Original article

Drug design of new anti-EBOV inhibitors: QSAR, homology modeling, molecular docking and molecular dynamics studies

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ABSTRACT

Ebola virus disease is a deadly pathogenic disease with a fatality rate of 25–90 % as recorded in previous outbreaks. The Ebola Virus glycoprotein (EBOV-GP) plays a crucial role in the entry of viruses into human cells, making it an interesting target for therapeutic discovery. Therefore, inhibiting this protein can directly limit the virus replication and disease progression at an early stage of infection. The present study focuses on the design of novel potent EBOV-GP inhibitors using multiple computational techniques. In this context, two QSAR models were built from a set of 86 amodiaquine derivatives as anti-EBOV-GP using Monte Carlo and genetic algorithm multiple linear regression methods. Both models confirmed their predictive performance with satisfactory statistical parameters of the validation ($R^2 = 0.9129$; $Q^2 = 0.8848$ for the CORAL model and $R^2 = 0.8848$; $Q^2 = 0.8148$ for the GA-MLR model). From the outputs of the CORAL model, the structural fragments responsible for increasing and decreasing the inhibition activity were extracted and interpreted. This molecular information was used to design 26 new potentially safe and active candidate drugs. Molecular docking and dynamics simulations have affirmed the efficacy of the designed compounds. Specifically, compounds **D2** ($pIC_{50\_coral} = 7.12$; $pIC_{50\_GA-MLR} = 7.07$), **D3** ($pIC_{50\_coral} = 7.83$; $pIC_{50\_GA-MLR} = 7.10$), and **D5** ($pIC_{50\_coral} = 7.26$; $pIC_{50\_GA-MLR} = 7.55$) displayed notable predicted inhibitory activity, according to both models. These compounds also exhibited conformational and structural stability, as well as a favorable binding profile. Furthermore, these potential drug candidates were found to be non-toxicity and have acceptable pharmacological properties.

1. Introduction

Ebola virus disease (EVD) is a severe and rapidly progressing hemorrhagic fever caused by the Ebola virus (EBOV) (hong Ma et al., 2023). Since the virus was first identified in the Democratic Republic of Congo in 1976, there have been several outbreaks in which it has been responsible for intermittent but highly destructive epidemics, mainly affecting regions in Central and West Africa (Dash et al., 2017; Garcia-Rubia et al., 2023). The most devastating of these outbreaks occurred in West Africa between 2013 and 2016 with over 28,000 infections and more than 11,000 deaths (hong Ma et al., 2023). The repeated and severe outbreaks have emphasized the significant risk that EBOV poses to human health. In the face of this disease, current treatment strategies focus on complementary treatment, as there is no specific approved antiviral therapy for widespread use. The high mortality rate associated with EBOV emphasizes the urgent need to develop drugs that can inhibit different stages of the EBOV replication cycle.

EBOV belongs to the Filoviridae family and is characterized by its filamentous structure and an 18 kb single-stranded RNA genome encoding seven structural proteins, including viral structural proteins

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(VP35, VP40, VP30 and VP24), nucleoprotein (NP), RNA-dependent RNA polymerase (L) and glycoprotein (GP) (Peng et al., 2022; Mali and Chaudhari, 2019; Volchkova et al., 1998; Volchkov and Klenk, 2018; Lee and Saphire, 2009). The GP gene of EBOV transcribes into three different GP forms. Full-length GP chains express the attachment protein (GP1) and the entry/fusion protein (GP2) from messenger RNAs (mRNAs) containing an additional adenosine that is not present in the template (Lee et al., 2008). The soluble GP (sGP), on the other hand, is synthesized from the primary RNA transcript. The small soluble GP (ssGP) is produced by the insertion of two additional adenosine residues (Volchkova et al., 1998). These GPs, which are located on the surface of the virion, play a crucial role in promoting membrane fusion and penetration into host cells (Lee and Saphire, 2009). Therefore, inhibition of this protein can prevent the virus from entering and infecting host cells, which is an important strategy for antiviral therapies and vaccine development.

In silico investigations represent a very promising methodology in drug discovery to develop new potent and safe anti-EBOV drugs in terms of time and cost. This shift towards these methods is evident in the growing importance of Computer-Aided Drug Design (CADD) in the field. CADD encompasses various computational approaches, including structure-based drug design (SBDD) and ligand-based drug design (LBDD) (Mallipeddi et al., 2014). Additionally, CADD involves the estimation of pharmacokinetics, therapeutic, and toxicological properties in drug discovery journey with computational approaches before the experimentations (Lipinski et al., 2012). Despite the advantages of CADD in modern drug design, there are still limitations, as many identified candidate molecules do not show the desired activity in biological systems. In fact, only 40 % of drug candidates identified via CADD make it through clinical trials and receive approval for clinical use. To overcome these limitations, using the most accurate tools available and combining multiple CADD techniques can increase the reliability of the predictions (Baig et al., 2018).

In the quest for new treatments for EVD, this study focused on the development of quantitative structure–activity relationships (QSAR) to design new inhibitors of EBOV-GP. The initial QSAR model employed the Monte Carlo optimization using simplified molecular input line representations (SMILES) to explore the molecular fragments associated with enhancing/reducing of the biological activity. Using this molecular information, we designed new molecules with potential inhibition against EBOV-GP. Subsequently, a Genetic Algorithm Multiple Linear Regression (GA-MLR) based QSAR model was applied to the newly designed molecules to confirm their potential inhibition activity. To thoroughly evaluate these compounds, we conducted molecular docking and molecular dynamics simulations (MD) together with Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) assessments to ensure a comprehensive evaluation of their interaction with the EBOV-GP protein, their stability, and their pharmacokinetic profiles.

2. Materials and methods

2.1. Data collection and preparation

A dataset of 86 amodiaquine derivatives with EBOV-GP inhibitory activity were collected from the published work by Sakurai et al. (Sakurai et al., 2018). After drawing the chemical structures of these derivatives using ChemDraw software (PerkinElmerInformatics, Inc, ChemDraw, 2021), their geometries were optimized in the gas phase using the AM1 semi-empirical method. The optimization procedure was performed using the Gaussian 09 software package (Gaussian 09, n.d.). The optimized molecular structures were converted into isomeric SMILES notations for the modeling process of the CORAL model using the Openbabel program (O'Boyle et al., 2011). For the GA-MLR model, the molecular descriptors of the optimized 3D structures were calculated using AlvaDesc (Mauri and Bertola, 2022). To avoid multicollinearity in the QSAR model, we reduced the number of generated variables by

removing descriptors with a correlation coefficient greater than 0.95 and retaining only one of the pairs. As a result, a total of 832 descriptors were selected from the original set of 4149 descriptors. The experimental data value of each molecule (half-maximal inhibitory concentration: IC_{50}) was converted into negative logarithmic scale (pIC_{50}). These converted data were then utilized as variables for building QSAR models. The molecular structures and corresponding IC_{50} data are listed in Table S1 and their SMILES notation and converted pIC_{50} can be found in Table S2.

2.2. CORAL QSAR model

CORAL QSAR modeling software (Toropova and Toropov, 2014) utilizes SMILES attributes for endpoint prediction, based on optimal descriptors, namely correlation weights (CWs), along with the balance-of-correlation approach. Four splits were randomly made from the entire dataset with each split in turn divided into four partitions: Training (Tr: 35 %), Invisible Training (Inv-Tr: 35 %), Calibration (Calib: 15 %), and Validation (Valid: 15 %). The specific functions of each set in the development of QSAR models are described in detail in the literature (Toropova and Toropov, 2014; Oubahmane et al., 2023). Table 1 illustrates the distribution and percentage of the identity of the compounds in the four splits.

The development of QSAR models based on SMILES notation uses the equation of the optimal descriptor of correlation weights (Eq.1).

$$^{SMILES}DCW(T, N_{epoch}) = \sum CW(S_K) + \sum CW(SS_K)$$
$$+ \sum CW(SSS_K) + CW(HARD) + CW(C_{max}) + CW(N_{max}) + CW(O_{max})$$

(1)

$^{SMILES}DCW(T, N_{epoch})$ integrates the attributes derived from SMILES with a correlation weight. The parameters T and N_{epoch} represent the threshold and the total number of epochs determined by the Monte Carlo optimization technique during the model construction (Oubahmane et al., 2023). The threshold coefficient is utilized to categorize molecular attributes derived from SMILES into two classes: (i) the active class, where CW is incorporated in model development, and (ii) the rare class, where CW is not employed in model development. The optimal statistical quality for the calibration set is determined by N_{epoch}. A detailed description of the SMILES attributes can be found in Table S3.

Table 1
Percentage distribution of compounds in the four splits.

Split	Set	Split 1 (%)	Split 2 (%)	Split 3 (%)	Split 4 (%)
Split 1	Total	100	29.1	25.6	32.6
	Tr	100	36.7	26.7	40.0
	Inv-Tr	100	33.3	33.3	36.7
	Calib	100	15.4	15.4	30.8
	Valid	100	15.4	15.4	7.7
Split 2	Total		100	33.7	24.4
	Tr		100	40.0	33.3
	Inv-Tr		100	33.3	23.3
	Calib		100	30.8	23.1
	Valid		100	23.1	7.7
Split 3	Total			100	33.7
	Tr			100	33.3
	Inv-Tr			100	43.3
	Calib			100	23.1
	Valid			100	23.1
Split 4	Total				100
	Tr				100
	Inv-Tr				100
	Calib				100
	Valid				100

Following the calculation of all CWs, the linear regression technique was then employed to develop QSAR models, as indicated in equation (Eq.2).

$$pIC_{50} = C_0 + C_1 \, ^{SMILES}DCW(T, N_{epoch}) \tag{2}$$

C_0 and C_1 are the intercept and slope of the regression equation respectively.

In order to optimize the QSAR modeling, based on the Monte Carlo method, two different target functions, namely TF_1 (without the IIC) and TF_2 (with value $W_{IIC} = 0.3$) were used to generate the models. TF_1 was calculated using the equilibrium of the correlation method (according to equation (Eq.3)), and the Index of Ideality of Correlation (IIC) (Liman et al., 2022; Toropov et al., 2019; Toropova and Toropov, 2017) was combined with TF_1 to formulate the modified target function TF_2 (Eq.4).

$$\mathbf{TF_1} = \mathbf{R_{Tr}} + \mathbf{R_{Inv.Tr}} - |\mathbf{R_{Tr}} - \mathbf{R_{Inv.Tr}}| \times 0.1 \tag{3}$$

$$\mathbf{TF_2} = \mathbf{TF_1} + \mathbf{IIC} \times \mathbf{W_{IIC}} \tag{4}$$

R_{Tr}, R_{Inv-Tr}, and R_{set} represent the correlation coefficients for the observed pIC_{50} versus the predicted pIC_{50} within the training set, invisible training set, and a specified set, respectively.

The IIC, given in equation (Eq.5), was proposed as a measure for evaluating the predictive ability of the developed QSAR models. In particular, it improves the precision of the model, which is determined by the determination coefficient (R^2) and the mean absolute error (MAE). The W_{IIC} coefficient, which represents the IIC weight, can change the extent of the influence of the IIC on the Monte Carlo optimization process. The optimal value of W_{IIC} is influenced by two aspects: the diversity of the molecules and the characteristics of the endpoint.

$$\mathbf{IIC} = \mathbf{R_{set}} \times \frac{\min(^-\mathbf{MAEset}, \, ^+\mathbf{MAEset})}{\max(^-\mathbf{MAEset}, \, ^+\mathbf{MAEset})} \tag{5}$$

$$^-\mathbf{MAEset} = \frac{1}{N}\sum_{k=1}^{N}|\Delta_k| \quad (\Delta_k < 0, \, \overline{N} \text{ is the the number of } \Delta_k \tag{6}$$

$$^+\mathbf{MAEset} = \frac{1}{^+\mathbf{N}}\sum_{k=1}^{N_+}|\Delta_k| \quad \Delta_k \geq 0, \, ^+\mathbf{N} \text{ is the number of } \Delta_k \geq 0 \tag{7}$$

Where;

$$\Delta_k = pIC_{50}(\text{observed}) - pIC_{50}(\text{predicted}) \tag{8}$$

Δ_k measures the quality prediction of the kth molecule.

To construct robust QSAR models, the optimal threshold (T^*) and the number of epochs (N^*) had to be determined by evaluating the most favorable statistical metrics for the calibration set. In the search for the ideal T^* and N^*, ranges from 1 to 10 were used for the threshold and 1 to 30 for the number of epochs in the optimization process, using three optimization probes. For this study, the W_{IIC} was set to 0 for TF_1 and adjusted to 0.3 for TF_2.

2.3. GA-MLR QSAR model

The selection of the most relevant descriptors, from the entire computed ones, is a crucial step in QSAR modeling. This selection was achieved by stepwise MLR technique via XLSTAT (Addinsoft, 2020). A total of 832 molecular descriptors were filtered out to get a final selection of five relevant molecular descriptors. Using these descriptors, the MLR method with the ordinary least squares (OLS) algorithm, implemented in the QSARINS software (Addinsoft, 2020; Gramatica et al., 2013) was applied to establish a linear correlation between the pIC_{50} endpoints of the molecules and their corresponding molecular descriptors. The dataset was divided into a training set with 60 molecules and a test set consisting of 26 molecules, with a distribution ratio of 70 % and 30 % accordingly. The GA-MLR models were developed using the

following parameters: all subsets up to a maximum of 5, a maximum generation of 10 000, and a mutation probability of 0.05. The remaining settings were configured with their default values.

2.4. QSAR model validation

The validation process is a crucial stage in QSAR establishment to assess the accuracy of the model and to make reliable predictions about the activity of new molecules. This process is considered the most important aspect in testing the robustness, predictability, and reliability of a QSAR model. Four steps are typically used to validate the generated model, including (a) internal validation or cross-validation using the training set, (b) Y-randomization, (c) independent validation using the test set, and (d) applicability domain (AD) evaluation. The validation procedures and criteria for the CORAL-based QSAR and GA-MLR QSAR models are well discussed in our earlier works (Gramatica et al., 2014; Hdoufane et al., 2019, 2022; Oubahmane et al., 2023; Toropova and Toropov, 2014).

2.5. EBOV-GP structure preparation

The experimental 3D structure of EBOV-GP (PDB ID: 5JQ7) has some missing residues that are essential for its functional mechanism in three regions (LYS191-SER210, THR284-GLY286 and LYS294-ARG302). To fill these missing residues and facilitate subsequent molecular docking and MD simulations, we used the SWISS-MODEL web server for homology modeling to reconstruct the full structure of EBOV-GP (Schwede et al., 2003). The server applies a rigorous protocol that includes the use of BLAST and HHblits to find structural templates from its extensive library, the SWISS-MODEL Template Library (SMTL), which is sourced from the PDB. This ensures that high quality templates are provided, as determined by the Global Model Quality Estimate (GMQE) and the Quaternary Structure Quality Estimate (QSQE). After selecting the most suitable template, which in this case was the same PDB ID due to its high similarity to the target structure, the incomplete EBOV-GP structure was aligned with the template. Subsequently, the missing loop regions were carefully filled in using OpenStructure and the ProMod3 modeling algorithm (Studer et al., 2021). The accuracy and reliability of the final EBOV-GP model was checked using the Qualitative Model Energy ANalysis (QMEAN) assessment function to ensure that the final model was of high quality and suitable for the intended advanced computational analyses (Benkert et al., 2011).

2.6. Molecular docking

Molecular docking analysis was performed to investigate the ligand–protein interactions of the designed compounds and the reference lead compound **(78)** within the binding site of the modeled EBOV-GP protein. Prior to the docking process, the co-crystallized ligand (Toremifene: TOR) was used to generate the grid-box coordinates of the binding site of the EBOV-GP protein. The grid box coordinates are as follows: xyz coordinates of −45, 16.75, −9, and grid box dimensions of 24 Å^3. The protein was then prepared by removing water molecules and the co-crystallized ligand and adding polar hydrogens and Gasteiger charges using AutodockTools (Morris et al., 2009). The protein and compounds were saved in PDBQT format using the same software. Molecular docking analysis were performed using AutoDock Vina software (Trott and Olson, 2010) with exhaustiveness of 20. The docking results were analyzed by the Discovery Studio visualizer and Pymol softwares (BIOVIA Discovery Studio Visualizer, n.d.; Yuan et al., 2017).

2.7. Molecular dynamics simulations

The apo form of the EBOV-GP protein and the designed compounds complexed with the EBOV-GP protein were subjected to all-atom molecular dynamic simulations using GROMACS 2021.3 software (Van Der

Spoel et al., 2005). Prior to the MD simulations, the CHARMM-GUI web server (Jo et al., 2008) was utilized to generate initial input parameters, implementing the CHARMM36 force field (Huang et al., 2017). Each complex was solvated in TIP3P water within a rectangular grid box (Jorgensen et al., 1983) and counterions (Na^+, Cl^-) were added to maintain a 0.15M salt concentration through Monte Carlo ion displacement. The size and shape of the systems were considered when the periodic boundary conditions (PBC) were imposed. Non-bound interactions were addressed using Lennard-Jones and Coulomb potentials with a cut-off distance of 12 Å, and the Verlet cut-off strategy was used to buffer the neighbor search list. The Particle-Mesh Ewald (PME) method (Darden et al., 1993) was used to address the long-range electrostatic interactions. The novel Linear Constraint Solver (LINCS) algorithm (Hess et al., 1997) constrained all covalent bonds, including hydrogen atoms. Energy minimization of each system was carried out using the steepest descent algorithm with a maximum of 50,000 steps and a maximum force of 10.0 KJ/mol. The systems were equilibrated using a two-step process: first, a canonical (NVT) ensemble was employed to equilibrate the temperature at 303 K for 500 ps, followed by an isothermal-isobaric (NPT) ensemble for another 500 ps to equilibrate the pressure, both set at 303 K and 1.01325 bar respectively. The Nose-Hoover thermostat (Hess et al., 1997; Nosé, 1984) and Parrinello-Rahman barostat (Parrinello and Rahman, 1981) were used to regulate the temperature and pressure respectively.

The production run was conducted for 100 ns to analyze the structural stability of the designed molecules within the binding site of EBOV-GP protein. The structural stability of the designed molecules within the EBOV-GP was assessed using the root mean square deviation (RMSD), the radius of gyration (Rg), the root mean square flexibility (RMSF), and the solvent accessibility area (SASA) based on the dynamics trajectory results. The data obtained were visualized using Xmgrace software (GRACE - GRaphing, Advanced Computation and Exploration of data, (n.d.). https://plasma-gate.weizmann.ac.il/Grace/ (accessed March 4, 2024).

2.8. Drug likeness and ADMET prediction

The evaluation of ADMET has a great importance in the initial phases of pharmaceutical exploration. It is expected that a therapeutic drug of better quality would demonstrate exceptional activity at the target receptor, as well as better ADMET profile at therapeutic dosage. Therefore, it is fundamental to assess the pharmacokinetic properties of hit compounds to minimize the risk of subsequent medication failure. The qualities related to drug-likeness are important to understand the distribution of a molecule in an organism, which in turn affects its pharmacological effectiveness. ADMET predictions for the designed compounds were performed via the AdmetLab2, ProTox-II, and Osiris Property Explorer servers (Xiong et al., 2021; Banerjee et al., 2018; Property explorer, 2024).

Table 2
Statistical parameters of the built QSAR models and their corresponding equations.

Split	TF	Set	n	R^2	CCC	IIC	Q^2	Q^2_{F1}	Q^2_{F2}	Q^2_{F3}	S	MAE	F	Avg Rm^2	ΔRm^2	Equation
1	TF$_1$	Tr	30	0.9472	0.9729	0.7442	0.9395				0.106	0.085	502			pIC$_{50}$ = 3.853
		Inv-Tr	30	0.9289	0.7204	0.5278	0.9211				0.328	0.261	366			($\pm$0.015) + 0.129
		Calib	13	0.8191	0.8338	**0.7272**	**0.7058**	0.7926	0.7414	0.7161	0.275	0.233	50	**0.5578**	**0.2363**	($\pm$0.001) × DCW
		Valid	13	**0.7919**	**0.8259**	**0.3625**	**0.7251**					0.250		**0.5721**	**0.2334**	(3,30)
	TF$_2$	Tr	30	0.8196	0.9009	0.6923	0.7922				0.197	0.148	127			pIC$_{50}$ = 3.498
		Inv-Tr	30	0.8209	0.8609	0.4263	0.7952				0.246	0.188	128			($\pm$0.040) +
		Calib	13	0.8623	0.8863	**0.9285**	**0.7672**	0.8538	0.8176	0.7998	0.231	0.181	69	**0.6406**	**0.1787**	0.110 ($\pm$0.002) ×
		Val	13	**0.8807**	**0.9333**	**0.7306**	**0.8463**					0.158		**0.8260**	**0.0745**	DCW(3,30)
2	TF$_1$	Tr	30	0.9684	0.9839	0.4920	0.9628				0.082	0.051	857			pIC$_{50}$ = 3.210
		Inv-Tr	30	0.9476	0.7806	0.4236	0.9433				0.298	0.237	506			($\pm$0.018) + 0.142
		Calib	13	0.6199	0.7704	**0.5066**	**0.4494**	0.6947	0.6193	0.5820	0.333	0.258	18	**0.4752**	**0.2594**	($\pm$0.001) × DCW
		Valid	13	**0.5718**	**0.7471**	**0.6509**	**0.2983**					0.311		**0.4290**	**0.1397**	(1,30)
	TF$_2$	Tr	30	0.8484	0.9180	0.6141	0.8243				0.180	0.139	157			pIC$_{50}$ = 4.152
		Inv-Tr	30	0.8352	0.8236	0.3810	0.8190				0.267	0.206	142			($\pm$0.027) + 0.079
		Calib	13	0.8731	0.8782	**0.9344**	**0.7877**	0.8524	0.8159	0.7978	0.232	0.188	76	**0.5765**	**0.2120**	($\pm$0.001) × DCW
		Valid	13	**0.8115**	**0.8836**	**0.8700**	**0.7540**					0.207		**0.6947**	**0.1769**	(3,30)
3	TF$_1$	Tr	30	0.9223	0.9596	0.7344	0.9099				0.153	0.102	332			pIC$_{50}$ = 2.322
		Inv-Tr	30	0.9219	0.9432	0.4511	0.9130				0.167	0.127	330			($\pm$0.038) + 0.173
		Calib	13	0.5525	0.6907	**0.2647**	**0.3255**	0.1773	0.1755	0.3708	0.428	0.309	14	**0.3950**	**0.2702**	($\pm$0.002) × DCW
		Valid	13	**0.7982**	**0.8892**	**0.7386**	**0.7127**					0.252		**0.7116**	**0.1171**	(4,30)
	TF$_2$	Tr	30	0.8618	0.9258	0.8123	0.8287				0.204	0.157	175			pIC$_{50}$ = 2.043
		Inv-Tr	30	0.7631	0.8716	0.7205	0.7376				0.261	0.203	90			($\pm$0.078) + 0.061
		Calib	13	0.8369	0.9116	**0.9148**	**0.7713**	0.8296	0.8293	0.8697	0.195	0.143	56	**0.8369**	**0.9116**	($\pm$0.001) × DCW
		Valid	13	**0.9129**	**0.9512**	**0.5608**	**0.8848**					0.147		**0.8288**	**0.0885**	(1,30)
4	TF$_1$	Tr	30	0.9103	0.9530	0.7296	0.9008				0.149	0.099	284			pIC$_{50}$ = 3.214
		Inv-Tr	30	0.9353	0.9664	0.8614	0.9267				0.154	0.113	405			($\pm$0.020) + 0.158
		Calib	13	0.3941	0.6212	**0.5782**	**0.1323**	0.1718	0.1364	0.3877	0.435	0.335	7	**0.2448**	**0.1002**	($\pm$0.001) × DCW
		Valid	13	**0.6518**	**0.7316**	**0.5470**	**0.3660**					0.405		**0.3837**	**0.3548**	(6,30)
	TF$_2$	Tr	30	0.7843	0.8791	0.3795	0.7608				0.231	0.163	102			pIC$_{50}$ = 2.543
		Inv-Tr	30	0.8346	0.8992	0.5306	0.8139				0.260	0.201	141			($\pm$0.044) + 0.089
		Calib	13	0.7857	0.8661	**0.8863**	**0.6641**	0.7449	0.7340	0.8114	0.241	0.176	40	**0.6958**	**0.0742**	($\pm$0.001) × DCW
		Valid	13	**0.7846**	**0.8787**	**0.3273**	**0.7097**					0.201		**0.6899**	**0.1885**	(1,30)

3. Results and discussion

3.1. CORAL-based QSAR model

A total of eight QSAR models were created by performing four random splits. The two different target functions, namely TF_1 and TF_2, were used to generate these models. The obtained statistical parameters from the analysis of these QSAR models suggest that the inclusion of $W_{IIC} = 0.3$ significantly increases the influence of IIC in the Monte Carlo optimization process. Table 2 presents the statistical parameters for all splits, indicating the robustness and validity of the models according to the criteria established by Tropsha et *al.* (Golbraikh and Tropsha, 2002) and Ojha et *al.* (Ojha et al., 2011). Fig. 1 displays the correlation between the experimental and predicted pIC_{50} values across the four splits. The QSAR model derived from split 3 was chosen as the optimal model based on its superior validation metrics ($R^2 = 0.9129$; $Q^2 = 0.8848$). The mathematical model equation for split 3 is given below (Eq.9):

$$pIC_{50} = 2.043(\pm 0.078) + 0.061(\pm 0.001)DCW(1,3) \quad (9)$$

Regarding the AD, all compounds are within the domain of the CORAL model built from split 3, with the exception of compound 2. The AD details for all four model splits are provided in Table S4.

3.2. GA-MLR QSAR model

The GA-MLR model was built based on five selected descriptors from a comprehensive set of descriptors, namely IC2, SpMin7_Bh(s), P_VSA_Charge_7, CATS2D_05_DD, and T(O..O). The description of each descriptor was given in Table S5. These descriptors were found to significantly explain the structure activity relationship (SAR) between the pIC_{50} activity and the studied compounds and were subsequently used to construct the QSAR model. The generated model using the GA-MLR approach (Eq.10) and its corresponding statistical parameters are shown below:

$$pIC_{50} = 2.0530 + 0.4612(IC2) + 1.3754(SpMin7\_Bh(s))$$
$$+ 0.0105(P\_VSA\_charge\_7) + 0.2552(CATS2D\_05\_DD) - 0.0132(T(O..O)) \quad (10)$$

$N_{Tr} = 60$, $R^2_{Tr} = 0.8490$, $Q^2_{LOO} = 0.8148$
$N_{ext} = 26$, $R^2_{ext} = 0.8661$, $MAE_{ext} = 0.2135$.
$Q^2_{F1} = 0.8681$, $Q^2_{F2} = 0.8599$, $Q^2_{F3} = 0.8840$, $CCC_{ext} = 0.9229$, $F = 77.6036$, $s = 0.3138$.

N_{Tr} and N_{ext} indicate the total number of samples used for the training and the test sets, respectively. CCCext is the external concordance correlation coefficient, while F refers to F-statistic. Additionally, the standard deviation is represented by "s" and the external validation criteria are expressed through Q^2_{F1}, Q^2_{F2} and Q^2_{F3} (Chirico and Gramatica, 2012; Hess et al., 1997; Nosé, 1984).

The evaluation of the indicated parameters in the established GA-MLR model satisfies the validation requirements outlined in the OECD guidelines. Moreover, the scatter plot shown in Fig. 2a displays a good correlation between the experimental and predicted pIC_{50} endpoints. To confirm the reliability of the built model, the AD was evaluated using the leverage method, and presented through the Williams plot in Fig. 2b. The graphic includes dashed lines to indicate the cutoff value of ± 3 s.d., and the warning line for the outliers (h*) was found to be 0.29. The findings from the Williams plot provide definitive evidence that the AD covers all compounds, except for compound **65**. This observation can be attributed to the low activity of compound **65**, as evidenced by its high value ($IC_{50} = 20$ μM), which is 69-fold higher than that of the lead compound ($IC_{50} = 0.29$ μM).
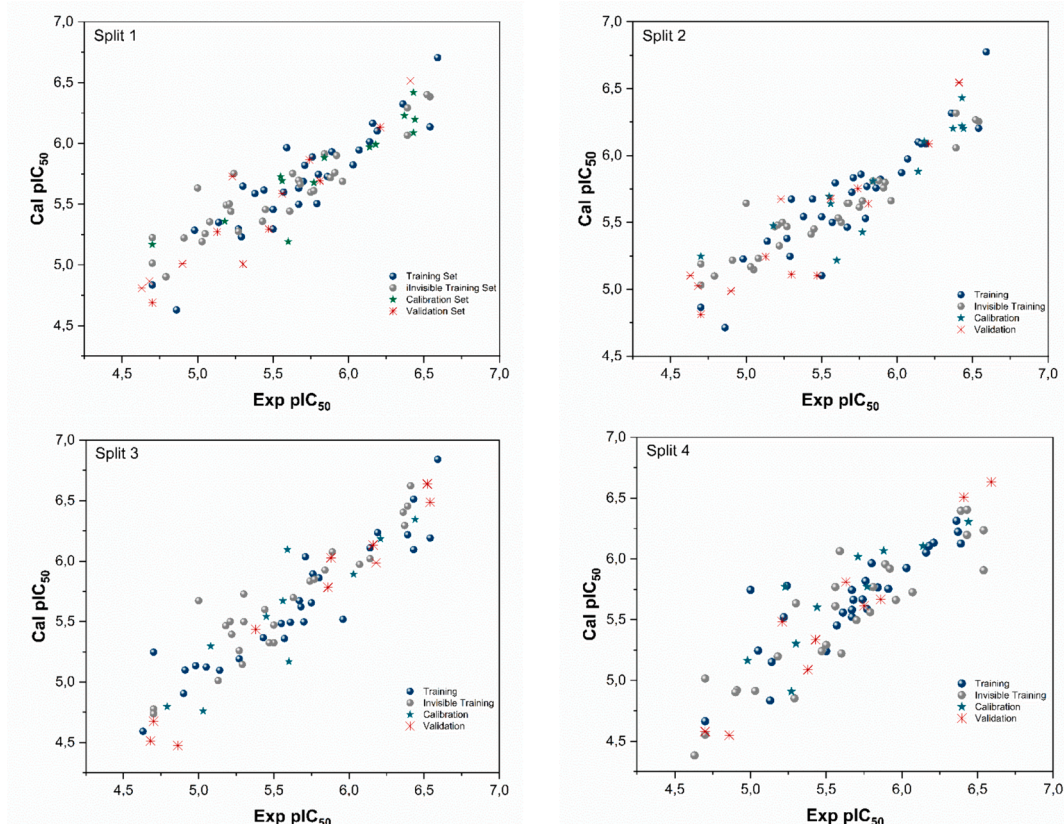

Fig. 1. Experimental vs. calculated pIC_{50} values for the four Splits.

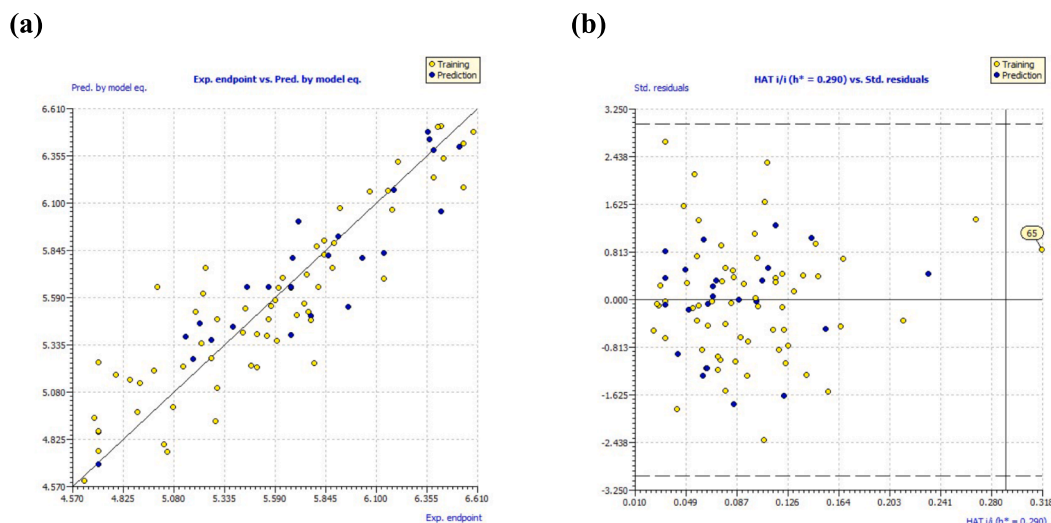**(a)** **(b)**

Fig. 2. (a) Experimental vs. predicted pIC$_{50}$ values; **(b)** William's plot.

3.3. Mechanistic interpretation

The integration of mechanistic interpretations is a pivotal component within the framework of the OECD. These interpretations are helpful for identifying and evaluating the chemical features that contribute to the increase or decrease of a defined endpoint value. To provide a comprehensive understanding of the mechanistic interpretation of the CORAL model, numerous iterations of Monte Carlo optimization were used. The chemical features, obtained from SMILES descriptors, display positive (CWs) and recognize factors that support an increase in the pIC$_{50}$ value. In contrast, negative CWs identify factors that encourage a reduction in the pIC$_{50}$ value. While SMILES qualities that include both positive and negative CWs values remain undefined. Table S6 presents a complete summary of the main factors that contribute to the increase or decrease of pIC$_{50}$ values, associated with their corresponding correlation weights (CWs). These results are derived from the three separate runs of the established QSAR model for split 3.

Based on the SAR study of Sakurai *et al.* (Sakurai et al., 2018) and on the insights obtained from Table S6, the factors increasing the inhibitory activity were incorporated into the lead compound 78 along with compounds 80 and 83. These two molecules exhibit low cytotoxicity and high pIC$_{50}$ values and are closely aligned with the lead compound. While the promoters associated with a decrease were omitted. The influential promoters were systematically investigated at three distinct sites (R$_1$, R$_2$, R$_3$) within the lead compound to strategically design novel inhibitors targeting the EBOV-GP, as depicted in Fig. 3. Therefore, 26 novel molecules were designed (Table S7). Table S8 gives the calculated activities of the newly designed molecules by the two QSAR models. The CORAL model predicted a pIC$_{50}$ range [7.1239–7.9595] for all the designed

compounds. The GA-MLR QSAR model confirmed the inhibitory potential of the newly developed compounds.

3.4. Modeling missing residues as loop regions

The loops are involved in many biological functions and constitute key components of protein structure. The loop modeling of the EBOV-GP (PDB ID: 5JQ7), successfully filled the missing residues in three critical regions (LYS191-SER210, THR284-GLY286 and LYS294-ARG302). These regions are essential for the functional mechanism of the EBOV-GP as depicted in Fig. 4. The process involved aligning the incomplete structure of EBOV-GP with its corresponding higher-resolution template, and the missing residues were completed using the ProMod3 modeling algorithm. The accuracy and reliability of the reconstructed EBOV-GP was confirmed by QMEAN and GMQE values of 0.69 and 0.85, respectively. Importantly, the loop model of the missing residues in region 1 is positioned and oriented upwards to allow the ligands to access the binding site. This structural arrangement is in agreement with the findings of previous research (Ren et al., 2018), suggesting that the modeled loop does not obstruct the binding pocket and thus facilitates potential inhibitor interactions. These findings indicate that the completed EBOV-GP structure is well constructed, confirming its suitability for subsequent molecular docking and MD simulations.

3.5. Molecular docking

To validate the efficacy of our design approach, we employed molecular docking methodology to explore the ligand–protein interactions involving the newly designed compounds, the reference lead compound,
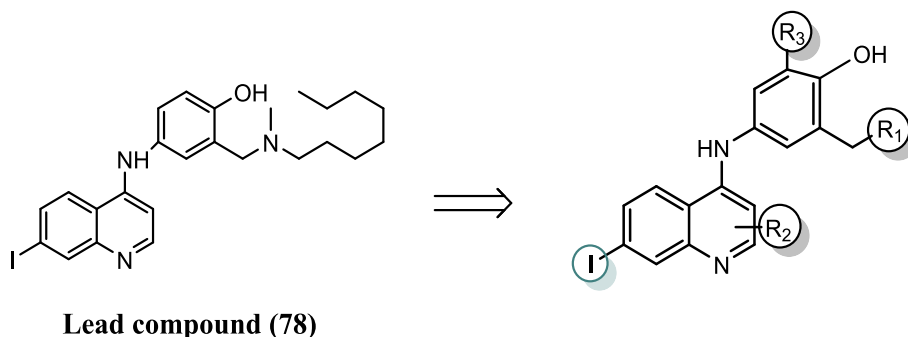

Lead compound (78)

Fig. 3. Scaffold chemical structure derived from the lead compound with highlighted substitution sites (R$_1$, R$_2$, R$_3$) maintaining crucial Iodine for inhibition activity.
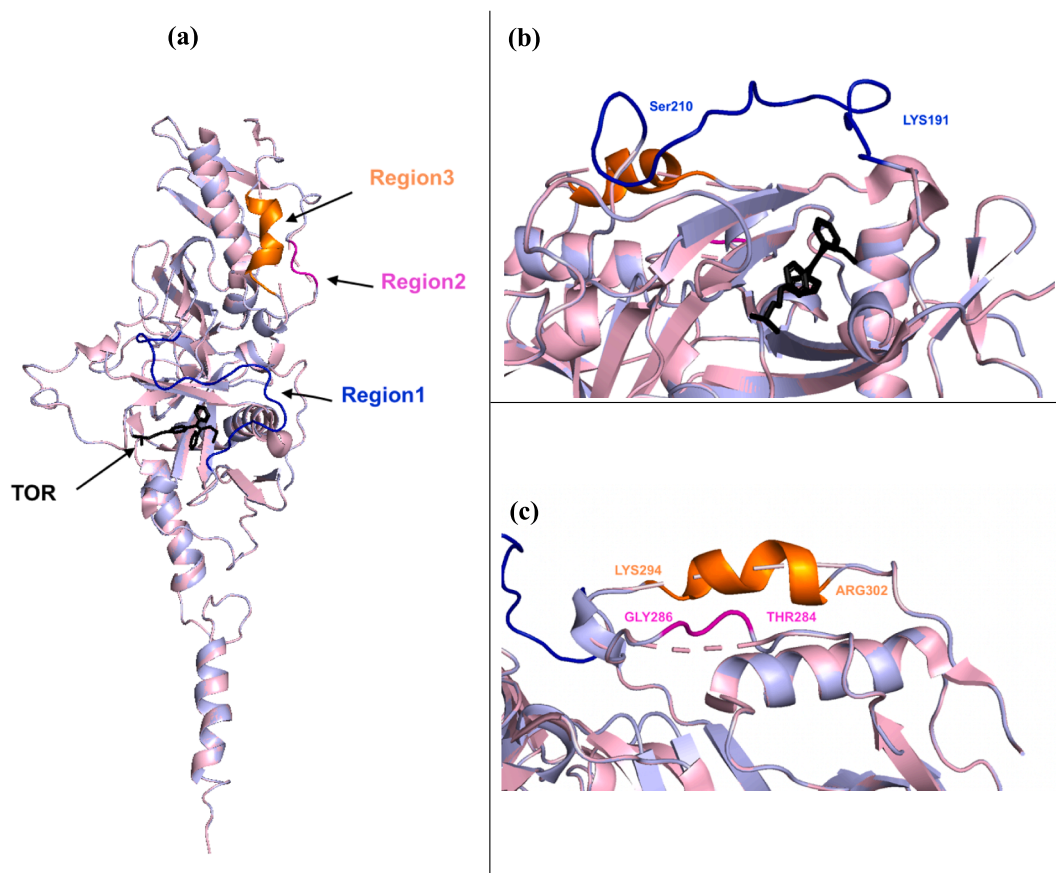
Fig. 4. (a) The alignment of the uncompleted structure of EBOV-GP (PDB ID: 5JQ7, light pink) and the modeled EBOV-GP (light blue) containing the co-crystalized ligand (TOR). The modeled structure of the missing residues in the three regions: **(b)** Region 1 (LYS191-SER210, blue), **(c)** Region 2 (THR284-GLY286, magenta) and Region 3 (LYS294-ARG302, orange).

and the co-crystallized ligand (TOR) with the modelled EBOV-GP protein. A crucial step in this validation process was the re-docking analysis of the TOR ligand to assess the accuracy of the docking protocol. The

RMSD between the x-ray and predicted poses of TOR was determined to be 0.664 Å (Figure S1), confirming the appropriateness of the docking protocol in reproducing native poses within the acceptable range of less
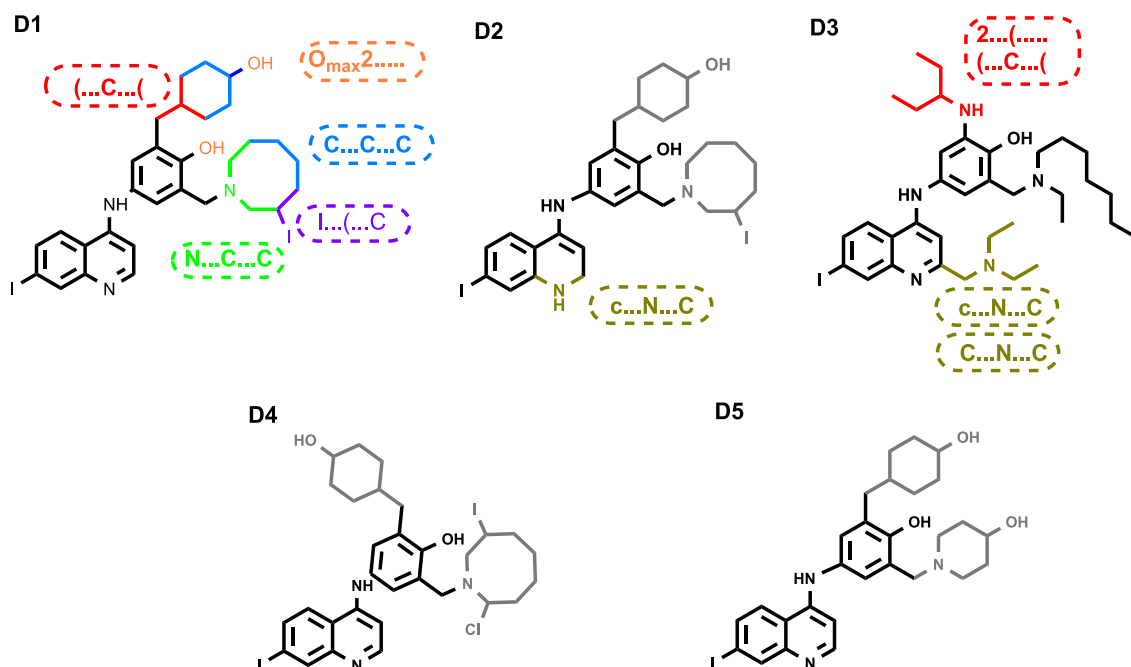
Fig. 5. Chemical structures of the top five newly designed compounds.

than 2 Å. Subsequently, a comprehensive docking study was conducted for all designed compounds against the modelled EBOV-GP, and the resulting binding affinity values are detailed in Table S8. Notably, ten designed molecules exhibited higher binding affinity values compared to both the co-crystallized ligand (TOR: −8.4 Kcal/mol) and the lead compound (**78**: −7.4 Kcal/mol). The chemical structures of the top five newly designed compounds (**D1**-**D5**) ranked based on their binding affinities are presented in Fig. 5. While, Fig. 6 illustrates their 2D and 3D representations within the binding site of EBOV-GP. Their binding affinity values and ligand–protein interactions details are provided in Table 3 and Table S9, respectively. Analysis of the docking results elucidates that compound **D1** exhibited a high binding affinity (−9.9 kcal. mol^{-1}), forming stable interactions with the key residues of the active site of EBOV-GP**.** The interactions formed by compound **D1** were three hydrogen bonds (with GLY B:45, TYR B:16, and VAL A:176), one Pi-Sulfur interaction with MET B:47, and three Alkyl and Pi-Alkyl interaction involving (ALA A:74), (LEU B:14), and (VAL A:39) residues. Compound **D2** exhibited stability through three hydrogen bonds (two conventional with (PRO A: 160) and (TYR B:16), one carbon hydrogen bound with (LEU B:46), one pi–sulfur interaction with (MET B:47), one pi-pi Stacked interaction with (TYP B: 16), and seven alkyl and pi-alkyl interactions. Similarly, compound **D3** formed interactions with (ARG A:37) and (VAL A:176) via conventional hydrogen bonds and with (GLY B:45) via carbon hydrogen bond. Furthermore, it engages in Pi-Donor hydrogen bonds with (TYR B:16), contributing to its structural stability. Additionally, **D3** exhibits hydrophobic interactions with (ALA A:74), (LYS A:163), (LYS A:164), (VAL A:39), and (LEU B:14), further enhancing its binding affinity and molecular interactions. Compound **D4** was stabilized by the formation of one carbon hydrogen bond with (LYS A:163) and eight hydrophobic interactions with (ALA A:74), (VAL A:39), (LEU A:41), (LEU B:14), (MET B:47) and (PHE A:167). Compound **D5** formed one conventional hydrogen bond with (THR B:18) and seven hydrophobic interactions with (ALA A:74), (LEU B:14), (LYS A:163), (MET B:47), (VAL A:39), (THR B: 18), and (TYR B:16).

3.6. Molecular dynamics simulations

Molecular dynamics simulations were employed to assess the stability of interactions between proteins and ligands, as well as to quantify the binding affinity of ligands. MD simulations were run for the top five compounds **(D1-D5)**. The study included the computation of diverse parameters (Table 4) such as RMSD, RMSF, Rg, and SASA metrics. The best three stable systems (**D2**, **D3**, and **D5**) that showed good stability with Apo form of the EBOV-GP and the EBOV-GP-lead compound complex are presented in the Table 4.

The RMSD serves as a measure to quantify the degree of deviation in a protein's backbone from its initial to final conformation during a simulation, providing valuable insights into its structural stability. A protein with consistent stability will exhibit minimal backbone deviation, while a less stable protein will show greater variation. Analysis of the MD results, as depicted in both the Fig. 7 and Table 4, reveals variations in the RMSD values for the Apo form of EBOV-GP and its complexes with different compounds. Interpreting these findings, the compound with the lowest average RMSD, namely compound **D2**, suggests a higher degree of stability compared to the complex protein-lead compound. Similarly, compound **D3** and compound **D5** also exhibit greater stability, as evidenced by their lower RMSD values. This implies that these compounds potentially contribute to maintaining the structural integrity of the protein during the simulation.

To further investigate the ligand stability within the binding site of EBOV-GP, the RMSD values of the ligands were monitored (Fig. 8). Monitoring these trajectories would provide valuable information about the conformation and orientation of the simulated ligands within the binding site of EBOV-GP throughout the simulation period. The RMSD plot shows that compound **D3** exhibits the most consistent and stable behavior, showing the least variation throughout the 100 ns MD

simulation. In contrast, compounds **D2** and **D5** show higher RMSD values than the lead compound, indicating greater mobility within the binding site before reaching a semblance of stability later at the end of the simulation.

Analyzing the RMSF is essential for identifying flexible areas within protein–ligand complexes. Higher RMSF values in regions with lower structural organization, such as loops and turns, contrast with lower fluctuations in more ordered segments like alpha helices and beta sheets. It is crucial to note that the RMSF assessment covered C-alpha atoms across the entire simulation for both the complexes and the EBOV-GP Apo form. In evaluating the flexibility of the top five compounds binding to the EBOV-GP, RMSF values from the lead compound complex served as a reference baseline. Remarkably, compound **D3** demonstrated the lowest RMSF (Table 4 and Fig. 9), corroborating the findings observed in the RMSD analysis. This underscores the consistent behavior of compound **D3**, not only in terms of structural stability (as indicated by the RMSD) but also in terms of exhibiting minimal fluctuations in flexible regions, further highlighting its potential as a stable and structurally sound ligand for EBOV-GP.

Radius of gyration, serving as an indicator of protein structure compactness, is employed to evaluate changes induced by ligand binding through a comparison of Rg values before and after binding. A lower radius of gyration signifies a more compact protein structure. Fig. 10 presents the Rg plot for the Apo state, lead compound, compound **D2**, compound **D3**, and compound **D5** unveiled average Rg values of 2.268, 2.293, 2.312, 2.291, and 2.277 nm, respectively. Particularly noteworthy is that compound **D5** exhibited Rg values slightly lower than those of the EBOV-GP bound to the lead compound. This suggests that compound **D5** may lead to a protein structure that is more densely packed compared to the lead compound, implying potential implications for the binding process and overall stability of the protein–ligand complex.

The SASA parameter refers to the surface area of a protein that engages with solvent molecules, measuring the fraction of a protein's surface available to such molecules.

The SASA values for the EBOV-GP Apo state, lead compound, compound **D2**, compound **D3**, and compound **D5** are 198.266, 205.813, 206.417, 203.612, and 204.020 nm^2, respectively. The Apo structure inherently represents solvent accessibility, and the marginal increase in SASA with the lead compound indicates alterations upon ligand binding. Notably, compound **D2,** as showed in Fig. 11**,** exhibits higher SASA values, suggesting modifications in the protein's surface accessibility, likely attributed to the binding of distinct ligands. These SASA variations offer insights into the protein's dynamic nature, highlighting structural adaptations and potential functional implications associated with specific ligand interactions.

3.7. ADMET

In drug discovery and development, the ADMET emerges as a pivotal phase and plays a vital role in circumventing potential complications during clinical trials. A successful drug candidate must not only exhibit efficacy against the targeted therapeutic endpoint but also demonstrate favorable drug-like qualities and pharmacokinetic characteristics. In the present study, *in silico* ADMET analysis results of our newly compounds are summarized in Table 5. All the five compounds exhibit a reassuring absence of risks of tumorigenicity, irritancy, mutagenicity, reproductive effects, carcinogenicity, or hepatotoxicity, underscoring their potential safety and efficacy in the drug development pipeline. The human intestinal absorption (HIA) of an oral drug is a critical determinant of its apparent efficacy. The scale of the five compounds ranges from excellent (0–0.3) to poor (0.7–1.0), as it is represented in red in Table 5. Caco-2 cell permeability, expressed as a log cm/s value, is a critical index for evaluating the potential in vivo drug permeability of a compound, with a predicted value >-5.15 log cm/s indicating adequate permeability across intestinal cell membranes via various transport processes. With
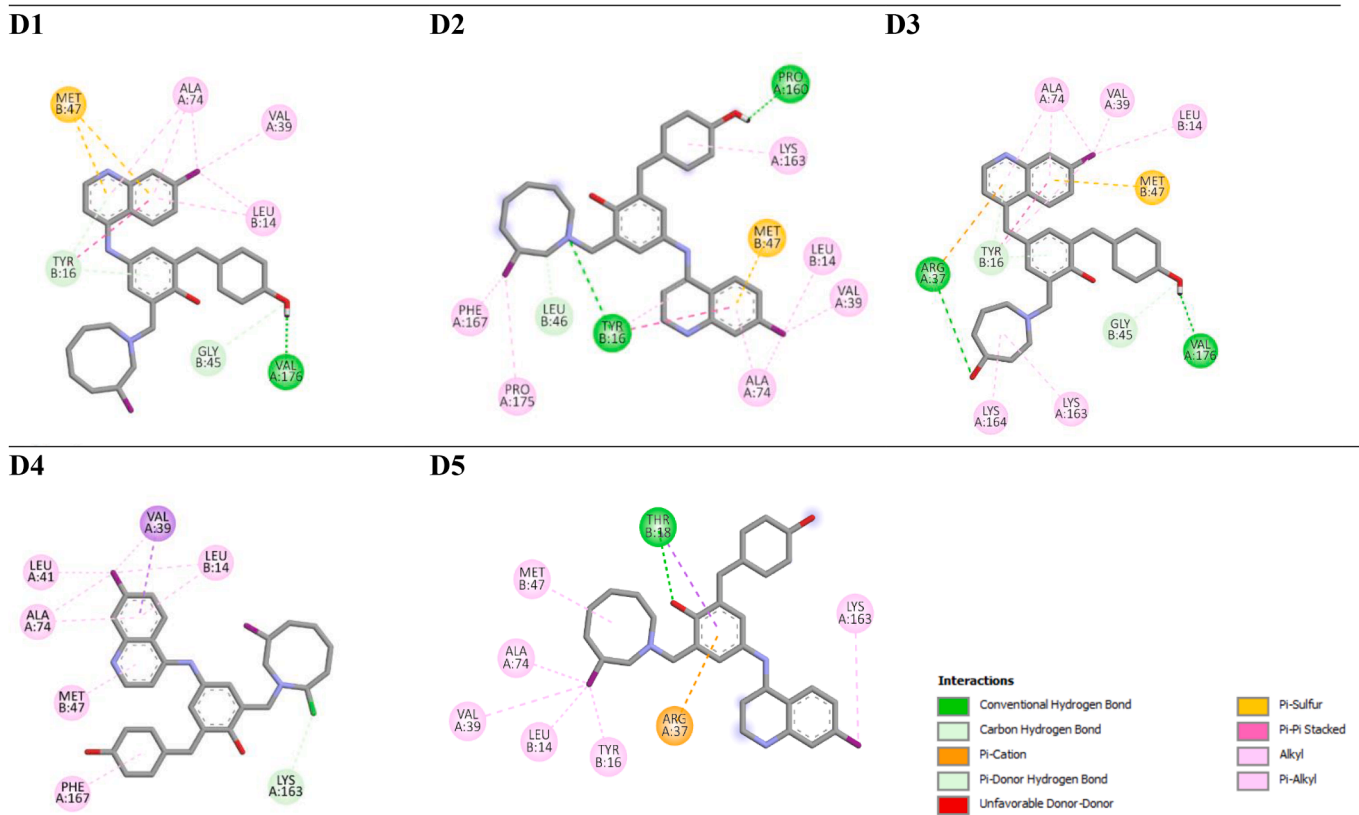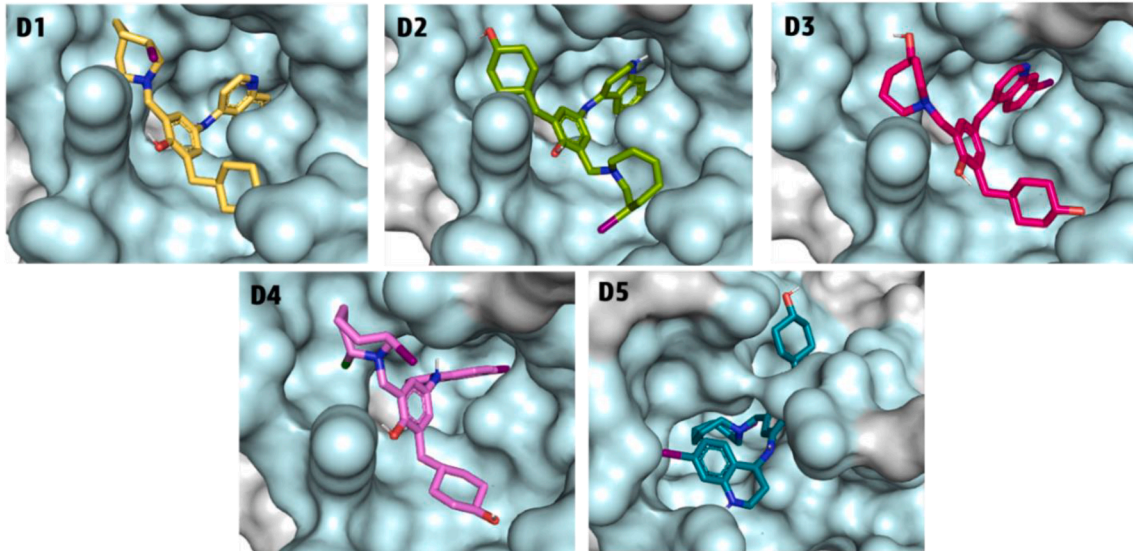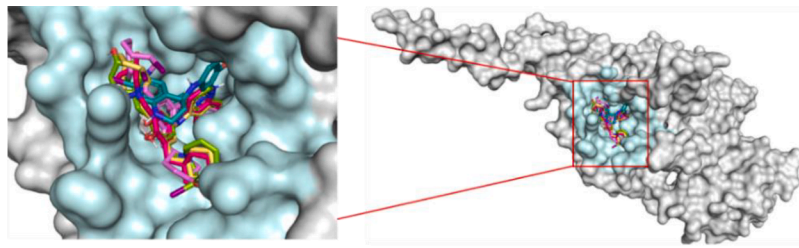
Fig. 6. 2D and 3D representation of the interactions of ligands **D1**-**D5** within EBOV-GP binding pocket.

Table 3

Top five designed compounds and their predicted pIC_{50} using the Monte Carlo optimization and the GA-MLR models and their docking scores.

Ligand	CORAL pIC_{50}	GA-MLR pIC_{50}	Docking Score (kcal/mol)
Lead compound	6.84	6.77	−7.4
D1	7.63	7.04	−9.9
D2	7.12	7.07	−9.8
D3	7.83	7.10	−9.6
D4	7.68	7.04	−9.5
D5	7.26	7.55	−9.4

Table 4

Calculated average parameters for all the systems throughout 100 ns MD simulations.

System	RMSD (nm)	RMSF (nm)	Rg (nm)	SASA (nm²)
Apo	0.399 ± 0.075	0.145 ± 0.117	2.268 ± 0.021	198.266 ± 31.119
Lead compound	0.532 ± 0.111	0.164 ± 0.149	2.293 ± 0.013	205.813 ± 32.156
D2	0.374 ± 0.081	0.181 ± 0.167	2.312 ± 0.018	206.417 ± 32.365
D3	0.416 ± 0.075	0.162 ± 0.146	2.291 ± 0.015	203.612 ± 31.916
D5	0.414 ± 0.078	0.178 ± 0.173	2.277 ± 0.014	204.020 ± 32.163

the exception of compounds D3 and D5, all compounds described have shown good predicted permeability (Barrett et al., 2022). In addition, solubility is a critical factor that influences the ADME of a drug candidate. The solubility is often expressed as the logarithm of its solubility in water (logS). A more negative logS value indicates lower solubility, while a less negative (or more positive) logS value indicates higher solubility. Compared to the lead compound, all the new compounds have higher solubility than the starting lead compound (−5.671), as indicated by their less negative logS values. This suggests an improvement in solubility, which is beneficial for drug development since higher solubility typically correlates with better bioavailability. D5, with the lowest permeability, had the highest solubility value (−4.409) as the permeability is inversely correlated with the solubility (Barrett et al., 2022). For drugs targeting the central nervous system (CNS), traversing the blood–brain barrier (BBB) is imperative to reach their molecular targets, while drugs with peripheral targets may require minimal or no BBB penetration to avoid CNS side effects. The evaluation criteria for BBB penetration are categorized as excellent (0–0.3), medium (0.3–0.7), and poor (0.7–1.0). As detailed in the table below all the proposed structures had excellent to medium values of BBB. Another essential parameter in ADMET analysis is the half-life of a drug ($T_{1/2}$), a composite measure of both clearance and volume of distribution. It is a better assessment with reliable estimates of these two properties. Excellent categorization was attributed to all molecules as they are in the range 0–0.3. Additionally, these drug-like molecules are easy to synthesis according to their excellent Synthetic Accessibility scores (SA
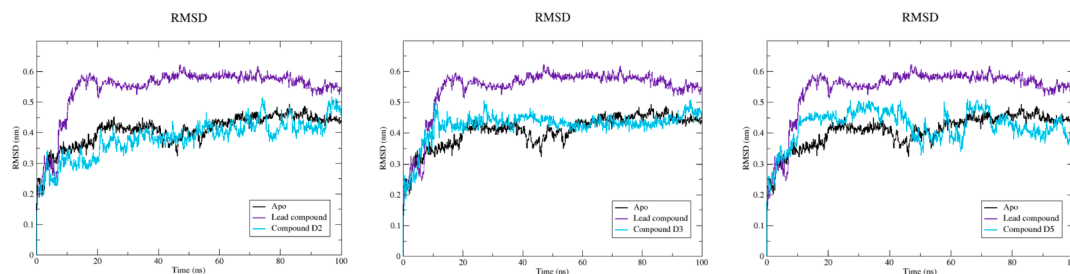

Fig. 7. Time-dependent RMSD of c-α backbone of EBOV-GP Apo, lead compound, compound **D2**, compound **D3**, and compound **D5**.
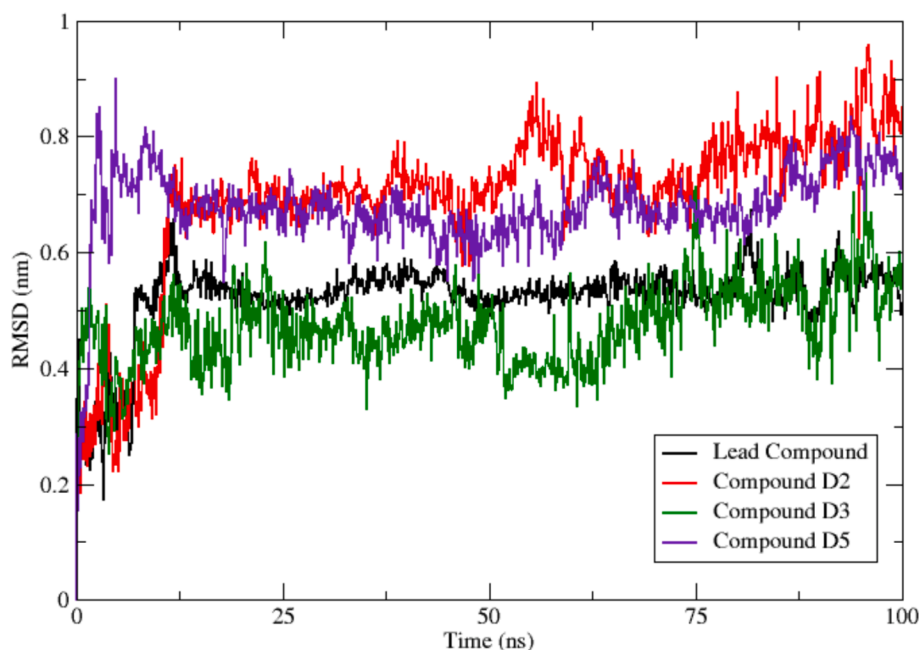

Fig. 8. RMSD of the ligands (reference compound **78** and designed compounds **D2**, **D3** and **D4**).
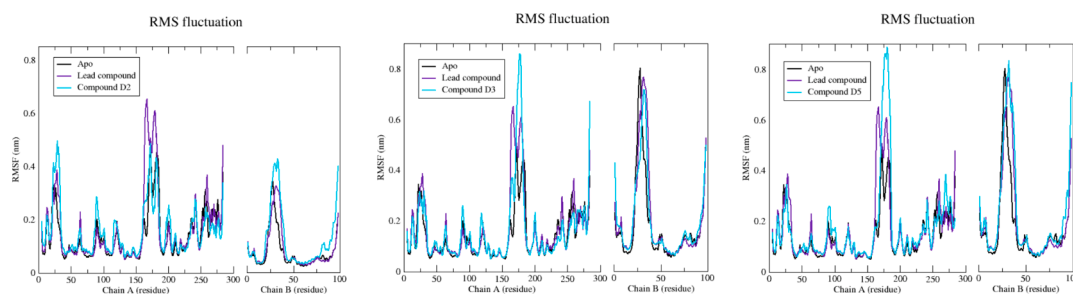
Fig. 9. Plot of RMSF for c-α atoms of EBOV-GP Apo, lead compound, compound **D2**, compound **D3**, and compound **D5**.
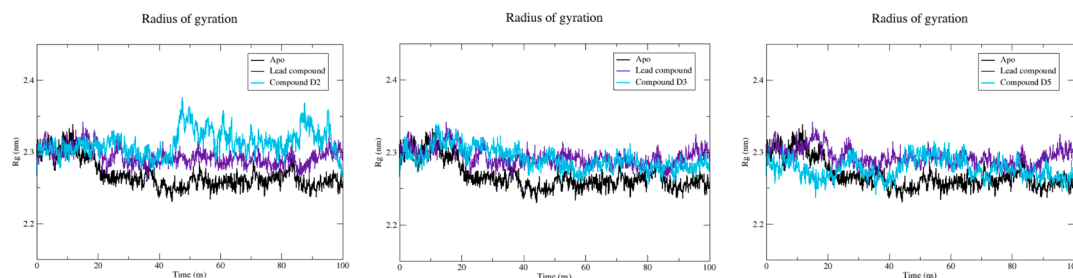

Fig. 10. Plot of Rg vs. time for EBOV-GP Apo, lead compound, compound **D2**, compound **D3**, and compound **D5**.
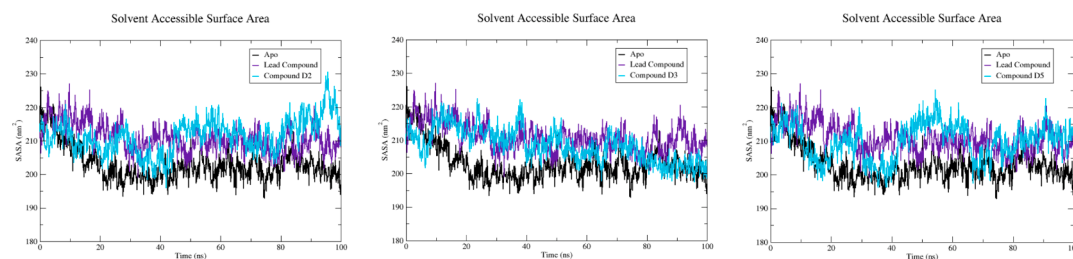

Fig. 11. The SASA profile of EBOV-GP Apo, lead compound, compound **D2**, compound **D3**, and compound **D5**.

Table 5
ADMET properties of the lead and the top five designed compounds.

	Cmpd.	Lead compound	D1	D2	D3	D4	D5
Physicochemical and ADME properties	TPSA (Å²)	48.39	68.62	67.76	88.85	58.97	63.66
	HBA	4	5	5	6	5	6
	HBD	2	3	4	4	3	3
	BBB	0.182	0.121	0.343	0.250	0.543	0.085
	HIA	0.004	0.010	0.029	**0.784**	0.028	0.004
	Solubility (log(S))	−5.671	−4.969	−4.953	−4.677	−4.694	−4.409
	Caco-2 Permeability	−4.730	−5.267	−5.585	−5.105	−5.071	−5.614
	CYP2C9 inhibitor/ CYP2C9 substrate	N/N	N/N	N/N	N/N	N/N	N/N
	$T_{1/2}$	0.068	0,02	0,03	0,057	0,031	0,026
Medicinal Chemistry	SA score	2.47	3.557	3.942	3.356	3.936	3.132
	Drug score	Reference	0.100	0.200	0.220	0.310	0.050
Toxicity properties	AMES Toxicity	N	N	N	N	N	N
	Tumorigenic	N	N	N	N	N	N
	Irritant	N	N	N	N	N	Y
	Reproductive affective	N	N	N	N	N	N
	Carcinogenicity	N	N	N	N	N	N
	Hepatotoxicity	N	N	N	N	N	N

N: No risk.

score ≤ 6). This score was estimated based on a combination of fragment contributions and a complexity penalty (Ertl and Schuffenhauer, 2009). Furthermore, neither inhibitory nor substrate interactions with the human cytochrome P450 family CYP450- 2C9 were observed, suggesting a favorable safety profile with minimal impact on drug metabolism mediated by CYP450-2C9, which is a positive characteristic in drug development. Regarding toxicity, all compounds pose no risk except compound **D5**, which may have an irritant effect.

4. Conclusion

This study was focused on designing novel and potent inhibitors for

the Ebola virus, specifically targeting EBOV-GP, the crucial protein involved in attachment and fusion. Utilizing a series of amodiaquine derivatives, two QSAR models, CORAL and GA-MLR were developed to gain insights into the design of potent inhibitors for EBOV-GP. The first model, the CORAL QSAR model, was employed to identify the key features involved in increasing and decreasing the inhibition activity against EBOV-GP. Using these features, 26 new molecules were designed with better inhibition activity than the lead compound. The second model, a GA-MLR model, served to confirm the predicted inhibition activity of the designed compounds. Computational validation through molecular docking and dynamics simulations confirmed the efficacy of the designed compounds. Before conducting the molecular docking study, homology modeling was used to fill the missing residues in the EBOV-GP structure. The modeled and completed EBOV-GP structure was docked against the designed compounds where three designed compounds (**D2**, **D3**, and **D5**) showed remarkable binding affinity profiles. Furthermore, molecular dynamics simulations corroborated the docking results, revealing their stability when they are complexed with EBOV-GP protein. Moreover, these drug candidates demonstrated non-toxic and acceptable pharmacological properties. The combined computational methods employed in this study facilitated the identification of new drug candidates, paving the way for further evaluation of their efficacy and safety. Further studies may explore in vitro experiments to validate and reinforce our computational modeling results. Nevertheless, the computational methods, showcased in this study, underscore their potential utility in expediting drug discovery and guiding future research endeavors against the Ebola virus.

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CRediT authorship contribution statement

Nouhaila Ait Lahcen: Writing – original draft, Investigation, Data curation, Conceptualization. **Wissal Liman:** Writing – original draft, Data curation. **Mehdi Oubahmane:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Ismail Hdoufane:** Writing – review & editing, Formal analysis, Conceptualization. **Youssef Habibi:** Writing – review & editing, Supervision. **Ashwag S. Alanazi:** Validation, Resources, Funding acquisition. **Mohammed M. Alanazi:** Writing – review & editing, Validation, Funding acquisition. **Christelle Delaite:** Validation, Resources. **Mohamed Maatallah:** Writing – review & editing, Supervision. **Driss Cherqaoui:** Writing – review & editing, Visualization, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.arabjc.2024.105870.

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