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Original Research Article

Computational design of phosphoinositide 3-kinase gamma (PI3Kg) inhibitors as a newer therapy for rheumatoid arthritis

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Abstract

Purpose: *To develop a potential therapy for rheumatoid arthritis (RA) by altering factors involved in the pathogenesis of the disease.*
Methods: *Molecular docking simulation-based virtual screening was performed against phosphoinositide-3-kinase gamma (PI3Kg) to identify potential leads that may serve as anti-rheumatoid arthritic agents through their interactions and binding energies with the target receptor, followed by their optimization for improvement of their pharmacokinetics and toxicity profiles.*
Results: *Molecular docking simulation-based virtual screening and computational toxicity profiling predicted that the lead compounds ZINC04376856, ZINC01729526, ZINC01045089, ZINC03954520, ZINC01738764, and ZINC01163259 were potent PI3Kg inhibitors.*
Conclusion: *These lead compounds exert potent inhibitory effects on human PI3Kg receptor. Thus, they need to be experimentally validated for use in the development of novel drugs for treating RA in humans.*

Keywords: *Phosphoinositide 3-kinases, Rheumatoid arthritis, PI3Kg, Molecular docking*

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints. About 1% of the total human population is afflicted with RA. The etiology and pathophysiology of this complex human disorder are still poorly understood. Available treatment for the disease merely produces symptomatic relief from joint pain, a prominent symptom of RA. Moreover, the use of steroidal anti-inflammatory agents is associated with serious adverse effects. Studies on existing anti-RA drugs using various animal models have revealed the mechanism involved in the pathogensis of RA. Elevated cellular infiltration, formation of pannus, synovial hyperplasia and cartilaginous erosions in distal joints are actively involved in the pathophysiology of RA [1,2].

The involvement of B and T cells of the inflamed joints in the initiation of RA via production of chemokines results in the biosynthesis of inflammatory agents responsible for RA-induced pain. Inflammatory agents such as leukocytes, T

cells and macrophages are responsible for the destructive processes involved in the pathogenesis of RA [3,4].

Ample of evidence indicate the involvement of mast cells and neutrophils in RA. Neutrophils are the most abundant cell types in the inflamed joints. They are also capable of initiating inflammatory damage and prolongation of the arthritic condition. Chemotaxis and leukocyte activation are inhibited either by inhibiting the biosynthesis of the chemo-attractants or by blocking their respective receptors [1,5].

The pathophysiological involvement of PI3Kg in enhancing leukocyte activation and chemotaxis, as well as degranulation of mast cells has been confirmed using gene targeting methods [6]. Thus, suppression of PI3Kg may be a novel therapeutic approach for the treatment of RA and other inflammatory disorders [7]. In the current study, *in silico* structure-based design approach was applied to design potential inhibitors of PI3Kg so as to develop novel anti-RA therapy.

A ligand library consisting of 1590 diverse ligand molecules were virtually screened against the PI3Kg enzyme to identify potential leads for use in suppressing inflammation in joints affected by RA, with a view to preventing tissue damage in both lymphocyte-dependent and lymphocyte-independent RA.

EXPERIMENTAL

Selection and preparation of macromolecule for docking

Human phosphoinositide 3-kinase (PI3Kg) bound to an antagonist AS605240 (QYT) (pdb code2a5u) was obtained from the RCSB protein data-bank (PDB) [8]. The three-dimensional (3D) structure of PI3Kg is shown in Figure.1. The ligand molecule was separated from the structural protein model of human PI3Kg receptor using software chimera. Redundant water molecules present in the macromolecular crystal structure were removed, and polar hydrogen atoms were added to the macromolecular structure model prior to performing docking simulations [4,9,10].

Preparation of ligand for molecular docking

Rotatable, unrotatable and non-rotatable bonds in the QYT ligand were endorsed in AutoDock prior to performing docking simulations [12-16].

Identification of ligand binding site

The binding site was identified within the structural model of human PI3Kg enzyme using the residues of the macromolecule that interact with the QYT ligand, with the help of PyMol software [17–19].

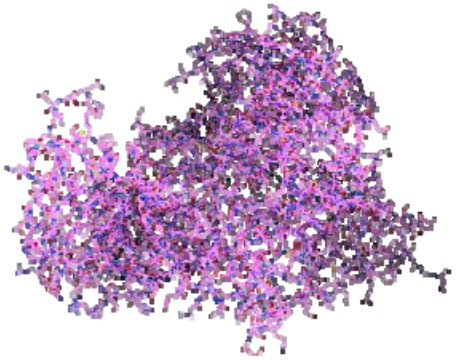


Figure 1: Structural model of protein phosphoinositide 3-kinase gamma (PI3Kg) complexed with an antagonist [4, 8, 11] (PDB ID-2a5u)

Molecular docking

The identified binding site within the human PI3Kg enzyme was further utilized to specify grid parameter points required to generate the grid box. The generated grid box was then utilized to perform all the docking cycles in the current *in silico* studies. The grid box was located by considering the ligand as a centre, and also by wrapping each of the macromolecular residues interacting with the ligand to make sure that every possible ligand conformation falls inside the grid box [12,20-22]. The grid box used in the current *in silico* studies is shown in Figure 2.

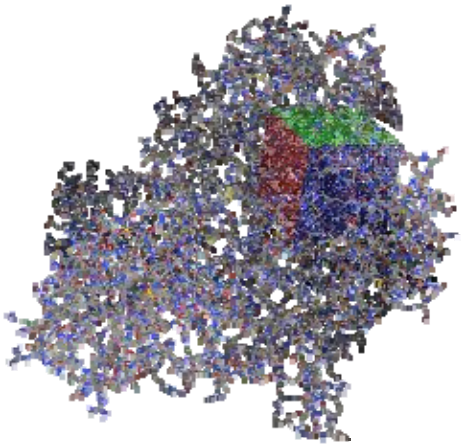


Figure 2: 3D grid-box utilized in the docking studies on human PI3Kg enzyme

The Autogrid software generates map files for different types of atoms present in the ligand and receptor. In the current study, map files for A C HD N OA SA NA were prepared using Autogrid. The prepared map files were utilized for performing molecular docking simulations with AutoDock software [23-25]. The AutoDock software utilizes Lamarckian genetic algorithm (LGA) as its primary conformational search algorithm for performing docking studies. Trajectory population of the possible conformations of the ligands and their mutational conformations were generated using LGA.

This was followed by exchange of various parameters so as to resist style-related consecutive generations of the biological evolutions for decisive selection of ligands with minimum binding energy values. The additional features of the ‘‘Lamarckian’’ aspect include individual and selective conformational search for local conformational space, identification of local minima, and transfer of the generated information to the later generations. Semi-empirical force field was utilized to predict ligand binding energy with reference to the specific macromolecular target.

The force field predicts the binding energy of the ligand by allowing integration of the intra-molecular energies through energetics of their bound and unbound states on the basis of a comprehensive thermodynamic model. The docking parameter file (DPF) consists of various parameters required for performing docking of each ligand molecule [20,24-26].

Validation of docking methodology

The probable binding patterns of ligands were obtained on the basis of their positions and orientations identified after the molecular docking simulations. The parameters included in the current *in silico* study were validated by performing docking of human PI3Kg enzyme against the crystallized ligand QYT [13, 27-29]. The *in silico* docking methodology was validated through overlay methods and chemical resemblance:

(a) Overlay methods

The ligand overlay methodology was applied for the validation of docking parameters utilized in the current study. The parameters utilized in the current docking study were deemed to be successfully validated if the docked conformation was perfectly overlaid over the crystallized bioactive conformation of the ligand available in the macromolecular complex [16, 26-28].

(b) Chemical resemblance

The parameters used in the current docking protocol were validated using resemblance between the chemical interactions observed in the conformation of the reference ligand docked with the macromolecular target, and the interactions of the bioactive crystallized conformation present in the bioactive crystallized macromolecular complex structure [14,22-25].

***In silico* virtual screening**

The ligand library i.e. diversity set II released by National Cancer Institute (NCI) was used in the current study to perform virtual screening against human PI3Kg enzyme. There were 1593 diverse ligands in diversity set II. Molecular docking simulation-based virtual screening was performed against validated human PI3Kg enzyme using these ligands so as to identify the potential leads [14,22,23].

Analysis of docking results

The evaluation of results of docking of all the ligands against human PI3Kg enzyme was performed by considering each interaction with the macromolecular binding residues. The free energy of bonding for each ligand ought to be well within the pre-defined empirical range of -5 to -15 kcal/mol.

The lead molecules were shortlisted based on minimum binding free energy. The LGA was utilized as a scoring function in the AutoDock tool [14,25,27]. Eq 1 was used to generate the binding affinity of the specific ligand against a specified macromolecular target:

$K_i = e\{(\Delta G/(RT)\}$ …… *(1)*

where ΔG = free energy change on binding, T = temperature in Kelvin, and R = universal gas constant.

Pharmacokinetics and toxicity studies

Pharmacokinetic assessment of all the shortlisted leads was performed by calculating some important physicochemical parameters using online platform Osiris Molecular Property Explorer. Osiris Molecular Property Explorer software was also used to identify key toxic effects such as reproductive effects, mutagenic effects, irritant effects and tumorigenicity in the shortlisted leads [13,23,29].

RESULTS

Macromolecular selection and preparation

The three-dimensional structural model of human PI3Kg consisting of a single polypeptide chain of 966 amino acid residues was resolved with X-ray diffraction method at a resolution of 2.7Å. The bound ligand molecule (QYT) was separated and the processed macromolecular structure model was saved in the AutoDock format (*. pdbqt) for use in performing docking simulations.

Ligand preparation

Eleven aromatic carbons with five rotatable bonds were present in the ligand QYT. All the five bonds of the QYT ligand were kept rotatable in the current computational study, and were also saved in the pdbqt format of the AutoDock software.

Identification of ligand binding site and grid box formation

The macromolecular binding residues Lys833, Ile831, Met953, Ile879 and Ile963 were involved in the active binding of the ligand QYT with human PI3Kg enzyme. The chemical interactions of ligand QYT with human PI3Kg enzyme are shown in Figure 3.

An imaginary grid box was arranged by wrapping up the ligand molecule QYT as well as all the binding residues of the PI3Kg enzyme. The grid coordinates utilized for the preparation of the grid-box are given in Table 1.

Validation of molecular docking

The results of docking the ligand QYT against human PI3Kg enzyme are shown in Table 2.

The parameters utilized in the molecular docking simulation of human PI3Kg enzyme were successfully validated through the following methods:

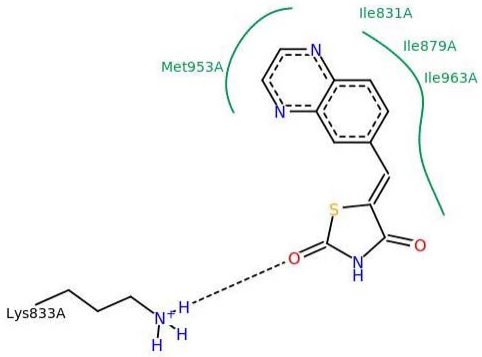


Figure 3: Chemical interactions of human PI3Kg enzyme with the bound ligand QYT

(a) Overlay

The docked conformation of the ligand QYT was perfectly overlaid over perfectly overlaid over the crystallized bioactive conformation, thereby successfully validating the molecular docking methodology in the current *in silico* studies [23, 28]. The perfectly overlaid conformation of the docked ligand QYT with respect to its crystallized conformation is presented in Figure 4.

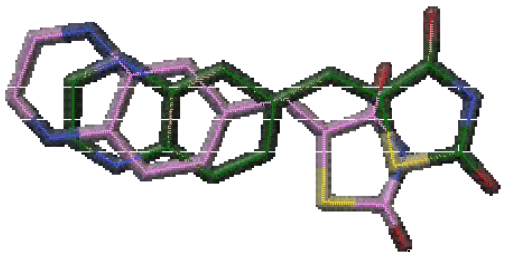


Figure 4: Superimposed overlaid conformation of the docked ligand QYT with respect to its crystallized conformation obtained from the bioactive complex structure

(b) Chemical resemblance

The docking of the human PI3Kg enzyme was further validated using resemblance of the chemical interactions of the docked conformation of the ligand.

Table 1: Coordinates of grid-box for the human PI3Kg enzyme

Macromolecule	X-axis	Y-axis	Z-axis	Spacing (Å)	X-centre	Y-centre	Z-centre
2a5u	40	40	40	0.447	42.465	14.195	31.784

Table 2: Docking results for ligand QYT against human PI3Kg enzyme (2a5u)

Macromolecule	Binding residues	RMSD	Binding energy (kcal/mol)
2a5u	Lys 833, Ile 831, Met 953, Ile 879 and Ile 963	1.6	-8.9

This resembled exactly the interactions present in the bioactive crystallized conformation of the ligand. The chemical interactions involved in the binding of the docked conformation of the ligand with respect to its crystallized bioactive conformation are shown in Figure 5.

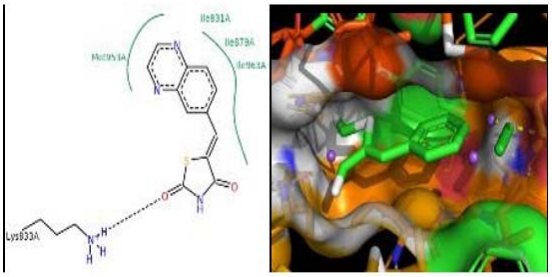
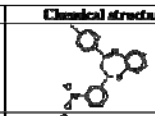
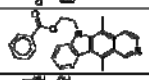
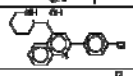
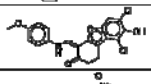
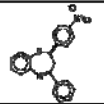
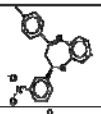
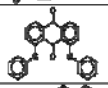
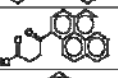
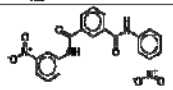
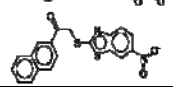


Figure 5: Chemical interactions involved in the binding of the ligand QYT within the PI3Kg binding site

Virtual screening

The leads were selected on the basis of their affinities for human PI3Kg enzyme. The binding energies obtained after docking-based virtual screening of the top 10 shortlisted ligand molecules are shown in Table 3.

Table 3: Binding energies of 10 shortlisted top leads for human PI3Kg enzyme

S/no.	Zinc code	Chemical structure	Binding energy
1	ZINC04376856		-11.35
2	ZINC01635676		-10.86
3	ZINC01729526		-10.60
4	ZINC05487838		-10.59
5	ZINC01045089		-10.36
6	ZINC03954520		-10.17
7	ZINC05124931		-10.11
8	ZINC00154888		-10.02
9	ZINC01738764		-10.01
10	ZINC01163259		-9.97

ADME-T profiling

Pharmacokinetic evaluation and the prediction of toxic effects of the shortlisted lead molecules against human PI3Kg enzyme were performed using online Osiris molecular property explorer server. The pharmacokinetic profiling of the leads was done through determination of physicochemical properties such as molecular weight, partition coefficient, solubility, hydrogen bond-donor (HBD) and hydrogen bond-acceptor (HBA) sites of the individual lead molecules in line with Lipinski's Rule of Five. The presence of major toxic effects (mutagenicity, tumorigenicity, irritability and reproductive effects) were predicted by considering the presence of specific functional groups already present in drugs with similar toxic effects. The results of toxicity profiling for all the shortlisted leads are shown in Table 4. The profiling of the ten shortlisted lead molecules for the presence of any major associated toxicity revealed that six molecules, i.e. ZINC04376856, ZINC01729526, ZINC01045089, ZINC03954520, ZINC01738764 and ZINC01163259 did not bear any functional group associated with key toxic effects such as mutagenicity, irritability, tumorigenicity and reproductive defects. Moreover, they had very good pharmacokinetic profiles.

Table 4: Toxicity profiles of the 10 lead molecules for human PI3Kg enzyme

S/no.	ZINC Id	Mut	Tum	Irr	Rep	MW	cLogP	TPSA	D-Liken	D-Score
1	ZINC04376856	Nil	Nil	Nil	Nil	374	4.57	83.48	-2.86	0.23
2	ZINC01635676	High	Nil	High	Nil	394	5.29	44.12	3.8	0.15
3	ZINC01729526	Nil	Nil	Nil	Nil	352	4.11	45.15	0.7	0.47
4	ZINC05487838	Nil	Nil	Nil	High	403	4.08	71.7	-0.65	0.19
5	ZINC01045089	Nil	Nil	Nil	Nil	360	4.23	83.47	-4.95	0.25
6	ZINC03954520	Nil	Nil	Nil	Nil	374	4.57	83.48	-2.86	0.23
7	ZINC05124931	Low	Nil	High	Nil	424	6.68	84.74	-1.9	0.07
8	ZINC00154888	High	High	Nil	Nil	302	4.19	54.37	-1.54	0.1
9	ZINC01738764	Nil	Nil	Nil	Nil	406	2.11	149.8	-5.59	0.29
10	ZINC01163259	Nil	Nil	Nil	Ni;	380	3.96	129.3	-8.16	0.22

DISCUSSION

The mast cell and neutrophils are involved in the initiation and progression of the inflammatory damage in the RA. The human PI3Kg is having a pronounced role in the inflammatory damage as well as progression of the diseased condition in RA. Thus, a computational framework has been developed and implemented in the current research protocol to target the human PI3Kg as a potential anti-inflammatory drug target for screening of a ligand library consisting of 1593 diverse ligand molecules intended to identify a potential inhibitor molecule based upon its interactions with the target receptor as well as optimized pharmacokinetic profile.

The three-dimensional structure model of PI3Kg complexed with a ligand QYT was procured from the RSCB protein data bank. The crystallized structure model was resolved with the help of X-ray diffraction method at a resolution of 2.7 Å. The ligand and the macromolecular target were separated with the help of software Chimera. The separated ligand and macromolecular target were again docked to validate the utilized docking protocols followed by the screening the ligand library by using the validated parameters.
The potential lead molecules shortlisted after performing the molecular docking simulation based virtual screening were evaluated for their pharmacokinetic as well as toxicity profile based upon their physicochemical and functional parameters. Those lead molecules which are having optimized pharmacokinetic profile without presence of any major toxic effects were proposed as a potential inhibitor molecule targeting human PI3Kg receptor as a novel therapy for the treatment of RA.

CONCLUSION

Molecular docking simulation-based *in silico* screening of large ligand libraries is a very useful method for the discovery of novel inhibitor molecules as well as establishment of the mechanisms of action of newly identified inhibitor molecules. Based on the binding energy of the ligand molecules predicted by observing their affinities to, and chemical interactions with human PI3Kg receptor, some potential lead molecules have been shortlisted from a ligand library of 1593 diverse ligands. The shortlisted lead molecules have been further screened for their pharmacokinetic profiles as well as presence of major potential toxic effects, based on their physicochemical properties and functional group analysis. The leads, ZINC04376856, ZINC01729526, ZINC01045089, ZINC03954520, ZINC01738764 and ZINC01163259, have very good pharmacokinetic profiles without the presence of any major toxic effects such as mutagenicity, tumorigenicity, irritability and reproductive effects. Moreover, they are believed to have potential inhibitory effects against human PI3Kg receptor. Therefore, these lead molecules need to be experimentally validated for use in the development of novel therapies for rheumatoid arthritis.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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