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# *IN SILICO* RATIONAL DRUG DESIGN FOR 2-PHENYL QUINAZOLIN-4(3*H*)-ONE AS SCAVENGER RECEPTOR CLASS B TYPE- I (SRCB 1) INHIBITORS

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**ABSTARCT**
In present research; we tried to confirm 2-phenyl Quinazolin-4(3*H*)-one derivatives, which are broadly reported in the literature as scavenging agent. The study was carried out on a selected set of 40 novel 2-phenyl quinazoline-4(3*H*)-one and consequently docked them into Scavenger receptor class B Type- I (SRCB 1). The analogues 7a-7a8 and 7b1-7b8 were found to be more potent inhibitor as they exhibit drug like activity. The entire test Compounds which have highest ligand energy compared to the Standard compounds. Structure based drug designing of these analogues may found a novel antioxidant for future study.
**Keywords:** Scavenging agent, inhibitor, receptor class B, antioxidant.


## INTRODUCTION

Two approaches are mainly well-known within the molecular docking community. One approach uses an identical technique that describes the protein and the ligand as complementary surfaces[1-3]. The second approach simulates the authentic docking process in which the ligand-protein pair wise interaction energies are calculated[4]. Both approaches have significant advantages as well as some restrictions.
Scavenger receptor class B member 1 (SRB1) also known as SRBI is a protein that in humans is encoded by the *SCARB1* gene. SR-BI functions as a receptor for high-density lipoprotein[4]. Scavenger receptor class B, Type- I (SRBI) is an integral membrane protein originate in numerous cell Type-s/tissues, together with the liver and adrenal. It is best known for its role in facilitating the uptake of cholesteryl esters from high-density lipoproteins in the liver. This process drives the movement of cholesterol from peripheral tissues towards the liver for excretion. This movement of cholesterol is known as reverse cholesterol transport and is a protective mechanism against the development of atherosclerosis, which is the principal cause of heart disease and stroke. SR-BI has also been identified in the livers of non-mammalian species (turtle, goldfish, shark, chicken, frog and skate), suggesting it emerged early in vertebrate evolutionary history.[5-6]

The principal objectives of the present research investigation are to model the protein target which is responsible for the human diseases, to validate the extracted chemical compound and to perform molecular docking studies. The above results are used to find out the best chemical compounds for the diseases based on the molecular drug binding affinities. Many of the drugs available in the market for the treatment of anti- diabetic and many nitrogen-containing heterocyclic compounds have been reported to posse's relatively high toxicity compared to other heterocyclic derivatives. Based on the literature survey we planned to dock some novel quinazoline derivatives, which are less toxic and more potent and which shows various biological activity.

## EXPERIMENTAL

### ChemDraw Ultra

In arrange to manner docking studies the structures of every ligands were prepared using Chem Draw Ultra 8.0, chemical drawing software developed by Cambridge Pvt. Ltd. The software is user-friendly, provides all details of drawn structures. It helped in calculate chemical properties, design professional reports and presentations.

### Protein Data Bank (PDB)

The PDB is the single, global archive for information about the 3D structure of biomacromolecules and their complexes, as determined by X-ray crystallography, NMR spectroscopy and cryoelectron microscopy. The crystal structure of Scavenger receptor class B Type- I was retrieved from the Protein Data Bank.

### Protein Preparation

A typical PDB structure file consists of heavy atoms, water molecules, cofactors, metal ions and can be multimeric. The structure generally has no information on bond orders, topologies, or formal atomic charges. These structures do not have the information about bond orders, topologies or formal atomic charges. So, the raw PDB structure should be prepared in a suitable manner for docking. The Protein Preparation Wizard module of Maestro was used to prepare the protein. During protein preparation, water molecules and peptide substrate (NAG) were deleted. This follows the optimized potential for Liquid Simulations-All Atoms (OPLS-AA) force fields for energy minimization[6].

### Ligand Preparation

The LigPrep process consists of a series of steps that perform conversions, apply corrections to the structures, generate variations on the structures, eliminate unwanted structures and optimize the structures. Many of the steps are optional and are controlled by selecting options in the LigPrep panel by specifying command-line options[7].

### Visualization and Analysis

The 1xbb molsoft molbrowser was used to analyze the hydrogen bond interactions and preparation of high resolution images.

We use Scoring based docking Tool -Scoring functions play a chief role in identifying a "good dock" and as such leftovers an area of active research. Several other considerations are worth noting including water molecules and ions in the binding site, flexibility of binding site residues, etc. Some docking programs (including AutoDock Vina) allow you to identify a subset of flexible side chains. Whilst this permits binding site rearrangement to accommodate distinct ligands, the computational search space increases many fold. Major water molecules that are important in the binding site also remains an area of active research. In this practical, we have considered only protein-ligand docking. Protein-protein docking is also widely used, but not well thought-out here due to the significantly higher search space that has to be considered. As the number of published and unpublished protein structures continue to grow, *in silico* docking will continue to play an important part in the drug discovery process.

## RESULTS AND DISCUSSION

Computer-assisted drug design (CADD) approach has contributed to the successful discovery of several novel small molecules as antidiabetic agents. The 40 quinazoline derivatives were docked into the Scavenger receptor class B Type- I binding site. 3 dimensional representations of the optimized binding models of the 40 compounds with the crystallographic structure and standard balaglitazone. The Results are given Table-1.

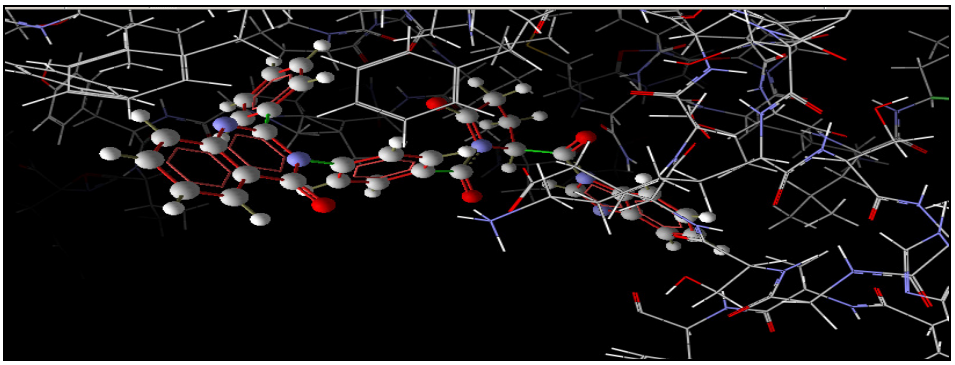
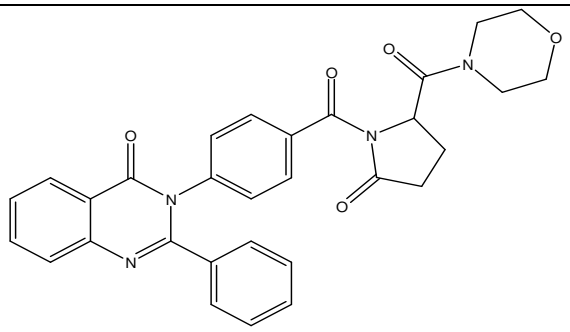
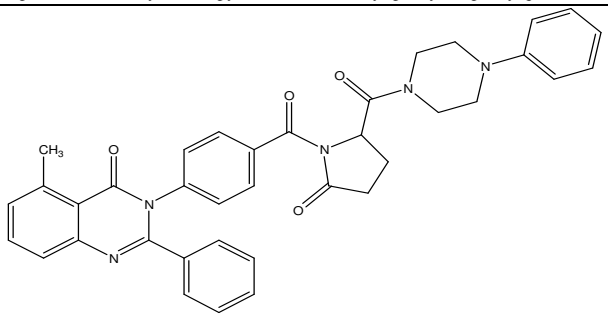
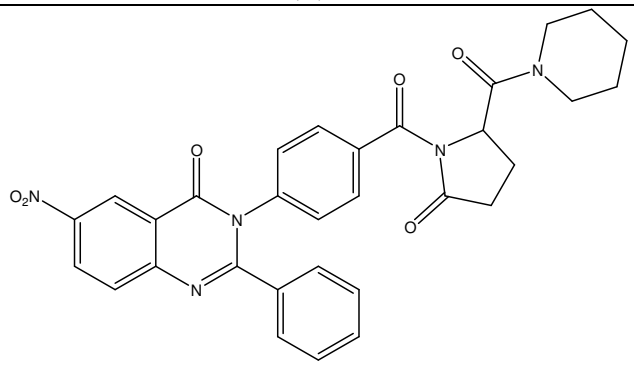
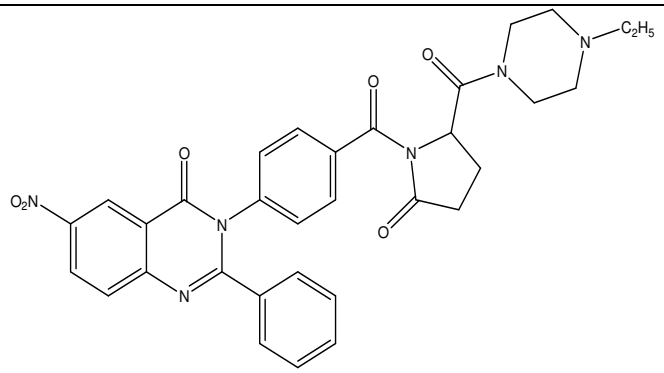
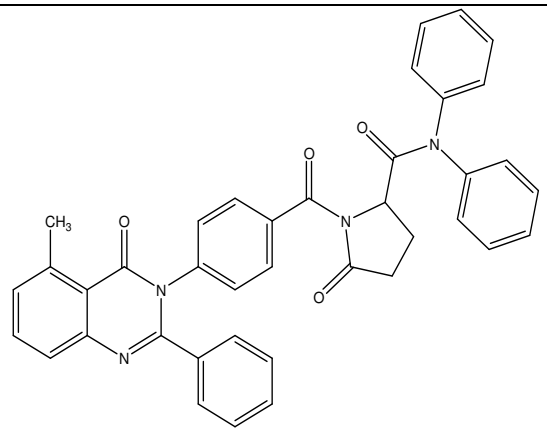
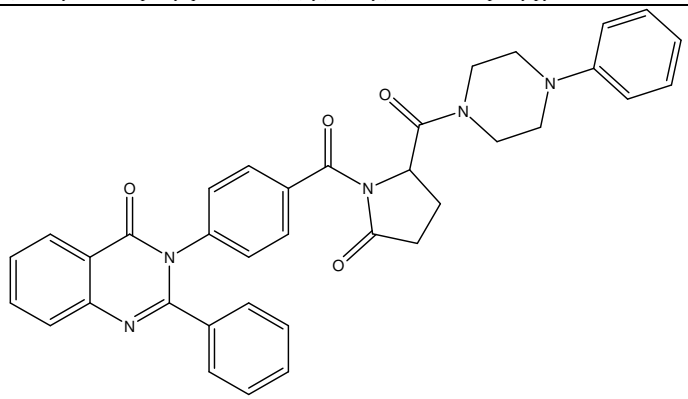
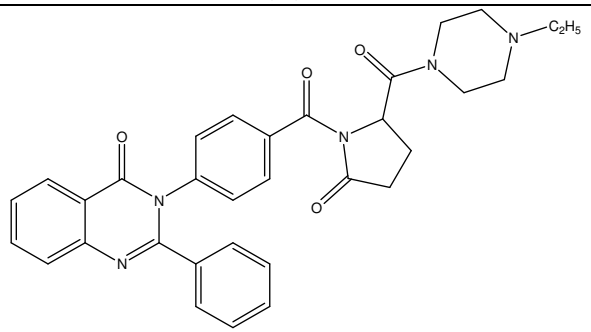
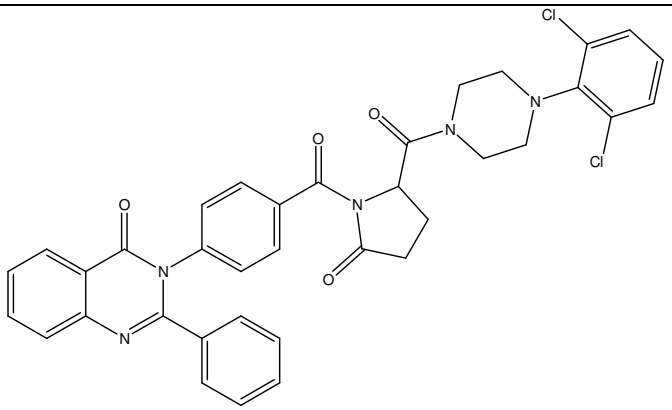
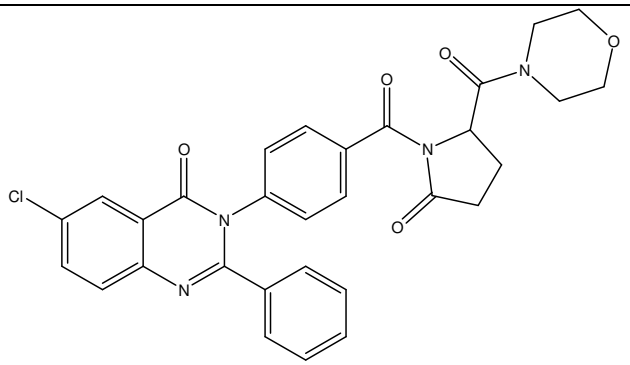
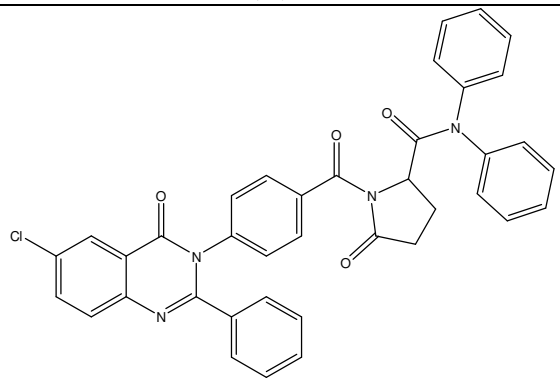
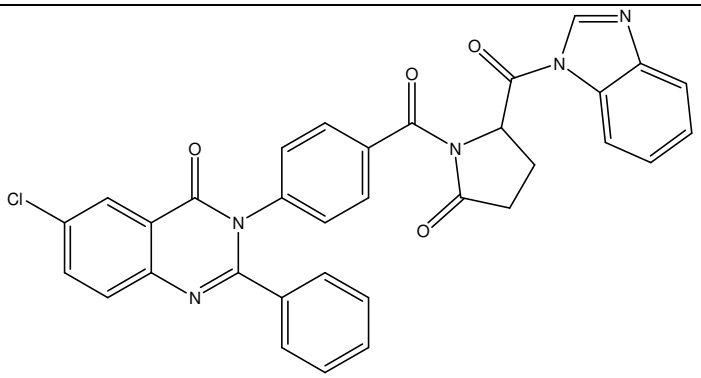


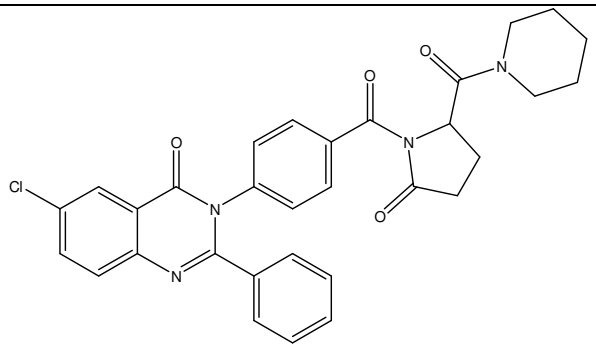
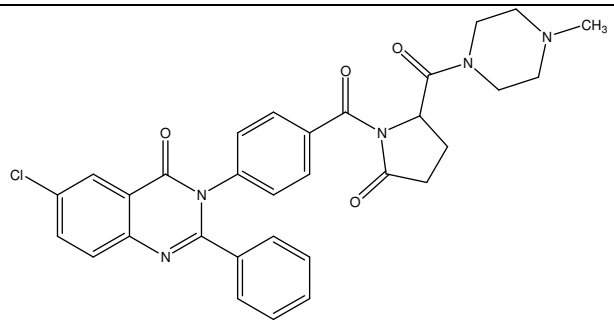
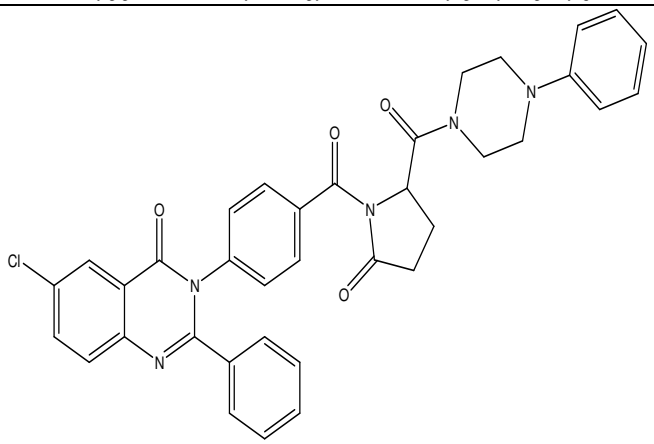
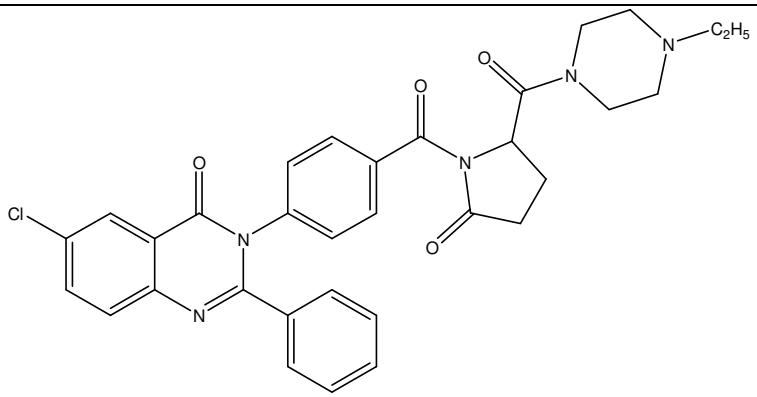
Fig.-1: 3D SRB1 (Scavenger receptor class B Type- I) and 3D ligand (Q1)

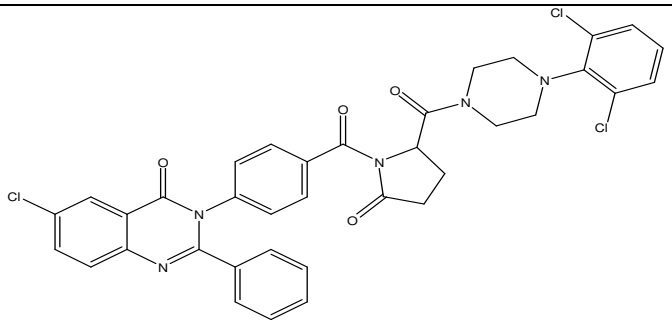
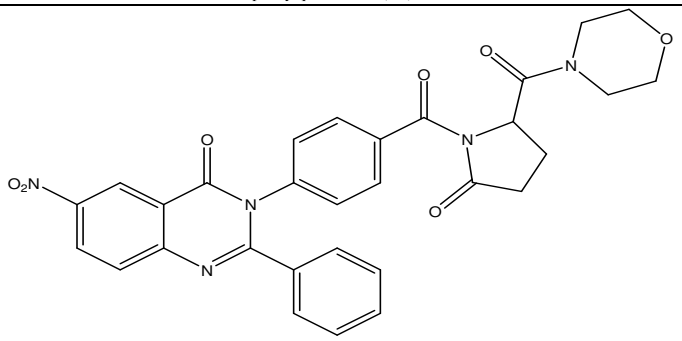
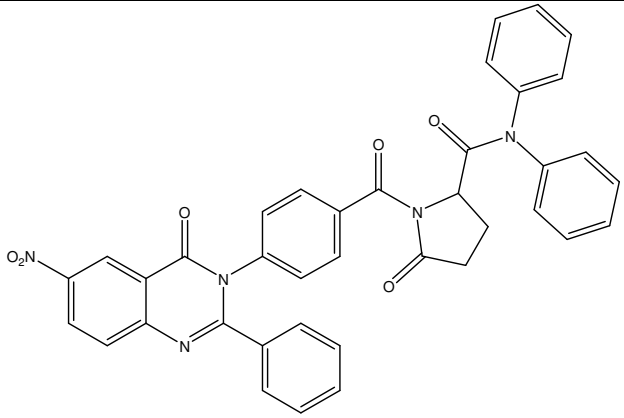
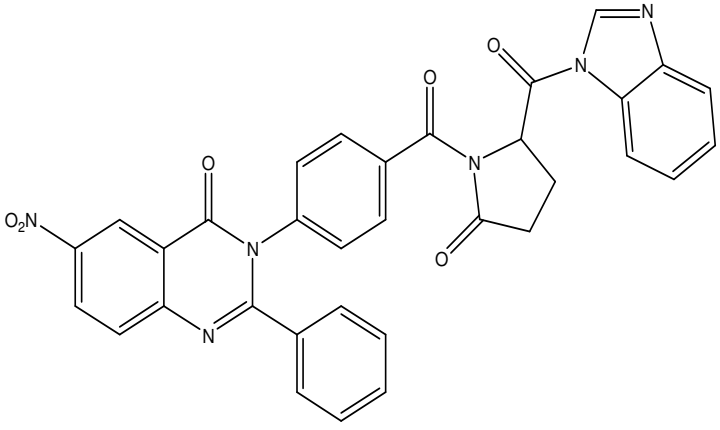
Table-1: Structure and Docked compounds with standard

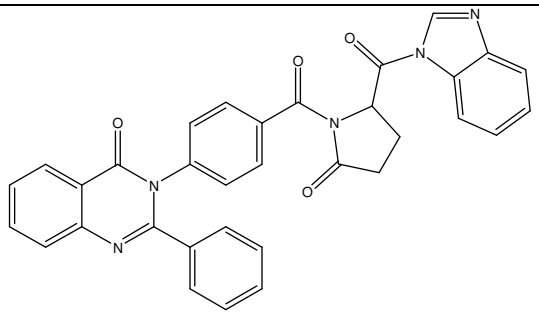
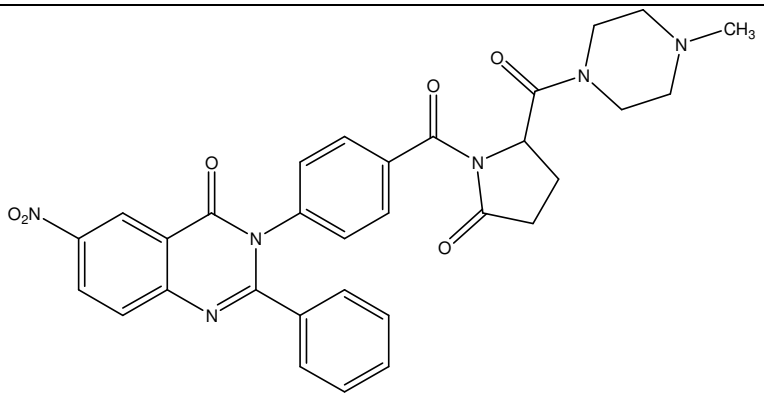
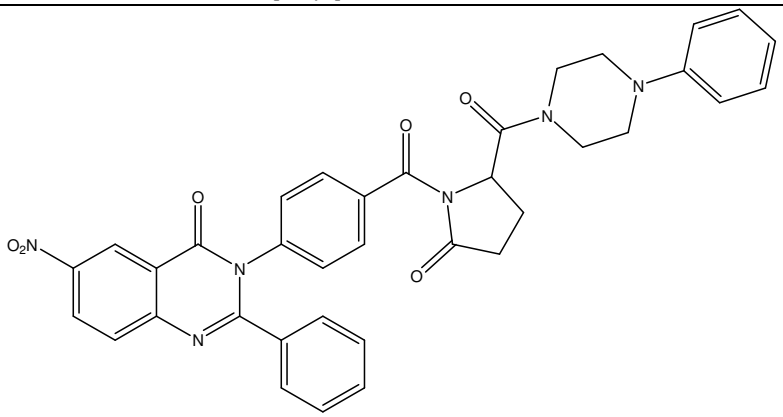
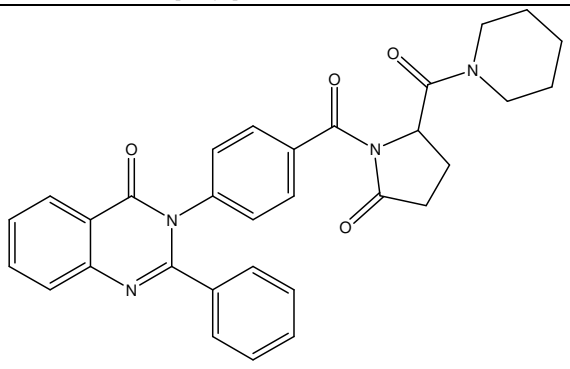
| S.No. | Compound Code | Structure | Binding values |
|---|---|---|---|
| 1 | 7a1 |  3-(4-(2-(morpholine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -9.9 |
| 2 | 7a2 |  5-methyl-3-(4-(2-oxo-5-(1-phenylpiperazine-4-carbonyl)pyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -9.7 |
| 3 | 7a3 |  6-nitro-3-(4-(2-oxo-5-(piperidine-1-carbonyl)pyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -9.7 |

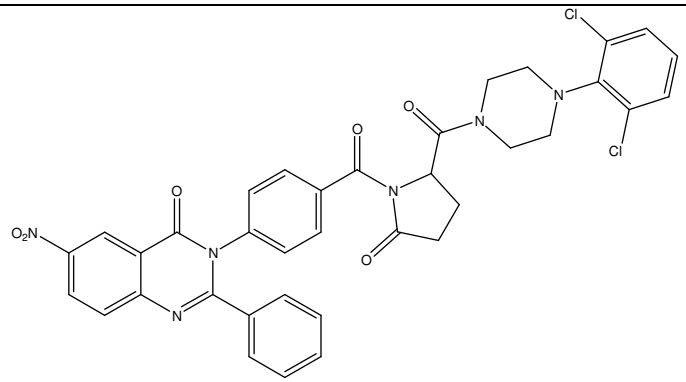
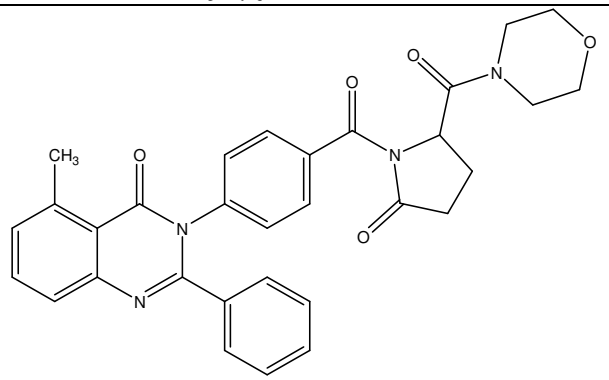
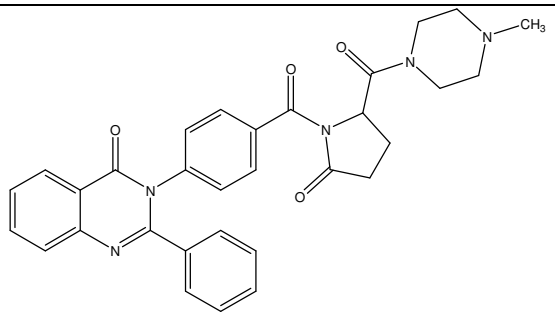
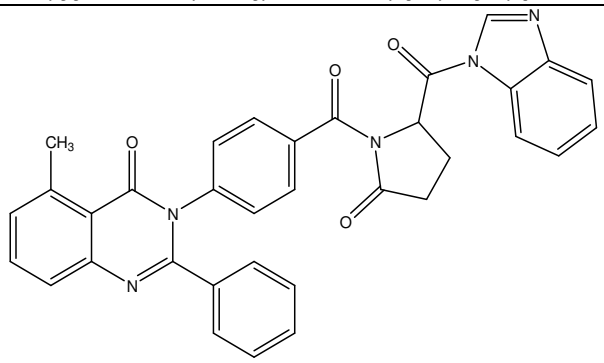
| | | | |
|---|---|---|---|
| 4 | 7a4 |  <br>3-(4-(2-(1-ethylpiperazine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-6-nitro-2-phenylquinazolin-4(3*H*)-one | -9.6 |
| 5 | 7a5 |  <br>1-(4-(5-methyl-4-oxo-2-phenylquinazolin-3(4*H*)-yl)benzoyl)-5-oxo-*N*,*N*-diphenylpyrrolidine-2-carboxamide | -9.5 |
| 6 | 7a6 |  <br>3-(4-(2-oxo-5-(1-phenylpiperazine-4-carbonyl)pyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -9.4 |
| 7 | 7a7 |  <br>3-(4-(2-(1-ethylpiperazine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -9.3 |

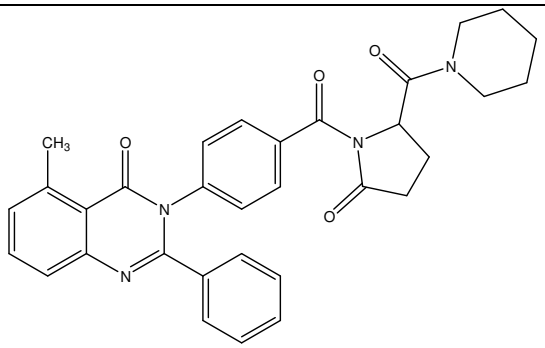
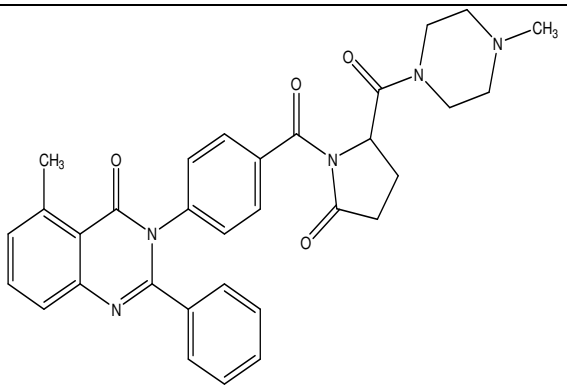
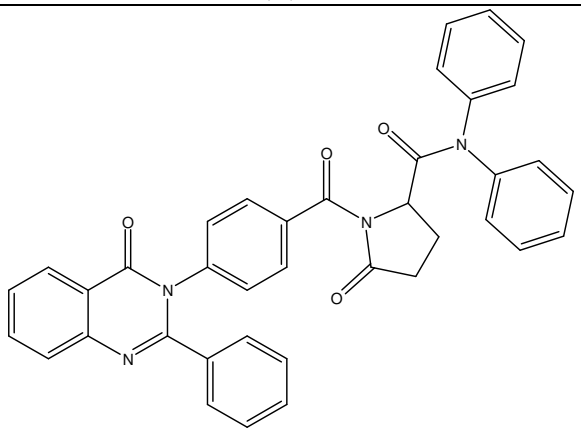
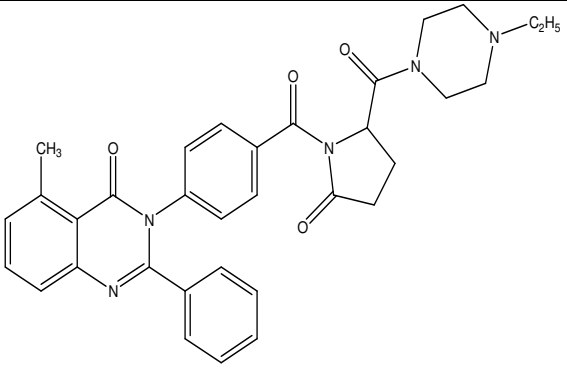
| | | | |
|---|---|---|---|
| 8 | 7a8 |  <br>3-(4-(2-(1-(2,6-dichlorophenyl)piperazine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -9.3 |
| 9 | 7b1 |  <br>6-chloro-3-(4-(2-(morpholine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -9.3 |
| 10 | 7b2 |  <br>1-(4-(6-chloro-4-oxo-2-phenylquinazolin-3(4*H*)-yl)benzoyl)-5-oxo-*N*,*N*-diphenylpyrrolidine-2-carboxamide | -9.3 |
| 11 | 7b3 |  <br>3-(4-(2-(1*H*-benzo[*d*]imidazole-1-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-6-chloro-2-phenylquinazolin-4(3*H*)-one | -9.3 |

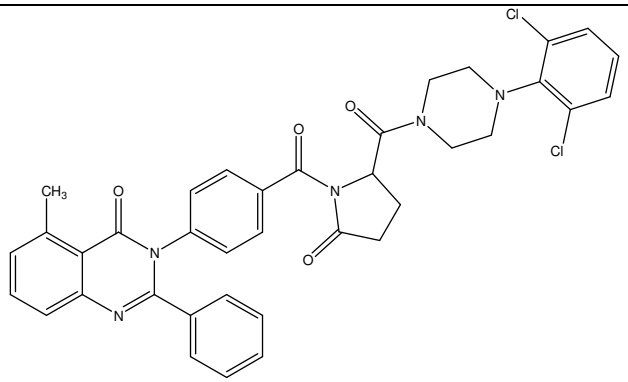
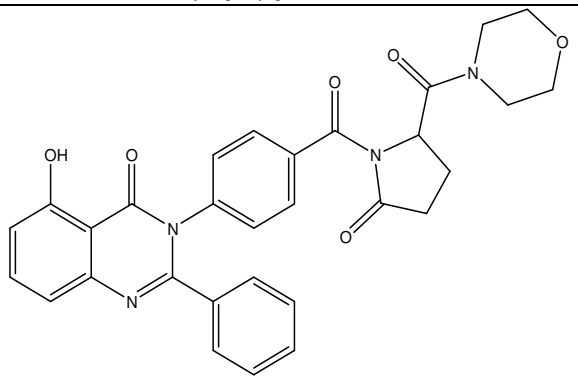
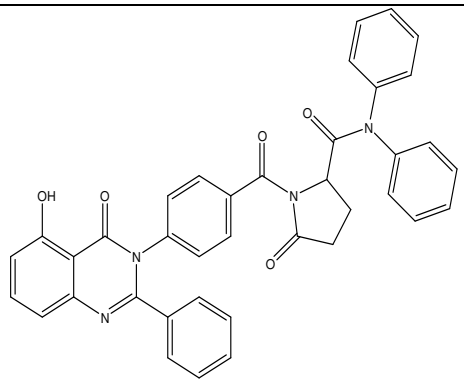
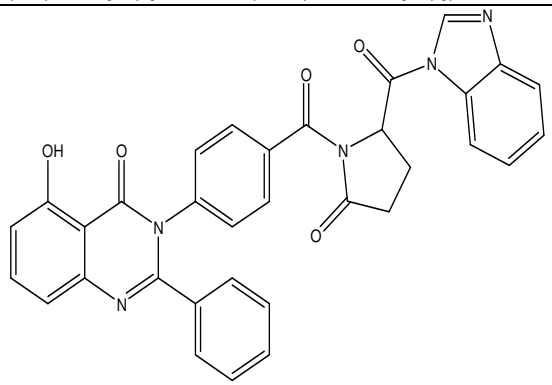
| | | | |
|---|---|---|---|
| 12 | 7b4 |  <br>6-chloro-3-(4-(2-oxo-5-(piperidine-1-carbonyl)pyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -9.2 |
| 13 | 7b5 |  <br>6-chloro-3-(4-(2-(1-methylpiperazine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -9.1 |
| 14 | 7b6 |  <br>6-chloro-3-(4-(2-oxo-5-(1-phenylpiperazine-4-carbonyl)pyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -9.1 |
| 15 | 7b7 |  <br>6-chloro-3-(4-(2-(1-ethylpiperazine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -9.0 |

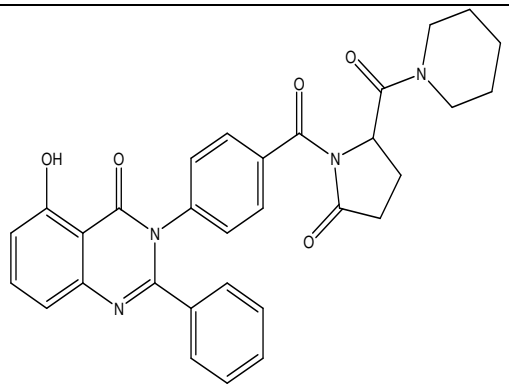
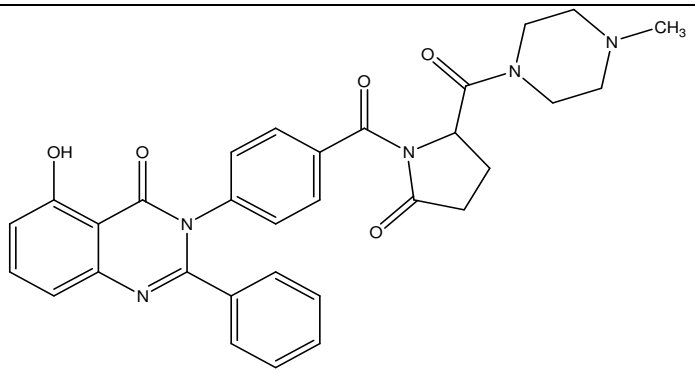
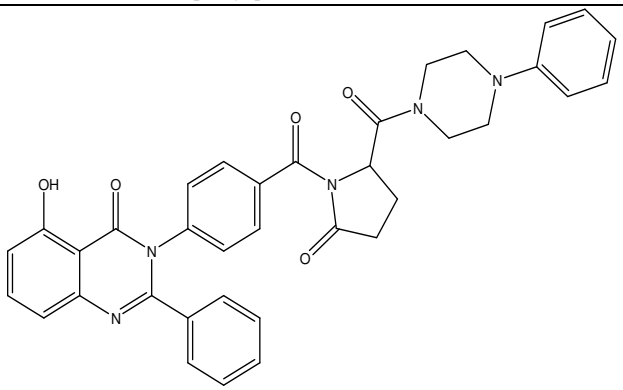
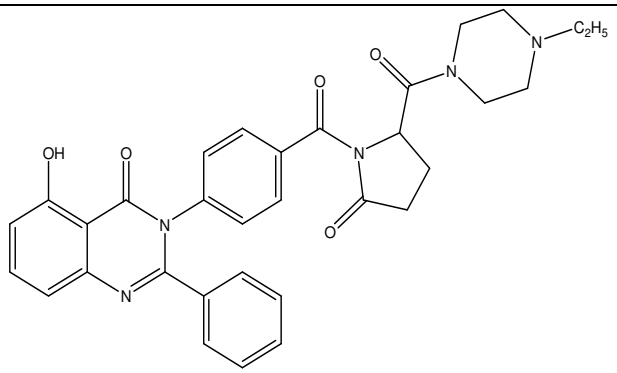
| | | | |
|---|---|---|---|
| 16 | 7b8 |  <br>6-chloro-3-(4-(2-(1-(2,6-dichlorophenyl)piperazine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -8.9 |
| 17 | 7c1 |  <br>3-(4-(2-(morpholine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-6-nitro-2-phenylquinazolin-4(3*H*)-one | -8.9 |
| 18 | 7c2 |  <br>1-(4-(6-nitro-4-oxo-2-phenylquinazolin-3(4*H*)-yl)benzoyl)-5-oxo-*N*,*N*-diphenylpyrrolidine-2-carboxamide | -8.9 |
| 19 | 7c3 |  <br>3-(4-(2-(1*H*-benzo[*d*]imidazole-1-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-6-nitro-2-phenylquinazolin-4(3*H*)-one | -8.8 |

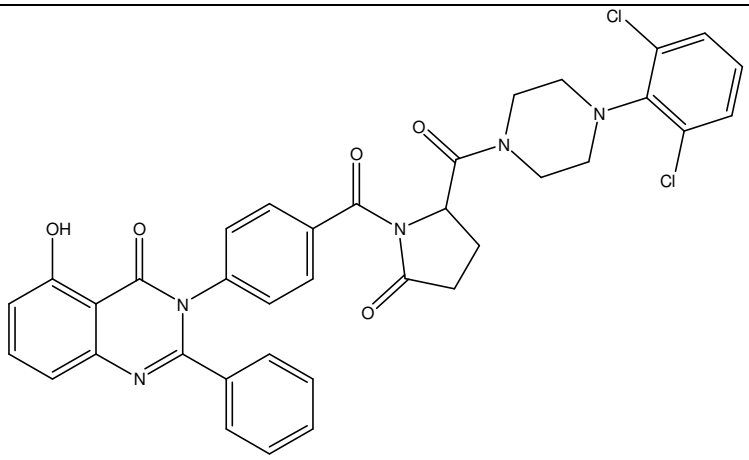
| | | | |
|---|---|---|---|
| 20 | 7c4 |  <br>3-(4-(2-(1*H*-benzo[*d*]imidazole-1-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -8.8 |
| 21 | 7c5 |  <br>3-(4-(2-(1-methylpiperazine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-6-nitro-2-phenylquinazolin-4(3*H*)-one | -8.8 |
| 22 | 7c6 |  <br>6-nitro-3-(4-(2-oxo-5-(1-phenylpiperazine-4-carbonyl)pyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -8.8 |
| 23 | 7c7 |  <br>3-(4-(2-oxo-5-(piperidine-1-carbonyl)pyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -8.7 |

| | | | |
|---|---|---|---|
| 24 | 7c8 |  <br>3-(4-(2-(1-(2,6-dichlorophenyl)piperazine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-6-nitro-2-phenylquinazolin-4(3*H*)-one | -8.6 |
| 25 | 7d1 |  <br>5-methyl-3-(4-(2-(morpholine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -8.5 |
| 26 | 7d2 |  <br>3-(4-(2-(1-methylpiperazine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -8.5 |
| 27 | 7d3 |  <br>3-(4-(2-(1*H*-benzo[*d*]imidazole-1-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-5-methyl-2-phenylquinazolin-4(3*H*)-one | -8.5 |

| | | | |
|---|---|---|---|
| 28 | 7d4 |  <br>5-methyl-3-(4-(2-oxo-5-(piperidine-1-carbonyl)pyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -8.2 |
| 29 | 7d5 |  <br>5-methyl-3-(4-(2-(1-methylpiperazine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -8.2 |
| 30 | 7d6 |  <br>5-oxo-1-(4-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)benzoyl)-*N*,*N*-diphenylpyrrolidine-2-carboxamide | -8.2 |
| 31 | 7d7 |  <br>3-(4-(2-(1-ethylpiperazine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-5-methyl-2-phenylquinazolin-4(3*H*)-one | -8.1 |

| | | | |
|---|---|---|---|
| 32 | 7d8 |  <br>3-(4-(2-(1-(2,6-dichlorophenyl)piperazine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-5-methyl-2-phenylquinazolin-4(3*H*)-one | -8.1 |
| 33 | 7e1 |  <br>5-hydroxy-3-(4-(2-(morpholine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -8.0 |
| 34 | 7e2 |  <br>1-(4-(5-hydroxy-4-oxo-2-phenylquinazolin-3(4*H*)-yl)benzoyl)-5-oxo-*N*,*N*-diphenylpyrrolidine-2-carboxamide | -7.9 |
| 35 | 7e3 |  <br>3-(4-(2-(1*H*-benzo[*d*]imidazole-1-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-5-hydroxy-2-phenylquinazolin-4(3*H*)-one | -7.8 |

| | | | |
|---|---|---|---|
| 36 | 7e4 |  <br>5-hydroxy-3-(4-(2-oxo-5-(piperidine-1-carbonyl)pyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -7.7 |
| 37 | 7e5 |  <br>5-hydroxy-3-(4-(2-(1-methylpiperazine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -7.7 |
| 38 | 7e6 |  <br>5-hydroxy-3-(4-(2-oxo-5-(1-phenylpiperazine-4-carbonyl)pyrrolidine-1-carbonyl)phenyl)-2-phenylquinazolin-4(3*H*)-one | -7.6 |
| 39 | 7e7 |  <br>3-(4-(2-(1-ethylpiperazine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-5-hydroxy-2-phenylquinazolin-4(3*H*)-one | -7.4 |

| | | | |
|---|---|---|---|
| 40 | 7e8 |  <br>3-(4-(2-(1-(2,6-dichlorophenyl)piperazine-4-carbonyl)-5-oxopyrrolidine-1-carbonyl)phenyl)-5-hydroxy-2-phenylquinazolin-4(3*H*)-one | -6.6 |

The introduced protein targets SRB1 (scavenger receptor, class B, Type- 1) are potential mutation genes involved in diabetes and obesity associated disorders in human. The use of computer and informational techniques applied to a range of problems in the field of chemistry. These *in silico* techniques are used in pharmaceutical companies in the process of drug discovery.

The application of docking and scoring has led to some remarkable successes; there are still some major challenges ahead, which were outlined in our thesis as well. Approaches to address some of these challenges and the latest developments in the area were presented. Some aspects of the assessment of docking program performance were discussed. A number of victorious applications of structure-based virtual screening were described.

The overall docking results show that the synthesized chemicals are made to inhibit SRB1 (scavenger receptor, class B, Type-I) proteins with help of automated docking servers (AUTODOCK VINA). Based on the docking results, we deduce that SRB1 have negatively high binding values. The standard drugs with SRB1 show a binding value which is negatively low. The complete automated drug docking results clear show how the synthesized chemicals and the standard drugs are bound to the target receptors.

## CONCLUSION

Thus based on ligand score, glide energy and interaction with residues in the active site of the SRCB1, compound 7a-7a8 and 7b1-7b8 was found to be more potent inhibitor as they exhibit drug like activity. The entire test Compounds which have highest ligand energy compared to the Standard compounds. The top 16 compounds with good docking score will be subjected to wet lab work viz., synthesis and evaluation using Scavenger receptor class B Type- I inhibitor assay studies. The outcome of dry lab work and wet lab work will be analyzed carefully to find out suitability of the rational used for the design of novel entity in general and optimization of pharmacophore for inhibition of Scavenger receptor class B Type- I.

## ACKNOWLEDGEMENT

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