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Computational prioritization of small molecule inhibitors targeting the E6AP LxxLL motif

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Abstract:

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Cervical cancer is primarily driven by infection from high-risk types of human papillomavirus that alter the p53 tumor suppressor regulation. Therefore, it is of interest to report the ranked small molecules from the ZINC15 data for predicted ADMET properties and molecular docking performance with the E6AP LxxLL motif. We show that (3S)-1-((S)-(6-benzamido-1H-indol-3-yl)–carboxymethyl)piperidine-3-carboxylic acid is a prioritized drug candidate with an ADMET score of -1.409, an AutoDock Vina score of -9.4 kcal/mol, a FastDock score of -153.251 and an MD-based score of -491.669 for further consideration.

Keywords: Molecular docking, human papillomavirus (HPV), absorption, distribution, metabolism, excretion and toxicity (ADMET), AutoDock Vina, SCIGRESS, ADMET score, *in silico*, binding affinity, binding score

Background:

Predicted ADMET properties (absorption, distribution, metabolism, excretion and toxicity) and molecular docking scores were used as computational filters for compound prioritization **[1, 2].** These outputs were interpreted only as relative scores and not as experimental evidence of bioavailability, safety, binding or therapeutic activity. The objective was to identify a computationally prioritized candidate for future cellular testing rather than to establish a validated inhibitor. Persistent infection with high-risk human papillomavirus, particularly HPV-16, is a major cause of cervical carcinogenesis **[3, 4].** The viral E6 oncoprotein promotes malignant cell survival by interfering with the p53 tumor-suppressor pathway **[3–7].** E6 binds the cellular E3 ubiquitin ligase E6-associated protein (E6AP) through a short leucine-rich LxxLL sequence **[5–7].** Binding of this motif changes the conformation of E6 and creates a surface capable of recruiting p53 **[5, 6].** In the resulting E6-E6AP-p53 complex, E6AP promotes p53 ubiquitination and subsequent proteasomal degradation **[5–7].** Loss of p53 weakens DNA-damage-induced cell-cycle arrest, DNA repair and apoptosis, allowing genetically damaged cells to survive and continue proliferating**.** Continued E6 activity therefore contributes to mutation accumulation and progression toward cervical malignancy **[3, 4]**. Beyond p53 degradation, the interaction between E6 and E6AP can also affect keratinocyte differentiation and YAP1 activation, indicating broader effects on epithelial homeostasis **[8].** Formation of the E6–E6AP complex is therefore an essential early step in the oncogenic mechanism**.** The LxxLL motif of E6AP is not only a structural docking region but also a biologically important regulator of p53 recognition **[5, 6]**. Molecules that disrupt this interface may prevent complex assembly, preserve p53 signaling and restore cellular responses to DNA damage. Previous studies have supported the targetability of this interaction through virtual screening **[9],** reactive peptide inhibitors **[10],** stapled covalent peptides **[11]** and covalent small-molecule inhibition of HPV16 E6 **[12].** Soumia *et al.* screened an anticancer-focused compound library against the E6 protein **[9].** Therefore, it is of interest to prioritize a chemically distinct small-molecule candidate for further testing of E6-E6AP disruption and its effects on HPV-positive cervical cancer cells.

Methods:

The candidate selection workflow combined chemical structure and ADMET property filtering and score analysis in assessing bioavailability and three docking/scoring outputs to prioritize compounds (**Figure 1**) **[12-14]**. This workflow ranks compounds computationally and does not establish experimental bioavailability, safety, binding or therapeutic activity. The crystal structural protein-Oncoprotein E6 in complex with LxxLL peptide of ubiquitin ligase E6AP in HPV 16 (RCSB ID - 4GIZ) was downloaded through the RCSB Protein Data Bank. Relevant predicted ADMET properties related to oral bioavailability were utilized to calculate an internal compound ranking score. Subsequently, weightings were applied to each endpoint value to account for the differences in the relative contribution of each property to the final score. The ADMET score was used to internally rank compounds relative to one another for compound prioritization prior to molecular docking and was not calibrated against experimental PK and toxicity data.

Formula 1: Formula to calculate ADMET Score

ADMET Score = Σ (Property Values × W_i) where $W_i = W_1 \times W_2 \times W_3$.

Formula 2: Formula for Kendall's coefficient of concordance

$$W = \frac{12S}{m^2(n^3 - n) - mT}$$

Table 1: Molecular docking/scoring results Ranking, Filename, Best Binding affinity/Score (kcal/mol), Lower score indicates a more favorable software score within that method.

Software	AutoDock Vina		SCIGRESS FastDock		SCIGRESS MD	
Rank	**File number**	**Binding Affinity (kcal/mol)**	**File number**	**Binding Score**	**File number**	**Binding Score**
1	47	-9.5	32	-176.45	21	-515.64
2	44	-9.4	21	-159.19	43	-513.61
3	36	-9	47	-157.91	44	-491.67
4	39	-9	44	-153.25	2	-475.09
5	29	-8.8	45	-152.11	32	-473.79
6	5	-8.8	29	-149.82	13	-471.18
7	43	-8.7	27	-148.96	24	-469.62
8	32	-8.6	33	-148.94	6	-464.04
9	49	-8.6	26	-144.44	26	-454.2
10	21	-8.5	12	-144.06	14	-446.1

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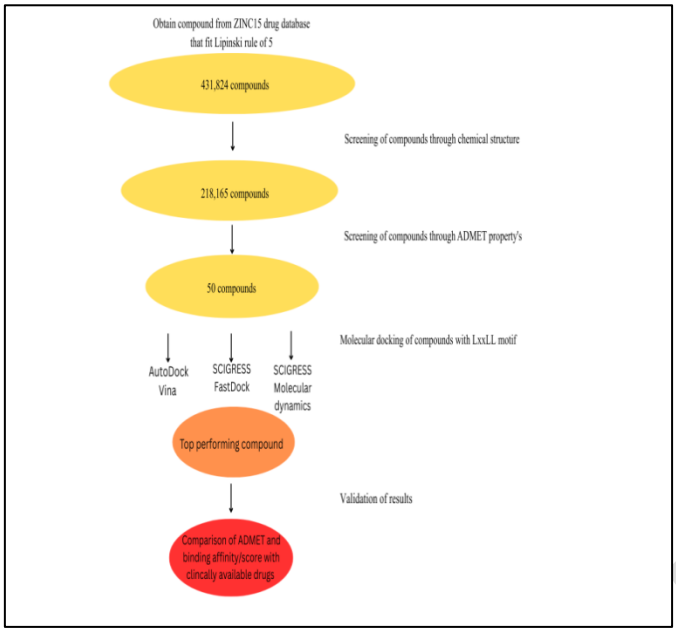

Figure 1: Methodology of flow chart for compound selection. Schematic built with Canva

Results and Discussion:

Among the 116 related endpoints, 18 related endpoints of the admetSAR 2.0 were available for use as a reference for our study **[13]**, thus necessitating an alternative strategy for assigning ADMET endpoint weightings. We utilized an AI-based approach which featured different AI tools (DeepSeek, Qwen, ChatGPT), data from the reference paper and public training data available on the admetSAR 3.0 website to generate all endpoint weightings **[1, 13]**. The intended role of the AI tools in this manuscript is solely for endpoint-weighting assistance for exploratory compound ranking, not as validated ADMET prediction models. The 116 endpoint weightings that were used to calculate the final ADMET score were subjected to cross-model agreement analysis using Kendall's coefficient of concordance (W) (Formula 2) to determine whether the AI-assisted weighting sets were internally consistent with one. After ADMET-score based ranking, molecular docking was used to analyze relative binding score performance at the E6AP LxxLL motif. Three scoring outputs were used in this study: AutoDock Scoring (AutoDock Vina), Fastdocking and MD-based scoring (SCIGRESS). A lower binding affinity/score indicates a stronger relative binding of the compound to the LxxLL motif. For AutoDock Vina, E6AP was isolated from the E6/E6AP complex where a grid box was centered on the LxxLL motif for targeted molecular docking. The binding affinity values were obtained for each compound from AutoDock Vina and used for relative ranking. A similar process was then applied in SCIGRESS FastDock and SCIGRESS MD-based scoring to compare compounds under consistent site conditions. The compounds were then ranked by their average rank across the three different scoring outputs. The agreement among docking outputs was interpreted conservatively and compounds with consistent favorable ranks across methods were prioritized. Ranking through ADMET scores identified ((S)-((1, 5-dimethyl-3-oxo-2-phenylpyrazol-4-yl) amino)-phenylmethyl) phosphonic acid as highest-ranked compound by internal ADMET score, which had an ADMET score of 0.311. To quantify the degree of agreement between the 3 different sets of weightings generated by the 3 AI models (ChatGPT, DeepSeek and Qwen), Kendall's Coefficient of Concordance (W) was employed. Kendall's coefficient of concordance (W) ranges from 0 to 1, with higher values indicating greater agreement **[16]**. From our calculated weightings obtained from each AI model, we obtained a Kendall's Coefficient of Concordance of 0.8, showing moderate to high levels of agreement in the relative importance of each of the 116 ADMET endpoint weightings. This agreement supports internal consistency of the weighting procedure, but it does not validate the biological accuracy of the weights. Binding scores/affinities were interpreted only as relative computational outputs, not as experimental binding affinities. For each docking method, the binding score/affinity value associated with the lowest RMSD/conformer number was used for ranking. The three docking/scoring outputs were then combined by average rank to identify compounds with highest consistent performance across methods. Results show that compound 44, (3S)-1-((S)-(6-benzamido-1H-indol-3-yl)-carboxymethyl) piperidine-3-carboxylic acid, ranked favorably across AutoDock Vina, SCIGRESS FastDock and MD-Based scoring. Therefore, this candidate was selected as the most prioritized drug candidate because it remained near the top ranks across all three outputs. All docking values in (**Table 1)** are predicted software outputs rather than experimentally measured binding affinities**.** Differences among predicted binding scores/affinities were expected because the scoring methods use different algorithms. The scoring function in AutoDock Vina utilizes a global optimization algorithm called Iterated Local Search (ILS) for its docking **[2]**. On the other hand, SCIGRESS Fastdock uses a genetic algorithm and SCIGRESS MD uses the LAMMPS interface **[14]**. Multiple tools were used to reduce dependence on one scoring function and identify compounds with consistent relative performance across scoring methods. To provide computational context for the selected compound, approved cervical-cancer treatment compounds, including Docetaxel, Paclitaxel, Vinorelbine, Topotecan and Fluorouracil were used as broad reference compounds to compare against our top performing compound. For molecular docking, the same binding site and grid-box used for the prioritized candidate were applied to each reference compound. This comparison was intended to place the candidate scores alongside known cervical-cancer treatment compounds under identical computational settings, not to establish mechanistic equivalence or therapeutic superiority. Limitations in this study do arise in terms of the accuracy of the *in silico* models *in vivo* and *in vitro*. First, the study is entirely computational and does not include *in vitro* binding assays, MM/PBSA, MM/GBSA or full trajectory-level molecular-dynamics analysis. Therefore, the predicted ADMET outputs, docking scores and rankings cannot establish experimental binding, PK, toxicity or therapeutic efficacy.

Secondly, the AI-assisted ADMET endpoint weighting was used only as an exploratory ranking aid and was not trained, externally validated, or calibrated against experimental PK or toxicity data. Although agreement among ChatGPT, DeepSeek and Qwen weightings suggests internal consistency, it should not be interpreted as evidence that the selected weights are pharmacologically accurate. Third, the anti-cancer reference drugs utilized for drug likeness validation only provide broad computational context. These drugs act through mechanisms different from the proposed E6AP LxxLL motif pathway, so binding scores/affinities should not be interpreted as mechanistic validation or therapeutic superiority. Recent experimental evidence indicates that E6AP supports the proliferation of HPV-positive cancer cells by preventing senescence **[15].** However, E6AP also performs important physiological functions, and E6AP dysfunction is associated with Angelman syndrome **[7].** Therefore, compounds targeting the E6AP LxxLL region require careful evaluation of target selectivity and possible effects on normal E6AP activity. Further *in vitro* and *in vivo* studies are needed to determine whether the prioritized compound can selectively disrupt the viral E6/E6AP interaction while minimizing effects on physiological E6AP function

Conclusion:
ADMET property analysis and molecular docking were used to prioritize small molecules targeting the HPV-16 E6/E6AP pathway. The top candidate, (3S)-1-((S)-(6-benzamido-1H-indol-3-yl)-carboxymethyl) piperidine-3-carboxylic acid, showed favorable predicted ADMET properties and consistent docking performance across three software outputs to further consideration.

Abbreviations:
ADMET: Absorption, Distribution, Metabolism, Excretion and Toxicity
MD: Molecular Dynamics
HPV: Human Papillomavirus
PK: Pharmacokinetic
Declarations:

Ethics approval and consent to participate:
This study did not involve human participants, human data, human tissue, animals or animal tissue.

Availability of data and materials:
The datasets generated and analysed during the current study are available from the corresponding author on request. The supporting files include the ADMET endpoint-weighting table, compound ranking table, full binding-score table and reference-compound comparison table.

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