Molecular docking studies of 4 – Piperidinopyridine and 4 – Piperidinopyrimidine derivatives as 2, 3 - Oxidosqualene Cyclase inhibitors

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Abstract

Lanosterol synthase belongs to the large family of oxidosqualene cyclases (OSCs), eukaryotic enzymes that catalyse the cyclization of 2,3-oxidosqualene(OS) into different cyclic compounds. A novel series of 4-piperidinopyridines and 4-piperidinopyrimidines showed potent and selective inhibition of 2,3-oxidosqualene cyclase-lanosterol synthase (OSC). The piperidinopyrimidine OSC inhibitors have a significantly lower pK(a) than the corresponding pyridine .This indicates that other novel OSC inhibitors may be found in analogues of this series across a broader pK(a) range (6.0-9.0). These series may yield novel hypocholesterolemic agents for the treatment of cardiovascular disease. Docking analysis of GOLD and GLIDE were performed to predict the binding properties of disease related target protein OSC with 4-Piperidinopyridine and 4-Piperidinopyrimidine derivatives as inhibitors. Virtual Screening has been done for all derivatives (inhibitors) and the ligands were chosen for induced fit docking based on their binding affinity, glide energy and glide score. The results revealed that the compound 25 *(1-(4-Pyrimidinyl)- 4-(1- (4-bromophenyl -sulfonyl) pipera zin-4ylcarbonyl) piperidine)* with more interaction and scores may afford novel hypocholesterolemic agents for the treatment of cardiovascular disease.

Keywords: Oxidosqualene Cyclase , docking, cardiovascular, hypocholesterolemic .

Introduction

Oxidosqualene cyclases (OSC) are crucial enzymes of sterol biosynthesis in eukaryotes as they transform 2,3-oxidosqualene, the last acyclic precursor of the metabolic path, into a variety of cyclized products (Nes ,1989 and Abe *et al.*,1993).Prokaryotes possess an enzyme Squalene - hopene cyclase (SHC) similar to OSCs that converts squalene into hopene or diplopterol, pentacyclic precursors of hopanoids (Wendt *et al.*, 2000). OSCs accept only 2,3- oxidosqualene as substrate, whereas SHC not only accepts its physiological substrate squalene, but also the eukaryotes substrate 2,3-oxidosqualene (Bosso *et al* .,2005). The knowledge of the inhibitor binding mode in SHC is likely to help develop more potent inhibitors for OSC (Lenhart *et al.* , 2002).

In addition to work on novel Squalene synthase (SQS) and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, Brown *et al* ., (2000) have considered the inhibition of other enzyme steps of the cholesterol biosynthesis pathway as potential targets for medicinal chemistry. In this approach inhibition of steps before SQS is avoided because they are involved in protein prenylation and the synthesis of key biosynthetic precursors such as ubiquinone.

Inhibition of steps after the formation of lanosterol is also avoided because it previously afforded toxic inhibitors by accumulation of higher sterols such as desmosterol. This analysis leads to squalene oxidation and the subsequent cyclization of 2,3-oxidosqualene by OSC, as optimal steps for enzyme inhibition (Brown *et al*., 2000).The OSC was also proved enormously successful in preventing cardiovascular disease (Menys and Durrington ,2007).Cholesterol has been implicated as the major contributor to this condition as atherosclerosis is strongly correlated with an increase in serum cholesterol levels (Chittur *et al* .,2008). This disorder is characterized by deposits of fatty substances, cholesterol, cellular waste products, calcium and other substances in the inner lining of an artery collectively known as plaques (Munro and Cotran, 1988).

The drugs may be designed that bind to the active region and inhibit the key molecule. Most proteins contain pockets, cavities, surface depressions and other geometrical regions where small-molecule compounds can easily bind (Gane and Dean, 2000). Drug design is the approach of finding drugs by design, based on the three dimensional structure of their biological targets. It aims to create a molecule that will bind to the active site of a targeted enzyme, thereby preventing the normal chemical reaction and ultimately halting the progression of the disease (Kuntz, 1992). Docking is a term used for computational schemes that attempt to find the "best" matching between two molecules: a receptor and a ligand.The results of docking can be extremely beneficial in finding drugs that are effective against particular diseases (Palma *et al* ., 2000).

Docking analysis of GOLD and GLIDE were used to predict the binding properties of disease related target protein OSC with 4-

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Piperidinopyridine and 4-Piperidinopyrimidine derivatives as inhibitors. The molecular docking software GOLD (Genetic Optimization for Ligand Docking) follows a genetic algorithm for calculating the solutions. GOLD allows for partial protein flexibility in all dockings.(Jones *et al.*, 1997). The two scoring functions available in the GOLD software are Gold Score fitness function and ChemScore fitness function. The results of the GOLD were analyzed using *SILVER* (Jones *et al.*, 1995). The molecular docking software *GLIDE* (Grid based Ligand Docking with Energetics) searches for favorable interactions between one or more typically small ligand molecules and a larger receptor molecule usually a protein .Three types of docking algorithm used for the present studies are HTVS(High Throughput Virtual Screening), XP(Extra Precision), and Induced fit docking (Friesner *et al.*, 2004; Abagyan and Totrov, 2001).

The prime aim of the study is to design a novel drug of hypocholesterolemic agents for the treatment of cardiovascular disease. The results obtained from this study would be useful in both understanding the inhibitory mode of the 4-Piperidinopyridine and 4-Piperidinopyrimidine derivatives as well as in predicting the activities of newly designed inhibitors on the basis of docking scores.

Materials And Methods

Docking plays an important role in structure based drug design minimizing the amount of money spent in the pharmacological field for developing the medicines against deadly diseases. (Kitchen *et al.*, 2004). The *molecular docking problem* can be defined as follows: Given the atomic coordinates of two molecules, predict their "correct" bound association (Inbal *et al* ., 2002).

Target Protein Identification: The protein molecule chosen for the docking studies was 2,3-Oxidosqualene Cyclase (OSC) or Lanosterol Synthase. The crystal structure of human OSC in complex lanosterol, was used as target structure in the current study. It was obtained from RCSB Protein Data Bank with the PDB ID: 1W6K. The structural details are as follows:

2,3-Oxidosqualene Cyclase	: (E.C. 5.4.99.7)
Crystal structure resolution	: 2.10
Chains present	: 1-(A)
Total residues	: 351 amino acids
Crystallography method	: X- ray diffraction
Space Group	: $C222_1$
R-value	: 0.147

Ligands

About 45 compounds (4-piperidinopyridines and 4-piperidinopyrimidines derivatives) were used for docking studies which were selected from literature studies(Brown *et al.*, 2000).The canonical structure or PDB files of the compounds were used for docking.

Docking Analysis Using Gold

GOLD is Genetic Optimization for Ligand Docking , it is a genetic algorithm for docking flexible ligands into protein binding sites. Specifically GOLD rotates the torsion angles of Ser, Thr and Tyr hydroxyl groups during docking in order to optimise H-bonding interactions of these residues with the ligand .GOLD offers a choice of scoring functions, GoldScore, ChemScore, ASP and User Defined Score which allows users to modify an existing function or implement their own scoring function. The results of GOLD were visualized in *SILVER*.

Preparation of Protein Molecule and Ligand

The experimental structure of human OSC was retrieved from the RCSB Protein Data Bank as a *pdb* file. The PDB code of the protein was 1W6K.The protein molecules were prepared mainly by using the software Swiss-pdb viewer. Active site residues with in a range of 3.5 Å were selected and saved in pdb format. Later, the active site residues were minimized in Argus lab after adding hydrogen bonds. The list of atoms in active site, were saved separately as a list file in text document format, which will be used as an input for GOLD. The ligand (4-Piperidinopyridine and 4-Piperidinopyrimidine derivatives) were taken from literature. The ligand structures were drawn using Chemsketch and saved in mol format. The saved ligand compounds were later import and minimized in Argus lab after adding hydrogen bonds. The molecules thus obtained were saved in pdb format.

Setting up Gold Parameter

The protein molecule and the ligands were imported into GOLD. GOLD was run in a particular way such that a particular atom number was given from the identified active site. The GOLD was setup to run at an active site radius of 3.5 Å. The output folder was also specified. All the other fitness function parameters and the genetic algorithm parameters were kept in default mode. The GOLD was run and the output was viewed using *Silver*.

Screening criteria

The output was produced as GOLD Fitness scores and different energy functions. The fitness scores were mainly considered for the results and the screening. The only ligands with scores of 25 (GOLD Fitness score for co-crystallized ligand) and above were considered. The output of these protein- ligand complexes were exported as PDB files using Gold.

Docking Analysis Using Glide

Maestro is the graphical user interface for all of Schrödinger's products CombiGlide™, Epik™, Glide™, Impact™, Liaison™ ,Ligprep™ MacroModel™ , Phase™, Prime™, QikProp™, Qsite™, and Strike™. GLIDE can be run in rigid or flexible docking modes; the latter automatically generates conformation for each input ligand. The combination of positions and orientation of the ligand relative to the

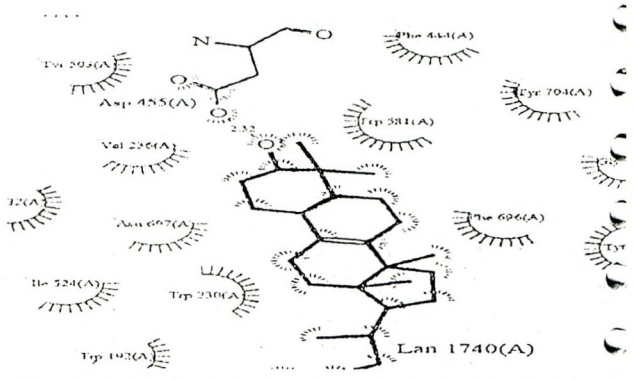
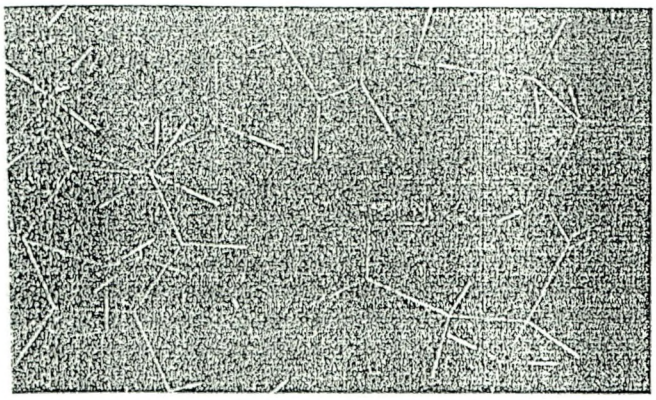


Figure 1: Ligplot interactions of co-crystal ligand (LAN) with the active of the target protein OSC (1W6K)



ure 2: Interaction of co-crystal ligand(LAN) with the active site of et protein OSC

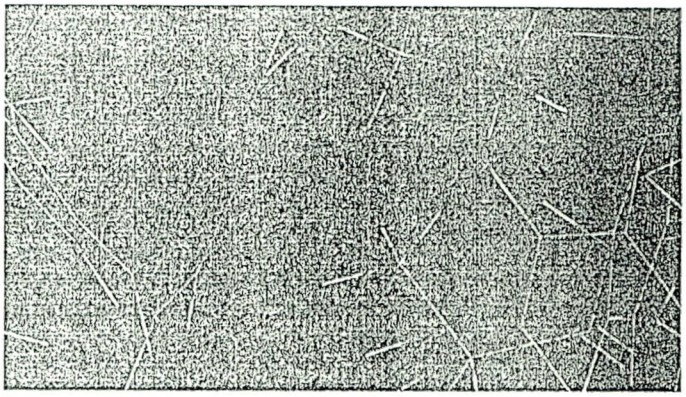
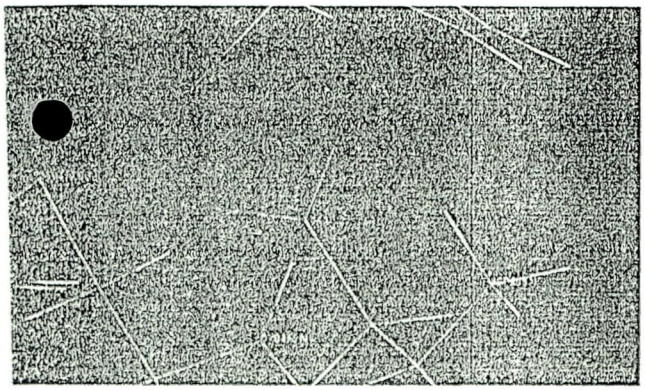


Figure 3: Interaction of Compound 4a with the active site of t arget protein OSC



e 4: Interaction of Compound 25 with the active site of t protein OSC

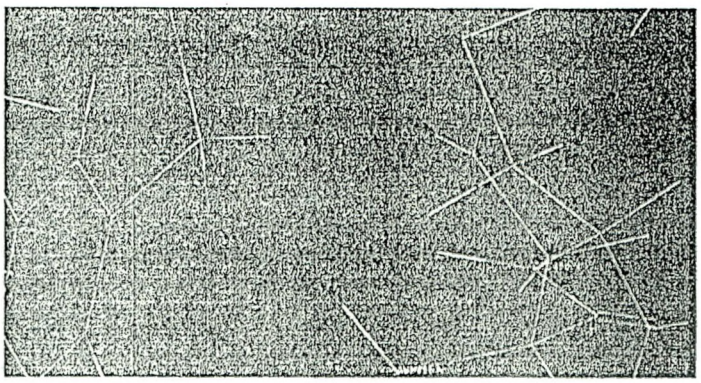
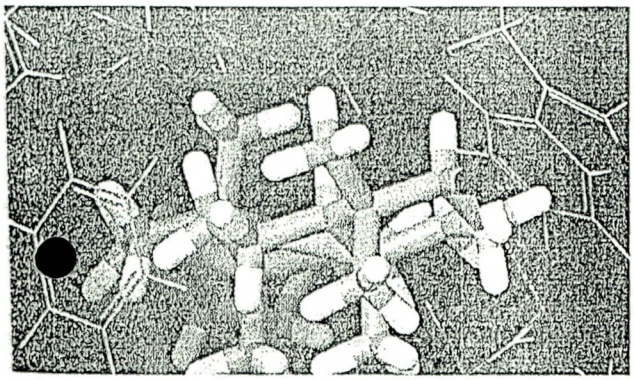


Figure 5. Interaction of Compound 26 with the active site of target protein OSC



e 8. Glide Interactions of Co-Crystal Ligand(LAN) docked e active site of OSC

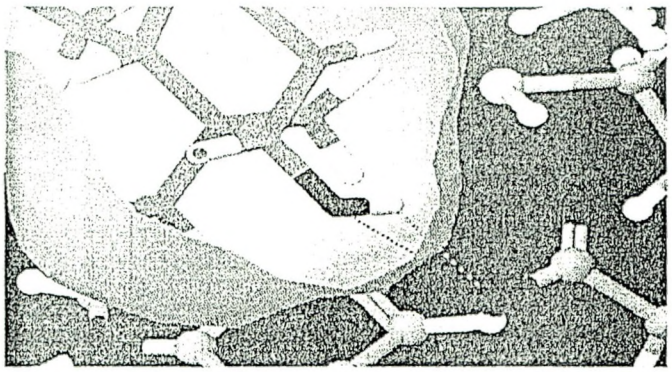
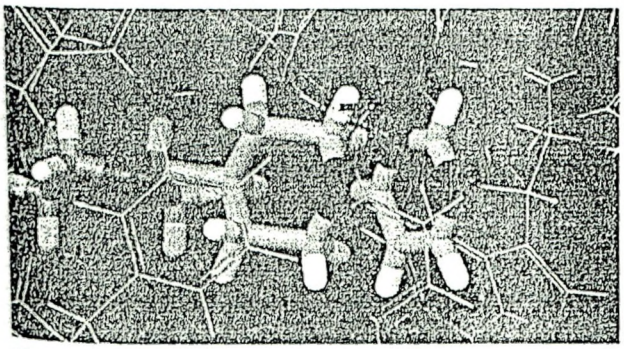


Figure 9 . Glide Pose viewer Interactions of Co-Crystal Ligand(LAN) docked into the active site of OSC



10. Glide Interactions of compound 25 docked into the active site

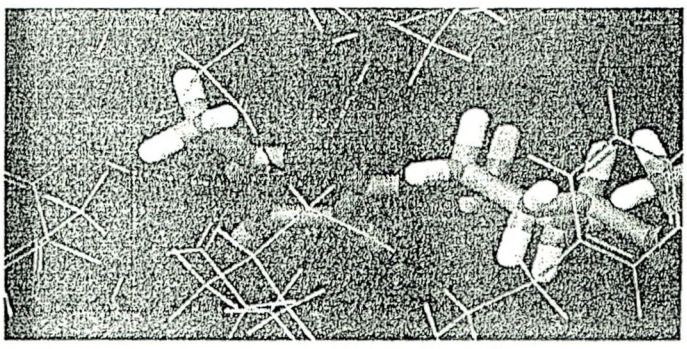
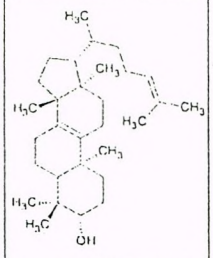
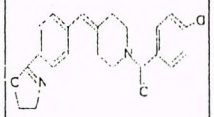
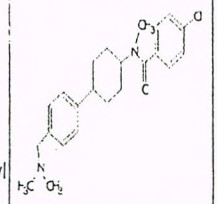
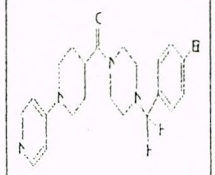
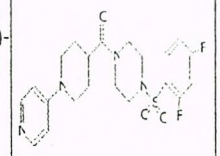
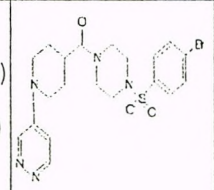
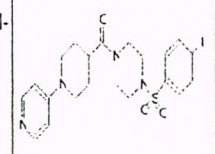


Figure 11. Glide Interactions of compound 26 docked into the active site of OSC

Compounds	Structures	Interactions (D-H...A)	Bond distance (Å)	Gold Score
CO-CRYSTAL LIGAND (Lanosterol) *4,4',14alpha-Trimethyl-5alpha-cholesta-8,24-dien-3beta-ol*		(O-H...O) ASP 455:O	2.642	25.93
Compound 4a 1-(4-chloro benzoyl)-4-((4-(2-oxazolin-2-yl) benzylidene)) Piperidine		(N-H...O) ASP 455:N	2.427	74.81
Compound 5 4-Chloro-N-[4-(4-dimethyl aminomethyl-phenyl)-cyclo hexyl]-N-methyl benzamide		(N-H...O) ASP 455:N	2.566	70.99
Compound 18 4-(4-Bromo phenylmethyl)-1-(1-(4-pyridyl) piperidin-4-ylcarbonyl) piperazine		(N-H...N) CYS 456:N	2.563	68.17
Compound 13 1-(2,4-di-fluoro phenylsulfonyl)-4-(1-(4-pyridyl) piperidin-4-ylcarbonyl) piperazine		N-H...O) CYS 456:N (N-H...O) ASP 455:N (S-H...O) CYS 456:S	2.593 2.406 2.619	67.48
Compound 24 1-(5-Pyridazinyl) -4-(1-(4-bromo phenyl-sulfonyl) piperazin-4-ylcarbonyl) piperidine		(N-H...N) CYS 456:N (N-H...N) ASP 455:N	2.396 2.464	66.03
Compound 7 1-(4-Iodophenyl-sulfonyl)-4-(1-(4-pyridyl) piperidin-4-ylcarbonyl) piperazine		(N-H...O) ASP 455:N (S-H...O) CYS 456:S	2.365 2.712	64.30

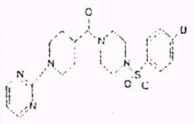
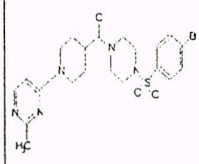
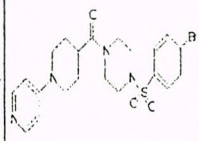
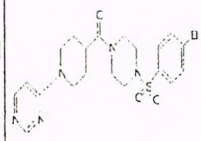
Compounds	Structures	Interactions (D-H...A)	Bond distance (Å)	Gold Score
Compound 23 1-(2-pyrimidin-yl)-4-(1-(4-bromophenyl sulfo-nyl) piperazin-4-ylcarbonyl) piperidine		(N-H...O) ASP 455:N (S-H...O) CYS 456:S	2.539 2.416	64.07
Compound 26 1-(2-Methyl-4-pyrimidinyl)4(1-(4-bromophenyl-sulfonyl)pipera-zin -4ylcarbonyl) piperidine		(N-H...O) ASP 455:N (S-H...O) CYS 456:S	2.383 2.641	63.81
Compound 9 1-(4-bromo phenylsulfonyl)-4-(1-(4-pyridyl) piperidin-4-yl carbonyl) piperazine		(N-H...O) CYS 456:N (N-H...O) ASP 455:N (S-H...O) CYS 456:S	2.664 2.431 2.610	66
Compound 25 1-(4-Pyrimidin yl)- 4-(1-(4-bromophenyl -sulfonyl) pipera zin-,4ylcarbonyl) piperidine		(N-H...O) CYS 456:N (N-H...O) ASP 455:N (S-H...O) CYS 456:S	2.578 2.369 2.427	62.15

Table 1. Structure, interaction, bond distance and gold fitness score of the selected compounds

receptor, along with its conformation in flexible docking, is referred to as a ligand pose. Maestro contains tools for building, displaying, and manipulating, chemical structures; for organizing, loading and storing these structures and associated data.

Preparation of target protein and ligand

The protein 3-D structure was taken from the PDB (www.rcsb.org) 1W6K and modified for Glide Docking calculations .2,3-Oxidosqualene cyclase protein complex was imported and prepared using the Protein Preparation Wizard in the Maestro .The protein was optimized and energy minimized using the amber forcefield. The output file generated was *Jobname.impref_ref.out*. All the small ligand molecule structures were drawn using the builder panel available in the Schrödinger software. The structures were then energy minimized using the OPLS 2005 force field until it reaches the RMSD 0.0018 kcal/mol. Three types of Docking Algorithm used for the current studies are:

1. **High Throughput Virtual Screening (HTVS)**
2. **Extra Precision (XP) docking**
3. **Induced Fit docking**

job name	docking score	glide lipo	glide hbond	glide esite	glide evdw	glide energ
impact_mini_ligand4b_sd	-10.249753	-4.540832	0.000000e+...	0.000000e+...	-81.529483	-51.082808
impact_mini_ligand14_sd	-10.193659	-4.277692	0.000000e+...	0.000000e+...	-87.952301	-57.290165
impact_mini_ligandnew12_...	-10.184518	-4.404314	0.000000e+...	0.000000e+...	-90.973875	-57.104078
impact_mini_ligand20_sd	-10.153573	-4.115180	0.000000e+...	0.000000e+...	-101.266466	-64.195940
impact_mini_ligand11_sd	-10.113387	-4.224371	0.000000e+...	0.000000e+...	-92.633044	-56.945875
impact_mini_ligand13_sd	-10.077347	-4.404984	0.000000e+...	0.000000e+...	-86.866033	-55.185735
impact_mini_ligand8_sd	-10.074329	-4.432026	0.000000e+...	0.000000e+...	-91.117210	-57.947570
impact_mini_ligand4a_sd	-10.064508	-4.892218	0.000000e+...	0.000000e+...	-87.384727	-54.960968
impact_mini_ligand25_sd	-10.027523	-4.265533	0.000000e+...	-0.062074	-102.544668	-65.825337
impact_mini_ligand23_sd	-9.965881	-4.184064	0.000000e+...	0.000000e+...	-92.496048	-59.841330
impact_mini_ligand24_sd	-9.937436	-4.351449	0.000000e+...	-0.092811	-93.117437	-61.134718
impact_mini_ligand22_sd	-9.896571	-4.210435	0.000000e+...	-0.076039	-99.907703	-63.656160
impact_mini_ligand9_sd	-9.874178	-4.439071	0.000000e+...	0.000000e+...	-89.145715	-57.978799
impact_mini_ligand26_sd	-9.851079	-4.283365	0.000000e+...	-0.022279	-92.756079	-60.551695
impact_mini_ligand21_sd	-9.807931	-3.964893	0.000000e+...	0.000000e+...	-96.240217	-61.244348
impact_mini_ligand10_sd	-9.788077	-4.678593	0.000000e+...	0.000000e+...	-81.373973	-53.452326
impact_mini_ligand7_sd	-9.764974	-4.633223	0.000000e+...	0.000000e+...	-79.282179	-52.550094
impact_mini_ligand19_sd	-9.757996	-4.588119	0.000000e+...	0.000000e+...	-91.521856	-60.662449
impact_mini_ligand17_sd	-9.674854	-4.362632	0.000000e+...	0.000000e+...	-84.795983	-54.356927
impact_mini_ligand30_sd	-9.668891	-3.890770	0.000000e+...	0.000000e+...	-93.467363	-60.851807
impact_mini_ligand18_sd	-9.638848	-4.754842	-0.030630	0.000000e+...	-86.332610	-57.581659
impact_mini_ligand6b_sd	-9.360982	-5.175209	0.000000e+...	0.000000e+...	-80.901000	-52.740129
impact_mini_ligand31_sd	-9.291447	-3.869242	0.000000e+...	-0.007977	-86.706915	-56.140585
impact_mini_ligand16_sd	-9.202854	-4.112502	0.000000e+...	0.000000e+...	-66.367479	-46.593099
impact_mini_ligand35a_sd	-9.124677	-4.159579	0.000000e+...	0.000000e+...	-74.316245	-48.030533

Figure 6. High Throughput Virtual Screening list the best score compounds at the top

(2)		XP:pdbligand_glide_dock_pv										
1	◇				1	X...						
2	◇	STRUCTURE OF HUMAN OSC IN COM...			2	1...	1W6K	pdbligandsdimpact_mini	-13.750449	-13.7504...	-13.750449	-36.128997
(2)		XP:ligand14_glide_dock_pv										
3	◇				3	X...						
4	◇	ligand_7			4	1...		impact_mini_ligand14_sd	-14.978137	-14.9781...	-14.978137	-57.041025
(2)		XP:ligand24_glide_dock_pv										
5	◇				5	X...						
6	◇	ligand_7			6	1...		impact_mini_ligand24_sd	-14.192513	-14.1925...	-14.192513	-59.336975
(2)		XP:ligand25_glide_dock_pv										
7	◇				7	X...						
8	◇	ligand_7			8	1...		impact_mini_ligand25_sd	-14.558838	-14.5588...	-14.558838	-54.796850
(2)		XP:ligand26_glide_dock_pv										
9	◇				9	X...						
10	◇	ligand_7			10	1...		impact_mini_ligand26_sd	-10.227364	-10.2273...	-10.227364	-48.316162
(2)		XP:ligand9_glide_dock_pv										
11	◇				11	X...						
12	◇	ligand_7			12	1...		impact_mini_ligand9_sd	-14.382653	-14.3826...	-14.382653	-54.822421
(2)		XP:ligand18_glide_dock_pv										
13	◇				13	X...						
14	◇	ligand_7			14	1...		impact_mini_ligand18_sd	-13.934348	-13.9343...	-13.934348	-53.689532
(2)		XP:ligand19_glide_dock_pv										
15	◇				15	X...						
16	◇	ligand_7			16	1...		impact_mini_ligand19_sd	-14.313329	-14.3133...	-14.313329	-56.006727
(2)		XP:ligand13_glide_dock_pv										
17	◇				17	X...						
18	◇	ligand_7			18	1...		impact_mini_ligand13_sd	-14.539578	-14.5395...	-14.539578	-52.524503
(2)		XP:ligand10_glide_dock_pv										
19	◇				19	X...						
20	◇	ligand_7			20	1...		impact_mini_ligand10_sd	-14.335577	-14.3356...	-14.335577	-53.076747

Figure 7. XP docking for the selected top 10 compounds

Receptor grid generation and Ligand docking: The grid was generated at the centroid of selected residue using *receptor grid generation* option in the Glide. The output file generated was *Jobname.zip*. The ligand docking was carried out using the output files obtained from the LigPrep (*Jobname_Ligprep.out*) and receptor grid generation (*Jobname.zip*). To specify precision in the docking section, we can choose, whether ligands to be docked by HTVS , XP (Extra Precision) or SP (Standard Precision) docking. In the current study, ligands were docked using HTVS and XP docking. *HTVS docking* is intended for the rapid screening of very large numbers of ligands. XP is designed to be used on ligand poses that have a high score using SP docking .Induced fit docking is carried out for detecting the potency of the ligand against the (OSC) target. Before performing the induced fit docking, all the ligands are undergone XP docking. Glide docking score was checked. *Ligplot* automatically generates schematic diagrams of protein-ligand interactions for a given PDB file.

Results

In the current study, 45 compounds were collected from the literature studies for docking analysis . Interaction studies were performed using GOLD and GLIDE docking program .

Pose	Glide Score	Glide Energy (Kcal/mol)	Hydrogen bond Interactions DH...A	Bond Distance (Å)
Co crystal ligand	-9.301634	-48.003928	.(OH...O) ASP455	2.705
Compound 7	-10.230094	-68.159547	TYR 503(OH...O)	2.803
Compound 14	-10.598645	-70.604390	TYR 503(OH...O) CYS 233(SH...N)	2.866 3.453
Compound 25	-10.950056	-67.653122	TYR 704 (OH...N) TYR 587 (OH...N) TYR 98 (OH...O)	2.845 2.780 2.997
Compound 26	-11.231711	-73.674332	TYR 704(OH...N) TYR 587(OH...N)	2.806 2.748

Table 2. Inducedfit docking result

Docking Results With Gold

Among the 45 compounds docked, top 10 compounds were selected in GOLD and tabulated based on the docking score. The Gold fitness score and interactions of selected compounds along with co-crystal ligand (LAN) were shown in the table 1.

Docking Results With Glide

In GLIDE the Crystal structure of Human OSC complexed with Lanosterol is downloaded from Protein Data Bank of PDB ID:1W6K and saved. It is imported in to the Maestro work space and water molecules are deleted and energy minimization procedures were performed for the target protein and the ligand compounds.

High Throughput Virtual Screening

All the 45 ligands taken from the literature studies were undergone HTVS. In HTVS , all the compounds were sorted according to their best possible docking scores and will be listed in the top. The screenshot for 25 compounds was shown in the figure 6

XP docking

XP docking were undergone for all the 45 ligands taken from the literature studies. . All the ligands were compared with the co-crystal ligand and top 10 compounds were selected based on their glide score and glide energy. The screenshot for top 10 compounds was shown in the figure 7.

Based on docking score and glide energy , best ligands were selected from HTVS and XP docking to perform induced fit docking.

Combining both HTVS and XP docking , four compounds (7,14,25 and 26) with best score and interaction were selected and tabulated (table 2) for Induced fit Docking .

Inducedfit Docking Result

Discussion

The present study is made with an objective to perform the interaction studies using GOLD and GLIDE to block the active site of the enzyme OSC with 4-Piperidinopyridine and 4-Piperidinopyrimidine derivatives. The results of GOLD and GLIDE were compared to generate a novel hypercholesterolemic drugs to prevent cardiovascular disease.

Interaction studies were performed for 45 compounds collected from the literature studies using GOLD and GLIDE. Among the 45 compounds docked, top 10 compounds were selected in GOLD and tabulated based on the docking score. The Gold fitness score and interactions of selected compounds along with co-crystal ligand (LAN) were shown in the table 1.In top 10 compounds, the compound 4a with highest score , compound 25 and compound 26 with more interaction compared to other compounds including co-crystallized ligand (LAN) .

Th co-crystallized ligand has given highest score of 25.93 by showing strong interaction with the residues ASP 455 having hydrogen bonds of length 2.642 Å (figure 2). The compound 4a has given highest score of 74.81 by showing strong interaction with the residues ASP 455 having hydrogen bonds of length 2.427 Å (figure 3). The compound 25 has given highest score of 62.15 by showing strong interaction with the residues CYS 456,ASP 455,CYS 456 having hydrogen bonds of length 2.578 Å, 2.369 Å and 2.427 Å respectively (figure 4). The compound 26 has given highest score of 63.81 by showing strong interaction with the residues ASP 455, CYS 456 having hydrogen bonds of length 2.383 Å and 2.641 Å respectively(figure 5).

From the literature studies, the oral inhibition of rat cholesterol biosynthesis for compound 25 and 26 was comparable with that found for the clinically used HMGCoA reductase inhibitors simvastatin[redacted]e results showed that ED80 values for compound 25(1.4 0.3 mg/Kg) and 26(1.2 0.3 mg/Kg) were similar to the results(1.2 0.3 mg/Kg) of simvastatin(Brown GR et al .,2000).The compounds that were similar to the simvastatin may be considered as the potent inhibitors of OSC. The docking analysis using GOLD showed that the compound 25 with three interaction which comes under the top 10 compounds. So the compound 25 similar to simvastatin can serve as the drug for the inhibition of OSC.

In Glide , all the ligands were undergone HTVS and XP docking .Glide docking score and glide energy is checked for both . Based on docking score and glide energy , best ligands were selected from HTVS(figure 6) and XP (figure 7) docking to perform induced fit docking. Best four ligands choosen for induced fit docking were compounds 7,14, 25 and 26. The co-crystal ligand (LAN) has given highest score of -9.301634 having hydrogen bonds of length 2.705 Å . The compound 7 has given highest score of -10.230094 greater than co-crystal showing strong interaction with the residues TYR 503 having hydrogen bonds of length 2.803 Å. The compound 14 has given highest score of -10.598645 greater than co-crystal showing strong interaction with the residues TYR 503 and CYS 233 having hydrogen bonds of length[redacted]66 Å and 3.453 Å respectively. The compound 25 has given highest score of -10.950056 greater than co-crystal showing strong interaction with the residues TYR 587, TYR 704, TYR 98 having hydrogen bonds of length 2.780 Å , 2.845 Å and 2.997 Å respectively. The compound 26 has given highest score of -11.231711 greater than co-crystal showing strong interaction with the residues TYR 587 and TYR 704 having hydrogen bonds of length 2.748 Å and 2.806 Å respectively.

Combining HTVS and XP docking , compounds (7,14,25 and 26) with best score and interaction were selected and tabulated (table 2) for Induced fit Docking . The co-crystal ligand has given highest score of highest score of –9.301634 by showing strong interaction with the residues ASP 455 having hydrogen bonds of length 2.705 Å (figure8) for best pose . The compound 25 has given highest score of highest score of of –10.950056 by showing strong interaction with the residues TYR 704 ,TYR 587and TYR 98 having hydrogen bonds of length 2.845 Å

2.780 Å and 2.997 Å respectively (figure 10) . The compound 26 has given highest score of highest score of of −10.950056 by showing strong interaction with the residues TYR 704 ,TYR 587and TYR 98 having hydrogen bonds of length 2.845 Å , 2.780 Å and 2.997 Å respectively (figure 11) .

A best pose was selected for each of the four compounds based on the interaction . Among the best four ligands , the compound 25 with three interaction at the active site residues may be a potent inhibitors of OSC and may afford a novel hypocholesterolemic agents for the cardiovascular disease.

Conclusion

By docking analysis of GOLD and GLIDE, the compound 25 was found to be a potent inhibitors of OSC comparable with that found for the clinically used HMGCoA reductase inhibitor. It exhibit more interaction with the active site residue TYR 704, TYR 587, TYR 98, CYS 456 and ASP 455. This shows that the compound 25 with ED80 values similar to the results of simvastatin (1.2 ± 0.3 mg/Kg) can serve as a potent inhibitors of OSC target for cardiovascular disease. This study evaluated and compared the docking accuracies of a commercial docking package, GOLD and GLIDE .

More research and development of the various docking and scoring modules definitely make this software a more popular one in educational circles. Computational generation of protein structures and the docking of modeled protein structures with potential interacting partners will have great impact on the life sciences.To conclude that the proposed compound *25 (1-(4-Pyrimidinyl)- 4-(1- (4-bromophenyl - sulfonyl) pipera zin-4ylcarbonyl) piperidine)* showed orientation close to the active site and this compound can be used as a lead for designing future pharmaceuticals that may be used as inhibitors of OSC.

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Citation : R. Rajasekaran *et al.*, 2011, Molecular docking studies of 4 – Piperidinopyridine and 4 – Piperidinopyrimidine derivatives as 2, 3 - Oxidosqualene Cyclase inhibitors. *Adv Bio Tech* 10 (10) : 37-43