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Molecular Docking Studies of Shc1 Protein: A Drug Target to Treat Obesity

Shobha Shouche[1], Sachin Rahangdale[1*], Ravikant Yadav[1], Harshad Sharma[2]
[1]*govt. Madhav science college, ujjain, madhya pradesh, india*
[2]*school of studies microbiology department vikram university ujjain, madhya pradesh, india*

Abstract: *Scientists recently identified the important role of SHC1 gene expression in causing obesity. SHC1 protein has been found to be highly active in fatty tissues. It could help to develop medicines to treat obesity and related diseases such as heart disease, diabetes, cancer etc. In this present work, based on protein-ligand interaction studies, we proposed interacting domain for SHC1 (PDBID: 1N3H) and further the interacting domain was chosen to screen with a set of natural compounds. At last the potent lead molecules with good docking score were screened for their ADMET properties. The best inhibitor has been reported here.*
Key words*: Inhibitor, Ligand, Docking, Interaction, Screen*

I. Introduction

Obesity is a complex disorder involving an excessive amount of body fat. Obesity isn't just a cosmetic concern. It increases your risk of diseases and health problems such as heart disease, diabetes and high blood pressure. In the present scenario, childhood obesity is a major public health problem. Globally, in 2010 there were 42 million children were estimated to be overweight below the age of 5, and 35 million of them are from urban areas of developing countries [11]. In India, nearly 15 to 20% of children are overweight. Many studies have shown that the prevalence of overweight among adolescents varies between 10% and 30% in India [12][13].

Obesity treatments may include changes in lifestyle, exercise, dieting and weight loss medicines or bariatricsurgery. The surgeryis reserved for people with severe obesity who has not responded to other weight loss therapy [14].

Some weight loss drugs are associated with dangerous heart and lung side effects. Many of the weight loss drugs known as sympathomimetic amines can stimulate the heart and lead to high blood pressure and tachycardia (fast heart beat). These drugs may be associated with constipation, dry mouth, restlessness, withdrawal effects, or insomnia (difficulty falling asleep) [6].

In this present work, based on protein-ligand interaction studies [9], we proposed interacting domain for SHC1 (PDBID: 1N3H) and further the interacting domain was chosen to screen with a set of natural compounds. At last the potent lead molecules with good docking score were screened for their ADMET properties.

II. Material And Methodology

Natural Ligands Collections

All natural ligands were collected from supernatural V II database **[1].** These ligands were of natural origin. These targets were selected from the pathway diabetes mellitus type-2.

Target Protein Preparations

Target protein with PDBID: 1N3H was downloaded from PDB **[2].** This protein was checked and fixed for any missing residues, loops, bond length in "macromolecule" module of SPDBV [v4.1.0][8]. Then this structure was optimized and minimized.In the crystal structure of SHC-transforming protein -1 PTB domain of chain A was taken as active site was chosen for grid generation as there was already a crystal inhibitor. Grid was made using "define site" module of MVD.

Ligandselection

All the collected ligands from supernatural V II database were checked on the basis of Lipinski's rule. This rule is helpful to identify the molecules. Whether it can be used as a drug like or not. It means that it can predict the success probability rate of a molecule.

The molecules should have the following properties according to rules.

MW ---------0 to 500
Xlogp----- --0 to 5
HBD---------0 to 5

HBA---------0 to 10

On the basis of above parameter we have selected 4 ligands for this study and found perfect for Potent and ADMET study.

Docking Studies And Interaction Studies

A molecular docking study was done with naturalligands and protein from Genetic optimization for ligand docking Molegro Virtual Docker (MVD 4.0.2)[7]. We find interactions from MVD in terms of good scoring function and search space. We find active sites from MVD and cross checked with Active site prediction [5]

ADME Analysis And Best Ligand Proposal

ADMET stands for Absorption, Distribution, Metabolism, Excretion and Toxicity. If a ligand follows ADMET properties then its likeness to become a drug molecule increases. Pharmacokinetics and Pharmacodynamic come under ADMET studies. We have used OSIRIS PROPERTY EXPLORER [3] to check whether they are obeying all the ADMET properties or not.

On the basis of non-bonded and bonded interactions, ADMET properties and scoring functions, we can propose these ligands as apotent inhibitors of SHC-transforming protein -1(PTB domain). OSIRIS PROPERTY EXPLORER [3] was used to know the mutagenicity, carcinogenicity, reproductively and toxicity. Red color indicates its unfavorability to consume as a drug while green color indicates its favorability to consume as druglike.

III. Result And Discussion

Total 80 natural ligands were collected which act as potent natural drugs for the following targets in diabetes mellitus type 2.

SN00000362, SN00001731, SN00001876, SN00002040, SN00002047,SN00000245, SN00002211, SN00002222, SN00002257, SN00002387, SN00002543, SN00003330, SN00005643, SN00005648, SN00005681, SN00006216, SN00006577, SN00008119, SN00011332, SN00011568, SN00014213, SN00017871, SN00017872, SN00017873, SN00017874, SN00021320, SN00024335, SN00024491, SN00027401, SN00029289, SN00030295, SN00030296, SN00032737, SN00032738, SN00032739, SN00032740, SN00035548, SN00037188, SN00037189, SN00037510, SN00037511, SN00037512, SN00037513, SN00038410, SN00038512, SN00038784, SN00038948, SN00039296, SN00039297, SN00041720, SN00041721, SN00048679, SN00048687, SN00048690, SN00048700, SN00050524, SN00050528, SN00050529, SN00050552,SN00051430, SN00051747, SN00064236, SN00064237, SN00064343, SN00064344, SN00064345, SN00064435, SN00064441, SN00064442, SN00064551, SN00067564, SN00078039, SN00078040, SN00089453, SN00121987, SN00126359, SN00127648, SN00127649, SN00001023, SN00000558

SHC-transforming protein -1 was downloaded from PDB with ID 1N3H and find the key active site residues from MVD and cross checked with active site prediction. (Volume of cavity = 640.99).

To propose ligands to inhibit SHC-transforming protein -1, we have selected 4 ligands compound, which follow the lipinski's rule of five.

The proposed best 4 ligands are given in Table 1.

Table 1: Best 4 compounds as inhibitor to SHC-transforming protein -1

Compound ID	Compound name
SN00000245	Resveratrol
SN00000362	6-hydroxy-2-(3-methoxyphenyl)chromen-4-one
SN00001023	cis-dihydroquercetin
SN00000558	2-(3,4-dimethoxyphenyl)benzo[h]chromen-4-one

Note: Highlighted compound is most important ligands following ADME properties and good scoring function.

Table 2: proposed ligands structure

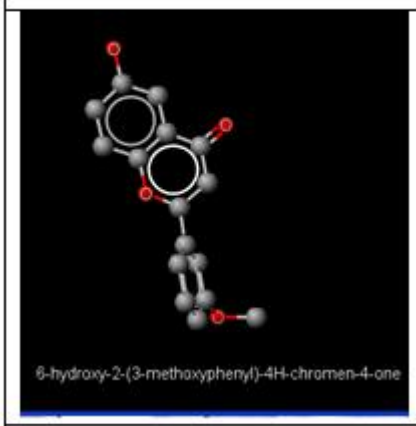
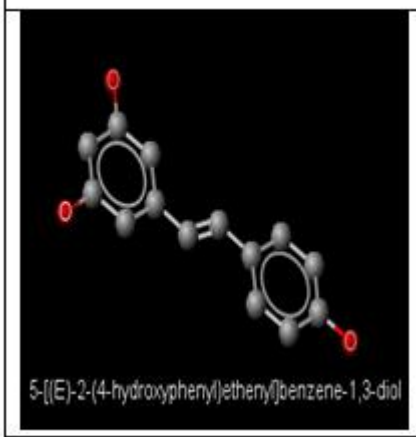
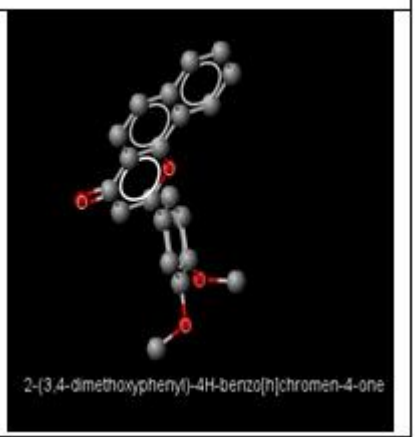
SN00000245	SN00000362
	
SN00001023	**SN00000558**
	

Table3: Basic descriptors for ligands is shown in Table 3

Ligand	Descriptors	
SN00000245	Name	resveratrol
	Molecular weight	228.079
	Formula	$C_{14}H_{12}O_3$
	desolv polar	-8.46
	desolv apolar	0.79
	H-bond donors	3
	H-bond acceptors	0
	TPSA	61
	Charge	0
	NRB	2
	logp	2.9738
	Ring count	2
	Atom count	29
	Bond count	18
	SMILES	c1cc(ccc1/C=C/c1cc(cc(c1)O)O)O
SN00000362	Name	6-hydroxy-2-(3-methoxyphenyl)chromen-4-one
	Molecular weight	268.074
	Formula	$C_{16}H_{12}O_4$
	desolv polar	-11.73
	desolv apolar	4.73
	H-bond donors	1
	H-bond acceptors	1
	TPSA	60
	Charge	0
	NRB	2
	logp	3.1742
	Ring count	3
	Atom count	32
	Bond count	22
	SMILES	COc1cccc(c1)c1cc(=O)c2cc(ccc2o1)O

SN00001023	

Name	cis-dihydroquercetin
Molecular weight	304.058
Formula	$C_{15}H_{12}O_7$
desolv polar	-13.46
desolv apolar	-4.11
H-bond donors	5
H-bond acceptors	2
TPSA	127
Charge	0
NRB	1
logp	1.1863
Ring count	3
Atom count	34
Bond count	24
SMILES	c1cc(c(cc1[C@H]1[C@H](C(=O)c2c(cc(cc2O1)O)O)O)C

SN00000558

Name	2-(3,4-dimethoxyphenyl)benzo[h]chromen-4-one
Molecular weight	332.105
Formula	$C_{21}H_{16}O_4$
desolv polar	-12.99
desolv apolar	2.6
H-bond donors	0
H-bond acceptors	1
TPSA	49
Charge	0
NRB	3
logp	4.6304
Ring count	4
Atom count	41
Bond count	28
SMILES	COc1ccc(cc1OC)c1cc(=O)c2ccc3ccccc3c2o1

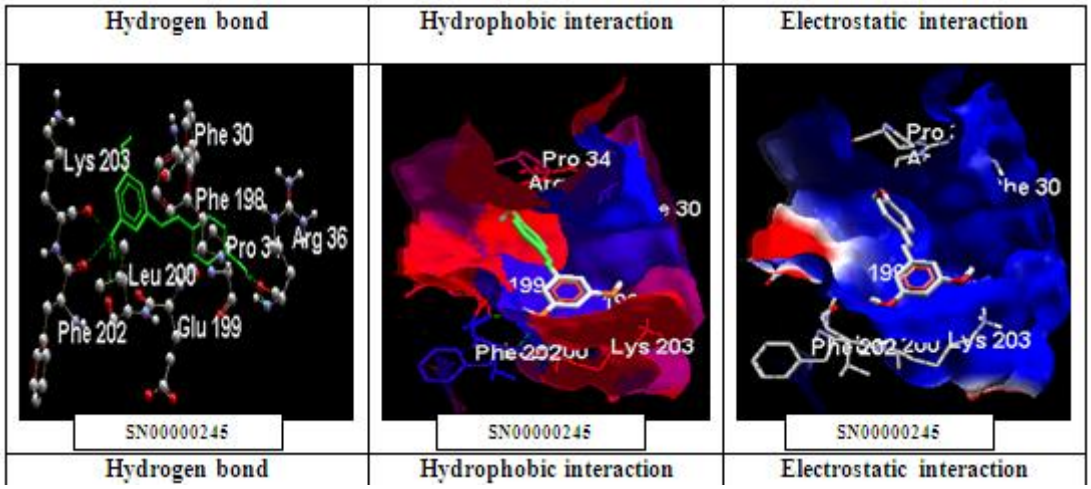
After ligands validation we performed Molecular docking studies of **SHC**-transforming protein -1with these proposed four ligands. Molecular Docking Score are given in Table 4.

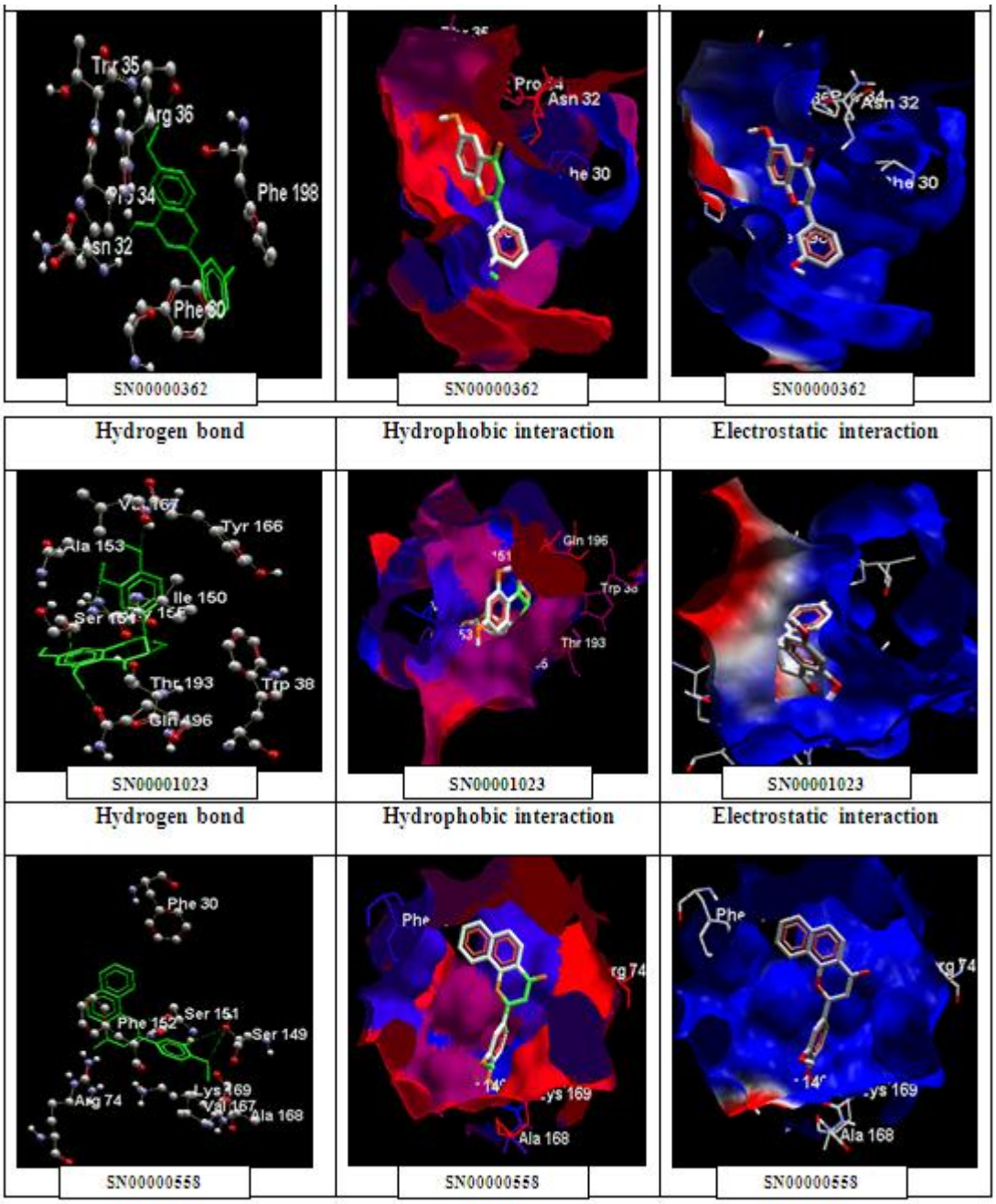
Table 4: Molecular docking Results

Ligand	H-bond	Moldock score (Energy)	RMSD
SN00000245	6	-84.86	0.0088
SN00000362	3	-99.05	0.33
SN00001023	6	-100.38	0.02
SN00000558	3	-76.13	0.008

The table 5 is shows the favorable interactions between ligand-protein. The following diagram labels are used in Molegro Virtual Docker (MVD 4.0.2). These Diagrams show Hydrogen bond interaction, hydrophobic interaction and Electrostatic interaction of 4 best ligands with target proteins.

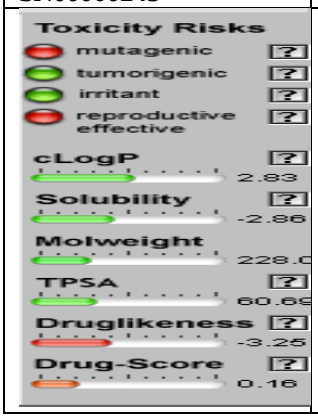
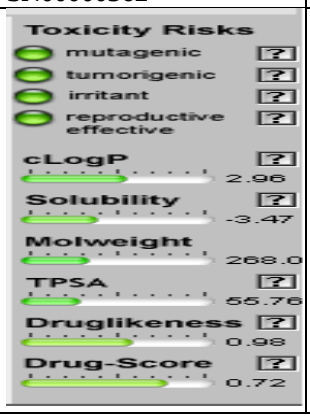
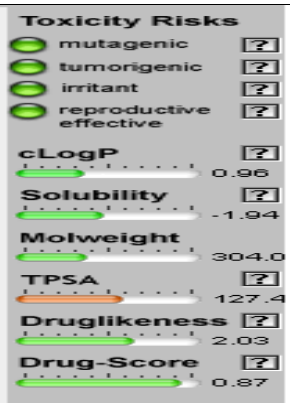
Table 5: Electrostatic, Hydrophobic and H bond interaction of 4 best ligands with target proteins.





These four ligands were checked in ADMET study and found that they follow ADMET properties very well. The bioactivity assessment of four ligands in human body is shown in table 6but onlySN00000362(6-hydroxy-2-(3-methoxyphenyl) chromen-4-one) ligand is the best.

Table 6: Osiris Property Explorer Result

SN00000245	SN00000362	SN00001023	SN00000558
			

As these four proposed ligands (**SN00000245**, **SN00000362**, **SN00001023, andSN00000558**) have no Lipinski failures, they are bioactive compounds and following ADMET properties .They are showing good interaction with of **SHC**-transforming protein -1, so they can be used as a potent and an active inhibitors to these domains.

IV. Conclusion

Drug Discovery process is a very important and crucial one in drug designing. As per interaction studies of these 80 natural compoundswithSHC-transforming protein-1, only fourligandswere found to be most energetically stable on the basis of moldock score and alsofound promisingin protein-ligandinteractions.

Out of these four screened ligands, SN00000362 (6-hydroxy-2-(3-methoxyphenyl) chromen-4-one) is quite promising at all ADMET properties except LogP. So we may conclude that SN00000362 ligand can work as SHC1 inhibitor and thus could be useful for controlling the obesity.

Acknowledgment

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