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Original Article

IN SILICO STUDIES ON FUNCTIONALIZED AZAGLYCINE DERIVATIVES CONTAINING 2, 4-THIAZOLIDINEDIONE SCAFFOLD ON MULTIPLE TARGETS

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ABSTRACT

Objective: The 2, 4-thiazolidinedione containing compounds could lead to most promising scaffolds with higher efficiency toward the targets recognized for its antidiabetic activity when combined with azaglycine moiety. The objective of the present work was to merge functionalized aza glycines with 2, 4-thiazolidinediones, perform *in silico* evaluation by molecular properties prediction and undertake the molecular docking studies with targets relevant to diabetes, bacterial and viral infections using Swiss Dock programme for unraveling the target identification which can be used for further designing.

Methods: (i) *In silico* studies were performed using Molinspiration online tool, Swiss ADME website and Swiss Target Prediction websites to compute the physicochemical descriptors, oral bioavailability and brain penetration. (ii) Molecular docking studies were performed using Swiss Dock web service for enumeration of binding affinities and assess their biological potentiality.

Results: The results predicted good drug likeness, solubility, permeability and oral bioavailability for the compounds. All the compounds showed good docking scores as compared to the reference drugs. The N-oleoyl functionalized aza glycine derivative demonstrated superior binding properties towards all the studied target reference proteins, suggesting its significance in pharmacological actions.

Conclusion: The binding interactions observed in the molecular docking studies suggest good binding affinity of the oleoyl functionalized aza glycine derivative, indicating that this derivative would be a promising lead for further investigations of anti-viral, anti-inflammatory and anti-diabetic activities.

Keywords: Functionalized aza glycine, 2, 4-thiazolidinediones, Molecular docking, human immuno deficiency virus-1 protease (HIV-1)

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INTRODUCTION

Functionalized amino acids have been widely studied for their anticonvulsant and other pharmacological properties. Lacosamide (N-benzyl-2-acetamido-3-methoxy propionamide) a functionalized amino acid is widely used for the partial onset seizures and diabetic neuropathic pain (fig. 1) [1]. Functionalized amino acids where the amino terminus was capped with acetyl moiety and carboxyl terminus was converted to N-benzyl amide (fig. 2) showed excellent protection against maximal electroshock (MES)-induced seizures [2]. Azaamino acids serve as an attractive tool for drug design leading to the development of aza-peptides, the most useful peptidomimetics drug molecules. Incorporation of aza glycine in place of glycine furnishes peptides with improved biological activity and metabolic stability [3]. Ester and amide derivatives of alpha-aza glycine (carbazic acid, $NH_2NHCOOH$), were reported as protease inhibitors [4]. Clinically active aza-peptide, Atazanavir is a human immunodeficiency virus-1(HIV-1) protease inhibitor recommended with another antiretroviral [5].

2,4-thiazolidinediones, the peroxisome proliferator activated receptors-γ (PPAR-γ) agonists also referred to as glitazones show significant anti-diabetic activity (fig. 3, 4). PPAR-γ agonists can inhibit the inflammatory cytokines: interleukin-1 beta (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor alpha (TNF-α), while suppressing the expression of cyclooxygenase-2 (COX-2). The significance of 2,4-thiazolidinediones as anti-inflammatory agents paves the path to repurposing these drugs for other conditions like liver diseases, stroke and cancer disorders. 2, 4-thiazolidinediones are known to inhibit cell proliferation through arrest at G0/G1 cycle and induction of apoptosis. Different classes of phenyl and heterocyclic based 2,4-thiazolidinedione derivatives are a potent class of PPAR-γ agonists and the suitable N-position substitution plays a key role in the aldose reductase inhibitory activity. The 2, 4-thiazoldinediones substituted at the 3rd and 5thposition have been reported to possess antioxidant, anti-microbial, anti-bacterial and anti-inflammatory activities [6-10].

Development of ligands with higher efficacy towards the targets may probably decrease the side effects and adverse reactions. This always remains the biggest challenge to the medicinal chemist. Molecular docking on the multiple targets provides insights into the most promising interactions between the designed ligand and the related target receptors and helps in providing potent target modulators for the derivatives. The aza scaffold imparts the preferential binding orientations owing to the nitrogen (N^{α}) insertion in place of the carbon (C^{α}). The literature review suggests that 2, 4-thiazolidinedione substituted at 3rd and 5th positions serves as an important scaffold by virtue of its key structural feature of hydrogen bonding donor and hydrogen bonding acceptor regions. It was therefore planned to link this privileged moiety via amide bond link to aza glycine and design few functionalized aza glycine derivatives, and exploit the efficiency of the designed derivatives towards the targets like HIV-1 protease, IL-1β and PPAR-γ which are well-known targets for aza derivatives and 2, 4-thiazolidinediones.

Prioritization of the designed compounds by performing *in silico* studies limits animal testing and reduces global pharmacokinetic failures at the later stages of drug development [11]. With this aim, the *in silico* studies were carried out for predicting the molecular property calculations and the molecular level interactions were analyzed by performing molecular docking studies.

The molecular docking studies were performed on a series of functionalized aza glycine derivatives with different N-acyl substituents and C-terminal amide bonding with 2,4-thiazolidinedione for predicting their binding affinities towards target proteins, related to the pharmacological potentiality of

azapeptides (protease and caspases) and 2,4-thiazolidinediones (diabetes mellitus). The target proteins were obtained from the protein data bank (PDB ID: 1A30, HIV-1 protease; PDB ID: 1BMQ, caspases-1/Interleukin-1 beta converting enzyme (IL-1) and PDB ID: 2PRG, PPAR-γ) and molecular docking was performed using http://www. swissdock. ch. Swiss Dock an online web service developed by Aurellen Grosdidier, Vincent Zoete and Olivier Michielin performs EADock based docking simulations. The application of EADock was illustrated by successful docking of Arg-Gly-Asp (RGD) cyclic pentapeptide on the $\alpha V\beta_3$ integrin [12].

MATERIALS AND METHODS

A set of compounds was designed by functionalizing the N-terminal of azaglycine with acetyl, benzoyl, cinnamoyl, oleoyl, palmitoyl, phenoxy and 2-(4-(2-methylpropyl) phenyl) propionyl derivatives, and C-terminal amide bond modification with 2, 4-thiazolidinedione scaffold.

Computational details

The computational technique of molecular docking, usually used to find the best orientation of ligand to a protein target, plays important role in rational drug design. The Swiss Dock, a web interface was developed to perform molecular docking, fragment based drug design and lead optimization [13].

Table 1: Structures and IUPAC names of functionalized azaglycyl-2, 4-thiazolidinediones

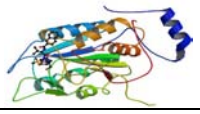
S. No.	Structure	IUPAC nomenclature
1		N'-acetyl-2,4-dioxothiazolidine-3-carbohydrazide
2		N'-benzoyl-2,4-dioxothiazolidine-3-carbohydrazide
3		N'-cinnamoyl-2,4-dioxothiazolidine-3-carbohydrazide
4		N'-oleoyl-2,4-dioxothiazolidine-3-carbohydrazide
5		N'-palmitoyl-2,4-dioxothiazolidine-3-carbohydrazide
6		N'-(2-phenoxyacetyl)-2,4-dioxothiazolidine-3-carbohydrazide
7		N'-(2-phenoxypropanoyl)-2,4-dioxothiazolidine-3-carbohydrazide
8		N'-(2-(4-isobutylphenyl)propanoyl)-2,4-dioxothiazolidine-3-carbohydrazide

Selection of target and ligand preparation

A set of eight compounds were designed and used for performing the molecular docking studies. Chemical structures were drawn using Chem and Bio Draw 12.0, an easy to use tool and saved as mol2 files using Chem and Bio 3D version 12.0. Table 1 illustrates the structures and the international union of pure and applied chemistry (IUPAC) nomenclature of these compounds. Crystallographic structures of the targets belonging to following categories anti-viral, anti-inflammatory and anti-diabetic were obtained from protein data bank [(PDB ID: 1A30, 1BMQ and 2PRG)]. The targets possessed inbuilt ligands and the active site residue for the same and details of the all studied targets were given in table 2. The binding site was defined to include all residues within 5.0 °A vicinity of the ligand.

The predicted binding modes with most favorable energies were evaluated with fast analytical continuum treatment of solvation (FACTS) and clustered and the most favorable clusters were visualized using the View Dock plug-in of UCSF chimera which can be launched directly from the web. Computation of molecular descriptors such as log P, topological surface area, number of hydrogen bond donors and acceptors and the bioactivity scores for G-protein coupled receptor (GPCR) ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor and enzyme inhibitor were calculated by using Molinspiration online tool (http://www. molinspiration. com/cgi-bin/properties) [14,15]. The gastrointestinal absorption (GI) and brain permeation (BBB) considered as crucial pharmacokinetic parameters were computed using Swiss ADME web service (http://www. swissadme. ch/). The Swiss target prediction studies were carried out for predicting the probable targets for the designed compounds using http://www. Swiss target prediction. ch a web server to accurately predict the targets of bioactive molecules based on a combination of 2D and 3D similarity measures with known ligand [16-18].

Table 2: Details of the target proteins retrieved from the protein data bank

Target enzymes	HIV-Protease	Protein (Interleukin-1 beta convertase)	Peroxisome proliferator activated receptor gamma
PDB ID	1A30	1BMQ	2PRG
EC number	3.4.23.16	3.4.22.36	2.3.1.48
Resolution	2.0 Å	2.5 Å	2.3 Å
Organism	HIV-1	Homo sapiens	Homo sapiens
Classification	Hydrolase	Hydrolase	Complex (Thiazolidinedione/Receptor)
Total structural weight	21985.18	29614.30	72105.70
Chains	A,B,C	A,B	A,B,C
Length (amino acids)	(99,99,3)	(167,88)	(271,271,88)
Amino acid residues present in the binding pocket	ASP25, ASP29,ASP30 GLY46, ARG8	SER339B, TRP340B, HIS342B, ARG341B and ARG179A	GLN286,SER289, HIS323, TYR473
3D structure			

RESULTS AND DISCUSSION

***In silico* molecular descriptor studies**

Lipinski's rule of five (RO5) is used to evaluate whether the chemical compound possess the properties of drug likeness (i.e. orally active) in humans. As per the rule the compound possessing Partition coefficient log P in −0.4 to +5.6 range, molar refractivity from 40 to 130, molecular weight from 180 to 500, number of atoms from 20 to 70 (includes H-bond donors [e. g.; OH's and NH's] and H-bond acceptors [e. g.; N's and O's]) Polar surface area not greater than 140 °A, 10 or fewer rotatable bonds and polar surface area equal to or less than 140 Å are predicted to have good oral bioavailability [19, 20].

All the designed compounds obeyed Lipinski rule of five suggesting good oral bioavailability for the title compounds (table 3). The compounds with bioactivity score>0 are considered to be active and those with scores ranging from-0.5 to 0 are considered to be moderately active [21]. The oleoyl, palmitoyl and 2-(4-(2-Methylpropyl) phenyl) propanoyl functionalized azaglycine derivatives showed moderate activity (bioactivity scores ranging from-0.23 to-0.3) towards protease and enzyme inhibition properties. The protease inhibition of the derivatives indicates their significance towards antibacterial activity (table 4) [22]. Oral bioavailability and GI absorption of all the derivatives were found to be high except for the oleoyl and the palmitoyl functionalized derivatives which showed low GI absorption. The oleoyl functionalized derivative was shown to be a P-glyco protein substrate and possessing relatively low GI absorption as per Swiss ADME studies. The bioavailability scores were found to be good for all the derivatives with the range of 0.50-0.55 and accordingly were predicted to possess drug likeness property. Permeation of the BBB is crucial for CNS drug candidates and the prior investigation of the BBB penetration for the drugs targeting the peripheral organs could avoid CNS side effects [23]. None of the derivatives showed BBB penetration showing that derivatives elicit no CNS side effects. The Swiss target predictions revealed preference of the designed ligands for the targets like cysteine protease and other targets related to pain and inflammation (table 5).

Table 3: Analysis of lipinski rule of 5 for the designed azaglycyl-2, 4 Thiazolidinediones

S. No	mi log P	TPSA	n atoms	Molecular weight	n ON	n OHNH	n Violations	n Rotatable bonds	Molar volume
1	-1.31	95.58	14	217.21	7	2	0	1	166.81
2	0.36	95.58	19	279.28	7	2	0	2	221.66
3	1.00	95.58	21	305.31	7	2	0	3	249.07
4	6.67	95.58	30	439.62	7	2	1	16	429.45
5	6.15	95.58	28	413.58	7	2	1	15	402.03
6	0.33	104.81	21	309.30	8	2	0	4	247.44
7	0.69	104.81	22	323.33	8	2	0	4	264.03
8	2.55	95.58	25	363.44	7	2	0	5	321.80

Table 4: Predicted bioactivity scores for the title compounds using Molinspiration online web server

S. No.	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	-0.86	-1.16	-1.90	-2.00	-1.24	-0.96
2	-0.37	-0.82	-1.11	-1.19	-0.66	-0.55
3	-0.28	-0.61	-0.97	-0.89	-0.61	-0.51
4	-0.06	-0.50	-0.70	-0.59	**-0.23**	**-0.23**
5	-0.10	-0.55	-0.73	-0.68	**-0.25**	**-0.30**
6	-0.37	-0.85	-1.15	-1.01	-0.60	-0.63
7	-0.40	-0.94	-1.08	-1.03	-0.55	-0.61
8	-0.09	-0.40	-0.84	-0.68	-0.23	-0.41

Table 5: The swiss ADME and swiss target prediction data for the title compounds

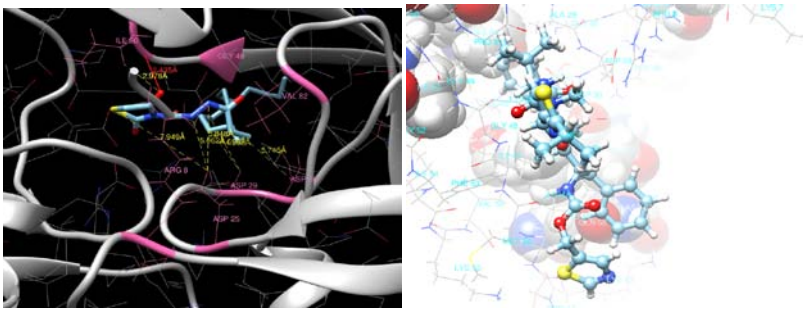
S. No.	Oral bioavailability	Blood brain barrier penetration	P-GP substrate	Drug likeness and bioavailability score	Swiss target prediction
1	High	No	No	Yes (0.55)	Cysteine protease (Caspases-3)
2	High	No	No	Yes (0.55)	Cysteine protease (Caspases-3)
3	High	No	No	Yes(0.55)	Prostaglandin g/h synthase-1 and 2
4	Low	No	**Yes**	Yes(0.55)	Fatty Acid Amide Hydrolase
5	Low	No	No	Yes(0.55)	Fatty Acid Amide Hydrolase
6	High	No	No	Yes(0.55)	Microtubule associated protein tau
7	High	No	No	Yes(0.55)	Cysteine protease
8	High	No	No	Yes(0.55)	Transient receptor potential cation channel subfamily V member 1

Molecular docking studies using Swiss dock program

Molecular docking studies of the designed ligands with HIV-1 protease complexed with a tripeptide inhibitor (PDB ID: 1A30)

HIV protease enzyme known to be highly essential for virus infectivity serves to be the major therapeutic target for AIDS treatment. Protease inhibitors are a class of anti-viral drugs used to treat HIV/AIDS and hepatitis C and the development of safer protease inhibitors with improved bioavailability is a challenging task to medicinal chemist [24].

Molecular docking was performed using HIV-1protase complexed with a tripeptide inhibitor (GLU-ASP-LEU) retrieved from the protein Data Bank (PDB ID: 1A30) [25]. The inhibitor contacting residues of HIV-1 protease are relatively conserved including ARG8, GLY27, ASP 29, ASP30, GLY48 and ILE50 [26]. The molecular interactions predicted that the molecule is embedded well in the loop area constituting amino acids from LEU24 to TRP42, beta sheet LYS 43 to GLY48 and loop region formed by GLY49 to ILE64. Critical amino acids like ARG 8, ASP29, ASP30 and GLY48 were within the 5 °A distance when observed in different binding modes. The carbonyl oxygen of the aza glycine residue was found to involve in the hydrogen bond formation with GLY48 and ASP29 with bond distances of 1.983 °A and 2.024 °A respectively. The hypothetical binding mode of the most interactive oleoyl functionalized derivative is depicted in fig. 5 (table 6). This derivative showed a good binding affinity of-9.30 K Cal/mol almost comparable to Ritonavir (-9.63 Kcal/mol) an antiretroviral agent for HIV/AIDS.



A **B**

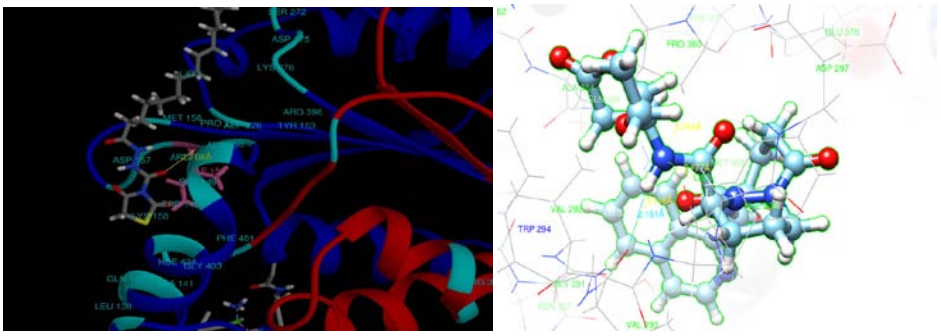
Fig. 5: A) Hypothetical biniding intractions of the N-oleoyl functionalised derivative in the relatively conserved residues of HIV-1Protease, interactive ribbons representation (PDB ID: 1A30) B) The interactive 2 (all atoms) representation of the standard drug ritonavir in the active binding site of HIV-1 protease

Table 6: Docking scores (binding affinity) obtained from Swiss dock molecular docking programme

S. No.	A130(HIV-1)		1BMQ(IL-1)		2PRG(PPAR-γ)	
	Full fitness	ΔG Kcal/mol	Full fitness	ΔG Kcal/mol	Full fitness	ΔG Kcal/mol
1	-1107.60	-7.22	-1466.98	-7.03	-3201.35	-7.91
2	-1080.51	-7.65	-1439.96	-7.63	-3180.64	-7.92
3	-1089.74	-8.13	-1447.56	-7.95	-3193.50	-8.42
4	-1113.58	**-9.30**	-1492.06	**-9.08**	**-3231.90**	**-10.72**
5	-1124.77	-8.55	-1491.86	-8.30	-3238.62	-10.01
6	-1075.67	-8.28	-1433.52	-7.94	-3174.59	-8.25
7	-1075.31	-7.91	-1434.61	-7.61	-3181.53	-8.38
8	-1080.48	-7.63	-1446.06	-7.66	-3192.62	-8.95
9	-1095.95 (Ritonavir)	-9.63	-1325.26 (Pralnacasan)	-8.59	-3190.48 (Rosiglitazone)	-8.85

Molecular docking studies of the designed ligands with crystal structure of the complex of interleukin-1beta converting enzyme (ice) with a peptide based inhibitor, (3s)-n-methanesulfonyl-3-({1-[n-(2-naphtoyl)-l-valyl]-l-prolyl } amino)-4-oxobutanamide (PDB ID: 1BMQ)

Interleukin-1β-converting enzyme (ICE) is a novel cysteine protease responsible for the cleavage of pre-interleukin-1β (pre-IL-1β) to the mature cytokine. The crystal structure of the complex of interleukin-1βeta converting enzyme with a peptide based inhibitor (PDB ID: 1BMQ) was used to perform the docking studies [27]. All the derivatives showed good binding affinity towards the target enzyme and the possible interactions were observed with ILE155, GLU241, ASP275, VAL293, TRP294, and GLY382 (fig. 6). The aza-amino nitrogens were found to involve in the hydrogen bonding with GLU241 and TRP294 with bond distances of 1.940 °A and 1.956 °A respectively. The 2, 4 thiazolidinediones was lying near the loop region of ILE152 to PRO154. Among all the derivatives, the oleoyl functionalized derivative showed the maximum binding affinity of-9.08 Kcal/mol, which was comparatively more than the binding affinity observed for Pralnacasan (-8.59 Kcal/mol) (table 6), the first orally available potent and selective interleukin-1beta converting enzyme inhibitor to enter clinical trials in the treatment of rheumatoid arthritis.



A B

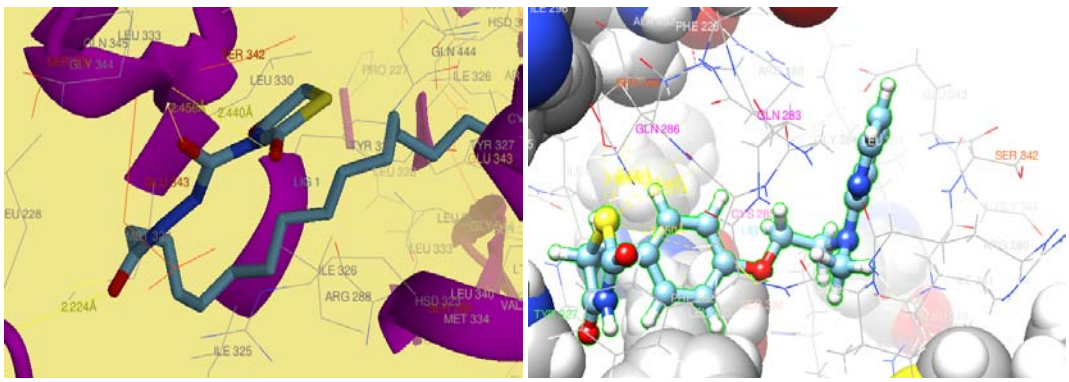
Fig. 6: A) Ribbon representation of the N-oleoyl functionalized derivative with the hyrogen bonding between O_3 of ligand with the ILE155 (2.104 °A) (PDB ID: 1BMQ) B) Interactive 2 (all atom) representation of pralnacasan featuring the interactions between its H_9 with VAL293 O atom with a hydrogen bonding (2.161 °A)

Molecular docking studies of the designed ligands with ligand-binding domain of the human peroxisome proliferator activated receptor gamma (PDB ID: 2PRG)

Peroxisome proliferator-activated receptors (PPAR-α and PPAR-γ) are the molecular targets of number of marketed drugs featured for disorders related to high triglycerides, insulin resistance and hyperlipidemia [28]. PPAR agonists elicit a detrimental effect in diabetes, adipocyte differentiation, inflammation, cancer, pain obesity etc [29]. The PPAR-γ which regulates energy storage is the major target of anti diabetic drugs [30].

Among the various classes of ligands the thiazolidinedione's are the most widely studied PPAR-γ agonists. Owing to the presence of the thiazolidinedione ring structure in the designed molecules, the molecular docking studies were carried on PPAR-γ (PDB ID: 2PRG) to predict the possible binding interactions and affinities of these compounds. Among all the compounds the oleoyl substituted derivative showed the highest binding affinity (ΔG-10.72 Kcal/mol) and the palmitoyl derivative also showed good binding affinity (ΔG-10.01 Kcal/mol). The binding affinity of the N-oleoyl and N-palmitoyl derivatives was found to be more than that of the rosiglitazone (ΔG-8.85 Kcal/mol).

The active binding site residues of PPAR-γ which were found to interact with the antidiabetic drug rosiglitazone were GLN286, SER289, HIS323 and TYR473. Moreover, rosiglitazone exhibited non bonded interactions with ILE281, PHE282, GLY284, CYS285, TYR327, LEU330, ILE341, MET348, MET364, HIS449 and LEU453 [31]. Similar observations were visualized for the designed compounds which were found to be embedded in the binding pocket of the target, similar to rosiglitazone with the amino acids ILE281, PHE282, GLY284, CYS285, GLN286, ARG288, and SER289. All the derivatives showed H bond formation with SER342 with bond lengths ranging from 2.337 °A to 2.551 °A (fig. 7) (table 7).



A B

Fig. 7: A) Hypothetical interactive 1 ribbon representation of the N-oleoyl functionalised derivative in the active site of the PPAR--γ receptor (PDB ID: 2PRG) B) Interactive 2 (all atoms) representation of rosiglitazone used as standard for comparison represented in ball and stick model with the bond distances from S atom to the nearest residues in the predicted binding pocket

Table 7: Depiction of interacting amino acids and the corresponding bond lengths between the designed ligands and the studied targets

S. No.	HIV-1 protease		Interleukin-1beta convertase (IL-1)		PPAR-γ	
	Interacting amino acids	Bond length	Interacting amino acids	Bond length	Interacting amino acids	Bond length
1	O_2 of LIG with GLY48	2.136 °A	N_2H of LIG with Glu241	1.940 °A	O_4 of LIG with SER342	2.403 °A
2	O_4 of LIG with GLY 48 and O_2 of LIG with ASP29	2.059 °A And 2.100 °A	O_4 of LIG with GLY382	2.125 °A	O_4 of LIG with SER342	2.393 °A
3	O_1 of LIG with ASP29 and O_4 of LIG with GLY48	2.2130A and 2.072 °A	N_3H of LIG with TRP294	1.956 °A	O_4 of LIG with SER342	2.398 °A
4	O_4 of LIG with NH of GLY48 and ASP 29 backbone	1.983 °A and 2.024 °A	O_3 of LIG with ILEU155	2.104 °A	O1 of LIG with SER342 and O_4 of LIG with GLU343	2.440 °A 2.456 °A
5	O_2 of LIG with GLY48 and N_2 of LIG with ASp29	2.185 °A And 2.107 °A	N_1 H of LIG with VAL 293	1.879 °A	O_4 of LIG with SER342	2.444 °A
6	O_2 of LIG with ASP29 and O_3 of LIG with GLY48	2.077 °A And 1.982 °A	O_3 of LIG with ASN259and N3 H of LIG with GLU241	2.091 °A 1.968 °A	O_4 of LIG with SER342	2.476 °A
7	O_3 of LIG with ASP29	2.104 °A	O_4 of LIG with GLY382	1.999 °A	O_4 of LIG with SER342	2.214 °A
8	O_3 of LIG with ASP29	2.013 °A	O_4 of LIG with GLY382	1.941 °A	O_2 of LIG with SER342 and O_4 of LIG with SER342	2.337 °A 2.551 °A

Based on the *in silico* molecular property predictions and the results obtained from the molecular docking studies using Swiss dock our future work is planned to perform the synthesis of the designed derivatives and also to explore their therapeutic potential in the treatment of pain and inflammatory disorders.

CONCLUSION

Majority of the compounds showed good oral bioavailability and no BBB penetration indicating that these derivatives would possess drug likeness and be devoid of CNS side effects. The designed derivatives were found to possess good binding affinities towards the studied target proteins (HIV-1 Protease, Interleukin-1beta Convertase and PPAR-γ). Among all these the N-oleoyl functionalized derivative showed high binding affinity towards all the studied targets, thus indicating its potentiality for further investigations as anti viral, anti inflammatory and anti diabetic agents. The highest binding affinity of the N-oleoyl derivative towards the PPAR-γ ensures this derivative could be a potent PPAR-γ modulator.

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CONFLICT OF INTERESTS

Declared none

AUTHOR CONTRIBUTION

Arifa Begum and Shaheen Begum provided substantial contributions in analysis and interpretation of the molecular docking studies. Bharathi K contributed in designing and supervision of the work along with drafting the article. Prasad KVSRG supported in critically evaluating the work and drafting the article.

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