

## DESIGNING OF COUMARIN DERIVATIVES AS SQUALENE SYNTHASE INHIBITORS

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Received: 02 May 2018, Revised and Accepted: 14 June 2018

## ABSTRACT

**Objective:** The importance of this research work is to design a library of novel coumarin derivatives by docking evaluation of the designed coumarin derivatives as squalene synthase inhibitor.

**Methods:** The three-dimensional structure of designed molecules of squalene synthase inhibitors was collected from Protein Data Bank. The designed molecules were docked onto the enzymes that are squalene synthase inhibitor - 3WCM, 3WCJ, and 3Q2Z protein using SYBYL-X 2.1. Using a standard protocol, the protein was subjected to minimization and protomol generation.

**Results:** By this method, we visualized the possible binding and also estimated the protein interactions with our intended coumarin library, using SYBYL-X 2.1 software. Into the active site of the selected enzymes, all the 20 coumarins were docked and then the docking scores revealed that the compounds possess high affinity toward the selected enzymes.

**Conclusion:** With the help of virtual evaluation, we have elaborated a fast synthetically accessible coumarin-based compounds, and it is an advanced and original scaffold in the area of probable human squalene synthase inhibitors. Some of the developed compounds show better binding property than ligand, and in 3q2Z, the compound 5d shows better binding property than the protein. Furthermore, 6g and 6c have good binding property. In 3 WCM, the compound 6f has better property. In 3 WCJ, the compounds 6g and 6f show better binding property than the protein.

**Keywords:** Coumarin derivatives, Squalene synthase inhibitors, Molecular docking, Docking score.

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## INTRODUCTION

The main intention of this research work is to design a library of novel coumarin derivatives by docking evaluation of the designed coumarin derivatives as squalene synthase inhibitor. Coumarins are the compounds which can be found in different levels all over the plant kingdom. Some significant coumarins were derived from several microorganisms such as from *Streptomyces* species [1]. Dyslipidemia is a main risk factor in the occurrence of coronary heart disease (CHD). In case of CHD, dyslipidemia is a major risk factor. According to the World Health Organization, there are around 4 million deaths per year due to the heart diseases which is caused by dyslipidemia [2,3].

Dyslipidemia leads to elevation of total cholesterol, low-density lipoproteins, high-density lipoprotein, and triglycerides. If the elevation of cholesterol occurred due to lipoprotein then it is termed as hyperlipidemia, whereas elevation is due to triglycerides, low-density lipoprotein and high-density lipoprotein are called as atherogenic dyslipidemia [2,3].

With the sudden and stark increase in population growth rates the cardiovascular disease, it got affected the developing countries like India. By 2020, about 2.6 million Indians are estimated to die due to coronary heart failure. Among Indians, it has been shown that it occurs too early at least a period of 10 years or two earlier than their counterparts in developed countries [4].

## Docking

Using docking method, we can find the favored orientation of one molecule to a second molecule when bound to each other to form a

stable complex. It is commonly used to forecast the binding orientation of small drug molecule to their protein targets to predict the affinity and action of the small drug molecule. Thus, docking plays a significant role in the rational drug design. The aim of docking is to find the three-dimensional (3D) structure of the macromolecular complex of interest as it would happen in a living organism. Candidate structures which are potential can have produced by the process of docking [5].

## Types of docking studies

- Protein-protein docking
- Protein-ligand docking
- Other docking programs: FlexX, GOLD, Hammerhead, FLOG [4].

## MATERIALS AND METHODS

## Molecular docking studies

SYBYL-X 2.1 software has used to carry out docking studies. This software for docking program helps to gain deep understanding of binding mode of the intended compounds and explains the effect of structural changes on the chosen protein in the direction of their inhibitory activities. The flow diagram for structure-based drug design is shown in Fig. 1. Crystallographic data of the selected enzyme were downloaded and were used for docking studies. In the case of protein and enzymes, the X-ray crystal structure was described and achieved an acceptance with X-ray crystal structure was achieved with the help of hydrogen bond interaction of amino acid residues [6]. Using SYBYL-X 2.1, the protein has been developed in the basis of preparation module in the software. By this, the bond orders have been allocated, water and other residues have been removed, H atoms have added, and the

protein model was charged with AMBER7 FF99. With the help of *in silico* screening, coumarin-based compounds have developed which are fast synthetically accessible compounds [7]. It is a featuring new method in the case of potential human squalene synthase inhibitors. Especially, we have designed a set of compounds from a common scaffold having various groups attached to the coumarin ring, by considering both the synthetic accessibility and affinity with ligand binding domain of squalene synthase [8]. A brief description about structure-based design is depicted in Fig. 1.

#### Protein minimization

The structure of human squalene synthase was acquired from the Protein Data Bank (PDB Code: 3WCM, 3WCJ, and 3Q2Z). Graphical representation of 3Q2Z, 3WCJ, and 3WCM is shown in Figs. 2-4, respectively. At 2.38Å resolution, this structure is resolved. We accomplished the minimization of human squalene synthase with a template using the prepare protein module in SYBYL [9]. The ligand substructure was extracted, and all water molecules were separated. Explicit hydrogens were added to the protein, and protein model was charged with AMBER7 FF99 and ligand using Gasteiger-Marsili charges. Relaxation of the loop region and energy minimization was accomplished using 300 iterations with AMBER7 FF99 as force field [10].

#### Protomol generation

Receptor active binding site (protomol) was generated around the cocrystallized ligands in SYBYL X.2.1 molecular modeling software using default parameters. Ligand was extracted from the protein. The active site was generated to fit the ligands similar in size to cocrystallized ligands. The cocrystallized ligands of 3WCJ and 3WCM are shown in Figs. 5-7, respectively [11].

#### Preparation of ligands

The ligand compound was designed using SYBYL software. Here, energy minimization was done using the software and preparation of ligand

includes the addition of Gasteiger-Huckel charges and explicit hydrogen [12]. A number of 20 coumarin derivative were used in the study, which were designed by *in silico* virtual screening. The library of compounds is listed in Table 1. 20 ligands were drawn in Chem draw. Ligand preparation is a beneficial of SYBYL software suit that links the tools for creating 3D structures from 2D, searching for tautomers and performing a geometry minimization of ligands. The energy minimization of the ligands was performed using minimize module of SYBYL with default parameters and applying molecular mechanics force fields [13].

#### Docking of ligands

SYBYL docking suite was helped for this study. The SYBYL docking processes carry out a set of graded examinations for positions of achievable ligand affinity within the binding site of a receptor. A rough arrangement and counting process are applied during the early examination step, come after torsional energy optimization on optimized potentials for liquid simulation-AA non-bonded potential energy grid for generating potential candidate poses. Selection of the final docked pose is done using a total score, which is a model energy function that joins the empirical and force field-based terms [14].

### RESULTS AND DISCUSSION

#### Results of molecular docking

The method was used to visualize the probable binding and also to learn and estimate the protein interactions with our intended coumarin library. Using SYBYL-X 2.1 software, the docking study was completed. In which, into the active site of the selected enzymes, all the 20 coumarins were docked. From the Brookhaven, PDB has downloaded the crystal structure of the enzyme along with its cocrystallized ligand and was used for docking studies.

#### Molecular docking studies on squalene synthase (3WCM)

The docking study of the designed substituted coumarin onto the active site of the enzyme squalene synthase (PDB: 3WCM) was encouraging (Fig. 8). The cocrystallized ligand ER4 ((3R)-3-[[2-benzyl-6-(3-methoxypropoxy) pyridin-3-yl] ethynyl]-1-azabicyclo [2.2.2] octan-3-ol) showed a score of 10.0858 Kcal/M with the interactions with the all-around residues Leu211A, Ile58A, Leu76A, Leu183A, Val179A, and Tyr73A strongly contributed to the stabilization.

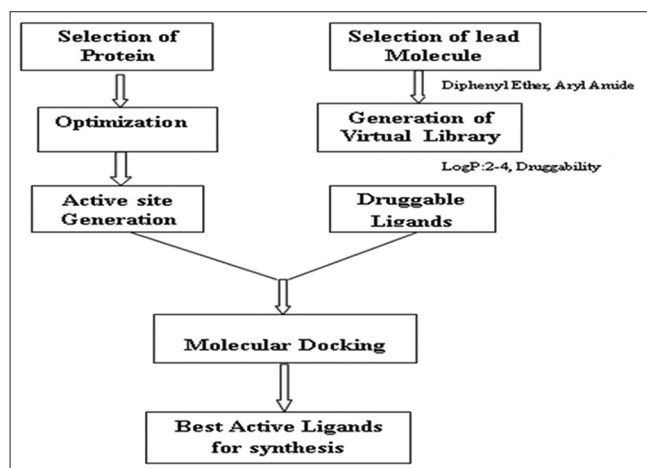


Fig. 1: Flow diagram for structure based drug design

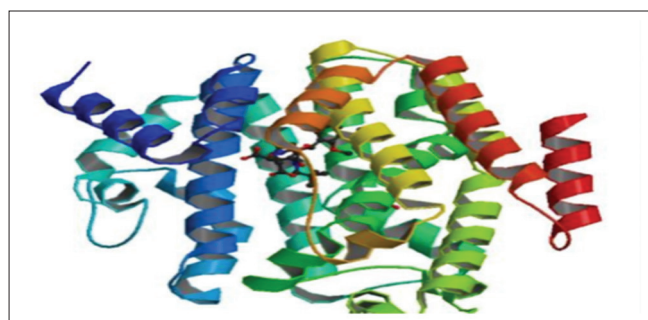


Fig. 2: Graphical representation of 3Q2Z

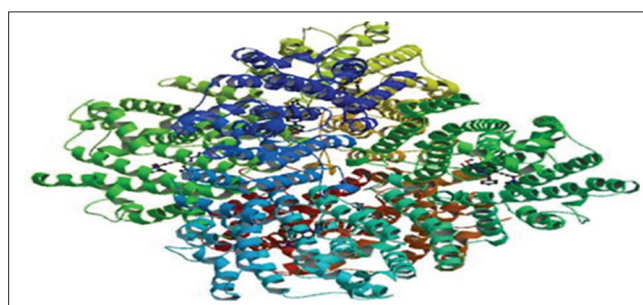


Fig. 3: Graphical representation of 3WCJ

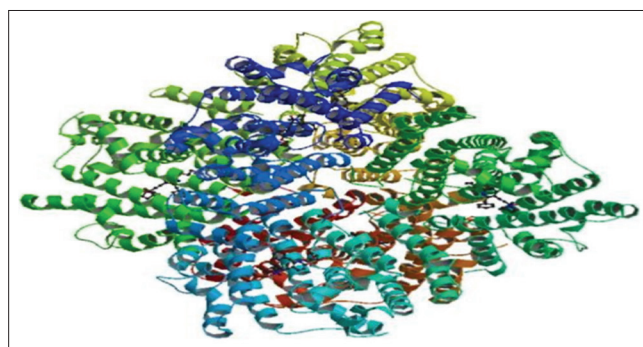


Fig. 4: Graphical representation of 3 WCM

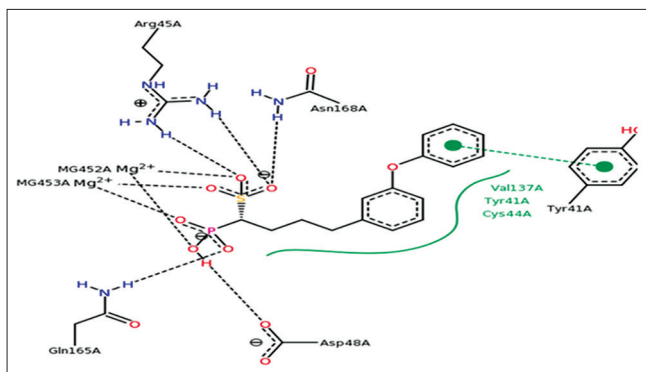


Fig. 5: Cocrystallized ligands of 3WCJ

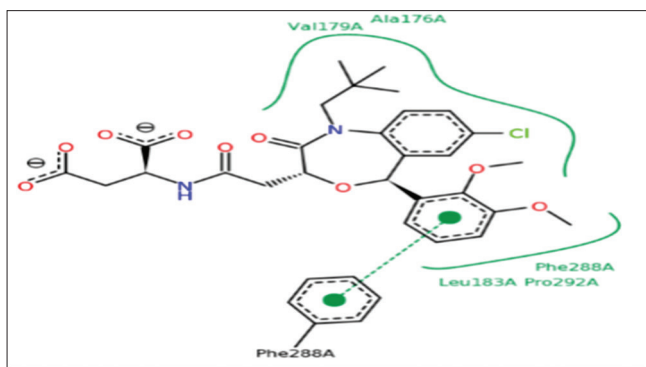


Fig. 6: Cocrystallized ligands of 3Q2Z

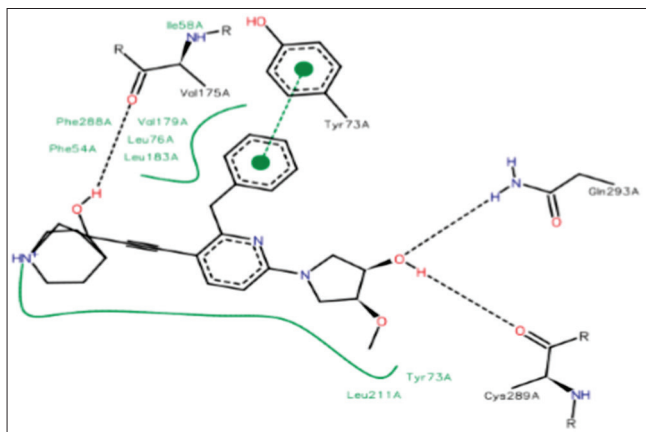


Fig. 7: Cocrystallized ligands of 3WCM

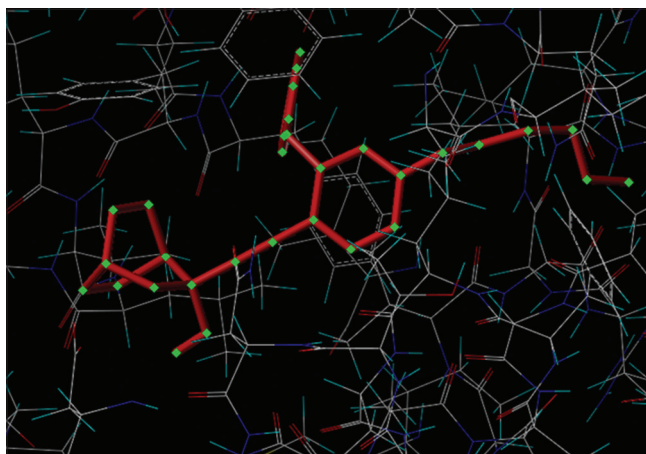


Fig. 8: Active binding in 3WCM

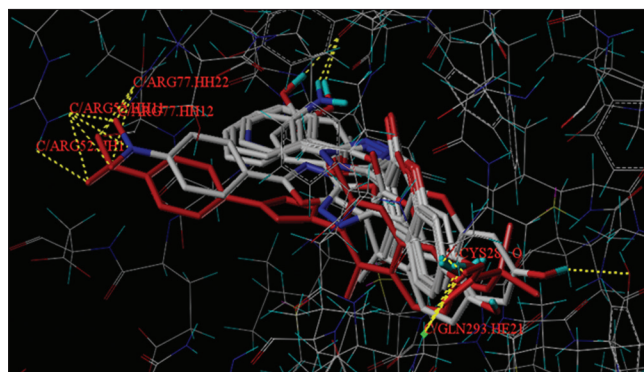


Fig. 9: Conformationally analyzed and energy minimized structures aligned against common atoms interacting with protomol 3WCM

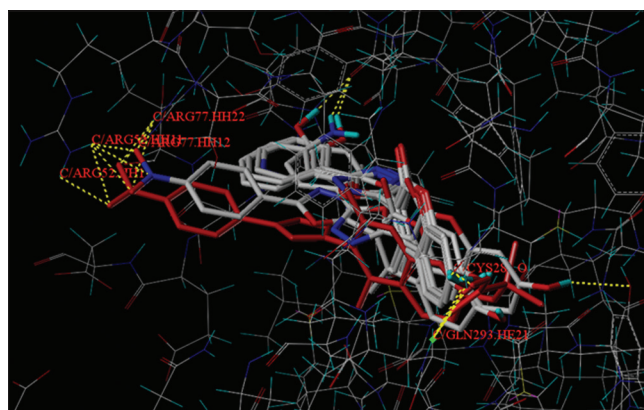


Fig. 10: Docking of 5 series with 3WCM.pdb

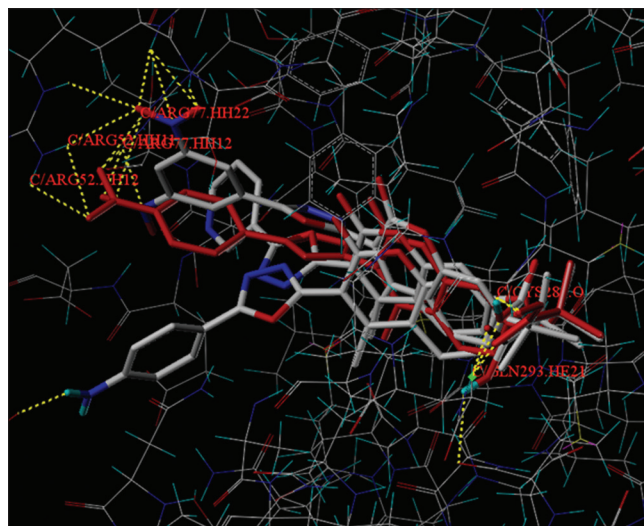
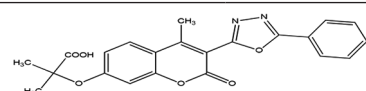
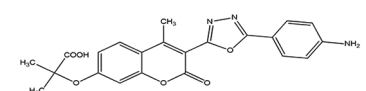
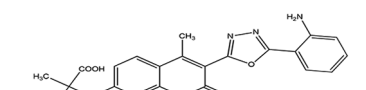
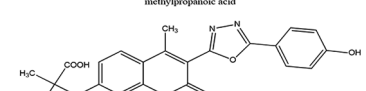
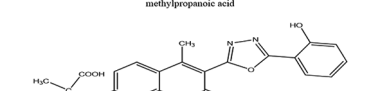
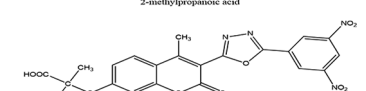
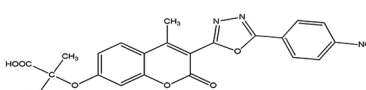
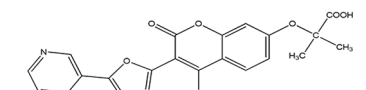
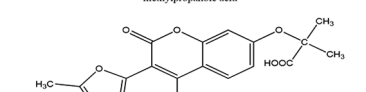
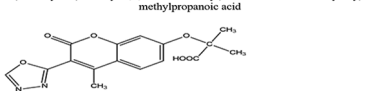
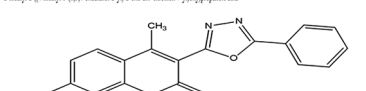
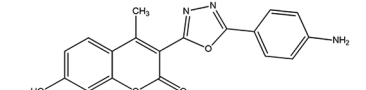
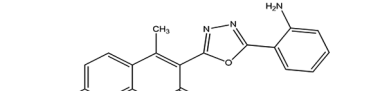
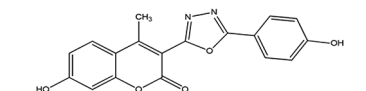


Fig. 11: Docking of 6 series with 3WCM.pdb

The docking study disclosed that the coumarin derivatives possessed high affinity in the directions 3WCM (Fig. 9). The docking score of coumarin derivatives 5a-5j and 6a-6j toward 3WCM is shown in Table 2. Among the derivatives, compounds 6f and 6e displayed a good docking score of 8.8778 and 7.6619 Kcal/M, respectively, show a better interaction with the protein squalene synthase, while the other coumarin derivatives exhibited a considerable score ranging from 3.8219 to 7.6015 Kcal/M (docking of 5 and 6 series with 3WCM.pdb is shown in Figs. 10 and 11, respectively, and also, 6g reference is shown in Fig. 12).

Table 1: Library of compounds

Library of compounds	Structure
5a	 2-(4-methyl-2-oxo-3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2H-chromen-7-yloxy)-2-methylpropanoic acid
5b	 2-(3-(5-(4-aminophenyl)-1,3,4-oxadiazol-2-yl)-4-methyl-2-oxo-2H-chromen-7-yloxy)-2-methylpropanoic acid
5c	 2-(3-(5-(2-aminophenyl)-1,3,4-oxadiazol-2-yl)-4-methyl-2-oxo-2H-chromen-7-yloxy)-2-methylpropanoic acid
5d	 2-(3-(5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)-4-methyl-2-oxo-2H-chromen-7-yloxy)-2-methylpropanoic acid
5e	 2-(3-(5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)-4-methyl-2-oxo-2H-chromen-7-yloxy)-2-methylpropanoic acid
5f	 2-(4-methyl-3-(5-(3,5-dinitrophenyl)-1,3,4-oxadiazol-2-yl)-2-oxo-2H-chromen-7-yloxy)-2-methylpropanoic acid
5g	 2-(4-methyl-3-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)-2-oxo-2H-chromen-7-yloxy)-2-methylpropanoic acid
5h	 2-(4-methyl-2-oxo-3-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)-2H-chromen-7-yloxy)-2-methylpropanoic acid
5i	 2-(4-methyl-3-(5-methyl-1,3,4-oxadiazol-2-yl)-2-oxo-2H-chromen-7-yloxy)-2-methylpropanoic acid
5j	 2-methyl-2-(4-methyl-3-(1,3,4-oxadiazol-2-yl)-2-oxo-2H-chromen-7-yloxy)propanoic acid
6a	 7-hydroxy-3-(5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)-4-methyl-2H-chromen-2-one
6b	 3-(5-(4-aminophenyl)-1,3,4-oxadiazol-2-yl)-7-hydroxy-4-methyl-2H-chromen-2-one
6c	 3-(5-(2-aminophenyl)-1,3,4-oxadiazol-2-yl)-7-hydroxy-4-methyl-2H-chromen-2-one
6d	 7-hydroxy-3-(5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)-4-methyl-2H-chromen-2-one

(Contd...)

Table 1: Continued...

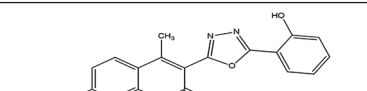
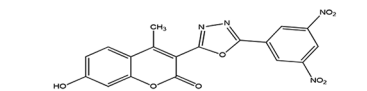
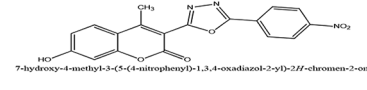
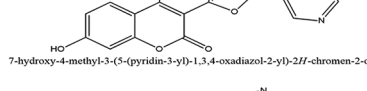
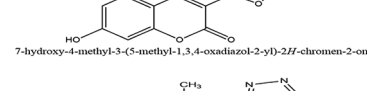
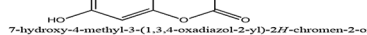
Library of compounds	Structure
6e	 7-hydroxy-3-(5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)-4-methyl-2H-chromen-2-one
6f	 7-hydroxy-4-methyl-3-(5-(3,5-dinitrophenyl)-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one
6g	 7-hydroxy-4-methyl-3-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one
6h	 7-hydroxy-4-methyl-3-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one
6i	 7-hydroxy-4-methyl-3-(5-methyl-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one
6j	 7-hydroxy-4-methyl-3-(1,3,4-oxadiazol-2-yl)-2H-chromen-2-one



Fig. 12: 6g reference

**Molecular docking studies on squalene synthase (3WCJ)**

The study of the designed substituted coumarin onto the active site of squalene synthase (PDB: 3WCJ) was encouraging (Fig. 13). The cocrystallized ligand, E5S (3R)-3-[(2-benzyl-6-[(3R,4S)-3-hydroxy-4-methoxy-pyrrolidin-1-yl]pyridin-3-yl)ethynyl]-1-azabicyclo [2.2.2] octan-3-ol, showed a score of 7.4301 cal/M with the interactions with the all-around residues Phe54A, Phe288A, Leu183A, Leu76A, Val179A, Val175A, Tyr73A, Gln293A, Cys 289A, Tyr73A, and Leu211A strongly contributed to the stabilization.

The study displayed that the coumarin derivatives possessed high affinity in the direction of 3WCJ (Fig. 14). The docking score of coumarin derivatives 5a-5j and 6a-6j toward 3WCJ is shown in Table 3. Among the derivatives, compound 6g, 6f, and 6d showed a good docking score of 8.355, 7.9677, and 7.5437 Kcal/M, respectively, greater than that of the cocrystallized ligand 3WCJ, indicating a greater interaction with the protein squalene synthase and spotlighting its capability to prevent the same and create a remarkable anti-dyslipidemia action, while the other coumarin derivatives showed a considerable score ranging from 4.0224 to 7.3892 Kcal/M. The

docking of 5 and 6 series with 3WCJ.pdb is shown in Figs. 15 and 16, respectively.

#### Molecular docking studies on squalene synthase (3Q2Z)

The study of the designed substituted coumarin onto the active site of the enzyme squalene synthase (PDB: 3Q2Z) was encouraging (Fig. 17). The cocrystallized ligand, D9A, N-[[[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]-L-aspartic acid, shows a score after docking, i.e., 7.7031 cal/M with the influence with the all-around the residues Val179A, Ala176A, Phen288A, Leu183A, Pro292A, and Phen288A strongly contributed to the stabilization.

Conformationally analyzed and energy minimized structures aligned against common atoms interacting with protomol 3Q2Z are shown

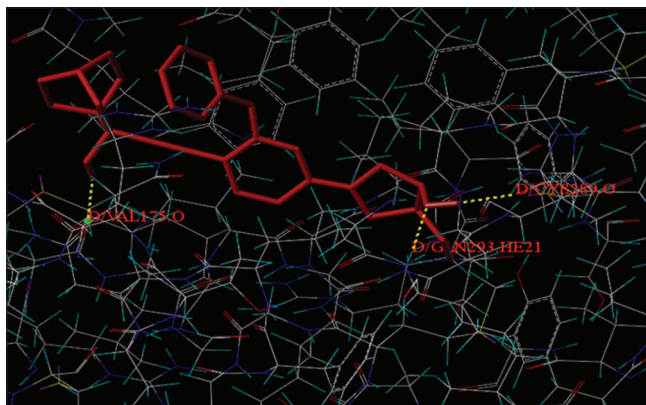


Fig. 13: Active binding in 3WCJ

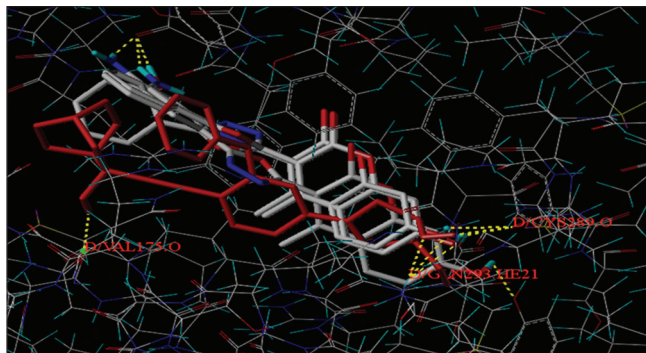


Fig. 14: Conformationally analysed and energy minimized structures aligned against atoms interacting with protomol 3WCJ

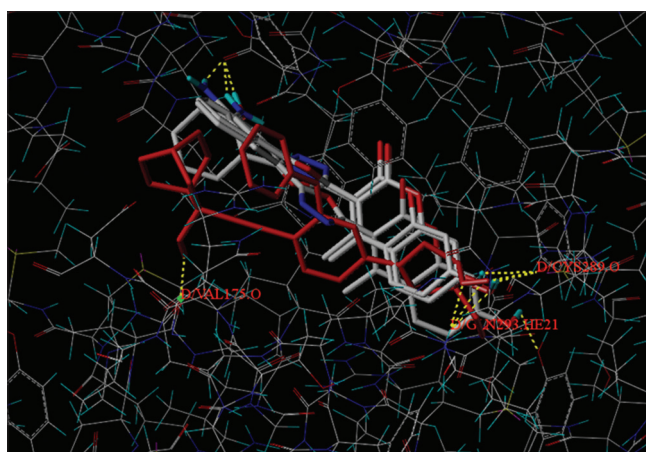


Fig. 15: Docking of 5 series with 3WCJ.pdb

in Fig. 18. Docking score of coumarin derivatives 5a–5j and 6a–6j toward 3Q2Z is shown in Table 4. The study disclosed that, among the derivatives, compound 5d showed a better score of 8.0496 Kcal/M, respectively, greater than that of the cocrystallized ligand 3Q2Z which shows a great interaction with the protein squalene synthase and draws special attention to its ability to inhibit the same and creates an important anti-dyslipidemic action, while the other coumarin derivatives showed a considerable docking score extend between 3.924 and 7.5023 Kcal/M. The docking of 5 and series with 3Q2Z.pdb is shown in Figs. 19 and 20, respectively.

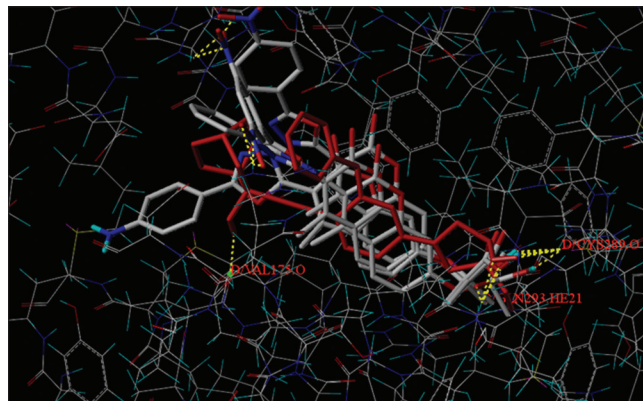


Fig. 16: Docking of 6 series with 3WCJ.pdb

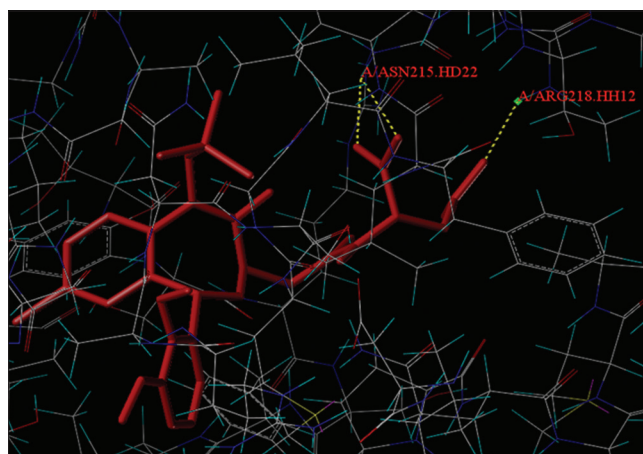


Fig. 17: Active binding in 3Q2Z

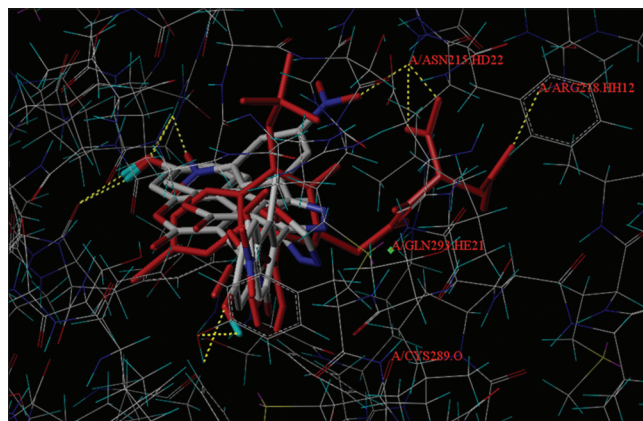


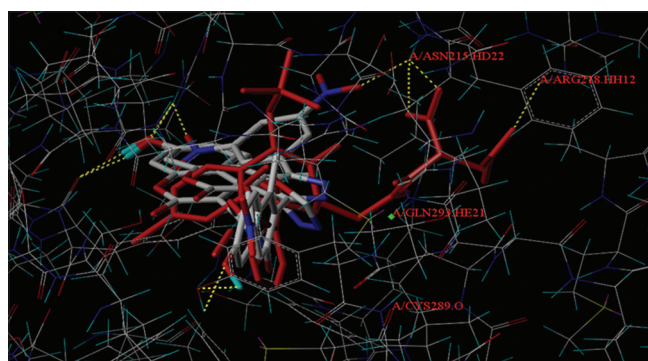
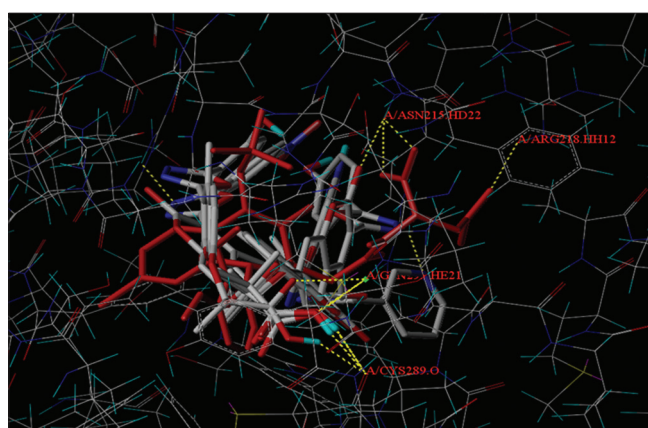
Fig. 18: Conformationally analyzed and energy minimized structures aligned against common atoms interacting with protomol 3Q2Z

**Table 2: Docking score of coumarin derivatives 5a–5j and 6a–6j toward 3WCM**

Name	Total score	Crash	Polar
3WCM	10.0858	-1.0032	0
5a	6.0303	-0.9745	0.6693
5b	6.2748	-1.0513	0.8472
5c	6.4401	-0.9485	1.5438
5d	6.7267	-1.4343	1.1061
5e	6.7664	-2.0112	1.9912
5f	6.0301	-1.874	3.6454
5g	6.1686	-0.9854	2.6787
5h	5.7272	-0.9888	0.7757
5i	4.6311	-0.9516	0.7607
5j	3.8219	-0.8645	0.9766
6a	6.8195	-1.9221	0.9764
6b	7.4204	-1.906	2.3131
6c	7.6015	-1.4632	1.0385
6d	7.3004	-3.1822	4.9339
6e	7.6619	-1.6783	1.0828
6f	8.8778	-2.8572	4.8447
6g	6.9703	-3.1642	3.4574
6h	6.6916	-2.8632	2.2597
6i	6.1307	-2.21	2.3035
6j	5.8351	-1.7756	3.0013

**Table 3: Docking score of coumarin derivatives 5a–5j and 6a–6j toward 3WCJ**

Name	Total score	Crash	Polar
3WCJ	7.4301	-1.8869	3.0632
5A	5.7669	-1.0303	0.1536
5B	7.0856	-1.5897	0.9592
5C	6.7155	-1.4323	2.0573
5D	6.5133	-0.725	1.3759
5E	6.3168	-1.5314	2.0522
5F	6.3762	-1.2533	4.3744
5G	5.7789	-1.2797	3.2303
5H	5.0926	-0.967	0
5I	4.3926	-0.5829	0.1326
5J	4.0224	-0.8375	1.0627
6A	7.3178	-3.0337	1.6263
6B	7.1507	-2.9978	2.1212
6C	7.1805	-4.5957	0.8395
6D	7.5437	-4.5924	1.2254
6E	7.3892	-1.6322	2.1942
6F	7.9677	-2.3664	5.8064
6G	8.355	-3.4986	5.3276
6H	6.8857	-2.2035	2.0567
6I	6.3393	-1.441	4.0459
6J	5.4802	-0.8153	1.0872

**Fig. 19: Docking of 5 series with 3Q2Z.pdb****Fig. 20: Docking of 6 series with 3Q2Z.pdb**

## CONCLUSION

With the help of virtual evaluation, we have elaborated fast synthetically accessible coumarin-based compounds, and it is an advanced and original scaffold in the area of probable human squalene synthase inhibitors. Especially, we have designed a group of compounds from a common scaffold having various groups attached to the coumarin ring, by considering the both the compatibility with ligand binding domain and synthetic accessibility of squalene synthase. Some of the developed

**Table 4: Docking score of coumarin derivatives 5a–5j and 6a–6j toward 3Q2Z**

Name	Total score	Crash	Polar
3Q2Z	7.7031	-1.8378	2.3055
5a	5.7563	-0.6161	0.0008
5b	6.6484	-1.0744	1.8029
5c	5.8023	-0.8269	0.0118
5d	8.0496	-1.2195	2.5386
5e	6.7664	-2.0112	1.9912
5f	5.1324	-0.7698	2.7422
5g	5.0874	-2.1981	1.869
5h	6.1545	-0.9184	2.1254
5i	4.4302	-1.6642	2.1496
5j	3.6924	-0.6029	2.0317
6a	6.2653	-1.2328	1.9052
6b	6.2263	-1.3705	1.8469
6c	6.9278	-1.1291	1.494
6d	6.3276	-1.0056	3.04
6e	6.4225	-2.0735	1.3061
6f	6.5614	-1.138	4.7483
6g	7.5023	-1.7564	4.1302
6h	6.3419	-1.9915	2.6184
6i	6.0045	-1.213	1.2191
6j	5.0727	-0.9799	1.714

compounds show better binding property than ligand, and in 3q2Z (score: 7.7031), the compound 5d shows better binding property than the protein with a score of 8.0496. Furthermore, 6g and 6c have good binding property. In 3WCM (10.0858), the compound 6f has a better property with a score of 8.355. In 3WCJ (7.4301), the compounds 6g and 6f show better binding property than the protein with score of 8.355 and 7.9677, respectively.

## ACKNOWLEDGMENTS

The authors express their gratitude to the JSS Academy of Higher Education and Research and JSS College of Pharmacy, Mysuru, for providing necessary support in due course of the work.

## AUTHOR'S CONTRIBUTIONS

Author is a faculty in the division of Pharmaceutics and Pharmaceutical Chemistry and the work contributed on faculty development program in the institution.

**CONFLICTS OF INTEREST**

The authors confirm that this article content has no conflict of interest.

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