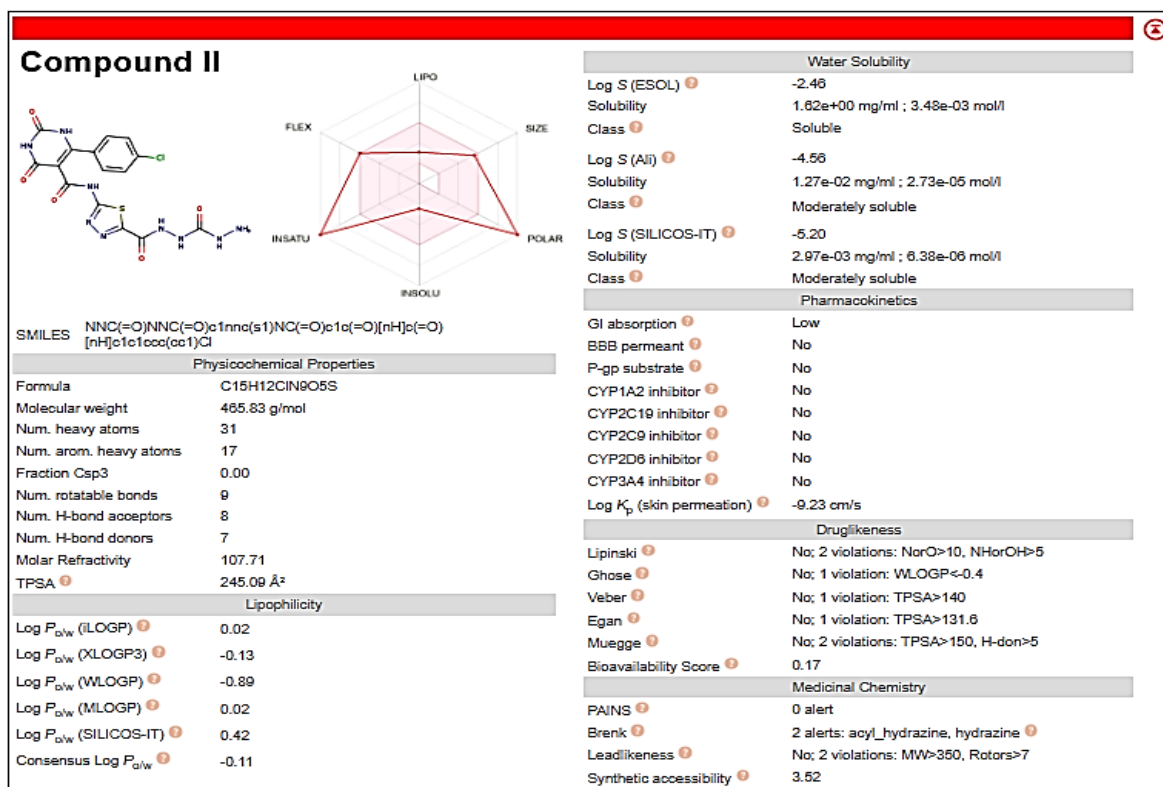


Figure 2: SwissADME prediction for the PK and drug-likeness characteristics of compound II

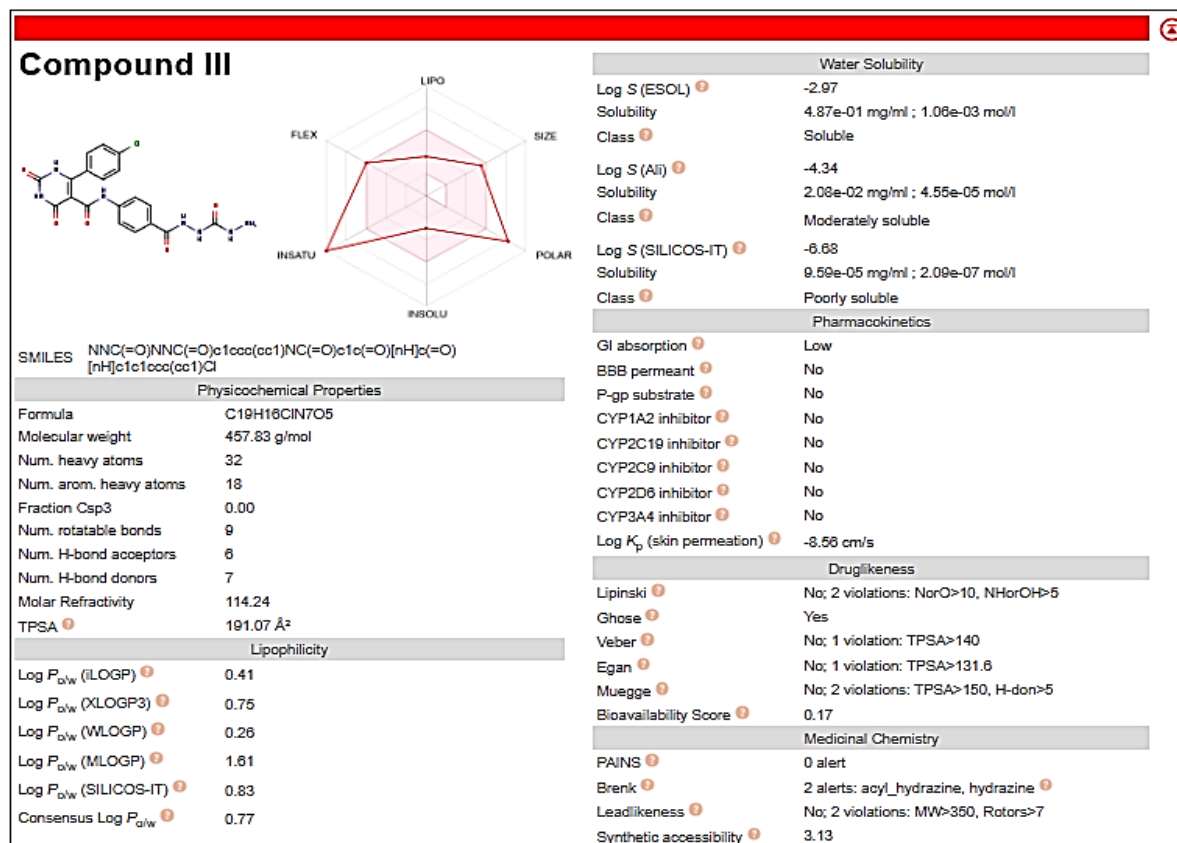


Figure 3: SwissADME prediction for the PK and drug-likeness characteristics of compound III

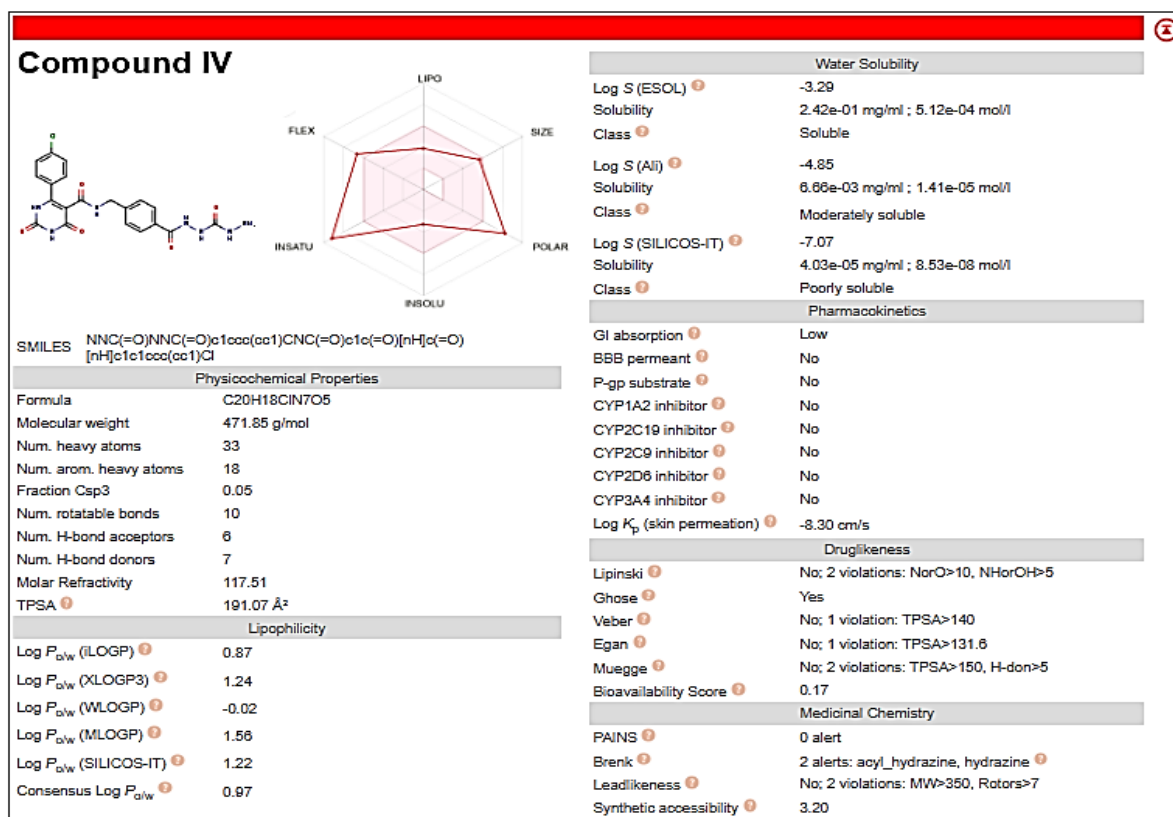


Figure 4: SwissADME prediction for the PK and drug-likeness characteristics of compound IV

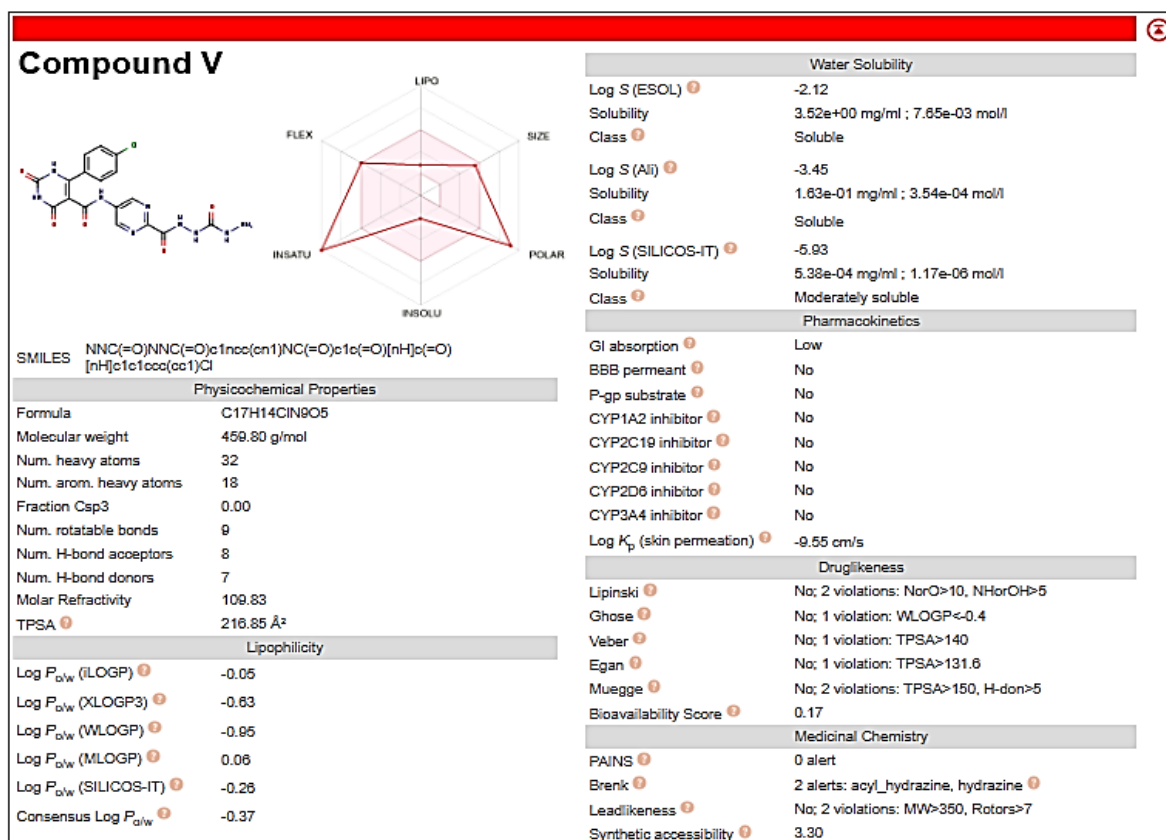


Figure 5: SwissADME prediction for the PK and drug-likeness characteristics of compound V

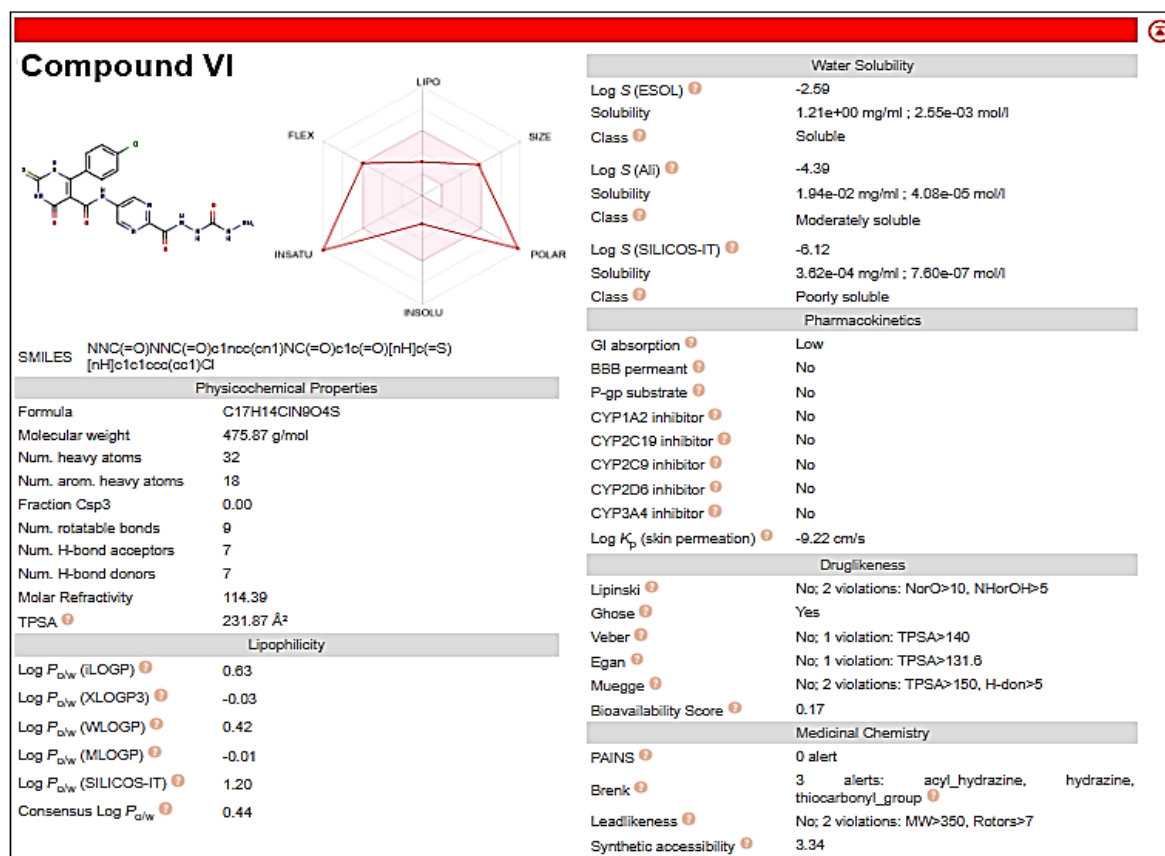


Figure 6: SwissADME prediction for the PK and drug-likeness characteristics of compound VI

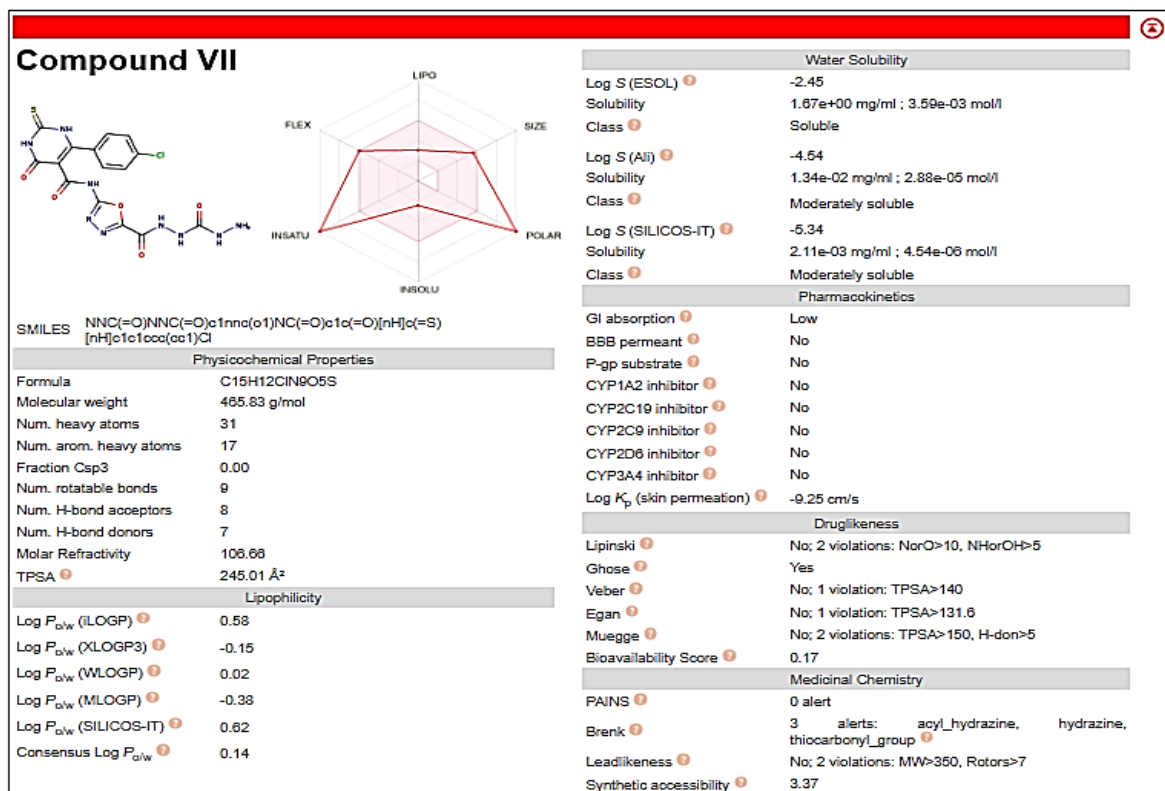


Figure 7: SwissADME prediction for the PK and drug-likeness characteristics of compound VII

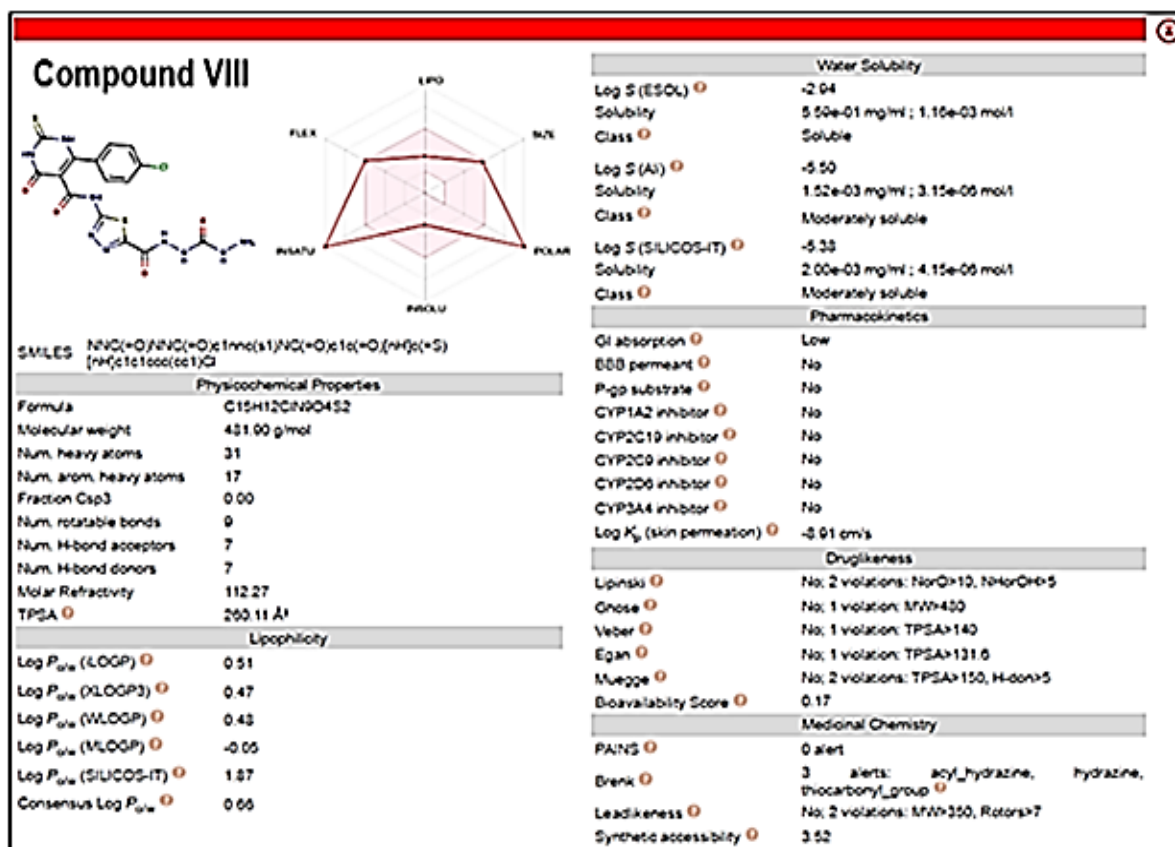


Figure 8: SwissADME prediction for the PK and drug-likeness characteristics of compound VII

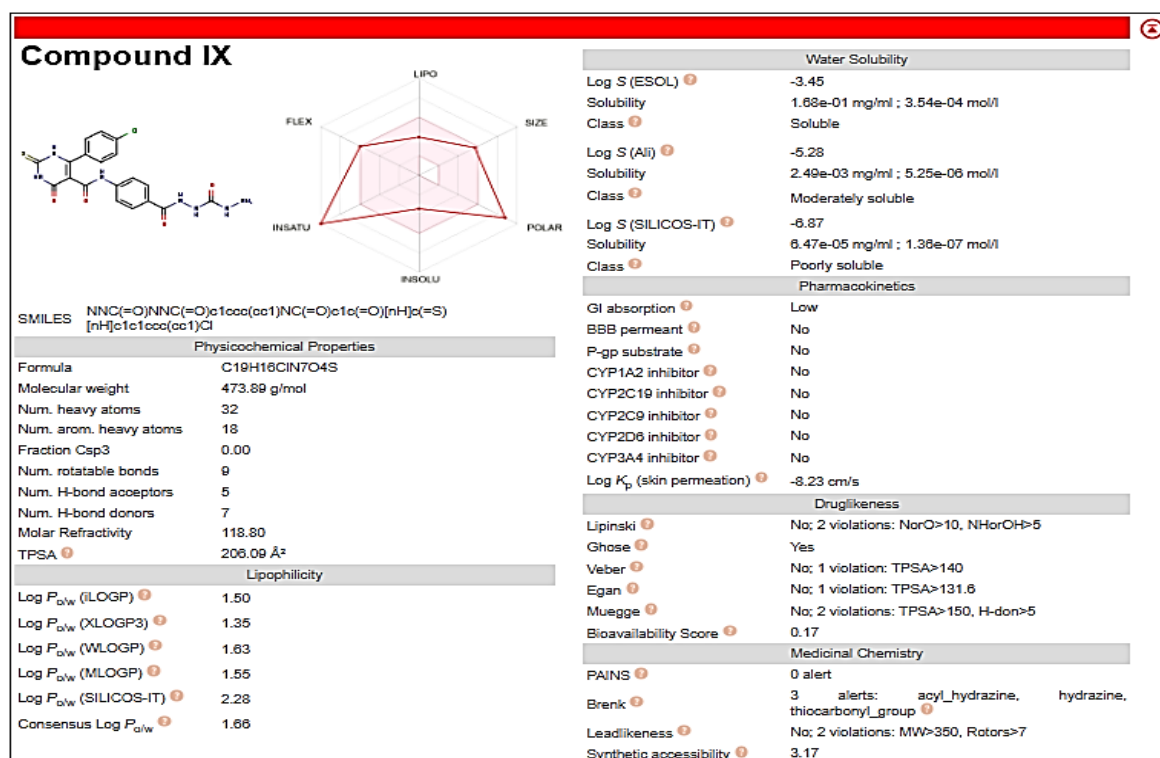


Figure 9: SwissADME prediction for the PK and drug-likeness characteristics of compound IX

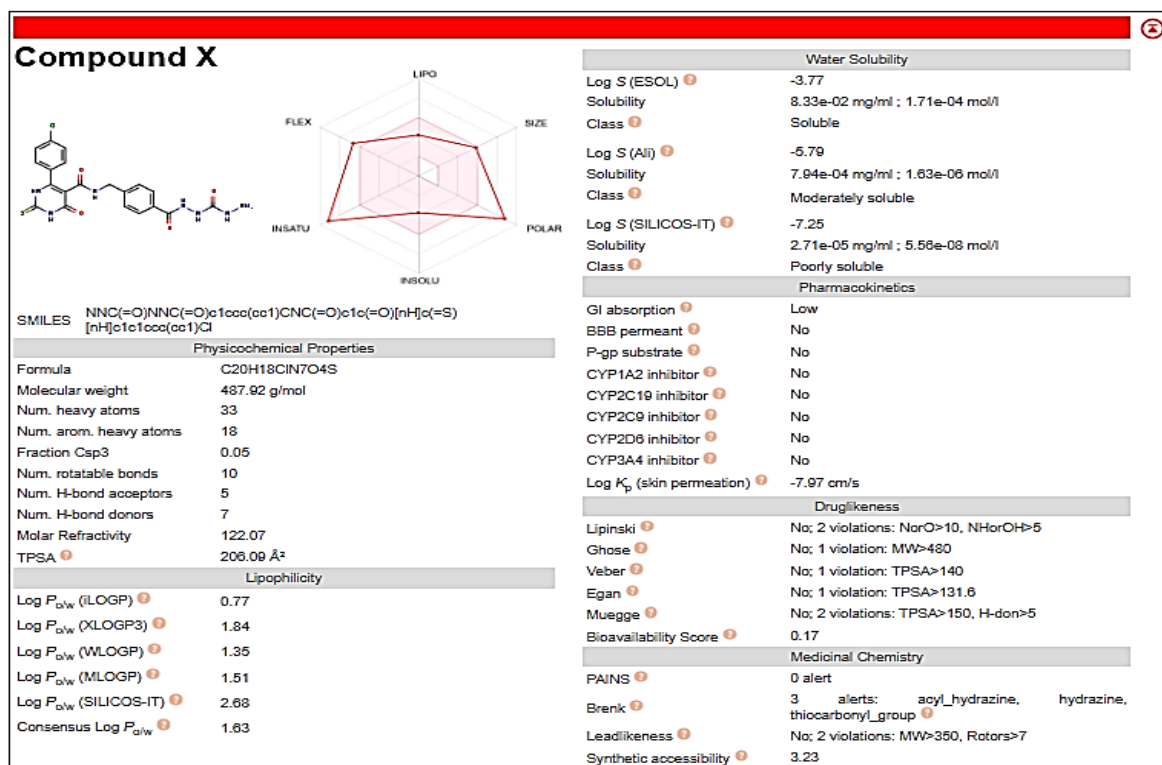


Figure 10: SwissADME prediction for the PK and drug-likeness characteristics of compound X

Synthetic route

A proposed synthetic route for the preparation of the investigated compounds is illustrated in Figure 13.

DISCUSSION

The investigated compounds were predicted to possess good aqueous solubility but low gastrointestinal absorption, a profile that may be advantageous for colon-targeted oral therapy, particularly in the management of colon cancer, by limiting systemic exposure. In addition, their

predicted inability to cross the blood–brain barrier suggests a reduced risk of central nervous system side effects, including dizziness and cognitive impairment. Lack of predicted CYP inhibition meant that they may not have an effect on the metabolism of other medications or diet, resulting in low incidence of drug–drug and diet interactions. The predicted lack of interaction with P-gp as a substrate may be advantageous in overcoming cancer cell resistance, given the critical role of this transporter in mediating multidrug resistance through enhanced drug efflux [9].

Table 1: Docking scores and amino acid residues involved in the ligand-HDAC8 interaction of compounds (I–X) and reference ligand (SAHA)

Compound no.	Docking scores (Kcal/mol)	Amino acid residues involved in the ligand-receptor interaction
I	-7.78	Gly151, Phe152, Asp178, His180, Gly206, Phe208, Tyr306, Zn378
II	-8.1	His142, His143, Gly151, Asp178, His180, Gly206, Phe208, Zn378,
III	-7.72	Phe152, Phe206, Gly303, Tyr306, Zn378
IV	-8.38	Gly151, His180, Gly206, Phe208, Tyr306, Zn378
V	-7.42	Gly151, Phe206, Tyr306, Zn378
VI	-7.24	Gly151, Phe152, Asp178, His180, Tyr306, Zn378
VII	-7.28	Gly151, Asp178, Phe207, Phe208, Tyr306, Zn378
IIIX	-7.37	Gly151, Phe152, Asp178, Phe207, Tyr306, Zn378
IX	-7.82	Gly151, Phe152, Gly303, Tyr306, Zn378
X	-8.51	Tyr100, Gly151, Asp178, Tyr306, Zn378
SAHA (reference ligand)	-5.54	Asp101, His142, Phe152, Tyr306, Zn378



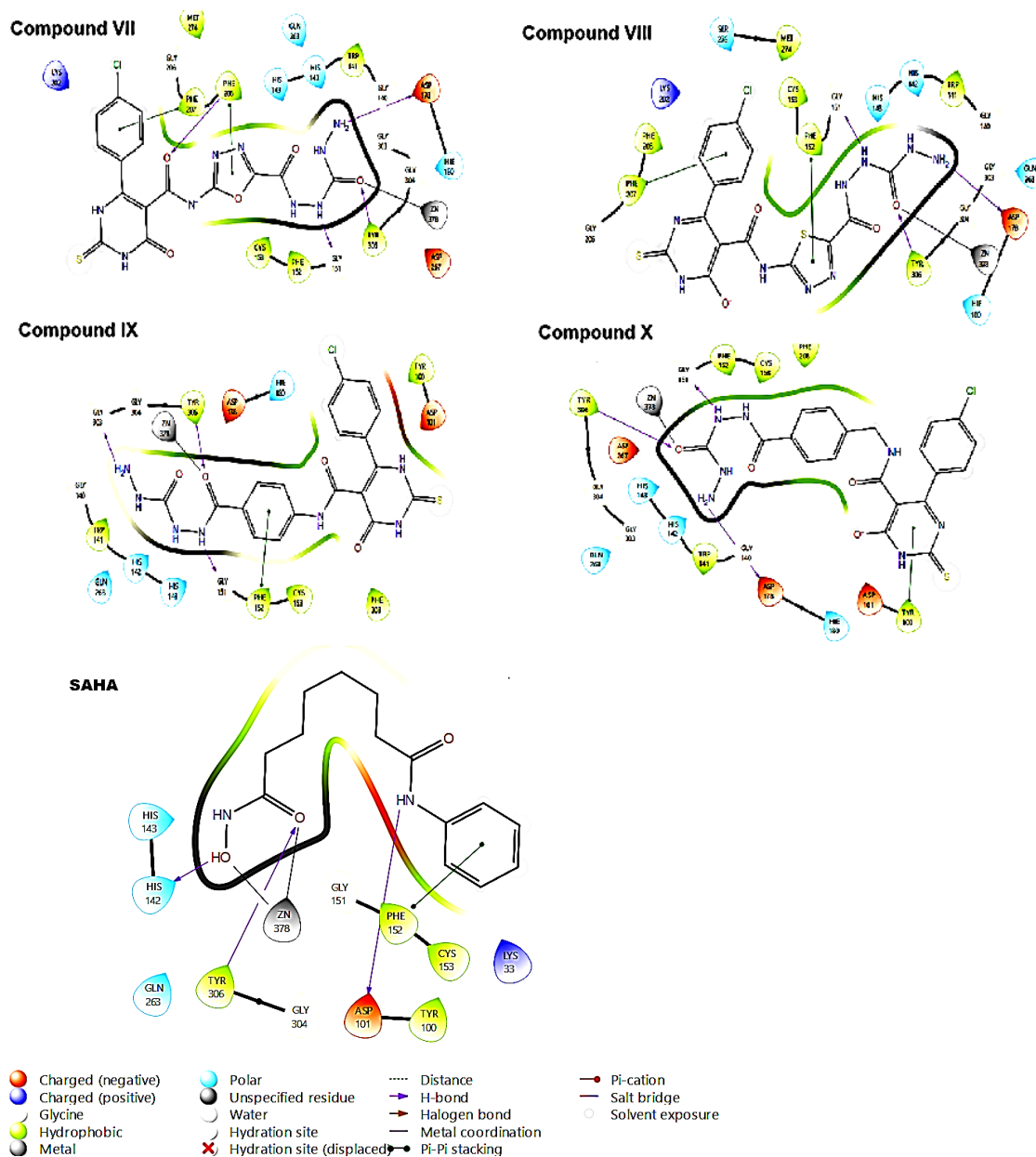


Figure 12: 2D visualization of compounds (VII-X) and SAHA-HDAC8 interaction (PDB ID: 1T69)

Regarding drug-likeness, compounds III, IV, VI, VII, and IX have acceptable properties according to Ghose parameters. Also, compounds (I-X) have acceptable medicinal chemistry characteristics according to PAINS parameters. The results further showed that all designed compounds (I-X) demonstrated comparable interactions with amino acid residues in the active site of HDAC8 enzyme with the reference ligand (SAHA). The compounds (I-X) also showed better predicted binding energies than SAHA (-5.54 kcal/mol), and demonstrated stable hydrogen bonding and hydrophobic interactions involving key residues within the HDAC8 catalytic pocket. Furthermore, compounds I-X have binding interactions with additional residues,

which may stabilize the ligand-receptor fit and produce high binding affinity to the active site of the enzyme [5,8]. Also, compounds with both the aromatic and heteroaromatic linkers showed high predicted binding affinity to the catalytic site of HDAC8. These findings provided promising preliminary evidence supporting further development of the compounds (I – X). Future studies should focus on synthesis and subsequent *in vitro* and *in vivo* pharmacological evaluation, particularly anticancer efficacy against colon cancer cell lines such as HCT116 and HT-29. This is especially relevant given the predicted physicochemical and pharmacokinetic properties suggesting the potential for colon-targeted activity.

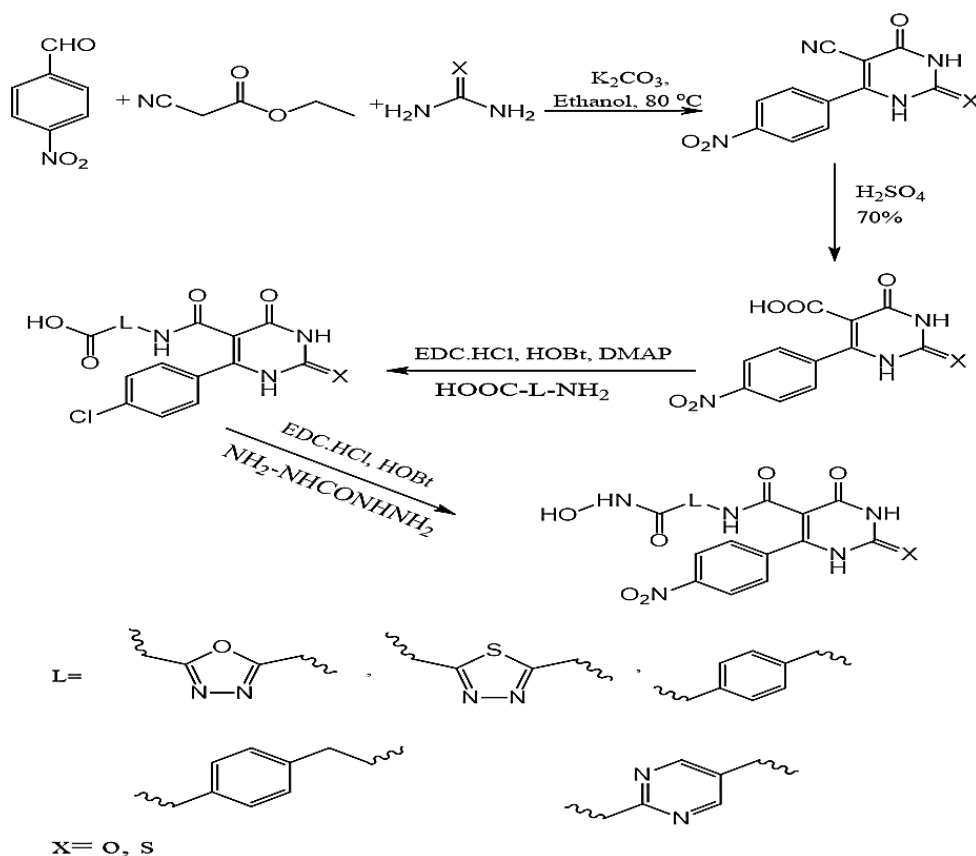


Figure 13: A suggested scheme for chemical synthesis of compounds I-X. EDC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide), ECF (ethyl chloroformate), HOBT (1-hydroxybenzotriazole), DMAP (4-Dimethylaminopyridine), hr (hours), r.t (room temperature)

CONCLUSION

The new series of 1,2,3,4-tetrahydropyrimines-carbohydrazide conjugated by different aromatic and heteroaromatic linkers showed promising pharmacokinetics, drug-likeness characteristics, and better binding affinity with HDAC8 than the reference ligand (SAHA).

DECLARATIONS

Acknowledgement

The authors would like to appreciate Albayan University for supporting this work.

Conflict of interest

None.

Data Availability

De-identified data supporting the findings of this study are available from the corresponding author upon reasonable request.

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