WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 8, 770-778. Research Article ISSN 2277– 7105

IN SILICO STUDY OF BENZIMIDAZOLE DERIVATIVES AS POTENTIAL INHIBITOR OF ACETYL COENZYME CARBOXYLASE

Nisha Devi[a], Deepika Choudhary[b] and Sukhbir Lal Khokra[b]*

[a]Dreamz College of Pharmacy, Himachal Pradesh Technical University, Khilra (Sundernagar), 175036, Himachal.

[b]*Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, 136119, Haryana, India.

Article Received on
01 June 2016,

Revised on 21 June 2016,
Accepted on 12 July 2016

DOI: 10.20959/wjpr20168-6710

***Corresponding Author**
Sukhbir Lal Khokra
Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, 136119, Haryana, India.

ABSTRACT

A series of total 12hypothetical benzimidazole derivatives, as shown in table 1 were designed having substituted sulphonamide at 2–position of benzimidazole ring. Acetyl coenzyme carboxylase (ACC) is catalyzes the carboxylation of acetyl-CoA to produce malonyl-CoA. To pre asses their potential to be effective against antioxidant activity, these 12 hypothetical butenolide derivatives were analysed by computational analysis, particularly docking studies using programme Molegro Virtual Docker 4.0.2. In this study we considered the hypothetical compounds as ligands and suitable target bio-molecules as receptors. When ligands bind to the receptor, the course of a biochemical process is modified. The protein receptors (PDBs) used in this study PDB ID-1UOk for antioxidant activity. The target protein receptor was found to be most suitable and actively involved as main trait for role and function of acetyl co-carboxylase. Results of docking studies revealed that almost all docked compounds have good mol dock score and showed strong interactions with the receptor in comparison to the standard drug ascorbic acid.

KEYWORDS: Molegro virtual docker, benzimidazole, biotin, biological function.

1. INTRODUCTION

Acetyl coenzyme carboxylase (ACC) is catalyzes the carboxylation of acetyl-CoA to produce malonyl-CoA. This enzyme was first discovered in nearly 50 years ago and has been studied extensively over the years.[1] Recently studies regarded to the obesity epidemic and

associated clinical manifestations such as type II diabetes, cardiovascular diseases and atherosclerosis, which are three terms known as the metabolic syndrome, insulin resistance syndrome or syndrome X [2] has been generated significant renewed interest in ACC. Mostly more than half of the population in the US is either overweight or obese. [3] In case changes life-style (less food intake and more physical activity) are an important component in reducing the obesity epidemic, there is also an urgent needs for new therapeutic agents. ACC has played important roles in fatty acid metabolism, and represents an effective target for new therapeutic development in the control of obesity and the treatment of metabolic syndrome.[4] The important regulatory and rate-limiting role of acetyl-CoA carboxylase makes this enzyme a powerful tool in a variety of biotechnological and medical projects It is shown as a multi-component system but it can be comprised in the two enzymes (AccC and AccAD) and also in biotin carrier protein (BCCP or AccB). Acetyl-CoA carboxylase (ACCs) are biotin-dependent enzymes in fatty acid de novo biosynthesis that irreversibly catalyze carboxylation of acetyl-CoA to malonyl-CoA[5] fig. 1

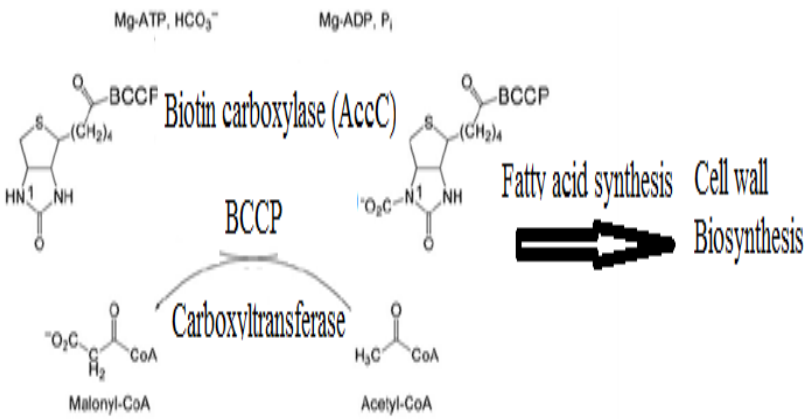

Fig.1-Role of Biotin in cell wall Biosynthesis

1.2 Biological Function

The ACCs protect many living organisms, underscoring the importance of their biological functions.[7] For example, the BC domain of human and other mammals contain in the ACC1 shares 37% amino acid sequence identity with the BC subunit of *E. coli* ACC and yeast ACC share 63% sequence identity.

The carboxylase enzyme are controlled by three global signals—glucagon, epinephrine, and insulin—that correspond to the overall energy status of the organism. Also in the low levels of citrate, palmitoyl CoA and AMP within a cell also exert to the carboxylase control in fig 2. Insulin stimulates the fatty acid synthesis by activating the carboxylase by causing its

dephosphorylation; whereas glucagon and epinephrine have producing the reverse effect because it is inhibits the phosphatase by phosphorylating it. Citrate is a signal that building blocks and energy are abundant, activates the carboxylase by the allosterically stimulated. Thus, this important enzyme is need to both global and fatty acid regulation.[8,9]

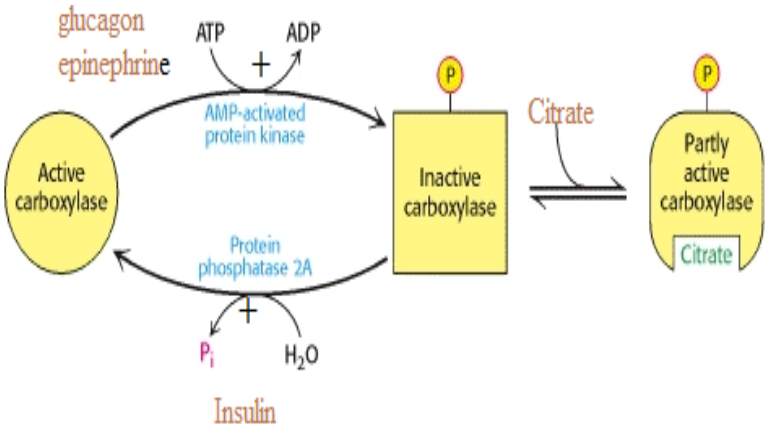

Fig. 2- Function & Regulation of Acetyl co-carboxylase

2. MATERIAL AND METHODS

2.1 The whole protocol followed during Molecular docking studies for cerebral malaria can be studied under following heads

- Selection of hypothetical compounds
- Selection of pdb done on the basis of literature based preference given by antimicrobial and antioxidant (PDB ID IUOK) work
- Importing a protein file, ligand file and preparation of ligands.
- Protein preparation and detecting cavities of protein molecules.
- Executing a docking set up through docking wizard panel.
- Determination of poses of protein-ligand complex.
- Calculation of Mol Dock Score and Hydrogen Bond Interaction.
- Interpretation of results.

2.2 Molecular docking on Molegro Virtual Docker 4.0.2

Molecular modelling for antibacterial and antioxidant activity on programme Molegro Virtual Docker 4.0.2- Methods for predicting modes of small organic molecules to protein receptors are widely used within drug discovery efforts. Ligand docking is typically achieved by generating a number of orientations (or poses) of a ligand within the active site, and scoring

of poses to identify one or more that closely approximate the bioactive conformation determined by X-ray crystallography.[10] Docking algorithms are also used for identifying putative binders from virtual chemical databases and for estimating the binding affinity of protein-ligand complexes.[11] Docking study has been performed with a set of 12 hypothetical butenolide derivatives using Molegro Virtual docker MVD 2010.4.2 for antioxidant for using (PDB ID: 1UOK).[12] The X-ray structures of which were accessed from the protein data bank (PDB).

2.2.1 Data-set selection- A series of total 12 hypothetical benzimidazole derivatives on the basis of literature explored, as shown in table 1 were designed, among these 12 compounds were having substituted sulphonamide moiety at 2–position of benzimidazole ring and 12 of them were having substituted hydrazine moieties at the same position of benzimidazole ring. General structures of hypothetical compounds are shown in table 1.

Table 1: The Sets of Structures of Hypothetical Compounds for docking studies

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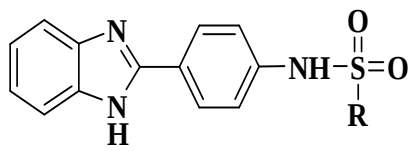
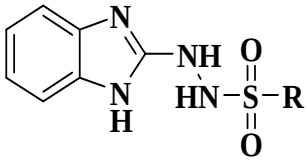
<tr><td> 
(I-VI)</td><td colspan="5"> 
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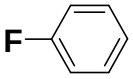
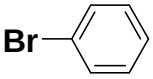
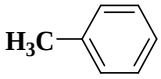
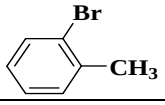
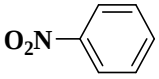
<tr><td>  </td><td>  </td><td>  </td><td>  </td><td>  </td><td>  </td></tr>
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2.2.2 Ligand preparation- The molecules were built in MarvinSketch 5.11.4.MarvinSketch is a robust collection of tools designed to prepare high quality, all-atom 3D structures for large numbers of drug like molecules, starting with the 2D structures in Marvin format. Before converting the 2D molecules into 3D; all hydrogen's in the structure were added. After converting the 2D molecules into 3D, the conformational energy of molecules was minimized. The resulting structures was saved in Marvin Sketch as MDL Molfile (*.mol). The simplest use of Marvin Sketch produces a single, low energy with 3D structure. Finally, the prepared 3D structures of molecules were imported by dragging or dropping a molecule structure file in the workspace.

2.3.3 Protein preparation and detecting cavities of protein molecules

The target selected for antioxidant was (PDB ID-1UOK). The corresponding X-ray structure for the protein targets were accessed from the protein data bank (PDB) and imported. The

protein structures were prepared using the protein preparation wizard in MVD. In this step, bond order were assigned, all hydrogen's in the structure were added and bonds to metals were deleted and adjust the formal charge on the metal and the neighbouring atoms and deleted waters that were more than 5Å specific distance. The energy of imported molecules was minimized using Ligand Energy inspector. The energy minimization supports in stability of molecules to be imported. In next, the protein surface was created using protein preparation. This step helps to inspect and change the protonation state for the residues. In order to determine the potential binding sites, a cavity prediction algorithm was performed.[13]

2.2.4 Executing a docking set up through docking wizard panel

Molegro searches for suitable interaction between one or more ligand molecules and the receptor. In next, all ligands were selected and docking was performed through the docking wizard panel. After then docking result were imported. Various orientation (or poses) of docked compounds were analysed by determination of Mol Dock Score and H-bond interaction. Compounds were arranged according to their Mol Dock scores and were visualized inside the pocket to view their fitting and closure to main residues. Molecular docking studies were revealed further insight into the nature of interactions between the compounds and the active site amino acids to rationalize the obtained biological results.

3. RESULTS AND DISCUSSION

Table 2: MolDock score and bonding interaction of benzimidazole derivatives with amino acid residues using PDB ID: 1UOK for determination of antioxidant activity.

Compounds	Mol Dock Score	No. of H-bond interaction	H-bond distance (A^0)	Amino acid involved	Structural feature
Ascorbic acid (Standard drug)	**-73.436**	**9**	3.19 2.59 3.57 3.25 2.53 2.58 2.75 3.10	His103 Asp60 Arg415 Gln167 Arg415 Asp199 Glu255 Glu255	O-OH O-OH O-CO O-OH O-CO O-OH O-OH O-OH
(I)	-129.874	2	3.23 2.95	Gln330 Lys293	N of benzimidazole N of benzimidazole
	-120.908	4	3.39 2.29 3.41 3.47	Gln330 Lys293 Asp329 Arg415	N of benzimidazole N of benzimidazole N-NH O –S
(II)	-122.778	4	2.92 2.96	Arg415 Asp329	O – S N-NH

			3.00 3.21	Lys293 Gln330	N of benzimidazole N of benzimidazole
(III)	**-126.919**	**5**	3.16 2.75 2.75 2.97 2.63	Arg415 Asp329 Lys293 Gln330 Gln330	N of benzimidazole N of benzimidazole O – S O – S N-NH
(IV)	-132.249	2	2.76 3.06	Asp329 Asp329	N of benzimidazole N-NH
(V)	**-133.554**	**6**	3.54 2.82 3.10 2.54 2.97 2.99	Arg336 Asp329 Arg336 Gln330 Gln330 Arg336	N of benzimidazole NH of benzimidazole O–NO_2 N-NO_2 O–NO_2 O–NO_2
	-118.182	**9**	3.18 3.31 2.73 3.10 3.52 3.57 2.60 3.03 2.88	Lys293 Arg336 Arg336 Gln330 Arg336 Lys413 Lys413 Ser288 Gly258	O–NO_2 O–NO_2 O–NO_2 O–NO_2 N-NO_2 N-NO_2 O–NO_2 O–NO_2 N of benzimidazole
(VI)	-125.978	3	3.42 3.00 2.89	Gln330 Lys293 Glu255	N of benzimidazole N of benzimidazole N-NH
(VII)	-106.842	4	3.22 3.32 2.68 3.11	Lys293 Lys293 Gln330 Asp329	N of benzimidazole O – S N of NH with S N of imdazole ring
(VIII)	-103.871	5	2.57 2.94 3.09 3.15 2.61	Glu 255 Glu 255 Asp199 Asp199 Arg415	N of imdazole ring N-NH NH of benzimidazole O-S O-S
(IX)	**-114.112**	**5**	2.56 2.92 3.07 3.10 2.64	Glu 255 Glu 255 Asp199 Asp199 Arg415	N of imdazole ring N-NH NH of benzimidazole O-S O-S
(X)	-101.436	6	3.50 3.52 **2.08** 3.51 2.95 2.60	Cys293 Arg415 **Gln330** Tyr324 Asn327 Asp329	O-S O-S **N-NH** N of imdazole ring N of imdazole ring NH of imdazole ring
(XI)	-107.912	6	3.10 3.16 2.37	Arg 331 Arg336 Gln330	O-NO_2 O-NO_2 O-NO_2

			2.74 2.97 3.31	Gln330 Glu255 Arg415	N-NO_2 NH of benzimidazole N of imdazole ring
(XII)	-106.3	4	3.40 2.40 2.91 3.02	Arg415 Glu255 Asp329 Asp329	O – S N of NH with S N of NH with S benzimidazole

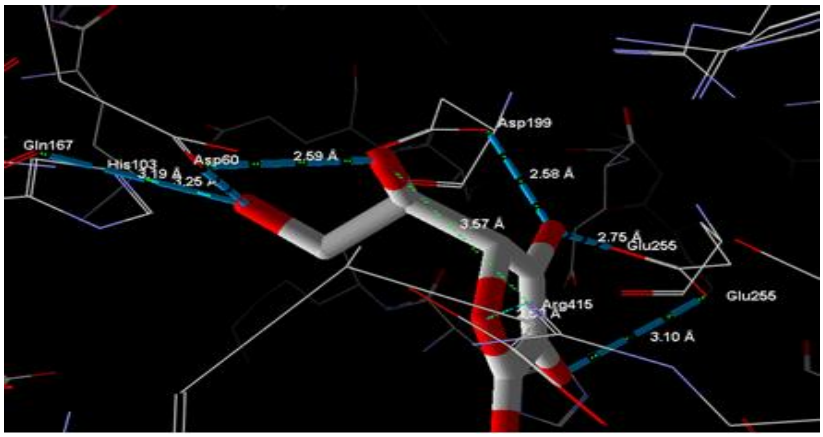

Fig.3-Binding mode of Ascorbic acid with 1UOK Antioxidant activity

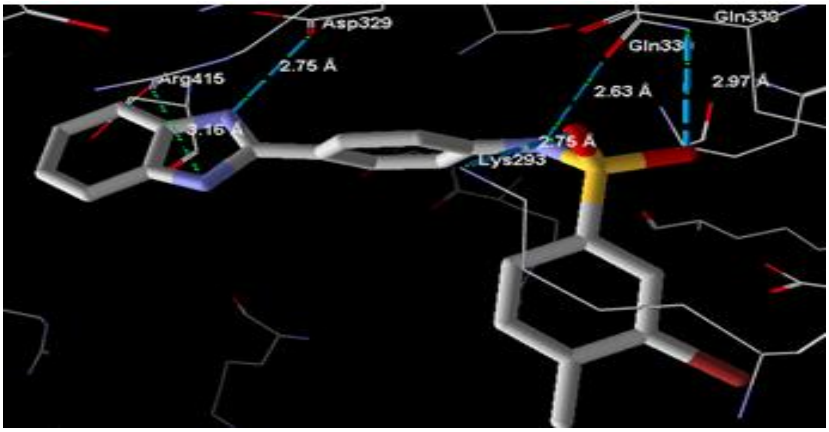

Fig.4-Binding mode of III with 1UOK for antioxidant activity

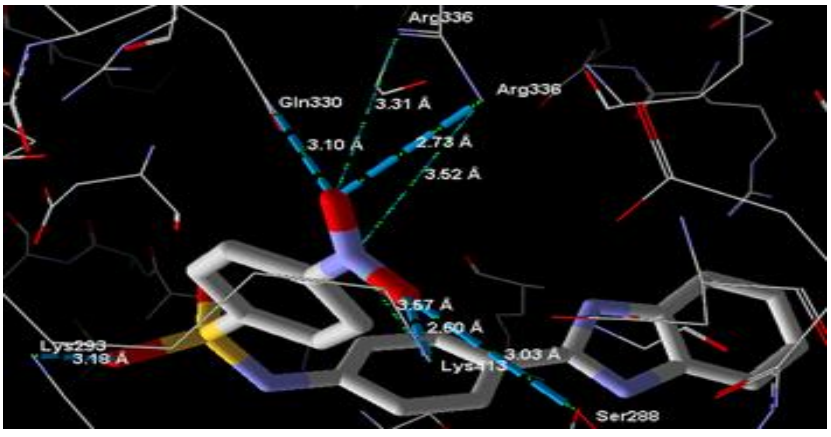

Fig.5-: Binding mode of V with 1UOK for antioxidant activity

Results of in *silico* analysis for antioxidant on receptor (PDB-1UOK) are shown in table 2 and it was observed that almost every derivative has better mol dock score than the standard drug Ascorbic acid having mol dock score **-73.436** and it forms nine interactions (H bond) with receptor as shown in as shown in fig 3. The compounds **I, II, III, IV, V** and **IX** were found best with mol dock score > -114and docking score > -133 and form > 4 no. of H-bond interactions with the receptor as shown in table 2. Binding mode of compound III and V with protein receptor 1UOK for antioxidant activity were shown in fig 4 and fig 5 respectively.

4. CONCLUSION

In present study, an approach of virtual screening based on docking study is applied to evaluate a set of designed hypothetical benzimidazole against receptor 1UOK, main target involved in the Acetyl co-enzyme function. From *In silico* analysis, it was concluded that among the 12 designed analogues, almost all compounds may be considered as potent and active derivatives, as antioxidant activity. In each series, compounds with R-group like sulphonamide & hydrazine showed very good binding affinities with protein receptors 1UOk. Hence should be explored as template to design some new potent hits and can be subjected to *in vitro* studies for further confirmation of their potential.

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