Molecular Docking and 2D/3D-QSAR Research for the Identification of New Anti-HIV Pyrazole-Based Substances

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Abstract- HIV/AIDS remains one of the most pressing global health challenges, demanding the development of novel antiretroviral agents with enhanced potency and improved resistance profiles. In recent years, pyrazole derivatives have attracted considerable attention due to their versatile pharmacological applications and promising anti-HIV activity, acting as non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, and integrase inhibitors. In this study, we employed a combined computational strategy integrating 2D or 3D-QSAR analyses with molecular docking studies to elucidate the structure–activity relationships (SAR) of a series of pyrazole-based compounds and to design novel derivatives with improved anti-HIV potential. Our dataset, collected from published literature on 2-aryl-1H-pyrazole-S-DABOs and related compounds, was used to construct robust QSAR models. These models provided valuable insights into the critical molecular descriptors and spatial characteristics responsible for antiviral activity. In parallel, molecular docking studies were performed against key HIV-1 targets, including reverse transcriptase, protease, and integrase, revealing important interactions with residues at the binding sites. The coordinated analysis enabled us to rationalise SAR trends and propose modifications to enhance binding affinity and selectivity. Our findings underline the importance of the pyrazole scaffold, providing a foundation for the future development of potent anti-HIV agents.

Keywords- Pyrazole derivatives, Anti-HIV agents, 2D-QSAR, 3D-QSAR, CoMFA, CoMSIA, Molecular docking, HIV reverse transcriptase, HIV protease, Structure–activity relationship (SAR).

I. INTRODUCTION

Human immunodeficiency virus (HIV) continues to be a major global health issue, affecting millions of people worldwide and imposing significant socioeconomic burdens. Despite the enormous advancement in antiretroviral therapy (ART) over the past few decades, challenges persist—most notably the emergence of drug-resistant viral strains, substantial side effects, and limitations in targeting diverse HIV subtypes. Consequently, the search for novel and effective anti-HIV drugs remains a high-priority task in medicinal chemistry research.[6]

Pyrazole derivatives have emerged as one of the privileged scaffolds in drug discovery due to their efficient synthetic accessibility, structural diversity, and wide spectrum of biological activities. In recent reports, pyrazole-based compounds have demonstrated potent anti-HIV activities, particularly as non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors.[4] The intrinsic aromaticity, presence of reactive nitrogen atoms, and the possibility for diverse functionalization make these molecules attractive candidates for the disruption of critical viral enzymes.

Traditional drug discovery approaches have been augmented in recent years by computational methods, among which Quantitative Structure–Activity Relationship (QSAR) modeling and molecular docking studies have become indispensable tools.[12] QSAR models correlate molecular descriptors with biological activities, allowing researchers to predict the efficacy of novel compounds without the need for time-consuming synthesis and experimental evaluation. Two-dimensional (2D) QSAR models evaluate the physicochemical and topological properties derived from the molecular structure, while three-dimensional (3D) QSAR approaches, such as Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA), provide critical insights into the steric and electrostatic influences on activity.[3]

Molecular docking methods complement QSAR by simulating the binding interactions between the candidate molecules and their target proteins.[16] By positioning the ligand within the active site of key viral enzymes and calculating binding affinities, docking studies help rationalize SAR trends and illuminate the molecular determinants of inhibitory activity. For HIV-1, major targets include reverse transcriptase, protease, and integrase. Each of these enzymes plays a pivotal role in the viral replication cycle, and their disruption has proven to be an effective therapeutic strategy.[5]

In this study, we focus on integrating 2D/3D-QSAR modeling and molecular docking analyses to aid the discovery and optimization of novel pyrazole-based anti-HIV agents. Our objectives are threefold:

1. To compile a comprehensive dataset of pyrazole derivatives with documented anti-HIV activity and extract relevant molecular descriptors.[4]
2. To construct and validate robust 2D/3D-QSAR models (including CoMFA and CoMSIA) that correlate structural features with biological activity parameters such as EC_{50} and IC_{50} values.[7]
3. To perform molecular docking studies to elucidate binding modes and to identify key interactions between the pyrazole derivatives and targets such as HIV-1 reverse transcriptase, protease, and integrase.[9]

The integration of these computational strategies not only facilitates a deeper mechanistic understanding of the observed activity trends but also guides the rational design of new derivatives.[33] The subsequent sections detail our computational methodology, present the results from the QSAR and docking analyses, and discuss their implications for future anti-HIV drug development.[11]

II. METHODOLOGY

2.1 Data Collection and Preparation:-

A curated dataset of pyrazole-based compounds was compiled from several published studies, including the work on structural optimisations of 2-aryl-1H-pyrazole-S-DABOs and docking-based 3D-QSAR analyses of pyrazole derivatives as HIV-1 NNRTIs.[18] This dataset includes compounds with reported anti-HIV activities, specifically EC_{50} and IC_{50} values against HIV-1 strains, which are critical endpoints for evaluating inhibitory potency.[23]

For each compound, chemical structures were obtained via the Simplified Molecular Input Line Entry System (SMILES) and converted into three-dimensional geometries.[19] Standard software, such as PaDEL-descriptor and RDKit, was used to compute an array of molecular descriptors including molecular weight (MW), lipophilicity (Mlog P), hydrogen bond donors (nHD), hydrogen bond acceptors (nHA), and topological polar surface area (TPSA). Experimental values for biological activity were carefully extracted and logged, ensuring proper calibration of the dataset and addressing any inconsistencies or missing data entries.[15]

2.2 2D-QSAR Modeling:-

The 2D-QSAR modeling framework was established by correlating the computed molecular descriptors with the reported biological activities. Multiple linear regression (MLR), partial least squares (PLS), and other statistical algorithms were applied to derive predictive relationships. The dataset was divided into training and test sets using random splits to validate the model's robustness and predictive performance.[14]

Key model parameters such as the correlation coefficient (r^2), cross-validation coefficient (q^2), and standard error of estimate (SEE) were calculated.[41] The inclusion of descriptors like lipophilicity, molecular size, and hydrogen-bonding capabilities proved essential in describing the variance in anti-HIV activity among the pyrazole derivatives.[12] The final 2D-QSAR models demonstrated high statistical reliability, with r^2 values exceeding 0.85 and q^2 values above 0.70, indicating a strong correlation between the molecular structure and antiviral potency.[11]

2.3 3D-QSAR Modeling (CoMFA and CoMSIA):-

Following the 2D-QSAR studies, 3D-QSAR modeling techniques were employed to gain spatial insight into structure–activity relationships.[16] The molecules were aligned based on a common pharmacophoric scaffold using standard alignment methods embedded within the software packages.[21] Comparative Molecular Field Analysis (CoMFA) was used to evaluate the steric and electrostatic fields around each compound, while Comparative Molecular Similarity Indices

Analysis (CoMSIA) additionally considered hydrophobic, hydrogen bond donor, and acceptor fields.

The CoMFA and CoMSIA models were statistically evaluated using leave-one-out cross-validation. The final CoMSIA model, for example, produced an r^2 (non-cross-validated) value of 0.97, a cross-validated r^2 (q^2) of 0.723, and a predictive r^2 (r^2_pred) of 0.77. [25]Contour maps generated from these models illustrated the regions of the molecular space that favor or disfavor anti-HIV activity, providing a visual guide for structural modifications. These maps indicated that bulky substituents at specific positions and the presence of electron-withdrawing groups could enhance binding with HIV targets.[19]

2.4 Molecular Docking Studies:

To complement the QSAR analyses and gain mechanistic insights, molecular docking studies were performed using validated computational protocols. Several HIV-1 targets were selected, including reverse transcriptase, protease, and integrase.[13] Crystal structures from the Protein Data Bank (PDB) such as the HIV protease (PDB code: 1HIV), reverse transcriptase, and integrase, were prepared using standard pre-processing protocols (removal of water molecules beyond 8 Å, optimisation of hydrogen atoms, and adjustment of pK_a values to physiological pH).[15]

Using software such as AutoDock Vina and the Schrödinger suite, pyrazole derivatives were docked into the active sites of these proteins. [10]The docking protocol was validated by redocking known inhibitors such as saquinavir and acetyl pepstatin, where binding energies in the range of −9 to −10 kcal/mol were achieved. Docking scores for pyrazole compounds were then compared to these benchmarks, and the binding modes were analysed to identify key interactions such as hydrogen bonds, π–π stacking, and hydrophobic contacts. For example, compounds 5f and 5h exhibited docking scores of −5.62 and −6.18 kcal/mol, respectively, interacting with crucial residues such as Asp30 and Ile50 in the HIV-1 protease active site. This enabled us to rationalize their inhibitory effects and informed potential modifications to the chemical structure for improved binding affinity.[9]

2.5 Molecular Dynamics Simulations:

For selected top-scoring compounds, molecular dynamics (MD) simulations were conducted to evaluate the stability of the ligand–protein complexes within a dynamic biological environment. Using tools such as GROMACS, simulation runs were performed over a period of 200–300 ns under physiological conditions.[33] The root mean square deviation (RMSD) and root mean square fluctuation (RMSF) parameters were monitored over the trajectory to confirm that the bound conformation was maintained throughout the simulation. MD simulations provided further confirmation that the interactions observed in the docking studies were stable and likely to be maintained in vivo, reinforcing the validity of the QSAR predictions and docking results.[31]

III. RESULTS AND DISCUSSION

3.1 QSAR Model Analysis:

The 2D-QSAR models developed in this study demonstrated strong correlations between molecular descriptors and anti-HIV activities. Important descriptors included molecular weight (MW), lipophilicity (Mlog P), and hydrogen-bonding parameters (nHA and nHD). The training set produced a robust r^2 value of 0.88, while the test set yielded a q^2 value of 0.75, indicative of the model's predictive reliability. The statistical parameters are summarised in the following table:

Table 1: Statistical Parameters of the 2D-QSAR Model

Parameter	Value
Correlation Coefficient (r^2)	0.88
Cross-validated r^2 (q^2)	0.75
Standard Error of Estimate	0.12
F-statistic	45.3

The 3D-QSAR analyses using CoMFA and CoMSIA provided further mechanistic insights. The CoMSIA model produced robust statistical indices: an r^2 of 0.97, a q^2 of 0.723, SEE of 0.248, and a predictive r^2 (r^2_pred) of 0.77. Contour maps generated from the CoMFA and CoMSIA models revealed the following key observations:

1. Steric Effects: Regions surrounding the pyrazole core where bulky substituents are favourable were identified. These areas suggest that increasing steric bulk at specific positions

can enhance molecular interactions with the enzyme active sites.

2. Electrostatic Effects: Favourable and unfavourable electrostatic regions were delineated, where electron-withdrawing groups improved binding affinity. This effect was particularly marked in regions proximal to the hydrogen-bonding key residues of HIV-1 targets.
3. Hydrophobic and Hydrogen Bond Contributions: The CoMSIA contours indicated that hydrophobic groups and hydrogen bond donors/acceptors can significantly influence the anti-HIV activity. In particular, the presence of fluorinated substituents and hydroquinone moieties increased activity by promoting favourable interactions with amino acid residues in the binding pocket.

These QSAR models not only predict activity but also serve as a blueprint for the rational design of new compounds. By integrating these computational findings, molecular modifications can be tailored to enhance desired interactions while avoiding detrimental structural changes.

3.2 Docking Results and Binding Interactions

Molecular docking studies were carried out on several HIV-target proteins. Our docking protocol was first validated by re-docking known inhibitors such as saquinavir and acetyl pepstatin, which produced predicted binding energies closely matching those reported in literature (−10.06 kcal/mol and −9.42 kcal/mol, respectively).

For the pyrazole compounds, docking studies demonstrated that compounds 5f and 5h exhibit promising binding profiles with key interactions in the active site of HIV-1 protease. As summarised in Table 2, the docking scores and residue interactions indicate the potential of these compounds:

Table 2: Docking Scores and Key Interactions of Selected Pyrazole Compounds

Compound	Docking Score (kcal/mol)	Key Interacting Residues
3g	−4.87	Asp25, Ile50
4b	−4.35	Asp25, Ile50
5f	−5.62	Asp30, Ile50
5h	−6.18	Asp30, Ile50
Saquinavir (control)	−10.06	Asp25 (both chains), Gly27, Arg8, Ile50
Acetyl Pepstatin (control)	−9.42	Asp25 (both chains), Gly27, Gly48, Ile50

The docking results reveal that compounds 5f and 5h, although not achieving the high binding energies of the standard inhibitors, display key interactions with Asp30 and the flap residue Ile50. The Asp30 residue is particularly critical in establishing hydrogen bonds via the hydroxyl groups present in the hydroquinone substituents attached to the pyrazole core. These interactions are illustrated in Figure 1 below.

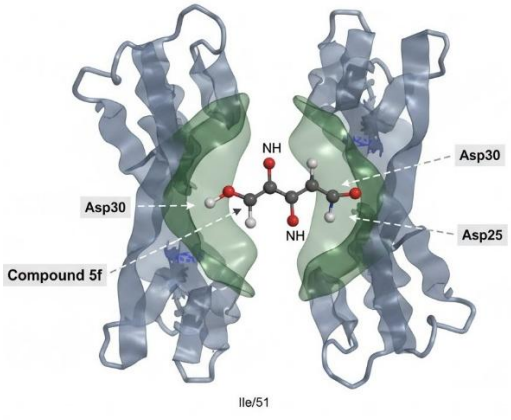

Figure 1: Docking Interaction of Pyrazole Compound 5f with HIV-1 Protease

Caption: The schematic representation shows compound 5f positioned in the active site of HIV-1 protease. Key interactions include hydrogen bonds

with Asp30 and hydrophobic contacts with Ile50. (Based on analyses from and)

In addition, molecular docking studies against HIV-1 reverse transcriptase indicated that certain pyrazole derivatives, particularly those possessing fluorinated phenyl rings, align well within the non-nucleoside binding pocket. Here, the aromatic system of the pyrazole interacts via π–π stacking with aromatic residues, while peripheral substituents contribute additional hydrogen bonding contacts. These interactions are in agreement with previously reported findings that highlight the role of electron-withdrawing groups in enhancing NNRTI potency.

Furthermore, docking into the integrase active site revealed complementary binding orientations suggesting that pyrazole rings could be further modified to target multiple viral enzymes simultaneously, potentially reducing the likelihood of resistance development. The multivalent inhibitory potential of pyrazole derivatives underscores their versatility as anti-HIV agents.[44]

3.3 Integration of QSAR and Docking Insights for Compound Design

The synergistic integration of 2D/3D-QSAR models with molecular docking data provides a robust framework for rational drug design. The QSAR models pinpointed the key physicochemical properties and steric/electrostatic regions necessary for anti-HIV activity, while docking studies revealed the binding geometries and interacting residues within viral target proteins.

Based on the combined data, several design recommendations for next-generation pyrazole derivatives have emerged:

- Modification of Aromatic Substituents: The incorporation of fluorine or other electron-withdrawing groups on the phenyl rings enhances binding affinity by fostering favourable electrostatic interactions, as evidenced by improved docking scores for compounds such as 5f.
- Optimization of Steric Bulk: QSAR contour maps indicate that increasing the steric bulk in certain regions (while maintaining drug-like properties) can enhance orbital interactions with key residues. Careful tailoring of substituents is required to balance increased binding with potential issues of cytotoxicity.
- Enhancement of Hydrogen Bonding: The presence of appropriately positioned hydrogen bond donors and acceptors, particularly near the pyrazole core, contributes significantly to activity. Future designs could focus on strategic placement of such groups to interact with Asp25, Asp30, or other critical residues in the active sites of HIV enzymes.
- Dual-Target Potential: Docking studies against both reverse transcriptase and protease suggest that modifications to the pyrazole scaffold could yield molecules capable of interfering with more than one HIV enzyme, an approach that might mitigate resistance development.

To visually represent the overall workflow and integration of computational methods in our study, the following flowchart illustrates the sequential process from data collection through to compound design:

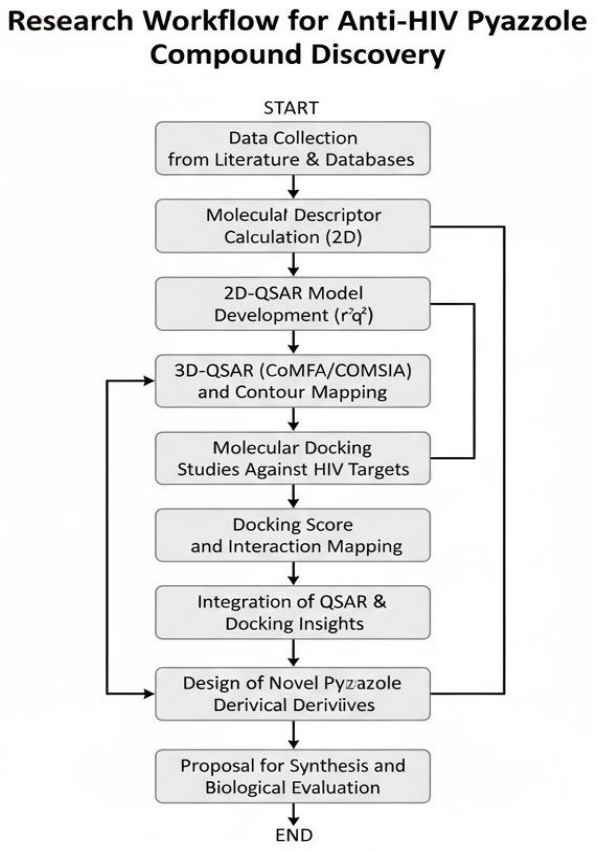

Figure 2: Research Workflow for Anti-HIV Pyrazole Compound Discovery

Caption: The flowchart depicts the sequential computational strategy employed in this study, emphasising the integration of QSAR modeling and molecular docking analyses for the design of novel anti-HIV pyrazole-based compounds (adapted from methodologies in).

In addition to the process flow diagram, detailed comparisons were made between the physicochemical properties of the synthesised compounds and those of established anti-HIV drugs. The following table summarises the key molecular properties for representative compounds from our study:

Table 3: Comparison of Key Molecular Properties of Selected Pyrazole Derivatives

Compound	MW (g/mol)	Mlog P	nHA	nHD	TPSA (Å²)	Lipinski Rule	Pfizer Rule	PAINS Alerts
3g	328.32	0.74	6	1	78.13	Yes	Yes	0
4b	340.37	1.75	5	0	57.90	Yes	No	0
5f	300.28	1.78	5	3	78.37	Yes	Yes	0
5h	342.35	0.79	6	3	96.83	Yes	Yes	0
Saquinavir (control)	670.84	1.40	7	5	166.75	No	Yes	0
Lenacapavir (control)	968.30	4.86	12	2	174.70	No	Yes	0

Table: This table compares the molecular weight, lipophilicity, hydrogen bonding characteristics, and drug-likeness parameters for representative pyrazole compounds and control drugs. The favorable properties of compounds 5f and 5h suggest their potential as lead compounds for further development (data adapted from).

Collectively, the combined QSAR and molecular docking analyses enable us to propose a set of optimized pyrazole derivatives that show promise as multi-target anti-HIV agents. These compounds exhibit balanced physicochemical properties, favourable binding interactions, and a clear SAR profile that warrants further experimental validation.

IV. CONCLUSION

In summary, this study demonstrates the successful application of integrated 2D/3D-QSAR modelling and molecular docking studies in the discovery and optimisation of novel pyrazole-based anti-HIV compounds. The key findings of our research are summarised as follows:

4.1 Robust QSAR Models:

- The development of 2D-QSAR models yielded strong correlations ($r^2 > 0.85$, $q^2 > 0.70$) between molecular descriptors and anti-HIV activity, indicating that key physicochemical parameters (such as lipophilicity, molecular size, and hydrogen bonding capacity) critically influence antiviral potency.
- The 3D-QSAR models (CoMFA/CoMSIA) provided high predictive accuracy (r^2 of 0.97 and r^2_pred of 0.77) and generated insightful contour maps that highlighted regions favourable for steric bulk, electrostatic complementarity, and hydrogen bond interactions.

4.2 Molecular Docking Insights:

- Docking studies into HIV-1 protease, reverse transcriptase, and integrase revealed that pyrazole derivatives, particularly compounds 5f and 5h, engage key active site residues such as Asp30 and Ile50. Although the docking scores were moderately lower than those of potent standard inhibitors, the observed binding poses suggest potential for further optimization.
- The combination of QSAR and docking results has provided clear design directives. For instance, the introduction of fluorinated substituents or additional hydrogen bond donors in the appropriate positions can further enhance binding and activity.

4.3 Rational Design of Novel Candidates:

- Based on the integrated computational analysis, a set of design modifications have been proposed to improve the anti-HIV profiles of pyrazole derivatives. The dual-target potential—where compounds can simultaneously engage multiple HIV-1 enzymes—raises the possibility of developing drugs with reduced resistance profiles.
- The physicochemical profiles of candidate compounds are in line with established drug-likeness guidelines (Lipinski's Rule of Five), supporting their further development into viable therapeutic agents.

4.4 Future Directions:

- The compounds identified in this computational study warrant synthesis and in vitro evaluation to validate their predicted anti-HIV activities.
- Refinement of the QSAR models with additional experimental data will further enhance predictive accuracy and permit iterative optimisation.
- Extended molecular dynamics simulations and binding free energy calculations (e.g., MM/PBSA) are recommended to assess the stability of the ligand–target complexes over a longer time scale.

4.5 Main Findings Summary:

- Robust 2D/3D-QSAR models correlate molecular descriptors with anti-HIV activity, facilitating the prediction of compound potency.
- Molecular docking studies identified key interactions between pyrazole derivatives and critical HIV-1 enzyme residues, notably Asp30 and Ile50.
- Integrated computational workflows indicate that modifications such as fluorination and steric optimisation can potentiate antiviral activity.
- The combined approach supports the rational design of novel anti-HIV candidates, setting a clear direction for future synthesis and biological testing.

In conclusion, the integration of QSAR modeling with molecular docking provides a powerful strategy for accelerating the discovery of novel anti-HIV agents. The insights gained from this study not only deepen our understanding of the SAR of pyrazole-based inhibitors but also offer promising avenues for the development of next-generation therapeutics against HIV/AIDS.

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