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IN SILICO EPITOPE PREDICTION AND HOMOLOGY MODELING OF ENVELOPE SURFACE GLYCOPROTEIN GP160, PRECURSOR REGION FROM HUMAN IMMUNO DEFICIENCY VIRUS -1

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ABSTRACT: The development of a highly effective AIDS vaccine will depend on the success of designing immunogens that will elicit immune response against broadly neutralizing antibodies to naturally circulating strains of HIV- can be done by reverse vaccinology. Reverse vaccinology is a good approach for provoking the broadly neutralizing antibody response by identifying the specific epitopes i.e. surface proteins. The 3D structure of a protein is a prerequisite for structure based drug design as well as for identifying the conformational epitopes that are essential for the designing vaccines. The objective of this study is to identify peptides that can be used as potential vaccines against HIV using bioinformatics approach. B-cell epitopes which are present in the structural, regulatory and accessory proteins encoded by Clade-B HIV-1 genome were predicted using epitope prediction servers (RANKPEP) available in the public domains. Homology modeling approach was used to determine the 3D structures of these predicted epitopes. In addition to these studies, modes of binding of these epitopes to broadly neutralizing antibodies 2G12, B12, 4E10 and PG9 were also investigated by docking studies.

INTRODUCTION: Acquired immunodeficiency syndrome (AIDS) was first described 30 years ago in a report from the US Centers for Disease Control. Two years later, it was found that virus responsible for it was Human immunodeficiency Virus (HIV) [1]. HIV spread throughout the world; it had already killed half of the 60 million people that had been infected so far. As of now, there are about 2 million new HIV infections each year and an equal number of deaths due to AIDS [2].

QUICK RESPONSE CODE

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Human immunodeficiency virus (HIV) is responsible for the cause of acquired immunodeficiency syndrome (AIDS) [3, 4] which is characterized by depletion of the immune cells mainly T helper cells [5]. According to the annual report of the Joint United Nations Program on HIV and AIDS (UNAIDS), it was reckoned that 34million people were infected with AIDS at the end of 2011. The percentage of people with AIDS has also substantially increased (~ 19%) from what it was in the year 2001. According to the UNAIDS report, about 1.7 million [1.5 million–1.9 million] people died due AIDS-related causes worldwide in 2011showing decrease in AIDS-related mortality compared with 2005 by 24% (when 2.3 million [2.1 million–2.6 million] deaths occurred) [6].

HIV can infect multiple cells like brain cells, but its main target is the CD4+ lymphocytes, also called T-cells. When HIV infects CD4+ cells, the virus goes through multiple steps to reproduce itself and produce more virus particles. HIV is quite genetically diverse, despite of its small genome. Its genome is composed of nine genes, but only two, *gag* and *env*, are reliable genes for vaccine development, since they are less affected by the high mutation rates of HIV [7.]

The 160 kD Env (gp160) is expressed from mRNA which is singly spliced. Env firstly synthesized in the endoplasmic reticulum then it migrates to Golgi complex where it undergoes glycosylation with the addition of 25 to 30 complex N-linked carbohydrate side chains that are added at asparagine residues. Env glycosylation is required for infectivity [8]. A cellular protease cleaves gp160 to generate gp41 and gp120. The gp41 moeity contains the Env transmembrane domain; gp120 is located on the infected cell surface and of the virion through noncovalent interactions with gp41. Trimer of Env exists on the surface of infected cells and virions [9]. Interactions between HIV and the virion receptor, are mediated through specific domains of gp120 [10].

Although no single immunogen has generated antibodies that can neutralize diverse isolates, progress has been made in understanding [11];

a. The structure of the HIV-1 envelope glycoprotein, which is targeted by neutralizing antibodies,

b. How HIV-1 gets entry into host cells,

c. How HIV-1 evade antibodies made by an infected host, and

d. How rare monoclonal antibodies can exhibit broadly neutralizing activity.

Humoral and T cell-based vaccine approaches each have their own clauses, the recent successful findings is the identification and production of bNAbs [12], new generation viral vectors, and the immunotechnology to detect highly specific responses, have facilitated the understanding in vaccinology that will ultimately be required to develop an effective HIV vaccine and meet the challenge of new and re-emerging pathogens. This can be easily achieved with the help of reverse vaccinology that uses the whole genome of the pathogen for the prediction of the surface proteins i.e. epitopes. The surface proteins will acts as candidate vaccines. Epitopes play an important role in development of a candidate vaccine. The major role played in immune system is by B and T lymphocyte. B cells are important in recognizing the epitopes of the antigens that can be identified by the paratopes of antibody. In some cases, T cells play a role in cell mediated immunity as the processed antigenic peptides interact with the T cell when they are presented in context of T cell. So the prediction of the epitopes of T and B cell plays an important role in determination of the candidate vaccine. The epitope prediction plays an important role in designing of epitope based vaccine.

The development of a highly effective AIDS vaccine will likely to depend on the success of designing immunogen that will elicit response to broadly neutralizing antibodies to naturally circulating strains of HIV- can be done by reverse vaccinology. Reverse vaccinology is a good approach for provoking the broadly neutralizing antibody response by identifying the particular specific epitopes i.e. surface proteins.

MATERIALS AND METHODS: In fulfilling the objectives of the project work, following steps were pursued;

1. Selection of proteins from HIV-1 genome database
2. Epitope prediction and selection
3. Homology modeling
4. Docking

1. **Retrieval of target sequences:** Selection of proteins from HIV-1 genome database [13]. Complete genome sequences of HIV-1 were downloaded from NCBI database. All proteins that are encoded by whole genome of HIV-1 were selected for further studies and their amino acid sequences were downloaded and saved in FASTA format. The following **table 1** depicts the attributes of selected proteins.

Name	Accession	Start	Stop	Gene Id	Locus	Locus Tag	Protein Product	Length
Envelope surface glycoprotein gp160, precursor	NC_001802.1	5771	8341	155971	env	HIV1gp8	NP_057856.1	856

2. **Epitope prediction and selection:** For the prediction of epitopes form the selected proteins web based program RANKPEP was used. The following steps of epitope prediction were based on the studies related to RANKPEP

   i. Home page of RANKPEP was opened- http://tools.immuneepitope.org/mhc.

Selection of home page depends on the prediction of the epitopes against MHC class I and MHC class II.

   ii. The amino acid sequence of the proteins which were selected from above step then pasted in the query window of RANKPEP. Selection of parameters like MHC source species, prediction method, and allele length was done.

   iii. Then the query was submitted to the RANKPEP database.

   iv. After this the result page was generated that contains different epitopes which were categorized on the basis of the percentile rank.

   v. Epitopes having highest percentile rank were selected for further studies.

3. **Homology modeling:** The ultimate goal of protein modeling is to predict a structure from its sequence with an accuracy that is comparable to the best results achieved experimentally. In addition, protein modeling is the only way to obtain structural information if experimental techniques fail. Many proteins are simply too large for NMR analysis and cannot be crystallized for X-ray diffraction. For this purpose, homology modeling of each predicted epitopes were done by MODELLER version 9.10. Modeller is a computer program that models three-dimensional structures of proteins and their assemblies by satisfaction of spatial restraints [14-17].

Amino acid sequence alignment of target and template proteins was derived using Modeller 9.10, a freely available tool for modeling. Structure refinement and model validation was done by energy minimization which was done by Swiss-PDBViewer and Ramachandran plot which was plotted using online server http://dicsoft1.physics.iisc.ernet.in/rp/

4. **Docking:** Molecular docking is the term used for computational schemes in which two molecules i.e. receptor and ligand, fit together in 3D space. It is initiated from folded protein chains and ligand conformations. There are three key ingredients in the docking:

   1. Representation of the system
   2. Conformational space search
   3. Ranking of potential solutions [18].

Docking can be achieved by probing the formation of inter-molecular complexes using various computational methods. Generally classical mechanics based force field methods are used in molecular docking. Monte Carlo and Molecular dynamics methods have also been employed to predict the best structural fit between protein and ligand molecules [19]. Molecular docking can also be used to test possible hypotheses before conducting costly laboratory experiments. The development of a vaccine would be facilitated by knowing what type of immune response is likely to be protective against infection and/or disease. Both IgG and IgA are protective at mucous membranes and protection can be achieved using relatively modest doses of NAbs that yield circulating levels achievable by active vaccination. Hence the broadly neutralizing antibodies which were isolated from HIV patients were used for docking with predicted epitopes; selected on their properties as [20];

- **2G12 (PDB ID: 1OM3)** [21]
- **B12 (PDB ID: 2NY7)** [22]
- **4E10 (PDB ID: 2FX7)** [23]
- **PG9 (PDB ID: 3U2S)** [24]

RESULTS AND DISCUSSION:

Vaccine design approach: Two essential elements required for preparation of an efficient vaccine design:

- The virus
- Host immune system.

The field has jumped from an early start using recombinant soluble antigen based upon the surface envelope glycoprotein (Env) gp120 to elicit antibody response, to focus on cytotoxic T cell (CTL)-based vaccine design [25, 26]. However, progress in two areas has galvanized the HIV-1 vaccine field into an unprecedented sense of purpose and activity. The isolation of a series of monoclonal antibodies (mAbs) that potently neutralize a broad spectrum of circulating HIV-1 strains, termed broadly neutralizing mAbs (bNmAb). Their existence testifies to the presence of highly conserved epitopes on the HIV-1 envelope glycoproteins (Env) and the ability of humans to make these responses [27, 28].

Epitope prediction by RANKPEP and modeling of selected epitopes: Server RANKPEP predicts and gives number of epitopes for selected protein but only those epitopes have been selected that have highest score value which was found to be above the predicted threshold. Following tables shows the list of the selected epitopes on the basis of highest percentile rank.

Table 1 shows the list of selected epitopes for ENV proteins of HIV-1 which targeted against MHC class I molecule showing epitope sequence, MHC class and percentile rank of respective epitope.

Table 2 shows the list of selected epitopes for ENV proteins of HIV-1 which targeted against MHC class II molecule showing epitope sequence, MHC class and percentile rank of respective epitope. Following table shows the list of predicted epitopes against MHC class I for Envelope surface glycoprotein gp160, precursor.

TABLE 2: SHOWS THE LIST OF SELECTED EPITOPES FOR ENV PROTEINS

Sr. No.	Epitope Sequence	MHC Class	MHC allele	Percentile Rank
1	PCVKLTPLCV	I	HLA-A*02:01,	32.40
2	NWLWYIKLFI	I	HLA-A*24:02,	31.04
3	QLTVWGIKQL	I	HLA-B*27:05,	29.55
4	HLLQLTVWGI	I	HLA-A*11:01,	26.76
5	AVGIGAL	I	HLA-B*40:02,	25.97
6	SLKPCVKLT	I	HLA-A*32:01	22.76
7	LWNWFNITNW	I	HLA-A*29:02,	48.36
8	QQHLLQLTVW	I	HLA-B*08:01,	17.69
9	KRRVVQREKR	I	HLA-A*68:02,	22.74
10	TQNFNMWKN	I	HLA-B*07:02,	12.78
11	MEWDREINNY	I	HLA-C*01:02,	15.53
12	MRDNWSERLY	I	HLA-G*01:04,	13.37
13	REINNYTSL	I	HLA-A*30:01	15.02

Following **table 3** shows the list of predicted epitopes against MHC class II for Envelope surface glycoprotein gp160, precursor.

The tables given below shows the selected epitopes which were targeted against MHC class I and MHC class II.

From the above results, it could be interpreted that selected epitopes were restricted by these MHC I alleles **HLA-A*02:01 HLA-A*29:02, HLA-B*27:05, HLA-B*08:01, HLA-A*68:02, HLA-B*07:02, HLA-C*01:02, HLA-G*01:04, HLA-A*30:01, HLA-A*68:02, HLA-A*24:02,HLA-B*27:05, HLA-A*11:01, HLA-B*40:02, HLA-A*32:01,**while in case of MHC II; the targeted alleles were found to be **HLA-DRB4*01:01, HLA-DPA1*01:03/DPB1*02:01, HLA-DRB1*01:04, HLA-DQA1*03:01/ DQB1* 03:02, HLA-DQA1*05:01/DQB1*03:01, HLA-DRB1*01:06, HLA-DRB1*01:16, HLA-DRB1*01:04, HLA-DRB1*01:17, HLA-DRB1*01:19, HLA-DRB1* 03:11, HLA-DRB1*03:35, HLA-DRB1* 04:71, HLA-DRB1*07:17.**

TABLE 3: SHOWS THE LIST OF PREDICTED EPITOPES AGAINST MHC CLASS II

Sr. No.	Epitope Sequence	MHC Class	MHC allele	Percentile Rank
1	LAEEEVVIR	II	HLA-DRB4*01:01, HLA-DPA1*01:03/DPB1*02:01, HLA-DRB1*01:04, HLA-DQA1*03:01/DQB1*03:02, HLA-DQA1*05:01/DQB1*03:01, HLA-DRB1*01:06, HLA-DRB1*01:16, HLA-DRB1*01:04, HLA-DRB1*01:17, HLA-DRB1*01:19, HLA-DRB1*03:11, HLA-DRB1*03:35, HLA-DRB1*04:71, HLA- DRB1*07:17.	33.33
2	MHEDIISLW	II		29.60
3	LLRAIEAQQ	II		26.37
4	AKWNNTLKQ	II		42.88
5	NWFNITNWL	II		31.27
6	LGAAGSTMG	II		32.54
7	YKYKVVKIE	II		64.70
8	FAILKCNNK	II		29.24
9	TTWMEWDRE	II		24.31
10	PISGQIRCS	II		27.89
11	PIHYCAPAG	II		25.44
12	VGIGALFLG	II		23.67
13	FFYCNSTQL	II		42.43
14	YAPPISGQI	II		33.18

The main objective of epitope prediction is to design a molecule that can replace an antigen in the process of either antibody production or antibody detection [12]. Identification of B cell and T cell epitope within protein antigens would aid in the rational development of an HIV subunit vaccine [29]. Ideally, such epitopes would be recognized by individuals with a variety of genetic background and would stimulate both T helper and cytotoxic T cell responses.

The major histocompatibility complex (MHC), a large genetic complex with multiple loci, is located on the short arm of chromosome 6. It has highly polymorphic human leucocyte antigen (HLA) genes. Loci within the MHC encode two major classes of membrane bound glycoproteins: class I and class II HLA molecules.

HLA class I molecules bind to endogenous antigenic epitopes and present them to CD8+ T lymphocytes, while HLA class II molecules present antigenic peptides to CD4+ T lymphocytes [30].

Homology Modeling: Modeler 9.10 was used for modeling of selected epitopes; every selected epitope have been modeled with by modeler. Modeler gave 5 best matches for selected epitope out of which best one is selected on the basis percentage identity and number of residues matching the template.

Table 3 shows list of predicted model for selected epitopes showing PDB ID of model that present in PDB data bank; percentage identity value and their energy value. The model of respective epitope was selected on the basis of lower energy value, highest percentage identity and depending on the number of amino acid matches the template.

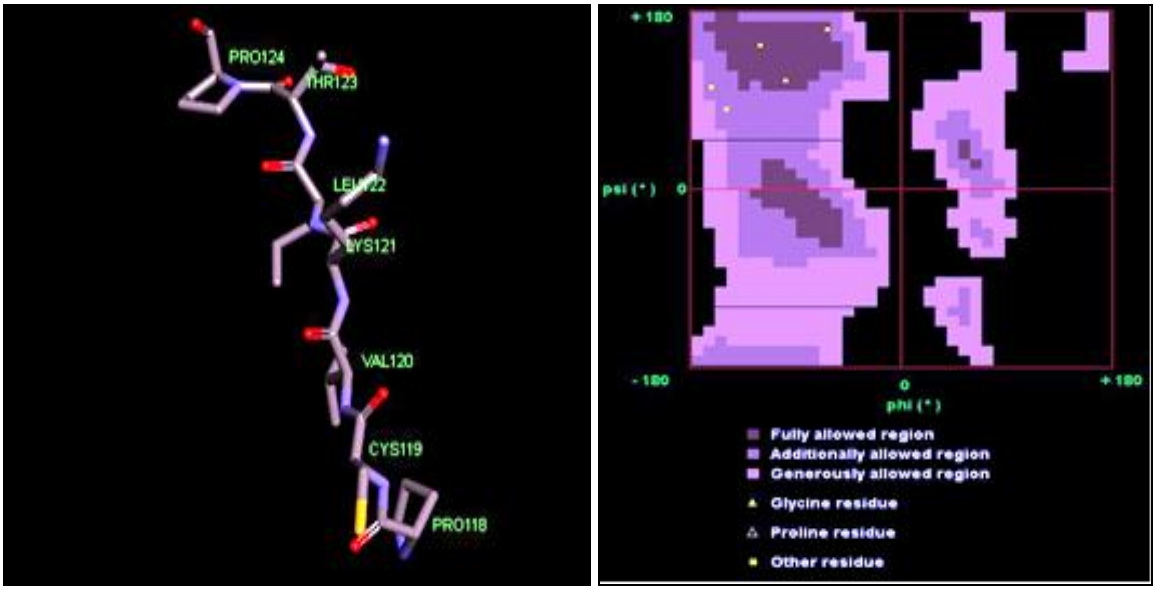
And their respective figure is given below the table giving the structure of model. Figure shows the structure of model; position of amino acids with their position number, name of amino acid, different color shows different groups present in side chain of amino acid residue. Their respective Ramachandran plot is given showing that amino acid present in allowed region which is most important for selection of epitope.

Ramachandran plot shows different colors which shows different regions for allowed and disallowed regions.

The List of predicted models of RANKPEP MHCI Env epitopes is given in the following **table 4** and their corresponding figures given below table.

TABLE 4: PREDICTED MODELS OF RANKPEP MHCI ENV EPITOPES

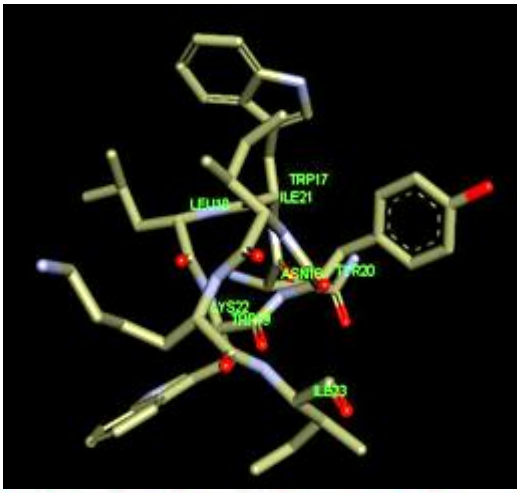
Sr. No.	Epitope No.	Epitope Sequence	PDB ID of Epitope Model	Position of Amino Acid	Percentage Identity	E-Value
1	Egp1	PCVKLTPLCV	3DNL	118-124	100%	3.04E-15
2	Egp2	NWLWYIKLFI	3G9R	17-23	96%	5.59E-9
3	Egp3	QLTVWGIKQL	2CMR	26-35	100%	6.82E-15
4	Egp4	HLLQLTVWGI	1AIK	564-571	100%	1.29E-13
5	Egp5	AVGIGAL	2ARI	1-7	100%	5.59E-9
6	Egp6	SLKPCVKLT	2QAD	115-123	97%	2.59E-14
7	Egp7	LWNWFNITNW	2PV6	8-17	100%	9.54E-9
8	Egp8	QQHLLQLTVW	2Z2T	562-571	97%	4.14E-12
9	Egp9	KRRVVQREKR	1MEQ	15-23	100%	1.68E-5
10	Egp10	TQNFNMWKN	2QAD	90-98	97%	2.59E-14
11	Egp11	MEWDREINNY	1AIK	630-639	100%	1.29E-13
12	Egp12	MRDNWSERLY	3DNL	475-482	100%	3.06E-15
13	Egp13	REINNYTSL	1AIK	633-641	100%	1.29E-13

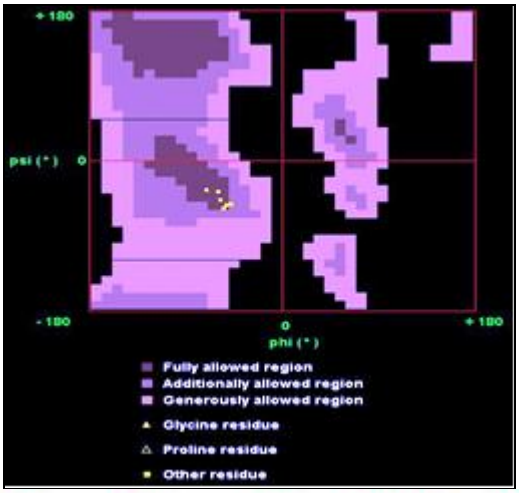


Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
CYS	0	0	0	0	1	0	0	1
LEU	0	1	0	1	0	0	0	1
LYS	0	0	0	0	1	0	0	1
THR	0	1	0	1	0	0	0	1
VAL	0	1	0	1	0	0	0	1
Total	0	3	0	3	2	0	0	5

Fully Allowed Region (3 residues) : 60.00 %
Additionally Allowed Region (2 residues) : 40.00 %
100.00 %

FIGURE 1: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp1 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).

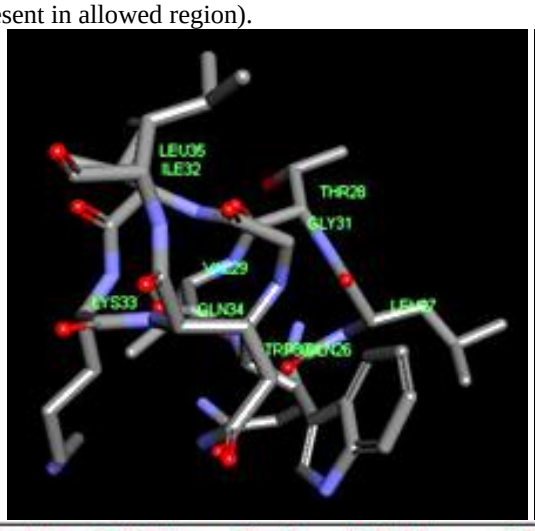


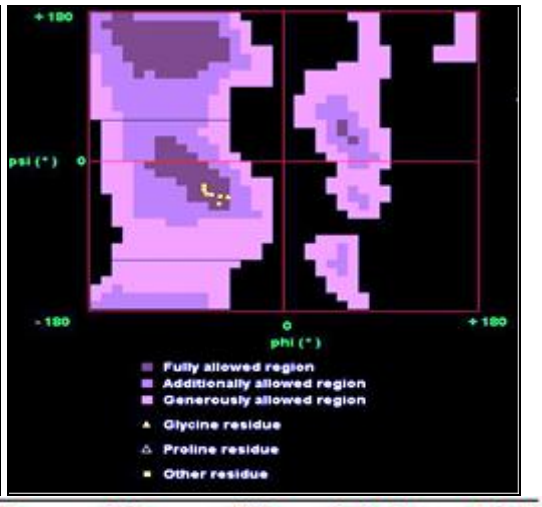


Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ILE	0	0	0	0	1	0	0	1
LEU	0	0	1	1	0	0	0	1
LYS	0	0	1	1	0	0	0	1
TRP	0	0	2	2	0	0	0	2
TYR	0	0	1	1	0	0	0	1
Total	0	0	5	5	1	0	0	6

Fully Allowed Region (5 residues) : 83.33 %
Additionally Allowed Region (1 residues) : 16.67 %
100.00 %

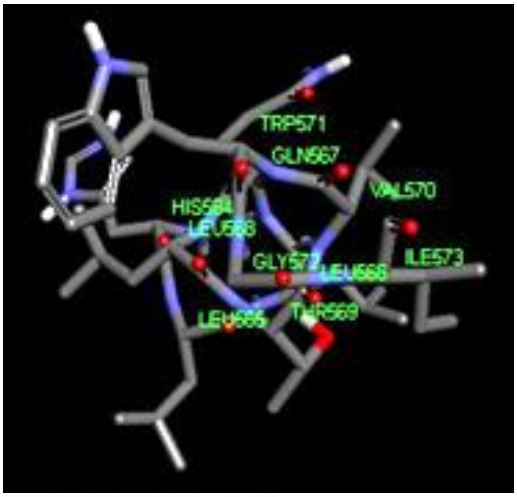
FIGURE 2: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp2 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).

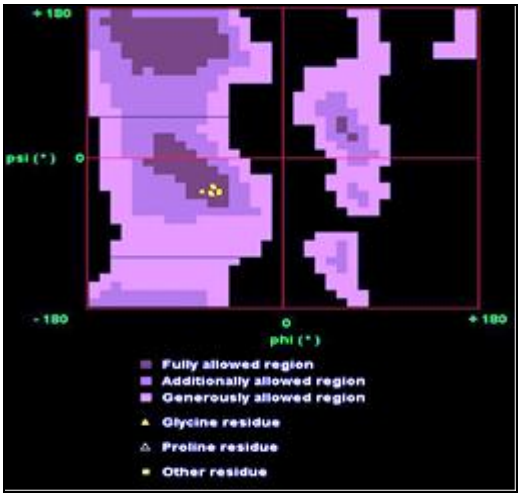




Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
GLN	0	0	1	1	0	0	0	1
GLY	0	0	1	1	0	0	0	1
ILE	0	0	1	1	0	0	0	1
LEU	0	0	1	1	0	0	0	1
LYS	0	0	1	1	0	0	0	1
THR	0	0	1	1	0	0	0	1
TRP	0	0	1	1	0	0	0	1
VAL	0	0	1	1	0	0	0	1
Total	0	0	8	8	0	0	0	8

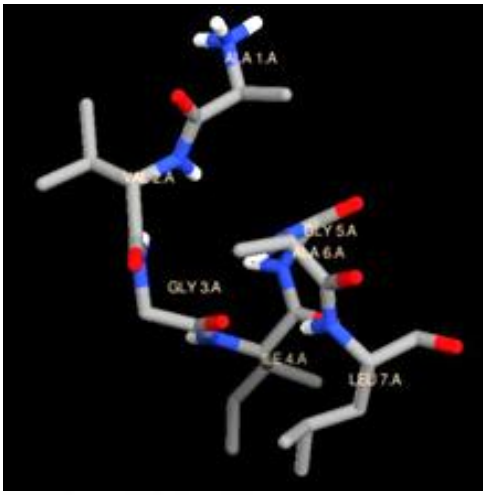
FIGURE 3: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp3 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).

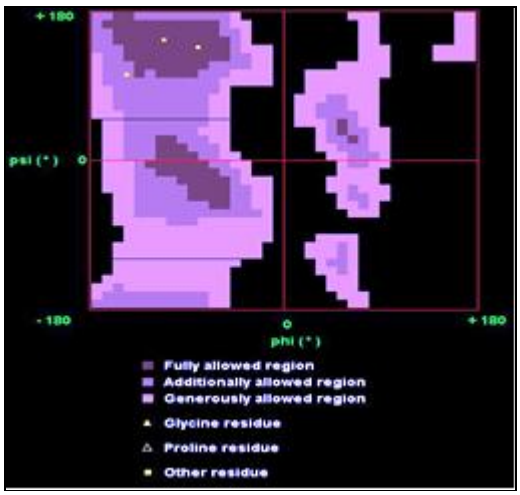




Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
GLN	0	0	1	1	0	0	0	1
GLY	0	0	1	1	0	0	0	1
LEU	0	0	3	3	0	0	0	3
THR	0	0	1	1	0	0	0	1
TRP	0	0	1	1	0	0	0	1
VAL	0	0	1	1	0	0	0	1
Total	0	0	8	8	0	0	0	8

FIGURE 4: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp4 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).





Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ASN	0	1	0	1	1	0	0	2
PHE	0	1	0	1	0	0	0	1
Total	0	2	0	2	1	0	0	3

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Fully Allowed Region (   2 residues)        :   66.67 %
Additionally Allowed Region (   1 residues) :   33.33 %
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                                              100.00 %
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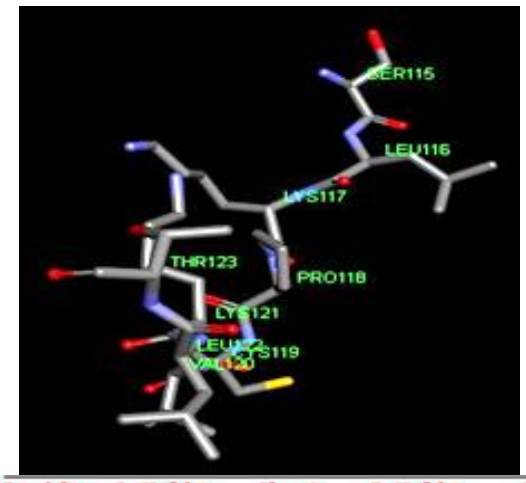
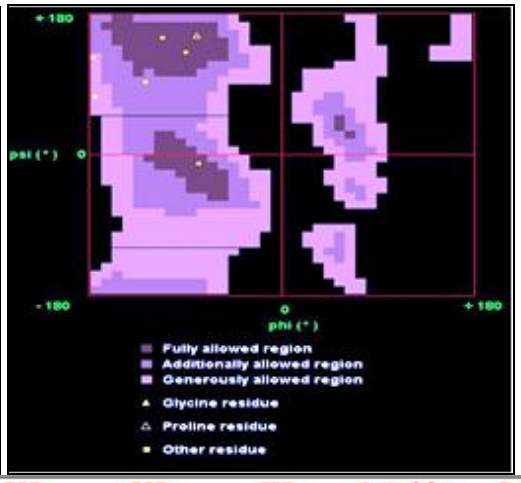
FIGURE 5: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp5 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).

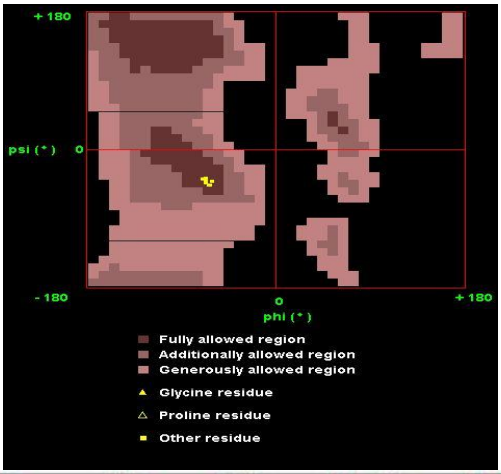




Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ASP	0	0	0	0	0	1	0	1
GLN	0	0	0	0	0	1	0	1
LEU	0	0	1	1	0	1	0	2
LYS	0	1	0	1	0	0	0	1
SER	0	0	1	1	1	0	0	2
TRP	0	0	1	1	0	0	0	1
Total	0	1	3	4	1	3	0	8

Fully Allowed Region (4 residues) : 50.00 %
Additionally Allowed Region (1 residues) : 12.50 %
Generously Allowed Region (3 residues) : 37.50 %
100.00 %

Figure 6: Predicted model and Ramachandran plot of Egp6 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).

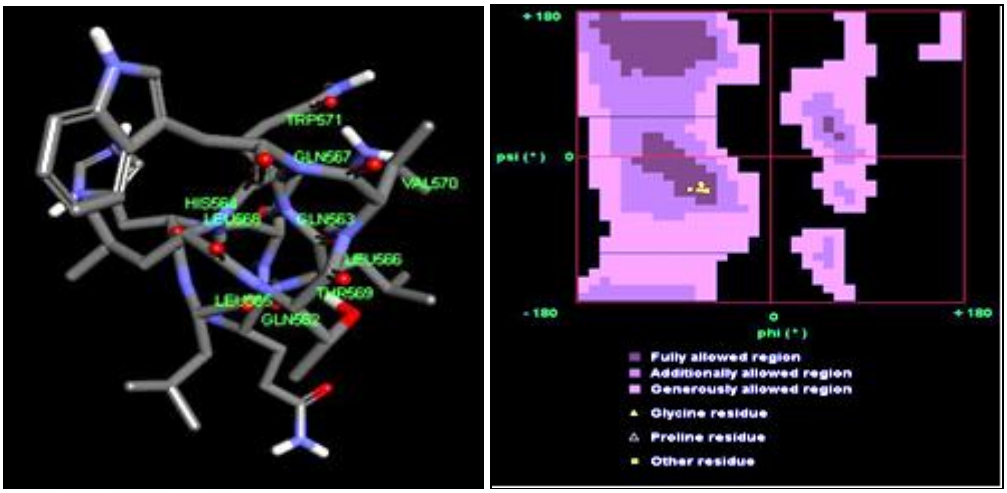


Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
CYS	0	0	1	1	0	0	0	1
LEU	0	0	0	0	1	1	0	2
LYS	0	2	0	2	0	0	0	2
PRO	0	1	0	1	0	0	0	1
VAL	0	0	0	0	0	1	0	1
Total	0	3	1	4	1	2	0	7

Fully Allowed Region (4 residues) : 57.14 %
Additionally Allowed Region (1 residues) : 14.29 %
Generously Allowed Region (2 residues) : 28.57 %
100.00 %

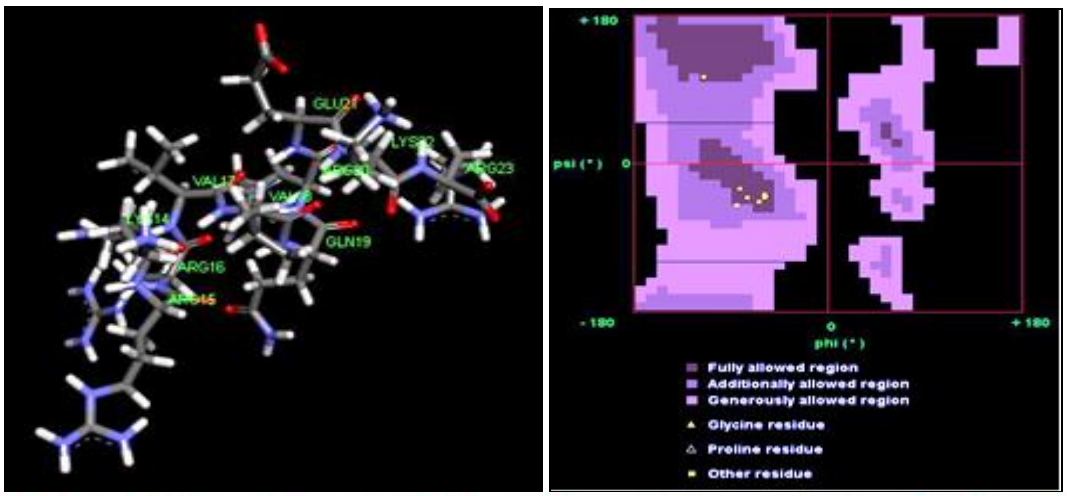
Alpha helical Region (1 residues) : 25.00 %
Beta sheet Region (3 residues) : 75.00 %
3-10 helical Region (0 residues) : 0.00 %
100.00 %

FIGURE 7: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp7 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).



Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ASN	0	0	3	3	0	0	0	3
ILE	0	0	1	1	0	0	0	1
PHE	0	0	1	1	0	0	0	1
THR	0	0	1	1	0	0	0	1
TRP	0	0	2	2	0	0	0	2
Total	0	0	8	8	0	0	0	8

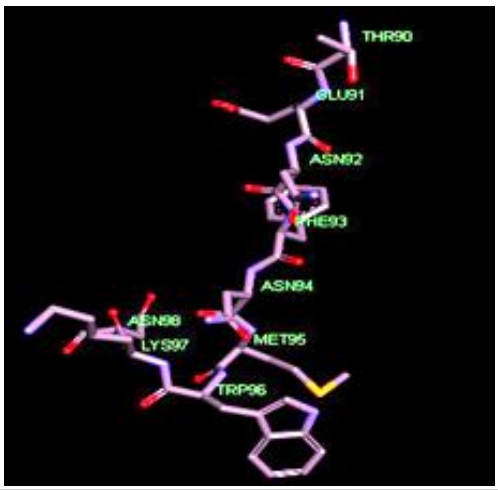
Figure 8: Predicted model and Ramachandran plot of Egp8 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).

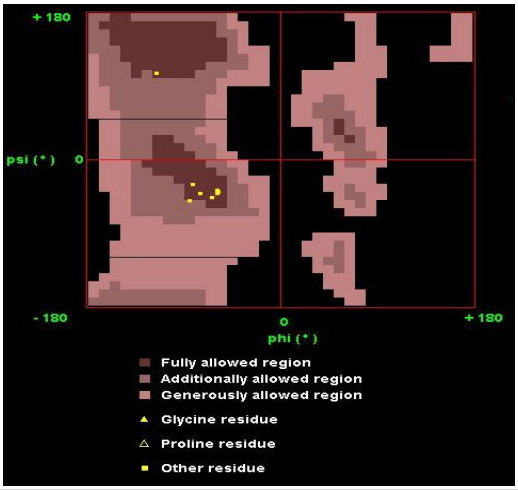


Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ASN	0	0	1	1	0	0	0	1
ILE	0	0	0	0	1	0	0	1
LEU	0	0	1	1	0	0	0	1
TRP	0	0	2	2	0	0	0	2
TYR	0	0	1	1	0	0	0	1
Total	0	0	5	5	1	0	0	6

Fully Allowed Region (5 residues) : 83.33 %
Additionally Allowed Region (1 residues) : 16.67 %
100.00 %

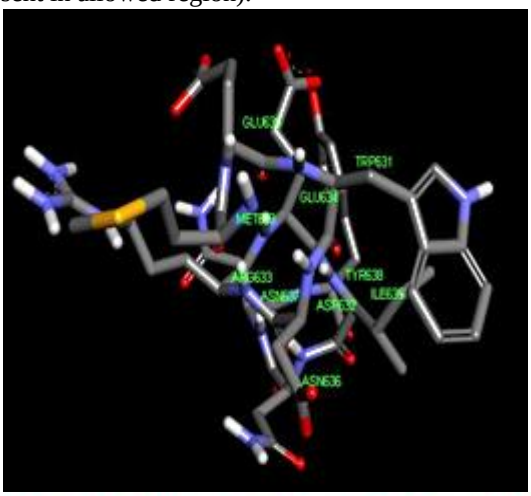
FIGURE 9: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp9 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).

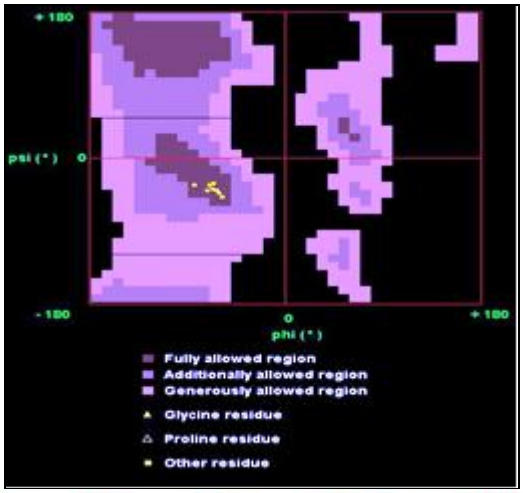




Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
GLN	0	0	2	2	0	0	0	2
HIS	0	0	1	1	0	0	0	1
LEU	0	0	3	3	0	0	0	3
THR	0	0	1	1	0	0	0	1
VAL	0	0	1	1	0	0	0	1
Total	0	0	8	8	0	0	0	8

FIGURE 10: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp10 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).



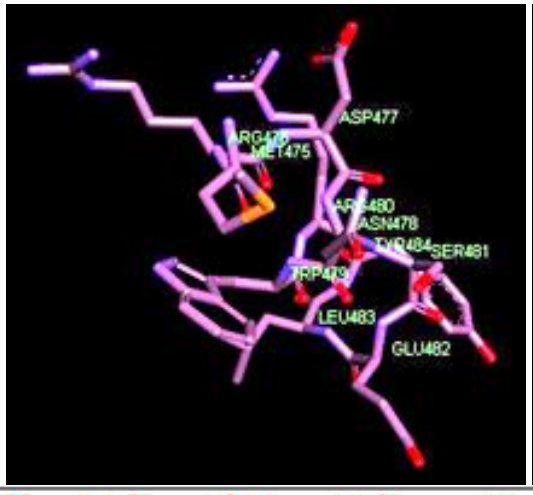


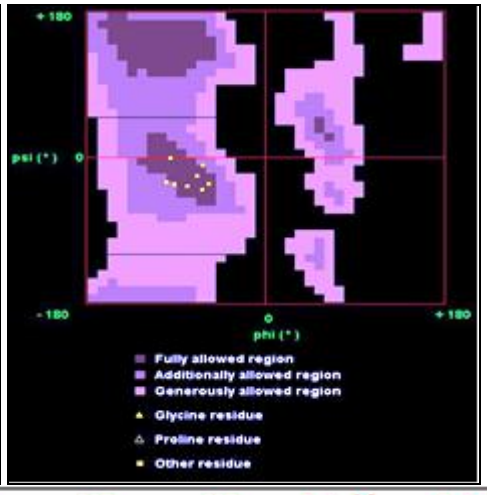
Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ARG	0	0	2	2	1	0	0	3
GLN	0	0	1	1	0	0	0	1
GLU	0	0	1	1	0	0	0	1
LYS	0	1	0	1	0	0	0	1
VAL	0	0	2	2	0	0	0	2
Total	0	1	6	7	1	0	0	8

Fully Allowed Region (7 residues)	:	87.50 %
Additionally Allowed Region (1 residues)	:	12.50 %
		100.00 %

Alpha helical Region (6 residues)	:	85.71 %
Beta sheet Region (1 residues)	:	14.29 %
3-10 helical Region (0 residues)	:	0.00 %
		100.00 %

FIGURE 11: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp11 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).



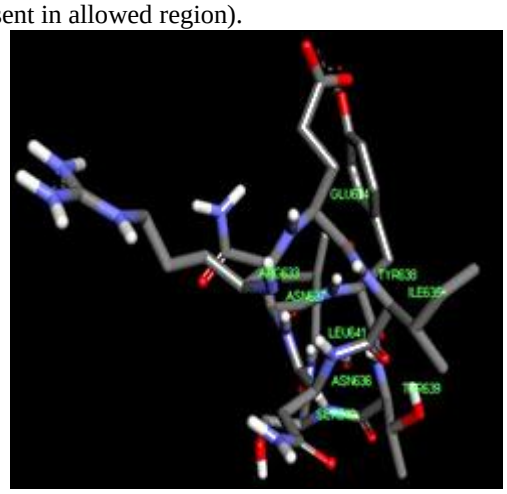


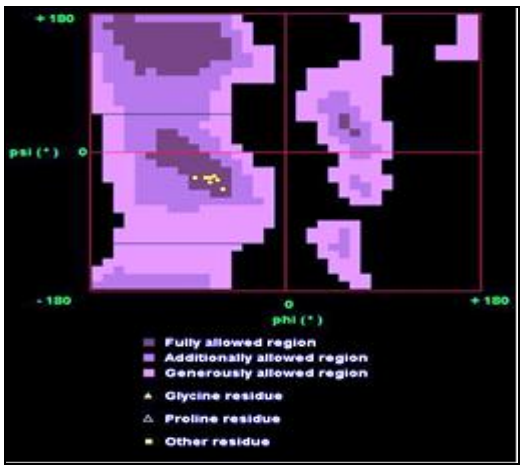
Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ARG	0	0	2	2	1	0	0	3
GLN	0	0	1	1	0	0	0	1
GLU	0	0	1	1	0	0	0	1
LYS	0	1	0	1	0	0	0	1
VAL	0	0	2	2	0	0	0	2
Total	0	1	6	7	1	0	0	8

Fully Allowed Region (7 residues) : 87.50 %
Additionally Allowed Region (1 residues) : 12.50 %
100.00 %

Alpha helical Region (6 residues) : 85.71 %
Beta sheet Region (1 residues) : 14.29 %
3-10 helical Region (0 residues) : 0.00 %
100.00 %

FIGURE 12: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp12 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).





Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ARG	0	0	1	1	0	0	0	1
ASN	0	0	2	2	0	0	0	2
ASP	0	0	1	1	0	0	0	1
GLU	0	0	2	2	0	0	0	2
ILE	0	0	1	1	0	0	0	1
TRP	0	0	1	1	0	0	0	1
Total	0	0	8	8	0	0	0	8

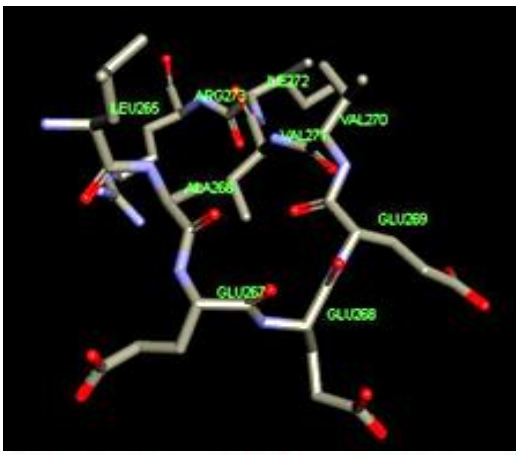
FIGURE 13: FIGURE PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp13 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).

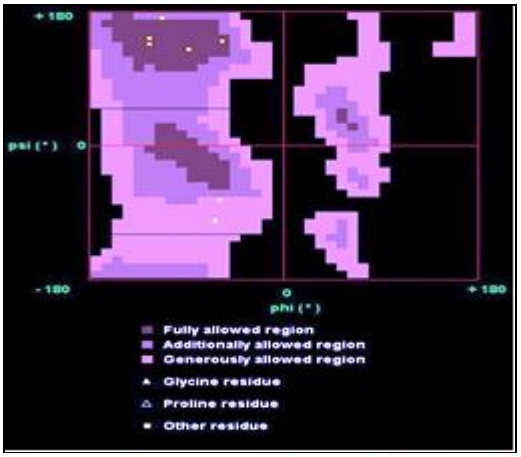
Table 5 shows list of predicted model for selected epitopes showing PDB ID of model that present in PDB data bank; percentage identity value and their energy value. The model of respective epitope was selected on the basis of lower energy value, highest percentage identity and depending on the number of amino acid matches the template.

The following table and figures shows the list of predicted models of RANKPEP MHCII Env epitopes.

TABLE 5: LIST OF PREDICTED MODELS OF RANKPEP MHCII Env EPITOPES

Sr. No.	Epitope No.	Epitope Sequence	PDB ID of Epitope Model	Position of Amino Acid	Percentage Identity	E-Value
1	Egp1	LAEEEVVIR	1G9M	265-273	90%	1.08E-15
2	Egp2	MHEDIISLW	3DNL	104-112	100%	3.06E-15
3	Egp3	LLRAIEAQQ	2CMR	14-22	100%	6.82E-15
4	Egp4	AKWNNTLKQ	1G9M	336-34	90%	1.08E-15
5	Egp5	NWFNITNWL	2PV6	10-18	100%	9.54E-9
6	Egp6	LGAAGSTMG	2ARI	13-21	100%	5.59E-9
7	Egp7	YKYKVVKIE	1G9M	485-492	90%	1.08E-15
8	Egp8	FAILKCNNK	1G9M	223-231	90%	1.08E-15
9	Egp9	TTWMEWDRE	1ENV	49-57	71%	1.61E-40
10	Egp10	PISGQIRCS	1G9M	438-446	99%	1.08E-15
11	Egp11	PIHYCAPAG	2NXY	214-222	90%	2.41E-151
12	Egp12	VGIGALFLG	2ARI	3-11	99%	5.59E-59
13	Egp13	FFYCNSTQL	2NXY	382-390	90%	2.41E-151
14	Egp14	YAPPISGQI	1G9M	435-554	90%	1.08E-15

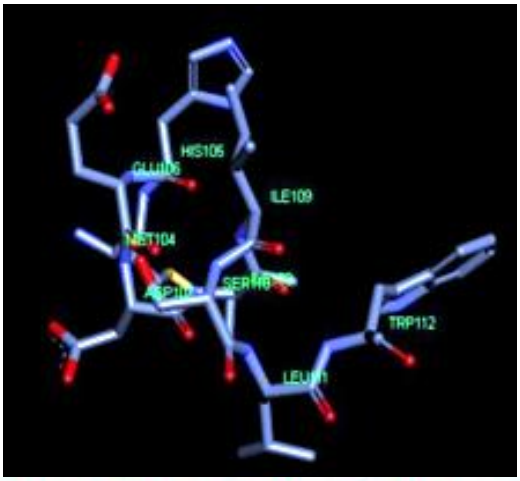


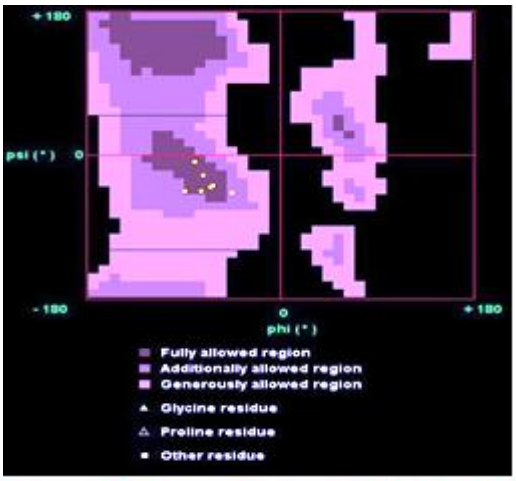


Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ALA	0	1	0	1	0	0	0	1
GLU	0	0	0	0	1	2	0	3
ILE	0	1	0	1	0	0	0	1
VAL	0	2	0	2	0	0	0	2
Total	0	4	0	4	1	2	0	7

Fully Allowed Region (4 residues) : 57.14 %
Additionally Allowed Region (1 residues) : 14.29 %
Generously Allowed Region (2 residues) : 28.57 %
100.00 %

FIGURE 14: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp1 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).

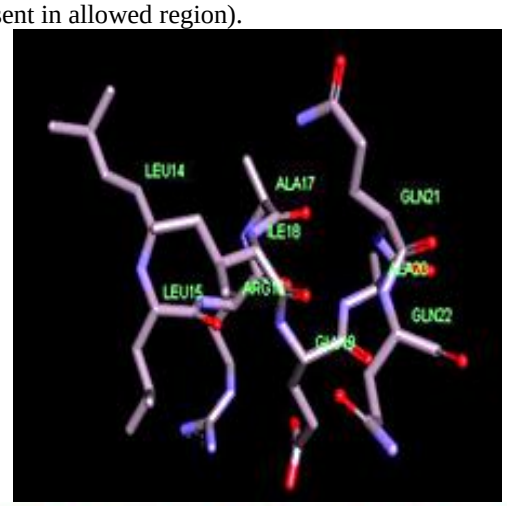


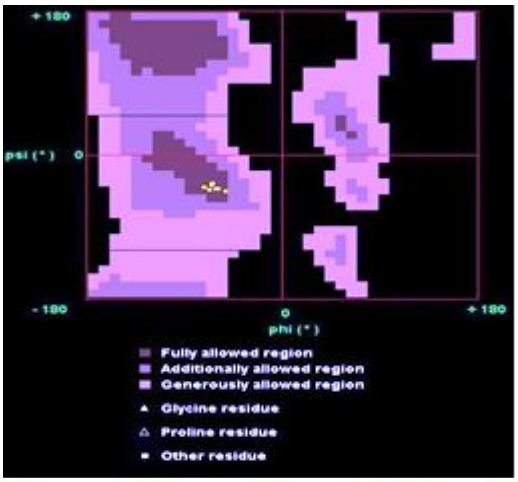


Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ASP	0	0	1	1	0	0	0	1
GLU	0	0	1	1	0	0	0	1
HIS	0	0	0	0	1	0	0	1
ILE	0	0	2	2	0	0	0	2
LEU	0	0	1	1	0	0	0	1
SER	0	0	1	1	0	0	0	1
Total	0	0	6	6	1	0	0	7

Fully Allowed Region (6 residues) : 85.71 %
Additionally Allowed Region (1 residues) : 14.29 %
100.00 %

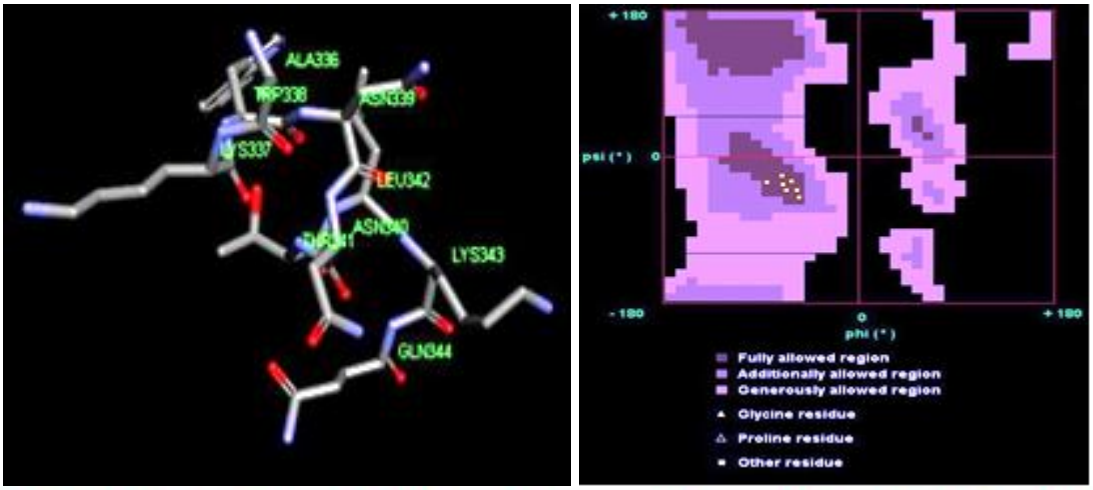
FIGURE 15: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp2 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).





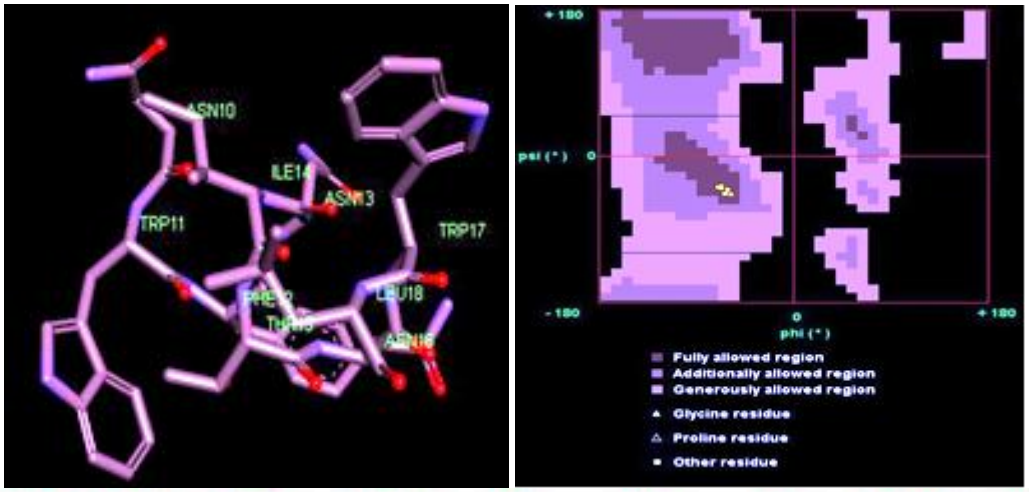
Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ALA	0	0	2	2	0	0	0	2
ARG	0	0	1	1	0	0	0	1
GLN	0	0	1	1	0	0	0	1
GLU	0	0	1	1	0	0	0	1
ILE	0	0	1	1	0	0	0	1
LEU	0	0	1	1	0	0	0	1
Total	0	0	7	7	0	0	0	7

FIGURE 16: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp3 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).



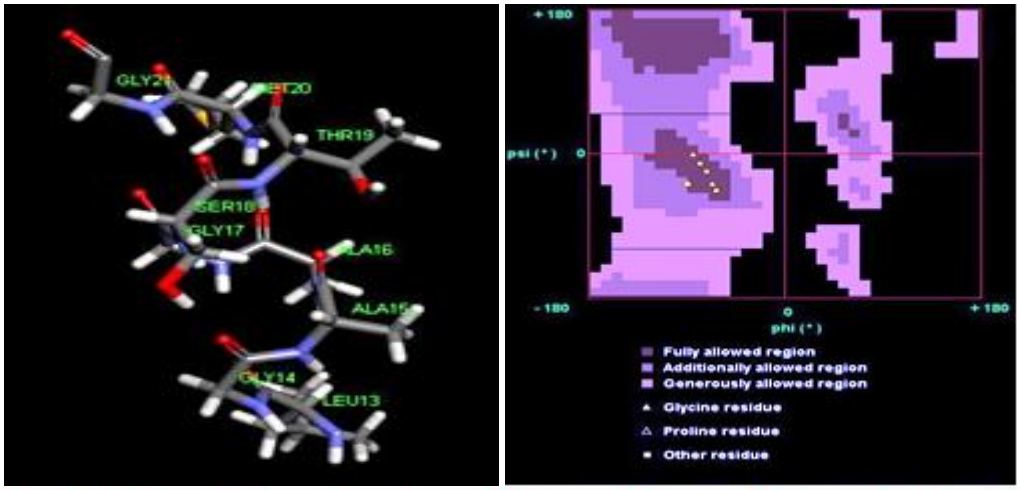
Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ASN	0	0	2	2	0	0	0	2
LEU	0	0	1	1	0	0	0	1
LYS	0	0	2	2	0	0	0	2
THR	0	0	1	1	0	0	0	1
TRP	0	0	1	1	0	0	0	1
Total	0	0	7	7	0	0	0	7

FIGURE 17: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp4 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).



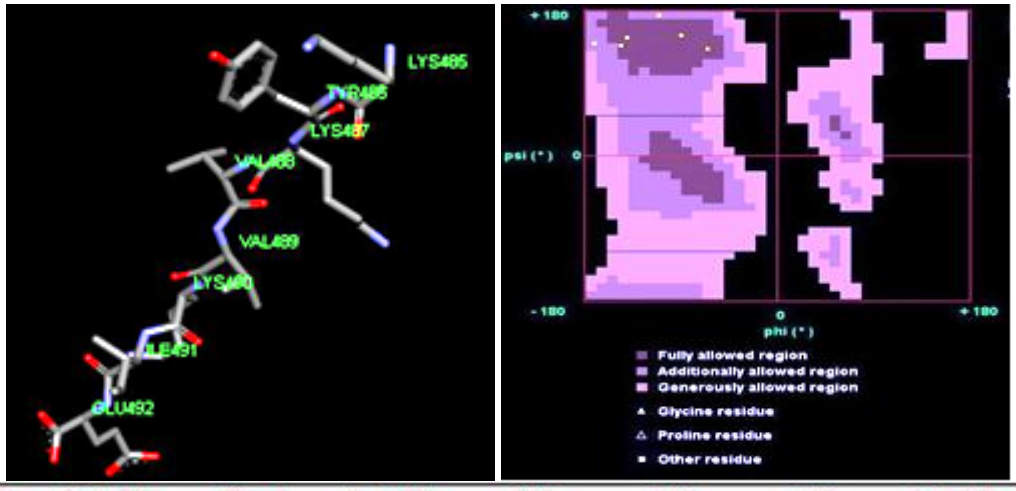
Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ASN	0	0	2	2	0	0	0	2
ILE	0	0	1	1	0	0	0	1
PHE	0	0	1	1	0	0	0	1
THR	0	0	1	1	0	0	0	1
TRP	0	0	2	2	0	0	0	2
Total	0	0	7	7	0	0	0	7

FIGURE 18: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp5 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).



Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ALA	0	0	2	2	0	0	0	2
GLY	0	0	2	2	0	0	0	2
MET	0	0	1	1	0	0	0	1
SER	0	0	1	1	0	0	0	1
THR	0	0	1	1	0	0	0	1
Total	0	0	7	7	0	0	0	7

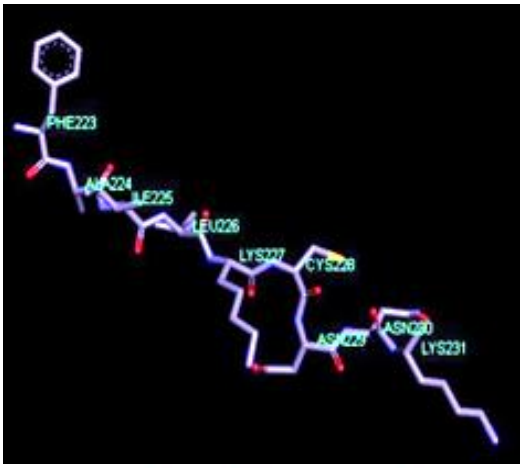
FIGURE 19: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp 6 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).

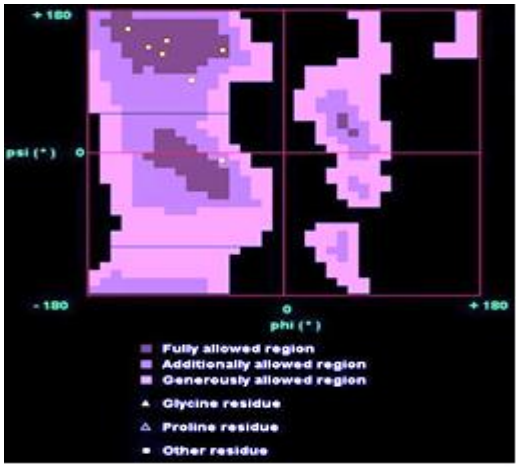


Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Tot.
ILE	0	1	0	1	0	0	0	1
LYS	0	1	0	1	1	0	0	2
TYR	0	0	0	0	1	0	0	1
VAL	0	2	0	2	0	0	0	2
Total	0	4	0	4	2	0	0	6

Fully Allowed Region (4 residues) : 66.67 %
Additionally Allowed Region (2 residues) : 33.33 %
100.00 %

FIGURE 20: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp7 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).

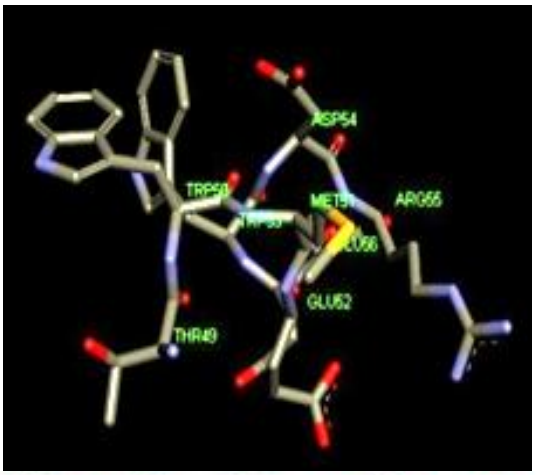


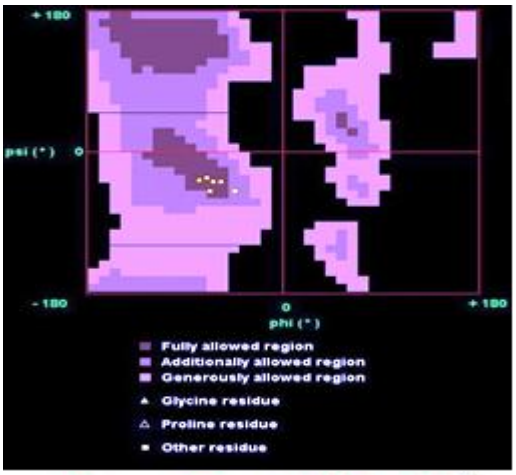


Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ALA	0	1	0	1	0	0	0	1
ASN	0	1	0	1	1	0	0	2
CYS	0	0	0	0	1	0	0	1
ILE	0	1	0	1	0	0	0	1
LEU	0	1	0	1	0	0	0	1
LYS	0	1	0	1	0	0	0	1
Total	0	5	0	5	2	0	0	7

Fully Allowed Region (5 residues) : 71.43 %
Additionally Allowed Region (2 residues) : 28.57 %
100.00 %

FIGURE 21: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp8 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).

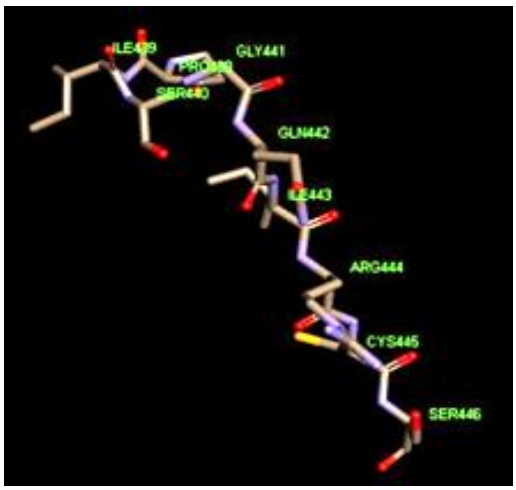


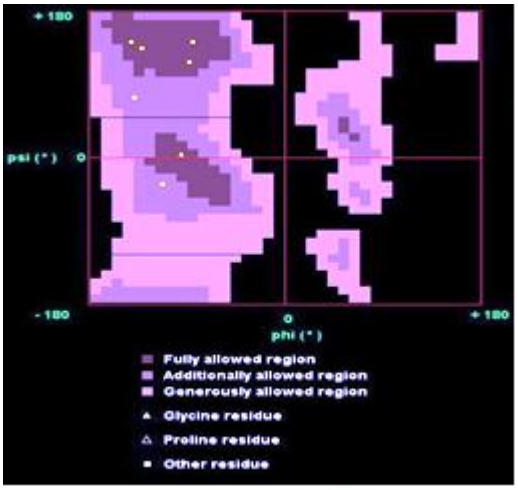


Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ARG	0	0	1	1	0	0	0	1
ASP	0	0	0	0	1	0	0	1
GLU	0	0	1	1	0	0	0	1
MET	0	0	1	1	0	0	0	1
TRP	0	0	2	2	0	0	0	2
Total	0	0	5	5	1	0	0	6

Fully Allowed Region (5 residues) : 83.33 %
Additionally Allowed Region (1 residues) : 16.67 %
100.00 %

FIGURE 22: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp9 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).



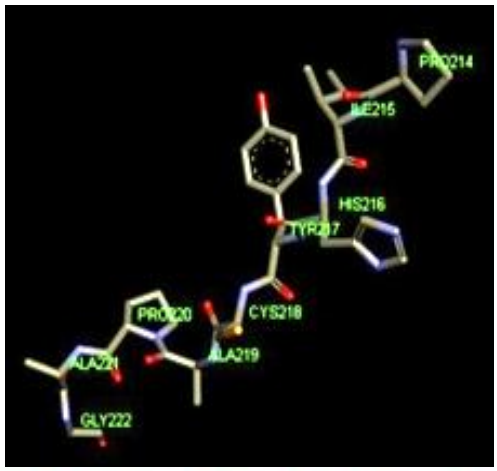


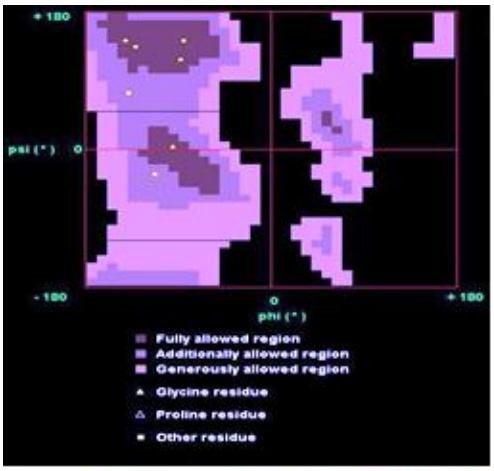
Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ARG	0	1	0	1	0	0	0	1
CYS	0	1	0	1	0	0	0	1
GLN	0	0	0	0	1	0	0	1
GLY	0	0	1	1	0	0	0	1
ILE	0	1	0	1	1	0	0	2
SER	0	1	0	1	0	0	0	1
Total	0	4	1	5	2	0	0	7

Fully Allowed Region (5 residues) : 71.43 %
Additionally Allowed Region (2 residues) : 28.57 %
100.00 %

Alpha helical Region (1 residues) : 20.00 %
Beta sheet Region (4 residues) : 80.00 %
3-10 helical Region (0 residues) : 0.00 %
100.00 %

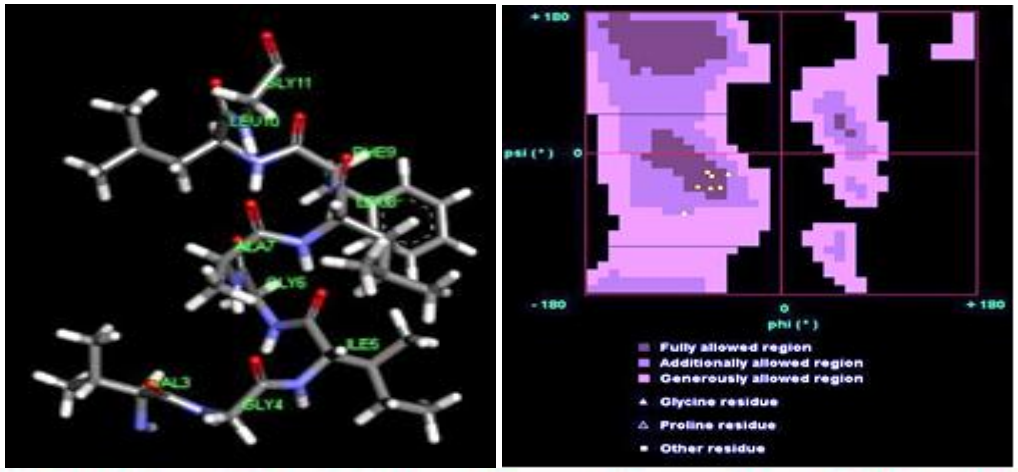
FIGURE 23: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp10 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).





Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ALA	0	2	0	2	0	0	0	2
CYS	0	1	0	1	0	0	0	1
HIS	0	1	0	1	0	0	0	1
ILE	0	1	0	1	0	0	0	1
PRO	0	1	0	1	0	0	0	1
TYR	0	1	0	1	0	0	0	1
Total	0	7	0	7	0	0	0	7

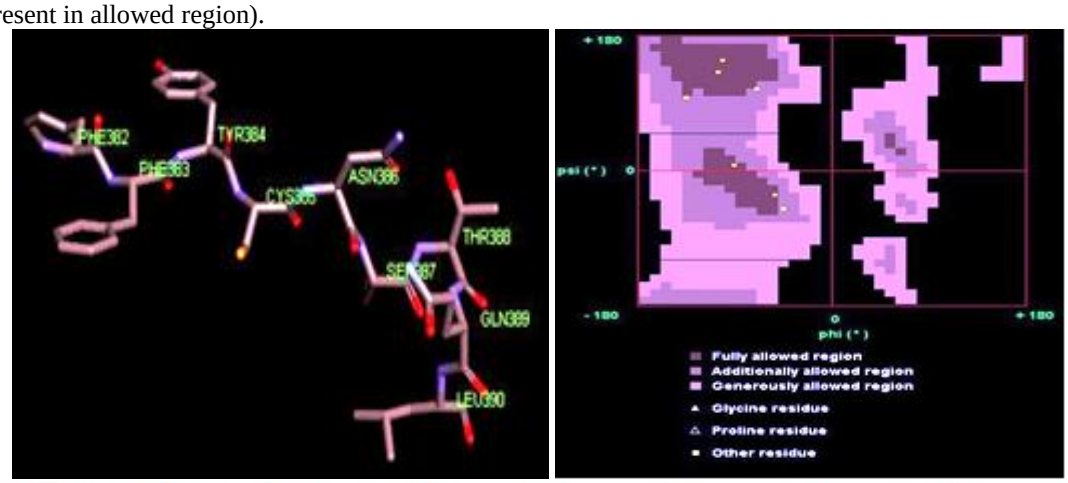
FIGURE 24: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp11 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).



Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ALA	0	0	1	1	0	0	0	1
GLY	0	0	0	0	2	0	0	2
ILE	0	0	1	1	0	0	0	1
LEU	0	0	2	2	0	0	0	2
PHE	0	0	1	1	0	0	0	1
Total	0	0	5	5	2	0	0	7

Fully Allowed Region (5 residues) : 71.43 %
Additionally Allowed Region (2 residues) : 28.57 %
100.00 %

FIGURE 25: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp12 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).

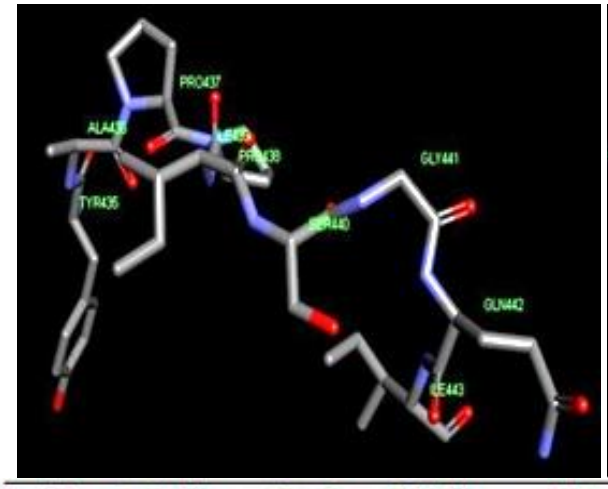


Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ASN	0	0	0	0	1	0	0	1
CYS	0	1	0	1	0	0	0	1
GLN	0	0	1	1	0	0	0	1
PHE	0	1	0	1	0	0	0	1
SER	0	0	1	1	0	0	0	1
THR	0	0	0	0	1	0	0	1
TYR	0	0	0	0	1	0	0	1
Total	0	2	2	4	3	0	0	7

Fully Allowed Region (4 residues) : 57.14 %
Additionally Allowed Region (3 residues) : 42.86 %
100.00 %

Alpha helical Region (2 residues) : 50.00 %
Beta sheet Region (2 residues) : 50.00 %
3-10 helical Region (0 residues) : 0.00 %
100.00 %

FIGURE 26: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp13 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).



Residue	L-Helix	Sheet	R-Helix	FAR	AAR	GAR	Outside	Total
ALA	0	1	0	1	0	0	0	1
GLN	0	0	0	0	1	0	0	1
GLY	0	0	1	1	0	0	0	1
ILE	0	0	0	0	1	0	0	1
PRO	0	2	0	2	0	0	0	2
SER	0	1	0	1	0	0	0	1
Total	0	4	1	5	2	0	0	7

Fully Allowed Region (5 residues) : 71.43 %
Additionally Allowed Region (2 residues) : 28.57 %
100.00 %

Alpha helical Region (1 residues) : 20.00 %
Beta sheet Region (4 residues) : 80.00 %
3-10 helical Region (0 residues) : 0.00 %
100.00 %

FIGURE 27: PREDICTED MODEL AND RAMACHANDRAN PLOT OF Egp14 (Figure shows the model of predicted structure of selected epitope and Ramachandran plot of that selected epitope shows that the amino acids present in epitope are found to be present in allowed region).

From table 3 epitopes sequence of Egp1, Egp11 and Egp13 targeting MHC I were found to be 100% similar with the template having E-value of 3.04E-15, 1.29E-13 and 1.49E-13 respectively while that of Egp2 and Egp10 targeting MHC II epitopes were 100% and 99% similar with the template having E- value of 3.08E-15 and 1.08E-15 respectively was given in Table 5.

Docking results of predicted B-cell based epitopes: Docking was done with help Autodock 4. It gives 10 best conformations according to docked energy. Out of best one selected on the basis of least docked score in KJ/mol.

Table 6 shows attributes of docking results of selected epitopes for class MHC I molecule against selected antibodies with respective docked score.

The docking results are of docking results of RANKPEP MHC I Env epitopes.

TABLE 6: DOCKING RESULTS OF RANKPEP MHC I Env EPITOPES

Sr. No.	Epitope	Antibody	Run	Lowest binding/ docked energy
1.	Egp1	2G12	9	-8.26
		4E10	5	-4.98
		B12	6	3266.83
		PG9	6	-5.29

2.	Egp2	2G12	6	78.08
		4E10	6	0.03
		B12	7	26142.44
		PG9	7	1970.34
3.	Egp3	2G12	7	41.38
		4E10	7	1.21
		B12	7	44808.19
		PG9	7	3974.06
4.	Egp4	2G12	7	91.02
		4E10	7	12.30
		B12	8	72303.59
		PG9	8	5229.02
5.	Egp5	2G12	8	3.85
		4E10	8	3.86
		B12	8	20.66
		PG9	8	2.75
6	Egp6	2G12	8	2935.51
		4E10	8	9.00
		B12	8	112872.30
		PG9	8	17.71
7	Egp7	2G12	9	256.35
		4E10	9	24.64
		B12	9	56633.02
		PG9	9	4534.17
8	Egp8	2G12	9	73.48
		4E10	9	38.79
		B12	9	79744.03
		PG9	9	25912.84
9	Egp9	2G12	9	1.31e+06
		4E10	9	1.79e+06
		B12	9	1.28e+06
		PG9	9	1.41e+06
10	Egp10	2G12	9	1.32e+06
		4E10	10	1.14e+06
		B12	10	1.78e+06
		PG9	10	1.41e+06

Interaction of epitope Egp1- antibody 2G12

Interaction of epitope Egp2- antibody

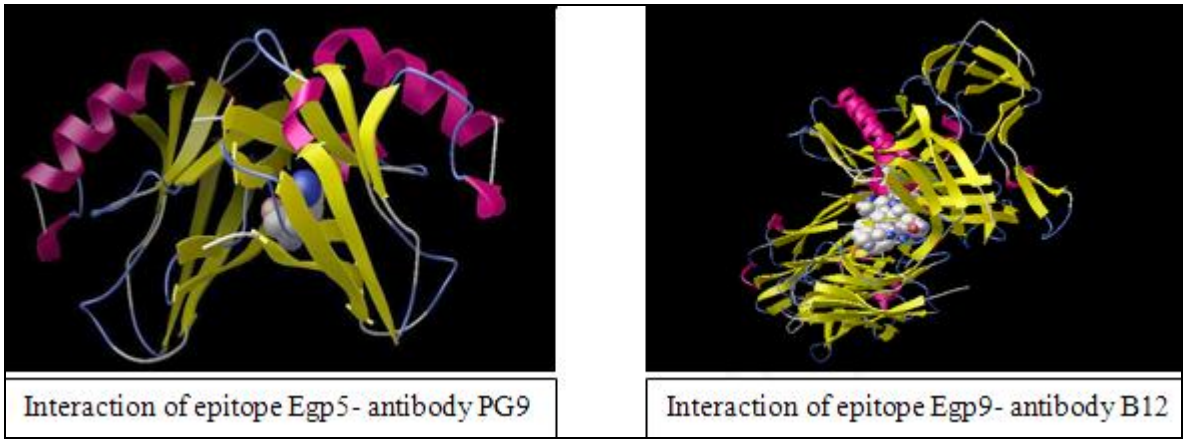


FIGURE 28: INTERACTION OF ANTIBODIES AND RESPECTIVE ANTIGENS. HERE SMALL MOLECULE IN CENTRE REPRESENTS SELECTED EPITOPES AND LARGE MOLECULE IS THE RESPECTIVE ANTIBODY.

Table 6 shows attributes of docking results of selected epitopes for class II MHC molecule against selected antibodies with respective docked score.

The following **table 7** and figures shows docking results of RANKPEP MHC II Env epitopes.

TABLE 7: DOCKING RESULTS OF RANKPEP MHC II ENV EPITOPES

Sr. No.	Epitope	Antibody	Run	Lowest binding/ docked energy
1.	Egp1	2G12	3	933.12
		4E10	10	24.41
		B12	9	130814.59
		PG9	10	14565.02
2.	Egp2	2G12	9	408.64
		4E10	3	44.50
		B12	4	96865.95
		PG9	10	12548.71
3.	Egp3	2G12	2	600.15
		4E10	1	17.25
		B12	5	137661.62
		PG9	9	26177.09
4.	Egp4	2G12	5	819.59
		4E10	5	6.43
		B12	2	114018.08
		PG9	6	39519.21
5.	Egp5	2G12	9	16.21
		4E10	2	0.06
		B12	9	27611.94
		PG9	1	141.38
6.	Egp6	2G12	8	2.25e+06
		4E10	1	1.1e+06
		B12	7	2.48e+06
		PG9	3	2.13e+06
7	Egp7	2G12	5	3.07e+06
		4E10	6	2.99e+06
		B12	7	3.29e+06
		PG9	3	3.28e+06

8	Egp8	2G12	6	1004.80
		4E10	2	78.23
		B12	9	86539.26
		PG9	3	23171.59
9	Egp9	2G12	9	229014.11
		4E10	2	134113.98
		B12	6	569331.44
		PG9	5	329988.88
10	Egp10	2G12	9	781767.31
		4E10	2	672732.50
		B12	6	1.06e+06
		PG9	4	798152.38
11	Egp11	2G12	5	80.33
		4E10	1	2.42
		B12	10	15686.97
		PG9	4	1069.22
12	Egp12	2G12	5	1.67e+06
		4E10	6	1.40e+06
		B12	7	2.01e+06
		PG9	3	1.57e+06
13	Egp13	2G12	6	479968.59
		4E10	2	397519.16
		B12	9	851523.50
		PG9	3	497579.34
14	Egp14	2G12	9	122.80
		4E10	2	33.23
		B12	6	44675.31
		PG9	5	12450.32

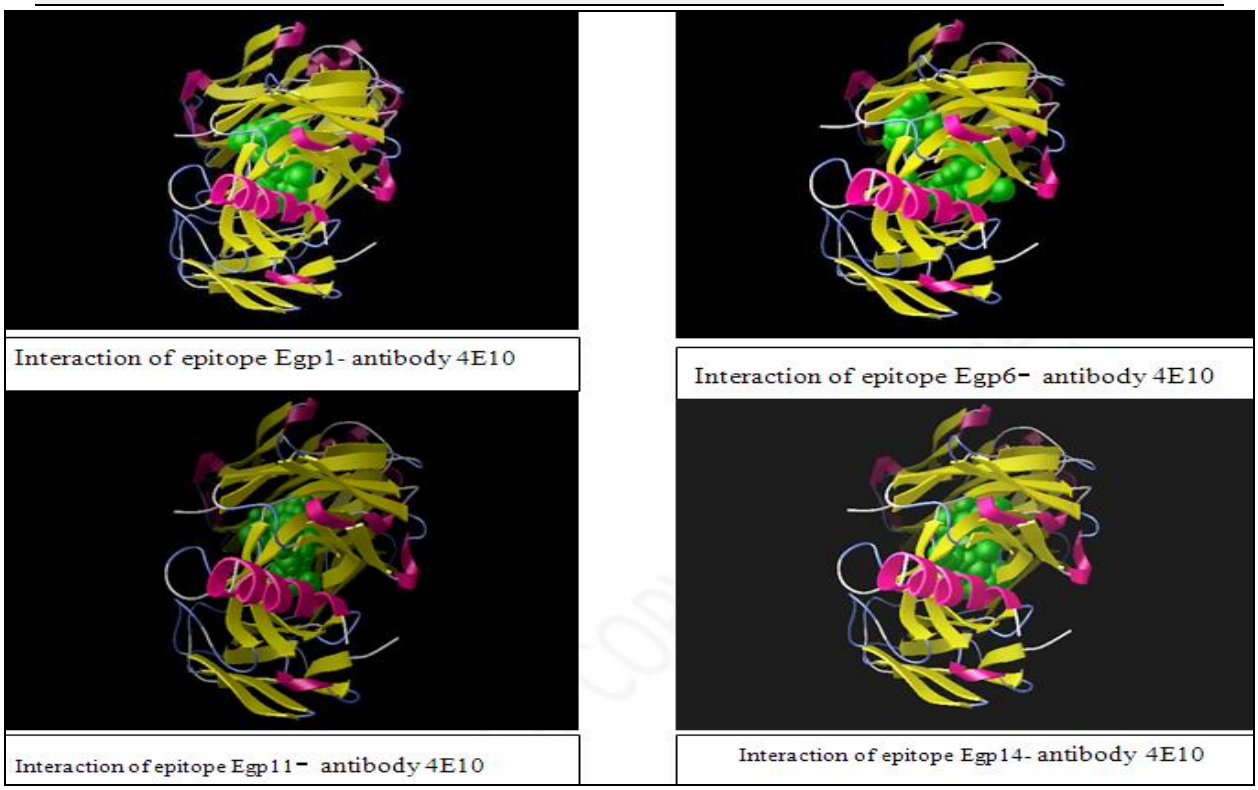


FIGURE 29: INTERACTION OF ANTIGEN AND RESPECTIVE ANTIBODIES. HERE SMALL MOLECULE IN CENTRE REPRESENTS SELECTED EPITOPES AND LARGE MOLECULE IS THE RESPECTIVE ANTIBODY.

To optimize the activity of the predicted epitopes; these epitopes were docked against the selected antibodies. For each docking, the lowest energy docked structure was selected from their respective runs which were shown in above table and respective figure shows the significant interaction of each epitope and the selected antibody. In case of MHC I, table shows all epitopes have least docked energy for 4E10 antibody except Egp1, Egp5, Egp9 have least docked energy for 2G12, PG9 and B12 respectively while in case of MHC II the given table shows all selected epitopes have least docked energy for 4E10 antibody. Egp1, Egp22, Pr6, Gp7, Gp14 of MHC I and Egp11, Pr3, Pr4, Gp11 of MHC II showed least docked score -8.26, 0.03, -0.59, -2.14, 3.79,-0.75 2.42, 7.59, -5.32 respectively.

CONCLUSION: The development of a highly effective AIDS vaccine will likely depend on success in designing immunogens that elicit broadly neutralizing antibodies to naturally circulating strains of HIV-1 and also stimulate the cell mediated immune response for the complete eradication of the HIV infection [28]. Hence, the present work gives the spotlight on developing an efficient candidate vaccine that is able to stimulate both immune responses.

The present work focuses on the development of vaccine that is able to stimulate humoral immune response hence B-cell epitope vaccines. It was found that all epitopes were targeting multiple MHC alleles. Docking was done with selected antibodies which were isolated from HIV infected patient to know their interaction. These antibodies were selected on the basis of their characteristic property of targeting specific regions on the HIV-1 surface.

Four antibodies were selected for docking 2G12 which targets glycan specific regions on the HIV envelop proteins, 4E10 targets membrane proximal domain and lipid region of envelop, B12 targets CD4 binding sites of HIV envelop while PG9 targets V1/V2 peptide glycan region of the envelop. As these are the most important regions on the surface of HIV-1 that are required for causing infection to human as they interact with hosts receptor. Hence blockage of these proteins could prevent infection of HIV-1 to host.

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