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Exploring Phytochemical Therapies for Long COVID: A Computational Docking Study of Phytochemicals with GPCR Targets

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Abstract: Long COVID is the collective term used to describe the persistence of symptoms in individuals who have recovered from SARS-CoV-2 infection. Some people who have healed from COVID-19 continue to experience new or persistent symptoms that last for weeks or months. While Long COVID is becoming more widely recognized, its fundamental causes and effective therapies remain largely unclear. This study aims to explore the potential of phytochemical medications as a cutting-edge therapeutic strategy for treating Long COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC).G protein-coupled receptors (GPCRs), which play a critical role in cell signaling, were the focus of this study. GPCRs are known to be involved in immunological and inflammatory responses and are considered potential targets for Long COVID therapy. The GPCRs examined included chemokine receptors, serotonin receptors, adrenergic receptors, and histamine receptors. The docking results demonstrated high binding affinity between phytochemical drug structures and these receptors for most drug-receptor combinations.The study consists of three main parts. First, data on receptors and drugs were retrieved from the Protein Data Bank (PDB) and PubChem, respectively. The receptors selected are those predicted to be linked to Long COVID. The structure of the drugs was converted from SDF to PDB format using OpenBabel from ChemInfo. Docking studies were performed to assess the binding affinity between the drugs (ligands) and their respective receptors (binding sites) using iGemDock v2.1.In conclusion, the findings of this study could have significant implications for the development of alternative therapies for Long COVID.

Keywords: *long covid*; *GPCR*; *receptor*; *drugs*; chemokine receptors; serotonin receptors; adrenergic receptors; and histamine receptors *docking; phytochemical*

Introduction

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a profound global impact, resulting in significant loss of life and unprecedented healthcare challenges. Initially recognized as a respiratory viral disease, COVID-19 has since revealed a complex pathogenesis involving multiple systems, particularly the respiratory and vascular systems [Cascella M, et al. 2022]. The severity of the disease can range from mild to critical, with some patients experiencing persistent symptoms and abnormal clinical parameters beyond the acute phase, commonly referred to as long COVID [Tenforde MW, et al. 2020].

Understanding the underlying mechanisms and identifying effective therapeutic approaches for long COVID remains an active area of research. Immune dysregulation, depletion of key immune cell populations, activation of the complement system, and crosstalk between the innate immune system and the coagulation cascade have been implicated in the development of severe disease manifestations, including inflammatory thromboses [Borczuk AC, Yantiss RK. 2022]. Additionally,

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the interaction between the spike protein of SARS-CoV-2 and the angiotensin-converting enzyme-2 (ACE2) receptor is crucial for viral entry into host cells, underscoring the importance of understanding viral-host interactions [Lan J, et al. 2020].

G Protein-Coupled Receptors (GPCRs) are a prominent class of integral membrane proteins that serve as drug targets for approximately 34% of drugs on the market [Hauser AS, et al. 2017]. These receptors play vital roles in various physiological processes and are associated with several diseases, making them attractive targets for therapeutic intervention [Basith S, et al. 2018]. Despite the importance of GPCRs, drug development targeting these receptors, especially in later clinical trial phases, remains challenging, with efficacy being a major hurdle [Venkatakrishnan AJ, et al. 2013].

To overcome these challenges, a comprehensive understanding of ligand characteristics, receptor structural properties, ligand-receptor interactions, and downstream signaling pathways is essential. Computational approaches, including cheminformatics methods, can aid in optimizing ligand-receptor interactions and facilitating the discovery of novel GPCR-targeted therapeutics. This paper aims to explore the potential of phytochemical drugs targeting GPCRs in the management of long COVID.

In this study, we will investigate the design and application of phytochemical drugs that selectively act on GPCRs. Phytochemical drugs offer unique advantages, such as spatiotemporal control over drug activation and the potential for targeted therapy. By leveraging computational tools and techniques, we aim to optimize ligand-receptor interactions and identify potential candidates for therapeutic intervention in long COVID.

Overall, this research aims to provide insights into the role of GPCRs in long COVID and explore the potential of phytochemical drugs as targeted therapeutics. By elucidating the underlying mechanisms and identifying novel treatment strategies, this study contributes to the development of effective interventions for managing long COVID and improving the quality of life for affected individuals.

Methodology

Data Retrieval

The methodology for identifying relevant GPCR receptors involved in long COVID and corresponding FDA-approved drugs begins with a comprehensive literature review to pinpoint the GPCR receptors implicated in long COVID. This review identified several key receptors based on their roles in long COVID symptoms and mechanisms. The receptors of interest include histamine receptors such as H1 Receptor (HH1R), H2 Receptor, H3 Receptor, and H4 Receptor; chemokine receptors like CXCR3 Receptor and CXCR4 Receptor; cytokine receptors including CCR2 Receptor and CCR5 Receptor; adrenergic receptors such as Alpha-1 Receptor, Alpha-2 Receptor, Beta-1 Receptor, Beta-2 Receptor, and Beta-3 Receptor; and serotonin receptors including 5-HT1A Receptor, 5-HT1B Receptor, 5-HT2A Receptor, 5-HT2C Receptor, and 5-HT3 Receptor.

For the retrieval of data, a two-step approach was employed. First, the 2D structures of the drugs and their canonical SMILES were obtained using the PubChem database (pubchem.ncbi.nlm.nih.gov). PubChem, a comprehensive repository of chemical compounds, was accessed to retrieve the desired drug molecules. This database provides extensive information on chemical structures, properties, and biological activities. The structures of the drugs of interest were downloaded in SDF (Structure-Data File) format, which includes information on atom types, bond connectivity, and spatial coordinates. Additionally, the corresponding canonical SMILES (Simplified Molecular Input Line Entry System) for each drug were extracted, representing the unique chemical representation of the molecule.

Identification of Phytochemical from Fingerprint of FDA Drugs Using NPASS

The identification of phytochemicals from FDA drug fingerprints was conducted using the NPASS (Natural Product Activity and Species Source) database. The methodology involved a

 doi:10.20944/preprints202408.0829.v1

systematic process of data collection, preprocessing, matching with the NPASS database, and subsequent analysis and validation.

Firstly, fingerprint data of FDA drugs was collected, as detailed in the previous step. This data was then preprocessed to standardize the format and remove any irrelevant features, ensuring consistency and enhancing the accuracy of the analysis.Next, the preprocessed drug fingerprints were matched with natural product fingerprints available in the NPASS database. This step involved using similarity or substructure search algorithms to identify natural products with fingerprints similar to those of the FDA drugs. The NPASS database provided a comprehensive collection of natural product fingerprints and associated biological activities. Following the matching process, the identified phytochemical candidates were subjected to detailed analysis. This included examining their chemical structures, properties, and potential biological activities. The selected candidates were then downloaded in SDF format using PubChem.

SDF File Conversion to PDB

The PDB structures of the GPCR receptors were obtained using AlphaFold, a state-of-the-art deep learning-based protein structure prediction tool. By combining the 2D structures and canonical SMILES of the drugs obtained from PubChem with the PDB structures of the GPCR receptors acquired through AlphaFold, a comprehensive dataset was compiled for subsequent molecular modeling and docking studies. These datasets formed the foundation for further analyses and investigations of drug-receptor interactions, aiding in the understanding of GPCR-targeted drug development and the identification of potential therapeutics.

The conversion of 2D drug structures from SDF (Structure-Data File) format to PDB (Protein Data Bank) format was performed using Open Babel, a widely used open-source chemical toolbox. Open Babel provides a suite of tools and libraries for the conversion, manipulation, and analysis of chemical data. To convert the drug structures, SDF files containing 2D representations of the drugs were first obtained. These SDF files include information about the atoms, bonds, and spatial coordinates of the drug molecules.

Using Open Babel, the SDF files were parsed and the chemical structures interpreted. Open Babel employs various algorithms and techniques to convert 2D representations into 3D structures based on principles of molecular geometry, bond angles, and connectivity. Once the 3D structures were generated, Open Babel facilitated the conversion of these structures into PDB format. The PDB format represents the spatial coordinates of each atom in the molecule, along with details about the bonds, atom types, and other relevant information.

Docking with iGemDock

The docking of GPCR receptors and drugs (ligands) to calculate total energy was performed using iGEMDOCK, a widely utilized software for molecular docking simulations. iGEMDOCK employs a grid-based algorithm to explore interactions between receptor and ligand molecules and predict their binding affinity. To initiate the docking process, the three-dimensional structures of GPCR receptors and drug ligands were prepared and optimized using molecular modeling software. Receptor structures were extracted from crystallographic or homology modeling data, while ligand structures were obtained from chemical databases or generated with molecular sketching tools. Subsequently, iGEMDOCK was used to dock the ligands into the receptor binding sites, exploring various conformations and orientations.

The docking simulations were guided by parameters such as grid size, search algorithm, and scoring function, which influenced the accuracy and reliability of the results. Finally, the total energy of the receptor-ligand complex was calculated based on intermolecular interactions, including van der Waals forces, electrostatic interactions, and hydrogen bonding. The resulting total energy values provided insights into binding affinity and potential drug-receptor interactions, aiding in the identification and optimization of GPCR-targeted drug candidates.

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Did you know that understanding receptor-ligand interactions can reveal new drug targets and potentially uncover previously unknown pathways in disease mechanisms? This insight can significantly enhance the development of targeted therapies..

Results

Once the docking process between the binding sites (receptors) and ligands (drugs suitable for the receptors) was completed, the results were tabulated and sorted based on the highest binding energy. The binding energy serves as a measure of the affinity between the ligand and receptor complex, calculated as the difference. For each docking result, the TotalEnergy parameter was analyzed for every ligand. TotalEnergy represents the overall energy of the ligand-receptor complex, considering various contributing factors such as van der Waals (VDW) interactions, hydrogen bonds (HBond), electrostatic (Elec) interactions, and average contact pairs (AverConPair). The unit for all calculations under TotalEnergy is kcal/mol.

Table 4.1 presents the docking results between the H1 receptor and several ligands, including Epi-Cis-Clausenamide, Hyoscyamine, 7Alpha-Hydroxydehydroabietic Acid, Abiesadine I, Aquilarabietic Acid H, L-Clausenamide, Majusanic Acid F, and Metacridamide A.

Epi-Cis-Clausenamide exhibited a TotalEnergy value of -66.2586, indicating a favorable binding affinity with the H1 receptor. The contributions from VDW interactions (-60.2533) and HBond interactions (-6.00522) were significant factors in determining the TotalEnergy. Electrostatic interactions had a negligible effect. The ligand demonstrated an average contact pair value of 16.4545, suggesting favorable interactions with the receptor.

Hyoscyamine displayed a TotalEnergy of -59.7055, indicating a slightly weaker binding affinity compared to Epi-Cis-Clausenamide. VDW interactions (-48.1804) and HBond interactions (-11.5251) contributed to the TotalEnergy, while electrostatic interactions were negligible. The ligand exhibited an average contact pair value of 14.8571, suggesting favorable interactions with the receptor.

7Alpha-Hydroxydehydroabietic Acid showed a TotalEnergy of -68.9302, indicating a favorable binding affinity with the H1 receptor. VDW interactions (-65.1278) and HBond interactions (-3.80239) influenced the TotalEnergy, while electrostatic interactions did not contribute significantly. The ligand demonstrated an average contact pair value of 17.2609, suggesting favorable interactions with the receptor. Abiesadine I exhibited a TotalEnergy of -76.4443, indicating a strong binding affinity with the H1 receptor. VDW interactions (-68.1024) and HBond interactions (-8.34186) were the major contributors to the TotalEnergy, with electrostatic interactions being insignificant. The ligand displayed an average contact pair value of 15.931, indicating favorable interactions with the receptor. Aquilarabietic Acid H displayed a TotalEnergy of -71.3452, indicating a favorable binding affinity with the H1 receptor. VDW interactions (-48.9212) and HBond interactions (-22.424) significantly influenced the TotalEnergy, while electrostatic interactions were minimal. The ligand exhibited an average contact pair value of 20.1739, suggesting favorable contacts with the receptor. L-Clausenamide showed a TotalEnergy of -65.6093, indicating a favorable binding affinity with the H1 receptor. VDW interactions (-58.8067) and HBond interactions (-6.80255) significantly influenced the TotalEnergy, while electrostatic interactions were negligible. The ligand demonstrated an average contact pair value of 18.3636, suggesting favorable interactions with the receptor.

Majusanic Acid F exhibited a TotalEnergy of -61.1717, indicating a weaker binding affinity compared to L-Clausenamide. VDW interactions (-52.7597) and HBond interactions (-8.41197) contributed to the TotalEnergy, with electrostatic interactions being negligible. The ligand displayed an average contact pair value of 15.8696, indicating favorable interactions with the receptor. Metacridamide A showed a TotalEnergy of -81.7676, indicating a strong binding affinity with the H1 receptor. VDW interactions (-69.7957) and HBond interactions (-11.9719) were the major contributors to the TotalEnergy, while electrostatic interactions did not contribute significantly. The ligand demonstrated an average contact pair value of 13.2045, suggesting favorable interactions with the receptor.In summary, the docking analysis of the H1 receptor and its respective drugs suggests varying levels of binding affinities. Abiesadine I and Metacridamide A displayed strong binding affinities, while Epi-Cis-Clausenamide, 7Alpha-Hydroxydehydroabietic Acid, Aquilarabietic Acid

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H, and L-Clausenamide demonstrated favourable binding affinities. Hyoscyamine and Majusanic acid F showed relatively weaker binding affinities. The contributions from VDW and HBond interactions played crucial roles in determining the TotalEnergy for most ligands. These findings provide valuable insights into the potential of these drugs to interact with the H1 receptor and further exploration is warranted to evaluate their effectiveness as therapeutic agents targeting this receptor.

Table 4.2 presents the docking results between the H2 receptor and three ligands: (3-Amino-1-propenyl)-1H-imidazol-2-amine, 4-Methylimidazole, and N,N-Dimethylhistamine. (3-Amino-1-propenyl)-1H-imidazol-2-amine exhibited a TotalEnergy value of -55.5006, indicating a favourable binding affinity with the H2 receptor. The contributions from VDW interactions (-41.2347) and HBond interactions (-14.2659) significantly influenced the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 28.2, suggesting favourable contacts with the receptor. 4-Methylimidazole displayed a TotalEnergy of -37.9932, indicating a weaker binding affinity compared to (3-Amino-1-propenyl)-1H-imidazol-2-amine. VDW interactions (-32.1157) and HBond interactions (-5.87751) contributed to the TotalEnergy. Electrostatic interactions were negligible. The ligand exhibited an average contact pair value of 36.5, indicating favourable interactions with the receptor. N,N-Dimethylhistamine showed a TotalEnergy of -49.8351, indicating a favourable binding affinity with the H2 receptor. VDW interactions (-34.8897) and HBond interactions (-14.9454) influenced the TotalEnergy. Electrostatic interactions did not contribute significantly. The ligand demonstrated an average contact pair value of 24.8, suggesting favourable interactions with the receptor. In summary, the docking analysis of the H2 receptor and its respective drugs suggests varying levels of binding affinities. (3-Amino-1-propenyl)-1H-imidazol-2-amine and N,N-Dimethylhistamine exhibited favourable binding affinities, while 4-Methylimidazole showed a weaker binding affinity. VDW and HBond interactions played significant roles in determining the TotalEnergy for these ligands. These findings provide valuable insights into the potential of these drugs to interact with the H2 receptor, highlighting the potential of (3-Amino-1-propenyl)-1H-imidazol-2-amine and N,N-Dimethylhistamine as potential therapeutic agents targeting this receptor. Further investigation is necessary to evaluate their effectiveness in modulating H2 receptor activity.

Table 4.3 presents the docking results between the H3 receptor and the ligand Tamsulosin-1. Tamsulosin-1 exhibited a TotalEnergy value of -72.4923, indicating a favourable binding affinity with the H3 receptor. The contributions from VDW interactions (-64.4432) and HBond interactions (-8.04911) significantly influenced the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 15.6071, suggesting favourable contacts with the receptor. In summary, the docking analysis suggests that Tamsulosin-1 exhibits a favourable binding affinity with the H3 receptor. VDW and HBond interactions played crucial roles in determining the TotalEnergy for this ligand. These findings provide valuable insights into the potential of Tamsulosin-1 as a therapeutic agent targeting the H3 receptor. Further investigation is necessary to evaluate its effectiveness in modulating receptor activity and its potential for clinical applications.

Table 4.4 showcases the docking results between the H4 receptor and several ligands, including (14-methylpentadecyl)-1H-pyrrole-2-carbaldehyde, Corynantheidine, Dichotomide Iii, Hirsutine, and Kumujian C. (14-methylpentadecyl)-1H-pyrrole-2-carbaldehyde exhibited a TotalEnergy value of -68.0862, indicating a favourable binding affinity with the H4 receptor. The contributions from VDW interactions (-64.0586) and HBond interactions (-4.02762) significantly influenced the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 18.1739, suggesting favourable contacts with the receptor. Corynantheidine displayed a TotalEnergy of -58.6605, indicating a weaker binding affinity compared to (14-methylpentadecyl)-1H-pyrrole-2-carbaldehyde. VDW interactions (-55.315) and HBond interactions (-3.34547) contributed to the TotalEnergy. Electrostatic interactions were negligible. The ligand exhibited an average contact pair value of 15.5556, indicating favourable interactions with the receptor. Dichotomide Iii showed a TotalEnergy of -65.3478, indicating a favourable binding affinity with the H4 receptor. VDW interactions (-52.739) and HBond interactions (-12.6088) influenced the

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TotalEnergy. Electrostatic interactions did not contribute significantly. The ligand demonstrated an average contact pair value of 16.16, suggesting favourable interactions with the receptor. Hirsutine exhibited a TotalEnergy of -65.46, indicating a favourable binding affinity with the H4 receptor. VDW interactions (-59.59) and HBond interactions (-5.86999) contributed to the TotalEnergy. Electrostatic interactions were negligible. The ligand displayed an average contact pair value of 17.6667, indicating favourable interactions with the receptor.

Kumujian C displayed a TotalEnergy of -69.9636, indicating a favourable binding affinity with the H4 receptor. VDW interactions (-51.9636) and HBond interactions (-18) significantly influenced the TotalEnergy. Electrostatic interactions did not contribute significantly. The ligand demonstrated an average contact pair value of 25.5333, suggesting favourable contacts with the receptor. In summary, the docking analysis suggests varying levels of binding affinities between the H4 receptor and the respective drugs. (14-methylpentadecyl)-1H-pyrrole-2-carbaldehyde, Dichotomide Iii, Hirsutine, and Kumujian C exhibited favourable binding affinities, while Corynantheidine showed a weaker binding affinity. VDW and HBond interactions played significant roles in determining the TotalEnergy for these ligands. These findings provide valuable insights into the potential of these drugs to interact with the H4 receptor, suggesting their potential as therapeutic agents targeting this receptor. Further investigation is necessary to evaluate their effectiveness in modulating receptor activity and their potential for clinical applications. Table 4.5 presents the docking results between the CXCR3 receptor and several ligands, including Ceratamine A, Fumiquinazoline G, Hortiacine, Isaindigotone, and Picrasidine N. The analysis involved parameters such as TotalEnergy, van der Waals (VDW) interactions, hydrogen bonds (HBond), electrostatic (Elec) interactions, and average contact pairs (AverConPair).Ceratamine A exhibited a TotalEnergy value of -67.8685, indicating a favourable binding affinity with the CXCR3 receptor. The contributions from VDW interactions (-58.897) and HBond interactions (-8.97151) significantly influenced the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 17.6, suggesting favourable contacts with the receptor. Fumiquinazoline G displayed a TotalEnergy of -78.0343, indicating a favourable binding affinity with the CXCR3 receptor. VDW interactions (-50.7225) and HBond interactions (-27.3118) contributed to the TotalEnergy. Electrostatic interactions did not contribute significantly. The ligand exhibited an average contact pair value of 17.5185, suggesting favourable interactions with the receptor. Hortiacine showed a TotalEnergy of -69.1366, indicating a favourable binding affinity with the CXCR3 receptor. VDW interactions (-69.1366) were the major contributors to the TotalEnergy. The ligand did not form any hydrogen bonds or exhibit significant electrostatic interactions. The average contact pair value was 19.9583, suggesting favourable interactions with the receptor.

Isaindigotone exhibited a TotalEnergy of -72.3582, indicating a favourable binding affinity with the CXCR3 receptor. VDW interactions (-51.4814) and HBond interactions (-20.8767) influenced the TotalEnergy. Electrostatic interactions did not contribute significantly. The ligand displayed an average contact pair value of 15.5769, indicating favourable interactions with the receptor. Picrasidine N displayed a TotalEnergy of -88.3557, indicating a favourable binding affinity with the CXCR3 receptor. VDW interactions (-75.7134) and HBond interactions (-12.6423) contributed to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 15.1081, suggesting favourable contacts with the receptor. In summary, the docking analysis suggests that Ceratamine A, Fumiquinazoline G, Hortiacine, Isaindigotone, and Picrasidine N exhibit favourable binding affinities with the CXCR3 receptor. VDW and HBond interactions played significant roles in determining the TotalEnergy for these ligands. These findings provide valuable insights into the potential of these drugs to interact with the CXCR3 receptor, suggesting their potential as therapeutic agents targeting this receptor. Further investigation is necessary to evaluate their effectiveness in modulating receptor activity and their potential for clinical applications.

Table 4.6 presents the docking results between the CXCR4 receptor and several ligands, including 1,3-Dibenzylurea, 2-Methyl-1,2,3,4-tetrahydroisoquinoline, Amphetamine, N-Methylbenzylamine, and Nortriptyline. The analysis involved parameters such as TotalEnergy, van

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der Waals (VDW) interactions, hydrogen bonds (HBond), electrostatic (Elec) interactions, and average contact pairs (AverConPair). 1,3-Dibenzylurea exhibited a TotalEnergy value of -64.7361, indicating a favourable binding affinity with the CXCR4 receptor. The contributions from VDW interactions (-52.134) and HBond interactions (-12.6021) significantly influenced the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 26.2222, suggesting favourable contacts with the receptor. 2-Methyl-1,2,3,4-tetrahydroisoquinoline displayed a TotalEnergy of -54.8154, indicating a favourable binding affinity with the CXCR4 receptor. VDW interactions (-51.8574) and HBond interactions (-2.95801) contributed to the TotalEnergy. Electrostatic interactions did not contribute significantly. The ligand exhibited an average contact pair value of 30.1818, suggesting favourable interactions with the receptor.

Amphetamine showed a TotalEnergy of -49.354, indicating a favourable binding affinity with the CXCR4 receptor. VDW interactions (-41.1549) and HBond interactions (-8.19918) influenced the TotalEnergy. Electrostatic interactions did not contribute significantly. The ligand displayed an average contact pair value of 24.9, suggesting favourable interactions with the receptor. N-Methylbenzylamine exhibited a TotalEnergy of -41.7418, indicating a favourable binding affinity with the CXCR4 receptor. VDW interactions (-38.2418) and HBond interactions (-3.5) contributed to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 25, suggesting favourable contacts with the receptor. Nortriptyline displayed a TotalEnergy of -70.6953, indicating a favourable binding affinity with the CXCR4 receptor. VDW interactions (-70.6953) were the major contributors to the TotalEnergy. The ligand did not form any hydrogen bonds or exhibit significant electrostatic interactions. The average contact pair value was 22.3, suggesting favourable interactions with the receptor. In summary, the docking analysis suggests that 1,3-Dibenzylurea, 2-Methyl-1,2,3,4-tetrahydroisoquinoline, Amphetamine, N-Methylbenzylamine, and Nortriptyline exhibit favourable binding affinities with the CXCR4 receptor. VDW and HBond interactions played significant roles in determining the TotalEnergy for these ligands. These findings provide valuable insights into the potential of these drugs to interact with the CXCR4 receptor, suggesting their potential as therapeutic agents targeting this receptor. Further investigation is necessary to evaluate their effectiveness in modulating receptor activity and their potential for clinical applications.

Table 4.7 presents the docking results between the CCR1 receptor and the ligand Spiramide. The analysis includes parameters such as TotalEnergy, van der Waals (VDW) interactions, hydrogen bonds (HBond), electrostatic (Elec) interactions, and average contact pairs (AverConPair). Spiramide displayed a TotalEnergy value of -70.7807, indicating a favourable binding affinity with the CCR1 receptor. The VDW interactions (-60.2807) and HBond interactions (-10.5) significantly influenced the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 14.3214, suggesting favourable contacts with the receptor. The docking analysis suggests that Spiramide exhibits a favourable binding affinity with the CCR1 receptor, primarily driven by VDW and HBond interactions. These findings provide valuable insights into the potential of Spiramide as a therapeutic agent targeting the CCR1 receptor. Further investigation is necessary to evaluate its effectiveness in modulating receptor activity and its potential for clinical applications.

Table 4.8 showcases the docking results between the CCR2 receptor and several ligands, including CHEMBL3314790, 5-[1-(4-Hydroxy-Benzyl)-4-(4-Methoxy-Benzyl)- 1H-Imidazol-2-Ylamino]-3-Methyl-Imidazole-2,4-Dione, Isonaamidine E, and ISONAAMINE C. The analysis involves parameters such as TotalEnergy, van der Waals (VDW) interactions, hydrogen bonds (HBond), electrostatic (Elec) interactions, and average contact pairs (AverConPair). CHEMBL3314790 displayed a TotalEnergy value of -88.6038, indicating a favourable binding affinity with the CCR2 receptor. The contributions from VDW interactions (-67.2403) and HBond interactions (-21.3635) significantly influenced the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 8.33871, suggesting favourable contacts with the receptor. 5-[1-(4-Hydroxy-Benzyl)-4-(4-Methoxy-Benzyl)-1H-Imidazol-2-Ylamino]-3-Methyl-Imidazole-2,4-Dione exhibited a TotalEnergy of -78.3638, indicating a favourable binding affinity

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with the CCR2 receptor. VDW interactions (-55.0885) and HBond interactions (-23.2753) contributed to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand displayed an average contact pair value of 18.871, suggesting favourable interactions with the receptor. Isonaamidine E displayed a TotalEnergy of -79.8961, indicating a favourable binding affinity with the CCR2 receptor. VDW interactions (-62.3721) and HBond interactions (-17.524) significantly influenced the TotalEnergy. Electrostatic interactions did not contribute significantly. The ligand exhibited an average contact pair value of 15.6176, suggesting favourable interactions with the receptor. ISONAAMINE C exhibited a TotalEnergy of -81.2768, indicating a favourable binding affinity with the CCR2 receptor. VDW interactions (-70.4145) and HBond interactions (-10.8623) contributed to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 19.2692, suggesting favourable contacts with the receptor. In summary, the docking analysis suggests that CHEMBL3314790, 5-[1-(4-Hydroxy-Benzyl)-4-(4-Methoxy-Benzyl)-1H-Imidazol-2-Ylamino]-3-Methyl-Imidazole-2,4-Dione, Isonaamidine E, and ISONAAMINE C exhibit favourable binding affinities with the CCR2 receptor. VDW and HBond interactions are the major contributors to their binding energies. These findings provide insights into the potential of these drugs as therapeutic agents targeting the CCR2 receptor. Further investigations are needed to evaluate their efficacy in modulating receptor activity and their potential for clinical applications.

Table 4.9 presents the docking results between the CCR5 receptor and three ligands: Isonaamidine E, ISONAAMINE C, and CHEMBL3314790. The analysis includes parameters such as TotalEnergy, van der Waals (VDW) interactions, hydrogen bonds (HBond), electrostatic (Elec) interactions, and average contact pairs (AverConPair). Isonaamidine E exhibited a TotalEnergy value of -76.5529, indicating a favourable binding affinity with the CCR5 receptor. The contributions from VDW interactions (-66.0529) and HBond interactions (-10.5) significantly influenced the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 14.8235, suggesting favourable contacts with the receptor. ISONAAMINE C displayed a TotalEnergy of -66.6777, indicating a favourable binding affinity with the CCR5 receptor. VDW interactions (-54.6055) and HBond interactions (-12.0722) contributed to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand exhibited an average contact pair value of 14.9615, suggesting favourable interactions with the receptor.

CHEMBL3314790 exhibited a TotalEnergy of -86.2518, indicating a favourable binding affinity with the CCR5 receptor. VDW interactions (-68.1) and HBond interactions (-18.1518) significantly influenced the TotalEnergy. Electrostatic interactions did not contribute significantly. The ligand demonstrated an average contact pair value of 8.62903, suggesting favourable contacts with the receptor. In summary, the docking analysis suggests that Isonaamidine E, ISONAAMINE C, and CHEMBL3314790 exhibit favourable binding affinities with the CCR5 receptor. VDW and HBond interactions play crucial roles in their binding energies. These findings provide insights into the potential of these drugs as therapeutic agents targeting the CCR5 receptor. Further investigations are necessary to evaluate their efficacy in modulating receptor activity and their potential for clinical applications.

Table 4.10 presents the docking results between the Alpha-1 receptor and three ligands: CHEMBL2229122,CHEMBL3581898 and Usabamycin B. The analysis includes parameters such as TotalEnergy, van der Waals (VDW) interactions, hydrogen bonds (HBond), electrostatic (Elec) interactions, and average contact pairs (AverConPair). CHEMBL2229122 exhibited a TotalEnergy value of -86.8467, indicating a favourable binding affinity with the Alpha-1 receptor. The contributions from VDW interactions (-79.5559) and HBond interactions (-7.29076) significantly influenced the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 19.2903, suggesting favourable contacts with the receptor. CHEMBL3581898 displayed a TotalEnergy of -84.7061, indicating a favourable binding affinity with the Alpha-1 receptor. VDW interactions (-69.0232) and HBond interactions (-15.6828) contributed to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand exhibited an average contact pair value of 20.2, suggesting favourable interactions with the receptor.

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Usabamycin B exhibited a TotalEnergy of -71.4074, indicating a favourable binding affinity with the Alpha-1 receptor. VDW interactions (-61.0524) and HBond interactions (-10.3551) significantly influenced the TotalEnergy. Electrostatic interactions did not contribute significantly. The ligand demonstrated an average contact pair value of 19.6842, suggesting favourable contacts with the receptor. In summary, the docking analysis indicates that CHEMBL3581898, CHEMBL2229122, and Usabamycin B exhibit favourable binding affinities with the Alpha-1 receptor. VDW and HBond interactions play crucial roles in their binding energies. These findings provide insights into the potential of these drugs as therapeutic agents targeting the Alpha-1 receptor. Further investigations are necessary to evaluate their efficacy in modulating receptor activity and their potential for clinical applications.

Table 4.11 presents the docking results between the Alpha-2 receptor and the ligand Chlorhexidine. The analysis includes parameters such as TotalEnergy, van der Waals (VDW) interactions, hydrogen bonds (HBond), electrostatic (Elec) interactions, and average contact pairs (AverConPair). Chlorhexidine displayed a TotalEnergy value of -94.6146, indicating a strong binding affinity with the Alpha-2 receptor. The contributions from VDW interactions (-73.5067) and HBond interactions (-21.108) significantly influenced the TotalEnergy, suggesting favourable interactions between the ligand and the receptor. Electrostatic interactions did not play a significant role in this case. The ligand demonstrated an average contact pair value of 16.3529, indicating favourable contacts with the receptor. The docking analysis suggests that Chlorhexidine has a high potential as a therapeutic agent targeting the Alpha-2 receptor due to its strong binding affinity. Further investigations are required to evaluate its effectiveness in modulating the receptor's activity and to explore its potential clinical applications.

Table 4.12 showcases the docking results between the Beta-1 receptor and five different ligands: 3-[4-(3-Methylbut-2-enoxy)phenyl]propan-1-ol, Lindoldhamine, Mescaline, p-Tolyl acetate, and Virolin-0. The analysis includes parameters such as TotalEnergy, van der Waals (VDW) interactions, hydrogen bonds (HBond), electrostatic (Elec) interactions, and average contact pairs (AverConPair).

3-[4-(3-Methylbut-2-enoxy)phenyl]propan-1-ol exhibited a TotalEnergy value of -53.3086, indicating a favourable binding affinity with the Beta-1 receptor. The contributions from VDW interactions (-50.8086) and HBond interactions (-2.5) influenced the TotalEnergy, suggesting favourable interactions between the ligand and the receptor. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 20.8125, indicating favourable contacts with the receptor. Lindoldhamine displayed a TotalEnergy of -81.045, suggesting a strong binding affinity with the Beta-1 receptor. VDW interactions (-65.9142) and HBond interactions (-15.1308) contributed to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand exhibited an average contact pair value of 15.4762, indicating favourable interactions with the receptor. Mescaline exhibited a TotalEnergy of -64.3843, indicating a favourable binding affinity with the Beta-1 receptor. VDW interactions (-56.6521) and HBond interactions (-7.73215) significantly influenced the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 26.1333, suggesting favourable contacts with the receptor. p-Tolyl acetate displayed a TotalEnergy of -52.087, indicating a favourable binding affinity with the Beta-1 receptor. VDW interactions (-42.9891) and HBond interactions (-9.09792) contributed to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand exhibited an average contact pair value of 26.5455, indicating favourable interactions with the receptor. Virolin-0 exhibited a TotalEnergy of -72.722, indicating a favourable binding affinity with the Beta-1 receptor. VDW interactions (-69.222) and HBond interactions (-3.5) influenced the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 17.6923, suggesting favourable contacts with the receptor. In summary, the docking analysis suggests that all five ligands, 3-[4-(3-Methylbut-2-enoxy)phenyl]propan-1-ol, Lindoldhamine, Mescaline, p-Tolyl acetate, and Virolin-0, exhibit favourable binding affinities with the Beta-1 receptor. These findings indicate their potential as therapeutic agents targeting the receptor. Further investigation is necessary to evaluate their effectiveness in modulating receptor activity and their potential for clinical applications.

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Table 4.13 presents the docking results between the Beta-2 receptor and five different ligands: 5-(12Z)-12-Nonadecen-1-yl-1,3-benzenediol, 5-(Pentadeca-8,11,14-trien-1-yl)resorcinol, Demethylbatatasin IV, Dihydropinosylvin, and Mescaline. The analysis includes parameters such as TotalEnergy, van der Waals (VDW) interactions, hydrogen bonds (HBond), electrostatic (Elec) interactions, and average contact pairs (AverConPair). 5-(12Z)-12-Nonadecen-1-yl-1,3-benzenediol exhibited a TotalEnergy of -67.9778, indicating a favourable binding affinity with the Beta-2 receptor. The ligand had significant van der Waals interactions (-67.9778), while other parameters, such as hydrogen bonds and electrostatic interactions, were not observed. The ligand demonstrated an average contact pair value of 17.9259, suggesting favourable contacts with the receptor. 5-(Pentadeca-8,11,14-trien-1-yl)resorcinol displayed a TotalEnergy of -71.47, suggesting a strong binding affinity with the Beta-2 receptor. The ligand had both van der Waals interactions (-67.3753) and hydrogen bonds (-4.09464) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand exhibited an average contact pair value of 19.3478, indicating favourable interactions with the receptor. Demethylbatatasin IV exhibited a TotalEnergy of -69.0439, indicating a favourable binding affinity with the Beta-2 receptor. The ligand had van der Waals interactions (-50.1972) and hydrogen bonds (-18.8467) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 23.8824, suggesting favourable contacts with the receptor. Dihydropinosylvin displayed a TotalEnergy of -65.8156, indicating a favourable binding affinity with the Beta-2 receptor. The ligand had van der Waals interactions (-56.9287) and hydrogen bonds (-8.88692) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand exhibited an average contact pair value of 23.875, indicating favourable interactions with the receptor. Mescaline exhibited a TotalEnergy of -69.4319, suggesting a strong binding affinity with the Beta-2 receptor. The ligand had van der Waals interactions (-56.8433) and hydrogen bonds (-12.5886) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 27.1333, indicating favourable contacts with the receptor. In summary, the docking analysis suggests that all five ligands, 5-(12Z)-12-Nonadecen-1-yl-1,3-benzenediol, 5-(Pentadeca-8,11,14-trien-1-yl)resorcinol, Demethylbatatasin IV, Dihydropinosylvin, and Mescaline, exhibit favourable binding affinities with the Beta-2 receptor. These findings indicate their potential as therapeutic agents targeting the receptor. Further investigation is necessary to evaluate their effectiveness in modulating receptor activity and their potential for clinical applications.

Table 4.14 presents the docking results between the Beta-3 receptor and the ligand Hydroxymatairesinol. The analysis includes parameters such as TotalEnergy, van der Waals (VDW) interactions, hydrogen bonds (HBond), electrostatic (Elec) interactions, and average contact pairs (AverConPair). Hydroxymatairesinol displayed a TotalEnergy value of -92.5233, indicating a strong binding affinity with the Beta-3 receptor. The contributions from VDW interactions (-81.6234) and HBond interactions (-10.8999) significantly influenced the TotalEnergy, suggesting favourable interactions between the ligand and the receptor. Electrostatic interactions did not play a significant role in this case, as the Elec value is listed as 0. The ligand demonstrated an average contact pair value of 22.5926, indicating favourable contacts with the receptor. Based on these docking results, Hydroxymatairesinol shows promising potential as a therapeutic agent targeting the Beta-3 receptor. Further studies are necessary to explore its efficacy in modulating the receptor's activity and to investigate its potential applications in the treatment of Beta-3 receptor-related conditions or diseases.

Table 4.15 presents the docking results between the 5-HT1A receptor and three different ligands: Caryachine, Dehydroevidiamine, and D-Tetrahydropalmatine. The analysis includes parameters such as TotalEnergy, van der Waals (VDW) interactions, hydrogen bonds (HBond), electrostatic (Elec) interactions, and average contact pairs (AverConPair). Caryachine exhibited a TotalEnergy of -71.9165, suggesting a favourable binding affinity with the 5-HT1A receptor. The ligand had significant van der Waals interactions (-65.816) and hydrogen bonds (-6.10049) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 19.2917, indicating favourable contacts with the receptor. Dehydroevidiamine displayed a TotalEnergy of -65.8062, indicating a favourable binding affinity

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with the 5-HT1A receptor. The ligand had van der Waals interactions (-62.3533) and hydrogen bonds (-3.45294) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand exhibited an average contact pair value of 17.6087, suggesting favourable interactions with the receptor. D-Tetrahydropalmatine exhibited a TotalEnergy of -72.6591, indicating a favourable binding affinity with the 5-HT1A receptor. The ligand had van der Waals interactions (-66.5162) and hydrogen bonds (-6.14289) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 16.3846, indicating favourable contacts with the receptor. These docking results suggest that Caryachine, Dehydroevidiamine, and D-Tetrahydropalmatine have favourable binding affinities with the 5-HT1A receptor. Further investigation is necessary to evaluate their potential as therapeutic agents targeting the receptor and their effectiveness in modulating receptor activity.

Table 4.16 presents the docking results between the 5-HT1B receptor and four different ligands: (1H-Indol-3-yl)methanamine, Corynantheidine, Gramine, and Kopsiyunnanine B. The analysis includes parameters such as TotalEnergy, van der Waals (VDW) interactions, hydrogen bonds (HBond), electrostatic (Elec) interactions, and average contact pairs (AverConPair). (1H-Indol-3-yl)methanamine exhibited a TotalEnergy of -52.0585, indicating a favourable binding affinity with the 5-HT1B receptor. The ligand had significant van der Waals interactions (-41.5585) and hydrogen bonds (-10.5) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 23.8182, suggesting favourable contacts with the receptor. Corynantheidine displayed a TotalEnergy of -72.6209, suggesting a favourable binding affinity with the 5-HT1B receptor. The ligand had van der Waals interactions (-59.6209) and hydrogen bonds (-13) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand exhibited an average contact pair value of 15.4815, indicating favourable interactions with the receptor. Gramine exhibited a TotalEnergy of -60.2025, indicating a favourable binding affinity with the 5-HT1B receptor. The ligand had van der Waals interactions (-53.2511) and hydrogen bonds (-6.95139) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 24.7692, suggesting favourable contacts with the receptor. Kopsiyunnanine B exhibited a TotalEnergy of -68.041, indicating a favourable binding affinity with the 5-HT1B receptor. The ligand had van der Waals interactions (-61.041) and hydrogen bonds (-7) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 19, suggesting favourable contacts with the receptor. These docking results suggest that (1H-Indol-3-yl)methanamine, Corynantheidine, Gramine, and Kopsiyunnanine B have favourable binding affinities with the 5-HT1B receptor. Further investigation is necessary to evaluate their potential as therapeutic agents targeting the receptor and their effectiveness in modulating receptor activity.

Table 4.17 presents the docking results between the 5-HT2A receptor and four different ligands: Arborine, Dehydroevidiamine, Fumiquinazoline G, and Rutaecarpine. The analysis includes parameters such as TotalEnergy, van der Waals (VDW) interactions, hydrogen bonds (HBond), electrostatic (Elec) interactions, and average contact pairs (AverConPair). Arborine exhibited a TotalEnergy of -68.1202, indicating a favourable binding affinity with the 5-HT2A receptor. The ligand had significant van der Waals interactions (-63.3219) and hydrogen bonds (-4.7983) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 21.4737, suggesting favourable contacts with the receptor. Dehydroevidiamine displayed a TotalEnergy of -71.4935, suggesting a favourable binding affinity with the 5-HT2A receptor. The ligand had van der Waals interactions (-64.5963) and hydrogen bonds (-6.89716) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand exhibited an average contact pair value of 18.7826, indicating favourable interactions with the receptor. Fumiquinazoline G exhibited a TotalEnergy of -69.8094, indicating a favourable binding affinity with the 5-HT2A receptor. The ligand had van der Waals interactions (-66.3094) and hydrogen bonds (-3.5) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 16.0741, suggesting favourable contacts with the receptor. Rutaecarpine exhibited a TotalEnergy of -71.526, indicating a

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favourable binding affinity with the 5-HT2A receptor. The ligand had van der Waals interactions (-71.526), indicating strong non-covalent interactions with the receptor. No hydrogen bonds or electrostatic interactions were observed. The ligand demonstrated an average contact pair value of 22.2727, suggesting favourable contacts with the receptor. These docking results suggest that Arborine, Dehydroevidiamine, Fumiquinazoline G, and Rutaecarpine have favourable binding affinities with the 5-HT2A receptor. Further investigation is necessary to evaluate their potential as therapeutic agents targeting the receptor and their effectiveness in modulating receptor activity.

Table 4.18 presents the docking results between the 5-HT2C receptor and four different ligands: Annomontine, Cyclolinopeptide G, Dichotomide Iii, and Kumujian C. The analysis includes parameters such as TotalEnergy, van der Waals (VDW) interactions, hydrogen bonds (HBond), electrostatic (Elec) interactions, and average contact pairs (AverConPair). Annomontine exhibited a TotalEnergy of -74.3285, indicating a favourable binding affinity with the 5-HT2C receptor. The ligand had significant van der Waals interactions (-51.4775) and hydrogen bonds (-22.8511) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 20.45, suggesting favourable contacts with the receptor. Cyclolinopeptide G displayed a TotalEnergy of -32.89, indicating a favourable binding affinity with the 5-HT2C receptor. The ligand had van der Waals interactions (-28.5531) and hydrogen bonds (-4.3369) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand exhibited an average contact pair value of 6.54878, indicating favourable contacts with the receptor. Dichotomide Iii exhibited a TotalEnergy of -64.7358, indicating a favourable binding affinity with the 5-HT2C receptor. The ligand had van der Waals interactions (-54.2583) and hydrogen bonds (-10.4775) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 16.08, suggesting favourable contacts with the receptor. Kumujian C exhibited a TotalEnergy of -66.0068, indicating a favourable binding affinity with the 5-HT2C receptor. The ligand had van der Waals interactions (-57.8377) and hydrogen bonds (-8.1691) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 25.3333, suggesting favourable contacts with the receptor. These docking results suggest that Annomontine, Cyclolinopeptide G, Dichotomide Iii, and Kumujian C have favourable binding affinities with the 5-HT2C receptor. Further investigation is necessary to evaluate their potential as therapeutic agents targeting the receptor and their effectiveness in modulating receptor activity.

Table 4.19 presents the docking results between the 5-HT3 receptor and several ligands: Acetyl-1H-indole-3-carbaldehyde, 5-HT3-Annomontine, 5-HT3-Dichotomide Iii PDB, 5-HT3-Evocarpine, and 5-HT3-Kumujian C. The analysis includes parameters such as TotalEnergy, van der Waals (VDW) interactions, hydrogen bonds (HBond), electrostatic (Elec) interactions, and average contact pairs (AverConPair). Acetyl-1H-indole-3-carbaldehyde exhibited a TotalEnergy of -50.2375, indicating a favourable binding affinity with the 5-HT3 receptor. The ligand had significant van der Waals interactions (-46.0334) and a minor contribution from hydrogen bonds (-4.2041) to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 22.8571, suggesting favourable contacts with the receptor. 5-HT3-Annomontine displayed a TotalEnergy of -71.2795, indicating a favourable binding affinity with the 5-HT3 receptor. The ligand had van der Waals interactions (-61.243) and hydrogen bonds (-10.0365) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand exhibited an average contact pair value of 21.3, suggesting favourable contacts with the receptor. 5-HT3-Dichotomide Iii PDB exhibited a TotalEnergy of -82.9235, indicating a favourable binding affinity with the 5-HT3 receptor. The ligand had van der Waals interactions (-65.9595) and hydrogen bonds (-16.964) contributing to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 16.48, suggesting favourable contacts with the receptor. 5-HT3-Evocarpine exhibited a TotalEnergy of -63.8447, indicating a favourable binding affinity with the 5-HT3 receptor. The ligand had van der Waals interactions (-60.3447) and a minor contribution from hydrogen bonds (-3.5) to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 17.12, suggesting

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favourable contacts with the receptor. 5-HT3-Kumujian C exhibited a TotalEnergy of -63.0381, indicating a favourable binding affinity with the 5-HT3 receptor. The ligand had van der Waals interactions (-59.9753) and a minor contribution from hydrogen bonds (-3.06284) to the TotalEnergy. Electrostatic interactions did not play a significant role. The ligand demonstrated an average contact pair value of 24.4, suggesting favourable contacts with the receptor. These docking results suggest that Acetyl-1H-indole-3-carbaldehyde, 5-HT3-Annomontine, 5-HT3-Dichotomide Iii PDB, 5-HT3-Evocarpine, and 5-HT3-Kumujian C have favourable binding affinities with the 5-HT3 receptor. Further investigation is necessary to evaluate their potential as therapeutic agents targeting the receptor and their effectiveness in modulating receptor activity.

Table 4.1. shows the docking results between H1 Receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
(+)-Hyoscyamine	-59.7055	-48.1804	-11.5251	0	14.8571
Majusanic acid F	-61.1717	-52.7597	-8.41197	0	15.8696
L-Clausenamide	-65.6093	-58.8067	-6.80255	0	18.3636
Epi-Cis-Clausenamide	-66.2586	-60.2533	-6.00522	0	16.4545
7Alpha-Hydroxydehydroabietic Acid	-68.9302	-65.1278	-3.80239	0	17.2609
Aquilarabietic Acid H	-71.3452	-48.9212	-22.424	0	20.1739
Abiesadine I	-76.4443	-68.1024	-8.34186	0	15.931
Metacridamide A	-81.7676	-69.7957	-11.9719	0	13.2045

Table 4.2. shows the docking results between H2 Receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
4-Methylimidazole	-37.9932	-32.1157	-5.87751	0	36.5
N,N-Dimethylhistamine	-49.8351	-34.8897	-14.9454	0	24.8

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(3-Amino-1-propenyl)-1H-imidazol-2-amin	-55.5006	-41.2347	-14.2659	0	28.2

Table 4.3. shows the docking results between H3 Receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
Tamsulosin-1	-72.4923	-64.4432	-8.04911	0	15.6071

Table 4.4. shows the docking results between H4 Receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
Corynantheidine	-58.6605	-55.315	-3.34547	0	15.5556
Dichotomide Iii	-65.3478	-52.739	-12.6088	0	16.16
Hirsutine	-65.46	-59.59	-5.86999	0	17.6667
(14-methylpentadecyl)-1H-pyrrole-2-carbaldehyde	-68.0862	-64.0586	-4.02762	0	18.1739
Kumujian C	-69.9636	-51.9636	-18	0	25.5333

Table 4.5. shows the docking results between CXCR3 Receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
Ceratamine A	-67.8685	-58.897	-8.97151	0	17.6
Hortiacine	-69.1366	-69.1366	0	0	19.9583
Isaindigotone	-72.3582	-51.4814	-20.8767	0	15.5769
Fumiquinazoline G	-78.0343	-50.7225	-27.3118	0	17.5185
Picrasidine N	-88.3557	-75.7134	-12.6423	0	15.1081

 doi:10.20944/preprints202408.0829.v1

Table 4.6. shows the docking results between CXCR4 Receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
N-Methylbenzylamine	-41.7418	-38.2418	-3.5	0	25
Amphetamine	-49.354	-41.1549	-8.19918	0	24.9
2-Methyl-1,2,3,4-tetrahydroisoquinoline	-54.8154	-51.8574	-2.95801	0	30.1818
1,3-Dibenzylurea	-64.7361	-52.134	-12.6021	0	26.2222
Nortriptyline	-70.6953	-70.6953	0	0	22.3

Table 4.7. shows the docking results between CCR1 Receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
Spiramide	-70.7807	-60.2807	-10.5	0	14.3214

Table 4.8. shows the docking results between CCR2 Receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
5-[1-(4-Hydroxy-Benzyl)-4-(4-Methoxy-Benzyl)-1H-Imidazol-2-Ylamino]	-78.3638	-55.0885	-23.2753	0	18.871
Isonaamidine E	-79.8961	-62.3721	-17.524	0	15.6176
ISONAAMINE C	-81.2768	-70.4145	-10.8623	0	19.2692
CHEMBL3314790	-88.6038	-67.2403	-21.3635	0	8.33871

Table 4.9. shows the docking results between CCR5 Receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
ISONAAMINE C	-66.6777	-54.6055	-12.0722	0	14.9615
Isonaamidine E	-76.5529	-66.0529	-10.5	0	14.8235

 doi:10.20944/preprints202408.0829.v1

CHEMBL3314790	-86.2518	-68.1	-18.1518	0	8.62903

Table 4.10. shows the docking results between Alpha-1 receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
Usabamycin B	-71.4074	-61.0524	-10.3551	0	19.6842
CHEMBL2229122	-84.7061	-69.0232	-15.6828	0	20.2
CHEMBL3581898	-86.8467	-79.5559	-7.29076	0	19.2903

Table 4.11. shows the docking results between Alpha-2 receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
Chlorhexidine	-94.6146	-73.5067	-21.108	0	16.3529

Table 4.12. shows the docking results between Beta-1 receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
p-Tolyl acetate	-52.087	-42.9891	-9.09792	0	26.5455
3-[4-(3-Methylbut-2-enoxy)phenyl]propan-1-ol	-53.3086	-50.8086	-2.5	0	20.8125
Mescaline	-64.3843	-56.6521	-7.73215	0	26.1333
Virolin	-72.722	-69.222	-3.5	0	17.6923
Lindoldhamine	-81.045	-65.9142	-15.1308	0	15.4762

Table 4.13. shows the docking results between Beta-2 receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
Dihydropinosylvin	-65.8156	-56.9287	-8.88692	0	23.875

 doi:10.20944/preprints202408.0829.v1

5-(12Z)-12-Nonadecen-1-yl-1,3-benzenediol	-67.9778	-67.9778	0	0	17.9259
Demethylbatatasin IV	-69.0439	-50.1972	-18.8467	0	23.8824
Mescaline	-69.4319	-56.8433	-12.5886	0	27.1333
5-(Pentadeca-8,11,14-trien-1-yl)resorcinol	-71.47	-67.3753	-4.09464	0	19.3478

Table 4.14. shows the docking results between Beta-3 receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
Hydroxymatairesinol	-92.5233	-81.6234	-10.8999	0	22.5926

Table 4.15. shows the docking results between 5-HT1A receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
Dehydroevidiamine	-65.8062	-62.3533	-3.45294	0	17.6087
Caryachine	-71.9165	-65.816	-6.10049	0	19.2917
D-Tetrahydropalmatine	-72.6591	-66.5162	-6.14289	0	16.3846

Table 4.16. shows the docking results between 5-HT1B receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
(1H-Indol-3-yl)methanamine	-52.0585	-41.5585	-10.5	0	23.8182
Gramine	-60.2025	-53.2511	-6.95139	0	24.7692
Kopsiyunnanine B	-68.041	-61.041	-7	0	19
Corynantheidine	-72.6209	-59.6209	-13	0	15.4815

 doi:10.20944/preprints202408.0829.v1

Table 4.17. shows the docking results between 5-HT2A receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
Arborine	-68.1202	-63.3219	-4.7983	0	21.4737
Fumiquinazoline G	-69.8094	-66.3094	-3.5	0	16.0741
Dehydroevidiamine	-71.4935	-64.5963	-6.89716	0	18.7826
Rutaecarpine	-71.526	-71.526	0	0	22.2727

Table 4.18. shows the docking results between 5-HT2C receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
Cyclolinopeptide G	-32.89	-28.5531	-4.3369	0	6.54878
Dichotomide Iii	-64.7358	-54.2583	-10.4775	0	16.08
Kumujian C	-66.0068	-57.8377	-8.1691	0	25.3333
Annomontine	-74.3285	-51.4775	-22.8511	0	20.45

Table 4.19. shows the docking results between 5-HT3 receptor and its respective drugs.

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
Acetyl-1H-indole-3-carbaldehyde	-50.2375	-46.0334	-4.2041	0	22.8571
Kumujian C	-63.0381	-59.9753	-3.06284	0	24.4
Evocarpine	-63.8447	-60.3447	-3.5	0	17.12
Annomontine	-71.2795	-61.243	-10.0365	0	21.3
Dichotomide Iii	-82.9235	-65.9595	-16.964	0	16.48

Discussion

Histamine receptors are involved in various physiological processes and have been linked to allergic responses, gastric acid secretion, immune modulation, and cognitive function. The four main

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histamine receptors are H1, H2, H3, and H4. In the context of long COVID, understanding the association between these receptors and the disease can provide insights into potential therapeutic options.

The H1 receptor (HH1R) is primarily associated with allergic responses and has been targeted for treating allergies, inflammation, and other conditions. H1 receptor antagonists, such as antihistamines, have been developed to alleviate symptoms. Recent studies suggest that H1 receptor antagonists may offer potential benefits in combating SARS-CoV-2 infection. Some H1 receptor antagonists, like mizolastine, have shown strong binding affinities with the SARS-CoV-2 protease Mpro. While the exact mechanisms are not fully understood, Metacridamide A shows potential in inhibiting viral entry. In the context of long COVID, modulating histamine signaling through the H1 receptor may contribute to symptom relief, particularly for respiratory symptoms.

The H2 receptor (HH2R) primarily stimulates gastric acid secretion and is involved in vasodilation and immune responses. H2 receptor antagonists, such as famotidine, are commonly used to treat conditions like peptic ulcers and asthma. In the context of long COVID, the interaction of 4-(3-Amino-1-propenyl)-1H-imidazol-2-amine with the H2 receptor may be relevant due to its influence on gastric acid production. Gastrointestinal symptoms, including nausea, diarrhea, and abdominal pain, have been reported in some long COVID patients. Inhibition of gastric acid secretion by 4-(3-Amino-1-propenyl)-1H-imidazol-2-amine may contribute to alleviating these symptoms.

The H3 receptor (HH3R) acts as a presynaptic autoreceptor on histamine-containing neurons in the central nervous system (CNS). It is widely distributed in the CNS and has implications for cognitive function and neurotransmitter modulation. Pesampator (BIIB-104/PF-04958242), a positive allosteric modulator of the AMPA receptor, is being developed for treating cognitive symptoms in schizophrenia. Based on this FDA drug, Tamsulosin-1's interaction with the H3 receptor suggests potential implications for cognitive impairments and sleep disturbances associated with long COVID.

The H4 receptor (HH4R) is predominantly expressed in immune cells and tissues and plays a role in allergic and inflammatory responses. Kumujian C, a selective antagonist of the H4 receptor, may demonstrate anti-inflammatory effects and superiority over traditional antihistamines in treating pruritus. Modulating histamine signaling through the H4 receptor may have implications for immune responses and inflammatory processes involved in long COVID. In summary, histamine receptors—H1, H2, H3, and H4—are involved in various physiological processes and have associations with long COVID. H1 receptor antagonists show potential antiviral effects and may alleviate respiratory symptoms, while H2 receptor antagonists, like famotidine, may help manage gastrointestinal symptoms. Modulating histamine signaling through the H3 and H4 receptors may have implications for cognitive function, sleep disturbances, and immune modulation in long COVID. Further research is needed to explore the therapeutic potential of targeting these receptors for treating long COVID.

Chemokines are molecules that attract immune cells to areas of inflammation and infection. They play a crucial role in combating viral infections by recruiting immune cells to the site of infection and enhancing their antiviral functions. However, some viruses have evolved mechanisms to manipulate chemokines for their own benefit.

Chemokines are classified into different classes based on the arrangement of conserved cysteine residues. The CXC chemokine receptor family, including CXCR3 and CXCR4, is particularly relevant in the context of viral infections such as SARS-CoV-2. CXCR3 is predominantly expressed on activated T lymphocytes and natural killer cells and is involved in recruiting effector T cells to inflamed tissues. In contrast, CXCR4 is widely distributed among various cell types and plays a role in several biological processes.

AMG 487 is a small molecule antagonist that specifically targets the CXCR3 receptor. It has been investigated as a potential drug for immune-related conditions such as autoimmune disorders and certain viral infections. Based on this drug's profile, a similar phytochemical drug known as Picrasidine N has been identified. In the context of long COVID, which is characterized by persistent immune activation and inflammation, blocking the CXCR3 receptor with Picrasidine N may help mitigate inflammatory processes and reduce immune cell recruitment to inflamed tissues.

 doi:10.20944/preprints202408.0829.v1

Plerixafor (AMD3100) is a CXCR4 antagonist approved for stem cell mobilization in certain medical procedures. It inhibits the interaction between CXCR4 and its ligand CXCL12, which plays a role in hematopoiesis and other biological processes. Based on this drug's profile, Nortriptyline has been chosen for its high binding affinity with the receptor and its potential to alleviate symptoms related to CXCR4.

CCR5 is another chemokine receptor predominantly expressed on white blood cells and involved in immune cell migration and inflammation. CHEMBL3314790 is a small molecule antagonist that targets the CCR5 receptor. By blocking CCR5, Cenicriviroc may help reduce inflammation and immune dysregulation. CCR2 is a chemotactic receptor primarily expressed on monocytes/macrophages and lymphocytes. It plays a role in recruiting immune cells to sites of inflammation. CCR2-mediated hyper-inflammatory reactions have been implicated in severe cases of COVID-19. CHEMBL3314790 also shows high binding affinity for this receptor, highlighting the need for further research on this phytochemical, as it may inhibit both CCR2 and CCR5 receptors. In summary, chemokine receptors such as CXCR3, CXCR4, CCR5, and CCR2 are involved in immune responses and inflammation. Drugs targeting these receptors, such as Picrasidine N, Nortriptyline, and CHEMBL3314790, hold promise as potential treatments for long COVID by modulating immune responses and mitigating inflammation. However, further research and clinical studies are needed to fully understand their efficacy and safety in managing long COVID.

Serotonin, a neurotransmitter involved in various physiological functions, is regulated by serotonin receptors. COVID-19 can lead to dysfunction in multiple organ systems, including the brain, and serotonin plays a crucial role in the immune system and inflammatory responses. Previous studies suggest that serotonin receptors, particularly 5-HT3 receptors, are involved in chronic inflammatory conditions and have been targeted in the treatment of rheumatic diseases. The 5-HT1A receptor is a prominent target for pharmacotherapy, especially in depression. Modulating the activity of this receptor with D-Tetrahydropalmatine, which showed the highest binding affinity among all the phytochemical compounds, can enhance stress resistance and improve the response to antidepressant treatment. Buspirone, a partial agonist of the 5-HT1A receptor, is used as an anxiolytic and may have implications for managing anxiety symptoms related to long COVID. The 5-HT1B receptor modulates neurotransmitter release and is involved in neural activity, pain perception, mood, and behavior. Corynanrheidine, an alkaloid phytochemical compound, is based on the FDA drug Methysergide. Corynanrheidine can modulate the 5-HT1B receptor and may be used for the acute treatment of migraines. Headaches, including migraines, are commonly reported in long COVID patients, and targeting the 5-HT1B receptor may offer potential for managing these headaches.

The 5-HT2A receptor mediates diverse effects on the cardiovascular and central nervous systems. Autoantibodies targeting the 5-HT2A receptor have been identified in individuals with acute COVID-19 infection. Rutaecarpine, a compound with the highest binding affinity towards the receptor, belongs to the Pyridoindoles chemical classification. It originates from the genus Persea and the genus Evodia from the families Lauraceae and Rutaceae, respectively, and may have implications in managing immune dysregulation and inflammatory manifestations in long COVID. The 5-HT2C receptor, primarily found in the central nervous system, is involved in various physiological processes. Agonists and antagonists of this receptor can modulate downstream signaling pathways. Annomontine, selected based on its fingerprint as a 5-HT2C antagonist, has the highest binding affinity for the receptor. Annomontine is also known as a harmala alkaloid. Targeting the 5-HT2C receptor may have potential therapeutic implications for managing obesity, addiction, and mood disorders.

Ondansetron, a selective antagonist of the serotonin 5-HT3 receptor, is primarily used for the prevention and treatment of nausea and vomiting (Lexicomp, 2021). Based on this FDA drug, Dichotomide III, an alkaloid derived from Stellaria dichotoma var. lanceolata (family Caryophyllaceae), has a similar fingerprint and the highest binding affinity for the receptor. In the context of long COVID, the interaction between Dichotomide III and the 5-HT3 receptor is intriguing due to the potential involvement of serotonin in gastrointestinal symptoms and dysautonomia.

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Gastrointestinal symptoms, including nausea and vomiting, have been reported in some long COVID patients (Nalbandian et al., 2021). Modulating serotonin signaling through the 5-HT3 receptor, as targeted by Dichotomide III, might offer a potential approach to managing gastrointestinal symptoms associated with long COVID. Further research is necessary to determine the efficacy and safety of Dichotomide III in addressing these symptoms specifically related to long COVID.

In summary, serotonin receptors, including 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2C, and 5-HT3, are involved in various physiological functions and have implications in treating conditions such as depression, migraines, and chronic inflammatory conditions. Modulating these receptors may offer potential therapeutic approaches for managing anxiety, headaches, immune dysregulation, and inflammatory manifestations associated with long COVID.

Adrenergic receptors are important targets for the treatment of cardiovascular disorders and play a role in various physiological responses. Drugs that target adrenergic receptors include beta blockers, beta-2 agonists, and alpha-2 agonists. The specific receptor subtypes and their effects vary, such as smooth muscle contraction, bronchial relaxation, and lipolysis.

The alpha-1 adrenergic receptor is involved in conditions characterized by reduced cardiac output or decreased systemic vascular resistance. Alpha-1 agonists like phenylephrine are used in shock, heart failure, and upper airway congestion. Alpha-antagonists, or alpha-blockers, are used for hypertension and urinary retention.

In the context of long COVID, CHEMBL3581898, a possible alpha-1A receptor blocker, may help manage lower urinary tract symptoms and vascular dysregulation. Chlorhexidine, a phytochemical with the highest binding affinity, could potentially address autonomic dysfunction and disrupted sympathetic activity. Beta-1 adrenergic receptors in the heart increase heart rate and contractility. Beta blockers have demonstrated clinical benefits in managing cardiovascular diseases and may have advantages in COVID-19 treatment. Modulating the Beta-1 receptor through Lindoldhamine presents a potential therapeutic approach for managing cardiovascular symptoms associated with long COVID. By blocking the Beta-1 receptor, Lindoldhamine can reduce heart rate and myocardial contractility, potentially alleviating symptoms and improving cardiac function. In the context of long COVID, the interaction between 5-(Pentadeca-8,11,14-trien-1-yl)resorcinol and the Beta-2 receptor is of interest due to its potential impact on respiratory symptoms and airway hyperresponsiveness (Lexicomp, 2021). Long COVID patients may experience persistent respiratory symptoms, including cough, shortness of breath, and chest tightness (Carfì et al., 2020). Modulating the Beta-2 receptor through 5-(Pentadeca-8,11,14-trien-1-yl)resorcinol presents a potential therapeutic approach for managing these respiratory symptoms associated with long COVID. By activating the Beta-2 receptor, 5-(Pentadeca-8,11,14-trien-1-yl)resorcinol promotes bronchodilation, improving airflow and relieving symptoms of airway constriction, thereby enhancing lung function.

Beta-3 adrenergic receptors regulate lipolysis and thermogenesis. Their direct involvement in COVID-19 and long COVID is not extensively studied. Based on the fingerprint of the FDA drug Ritobegron, we identified Hydroxymatairesinol as the phytochemical drug. Hydroxymatairesinol is derived from plants in the Apiaceae, Pinaceae, and Asteraceae families. Findings suggest that plants from the Asteraceae and Apiaceae families are used for gastrointestinal disorders, while plants from the Apocynaceae and Euphorbiaceae families are used for dermatological problems (Hosseini et al., 2021). These interactions between adrenergic receptors and drugs suggest potential therapeutic approaches for managing specific symptoms associated with long COVID. However, further investigation through clinical studies and trials is necessary to determine their specific roles and benefits in addressing long COVID symptoms.

Conclusion

The exact cause of Long COVID remains unclear, but it is thought to result from a combination of factors, including direct viral effects on various organs, an overactive immune response, and potential damage to blood vessels and nerves. G-protein coupled receptors (GPCRs), a large family of cell surface proteins, are crucial for cellular signaling and are involved in a wide range of physiological processes. Given their central role, GPCRs have been targeted to explore potential

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treatments for Long COVID. Our analysis focused on these receptors to identify suitable drugs for managing Long COVID. Different receptors exhibit varying binding affinities with different drugs, and the TotalEnergy parameter, reflecting overall binding affinity, can differ significantly among ligands for the same receptor. Docking results offer valuable insights into the potential of these drugs to modulate receptor activity. Ligands with favorable docking scores and interaction patterns may hold therapeutic potential for the targeted receptor. Overall, the docking studies underscore the diverse interactions between ligands and receptors, providing important information for drug discovery and development. To validate and confirm the binding affinities and functional effects of these ligands, further experimental studies, including in vitro and in vivo assays, are necessary.

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