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REPURPOSING OF SLEEP INDUCING ZOPICLONE VIA GABA FOR TREATMENT MODULATORY OF RHEUMATOID ARTHRITIS BY USING DRUGREP

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Keywords:

Rheumatoid Arthritis, Baricitinib, JAK Inhibitors, Drug Design, Molecular Docking, Zopiclone, Sleep-Inducing Agents, Therapeutic Strategies, Protein-Ligand Interactions

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ABSTRACT

This study explores the applicability of Baricitinib as a primary ligand in the design of new therapeutic agents for rheumatoid arthritis (RA), laying emphasis on its remarkable binding efficacy across numerous JAK targets. Baricitinib with the score of 1.000 serves as a reference for future drug design toward enhancing patient outcomes. Mechanistic studies indicate that the action of Baricitinib is through inhibition of JAK1 and JAK2, critical pathways to inflammation and joint degradation. In the comparative docking studies, other compounds such as Upadacitinib and Vemurafenib possess strong affinities, but nothing goes beyond Baricitinib in efficacy. Furthermore, the PDB-REDO refinement contributes greatly to the structural model's refinement, giving many pointers regarding protein-ligand interactions. Moreover, the study delves into the possibility of repurposing sleep-inducing drugs such as Zopiclone and suggests that their integration into the treatment regime may promote sleep quality and overall adherence to RA therapy. This study lays the groundwork for future investigators to maximize therapeutic strategies for RA through various pharmacological pathways.

1. Introduction

Rheumatoid arthritis (RA) refers to chronic autoimmune disease, which mostly affects the synovial joints , and is characterized as inflammation which usually leads to damage of cartilage and bone and soft surrounding tissues [1]. The intervention of immune system involves the immune-modulating factors leading to dysregulation of immune responses by immune cells such as T and B lymphocytes and macrophages along with a number of cytokines- TNF-α, IL-1, and IL-6- fueling an inflammatory response[2]. Such autoantibodies included rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies which are highly expressed in RA, contributing to synovial hyperplasia and heightened inflammation [3]. Variably, also showing the close clinical manifestations of the persistence of joint pain, stiffness, and swelling, along with progressive deformities that may even limit movement considerably and worsen patients' quality of life[4]. In addition, it has systemic consequences, such as fatigue, establishing complications in the cardiovascular system, and risk to osteoporosis, which have high burden impacts like many other diseases [5]. Traditional disease-modifying anti-rheumatic drugs (DMARDs) like methotrexate, sulfasalazine, and leflunomide, as well as biologics targeting TNF, IL-6, and B cells, continue to be cornerstones in the treatment of rheumatoid arthritis, but all these treatments have relatively limited efficacy [6]. A partial relief in many patients, with resistance or adverse effects in others [7]. Biologic therapies are challenging to undertake because they can be effective but are very costly and immunosuppressive, thus increasing infection potential [8]. With around 30% of the population not responding sufficiently, there is an urgent need to discover new alternatives that are expected to be safe and inexpensive [9].Against this background, a new therapeutic space that may contribute potential leads includes the GABAergic system. This system has for long been accepted as an inhibitory neurotransmitter in the central nervous system (CNS), regulating both neural excitability and synaptic transmission [10]. Evidence supports the existence of GABA receptors and relevant enzymes outside the CNS, especially in immune cells such as T cells, macrophages, and dendritic cells, suggesting a more extensive immunoregulatory function [11]. GABA and its receptors negatively regulate the production of pro-inflammatory cytokines and also modulate the activity of immune cells, as shown in several recent publications[12]. In models of autoimmune disease, GABAergic signaling appeared to dampen immune responses, suggesting a potential path for targeting autoimmune diseases such as RA [13]. In the light of this information, zopiclone, a well-known non-benzodiazepine insomnia drug, becomes an attractive candidate for drug repositioning [14]. Zopiclone, a GABA-A receptor agonist, binds to a unique allosteric site and enhances GABA's effects [15]. This

mechanism induces sedation and anxiolysis with side effects less common than traditional benzodiazepines[16]. Given the involvement of GABA in immune modulation, zopiclone is therefore hypothesized to have immune-reducing effects on target immune cells through GABA-A receptor activation [17]. Zopiclone can thus reduce cytokine production and alter immune cell signaling by normalizing GABAergic activity in the immune system, contributing to the alleviation of RA symptomatology.

The aim of this trial is to evaluate the ability and safety of zopiclone on RA pathophysiology via its GABAergic effects and thus open a new therapeutic window via drug repurposing [18]. This has proved successful in rheumatology, where drugs for conditions other than RA had been put to successful use. For example, tofacitinib was specifically developed to avoid transplant rejection, while hydroxychloroquine was introduced as an antimalarial agent; both are now widely used for RA and lupus [19]. Minocycline is an antibiotic with reported early-stage RA benefit due to its anti-inflammatory properties [20]. Repurposing confers advantages like a shorter timeframe for drug development, lesser costs, and an established safety record, thus rendering this strategy apt for fulfilling the unmet needs of RA management [21]. Zopiclone enhances the GABA-A receptor function in such a way that its binding increases GABA-aided chloride influx into the cell. Such an intracellular environment may help establish an immune response characterized by sedation [22]. Preliminary evidence has pointed towards the role the GABAergic sedatives might play in altering the release of cytokines and activity of T cells, underlying the potential immune-modulating effects of zopiclone [23]. GABAergic signaling has been found responsible for inhibition of the pathway of T cell activation and the release of inflammatory cytokines such as IL-6 and TNF-α [24]. GABA will most probably translate similarly into RA applications, with effects of reducing immune cell infiltration and infiltration shown in animal models of autoimmune diseases ranging from multiple sclerosis to lupus [25]. Furthermore, GABA receptors mediated in the joints affected by RA may restrain joint inflammation and cytokine release; GABAergic drugs have already been shown to decrease inflammatory cytokine production and prevent immune cell migration to sites of inflammation [26]. Taken together, this evidence favors the potential use of zopiclone in RA treatment [27].

2. Materials and Methods

2.1 Data Preparation

Baricitinib as the Ligand:

The justification for the selection of baricitinib says- Baricitinib is an FDA approved drug for Janus Kinase inhibitor and has been chosen as an active ligand for this study. Originally it was indicated for rheumatoid arthritis but later it exhibited significant action with the JAK-STAT signaling pathway which is involved in various immune disorders. It was approved for the

treatment of severe COVID-19, which further authenticates its nature as an immune-modulator. With proven inhibition of JAK1 and JAK2, baricitinib is a highly valid candidate for the repurposing study as the possible compound to target JAK in various diseases.The 3D configuration of baricitinib was obtained from a public chemical database such as PubChem or DrugBank. These databases provide quality experimentally validated structural information in terms of atomic coordinates and bond orientations. Chemical Structure of Baricitinib (PubChem CID: 44205240) can be downloaded in standard file formats like SDF (Structure Data File) or PDB (Protein Data Bank format) and used for virtual screening and docking simulations. Further, the structure was prepared by geometrical optimization and removal of solvent molecules, if they exist, or co-crystallized ligands to obtain an accurate model for virtual screening.

2.2 Ligand-Based Virtual Screening Using DrugRep Platform

Morgan Fingerprint Method:

The Morgan Fingerprint algorithm is a circular fingerprinting method that encodes the molecular structure into binary understandable lines that reflect the chemical environment surrounding each atom. The structure is represented as a series of substructures with the center at the atom under consideration, which radiate outwards, say, for a specified radius of 2 or 3 bonds. So wherever these substructures go, unique identifiers (or a bit string) are calculated, which then are amenable to comparison with other molecules in a database under which structural similarity will be assessed. The most common way to determine the structural similarity between the molecules is using the Tanimoto coefficient, which accounts for values ranging from 0 to 1. The nearer to 1 the Tanimoto score is, the greater is the similarity between two compounds. Here in this work, using Morgan Fingerprint, the comparison between baricitinib and those with similar structures from the FDA-approved drug library was undertaken.

2.3 FDA-Approved Drug Library:

Composition of the library: Virtual screening was carried out under the umbrella of the FDA-approved drug library, containing compounds that have been approved for use in humans in various therapeutic areas. The library obtained substances from such databases as DrugBank, ZINC (ZINC15 FDA-approved subset), or PubChem, which all compile complete collections of FDA-approved drugs. This library typically contains several thousand compounds with experimental proof of pharmacological data and safety evaluation; a good candidate for repurposing.

Approximately 1,600–2,000 FDA-approved compounds were maintained in the library. Each compound's structure was standardized (e.g., removing the salts and normalizing bond orders) so that drugs could properly run through the virtual screening workflow.

2.4 The Virtual Screening Workflow on the DrugRep platform:

The Virtual Screening Workflow on the DrugRep platform: DrugRep was used in ligand-based virtual screening. This involved the following steps in the workflow:

Input preparation: The platform loaded the 3D structure of baricitinib and the FDA-approved drug library for comparison. Morgan Fingerprint calculation: For each compound in the drug library, calculated Morgan Fingerprint generating binary representation of its structure. Similarity search: The fingerprint of baricitinib was compared against all fingerprints of FDA-approved drugs in the library using the Tanimoto similarity coefficient. Ranking of compounds: Based on similarity scores comparing compounds to baricitinib, compounds were ranked. The system then provided a list of top-ranked substances with Tanimoto scores exceeding the defined threshold. Data export: The resulting compounds and similar scores were exported for subsequent validation of molecular docking studies.

3. Result and Discussion

Justification for selecting Baricitinib as the primary ligand

Table 1: Justification for selecting Baricitinib as the primary ligand for designing new Rumartho Arthritis targeting agent

Justification Factor	Description
Mechanism of Action	JAK1 and JAK2 inhibition reduces inflammation and joint damage in RA.
Clinical Efficacy	Demonstrated significant improvement in disease activity and quality of life in clinical trials.
Safety Profile	Well-documented adverse effects, providing insights for improving safety in new agents.
Pharmacokinetics	Favorable oral bioavailability and manageable half-life, serving as a practical model for new designs.
Targeting Mechanism	Reference for developing compounds with enhanced efficacy or alternative pathways for synergy.
Structure-Activity Relationship (SAR)	Known chemical structure allows for effective SAR studies to inform new compound development.
Market Experience	Insights into patient needs and treatment adherence from Baricitinib's real-world use.
Research and Development Context	Ongoing studies on Baricitinib provide valuable information on resistance mechanisms and combination therapies.

Results of Ligand-Based virtual screening by DrugRep

Table 2: Binding Affinities and Target Profiles of Compounds Identified through Ligand-Based Virtual Screening

No.	Compounds	Name	Score
1	DB11817	Baricitinib	1.000
2	DB08877	Ruxolitinib	0.469
3	DB08895	Tofacitinib	0.314
4	DB15091	Upadacitinib	0.242
5	DB00918	Almotriptan	0.221
6	DB00962	Zaleplon	0.211
7	DB08932	Macitentan	0.206
8	DB08881	Vemurafenib	0.204
9	DB01299	Sulfadoxine	0.202
10	DB00952	Naratriptan	0.200
11	DB06821	Sulfameter	0.200
12	DB01382	Glymidine	0.198
13	DB11336	Kinetin	0.198
14	DB01628	Etoricoxib	0.197
15	DB00969	Alosetron	0.193
16	DB00953	Rizatriptan	0.191
17	DB01198	Zopiclone	0.190
18	DB00402	Eszopiclone	0.190
19	DB00216	Eletriptan	0.189
20	DB00664	Sulfametopyrazine	0.189

From the table 1 and table 2, Baricitinib stands out as one of the best JAK inhibitors for rheumatoid arthritis with a score of 1.000 due to its very high binding affinity on various JAK targets (JAK1, JAK2, JAK3 and TYK2) defined by a broad spectrum of therapeutic activity. Ruxolitinib and Tofacitinib score lower (0.469 and 0.314, respectively) for a lesser degree of efficacy, while Upadacitinib scores 0.242, being highly selective for JAK1. Other compounds, ranging from Almotriptan to Zaleplon, were more directed against non-JAK pathways like serotonin receptors, possibly addressing pain but not pro-inflammatory pathways. Such heterogeneity in compounds underscores the trend in developing therapies for RA, which makes receptor binding affinities and receptor specificity crucial factors for effective treatment and combination therapy development. Baricitinib can thus be viewed as a reference compound for future drug development with an eye toward improving patient outcome in rheumatoid arthritis.

3 Docking:

Protein preparation and refinement

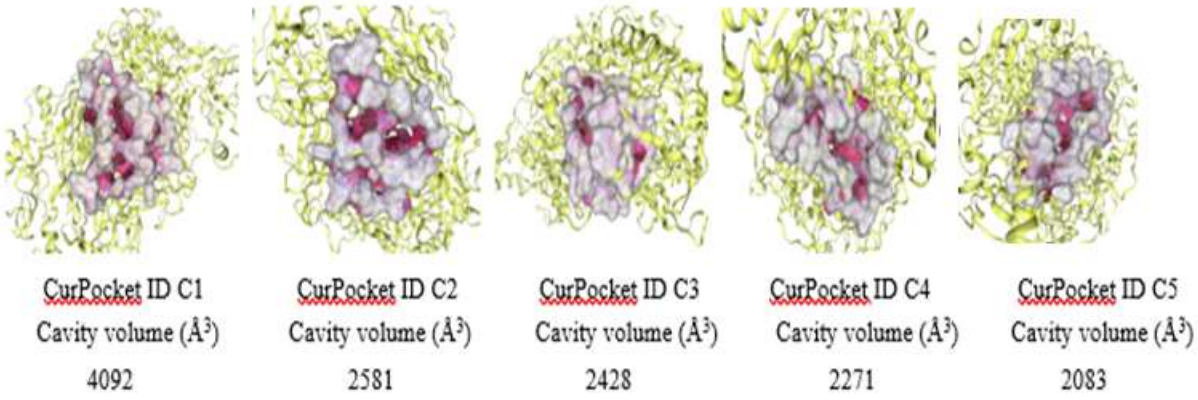

Figure 1: Visualization of Protein Binding Pockets (CurPocket ID C1-C5) with Corresponding Cavity Volumes

Figure 01 represents the mapping and analysis of five protein-binding cavities (CurPocket IDs C1 to C5) that vary in volume from 4092 Å³ to 2083 Å³. These imaged cavities are places where ligands interact with the protein, with larger cavities such as C1 (4092 Å³) favoring large ligands which may be significant for protein-ligand interactions. In contrast, smaller cavities such as C5 (2083 Å³) would accommodate small or specific molecules. Such cavity analysis is extremely valuable towards understanding protein functions and possibly offers help towards drug design by filtering the right binding sites for therapeutic molecules.

Result of refinement by PDB-REDO

Table 3: Validation metrics from PDB-REDO

Validation Metrics	Original	PDB-REDO
Crystallographic Refinement		
R	0.1841	0.1753
R-free	0.2204	0.2005
Bond Length RMS Z-score	1.369	0.425
Bond Angle RMS Z-score	1.086	0.637
Model Quality		
Ramachandran Plot Normality	17	45
Rotamer Normality	24	65
Coarse Packing	41	41
Fine Packing	6	10
Bump Severity	2	3
Hydrogen Bond Satisfaction	20	21

Table 03 gives validation statistics that showing significant improvement in the crystallographic model after refinement by PDB-REDO. The key metrics R-factor and R-free decreased from 0.1841 to 0.1753 and from 0.2204 to 0.2005, respectively, indicating close correspondence between observed and calculated values. Furthermore, a dramatic improvement in the Bond Length RMS Z-score from 1.369 to 0.425 and from 1.086 to 0.637 for the Bond Angle RMS Z-score was achieved, showing much better accuracy of bond geometry. The higher value in Ramachandran plot normality from 17 to 45 indicates higher proportions of residue in favorable conformations, while rotamer normality similarly increased from 24 to 65, suggesting better arrangements of side chains. While coarse packing remained stable at 41, fine packing increased from 6 to 10, suggesting improved atomic arrangements. Although the severity bumping slightly increases from 2 to 3, the overall improvement in hydrogen bond satisfaction from 20 to 21 increases stability. In summary, these parameters collectively shows that the results of refinement by PDB-REDO provide a structure that is more accurate and useful for understanding function and for facilitating additional research and drug design.

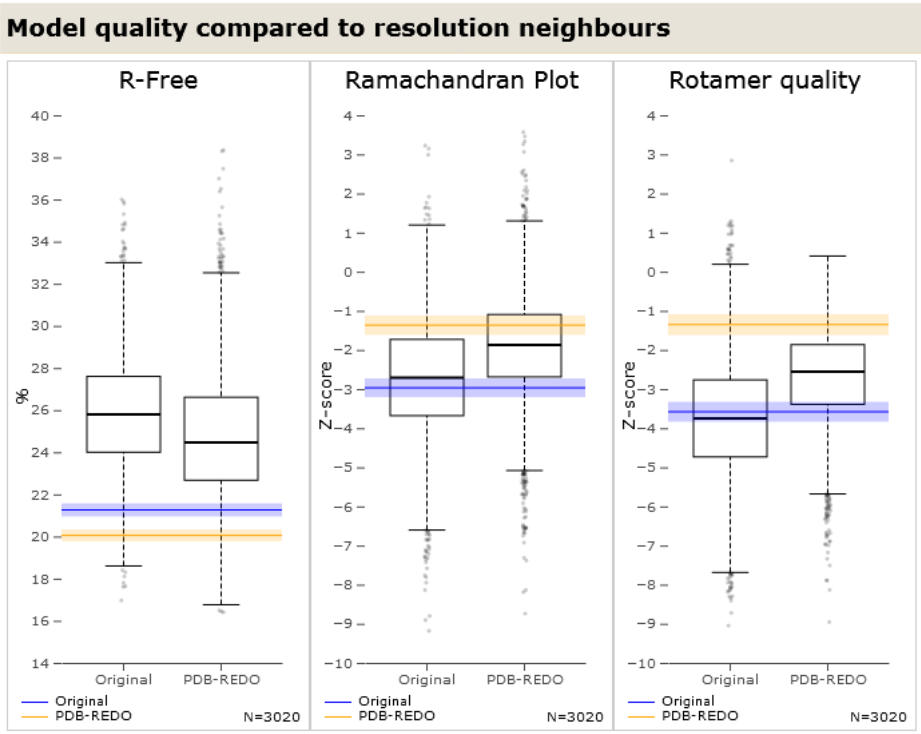

Figure 2: Comparison of Protein Model Quality Metrics: R-Free, Ramachandran Plot, and Rotamer Quality for Original vs PDB-REDO Models

Model comparison will be made for protein quality metrics including R-Free, Ramachandran plot, and rotamer quality, between the original and the PDB-REDO refined models, using box plots. All three metrics favor PDB-REDO: R-Free-

indicating a better fit for experimental data; better Ramachandran plot statistics-positive in favor of residues in more favorable dihedral angle regions-improved rotamer quality-likely achieving side-chain conformations with better accuracy. Overall, PDB-REDO improves the structure refinement compared to the original model (Figure 2).

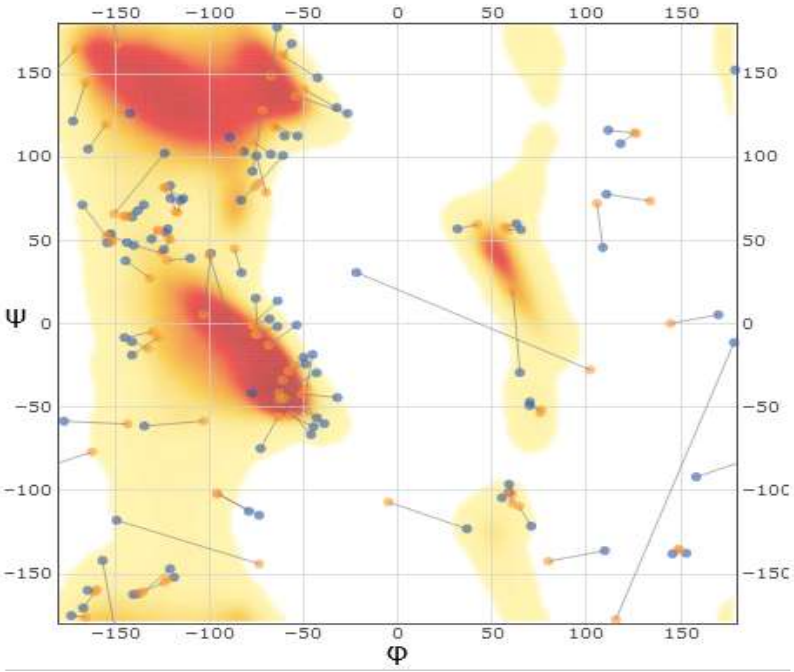

Figure 3: Keywegt-like plot

Box plots of model quality metrics such as R-Free, Ramachandran plot statistics, and rotamer quality compare the original versus PDB-REDO refined models. All three show PDB-REDO to be superior: further decrease in R-Free gives better agreement with experimental data, Ramachandran plot statistics were better, indicating more residues in favorable dihedral angle regions, and rotamer quality clearly indicates more accurate side-chain configurations. Hence, the PDB-REDO process achieves better structural refinement than the original model (Figure 3).

Molecular Docking results

Table 4: Docking Scores and Binding Affinities of Compounds Against Target Pockets

Drug Bank ID	Drug	Pocket	Score	Drug Bank ID	Drug	Pocket	Score
DB11817	Baricitinib	C3	–9.2	DB06821	Sulfameter	C1	–7.5
DB08877	Ruxolitinib	C4	–9.1	DB01382	Glymidine	C1	–7.5

DB08895	Tofacitinib	C5	–8.8	DB11336	Kinetin	C1	–7.3
DB15091	Upadacitinib	C5	–9.9	DB01628	Etoricoxib	C1	–8.5
DB00918	Almotriptan	C5	–8.0	DB00969	Alosetron	C1	–8.5
DB00962	Zaleplon	C5	–9.0	DB00953	Rizatriptan	C1	–9.6
DB08932	Macitentan	C3	–8.7	DB01198	Zopiclone	C1	–9.6
DB08881	Vemurafenib	C3	–9.8	DB00402	Eszopiclone	C1	–9.0
DB01299	Sulfadoxine	C3	–7.4	DB00216	Eletriptan	C1	–9.4
DB00952	Naratriptan	C1	–8.8	DB00664	Rizatriptan	C3	–7.4

The table 4 and figure 4 describes the binding affinities of different compounds in different pockets with respect to their possible behavior as therapeutic agents. With a binding affinity of -9.9 in pocket C5, Upadacitinib shows the greatest affinity for binding, followed closely by Vemurafenib with a binding affinity of -9.8 in pocket C3. This strong interaction may indeed contribute to their greater efficacy as therapeutic agents. Baricitinib and Ruxolitinib are two known JAK inhibitors that also bind with considerable affinity with -9.2 and -9.1, respectively. On the contrary, less favorable binding affinities were exhibited by Sulfadoxine and Glymidine at -7.4 and -7.5, respectively, which may limit their therapeutic usefulness. The variability in binding scores in different pockets underscores the importance of specific interactions in drug design, such that lower scores correspond to higher likely efficacies. The overall data reiterate the significance of pocket selection and binding affinity in the optimization of effective pharmacological agents.

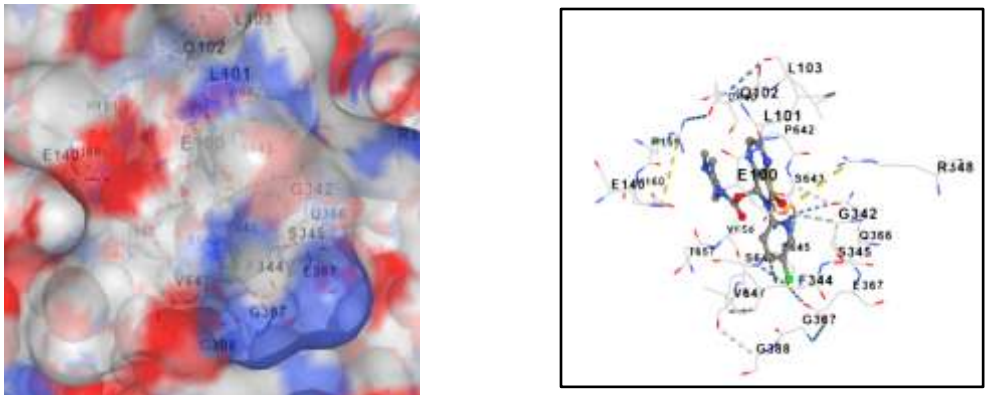

Figure 4: Molecular Docking of Ligand within the Active Site of a Protein: Electrostatic Surface and Ligand-Protein Interaction Visualization"

An illustration of protein-ligand interactions shows protein-ligand surfaces on the left, and an interactive map showing details of the interactions on the right. The surface model painting of red, blue, and white is likely a representation of charge distributions

within the binding cavity and insight into interactions of the ligand with the electrostatic environment around the protein. The right side shows the 2D diagrammatic representation of various molecular interactions, such as hydrogen bonds and hydrophobic contacts between the ligand and key residues within the binding site of the protein. In essence, overall, the images provide a fundamentally expanded view of the mechanism of ligand binding, which is important for protein-ligand interaction study and the subsequent drug design or examination of biochemical paradigms.

4. CONCLUSION

The analysis highlights the promising role of Baricitinib as a primary ligand in developing new therapeutic agents for rheumatoid arthritis (RA). Its exceptional binding affinity across multiple JAK targets—scoring 1.000—demonstrates broad therapeutic efficacy, positioning Baricitinib as a benchmark for future drug design aimed at enhancing patient outcomes in RA treatment.

The mechanism of action reveals that Baricitinib's inhibition of JAK1 and JAK2 is crucial in reducing inflammation and joint damage, aligning with therapeutic goals for RA management. Comparative binding affinities from docking results show that other compounds, such as Upadacitinib and Vemurafenib, exhibited strong affinities, yet none matched Baricitinib's efficacy, with Upadacitinib scoring -9.9 in pocket C5, indicating its potential as an alternative treatment option.

Additionally, the PDB-REDO refinement process significantly improved the structural model, with key metrics like the R-factor and Ramachandran plot normality showing marked enhancements, which are vital for accurate modeling of protein-ligand interactions and informing future drug design efforts.

The presence of non-JAK compounds in the docking analysis suggests avenues for combination therapies; while Zopiclone, primarily a GABA receptor modulator, scored lower in binding affinity, its sleep-inducing properties could help address the quality of life issues often experienced by RA patients.

Furthermore, the visualization of ligand-protein interactions underscores the importance of electrostatic interactions in binding efficacy, guiding future modifications to enhance the therapeutic potential of sleep-inducing agents like Zopiclone for RA treatment modulation.

Overall, this analysis establishes a foundation for future research into the repurposing of sleep-inducing agents in conjunction with established RA treatments, suggesting that, while Zopiclone alone may not exhibit strong anti-inflammatory effects, its ability to improve sleep and overall patient quality of life could significantly enhance treatment adherence and outcomes in a multimodal therapeutic strategy. The integration of sleep-modulating treatments could provide a novel approach to managing the

multifaceted challenges posed by rheumatoid arthritis.

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