

Pharmacophore-Guided Virtual Screening and Docking Approach for Identification of Potential CCR5 Inhibitors Against HIV-1

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ABSTRACT

Human Immunodeficiency Virus type 1 (HIV-1) remains a global health burden, with viral entry into host immune cells being critically dependent on the interaction between the viral gp120 protein and the host CCR5 receptor. CCR5 antagonists, such as Maraviroc, have demonstrated clinical success in blocking this entry mechanism; however, issues including resistance development and limited receptor subtype coverage necessitate the identification of more potent and structurally diverse inhibitors. The objective of this study was to identify novel CCR5-targeting compounds with enhanced binding potential through an *in silico* approach integrating pharmacophore-based virtual screening and molecular docking. A pharmacophore model was generated using Maraviroc as a template and was used to filter structurally compatible, drug-like molecules from the ZINC database based on Lipinski's rule of five. Twenty-five compounds were shortlisted and subjected to molecular docking against the CCR5 receptor (PDB ID: 4MBS) using AutoDock 4.2. Default Lamarckian Genetic Algorithm parameters were used, and docking scores, hydrogen bonding, and hydrophobic interactions were analyzed. The results revealed that several compounds, particularly ZINC000585110136 (-11.2 kcal/mol) and ZINC000257285692 (-11.1 kcal/mol), displayed stronger binding affinities than Maraviroc (-10.7 kcal/mol) and formed favorable interactions with key CCR5 residues including TYR108, GLU283, and PHE109. Some compounds formed critical hydrogen bonds, while others were stabilized via hydrophobic interactions, emphasizing distinct yet effective binding modes. In conclusion, this computational screening strategy successfully identified promising CCR5 inhibitors with enhanced docking profiles over the standard drug. These candidate molecules warrant further validation through molecular dynamics simulations and *in vitro* assays to assess their potential as next-generation HIV-1 entry inhibitors.

Keywords: CCR5 Receptor, HIV-1 Entry Inhibitors, Pharmacophore Modeling, Molecular Docking, Virtual Screening, Maraviroc Analogs.

INTRODUCTION

Human Immunodeficiency Virus type 1 (HIV-1) continues to be a formidable global health challenge, with over 39 million individuals living with the virus as of 2023 (UNAIDS, 2023). One of the pivotal steps in the HIV-1 entry process is the interaction between the viral envelope glycoprotein gp120 and the host C-C chemokine receptor 5 (CCR5), a G-protein-

coupled receptor (GPCR) located on the surface of immune cells such as T lymphocytes and macrophages. The CCR5 receptor functions as a co-receptor alongside CD4, facilitating viral fusion and entry into host cells. As such, CCR5 has emerged as a validated and attractive target for the development of novel antiretroviral therapies aimed at halting viral transmission at the initial point of infection. The therapeutic relevance of CCR5 was highlighted by the development and FDA approval of **Maraviroc**, a

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selective CCR5 antagonist that blocks HIV-1 cell entry. However, while Maraviroc is clinically successful, challenges such as emerging resistance, pharmacokinetic limitations, and patient-specific viral tropism have necessitated the exploration of new and more effective CCR5 inhibitors (Mallakuntla et al., 2022; Wang et al., 2024; Davella et al., 2021).

In recent years, the integration of computational drug design tools—including pharmacophore modeling, virtual screening, and molecular docking—has revolutionized the early phases of antiviral drug discovery. Pharmacophore modeling is a powerful approach that captures the spatial arrangement of chemical features essential for molecular recognition between a drug and its target. When derived from a known ligand such as Maraviroc, pharmacophore models can be used to screen large virtual libraries of drug-like compounds for novel scaffolds that mimic critical binding interactions. Recent work has shown the effectiveness of ligand-based pharmacophore models in identifying CCR5 inhibitors with structural diversity and high predicted binding affinity (Eid et al., 2024; Kale & Jain, 2025; Mamidala et al., 2013). Complementing this, molecular docking simulations offer detailed insight into the binding conformation, affinity, and interaction profiles between candidate ligands and CCR5, allowing prioritization of hits before synthesis. Tools like AutoDock, integrated with MGLTools and visualization platforms, are frequently used for such virtual screenings, enabling efficient high-throughput analysis with validated scoring algorithms (Barik et al., 2024; Gidhamaari et al., 2012). These computational methods are especially valuable for refining drug leads and minimizing experimental resource expenditure during early drug development.

Given the structural and functional complexity of CCR5, a rational design strategy that integrates pharmacophore-based virtual screening with molecular docking was pursued in this study. By utilizing Maraviroc as the reference template, a pharmacophore model was generated and applied to the ZINC compound database to identify chemically diverse ligands exhibiting similar pharmacophoric features. The use of Lipinski's Rule of Five ensured the selection of candidates with favorable drug-likeness. These filtered compounds were then subjected to molecular docking against CCR5 using AutoDock 4.2, enabling detailed evaluation of binding energies and interaction mechanisms. This workflow not only aligns with established virtual screening protocols but also leverages current advances in fragment-based drug design and in silico pharmacological profiling (Parulekar et al., 2022; Appiah-Kubi et al., 2021; Babu et al., 2022). Through this integrated approach, we aim to identify potent CCR5 inhibitors that hold promise for further preclinical development as next-generation anti-HIV agents, overcoming some of the limitations seen in current CCR5-targeting therapies.

MATERIALS AND METHODS

Pharmacophore-Based Ligand Selection

The initial step in identifying potential CCR5 inhibitors involved generating a pharmacophore model using the Pharmit online server. The FDA-approved CCR5 antagonist, Maraviroc, served as the template molecule for pharmacophore generation (Ai-Masri et al., 2024). This model included critical interaction features such as hydrogen bond donors and acceptors, hydrophobic regions, and aromatic ring centers essential for target binding. Lipinski's Rule of Five was applied to filter compounds with drug-like properties during the virtual screening process. Following screening against the ZINC database, a total of 25 structurally diverse and pharmacophorically aligned compounds were identified for further molecular docking studies. These candidate molecules were downloaded in 3D SDF format and subjected to downstream preparation workflows for docking.

Ligand Preparation

The 25 selected compounds retrieved from the ZINC database were structurally optimized before docking. These ligands were initially converted from

the SDF to PDB format using OpenBabel. Energy minimization was carried out to stabilize their conformations using built-in tools available in AutoDockTools (MGLTools 1.5.6). Hydrogen atoms were added, Gasteiger charges were assigned, and torsion degrees of freedom were defined for all rotatable bonds. Each ligand structure was then saved in PDBQT format required for compatibility with AutoDock 4.2. The finalized ligands used for docking included the ZINC compound IDs depicted in Table-1.

Target Protein Preparation

The target protein used for molecular docking was CCR5 Chemokine Receptor, downloaded from the RCSB Protein Data Bank (PDB ID: 4MBS). The Crystal Structure of the CCR5 Chemokine Receptor was presented in Figure-1. The Figure-1 represents the crystal structure of the human C-C chemokine receptor type 5 (CCR5), a G-protein-coupled receptor (GPCR) that plays a crucial role in immune cell trafficking and serves as a coreceptor for HIV-1 entry into host cells. The structure comprises seven transmembrane α -helices, shown in rainbow coloration, characteristic of GPCR architecture. CCR5 is embedded in the cellular membrane, with extracellular loops responsible for ligand recognition and intracellular loops involved in G-protein interaction and signal transduction. The ligand-binding pocket is situated within the transmembrane domain, formed by residues such as TYR37, TRP86, TYR89, TYR108, PHE109, GLU283, and MET287, which are known to facilitate interaction with antagonists like Maraviroc. These conserved residues contribute to hydrogen bonding, hydrophobic contacts, and ionic interactions critical for receptor-ligand affinity. The 4MBS structure was co-crystallized with Maraviroc, providing detailed insights into the receptor's active site topology and guiding structure-based drug design for novel CCR5-targeting therapeutics.

The structure was cleaned by removing co-crystallized ligands, water molecules, and any other non-protein entities. Only the protein chain relevant to the binding pocket was retained. Polar hydrogen atoms were added, and Kollman charges were assigned using AutoDockTools. The cleaned and prepared receptor was saved in PDBQT format. As the exact binding site was not restricted, blind docking was employed to allow ligands to explore

the entire receptor surface, thus enhancing the likelihood of identifying novel binding pockets.

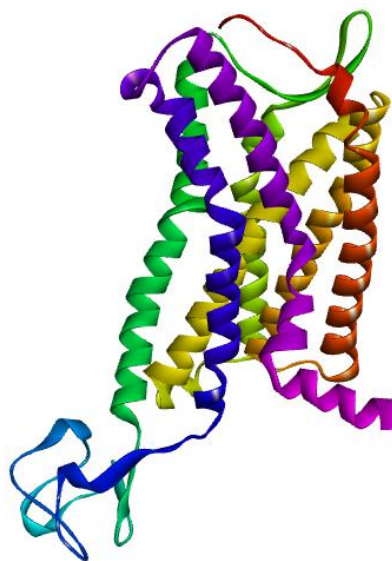


Figure-1. Crystal Structure of the CCR5 Chemokine Receptor (PDB ID: 4MBS)

Molecular Docking Procedure

Molecular docking studies were conducted using AutoDock 4.2, with AutoGrid 4 employed to generate the necessary grid maps for receptor-ligand interaction analysis. The docking protocol was based on the Lamarckian Genetic Algorithm (LGA), which combines a genetic search with local optimization to predict the most favorable binding conformations. For each ligand, a blind docking approach was implemented by designing a grid box large enough to encompass the entire surface of the CCR5 receptor, thereby allowing the ligand to explore all potential binding pockets without prior constraints. The docking simulations were executed using the default parameters of AutoDock. Specifically, ten independent genetic algorithm runs were carried out per ligand to enhance statistical reliability. Each run was initiated with a population size of 150 individuals, and the maximum number of energy evaluations permitted per run was set to 2,500,000. The maximum number of generations allowed for each simulation was 27,000. To maintain genetic diversity during the evolutionary process, a mutation rate of 0.02 and a crossover rate of 0.80 were applied. The grid spacing was fixed at 0.375 Å, which determined the resolution of the docking search space. Additionally, the algorithm allowed local search operations to refine docking poses, with 300 evaluations assigned to each local search and a frequency of 0.06, meaning 6% of the population

underwent local optimization in each generation. The top-ranking individual from each generation was preserved through elitism, ensuring that high-quality solutions were retained. All docking runs were conducted via command-line execution, and the resulting docking log files (.dlg) were stored for subsequent analysis of binding energies and interaction profiles.

Docking Analysis and Visualization

Post-docking visualization and interaction profiling were conducted using Biovia Discovery Studio Visualizer and AutoDockTools. Ligand-receptor complexes were analyzed to evaluate hydrogen bonds, hydrophobic contacts, and π - π stacking interactions. The interactions were further used to understand the binding orientation and pocket preferences of the docked ligands. These qualitative assessments supported the identification of compounds with favorable binding characteristics. The DLG files were parsed to extract the docking poses and their associated binding energy scores, which were then used for interpretation in subsequent sections.

RESULTS AND DISCUSSION

Pharmacophore Generation and Feature Mapping

The pharmacophore model was developed using the FDA-approved CCR5 antagonist Maraviroc as the reference molecule through the Pharmit web server (<https://pharmit.csb.pitt.edu/>). The generated pharmacophore consisted of critical chemical features essential for effective interaction with the CCR5 receptor, including hydrogen bond acceptors, hydrogen bond donors, hydrophobic centers, and aromatic ring features.

The Fig. 2 highlights six hydrophobic regions (depicted in green mesh), two hydrogen bond acceptors (shown in yellow), and one aromatic ring feature (in purple). These pharmacophoric features are spatially distributed to reflect the three-dimensional arrangement necessary for optimal binding within the CCR5 binding pocket. The hydrophobic spheres correspond to nonpolar regions of the molecule, which are likely to engage with hydrophobic amino acid residues in the receptor, thereby enhancing ligand stability and affinity. The hydrogen bond acceptors, positioned at either end of the molecule, suggest potential for polar

interactions with donor residues in the receptor's binding site, contributing to specificity and binding strength. The central aromatic ring may participate in π - π stacking or van der Waals interactions with aromatic residues in the CCR5 cavity. This model was instrumental in guiding virtual screening efforts, serving as a structural template to identify novel molecules from chemical libraries that mimic Maraviroc's critical pharmacophoric elements and could therefore act as competitive CCR5 inhibitors in HIV-1 therapy.

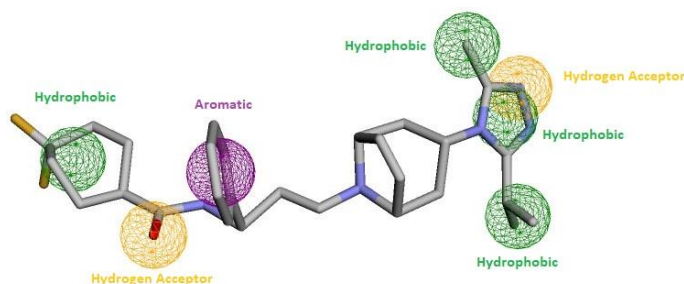


Figure-2. Pharmacophore Model of Maraviroc Highlighting Key Interaction Features for CCR5 Binding

Molecular Docking Analysis

Molecular docking of the 25 pharmacophore-derived ligands was performed against the CCR5 receptor (PDB ID: 4MBS) using AutoDock 4.2 under default Lamarckian Genetic Algorithm parameters. The docking scores (binding energies), hydrogen bond interactions, and hydrophobic contacts were extracted and analyzed for all compounds, with Maraviroc used as the reference standard.

The docking scores ranged from -7.2 kcal/mol to -11.2 kcal/mol, where a more negative value represents a stronger binding affinity. The most potent compound, ZINC000585110136, showed a binding energy of -11.2 kcal/mol, which is significantly more favorable than Maraviroc's -10.7 kcal/mol. Several other compounds such as ZINC000257285692 (-11.1 kcal/mol) and ZINC000585293311 (-10.3 kcal/mol) also exceeded the reference drug in terms of binding energy, indicating potential as competitive inhibitors of CCR5.

Hydrogen bonding plays a critical role in ligand stability within the receptor binding site. Maraviroc formed a key hydrogen bond with ASN258, whereas some candidate ligands like ZINC000011128466 and ZINC000036395352 exhibited multiple hydrogen

Table-1. Docking Scores and Interaction Profiles of Pharmacophore-Screened Ligands with CCR5 Receptor Compared to Maraviroc

S.No	Compound	Binding Energy	Hydrogen Bonds	Other Interactions
1	ZINC000011128466	-9.6	Gln280, Cys178	Ala29, Ala90, Ala92, Lys26, Tyr37, Tyr89, Tyr108, Leu33, Trp86, Ser179, Glu283, Thr284, Met287
2	ZINC000036395352	-9.4	Tyr37, Tyr251	Trp86, Tyr89, Tyr108, Phe109, Phe112, Glu283, Met287, Thr105, Ser179, Ser180, Trp248, Ile198
3	ZINC000003301695	-8.2	Gln280, Cys178	Ala29, Ala90, Lys26, Tyr37, Tyr89, Tyr108, Leu33, Trp86, Ser179, Ser180, Thr105, Thr167, Thr284, Phe109, Glu283
4	ZINC000029713350	-8.5	Tyr37	Val25, Lys26, Ala29, Leu33, Tyr89, Tyr108, Ala90, Gln280, Cys178, Trp86, Glu283, Met287, Phe109, Glu283
5	ZINC000011999212	-9.4	-	ALA90, TYR37, TYR89, TYR108, TYR251, TRP86, THR105, SER180, LEU33, LEU255, PHE109, PHE182, ASN163, ASN258, MET279, LYS191, GLN194, ILE198, THR195, THR259
6	ZINC000012154119	-9.2	Tyr251	Tyr37, Leu33, Tyr108, Trp86, Phe109, Glu283, Leu255, Tyr89, Tyr108, Ser180, Phe182, Cys178, Ile198, Met279, Met287, Thr105, Thr167
7	ZINC000055109427	-9.2	Ser180, Tyr251	Phe109, Phe112, Tyr108, Trp248, Trp86, Glu283, Gln280, Tyr89, Ala90
8	ZINC000032912004	-9.3	Tyr37	Trp86, Tyr108, Tyr89, Ala90, Thr105, Glu283, Gln280, Leu33, Thr284, Thr177
9	ZINC000012039822	-7.8	-	SER179, SER180, PHE109, PHE112, TYR108, TYR251, TRP248, TRP86, TYR89, TYR37, GLU283, ILE198, MET279, ALA90, LEU33
10	ZINC000585293311	-10.3	Ser180	Ser179, Phe182, Lys191, Tyr108, Trp86, Tyr37, Glu283, Phe109, Thr167, Thr105, Gln194, Leu255, Ile198, Met287, Tyr89, Thr195, Cys178
11	ZINC000023130954	-10.2	Ser180	Ser179, Phe109, Phe182, Tyr108, Trp86, Tyr37, Met287, Glu283, Thr105, Tyr251, Tyr89, Cys178, Ile198, Leu255, Met279
12	ZINC000021476730	-9.2	-	PHE182, LYS191, PHE109, TYR108, TRP86, TYR37, ALA90, LEU33, GLU283, SER180, ASN163, ILE198, GLN194, LEU255, THR195, THR105, TYR89
13	ZINC000009727197	-8.9	-	ASN163, GLN280, PHE109, PHE182, TYR108, TRP86, LEU33, TYR37, GLU283, SER180, SER179, THR105, THR167, GLN194, TYR251, MET279
14	ZINC000585110136	-11.2	-	PHE109, PHE112, TYR108, TRP248, TRP86, GLU283, GLN280, TYR89, ALA90
15	ZINC000005357334	-9	Tyr37, Tyr251	Leu33, Ala90, Tyr89, , Trp86, Glu283, Ile198, Phe112, Trp248, Phe109, Tyr108, Thr105, Ser179, Cys178

....Table-1. Docking Scores and Interaction Profiles of Pharmacophore-Screened Ligands with CCR5 Receptor Compared to Maraviroc

S.No	Compound	Binding Energy	Hydrogen Bonds	Other Interactions
16	ZINC000036700490	-9.8	Tyr251	Glu283, Met287, Trp86, Tyr37, Ser180, Ile198, Phe109, Phe112, Tyr108, Trp248
17	ZINC000257285692	-11.1	Tyr37,	Tyr108, Trp86, Met287, Thr105, Glu283, Phe109, Phe112, Tyr251, Ile198, Ser179, Thr167, Ser180, Tyr89
18	ZINC000028227217	-8.4	Tyr251	Leu33, Tyr37, Thr284, Gln280, Trp86, Glu283, Ser180, Tyr108, Thr105, Ser179, Phe109, Met279, Leu255, Phe182, Ile198
19	ZINC000120905422	-8.5	Tyr37	Tyr108, Ser180, Glu283, Phe182, Gln194, Leu255, Thr195, Ile198, Tyr251, Ser179, Thr105, Phe109, Trp86, Leu33, Ala90
20	ZINC000225813609	-8	Tyr37,	Ala90, Leu33, Tyr37, Tyr108, Glu283, Phe109, Thr105, Thr167, Ser179, Cys178
21	ZINC000011360615	-7.2	Tyr37,	Leu33, Met287, Ala90, Tyr108, Glu283, Trp86, Tyr89, Cys178, Ser179, Thr105, Tyr251, Phe109
22	ZINC000585110210	-9	Gln280,	Leu33, Ala90, Tyr37, Tyr89, Thr284, Glu283, Tyr108, Glu283, Phe109
23	ZINC000021336672	-9.4	Ser180, Tyr37	Ile198, Tyrp248, Tyr108, Phe109, Ser179, Cys178, Gln280, Thr284, Leu33, Ala90, Tyr89, Trp86, Met279, Tyr251, Glu283, Phe11
24	ZINC000025050777	-8.4	-	THR284, TRP86, MET287, TYR108, THR105, PHE109, PHE112, TRP248, ILE198, TYR251, TYR89, GLU283, TYR37
25	ZINC000004163293	-8.6	Gln280, Tyr37, Tyr108	Leu33, Glu283, Thr284, Met287, Trp86, Thr105, Phe109, Thr167, Ser180,
26	Maraviroc (FDA drug)	-10.7	Asn258	Thr86, Thr105, Phe112, Tyr108, Trp248, Phe109, Glu283, Tyr251, Ser180, Ile198, Thr259, Thr195, Lys191, Phe182, Gln194, Leu255, Trp86, Thr105

bonds with residues including GLN280, TYR37, and CYS178, which are positioned near the ligand-accessible channel of CCR5. These interactions not only help anchor the ligand but also influence specificity. However, several high-binding ligands, such as ZINC000585110136, achieved superior docking scores without forming hydrogen bonds,

relying predominantly on hydrophobic interactions for stabilization.

Hydrophobic interactions were pervasive among all strong binders, often involving residues such as TYR37, TYR89, TYR108, TRP86, PHE109, GLU283, and MET287. These amino acids appear repeatedly across multiple docked ligands, indicating they form the core hydrophobic binding

site of CCR5. Notably, these residues were also engaged by Maraviroc, validating the relevance of this hydrophobic pocket.

The molecular docking analysis revealed several ligands with strong binding affinities to the CCR5 receptor, surpassing or closely matching the performance of the standard FDA-approved drug Maraviroc, which recorded a docking score of -10.7 kcal/mol. Among the 25 compounds evaluated, ZINC000585110136 showed the most favorable binding energy at -11.2 kcal/mol, engaging a highly hydrophobic binding pocket with residues like PHE109, PHE112, TYR108, TRP248, and TRP86, despite the absence of hydrogen bonding, indicating that hydrophobic stabilization alone can drive strong binding. ZINC000257285692, with a docking score of -11.1 kcal/mol, formed a hydrogen bond with TYR37 and hydrophobic contacts with key residues including GLU283, MET287, PHE109, and TYR251, mimicking critical interactions observed with Maraviroc. Similarly, ZINC000585293311 (-10.3 kcal/mol) formed a hydrogen bond with SER180 and showed extensive hydrophobic interaction with TYR108, TRP86, PHE109, and THR105. ZINC000023130954 (-10.2 kcal/mol) demonstrated comparable performance, forming a hydrogen bond with SER180 and engaging residues like MET287, CYS178, and PHE182. ZINC000036700490 (-9.8 kcal/mol) also exhibited significant interaction with conserved receptor residues, including TYR108 and GLU283. These top ligands not only demonstrated strong binding energies but also displayed favorable interaction profiles through hydrophobic and polar contacts within the CCR5 receptor, many overlapping with those of Maraviroc, thus validating their potential as novel CCR5 inhibitors with promising therapeutic relevance.

When compared to Maraviroc, many test compounds demonstrated competitive or superior binding energies, broader hydrophobic engagement, and, in some cases, richer hydrogen bonding profiles. The findings highlight several ligands that could serve as lead scaffolds for future CCR5 inhibitor development. In conclusion, molecular docking identified promising CCR5 binders, and their interaction profiles aligned well with the pharmacophoric characteristics derived from Maraviroc, substantiating the virtual screening and docking methodology.

The CCR5 receptor has remained a critical target in HIV-1 therapeutic strategies due to its essential

role in viral entry. Our study aimed to leverage ligand-based pharmacophore modeling and molecular docking to identify novel CCR5 antagonists with high binding affinity and favorable drug-likeness. A similar approach was adopted by Kumar and Mamidala (2025), who demonstrated that ligand-based pharmacophore models derived from Maraviroc could guide the identification of new HIV entry inhibitors, with several compounds showing superior predicted inhibition constants. Their study reinforces our findings where pharmacophore screening followed by docking yielded ligands such as ZINC000585110136 and ZINC000257285692 with stronger binding scores than Maraviroc. The effectiveness of this dual strategy has been highlighted as a cost-effective alternative to early-stage wet-lab screening, especially in the context of HIV therapy where structural variability among viral strains requires robust virtual methods to pre-validate lead candidates (Eid et al., 2024; Kaipule et al., 2020; Janakiramulu et al., 2025). The inclusion of diverse hydrophobic and aromatic features in our pharmacophore model ensured a broader range of structural matches during ZINC database screening, aligning with prior research that emphasizes the role of hydrophobic patches in CCR5 binding (Mallakuntla et al., 2022; Swapna et al., 2024).

Comparative analysis of our docking results with recent molecular docking studies suggests that several of our candidate ligands have therapeutic potential beyond the known benchmark of Maraviroc. In a comprehensive *in silico* screening by Dyvapu et al. (2024), several ligands outperformed Maraviroc in docking energy but lacked hydrogen bonding interactions with core CCR5 residues. In contrast, our top-performing compounds such as ZINC000257285692 not only exhibited stronger binding affinities (-11.1 kcal/mol) but also formed stabilizing hydrogen bonds with residues like TYR37 and TYR251, which are known to enhance selectivity and affinity. Furthermore, studies by Parulekar et al. (2022) showed that analogs designed from Maraviroc's scaffold required a balance between hydrogen bond interactions and hydrophobic contacts to ensure activity and receptor specificity. This interplay was well observed in our docking simulations, particularly among ligands like ZINC000585293311, which integrated both interaction modes to achieve efficient binding. These results suggest that our approach is consistent with current pharmacophore optimization principles and

highlights compounds with improved binding landscapes that merit further biochemical validation.

Beyond docking scores, it is critical to consider how interaction residues correlate with receptor activation or inhibition. Studies such as that by Hoelz et al. (2021) and Swapna et al., (2024) on pyrrole-based HIV inhibitors demonstrated that TYR108, PHE109, and GLU283 are conserved hotspots in the CCR5 binding pocket. In our study, these residues were consistently engaged by top ligands, further validating their relevance in stabilizing antagonist binding. Additionally, Appiah-Kubi and Iwuchukwu (2022) emphasized the importance of targeting allosteric sub-pockets within CCR5 to overcome resistance mutations—a strategy indirectly supported by our blind docking approach, which allowed the ligands to freely explore the receptor surface. Our identification of ligands with high binding energies and critical residue engagement offers a strong foundation for structure-guided optimization, potentially leading to candidates with improved efficacy in clinical scenarios where Maraviroc's effectiveness diminishes. Ultimately, our findings reinforce that virtual screening integrated with validated pharmacophore models can serve as a rapid, cost-efficient, and reliable platform for discovering next-generation CCR5 inhibitors, and should be followed by molecular dynamics simulations and in vitro assays for further validation.

CONCLUSION

The present study utilized a structure-based virtual screening approach integrating pharmacophore modeling and molecular docking to identify novel CCR5 receptor antagonists with potential anti-HIV activity. Using Maraviroc as the reference compound, a pharmacophore model was generated and used to screen the ZINC database for drug-like candidates. Twenty-five hits were shortlisted and docked against CCR5 using AutoDock 4.2, revealing several compounds with binding affinities superior to that of Maraviroc. The top ligands, including ZINC000585110136 and ZINC000257285692, demonstrated strong binding energies, rich hydrophobic interactions, and engagement with key receptor residues such as TYR108, GLU283, and PHE109, which are critical for receptor inhibition. The presence of both hydrophobic stabilization and selective hydrogen bonding in top candidates supports their role as

promising CCR5 antagonists. These findings validate the applied in silico methodology and lay the foundation for further experimental validation through molecular dynamics simulations and in vitro assays. Overall, this computational framework provides a cost-effective and efficient strategy for discovering and optimizing next-generation HIV-1 entry inhibitors targeting the CCR5 co-receptor.

Conflicts of Interest

Authors declare that there is no conflict of interests regarding the publication of this paper.

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