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Research Article

Small Molecule Inhibitors Targeting Endothelial IL-1β Receptor (IL-1R1): A Novel Approach to Atherosclerosis Therapy

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Abstract

The current study identifies small molecules targeting the endothelial IL-1β receptor (IL-1R1), thereby ameliorating atherosclerosis progression. Macrophage IL-1β plays an essential role in the advancement of atherosclerosis by binding to the IL-1R1 thereby increasing endothelial junction permeability. IL-1RA is a IL-1R1 antagonist which binds to it and limits its interaction with the IL-1β. We investigated the critical binding residues on the IL-1R1 binding site, interacting with IL-1RA and a total of 12 important IL-1R1 residues were identified at the interface (4Å region). These findings helped us design potent antagonists for IL-1R1 post screening a small molecule library targeting these 12 residues on the IL-1R1. Virtual screening using various state-of-art softwares suggested six compounds interacting with most of the essential residues on the IL-1R1 with significantly high docking energy. The compounds were found to have excellent physicochemical and ADMET properties for therapeutic purposes. Thus, the screened compounds hold excellent potential as IL-1β receptor inhibitors thereby limiting the progression of atherosclerosis. Further studies are required to determine the efficacy and effectiveness of the compounds at the in-vitro and in-vivo levels.

Keywords: IL-1β; IL-1R1; Small molecule inhibitor; Virtual screening; Atherosclerosis

Introduction

Atherosclerosis is a chronic inflammatory disease in which plaque builds up in the wall of the arteries, leading to plaque formation. Rupture of this plaque leads to blood clot formation, and subsequently leads to sudden cardiac arrest. Thus, understanding the mechanism of plaque formation can help design a therapeutic strategy to limit its progression [1,2]. Macrophage plays an important role in foam cell formation and certain pro-inflammatory cytokines released by macrophage leads to further chronic consequences in development of plaque [3]. One such cytokines is IL-1β. IL-1β plays an important role in development of atherosclerosis. Uptake of Ox-LDL by macrophage leads to activation of signaling cascade, leading to IL-1β expression [4]. IL-1β induces expression of adhesion factors (such as ICAM-1 and VCAM-1) and chemokines (such as MCP-1), which helps in the adhesion and accumulation of inflammatory cells to the intimal site, initiating the plaque formation [5]. Cytokines such as IL-6 and MMPs are also induced by IL-1β. IL-6 helps in formation of thrombosis while MMPs (such as MMP-1, 8 and 13)

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ruptures the fibrous cap, leading to thrombus formation [6,7]. Recent study has also investigated the role of Nitric Oxide Synthase (NOS)-1 mediated expression of IL-1β in macrophage after Ox-LDL uptake and the expression of adhesion molecules on the endothelial cells [8,9]. Thus, therapeutic strategy targeting IL-1β would play an important role in decreasing the foam cell formation by the macrophage and in inhibition of atherosclerosis at every stage of the disease.

Several therapeutic strategies such as recombinant proteins, monoclonal antibodies and vaccines have been used to target the IL-1β signaling in atherosclerosis [4]. Anakinra, a recombinant human interleukin receptor antagonist which can antagonize IL-1β by binding to the IL-1β binding site on the IL-1R1 receptor and limits the binding of the IL-1β to the receptor [10]. For instance, in phase 2 trial, anakinra was found to reduce the plaque by 30% in atherosclerotic mice, decrease triglyceride levels and macrophage infiltration in $ApoE^{-/-}$ mice [11]. But it requires regular injections which can led to adverse drug effects and block both IL-1α and IL-1β binding, which can be detrimental [12]. Hence, the non-specificity and case of daily administration limits its usage. Another approach is the usage of monoclonal antibodies. Canakinumab and Gevokizumab are the monoclonal antibodies which have been used to selectively target IL-1β by forming antigen-antibody complex and sequestering the IL1β binding to the receptor [13]. They have also shown prolonged half-life and doesn't require daily administration [14]. But, during the in-vitro studies they have been found to be leading to the plaque instability in $ApoE^{-/-}$ mice [15]. Thus, alternative therapeutic strategies are required which provides higher specificity as well as doesn't require daily administration to overcome the limitations of already known inhibitors.

Drug discovery is a time-consuming and expensive process. Structure Based Virtual Screening (SBVS) can help reduce the time and cost involved in researching new drugs. SBVS predicts the best interaction mode between the two molecules to form a stable complex, and uses scoring functions to estimate the non-covalent forces between the target and the ligand. The technique helps in prediction of the active lead molecules before their synthesis [16]. Other factors such as toxicity, bioavailability and efficacy of the compound can also be checked before moving to the in-vitro and in-vivo process, thus saving time and effort. The process starts with the identification of molecular target for a given compound followed by virtual screening to identify the active drug candidate. This is followed by lead optimization by improving the binding and physicochemical properties of the compound [16]. Many compounds have been in the market through virtual screening such as saquinavir, ritonavir and indinavir (treatment for HIV), dorzolamide (for glaucoma), boceprevir (for Hepatitis C), among others [16,17]. Thus, the current study undertook the approach of SBVS to identify the lead molecule(s) against the target receptor.

Thus, the current study deals with the identification of novel molecule inhibitors against IL-1β receptor (IL-1R1), leading to the blockage of signaling with the IL-1β. Critical residues on the IL-1β mediating the interaction with the receptor were identified and virtual screening was done to identify lead compounds blocking receptor-ligand interaction. Further, physicochemical and ADMET analysis of the compounds were done to check the pharmacokinetics and toxicity profile of the compounds. The screened compounds showed promising results in the in-silico study, but the in-vitro and in-vivo studies are required to check the efficacy and effectivity of the compounds with the IL-1β receptor to limit the IL-1β signaling in atherosclerosis, leading to deceases in the atherosclerosis progression.

Methods

Analyses of the crystal structure of IL-1β and IL-1R1-Crystal structure of the IL-1β and IL-1R1 was retrieved from RCSB PDB (https://www.rcsb.org/) (PDB 4DEP). The structure consists of ternary complex of IL-1β-IL-1R1-IL-1RAcP. Single chain of IL-1β (Chain D) and IL-1R1 (Chain E) were considered for further study, deleting the other chains from the complex. The structures were further processed by deleting water molecules and heteroatoms and used for further study. Analysis of the crystal structure between IL-1RA-IL-1R1 was also done to compare the common interacting residues between the IL-1β and IL-1RA with the IL-1R1. Crystal structure of IL-1RA-IL-1R1 complex was downloaded from RCSB PDB (PDB 1IRA). The structure consists of single chain of IL-1RA (Chain A) and IL-1R1 (Chain B) interacting with each other. Water molecules and heteroatoms were deleted from the structure and used for further studies. 4Å interacting residues between both the complexes were analyzed in UCSF Chimera [20] to check the difference in the binding of the ligand(s) with the domains of the IL-1R1 receptor and to decipher the common interacting residues between the complex.

Screening of small molecule inhibitor against IL-1R1 receptor- Interaction of IL-1β with the domain 1 and 2 of the IL-1R1 receptor is critical for its activity [18]. Hence, critical interacting residues in domain 1 and 2 of IL-1R1 with the IL-1β in the crystal structure were analyzed in UCSF Chimera [20]. Targeting these residues in the complex can help in the inhibition of the interaction of the receptor with the IL-1β. Hence, library of FDA-approved compounds was downloaded from ZINC-15 [22]. A total of 1614 compounds were retrieved from the database in SDF format. The resultant compounds were then converted to pdbqt by OpenBabel [29]. The ligands were then subsequently used for docking in Schrodinger [24] and AutoDockVina v1.2.0 [25,26]. Glide module of the Schrodinger suite was used for docking [23]. Crystal structure of the IL-1R1 (PDB 4DEP; Chain E) was retrieved from RCSB PDB (https://www.rcsb.org/). Protein preparation wizard of Schrodinger suite [30] was used to prepare the structure of the protein for docking. Structure was then refined and optimized in PROPKA at pH 7.0 [31] followed by minimization using OPLS4 force-field [32]. Receptor grid was then generated around the receptor covering the domain 1 and 2 of the receptor. LigPrep module of Schrodinger suite [33] was used to prepare ligands for docking in Schrodinger. For docking in AutoDockVina, polar hydrogen atoms and Kolmann charges were added on the crystal structure of IL-1R1 (PDB 4DEP; Chain E) in AutoDock 4 [34]. Grid box was then generated around the receptor covering the whole molecule (blind docking) and ligands were then docked with the receptor in AutoDockVina v1.2.0 [26]. Ligands were converted to pdbqt in OpenBabel [29] and used for docking in AutoDockVina. For short listing the compounds, the compounds positive in both the platforms were considered. Dock score up to -5 were considered for Schrodinger and its corresponding dock score up to -6 in AutoDockVina. Further, the compounds were selected based on its interaction with the 12 critical residues on the receptor. This was followed by ADMET analysis of the compounds to derive its pharmacokinetic properties.

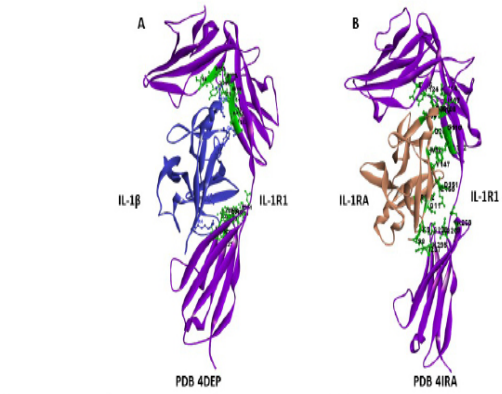
ADMET analysis of the screened compounds- pkCSM server (https://biosig.lab.uq.edu.au/pkcsm/) [28] was used to analyze the physicochemical and ADMET properties of the compounds. pkCSM uses graph-based signatures of the compounds to ana-

lyze the ADMET properties of the compounds by comparing it with the available in-vitro data on the server. The compounds positive in the physiochemical and ADMET properties were finalized as a therapeutic molecule in inhibiting the IL-1β interaction with the receptor.

Result and Discussion

Analyses of the crystal structure of IL-1β and IL-1RA with IL-1R1-IL-1β plays an important role as a pro-inflammatory cytokine in atherosclerosis. It is expressed as inactive pro-IL-1β form in macrophages stimulated by Ox-LDL, which later gets activated by various caspases. The active IL-1β can then bind to the IL-1R1 receptor and leads to its dimerization with IL-1RaP, further activating transcription factor NF-κB and contributes to the expression of pro-inflammatory cytokines [18]. IL-1β also leads to the expression of IL-6, ICAM-1, VCAM-1 and various MMPs (such as MMP-1, 8 and 13) which causes infiltration of various immune cells into the intima as well as leads to event of plaque instability and thrombosis [5,6]. Thus, it becomes evident to design a therapeutic strategy targeting the binding of the IL-1β with the receptor which can limit the chronic consequences of the atherosclerosis. IL-1RA is a natural antagonist present in the cellular system which binds to IL-1R1 receptor and inhibits the interaction of the receptor with the IL-1β, thus limiting the inflammatory signaling process [19]. Hence, it becomes important to study the common interacting residues between the IL-1β and IL-1RA with the IL-1R1 to design a therapeutic strategy against those residues. PDB structure of IL-1β and IL-1R1 was retrieved from RCSB PDB (PDB 4DEP) and 4Å interacting residues between the complex were analyzed in UCSF Chimera [20]. To compare the interaction of the IL-1β with the antagonist IL-1RA, 4Å residues between the IL-1RA and IL-1R1 complex (PDB 1IRA) were also analyzed in UCSF Chimera. Analysis of the interacting interface between the IL-1β and IL-1RA with the IL-1R1 receptor indicated that IL-1β interacted with most of the residues in the domain 1, 2 and 3 of the receptor, while IL-1RA interacted with domain 1 and 2 with minimal interaction in domain 3 of the receptor. Interaction of IL-1β with domain 3 of the receptor is important in mediating the function of the receptor. Binding of the IL-1β with the domain 3 of receptor changes the conformation of the receptor to a 20° from its actual orientation, which helps in the recruitment of IL1-RAcP adaptor protein onto the receptor further activating the signaling cascade [21]. As IL-1RA interact minimally with the domain 3, it does not govern the change in the orientation of the receptor, hence signaling remains inactivated. Our approach was to target the domain 1 and 2 of the IL-1R1 receptor as there were maximum numbers of critical interacting residues between the IL-1β and IL-1RA with the IL-1R1 receptor in the 4Å region. Thus, domain 1 and 2 on the receptor was used as a target to which both IL-1β and IL-1RA binds. Analyses of the 4Å interacting residues between the IL-1β and IL-1RA in domain 1 and 2 of the receptor indicated significant similarity between the residues, with 17 residues found common in both the complex (Figure 1).

In-vitro analysis have identified 12 critical residues on the domain 1 and 2 of IL-1R1 interacting with IL-1β [21]. Our analysis of 4Å interacting residues also found 12 critical residues on the IL-1R1 interacting with the IL-1β (Figure 1). Thus, targeting these critical residues on the IL-1R1 can limit the binding of the IL-1β with the receptor.



Domain 1	Domain 2	Domain 3
E11, K12, I13, I14, L15, V16, P28, **N30**, P31	Q108, A109, I110, F111, K112, Q113, K114, L115, G122, V124, P126, Y127, E129, R163	N204, K205, P206, Q236, L237, **S238**, D239, **I240**, Y242, K244, V249, I250, E252, E259, D260, Y261, Y262, S263, **R271**, L275, **K298, T300, H301**

4Å residues (IL-1R1)

Domain 1	Domain 2	Domain 3
R6, F8, **K9**, I10, I11, L12, V13, **N27, P28**	A106, I107, **F108**, Q110, K111, L112, P113, G119, V121, Y124, E126, R160, L198	Q283, S285, I287, K267, **R268, K295**, N296, **T297**, H298, G299, I300

4Å residues (IL-1R1)

Figure 1: Crystal structure analyses of interaction of IL-1β and IL-1RA with the IL-1R1 receptor: A.) Schematic representation of the interaction of IL-1β with the domain 1, 2 and 3 of the IL-1R1 (PDB 4DEP) and the 4Å interacting residues of domain 1, 2 and 3 of the IL-1R1 with the IL1β. **B.) Schematic representation of the interac**tion of IL-1RA with the IL-1R1 (PDB 4IRA) and the 4Å interacting residues of domain 1, 2 and 3 of the IL-1R1 with the IL-1RA. Residues in bold indicates common residues between the complex while underlined residues are the critical residues in the domain 1 and 2 of IL-1R1 interacting with the IL-1β. IL1-R1 is highlighted as purple, IL-1β is highlighted as blue and IL-1RA is highlighted as orange. 4Å interacting residues between the complex is highlighted as green.

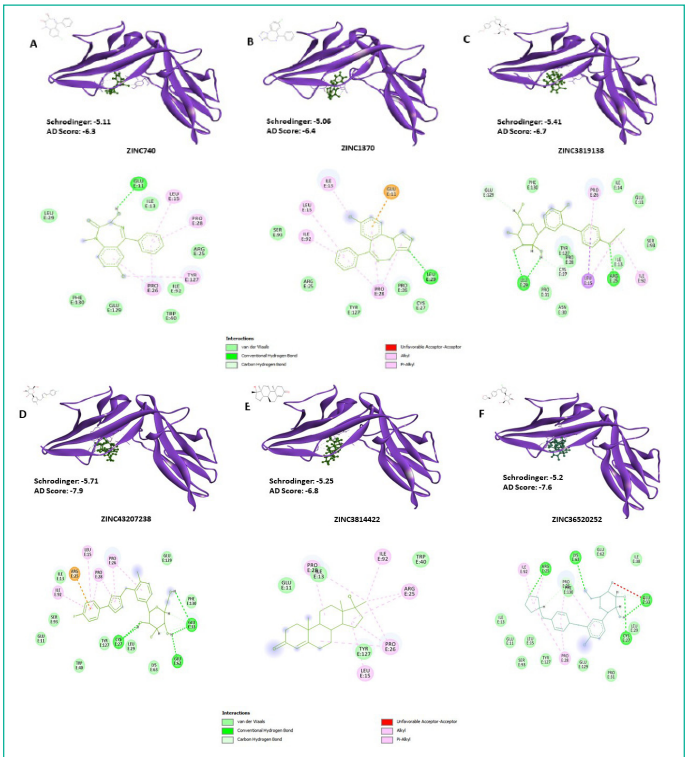


Figure 2: Docking of compounds with the IL-1R1 receptor. Schematic representation of docking of the compounds with the IL-1R1 receptor along with the 2D interaction diagram. A.) ZINC740, B.) ZINC1370, C.) ZINC3819138, D.) ZINC43207238, E.) ZINC3814422, and F.) ZINC36520252. Structures of the individual compounds are shown adjacent to the docked structures. Bonding interaction has been shown in different colour codes. IL-1R1 receptor is highlighted as purple while individual compounds have been highlighted as green.

Screening of small molecule inhibitors against IL-1R1: In-silico virtual screening approach was taken to screen small molecule inhibitors which can interact with the critical residues on the receptor, inhibiting its interaction with the IL-1β. A total of 1614 FDA-approved compounds were downloaded from the ZINC15 library [22] and docked onto the IL-1R1 receptor in Schrodinger [23,24] and AutoDockVina v1.2.0 [25,26]. Compounds were short-listed based on its interaction with the critical residues on the domain 1 and 2 of the receptor with dock scores upto -5.0 for Schrodinger and its corresponding dock scores upto -6.0 in AutoDockVina. Out of 1614 compounds, six compounds were found to be interacting with at least 1 or more out of 12 critical residues on the receptor (Figure 2 & Table 1). Thus, these compounds were further used to derive the physicochemical and ADMET properties.

Table 1: Docking summary of the compounds interacting with the critical residues of IL-1R1.

Compounds	ZINC ID	Schrodinger		AutoDockVina	
		Dock Scores	Interacting residues	Dock Scores	Interacting residues
Restoril	ZINC740	-5.11	111, 113, 124, 126, 127	-6.3	15, 127
Estazolam	ZINC1370	-5.06	111, 113, 124, 126, 127	-6.4	15, 127
Dapagliflozin	ZINC3819138	-5.41	14, 15, 127	-6.7	15, 127
Canagliflozin	ZINC43207238	-5.71	15, 127	-7.9	15, 127
Android	ZINC3814422	-5.25	15, 127	-6.8	15, 127
Empagliflozin	ZINC36520252	-5.2	15, 127	-7.6	15, 127

**Bold residue indicates H-bond*

Physicochemical and ADMET analysis of the top compounds: Analyzing the physicochemical and ADMET properties of the compounds can help in decreasing the risks during the clinical development, as it helps in evaluating the efficacy and safety of the drug during the development process. It also helps in limiting the failure of the drug during the pre-clinical and clinical trials [27]. Thus, in-silico approach was taken to determine the physicochemical and ADMET properties of the compounds using pkCSM server (https://biosig.lab.uq.edu.au/pkcsm/) [28]. pkCSM uses graph-based signature to determine the physicochemical and ADMET properties of the compound by comparing with the available database on the server. The result indicated that all six compounds were having positive value in terms of physiochemical and ADMET properties (Table 2). All six compounds were following Lipinski rule of five. In absorption parameter, water solubility, Caco2 permeability, intestinal absorption and skin permeability were determined, in which all the parameters showed values above threshold. In distribution parameter, fraction unbound, blood-brain permeability and central nervous system permeability were determined. In metabolism, CYP2D6 substrate and CYP2D6 inhibitor were determined. In the excretion parameter, total clearance was determined, while in toxicity parameter, AMES toxicity, hepatotoxicity and skin sensitization were determined. Thus, the result suggests the effectivity of the screened compounds against inhibiting the IL-1β binding to the receptor.

Further studies would be to check these six compounds at the in-vitro and in-vivo level to confirm the efficacy of the inhibition of the IL-1β binding with the IL-1R1 receptor, which could lead to decrease in the atherosclerosis progression.

Table 2: Physicochemical and ADMET properties of the selected compounds.

Parameters		ZINC740	ZINC1370	ZINC3819138	ZINC43207238	ZINC3814422	ZINC36520252
Physiochemical properties	M.W.	300.75	294.75	408.88	444.52	302.46	450.92
	LogP	2.47	3.27	1.84	2.97	4.27	1.61
	Rotatable bond	1	1	6	5	0	6
	Acceptor bond	3	4	6	6	2	7
	Donor bond	1	0	4	4	1	4
Absorption	Water Solubility	-3.607	-4.274	-4.346	-4.447	-4.33	-3.096
	CaCo2 permeability	1.32	1.722	0.939	0.711	1.4	-0.035
	Intestinal absorption	95.46	99.154	51.729	98.263	96.705	59.225
	Skin permeability	-2.873	-2.438	-2.738	-2.735	-3.035	-2.765
Distribution	Fraction unbound	0.007	0.163	0.096	0.029	0.029	0.187
	BBB permeability	0.316	0.506	-1.224	-1.186	0.184	-1.18
	CNS permeability	-2.033	-1.425	-3.632	-3.303	-1.711	-3.7
Metabolism	CYP2D6 substrate	No	No	No	No	No	No
	CYP2D6 inhibitor	No	No	No	No	No	No
Excretion	Total Clearance	0.21	0.266	0.198	0.039	0.625	0.402
Toxicity	AMES toxicity	No	No	No	No	No	No
	Hepatotoxicity	No	No	No	No	No	No
	Skin sensitization	No	No	No	No	No	No

Water solubility (logS)- defines solubility in water at 25°C; Skin permeability- logkp > – 2.5 classifies low skin permeability; Fraction unbound- defines unbound state in plasma protein remaining for pharmacological action; BBB permeability- logBB < – 1 classifies poorly distributed to the brain; CNS permeability- logPS > – 2 classifies CNS penetration and logPS < – 3 classifies no CNS penetration; Total clearance- includes both hepatic and renal clearance

Conclusion

The study identified novel small molecule inhibitors targeting critical residues on the IL-1R1 receptor, which helps to bind with IL-1β. IL-1β plays an essential role as a pro-inflammatory cytokine in the progression of atherosclerosis, and targeting its interaction with the IL-1R1 receptor can help decrease atherosclerosis progression. The identified small-molecule inhibitors through in-silico screening can work as an inhibitor of IL-1β by analyzing its binding affinity and physicochemical and ADMET properties. Although these in-silico studies have limitations, in-vitro and in-vivo studies are required to validate these computational findings.

Consent for Publication

All the authors have consented for the publication in the CMLS.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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Author Contributions

Conceptualization and investigation: MSB; Experiments: KS, RA, and RS; Writing (Original Draft): MSB, KS; Reviewing and editing MSB, EB, KS, RA, and RS. All authors have read and agreed to the published version of the manuscript.

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