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Deciphering Insulin Resistance through molecular docking of Short-Chain Fatty Acid Docking with associated Receptors

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ABSTRACT:
Proteins and ligands binding is essential for signal transduction, immunoreactivity, and gene regulation. Investigation of these interactions is crucial for comprehending the mechanisms underlying biological regulation, and it lays the groundwork for identifying and developing new drug targets. In the present article molecular interactions are investigated between the protein receptors associated with insulin resistance and postbiotics which are generally released by the gut biome, using MOE software. In molecular docking, two key objectives are identifying accurate binding poses and precisely predicting binding affinity. This analysis aids in comprehending and addressing pivotal inquiries, particularly those concerning the diversity of binding affinity and specificity.

KEYWORDS: FFAR1,FFAR2, GPCR, Receptors, Insulin resistance, SCFA.

I. INTRODUCTION

Molecular docking is a structure-based computational method that generates the binding pose and affinity between ligands and targets. There are many prevailing docking programs. Yet, there is no single program that is suitable for every system. Thus, an appropriate program is chosen based on availability, need, and computer capacity. Molecular docking has clear steps that should be followed carefully to get a good result [1] It holds great significance and is extensively employed in projects focused on designing and discovering new drugs [2]. Molecular docking has played a crucial role in making drug discovery faster, cheaper, and more effective.

Insulin resistance, characterised by the hindrance of insulin's ability to stimulate various metabolic processes such as glucose transport, glycogen synthesis, and inhibition of lipolysis, holds significant clinical importance due to its pathophysiological connection to various serious medical conditions [3]. These include type 2 diabetes [T2DM], hypertension, atherogenic dyslipidemia, abnormalities in blood coagulation and fibrinolysis, non-alcoholic fatty liver disease, polycystic ovarian syndrome, immunomodulation etc. [3].

Free Fatty Acid Receptor 1 [FFAR1], also referred to as GPR40, is expressed in human pancreatic β-islet cells and Free Fatty Acid Receptor 2 [FFAR2], known as GPR43 [G-protein coupled receptor functioning as a detector of surplus dietary energy,] are the types of G-protein-coupled receptors [GPCRs] that detect free fatty acids [FFAs] within the body. The primary locations and its functions in humans is as shown in the table **Fig. 1** [4]

GPCR [Free Fatty Acid Receptor]	Location	Function
FFAR1 [GPR40]	Mainly present in pancreatic beta cells, the gastrointestinal tract, adipose tissue, and the central nervous system [5].	Stimulates insulin secretion in response to glucose, aids in regulating blood sugar levels, participates in diverse metabolic processes, and helps maintain energy balance [6].

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FFAR2 [GPR43]	Predominantly found in immune cells [neutrophils, macrophages, and dendritic cells], gastrointestinal tract, and adipose tissue [6,7]	Modulates immune responses and inflammation when activated by short-chain fatty acids [SCFAs] like acetate, propionate, and butyrate, regulates the secretion of gut hormones and intestinal motility influences the regulation of energy expenditure and adiposity [8].

Fig. 1 Types of G-protein Coupled Receptor

SCFAs are produced by anaerobic gut bacteria through saccharolytic fermentation of complex resistant carbohydrates, which escape digestion and absorption in the small intestine [9]. These SCFA play crucial roles not only in gut health and as signaling molecules but also have the potential to enter the systemic circulation and directly impact metabolism or the function of peripheral tissues[10][11]

Butyrate serves as the primary fuel source in the intestines, providing approximately 60–70% of the energy requirements for isolated colonocytes. Additionally, acetate, propionate, and butyrate promote the proliferation of epithelial cells[12].

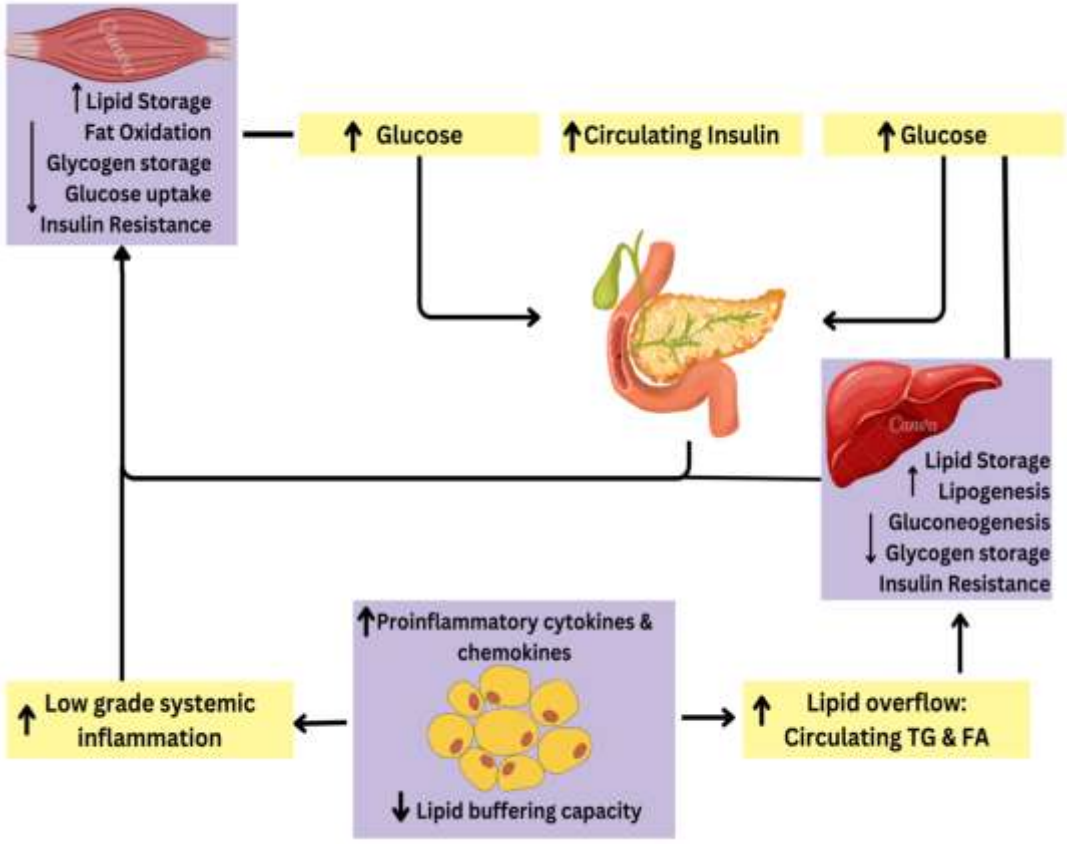

Fig. 2 Interorgan communication and insulin resistance triggered by obesity

The overall concentration of short-chain fatty acids [SCFAs] in the gut ranges from 0.5 to 0.6 Mol/day [13], depending on factors such as diet, gut bacterial composition, and intestinal transit time [14]. Acetate [C2], propionate [C3], and butyrate [C4] represent the most prevalent SCFAs in the gut, accounting for over 95% of the total, with a molar ratio of approximately 3:1:1,

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respectively [15]. SCFAs produced in the gastrointestinal tract are swiftly absorbed by colonocytes, with less than 10% being excreted in faeces [16]. Colonocytes primarily absorb SCFAs through four transport mechanisms: passive diffusion, exchange with bicarbonate, monocarboxylate transporters [MCTs], and sodium-coupled MCT1 transport [17].

Various short-chain fatty acids [SCFAs] and their receptors exhibit distinct affinities, for example in humans, FFAR2 shows an affinity ranking of C2=C3>C4>C5=C1, while FFAR3 has an affinity ranking of C3=C4=C5>C2>C1. Both FFAR2 and FFAR3 are linked to metabolic disorders, making them promising targets for treating type 2 diabetes [18][19]

Short-chain fatty acids [SCFAs] serve as natural inhibitors of histone deacetylases [HDACs]. They can directly impact HDACs by penetrating cells via transporters or indirectly influence HDACs through the activation of G protein-coupled receptors [GPCRs] [20].

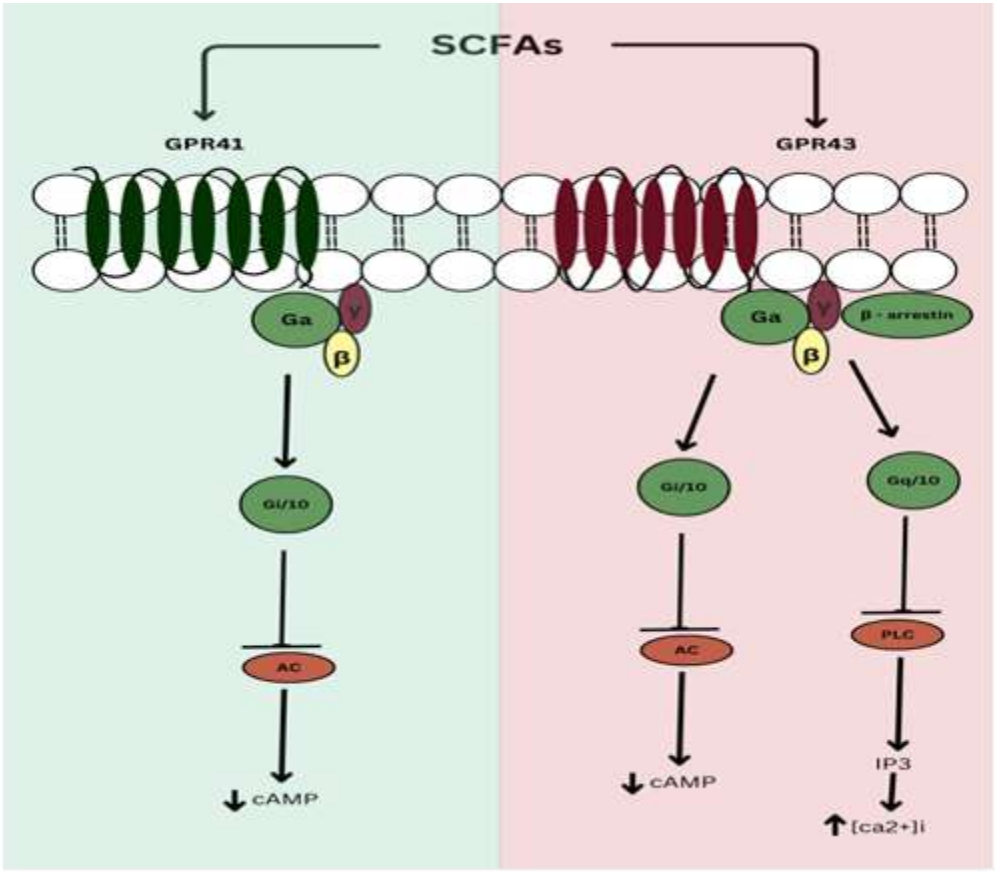

Fig. 3 Signalling pathways initiated by SCFA activation of GPR41 and GPR43

The signalling pathways initiated by SCFA activation of GPR41 and GPR43 are depicted. The downstream signalling pathways for each receptor are outlined. AC stands for adenylate cyclase, [Ca2+]i represents intracellular calcium concentration, GPR refers to G protein-coupled receptor, IP3 stands for inositol trisphosphate, PLC represents phospholipase C, and SCFAs denote short-chain fatty acids.

GPR41 and GPR43 are extensively researched receptors for short-chain fatty acids [SCFAs], known as free fatty acid [FFA] receptor 3 [FFAR3] and FFAR2, respectively [21]. These receptors belong to the G protein-coupled receptors [GPCRs] family, characterized by seven transmembrane-spanning domains that detect extracellular molecules and initiate intracellular signalling pathways and cellular responses mediated by different G protein heterotrimers or arrestins [22]. Upon ligand binding, GPRs trigger the dissociation of the Gα subunit from the Gβγ subunits of the heterotrimers, primarily influencing intracellular signalling proteins based on the type of Gα subunit [such as Gαi/o and Gαq/11][23].

International Journal of Pharmaceutical Research and Applications
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GPR41 primarily associates with pertussis toxin-sensitive Gαi/o proteins, while GPR43 couples with both pertussis toxin-sensitive Gαi/o and pertussis toxin-insensitive Gαq/11 proteins [24]. Activation of GPR41 and GPR43 by SCFAs via Gαi/o inhibits adenylate cyclase [AC] activity, leading to decreased cyclic adenosine monophosphate [cAMP] production. Conversely, SCFA activation of GPR43 via Gαq/11 stimulates phospholipase C [PLC], resulting in inositol trisphosphate [IP3] receptor activation on the endoplasmic reticulum and subsequent calcium [Ca2+] release from the endoplasmic reticulum [21].

Butyrate serves as the primary energy source for colonocytes [25], while propionate acts as a substrate for gluconeogenesis[26]. SCFAs that are not metabolized in colonocytes are transported to the liver via the portal circulation, where they serve as energy substrates for hepatocytes through acetyl-CoA synthetases [ACS [27]. Moreover, in the liver, acetate, and butyrate are utilized as substrates for synthesizing cholesterol and long-chain fatty acids [28], whereas propionate undergoes conversion into glucose via the tricarboxylic acid [TCA] cycle [17]. While acetate uptake is minimal, the liver absorbs a substantial amount of propionate and butyrate [15].

An insufficiency of short-chain fatty acids [SCFAs] plays a pivotal role in the development of type 2 diabetes mellitus [T2DM] [29]. The generation of short-chain fatty acids [SCFAs] prompted by dietary fibre and resistant starch has the potential to enhance insulin sensitivity and maintain glucose homeostasis in humans.

Moreover, the provision of dietary fibre to patients with type 2 diabetes mellitus [T2DM] augmented a subset of short-chain fatty acid [SCFA] producers and ameliorated glycated haemoglobin levels. This effect was partially attributed to heightened GLP-1 production, contributing to the alleviation of T2DM [30]

It is found that propionate and butyrate suppressed the apoptosis of pancreatic β-cells and stimulated their proliferation, resulting in an augmentation of pancreatic β-cell mass and enhancement of glucose homeostasis. This effect may be attributed to the HDAC inhibitory activity mediated by SCFAs, leading to the activation of the MAPK pathway [31], as well as the suppression of the endoplasmic reticulum stress-related protein kinase R-like ER kinase [PERK]-CCAAT/enhancer-binding protein homologous protein [CHOP] pathway [32]. The MAPK pathway plays a crucial role in the proliferation and differentiation of pancreatic β-cells, while the PERK-CHOP pathway is significant in the apoptosis of pancreatic β-cells [32].

II. MATERIAL AND METHOD

The present study includes the in-silico study using MOE software. Ligand structures were obtained from Pub chem Library and Receptor structures were obtained from the three-dimensional [3D] structures of FFAR1 [PDB ID : 3BU3, 8EIT, 4PHU] & FFAR2 [PDB ID : 8T3S]

SCFA used for docking studies:

SCFAs	Precursors	Pathways	Protein
Acetate a. Sodium acetate b. Calcium acetate	Pyruvate	Acetyl - CoA	3BU3, 8EIT, 4PHU, and 8T3S
Propionate	Phosphoenol Pyruvate	Succinic pathway	3BU3, 8EIT, 4PHU, and 8T3S
Butyrate Isobutyric Acid	Acetyl CoA	Acetyl CoA - transferase	3BU3, 8EIT, 4PHU, and 8T3S

The procedure involves utilizing MOE 2015.10 software for the docking process, employing the canonical smiles of Short-Chain Fatty Acids (SCFAs) for docking purposes, and detecting binding pockets. Following this, the protein was prepared, with its structure imported

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from PubChem. Docking was then conducted, followed by energy minimization. Molecules are imported from the Protein Data Bank (PDB) for further analysis. Finally, the results were meticulously analyzed to ascertain the best binding stability.

2.1 Receptor Protein Refinement: Prior to docking investigations, the protein structures of receptor proteins were fine-tuned using MOE software. After being made and optimised, the receptor proteins were cleared of ligands and water molecules. Additionally, the energy of the receptor proteins was reduced, and 3D protonation was carried out using a force field gradient parameter of 0.05.

III. RESULTS & DISCUSSIONS

Comprehending the molecular mechanisms governing SCFA-GPCR interactions is vital for clarifying their physiological functions and investigating their therapeutic applications for insulin resistance and metabolic disorders. These computational analysis aims to offer significant insights into the structural foundation of SCFA-GPCR interactions, thus laying the groundwork for the strategic development of innovative therapeutics aimed at targeting these receptors for therapeutic interventions. In the following sections, we present the outcomes of our docking simulations, offering a thorough examination and discourse on the interactions between SCFAs and GPCRs, as well as their binding affinities.

3.1 Binding Of FFAR1 receptors

1. Binding of Metformin with - 3BU3.

3BU3 is a protein that defines the KRLB region within insulin receptor substrate-2. It is a 297-amino acid-long insulin receptor subunit beta protein identified in Homo sapiens.

3BU3.

Met1120, Asp1123, Lys1150, Gly1149,Cyc 1138, and His1130 were found to be the leading interactive residues in this interaction.

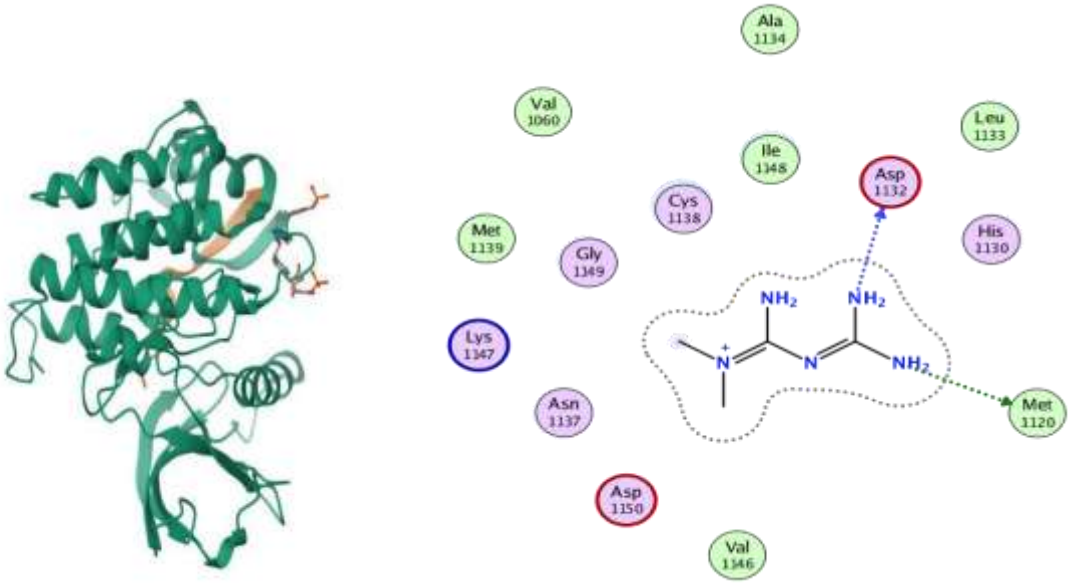

Fig. 4 Ligand Interaction of Metformin with 3BU3

Database Viewer : $HOME/dock.mdb

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	mol	rseq	mseq	S	rmsd	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1		1	1	-6.4301	0.1434	0.8679	-297.4231	-30.2704	-8.5066	-24.6966	-6.4301
2		1	1	-6.1027	4.2685	0.6530	-295.6543	-40.8759	-8.3385	-24.1398	-6.1027
3		1	1	-6.0845	3.6836	1.6187	-294.0490	-25.9310	-8.8145	-24.1097	-6.0845
4		1	1	-6.0475	3.5842	1.5278	-297.1178	-26.5878	-8.7374	-20.2390	-6.0475
5		1	1	-6.0088	1.8533	1.8019	-291.0527	-15.8525	-8.3939	-22.6000	-6.0088

Fig. 5 Energy Chart for Metformin with 3BU3

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2. Binding of Glipizide with - 8EIT

8EIT - FFAR1, a G-protein-coupled receptor [GPCR], reacts to circulating free fatty acids, boosting glucose-stimulated insulin secretion and the release of incretin hormones. The activation of FFAR1 has a glucose-lowering effect, leading to the development of potent agonists targeting this receptor for diabetes treatment. TrpB339, LysB57, LysB337, HisB311, ThrB329, ArgB52, HisB54 these emerged as the primary interactive components in this interaction.

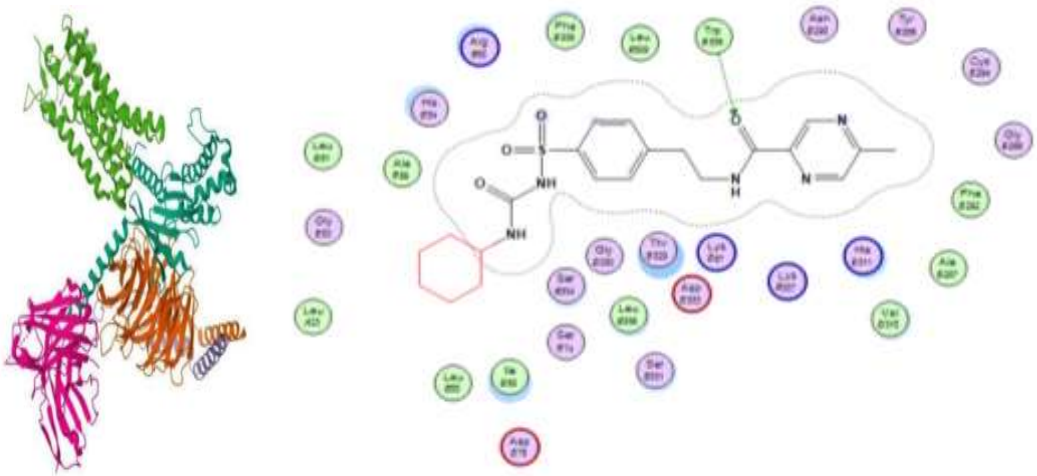

Fig. 6 Ligand Interaction of Glipizide with 8EIT

Database Viewer : $HOME/dock.mdb

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	mol	rseq	mseq	S	rmsd	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1		1	1	-8.8567	3.8047	1.6137	-121.0237	-60.3250	-11.2191	-45.2075	-8.8567
2		1	1	-8.8445	3.3766	1.7259	-99.8117	-96.2578	-10.8004	-42.1992	-8.8445
3		1	1	-8.7797	3.6478	1.5112	-118.6607	-66.0415	-10.5527	-44.3576	-8.7797
4		1	1	-8.7327	3.9029	1.4962	-121.2080	-93.8703	-13.3223	-45.0347	-8.7327
5		1	1	-8.5583	3.7429	2.0213	-117.4324	-71.7756	-11.3315	-39.0697	-8.5583

Fig. 7 Energy Chart for Glipizide with 8EIT

3. Binding of Sodium Acetate with - 8EIT

In insulin-resistant individuals, sodium acetate improves hepatic triglyceride levels and dysregulated glucose homeostasis. FFA1 is highly expressed in pancreatic cells, which regulates glycemic levels by promoting glucose-stimulated insulin secretion to avoid the side effect of hypoglycemia. Arg52, Ser72, His54, Gly53 may be the primary interactive residues in this interaction.

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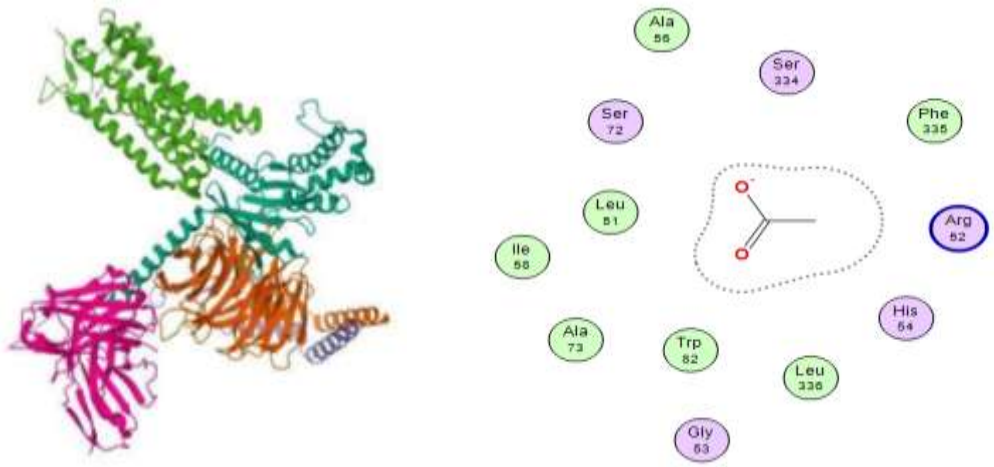

Fig. 8 Ligand Interaction of Sodium Acetate with 8EIT

Database Viewer : $HOME/dock.mdb

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	mol	rseq	mseq	S	rmsd	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1		1	1	-4.2908	2.1318	0.9431	-132.7174	-26.2454	-5.5490	-11.5621	-4.2908
2		1	1	-4.1278	2.1690	0.6123	-132.0993	-20.1363	-6.2405	-7.9472	-4.1278
3		1	1	-4.0376	0.7662	1.2989	-132.4855	-13.9994	-5.6334	-7.8374	-4.0376
4		1	1	-3.1303	12.8815	4.8374	-132.6730	-18.1827	-5.1879	-12.8061	-3.1303
5		1	1	-2.9014	12.1998	1.6762	-132.7007	-20.4234	-5.6223	-7.0072	-2.9014

Fig. 9 Energy Chart for Sodium Acetate with 8EIT

4. Binding of Acetate with - 4PHU

4PHU - The human GPR40 receptor [hGPR40], alternatively referred to as free fatty acid receptor 1 [FFAR1], is a G-protein-coupled receptor that binds long-chain free fatty acids, thereby amplifying glucose-dependent insulin secretion. Targeting hGPR40 with partial or full agonists offers potential for novel treatments in type-2 diabetes mellitus. Met1106 shows a side chain interaction with acetate.

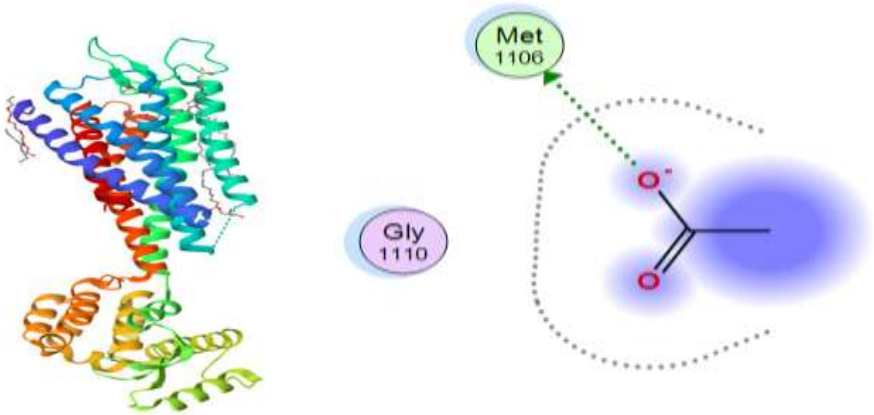

Fig. 10 Ligand Interaction of Acetate with 4PHU

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 430-451 www.ijprajournal.com ISSN: 2249-7781

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1		1	1	-3.0590	5.1288	1.8310	-91.5713	-21.8182	-4.7347	-6.0937	-3.0590
2		1	1	-2.8368	6.0230	3.5521	-91.6772	-14.1905	-4.6224	-7.6140	-2.8368

Fig. 11 Energy Chart for Acetate with 4PHU

5. Binding of Calcium Acetate with - 8EIT

Calcium ions have indirect effects on GPCR signalling through diverse mechanisms. For instance, they regulate the activity of enzymes like protein kinases and phosphatases, crucial players in GPCR signalling pathways. HisB54 is a basic in nature that is not a sidechain acceptor. AspB333 is polar in nature.

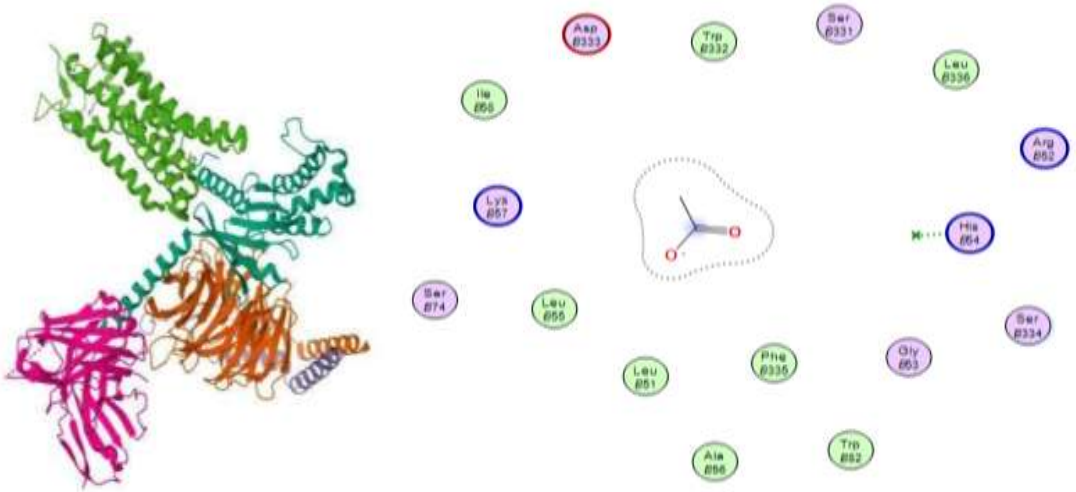

Fig. 12 Ligand Interaction of Calcium Acetate with 8EIT

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	mol	rseq	mseq	S	rmsd	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1		1	1	-3.6914	1.5796	1.9140	-132.6539	-21.2585	-5.9145	-12.4662	-3.6914
2		1	1	-3.5817	1.9188	1.8040	-132.1914	-20.0866	-5.9323	-9.0152	-3.5817
3		1	1	-3.2884	4.3255	3.2602	-132.8001	-18.4195	-4.2916	-9.9844	-3.2884
4		2	1	-3.6914	3.9583	1.9134	-132.6540	-21.2738	-5.9139	-12.4661	-3.6914
5		2	1	-3.6857	4.5600	2.4239	-132.4652	-20.0866	-5.9319	-9.5750	-3.6857
6		2	1	-3.2911	7.3418	3.2609	-132.7999	-18.4195	-4.2914	-9.9839	-3.2911

Fig. 13 Energy Chart for Acetate with 8EIT

6. Binding of Butyrate with - 8EIT

The mechanism underlying the action of butyrate is associated with the stimulation of energy expenditure and the induction of mitochondrial function. Butyrate may show binding with Arg52.

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Volume 9, Issue 2 Mar-Apr 2024, pp: 430-451 www.ijprajournal.com ISSN: 2249-7781

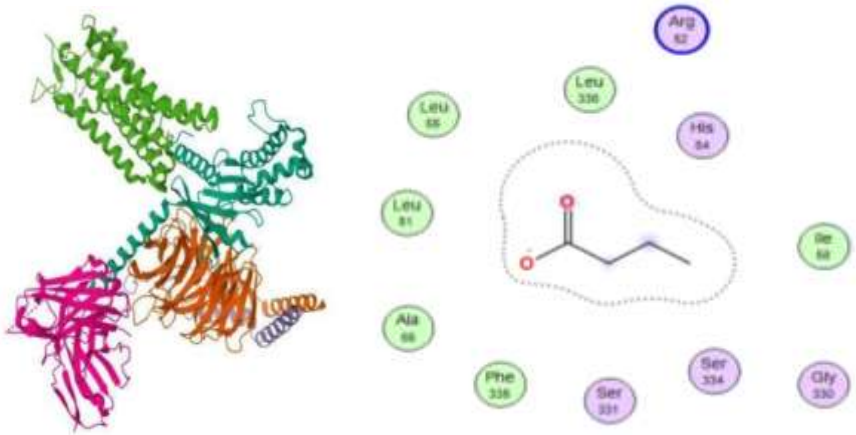

Fig. 14 Ligand Interaction of Butyrate with 8EIT

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	mol	rseq	mseq	S	rmsd	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
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2	٢	1	1	-4.5473	2.6113	1.8783	-100.7188	-14.8672	-6.3330	-13.4435	-4.5473
3	٣	1	1	-4.5372	2.9887	1.8450	-101.5573	-25.3127	-6.5405	-18.1273	-4.5372
4	٤	1	1	-4.5317	3.2854	0.9657	-103.2143	-36.6996	-6.6164	-16.2421	-4.5317
5	٥	1	1	-4.5118	2.9475	2.0157	-102.5161	-16.8096	-6.3060	-16.5396	-4.5118

Fig. 15 Energy Chart for Butyrate with 8EIT

7. Binding of Butyrate with - 4PHU

There was a binding energy difference observed when butyrate was bound with 4PHU the energy level was slightly increased from -4.7490 to -4.9175. This showed that there could be an improvement in the binding of 4PHU than 8EIT.

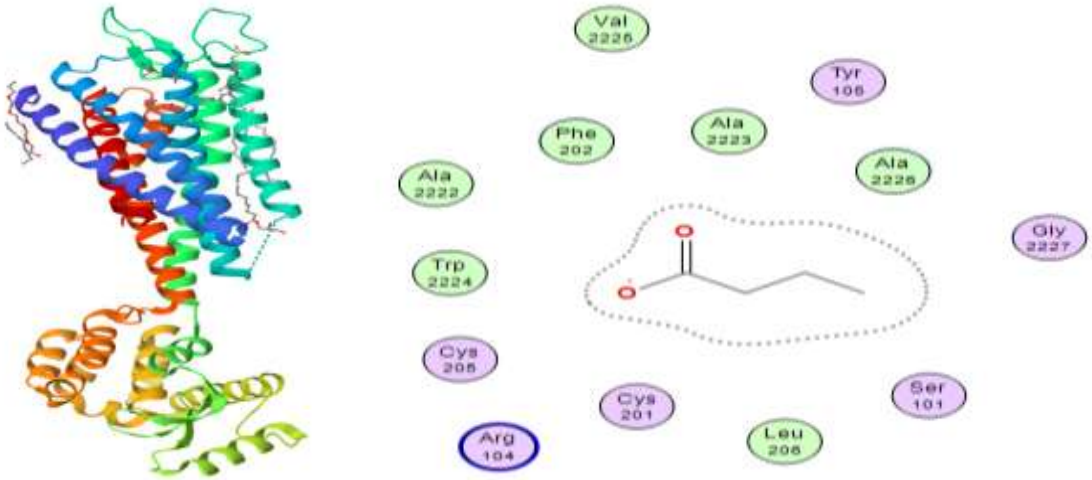

Fig. 16 Ligand Interaction of Butyrate with 4PHU

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 430-451 www.ijprajournal.com ISSN: 2249-7781

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2		1	1	-4.5372	0.7235	2.3159	-100.6730	-3.2753	-5.2565	-15.2051	-4.5372
3		1	1	-4.5236	0.9292	1.5549	-103.1272	-14.0200	-5.3438	-12.5734	-4.5236
4		1	1	-4.5033	1.6365	1.1175	-98.1702	-19.3144	-6.7034	-15.3215	-4.5033
5		1	1	-4.3655	0.9611	1.9404	-101.6814	-17.6885	-6.4433	-13.9228	-4.3655

Fig. 17 Energy Chart for Butyrate with 4PHU

8. Binding of Isobutyric Acid with - 8EIT

Butyrate reverses the insulin resistance induced by palmitate. Enhancement observed in insulin signallingand glycolysis. The insulin-sensitizing effect of the short-chain fatty acid [SCFA] is indirectly diminished by butyrate oxidation. Arg52, Ser334, His54, Gly53 were the sites that were found to have affinity towards Isobutyric acid.

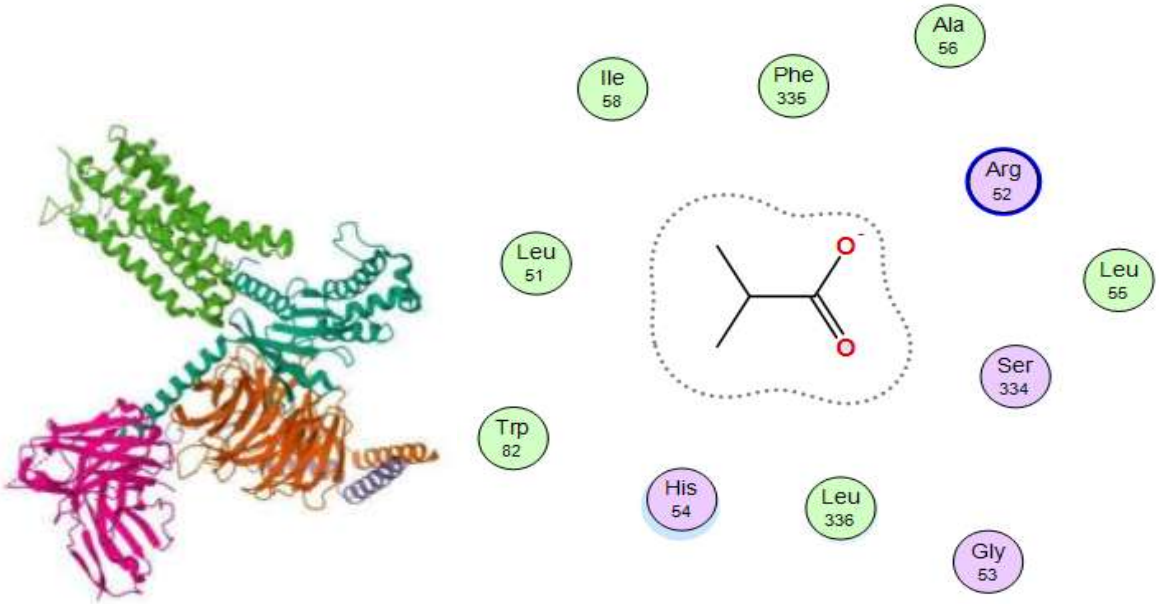

Fig. 18 Ligand Interaction of Isobutyric Acid with 8EIT

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2		1	1	-4.6146	0.6140	1.3269	-69.8768	-21.9982	-5.8518	-16.7774	-4.6146
3		1	1	-4.5469	1.8032	1.9414	-71.1444	-18.4012	-6.3321	-12.4843	-4.5469
4		1	1	-4.5142	2.9254	1.9820	-67.4936	-20.6728	-5.9870	-11.3941	-4.5142
5		1	1	-4.5061	2.7599	1.3266	-68.9436	-25.4501	-6.3215	-15.9346	-4.5061

Fig. 19 Energy Chart for Isobutyric Acid with 8EIT

9. Binding of Propionate with - 8EIT

Therefore, propionate might initiate a catecholamine-mediated elevation in insulin counter-regulatory signals, inducing insulin resistance and hyperinsulinemia. Over time, this could contribute to the development of adiposity

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 430-451 www.ijprajournal.com ISSN: 2249-7781

and metabolic irregularities. Backbone interaction was seen between the carbonyl group and His54, whereas Arg53 is an backbone acceptor.

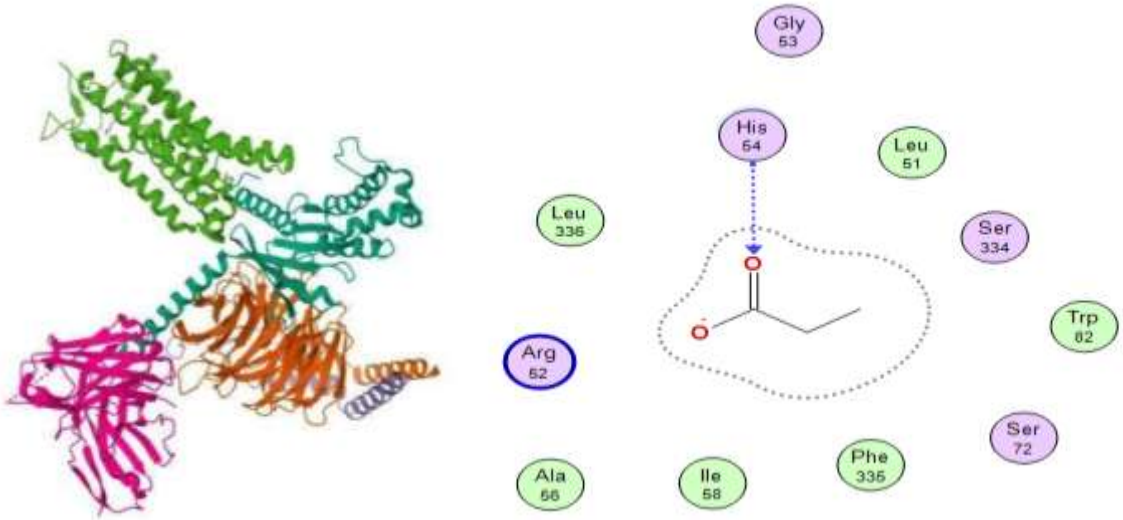

Fig. 20 Ligand Interaction of Propionate with 8EIT

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	mol	rseq	mseq	S	rmsd	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1		1	1	-4.7756	1.3985	0.7349	-94.3270	-21.2654	-6.7283	-12.3548	-4.7756
2		1	1	-4.7519	0.4870	0.9236	-97.1062	-17.9755	-6.6578	-14.1879	-4.7519
3		1	1	-4.6949	2.9382	1.8599	-97.7250	-25.6961	-6.4886	-10.0268	-4.6949
4		1	1	-4.5890	2.8603	1.1272	-98.3489	-35.8403	-7.1822	-10.6913	-4.5890
5		1	1	-4.5840	2.6717	1.3594	-96.6992	-32.8069	-6.6255	-12.9576	-4.5840

Fig. 21 Energy Chart for Propionate with 8EIT

10. Binding of Valerate with - 8EIT

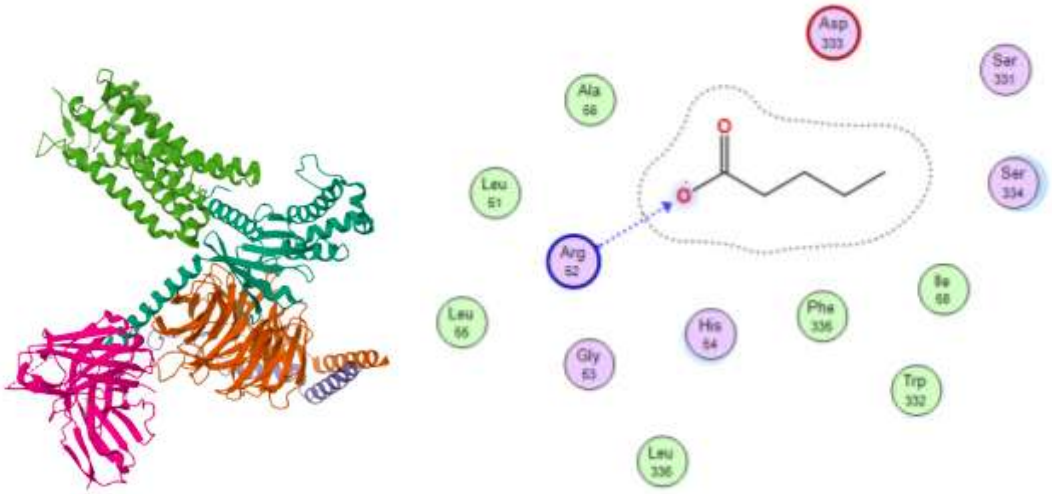

Fig. 22 Ligand Interaction of Valerate with 8EIT

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 430-451 www.ijprajournal.com ISSN: 2249-7781

Valeric acid enhanced insulin-stimulated glucose uptake in 3T3-L1 adipocytes, an effect not observed in cells transfected with siRNA for GPR41 [siGPR41]. These short-chain fatty acids [SCFAs] improved the absorption of glucose in C2C12 myotubes at rest, but not in response to insulin. Treatment with siGPR41 reduced valerate-stimulated basal glucose uptake. Arg52 is a backbone acceptor.

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	mol	rseq	mseq	$	rmsd	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1		1	1	-5.2277	1.0030	1.0124	-100.5817	-23.5612	-7.4543	-18.6587	-5.2277
2		1	1	-5.1013	4.3560	1.4521	-101.2083	-47.4189	-7.6850	-20.2580	-5.1013
3		1	1	-4.9842	4.3380	0.9007	-99.7491	-37.5608	-7.4019	-18.9731	-4.9842
4		1	1	-4.9105	4.3548	1.6496	-100.5252	-27.6490	-7.5216	-14.3676	-4.9105
5		1	1	-4.8975	0.1078	1.1187	-102.2131	-25.8748	-7.2439	-17.9414	-4.8975

Fig. 23 Energy Chart for Valerate with 8EIT

3.2 Binding Of FFAR2 receptor

1. Binding of METFORMIN with - 8T3S

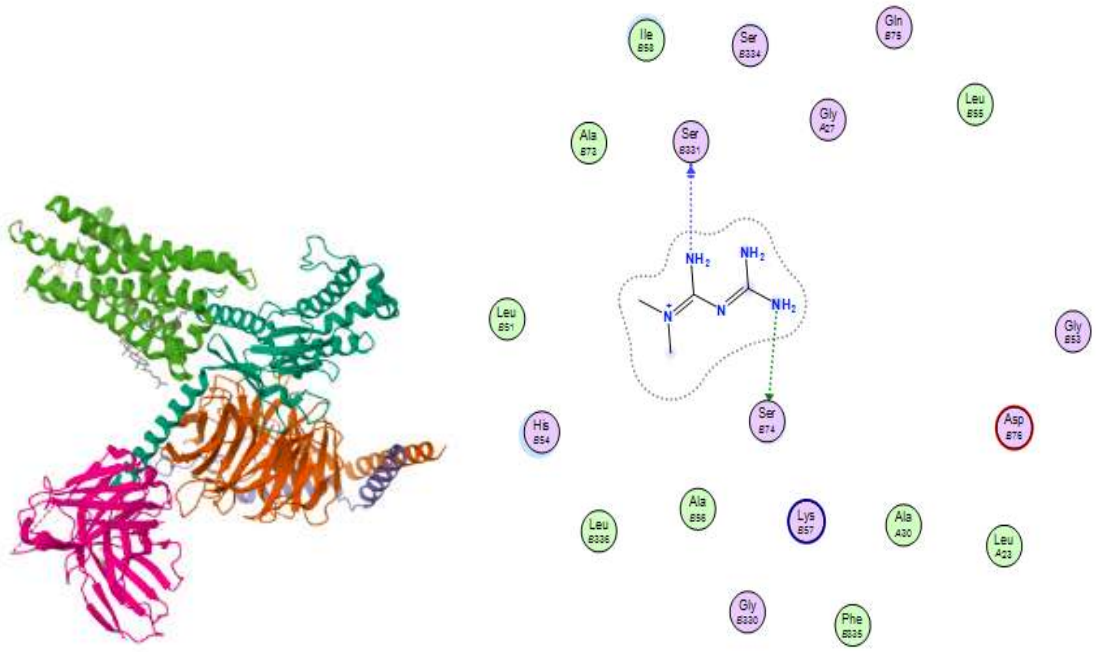

Fig. 24 Ligand Interaction of Metformin with 83TS

Class A G protein-coupled receptors [GPCRs] encompass free fatty acid receptors 1 to 4 [FFA1 to FFA4]. FFA1 to FFA3 exhibit significant sequence similarity, while FFA4 is distinct. But although FFA2 and FFA3 are triggered by short-chain fatty acids generated by the gut microbiota, FFA1 and FFA4 both react to long-chain fatty acids.

FFA1, FFA2, and FFA4 represent potential targets for therapeutic intervention in metabolic and inflammatory conditions. SerB331 is polar in nature as well as backbone donor, SerB74 polar in nature and is a sidechain donor. Receptor exposure was found to be HisB54.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 430-451 www.ijprajournal.com ISSN: 2249-7781

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	mol	rseq	mseq	S	rmsd	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1		1	1	-5.3399	8.1590	0.6464	-298.2320	-62.3445	-8.9864	-24.6025	-5.3399
2		1	1	-5.1792	7.5201	1.9200	-297.5666	-52.1872	-8.7152	-19.3556	-5.1792
3		1	1	-5.1388	7.7400	0.5531	-296.6451	-60.5260	-9.2364	-17.7847	-5.1388
4		1	1	-5.0619	8.2223	1.7882	-297.6952	-48.6086	-8.6008	-20.8075	-5.0619
5		1	1	-5.0288	7.3331	1.1940	-292.8448	-48.1633	-8.3865	-18.1877	-5.0288

Fig. 25 Energy Chart for Metformin with 83TS

2. Binding of GLIPIZIDE with - 8T3S

It was discovered that HisB54, AspB76, AspA26, SerB74, and PheB335 were receptors exposed. The backbone acceptors include AlaB56, PheB335, SerB334, and LeuB55. AspB76, AspA26, and AspB333 are acidic in nature, however LysB57 and LysB337 are basic.

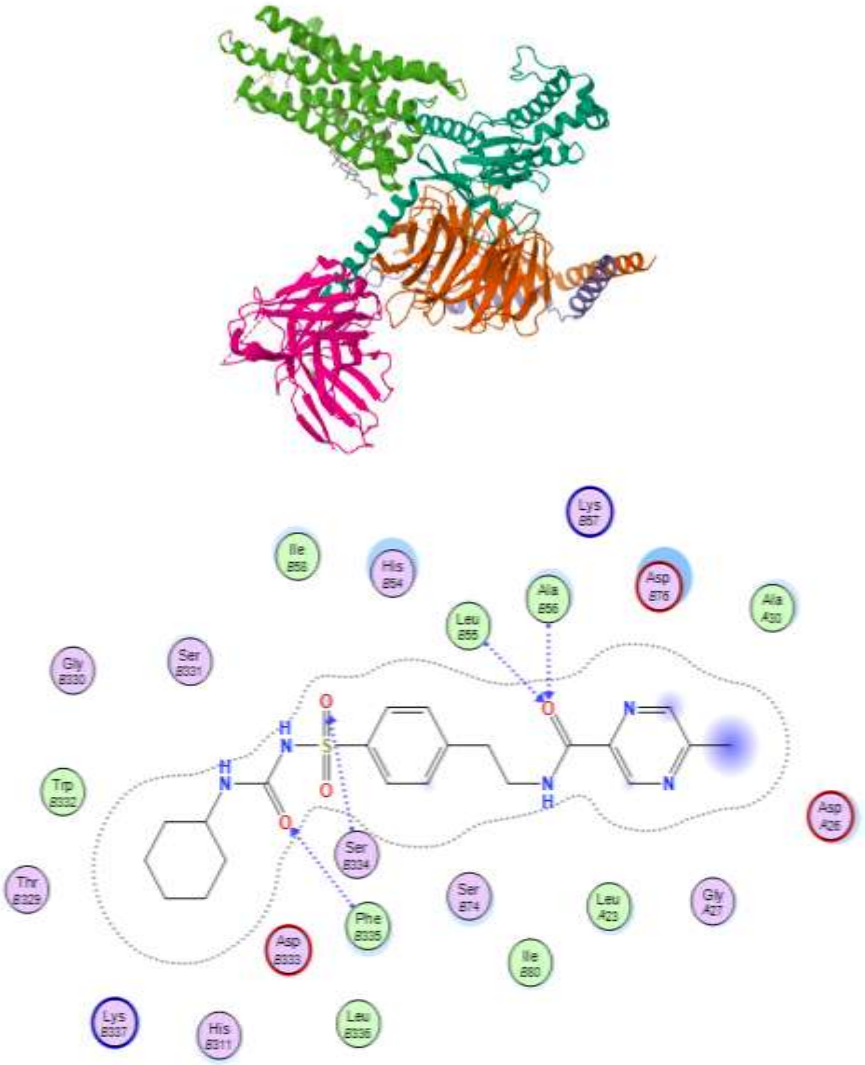

Fig. 26 Ligand Interaction of Glipizide with 83TS

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 430-451 www.ijprajournal.com ISSN: 2249-7781

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	mol	rseq	mseq	S	rmsd	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1		1	1	-9.8786	12.5447	1.8542	-96.4807	-52.3690	-11.2702	-45.8572	-9.8786
2		1	1	-9.6445	12.4905	1.3193	-103.6745	-124.5660	-11.9507	-43.6931	-9.6445
3		1	1	-9.1056	1.0761	2.3507	-70.5775	-73.6927	-10.3449	-28.9279	-9.1056
4		1	1	-8.6485	13.6671	2.3860	-122.4620	-72.7013	-11.2780	-43.1718	-8.6485
5		1	1	-8.5676	11.9147	1.2126	-79.2683	-127.5246	-14.2416	-30.7076	-8.5676

Fig. 27 Energy Chart for Glipizide with 83TS

3. Binding of Calcium Acetate with - 8T3S

The possible effect of calcium acetate, a substance frequently used to treat hyperphosphatemia in individuals with chronic kidney disease, in insulin resistance has been investigated. Via a variety of channels, calcium ions can indirectly affect insulin signalling. They control the activity of enzymes that are essential to insulin signalling cascades, such as protein phosphatases and kinases. Neither SerB354 nor PheB335 are acceptors. AspB333, LysB57, and ArgB52 are acidic, basic, and basic, respectively.
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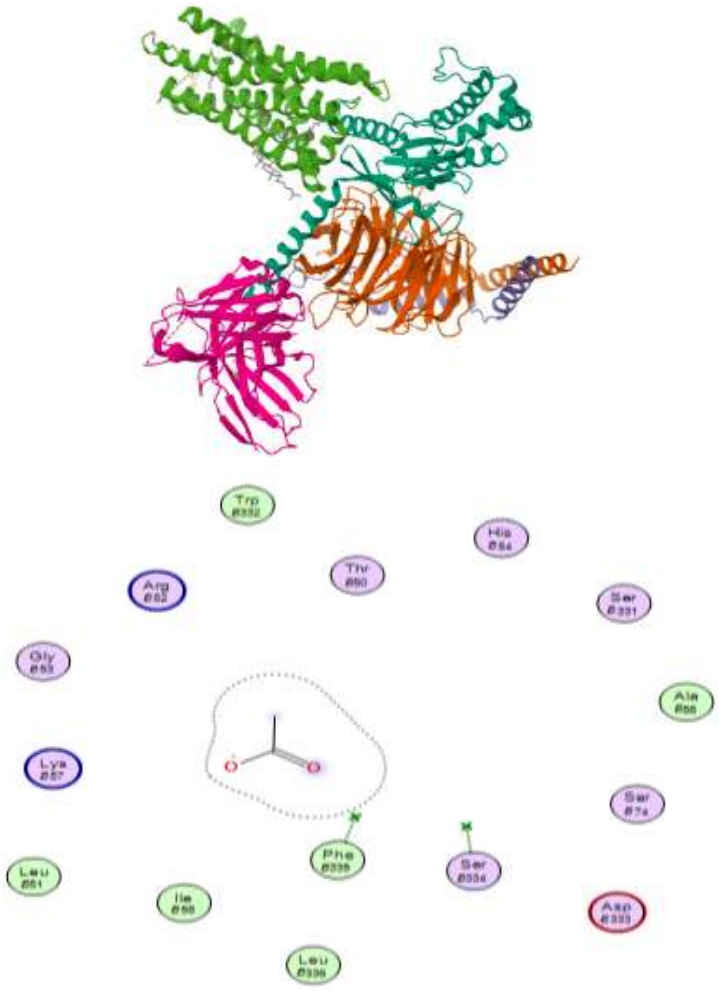

Fig. 28 Ligand Interaction of Calcium Acetate with 83TS

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 430-451 www.ijprajournal.com ISSN: 2249-7781

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	mol	rseq	mseq	S	rmsd	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1		1	1	-3.9133	4.1420	0.9250	-132.6264	-20.0771	-5.7999	-12.7134	-3.9133
2		1	1	-3.8283	4.3079	0.5526	-132.6044	-30.7436	-5.9828	-11.8064	-3.8283
3		1	1	-3.7983	4.3143	0.4931	-132.5638	-18.9968	-5.8992	-11.6838	-3.7983
4		1	1	-3.7825	4.6527	0.6812	-132.6789	-31.0824	-5.8456	-13.1671	-3.7825
5		1	1	-3.7597	3.0930	0.9696	-132.6982	-20.5477	-5.6281	-12.9263	-3.7597
6		2	1	-3.9133	0.3585	0.9252	-132.6265	-20.0771	-5.8003	-12.7119	-3.9133
7		2	1	-3.8282	1.3757	0.5531	-132.6041	-30.7436	-5.9832	-11.8050	-3.8282
8		2	1	-3.7983	1.7846	0.6811	-132.5636	-18.0177	-5.7692	-11.6842	-3.7983
9		2	1	-3.7824	1.4484	0.6811	-132.6789	-31.0824	-5.8459	-13.1661	-3.7824
10		2	1	-3.7596	1.9478	0.9698	-132.6982	-20.5477	-5.6285	-12.9264	-3.7596

Fig. 29 Energy Chart for Calcium Acetate with 83TS

4. Binding of Butyrate with - 8T3S

Research has demonstrated that butyrate stimulates the secretion of gut hormones like glucagon-like peptide-1 [GLP-1] and peptide YY [PYY] from enteroendocrine cells in the gastrointestinal tract. Subsequently, these hormones can bind to their specific G protein-coupled receptors [GPCRs] on pancreatic beta cells, which enhances insulin secretion and aids in maintaining glucose balance. These indirect influences on GPCR signalling pathways play a part in its diverse physiological functions, potentially including its involvement in regulating metabolism and insulin sensitivity. Ser331 is a backbone acceptor. Arg52, Lys57 are basic in nature. Receptor exposure can be found around His54 & Ser334

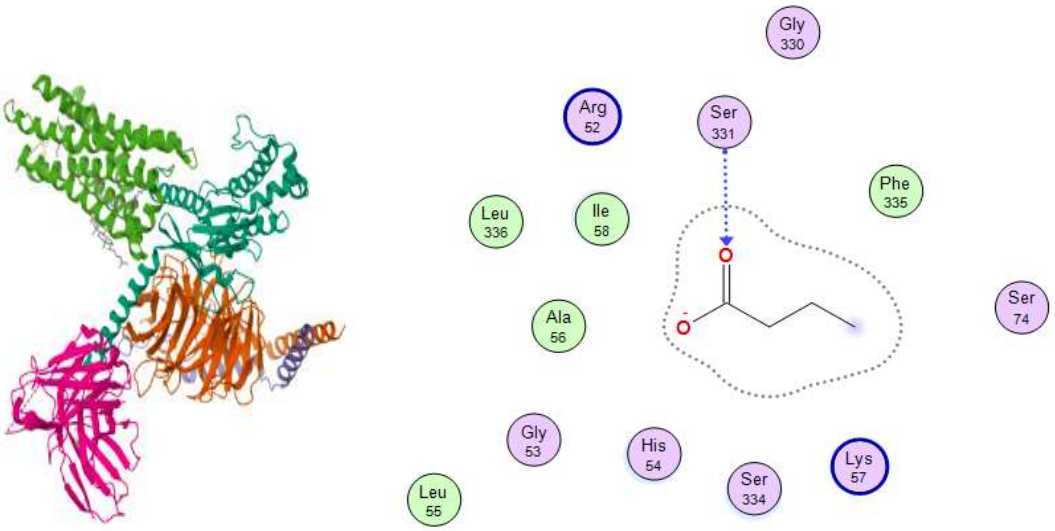


Fig. 30 Ligand Interaction of Butyrate with 83TS

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 430-451 www.ijprajournal.com ISSN: 2249-7781

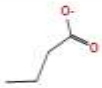
	mol	rseq	mseq	S	rmsd	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1		1	1	-4.7336	1.3878	2.0965	-100.6567	-21.0000	-6.1871	-17.0055	-4.7336
2		1	1	-4.7329	1.9433	0.9936	-101.7651	-36.9213	-6.7411	-16.4540	-4.7329
3		1	1	-4.6500	3.6676	1.3558	-100.4357	-21.2245	-6.5724	-15.9766	-4.6500
4		1	1	-4.5182	3.5772	1.3054	-102.6400	-22.0467	-6.4100	-13.9250	-4.5182
5		1	1	-4.4165	1.6952	1.3123	-101.2851	-37.6381	-7.0605	-13.5350	-4.4165

Fig. 31 Energy Chart for Butyrate with 83TS

5. Binding of Iso-butyric Acid with - 8T3S

Isobutyric acid serves as signallingmolecule by attaching to particular receptors like GPCRs, such as GPR41 and GPR43, alternatively termed as free fatty acid receptors 3 and 2 [FFAR3 and FFAR2], respectively. Ser72 is a sidechain acceptor. Receptor exposure was found around His54 & Ser334.

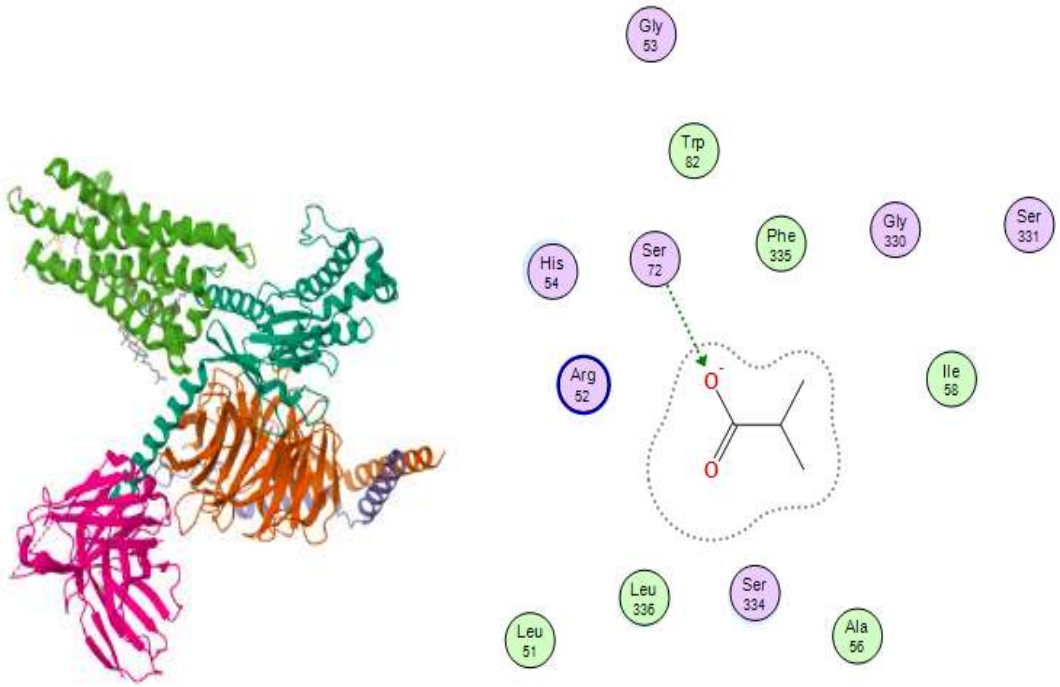


Fig. 32 Ligand Interaction of Iso - Butyric acid with 83TS

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 430-451 www.ijprajournal.com ISSN: 2249-7781

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	mol	rseq	mseq	S	rmsd	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1	٢	1	1	-4.8507	0.0655	0.9335	-72.6717	-31.0067	-6.0935	-20.2678	-4.8507
2	٢	1	1	-4.6033	2.0852	0.8102	-70.8116	-28.2513	-6.2912	-17.1641	-4.6033
3	٢	1	1	-4.5326	0.5646	0.7478	-71.7028	-31.5876	-6.7496	-17.4331	-4.5326
4	٢	1	1	-4.5103	2.8840	1.3564	-71.3075	-30.5351	-6.7892	-17.4155	-4.5103
5	٢	1	1	-4.4962	2.6312	1.2961	-70.4071	-21.8208	-6.5328	-13.1681	-4.4962

Fig. 33 Energy Chart for Iso - Butyric acid with 83TS

6. Binding of Propionate with - 8T3S

Propionate by interacting with FFAR2 and potentially other GPCRs, propionate influences metabolic regulation and insulin sensitivity. For instance, propionate-triggered activation of FFAR2 in enteroendocrine cells may prompt the secretion of gut hormones like peptide YY [PYY] and glucagon-like peptide-1 [GLP-1]. These hormones are involved in regulating appetite, glucose metabolism, and insulin release.

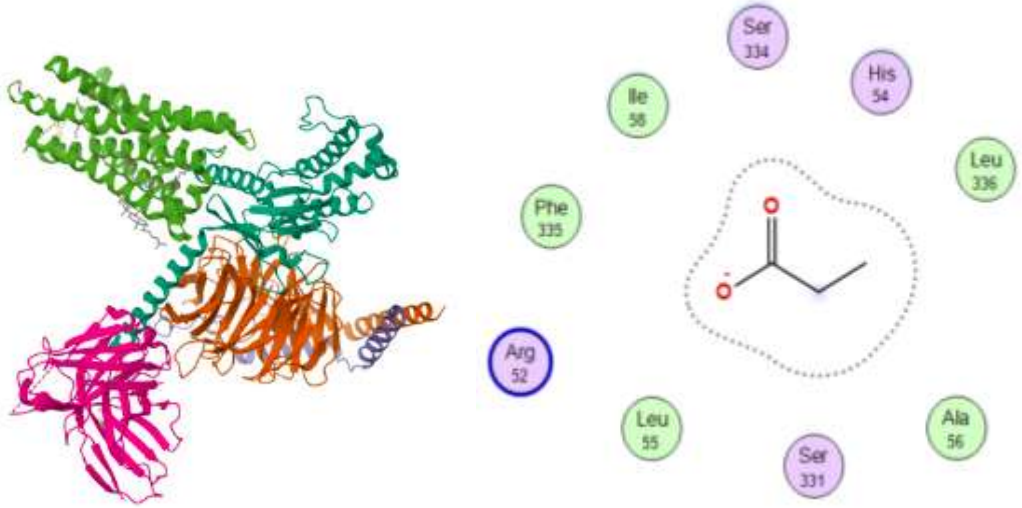

Fig. 34 Ligand Interaction of Propionate with 83TS

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	mol	rseq	mseq	S	rmsd	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1	٢	1	1	-3.7205	5.8208	0.8410	-98.3513	-18.3610	-5.1603	-11.7137	-3.7205
2	٢	1	1	-3.6720	8.6132	3.7904	-98.8850	-19.3800	-5.1115	-13.1742	-3.6720
3	٢	1	1	-3.4940	8.8002	3.4348	-98.5887	-25.5672	-5.1361	-11.8059	-3.4940

Fig. 35 Energy Chart for Propionate with 83TS

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 430-451 www.ijprajournal.com ISSN: 2249-7781

7. Binding of Valerate with - 8T3S

Valerate, like other short-chain fatty acids, is identified as capable of activating specific free fatty acid receptors [FFARs], notably FFAR2 [or GPR43] and FFAR3 [or GPR41].

This activation of FFARs by valerate and similar short-chain fatty acids can set off intracellular signalling pathways, thereby regulating a range of physiological processes including energy metabolism, inflammation, and the secretion of gut hormones. Receptor exposure was seen around His54.

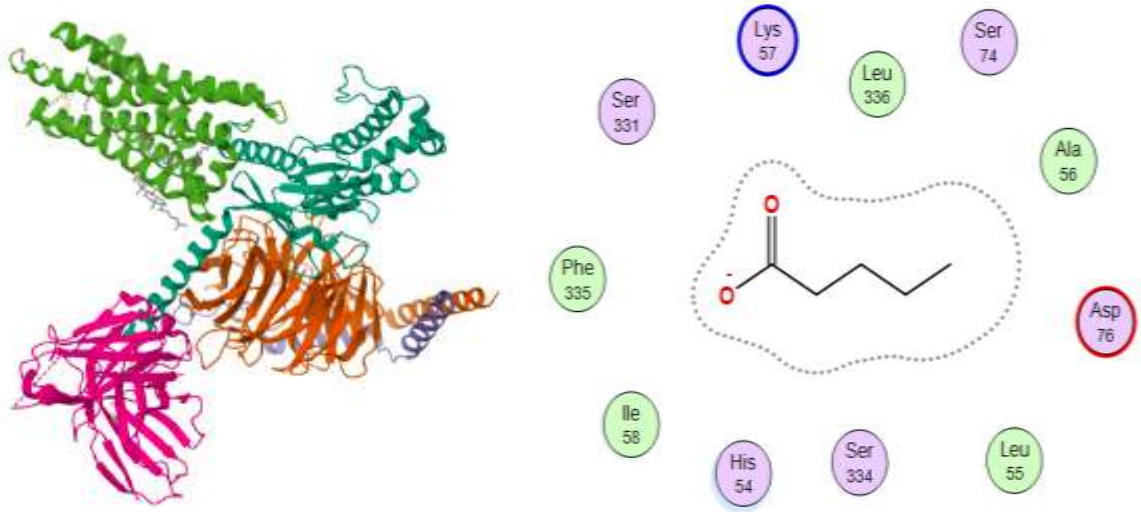

Fig. 36 Ligand Interaction of Valerate with 83TS

Database Viewer : SDESKTOP/pdb/dock.mdb

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	mol	rseq	mseq	S	rmsd	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1		1	1	-5.5481	0.0375	1.0420	-101.3298	-29.4803	-8.0146	-21.5433	-5.5481
2		1	1	-5.4753	0.4490	1.1699	-98.0199	-15.5745	-7.4112	-20.4403	-5.4753
3		1	1	-5.1713	0.9382	0.7004	-95.4106	-18.0759	-7.9373	-17.1003	-5.1713
4		1	1	-5.1468	1.1251	1.9236	-100.8986	-19.9863	-7.6694	-16.5760	-5.1468
5		1	1	-5.1092	4.5340	1.4023	-101.7172	-25.8819	-8.1887	-15.8507	-5.1092

Fig. 37 Energy Chart for Valerate with 83TS

3.3 Binding Energy Table

Binding Energy Table For Standard			
Standard	Receptor	Binding Energy	
		Minimum	Maximum
Metformin	3BU3	-6.0088	-6.4301
	8T3S	-5.0288	-5.3399
Glipizide	8EIT	-8.5583	-8.8567
	8T3S	-8.5676	-9.8786

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 430-451 www.ijprajournal.com ISSN: 2249-7781

Binding Energy Table For Metabolites			
Receptor	Metabolites	Binding Energy	
		Minimum	Maximum
8EIT	Sodium Acetate	-2.9014	-4.2908
	Calcium Acetate	-3.2911	-3.6914
	Butyrate	-4.5118	-4.749
	Isobutyric Acid	-4.5061	-4.6282
	Propionate	-4.584	-4.7756
	Valerate	0.1078	-4.356
4PHU	Acetate	-2.8368	-3.059
	Butyrate	-4.3655	-4.9175
8T3S	Calcium Acetate	-3.7596	-3.9133
	Butyrate	-4.4165	-4.7336
	Isobutyric Acid	-4.4962	-4.8507
	Propionate	-3.494	-3.7205
	Valerate	-5.1092	-5.5481

IV. CONCLUSION:

In conclusion, the docking study presented here sheds light on the interaction between the Short-chain fatty acid metabolites and G-protein Coupled receptors (FFAR1 & FFAR2). The study provided valuable insights into the interaction between ligands and receptors, and their potential binding sites and it can be concluded that metabolites have good interaction in favourable pose with G-protein Coupled receptor which was explained by high binding energy, strong bond length. The primary interactive residues in this interaction were determined as Arg52, Ser72, His54, Gly53. The receptor exposure sites for the activity with SCFA were established as HisB54, AspB76, AspA26, SerB74, PheB335, His54 & Ser334. These discoveries enhance our comprehension of the molecular mechanisms underlying SCFA-GPCR interactions and offer potential for the development of innovative therapeutics aimed at addressing metabolic and inflammatory conditions.

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ETHICAL STATEMENT:

1. Funding - NA
2. Conflict of Interest - The authors affirm that they do not have any conflicts of interest related to the publication of this article.
3. Ethical Approval - NA
4. Informed Consent - NA
5. Author Contribution - Nadar Madonna and Khan Ubaidur, studied the MOE software and performed docking with the guidance of Sohani Solanke and Priyanka Kalamkar. Punjabi Simran and Yadav Mahima prepared the introductory and related diagrammatic as well as referencing part.
6. Data Availability Statement - The data underpinning the findings of this study are accessible through the references mentioned.

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