



Investigation of the interaction of allergens of *Glycine max* with IgE-antibody for designing of peptidomimetics based anti-allergen

Vishvanath Tiwari*, Debarghya Mitra, Monalisa Tiwari

Department of Biochemistry, Central University of Rajasthan, Bandarsindri, Ajmer 305817, India

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ABSTRACT

Allergen induced IgE dependent type I hypersensitivity is the main cause of the allergy, which would be a burden on medical setup in coming years. Allergens of *Glycine max* have been isolated, and their disease relationships are documented. Therefore, it becomes important to investigate the interaction of different allergens of *Glycine max* with IgE and also screen suitable therapeutics to prevent this interaction. The amino acid sequences of all allergens of *Glycine max* and their isoallergens have been taken, and 3D structure of allergens (Gly m 3, Gly m 4, Gly m 5, Gly m 6 and Gly m 8) and their isoallergens were generated using Modeller v9.17. The modeled structures were further validated using PSVS, ProSA, RAMPAGE, and PDBsum. HL domain of Fab region of human IgE (PDBID: 2R56) was generated using UCSFchimera. The HL domain was minimized by Schrodinger software using the OPLS 2005 force field. SiteMap identified epitope binding site of the minimized domain. All the predicted epitopes of different allergens were docked to the binding site of HL domain using the Patchdock server. We have also designed a peptidomimetics based inhibitor targeted at interaction interface of Gly m8 and IgE, using *in-silico* virtual screening, molecular mechanics, and molecular dynamics simulation studies. These studies identified BDE32166344 ((N-(1-([1-(1-aminocyclopentanecarbonyl)-3-hydroxypyrrolidin-3-yl)methyl]piperidin-4-yl)acetamide) as a peptidomimetics based lead with binding energy of -72.77 kcal/mol. Therefore, the present study investigates the interaction between different Gly m allergens and IgE antibody and identifies peptidomimetics based lead that might be developed as a suitable therapeutics against allergy caused by allergen of *Glycine max*.

1. Introduction

Allergy is an overreaction of the immune system against antigen or molecules, which are otherwise considered harmless. Allergen induces IgE dependent type I hypersensitivity and is the leading cause of allergy in an individual. They indeed have grown in number with many allergens having been isolated from plants and animal alike. Allergens have evolved along with time and now have a much more crucial influence on human health alongside climate change [20]. It is responsible for a number of varied symptoms extending from boils, rashes, eczema, asthma and in some instances violent anaphylactic shocks leading to death. Not always life-threatening but allergies are no less a grave danger than any disease. Allergy can be contributed to a number of sources that range from plants, animals, and even dust. Minuscule in size, allergens have been identified as an emerging burden upon the health economy across not only developing countries but also developed countries as individuals afflicted with allergy have to carry on with medications throughout their life. Several methods aimed at

curbing this menace have been described [35]. Owing to the unique identification of different forms of allergens and their varied sources, to streamline the nomenclature of these allergens, the International Union of Immunological Societies (IUIS) has defined the nomenclature of allergens identified and has categorically listed them on allergen database www.allergen.org. [39].

Among the total number of listed and identified allergens around the world, nearly all the pollen allergens are ambiguously distributed in 29 protein families among the 2615 seed plant families [5]. The maximum number of allergens have been isolated from plants and range from grapes to climbers. Not only the plants but their products are equally susceptible to sensitizing Type I hypersensitivity among individuals [5]. Several allergen structures have been made available in the Protein Data Bank [4,19,25,32]. The allergenicity can be attributed in most cases to the structural aspects of the allergen. Allergens also have various isoforms, termed as isoallergens that show nearly 70% sequence similarity with the allergen and similar cross-reactivity with IgE. Till date, only two-documented interaction [23,31] studies

* Corresponding author.

E-mail addresses: vishvanath7@yahoo.co.in, vishvanath@curaj.ac.in (V. Tiwari).

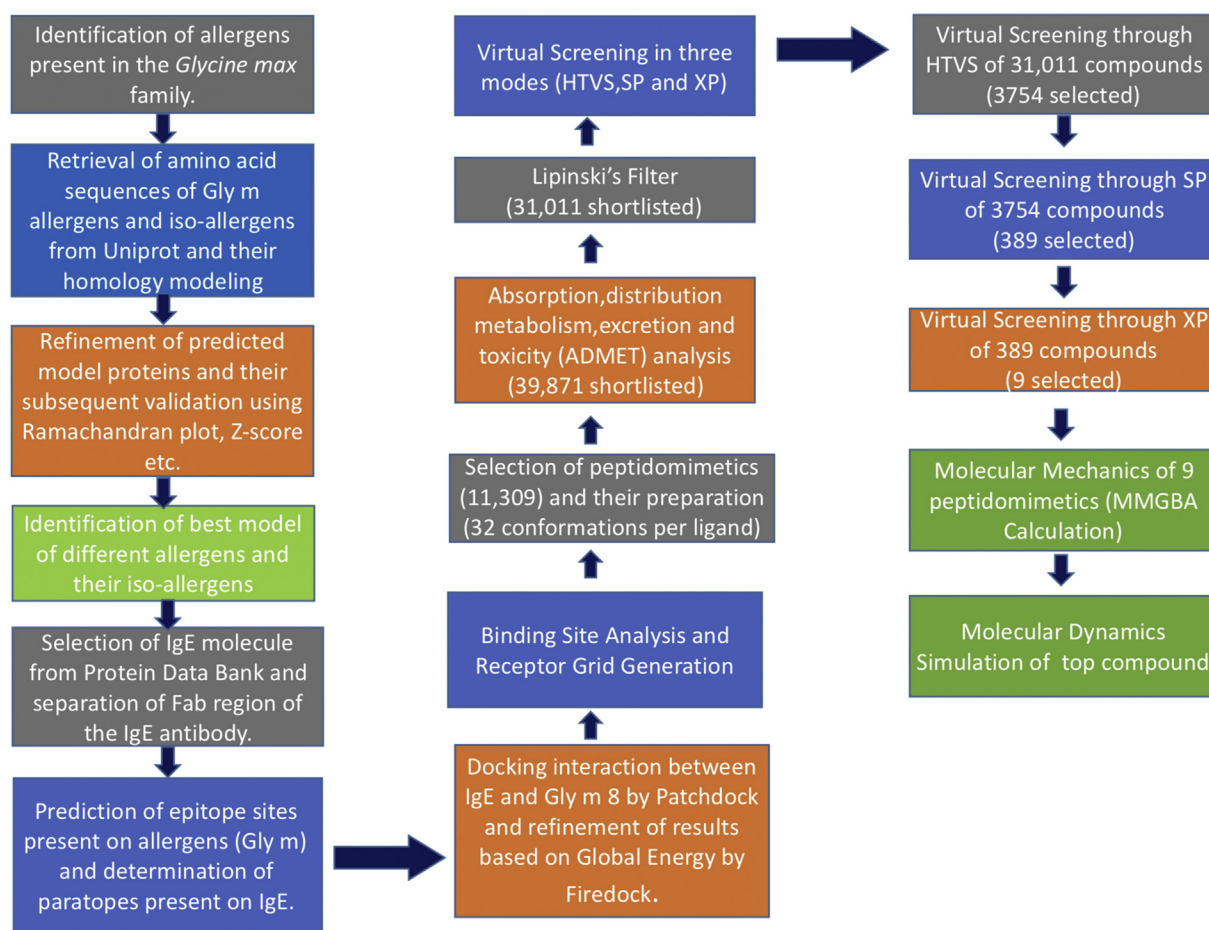


Fig. 1. The flowchart represents the outline of different steps of the methodology used in the present study.

Table 1

Results of refinement of modeled Gly m 8 using Galaxy web.

Model	GDT-HA	RMSD	MolProbity	Clash score	Poor rotamers	Rama favored	Z-score
Initial	1.0000	0.0000	3.378	89.6	3.4	89.7	
MODEL 1	0.9335	0.475	2.085	18.9	0.7	95.5	−3.23
MODEL 2	0.9383	0.458	1.939	13.1	0.7	95.5	−3.13
MODEL 3	0.9430	0.447	2.346	16.6	2.0	94.2	−3.17
MODEL 4	0.9446	0.432	2.204	17.8	1.4	94.9	−3.37
MODEL 5	0.9304	0.469	2.128	18.5	1.4	96.2	−3.19

between allergen and IgE have been made.

In the present study, we concentrate upon the soybean plant, a source of highly proteinaceous food. The plant *Glycine max* has been found to have different allergens. As specified by IUIS, the allergen present in the soybean plant has been named as Gly m followed by either one of the eight forms of iso-allergens [18]. Soybean allergy has already been reported before with well-documented cases for different allergens such as Gly m 1 [13], Gly m 2 [6], Gly m 3 [41], Gly m 4 [8], Gly m 5 [27,28], Gly m 6 [1,45], Gly m 7 [40] and Gly m 8 [10]. These allergens have been documented to show cross-reactivity [21]. A study conducted on the impression of soy allergy on individuals (with Gly m 8 allergen) indicates that it can occur at any age and the individuals with soy allergy are most certainly susceptible to peanut allergen (nearly 89% of tested individuals) [21].

In this fast-paced 21st century the need behind faster results has attributed to the success of bioinformatics which certainly outpaces experimental method and complements the experiment being conducted leading it to a number of avenues exclusively tailored to meet the demands of the experiment concerned. The sequences of most of the

allergens of the *Glycine max* are known but their structures are not available in the database (WHO/IUIS). Homology modeling has provided to be a boon in allergen-specific research; this can be attributed to the importance of structural properties behind allergenic stimulation. Docking interactions help provide insights into the interaction between IgE and the allergen concerned. The study also uses the approaches for epitope prediction, which subsequently aid in protein interaction between IgE and Gly m allergens family found in *Glycine max*. Therefore, the present study aims to generate models of different protein allergens present in *Glycine max* and their subsequent interaction studies of allergens with human immunoglobulin E (IgE). Gly m 8 has been selected because it showed the best clinical reactivity among the different allergens of *Glycine max* [21]. A comparative study of all other isoallergens found in *Glycine max* was also made. Using *in-silico* virtual screening, molecular mechanics, and molecular dynamics simulation approach, we have also designed peptidomimetics based lead, targeted at interaction interface of Gly m8 with Fab region of IgE.

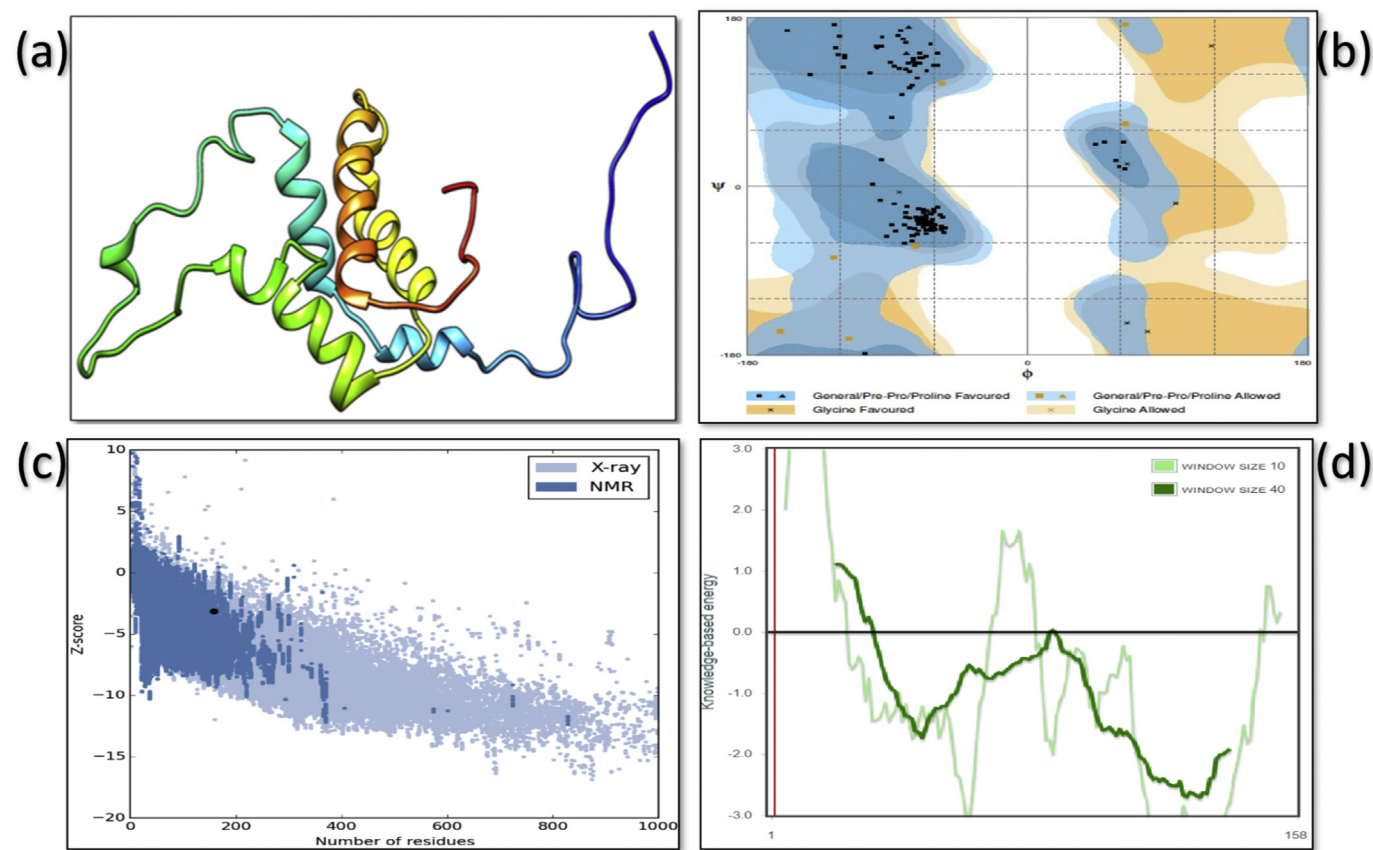


Fig. 2. Validation of allergen Gly m 8. 2(a) represents the predicted three-dimensional structure of allergen Gly m-8 obtained by Homology Modeling. 2(b) represents the Ramachandran Plot of the structure with nearly 95.5% of the amino acid residues lying in the favored region, 4.5% lying in the allowed region and none of the residues lie in the outlier region. 2(c) the plot represents the Z-score of the predicted model, which came to be around -3.13 . 2(d) the graph represents the plot of the amino acid residues with knowledge-based energy score, which determines the model quality.

Table 2
Predicted conformational epitope sites on Gly m 8 using Ellipro.

Sl. no.	Residues	Number of residues	Score
1	M1, T2, K3	3	0.987
2	R72, G73, R74, I75, N76	5	0.884
3	F4, T5, I6, L7, L8, I9, S10, L11, L12, F13, C14, I15, A16, H17, T18, C19, S20, A21, S22, K23	20	0.845
4	Q25, H26, Q28, D29, S30	5	0.696
5	Y77, I78, R79, N81, E82, G83	6	0.692
6	Q52, G53, R54, G55, D56, D57, D58, D59	8	0.665
7	D60, D61, D62, D63, D64, N65, H66, I67, L68, R69, T70, M71	12	0.616
8	F146, G147, P148, M149, I150, Q151, C152, D153	8	0.608
9	E103, L104, R105	3	0.563
10	S122, E124, L125, E126, E127, K128	6	0.502

2. Methods

The interaction study has been performed for the all the eight allergens (Gly m1 to Gly m8) found in the *Glycine max*. In this section, we have explained the approaches used for the Gly m 8. Similar approaches have been used for remaining isoforms of Gly m allergen. The Gly m 8-Fab complex was used for designing of peptidomimetics based lead. The different experimental setup is shown in Fig. 1.

2.1. Selection of allergens and their sequence

The different isoallergens (Gly m) of the *Glycine max* has been taken

from WHO/IUIS allergen database. This database showed the presence of eight allergens in the *Glycine max* (Gly m 1 to Gly m8). This database also provided the information about the isoallergens and protein sequence, available structure and documented literature of the analyzed allergens. The information was further validated from the SDAP (structural database of allergenic protein) database [18].

2.2. Molecular modeling of Gly m 8, its refinements and validations

The amino acid sequence of the protein allergen, Gly m 8 was derived from the UniProt link [Uniprot ID: P19594] [7]. This amino acid sequence was used for pBLAST [2] against the Protein Data Bank database to identify the templates based on which homology modeling of the allergen protein can be carried out. Based on the results of the protein BLAST, two templates were used in the homology modeling on the MODELLER v9.17 [42] using an approach similar to our published methods [47] and the three-dimensional model was predicted based on the DOPE score. The predicted model was refined using Galaxy Web Server [43], followed by structures validation using Prosa Web [50] and RAMPAGE [24] and PSVS server [3]. The template quality is validated using TM align [53]. The predicted structure was visualized on UCSF Chimera [36]. Similar approach was used to model other allergens and iso-allergens of *Glycine max*.

2.3. Selection of Fab domain of immunoglobulin E (IgE)

The IgE which acts as the receptor in the upcoming molecular docking was retrieved from the Protein Data Bank (PDB ID: 2R56). The unnecessary ligands were removed by using UCSF Chimera, and the

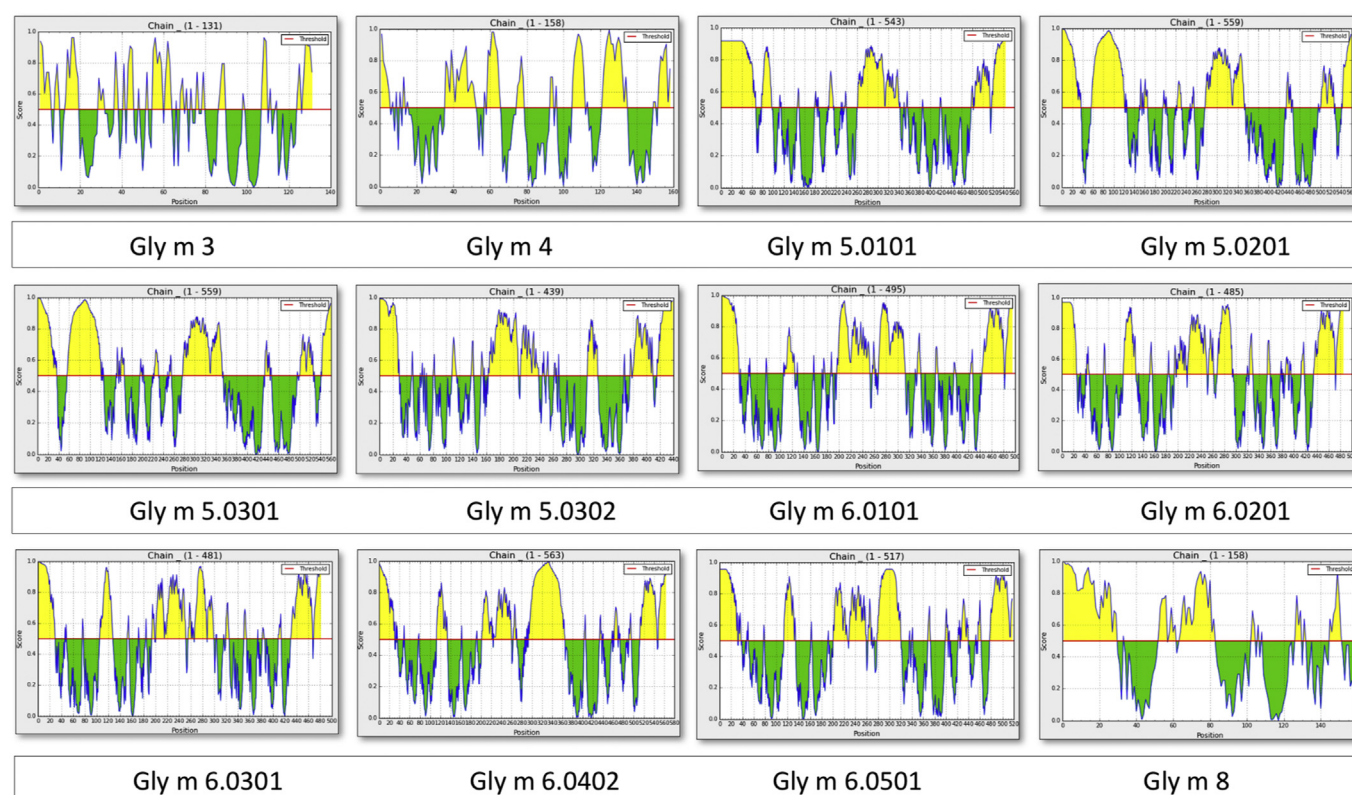


Fig. 3. The graph represents the scores obtained by the amino acid residues of different allergen of Gly m and their isoallergen. The yellow regions above the plane are the amino acid residues that form the conformational epitopes present on the allergen. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

heavy-light chain present in the antigen-binding fragment (Fab) of IgE was selected for the docking study. The left side of Fab is designated, as chain HL and right side of the chain is designated as MI chain (Supplementary Fig. 1).

2.4. Epitope and active site prediction

Before proceeding for protein-protein interaction, we predicted the epitope sites on the Gly m allergen, modeled allergen using ElliPro, a structure based tool for prediction of epitope sites [37] and correspondingly the paratopes or binding site on the receptor, Fab of IgE were detected using Sitemap [15]. The predicted sites were used for protein-protein docking.

2.5. Protein-protein docking between allergen and Fab of IgE

The protein-protein interaction between the allergen protein (ligand) and the Fab of IgE (receptor) was studied via molecular docking using PatchDock v1.3 server [9]. Predicted epitope site of allergen (from ElliPro) and predicted binding site of HL and MI chain were used in protein-protein docking to provide the PDB file of best-docked pose, geometric shape complementarity score (score), approximate interface area of the complex (area), atomic contact energy (ACE). The results of PatchDock were refined by Firedock server [29] into the top 10 pose PatchDock result based on global energy values. The interaction with the most negative global energy was the most spontaneous among all the receptor-allergen interactions and selected as the best model. The selected best docked model was used for the peptidomimetics designing.

2.6. Receptor grid generation for peptidomimetics designing

The peptidomimetics binding site in docked Gly m8-Fab complex was detected using Sitemap [15]. It is an energy-based method for the prediction of the protein-ligand binding site. It uses the interaction energy between the protein and simple van der Waals probe to locate the energetically favorable binding site. The binding site was selected based on its presence at the interface of the Gly m8 and Fab domain of IgE.

2.7. Selection of peptidomimetics ligands from Asinex database

Peptidomimetics are compounds with essential elements (pharmacophore) that mimic a natural peptide or protein in 3D space and retain the ability to interact with a biological target and produce the same biological effect [48]. We have selected a total of 11,309 peptidomimetics leads from the Asinex library.

2.8. Preparation of peptidomimetics

All the peptidomimetics compounds were subjected to LigPrep based ligand preparation. The LigPrep module prepares three-dimensional structures of compounds with high quality and corrects chiralities. Ionization states for the compounds were generated at pH of 7.0 ± 2.0 . The Epik and tautomeric states were generated followed by the desaltation of ligands. An OPLS_2005 force field was used for the minimization of the compounds. Maximum of 32 stereoisomers were generated for each ligand and five lower energy ring conformations per ligand were selected.

Table 3
Result of protein-protein docking between Gly m 8 (predicted epitopes) and HL chain domain of IgE.

Sl. no.	Epitope sites	Global energy value (kJ/mol)	Score	Area	ACE	HB energy
1	M1, T2, K3	4.14	9910	1622.10	78.96	0.00
2	R72, G73, R74, I75, N76	−24.64	12,820	1722.30	450.51	−5.27
3	F4, T5, I6, L7, I8, I9, S10, L11, L12, F13, C14, I15, A16, H17, T18, C19, S20, A21, S22, K23	2.92	15,270	2982.60	31.87	0.00
4	Q25, H26, Q28, D29, S30	−21.06	11,118	1560.20	−252.05	−1.67
5	Y77, I78, R79, N81, E82, G83	−47.90	9482	1202.70	−219.47	−2.88
6	Q52, G53, R54, G55, D56, D57, D58, D59	8.50	12,358	1641.50	463.88	−3.89
7	D60, D61, D62, D63, D64, N65, H66, I67, L68, R69, I70, M71	−12.59	12,170	1578.20	449.40	−3.79
8	F146, G147, P148, M149, I150, Q151, C152, D153	−21.63	13,294	2182.90	−67.67	−3.71
9	E103, L104, R105	−24.30	10,536	1331.70	122.39	−9.28
10	S122, E124, L125, E126, E127, K128	−26.41	11,050	1460.20	359.93	−3.32
11 ^a	M1, T2, K3, F4	−65.00	11,822	1674.50	−11.70	−0.43
12 ^a	M1, T2, K3, F4, T5, I6, L7, I8, I9	−55.16	14,458	1784.70	−12.79	−2.45
13 ^a	I6, L7, I8	−57.71	11,822	1674.50	−10.83	−0.89
14 ^a	K3, F4, T5, I6, L7, I8, I9, S10	−55.16	14,458	1784.70	−12.79	−2.45
15 ^a	M1, T2, K3, F4, G92, H93, M94, Q95, K96, C97, Q121, S122, E123, E124, L125, E126, E127, K128, Q129, L130, L131, L132, M133, E134	−55.16	12,722	2238.80	−12.79	−2.45

^a Hybrid epitopes generated after manual comparison.

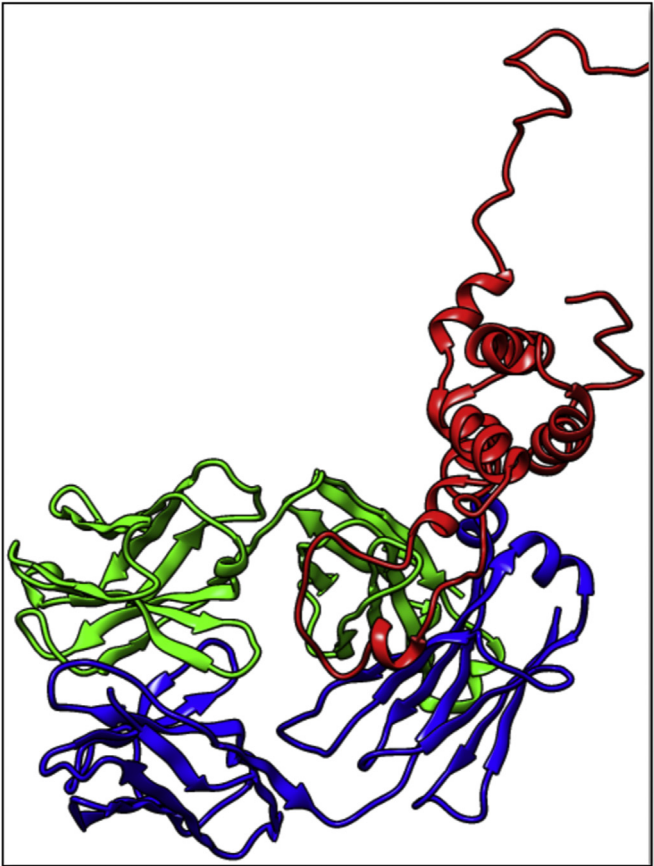


Fig. 4. The docked pose of Gly m 8 (red) and HL domain of Fab region of Immunoglobulin E (IgE). Protein-Protein docking was performed using PatchDock and refined by Firedock. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.9. High throughput virtual screening (HTVS) and ADMET analysis

The virtual screening workflow of Maestro v11 was used to screen the peptidomimetic library against the binding site of Gly m8-Fab(IgE) complex. We have skipped the ligand preparation step included in the virtual screening workflow due to their prior preparation using Ligprep. The first step of virtual screening involves the evaluation of drug-likeness of small molecules. Drug-like molecules exhibit favorable absorption, distribution, metabolism, excretion, toxicological (ADMET) parameters using QuikProp as per our published protocol [47]. This analysis was followed by three modes of docking i.e. HTVS, SP and XP docking.

2.10. Molecular mechanics/generalized born surface area (MM-GBSA) calculations of selected library compounds

The docking studies are not always considered as the most validated or successful method. Therefore, for the lead hit identification, comparatively more accurate computational method is required. The estimation of free binding energies for the best hit docked complexes using MM force fields, and implicit solvation was done using the Molecular mechanics/generalized born surface area (MMGBSA) method using the Prime module of Schrodinger suite v11. The protein-ligand complexes were ranked based on their binding free energy calculation.

2.11. Molecular dynamics simulation

For the molecular dynamics simulations (MDS), we have used the

Table 4

Result of IgE interaction with other allergens of Gly m Family identified from protein-protein docking. Only best global energy score epitopes have been listed here.

Allergen protein	Epitope site	Global energy (kJ/mol)	Score	Area	ACE	HB
Gly m 3	T97, G98, A99, D124, Y125, I127, D128, Q129, G130, Y131	−37.25	10,222	1236.60	−1.04	−5.23
Gly m 4	V14, A15, L104, V105, A106, G107, P108, N109, G110, G111, A113	−34.37	11,196	1989.90	−9.08	−9.54
Gly m 5.0101	D36, E37, Q38, P39	−43.49	8632	1314.60	−1.66	−2.53
Gly m 5.0201	R556, A557, F558, Y559	−37.34	10,460	2274.80	−0.96	−5.34
Gly m 5.0301	R3, V4, R5, F6, P7, L8, L9, V10, L11, L12, G13, T14, V15, F16, L17, A18, S19, V20, C21, V22, S23, L24, K25, V26, R27, E28, D29, E30, N31	−51.77	11,568	1616.90	−6.66	−5.29
Gly m 5.0302	M1, M2, V4, R5	−29.74	10,018	1599	−7.74	−1.75
Gly m 6.0101	M1, A2, K3, L4, V5, F6, S7, L8, C9	−36.61	8698	1337.40	−12.09	−1.25
Gly m 6.0201	M1, A2, K3, L4, V5, L6, S7, L8, C9, F10, L11, L12, F13, S14, G15, C16, F17, A18, L19	−53.63	9760	1255.90	−12.45	−3.96
Gly m 6.0301	M1, A2, K3	−37.77	8472	1157.70	−6.27	−1.51
Gly m 6.0401	R325, P326, S327, Q328, G329, K330	−77.46	10,246	1199.10	8.52	−8.90
Gly m 6.0501	M1, G2, K3, P4	−52.54	7644	1054.80	−8.06	0.00
Gly m 8	Y77, I78, R79, N81, E82, G83	−47.90	9482	1202.70	−219.47	−2.88
Gly m 8 ^a	M1, T2, K3, F4	−65.00	11,822	1674.50	−11.70	−0.43

^a Hybrid epitopes generated after manual comparison.

GROMACS version 5.1.4 (Mark James [26]). It helps in determining the interatomic motions as well as the dynamics of protein and protein-ligand complex [46]. Our published methods were used for MDS analysis of the ligand with Gly m8-Fab(IgE) complex for 10 ns.

3. Results and discussion

According to WHO statistics, hundreds of millions suffer from allergy, and it is estimated that 300 million have asthma, markedly affecting the quality of life of these individuals and their families, and negatively impacting the socio-economic welfare of society [49]. According to WHO/IUIS, *Glycine max* (dicotyledonous weeds of Fabaceae family) is the source of allergens namely ranging from Gly m 1 to Gly m 8 and each of these has been characterized as a potential allergen. It is a food-borne allergen and identified as a type I hypersensitive allergen [14]. *Glycine max* pollens have been reported to be the most common cause of allergy. Molecular interaction of these allergens is not well documented, with the increase in consumption of soybean; we might be looking at cases of increased allergenicity towards the plant. The Gly m family of protein allergens are listed (Supplementary Table 1) on the allergen databases, Structural Databases of Allergenic Proteins (SDAP) and allergen.org (maintained by WHO and IUIS). In this study, we have identified the epitope sites present in the allergen protein (Gly m 8) found in the *Glycine max*. Following similar step, we have been able to identify similar epitope sites on other allergen proteins present in the Gly m family. The identification of epitope sites opens up the avenue for understanding allergen interaction with IgE and design of peptidomimetics based therapeutics.

3.1. Modeled structure and validation

The template of allergen proteins were identified by protein BLAST, which yielded the best query cover. The identified templates 1W2Q 'A' and 3OB4 'A' are peanut allergens (Ara h 6 and Ara h 2), which have been used for determination of the three-dimensional structure of Gly m 8 (Supplementary Table 2). The Modeller v9.17 predicted the best model based on the DOPE score, which underwent refinement and subsequent validations. The best among the five refined generated models was determined on the basis of low RMSD, low MolProbity, less poor rotamer, high Ramachandran score and Z-score (Table 1, Fig. 2). Based on these parameters, model 2 was selected as a model for Gly m 8 allergen. The template used for modeling was further validated by TM align that shows that template (1W2Q) has good RMSD value (2.13) and good TM score (0.83), which further validates our template selection. Similarly, using homology modeling, we modeled the other allergens present in the Gly m allergen family using Modeller v9.17. Gly

m 3 was modeled on the basis of a monomeric allergen Profilin (Hv b 8) template 5FDS'A'. The allergen Gly m 4, had a defined PDB structure, but we conducted homology modeling based on the template 2K7H'A' which had a 99% similar query cover with the allergen. Gly m 5 has four isoallergens. The Gly m 5.0101 and Gly m 5.0201 were modeled using Adzuki bean 7s Globulin-3 template 2EAA 'A' that showed 76% and 79% sequence similarity respectively. Gly m 5.0301 and Gly m 5.0401 have PDB structures and were modeled using the respective templates 1IPJ'A' and 1IPK'A'. Gly m 6 has five isoallergens, which were modeled using homology modeling. Gly m 6.0101 showed maximum sequence similarity with its validated crystallographic PDB structure 1FXZ 'A'. Gly m 6.0201 and Gly m 6.0301 were modeled on the same template Soybean proglycinin A1ab1b homotrimer 1FXZ 'A' as they showed nearly 96% sequence similarity with it. Gly m 6.0401 and Gly m 6.0501 were modeled on the crystal structure of glycinin a3b4 subunit homohexamer 1OD5'A'. However, the allergens Gly m 1 and Gly m 2 could not be modeled because of their incomplete amino acid sequence. The allergen Gly m 7 did not produce any significant sequence similarity with any template and could not be modeled using homology modeling. The modeled structures were visualized on the UCSF Chimera software.

3.2. Selection of epitopes in the different allergen

Molecular docking requires predicted epitope sites of the ligand i.e. allergen and predicted binding sites on the receptor, Fab of IgE. This is necessary to determine whether binding occurs at these specified sites during the protein-protein interaction. The discontinuous or conformational epitope sites present on Gly m 8 and other Gly m allergen were included (Table 2, Fig. 3, Supplementary Fig. 2). The Ellipro score represents the probability of the sequence to become epitope, and its value varies from zero to one. Zero represents probable non-epitope sequence while 1 represents best probable epitope sequence. These epitope sites were used for the protein-protein docking.

3.3. Selection of IgE chain receptor and binding sites

The Fab fragment of IgE consists of HL (left side) and MI chain (right side). The HL and MI chain was separated using Chimera. The predicted sites on Gly m 8 were utilized for non-specific docking at multiple sites of antigen binding fragment (Fab) region, the HL chain and also with the MI chain of IgE. The results obtained for the interaction of Gly m 8, showed maximum negative global energy value of −24.53 kJ/mol in case of interaction with HL chain of Fab region of IgE whereas weak interaction was shown with MI chain (−2.43 kJ/mol) and Fab region (−1.10 kJ/mol) of IgE respectively. The present result showed that the

Table 5
Result of molecular docking and binding free energies of docked complexes.

Compound IDs	Name	Docking score ₁	Glide G-score ₁	Glide E-model ₁	XP G-score ₁	Complex energy ₂	dG_Bind (kcal/mol) ₂
BDH 34060020	N-[(1R,2S,3R,4R)-2-[benzyl(methyl)amino]-3-hydroxy-4-[3-(trifluoromethyl)phenoxy]cyclopentyl]-2-(methylamino)acetamide	-9.6147	-10.1024	-88.3991	-10.1024	-24,472.88	-58.50
BDE 32166344	N-[(1-[(1-aminocyclopentanecarbonyl)-3-hydroxy-pyrrolidin-3-yl]methyl]piperidin-4-yl]acetamide	-9.53971	-9.62471	-82.0148	-9.62471	-24,475.64	-72.77
LAS 57287831	(2R,3R,4S)-2-(hydroxymethyl)-1-[(3-{(2-methyl-1H-imidazol-1-yl)propoxy}phenyl)methyl]-4-phenylpyrrolidin-3-ol	-9.34469	-9.47659	-68.2619	-9.47659	-24,471.05	-71.04
LAS 34125414	2-amino-N-[(1R,4S,5S)-4-hydroxy-5-(4-hydroxypiperidin-1-yl)-1-phenylcycloheptyl]methyl]acetamide	-8.90636	-9.01076	-67.497	-9.01076	-24,491.26	-60.62
BDI 34017289	(2S)-2,6-diamino-1-[(3S,4S)-3-hydroxy-4-(1,5-naphthylidene-4-ylmethyl)pyrrolidin-1-yl]hexan-1-one	-8.89101	-8.98441	-80.9257	-8.98441	-24,483.96	-66.21
BDI 34017296	(2S)-2,6-diamino-1-[(3S,4S)-3-hydroxy-4-(pyrrol-1,2- α -pyrazin-3-ylmethyl)pyrrolidin-1-yl]hexan-1-one	-8.73167	-8.85157	-76.3292	-8.85157	-24,538.46	-65.28
BDG 34055894	3-amino-N-[(1R,2S,3R,4R)-4-(3-fluorophenoxy)-3-hydroxy-2-(1,2,3,4-tetrahydroisoquinolin-2-yl)cyclopentyl]propanamide	-8.61124	-8.77594	-78.5234	-8.77594	-24,464.02	-50.06
LAS 34136776	2-[4-(benzyloxy)-2-[(3R,4S)-4-(dimethylamino)-3-hydroxy-3-methyl-1-oxa-9-azaspiro[5.5]undecan-9-yl]methyl]phenyl]acetamide	-8.56707	-8.58737	-94.0947	-8.58737	-24,500.74	-66.13

energy difference between HL and MI chain is large and in favor of interaction with HL chain. It is reported by experimental result that allergens show maximum interaction with HL chain of Fab region of IgE [11,23]. Thus, in all of our docking interactions, we have used HL chain for studying interactions with all the epitopes of different allergens of Gly m family. We have used SiteMap to predict the active site on the HL chain of IgE. Predicted active sites of HL chain contain 38 amino acid residues which include Q38, K39, P40, G41, K42, T85, Y87, Q100, G101, T102 in L chain and E6, S7, G8, G9, G10, Q39, A40, P41, G42, K43, G44, I93, Y95, R113, G114, T115, L116, Y153, E156, P157, V158, T159, F174, P175, A176, L186, K209, P210 residues in H chain of Fab of IgE. These residues were also found in previous reported interactions between allergens and IgE [33]. Hence, these active site residues were used to dock the allergen with IgE.

3.4. Molecular docking of epitope of allergen and HL chain domain of Fab region of IgE

The protein-protein interaction between receptor (IgE) and ligand (Gly m 8 and other allergens) was conducted. The predicted active sites of HL chain and different epitope sites were utilized in specific binding of ligand and receptor. The results were obtained on the basis of global energy score, which represent docking energy score. The lower the global energy score, the better is the interaction between the proteins. All the ten epitopes and their designed hybrid epitopes of the Gly m8 were docked individually with HL chain of IgE (Table 3 and Fig. 4), and epitope 5 (Y77, I78, R79, N81, E82, G83) of Gly m 8 showed good results with global energy score of -47.90 kcal/mol among all predicted epitope site of Gly m 8. The designed hybrid epitope sequence M1, T2, K3, F4 showed global energy score of -65.00 kcal/mol. Similarly, interactions of other Gly m allergens (m3, m4, m5, m6) were also studied protein docking approach using binding site of HL chain of Fab region of IgE.

The results of epitopes showing best interaction among all these isoallergens are shown in Table 4. The global energy values on their interaction with predicted active sites of the Fab region of HL chain of IgE and their respective docked poses are shown in supplementary Fig. 3. The epitope sequence T97, G98, A99, D124, Y125, I127, D128, Q129, G130, Y131 showed the least global energy of -37.25 for Gly m 3. The epitope sequence V14, A15, L104, V105, A106, G107, P108, N109, G110, G111, A113 shows a negative global energy of -34.37 for the interaction of Gly m 4 with the predicted active sites of IgE. A global energy score of -43.49, -37.34, -51.77 and -29.74 were seen in the interaction of Gly m 5.0101 (D36, E37, Q38, P39), 5.0201 (R556, A557, F558, Y559), Gly m 5.0301 (R3, V4, R5, F6, P7, L8, L9, V10, L11, L12, G13, T14, V15, F16, L17, A18, S19, V20, C21, V22, S23, L24, K25, V26, R27, E28, D29, E30, N31), Gly m 5.0302 (M1, M2, V4, R5) with HL domain IgE respectively. The epitope sequence of Gly m 6.0101 (M1, A2, K3, L4, V5, F6, S7, L8, C9), Gly m 6.0201 (M1, A2, K3, L4, V5, L6, S7, L8, C9, F10, L11, L12, F13, S14, G15, C16, F17, A18, L19), Gly m 6.0301 (M1, A2, K3), Gly m 6.0401 (R325, P326, S327, Q328, G329, K330), Gly m 6.0501 (M1, G2, K3, P4) showed a negative global energy of -36.61, -53.63, -37.77, -77.46, and -52.54 respectability.

We have also identified the pattern among the residues involved in the interaction. The comparative study of best epitopes among all isoallergens showed that N-terminal conformational epitopes showed better interaction with the HL chain domain Fab of the IgE (Supplementary Fig. 4). It is also seen that at least one polar amino acid such as Glu or Asp, or Lys must be present in the epitope. This showed that polar amino acid-rich epitopes are more preferred epitope for the interaction with HL chain of IgE.

3.5. In-silico drug designing of peptidomimetics that inhibit the Glym8 and IgE interaction

Out of all different sites provided by sitemap for Glym8-Fab (IgE)

Table 6

Table represents physio-chemical properties of selected compounds.

Compounds	Molecular weight (g/mol)	H-bond donors	H-bond acceptors	EA (eV)	PSA	Rotatable bonds	QPlogKhsa
BDH 34060020	451.488	3	8.45	0.583	82.02	11	−0.023
BDE 32166344	352.476	4	9.25	−1.048	109.598	7	−0.829
LAS 57287831	421.538	2	7.65	−0.072	70.766	11	0.438
LAS 34125414	375.51	5	8.9	−0.139	108.629	8	−0.419
BDI 34017289	357.455	5	8.7	1.524	120.418	9	−0.661
BDI 34017296	345.444	5	7.7	0.611	114.472	9	−0.592
BDG 34055894	413.491	3	6.95	0.293	94.431	8	0.107
LAS 34136776	497.633	3	9.5	−0.123	103.169	10	0.231

Table 7

Physiochemical properties (ADMET) with standard limits of the selected ligands obtained from the docking study.

Compounds	QPolrz	QPlogP16	QPlogPoct	QPlogPw	QPlogPo/w	QPlogS	QPlogKp	Human oral absorption (%)
BDH 34060020	47.1	14.194	24.801	16.982	2.735	−3.005	−5.35	73.842
BDE 32166344	37.565	11.119	22.992	19.85	−0.65	0.105	−7.551	42.548
LAS 57287831	46.892	15.207	22.733	13.19	3.849	−4.474	−3.308	91.408
LAS 34125414	40.373	13.052	25.504	19.863	−0.016	−1.094	−7.948	42.595
BDI 34017289	37.353	13.428	24.734	20.118	−0.19	−0.288	−7.651	37.134
BDI 34017296	36.16	12.995	23.433	18.961	0.085	−0.242	−7.413	41.162
BDG 34055894	44.85	14.046	23.572	15.288	2.206	−3.047	−6.42	64.298
LAS 34136776	54.02	17.014	27.902	18.15	2.694	−3.37	−6.262	64.977

complex, the site with the highest site score was selected, and this site lies at the interface of the Glym8 and Fab of IgE interaction. In the present study, all the residues present within the 4 Å surrounding of binding site were considered and used for generation of docking grid. Similarly, all conformers of different peptidomimetics leads were initially screened for their ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties via computational approach. On the basis of these properties and toxicity, the filtered 39,871 leads were selected. The selected ligands underwent Lipinski's filtering, which selects 31,011 conformers and used for high throughput virtual screening. Virtual screening was done to design effective peptidomimetics that inhibit the interaction of Glym8 with Fab of IgE complex. This is initiated by HTVS ligand docking of 31,011 probable leads with Glym8-Fab complex. This step shortlisted 3754 leads. It was followed by SP and XP docking, which filtered the number of leads to 389 and 9 respectively (Table 5).

3.6. Binding free energy calculations using molecular mechanics with generalized born and surface area solvation (MM-GBSA)

All nine peptidomimetics leads were then subjected to binding free energy calculations using MM-GBSA approach. The MMGBSA analysis of selected nine peptidomimetics is listed in Table 5. As evident from Table 5, peptidomimetics BDE32166344 (N-(1-([1-(1-aminocyclopentanecarbonyl)-3-hydroxypyrrolidin-3-yl]methyl)piperidin-4-yl)acetamide) showed lowest binding energy (−72.77 kcal/mol) among all 9 leads. The physical and chemical properties of these leads at physiological pH have been shown in Tables 6 and 7. The interactions of BDE32166344 with the Glym8-Fab complex are shown in Fig. 5. Hence, *in-silico* virtual screening identified peptidomimetics BDE32166344 as a lead that may inhibits the interaction of Gly m8 with Fab of IgE.

3.7. Molecular dynamics simulation (MDS) analysis

The MDS result (Fig. 6) showed that BDE32166344 interact with the Glym8-Fab complex. Glym8-Fab-BDE32166344 complex showed multiphasic stability and the complex stabilizes at 8 ns but have high RMSD. This showed that BDE32166344 might reduce the interaction of Glym8 with Fab (IgE) protein and further validates the designed peptidomimetics.

The use of peptides as immune-modulators or in immunotherapy

against various inflammatory associated disorders (particularly autoimmune disorders) through the disruption of transient protein-protein interactions has been investigated [12]. Peptidomimetics compounds are designed specifically along the same lines and function with the purpose of destroying the short-lived interactions between two proteins [34]. They also overcome the shortcomings of peptide-based therapeutics by having low molecular weight and lower immunogenicity. In the case of allergen-antibody complex exhibited here, the use of the peptidomimetics compound prevents any form of cross-reactivity that might be prevalent in case of use of a peptide as anti-allergen.

Allergy induced by *Glycine max* is associated with mast cell degranulation prompted by IgE mediated allergen cross-linking that releases various immune-regulatory molecules like leukotrienes and cytokines responsible for initiating the inflammatory response generated in type-I hypersensitivity. Mast cell degranulation involves intracellular calcium signaling and mobilization of extracellular and ER calcium channels [51]. Therefore, calcium channel inhibitors play a significant role in preventing allergy induced hypersensitivity reactions. It has been experimentally verified that N-piperidinyl acetamide derivatives are used as calcium channel blockers [34,52]. The calcium channel signaling is effectively inhibited by the peptidomimetic based approach using a piperidine acetamide derivative; by disrupting protein-protein interaction exhibited in type I hypersensitivity. Certain calcium channel blockers that are used in various cardiovascular disorders and inflammatory-mediated autoimmune disorders include Amlodopine and Nifedipine which are also pyridine carboxylate derivatives. Recently, it is also seen the use of peptidomimetic compound i.e. icatibant (5-diaminomethylideneamino pentanoic acid) against angioedema, a symptom of allergy [38,54] and hence have anti-allergenic property. Therefore, the present designed anti-allergen peptidomimetic compound that is a derivative of acetamide i.e. N-(1-([1-(1-aminocyclopentanecarbonyl)-3-hydroxypyrrolidin-3-yl]methyl)piperidin-4-yl)acetamide] have more chance to block the crucial allergen-antibody complex (Gly m 8-IgE) interaction that is required for the allergic reaction, hence can be developed as an anti-allergen molecule.

4. Conclusions and future perspective

Glycine max is the source of allergens namely ranging from Gly m 1 to Gly m 8 and each of which has been characterized as a potential allergen. The predicted epitope sites based on the protein-protein

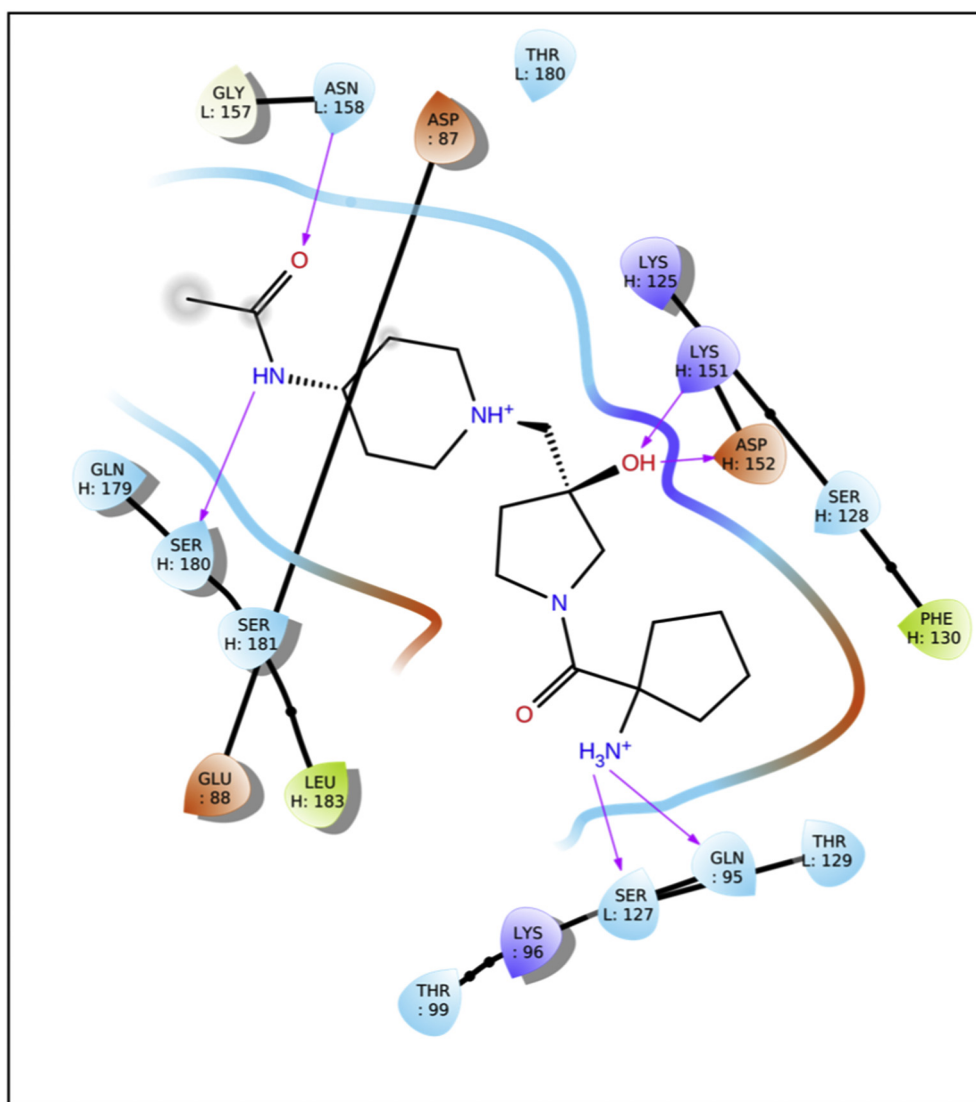


Fig. 5. Diagrammatic representation of the interaction between BDE32166344 with Gly m8-Fab complex. Purple colour lines denote the H-bond. Interacting residues of Gly m8-Fab complex and corresponding interacting atoms of peptidomimetic compound (BDE32166344) are shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

interaction through docking on the Patchdock Server between allergen protein Gly m and human IgE resulted in the manifestation of epitope sites for all the other allergen proteins present in the *Glycine max* family. The predicted interactions markedly determine the intensity of interaction between the various allergens and IgE. This was followed by peptidomimetics designing using *in-silico* virtual screening, molecular mechanics and molecular dynamics simulation studies that suggest the BDE32166344 as a lead that might suitably cure allergy caused by allergen of *Glycine max* via inhibiting the allergens (Gly m8) and IgE (Fab) interaction. Therefore, the present study that attempts to understand allergenic inception of Gly m protein allergens, and the subsequent methods through which it attaches itself to IgE receptors in humans would help us understand the workings of the allergen.

The designed peptidomimetics compound need to be experimentally validated before use as an anti-allergen. Allergen needs to be purified from the *Glycine max*. The strength of interaction of the purified allergen with IgE needs to be determined using surface plasmon resonance (SPR) or ELISA or mass-spectrometry after isolation of allergen-IgE complex. Experimental validation of designed peptidomimetics compound requires monitoring of allergen-IgE (protein-protein) interaction in its presence and absence. Interaction of

allergen with the IgE also induces type-I hypersensitivity that is associated with inflammation, therefore, the effect of designed peptidomimetic compound may also be validated on its inhibitory effects on various inflammation biomarkers like c-AMP level [16], levels of eosinophil [17,22], upregulation of pro-inflammatory molecules like IL-4 and IL-13 [44], mast cell degranulation and release of leukotrienes and histamines [30]. This study also stimulates further research aimed at the development of anti-allergenic drugs or recombinant vaccines to cure allergy caused by Gly m allergens.

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Author contributions

Conceived and designed the experiments: VT, Performed the experiments: VT (Peptidomimetics designing, and Molecular Dynamics Simulation), DM (literature survey and initial *in-silico* work), MT (*in-*

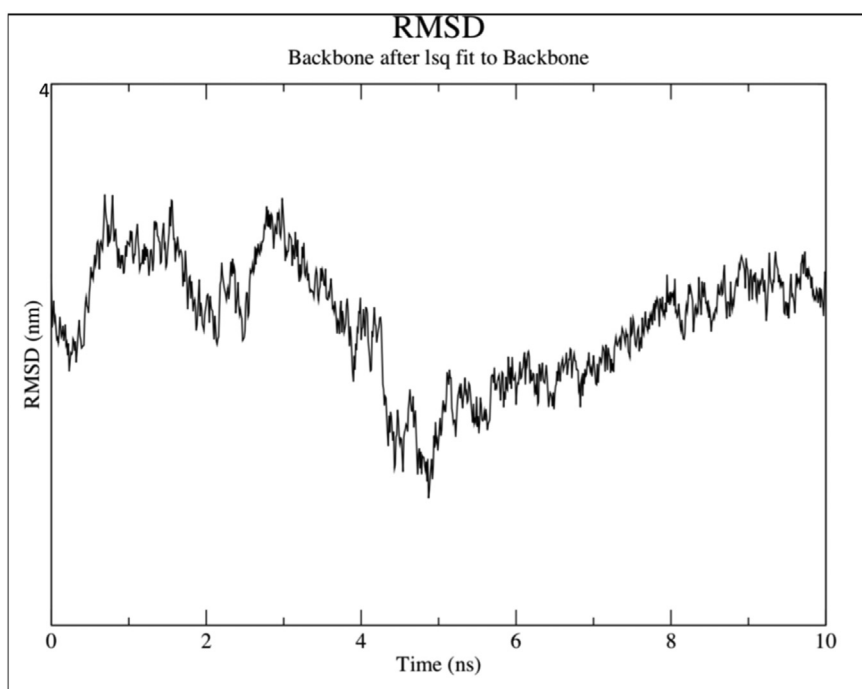


Fig. 6. Molecular dynamics simulation of BDE32166344-Glym8-Fab complex depicting their root mean square deviation (RMSD) with time (ns). MDS was run for 10 ns using GROMACS software.

silico work). Analyzed the data: VT, Wrote the manuscript: VT, DM & MT, Proofread of final version: MT & VT.

Author disclosure statement

The authors have declared that no competing interests exist.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.intimp.2018.06.023>.

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Supplementary Data

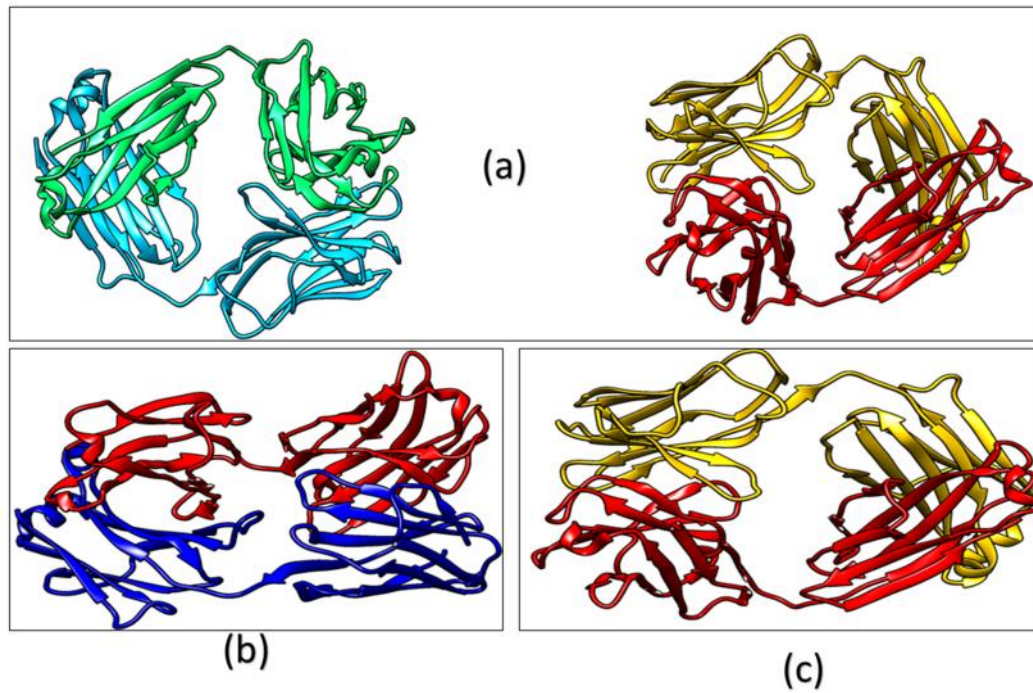
Supplementary Table 1: List of allergens (Gly m Family) found in *Glycine max* from WHO/IUIS database.

Name of Allergen	Isoallergens
Gly m 1	Gly m 1.0101; Gly m 1.0102
Gly m 2	Gly m 2.0101
Gly m 3	Gly m 3.0101; Gly m 3.0102
Gly m 4	Gly m 4.0101
Gly m 5	Gly m 5.0101; Gly m 5.0201; Gly m 5.0301; Gly m 5.0302
Gly m 6	Gly m 6.0101; Gly m 6.0201; Gly m 6.0301; Gly m 6.0401; Gly m 6.0501
Gly m 7	Gly m 7.0101
Gly m 8	Gly m 8.0101

Supplementary Table 2: Selection of template via Protein BLAST of allergen protein Gly m 8.

Sl No.	Description	Max Score	Total Score	Query Cover	E Value	Identity	Accession Code
1	Mbp-Fusion protein of the major Peanut Allergen Ara H 2	82.4	82.4	78%	9e-19	37%	3OB4_A
2	Allergen Ara h 6 from Peanut	66.6	66.6	79%	2e-14	35%	1W2Q_A

Supplementary Figure 1: The antigen binding fragment (Fab) of the Immunoglobulin E. (a) The Fab region of IgE representing the light chains (L,M) and the heavy chains (H,I). (b) The HL chain. (c) The MI chain.



Supplementary Figure 2: The predicted discontinuous epitopes by Ellipro for different allergen

2.1 Gly m 3:

Predicted Discontinuous Epitope(s):

No. ↕	Residues	Number of residues ↕	Score ↕
1	_M1, _S2, _W3, _Q4, _A5, _Y6, _D8, _D9, _H10, _L12, _C13, _D14, _I15, _E16, _G17, _N18, _H19, _L20, _K87, _G88, _P89, _D107, _E108, _P109, _M110, _T111, _Q114	27	0.703
2	_I197, _G98, _A99, _D124, _Y125, _I127, _D128, _Q129, _G130, _Y131	10	0.698
3	_P40, _Q41, _F42, _K43, _P44, _E45, _T48, _N52, _N55, _E56, _P57, _G58, _S59, _L60, _A61, _P62, _T63, _G64, _Y66, _G68, _G69, _K71, _G77, _E78, _P79, _G80	26	0.679
4	_D29, _G30, _S31	3	0.631
5	_T21, _S36, _T37, _D38	4	0.559

2.2 Gly m 4:

Predicted Discontinuous Epitope(s):

No. ↕	Residues	Number of residues ↕	Score ↕
1	_A149, _Y150, _L152, _A153, _H154, _P155, _D156	7	0.739
2	_M1, _G7, _V3, _F4, _P97, _D93, _T94, _A95, _F96, _K97, _F121, _T122, _K123, _G124, _D125, _A126, _F127, _P128, _N129, _O130, _D131, _F132, _I133, _K134	24	0.738
3	_L35, _D36, _S37, _F38, _K30, _S40, _V41, _E42, _N43, _V44, _E45, _Q46, _N47, _C48, _C49, _F50, _C51, _T52, _T57, _L59, _E60, _D61, _C62, _E63, _T64, _K65	26	0.733
4	_V14, _A15, _L104, _V105, _A106, _G107, _P108, _N109, _G110, _G111, _A113	11	0.707
5	_D75, _F76, _A77, _N78, _I79	5	0.644

2.3 Gly m 5.0101:

No. ↕	Residues	Number of residues ↕	Score ↕
1	_K3, _E4, _E5, _C6, _E7, _E8, _G9, _E10	8	0.917
2	_R13, _P14, _R15, _P16, _R17, _P18, _Q19	7	0.917
3	_H20, _P21, _E22	3	0.917
4	_E24, _P25, _Q26	3	0.917
5	_Q27, _P28, _G29, _E30, _K31, _E32	6	0.917
6	_E33, _D34, _E35	3	0.917
7	_D36, _E37, _Q38, _P39	4	0.917
8	_R540, _A541, _F542, _Y543	4	0.917
9	_R40, _P41, _I42, _P43	4	0.913
10	_K529, _G530, _R531, _K532, _G533, _P534, _L535, _S536, _S537, _I538, _L539	11	0.899
11	_D83, _E84, _E85, _Q86, _D87, _E88	6	0.844
12	_Q90, _F91, _P92	3	0.818
13	_E54, _E56, _Q57	3	0.787
14	_K146, _N147, _Q148, _Y149, _K179, _P180, _N181, _T182, _L183, _L185, _P186, _T201, _P236, _D237, _N238, _N239, _E240, _L262, _S263, _S264, _T265, _E266, _A267, _Q268, _Q269, _S270, _Y271, _L272, _Q273, _G274, _F275, _S276, _R277, _N278, _I279, _L280, _E281, _A282, _S283, _Y284, _D285, _T286, _K287, _F288, _E289, _E290, _I291, _N292, _K293, _Y294, _L295, _F296, _S297, _R298, _E299, _E300, _G301, _Q302, _Q303, _Q304, _G305, _E306, _Q307, _R308, _L309, _Q310, _E311, _S312, _V313, _I314, _V315, _E316, _I317, _S318, _K319, _E320, _Q321, _I322, _R323	79	0.709
15	_E59, _E60, _O61, _E62, _W63, _P64, _R65, _S354, _N355, _K356, _L357, _N384, _E385, _G386, _L390, _P391, _S458, _L477, _A478, _G479, _S480, _Q481, _D482, _N483, _V484, _L485, _S486, _Q487, _I488, _P489, _S490, _Q491, _Q492, _Q493, _E494, _L495, _A496, _F497, _P498, _G499, _S500, _A501, _D502, _A503, _V504, _E505, _K506, _L507, _L508, _R509, _N510, _D511, _E513, _S514, _Y515, _V517, _D518, _A519, _O520, _P521, _K522, _K523, _K524, _E525, _E526, _G527, _N528	67	0.642
16	_E77, _E78, _D79, _E80, _D81, _E82	6	0.605
17	_S205, _V207, _N208, _N209, _D210, _D211, _R212, _D213, _S214, _R216, _G228, _T229, _T230, _Y232, _A324, _L325, _S326, _K327, _R328, _A329, _K330, _S331, _S332, _S333, _R334, _K335, _T336, _I337, _S338, _S339, _E340, _D341, _K342, _P343, _R368	35	0.595
18	_K73, _G74, _S75, _E76, _R95, _P96, _P97	7	0.5

2.4 Gly m 5.0201:

1	_V1,_E2,_E3,_E4,_E5	3	0.993
2	_E6,_D7,_C8	3	0.98
3	_H64,_P66,_R68,_P87,_H88,_Q89,_P90,_I91,_Q92	9	0.977
4	_K83,_E84,_E93,_E90,_K97	5	0.902
5	_F78,_Q79,_P80,_P81	4	0.947
6	_R60,_A697,_P698,_V709	4	0.841
7	_E9,_G16,_Q15,_H12,_P13,_R14,_P15	7	0.938
8	_H85,_E89,_W100	3	0.825
9	_E67,_E68,_H80,_H76,_G71,_G72,_K73,_G74,_S75,_E78	10	0.009
10	_Q101,_H102,_K103,_Q104	4	0.804
11	_R16,_P17,_Q18	3	0.807
12	_K105,_H197,_Q108,_G109,_K110	5	0.859
13	_H119,_P20,_C21,_P22,_C23,_P24,_Q25,_C28	9	0.021
14	_E111,_S112,_E113,_E114,_E115	5	0.789
15	_H61,_C82,_V83,_H84,_P85,_C118,_C117,_D113,_Q119,_D120,_C121,_D122	12	0.891
16	_F140,_I141,_S142,_K143,_H144,_A145,_K146,_S147,_S148,_S149,_R150,_K151,_T152,_R153,_S154,_S155,_P156	17	0.687
17	_E157,_H161,_F162,_H163,_S164,_F165,_F166,_Q167,_L168,_F169,_K169,_N169,_Q164,_V165,_K165,_F166,_H167,_T168,_I169,_I166,_I161,_P162,_T167,_T161,_V165,_N164,_A165,_D168,_D167,_D163,_D160,_D161,_D162,_D163,_D164,_D165,_D166,_D167,_D168,_D169,_D170,_D171,_D172,_D173,_D174,_D175,_D176,_D177,_D178,_D179,_D180,_D181,_D182,_D183,_D184,_D185,_D186,_D187,_D188,_D189,_D190,_D191,_D192,_D193,_D194,_D195,_D196,_D197,_D198,_D199,_D200,_D201,_D202,_D203,_D204,_D205,_D206,_D207,_D208,_D209,_D210,_D211,_D212,_D213,_D214,_D215,_D216,_D217,_D218,_D219,_D220,_D221,_D222,_D223,_D224,_D225,_D226,_D227,_D228,_D229,_D230,_D231,_D232,_D233,_D234,_D235,_D236,_D237,_D238,_D239,_D240,_D241,_D242,_D243,_D244,_D245,_D246,_D247,_D248,_D249,_D250,_D251,_D252,_D253,_D254,_D255,_D256,_D257,_D258,_D259,_D260,_D261,_D262,_D263,_D264,_D265,_D266,_D267,_D268,_D269,_D270,_D271,_D272,_D273,_D274,_D275,_D276,_D277,_D278,_D279,_D280,_D281,_D282,_D283,_D284,_D285,_D286,_D287,_D288,_D289,_D290,_D291,_D292,_D293,_D294,_D295,_D296,_D297,_D298,_D299,_D300,_D301,_D302,_D303,_D304,_D305,_D306,_D307,_D308,_D309,_D310,_D311,_D312,_D313,_D314,_D315,_D316,_D317,_D318,_D319,_D320,_D321,_D322,_D323,_D324,_D325,_D326,_D327,_D328,_D329,_D330,_D331,_D332,_D333,_D334,_D335,_D336,_D337,_D338,_D339,_D340,_D341,_D342,_D343,_D344,_D345,_D346,_D347,_D348,_D349,_D350,_D351,_D352,_D353,_D354,_D355,_D356,_D357,_D358,_D359,_D360,_D361,_D362,_D363,_D364,_D365,_D366,_D367,_D368,_D369,_D370,_D371,_D372,_D373,_D374,_D375,_D376,_D377,_D378,_D379,_D380,_D381,_D382,_D383,_D384,_D385,_D386,_D387,_D388,_D389,_D390,_D391,_D392,_D393,_D394,_D395,_D396,_D397,_D398,_D399,_D400,_D401,_D402,_D403,_D404,_D405,_D406,_D407,_D408,_D409,_D410,_D411,_D412,_D413,_D414,_D415,_D416,_D417,_D418,_D419,_D420,_D421,_D422,_D423,_D424,_D425,_D426,_D427,_D428,_D429,_D430,_D431,_D432,_D433,_D434,_D435,_D436,_D437,_D438,_D439,_D440,_D441,_D442,_D443,_D444,_D445,_D446,_D447,_D448,_D449,_D450,_D451,_D452,_D453,_D454,_D455,_D456,_D457,_D458,_D459,_D460,_D461,_D462,_D463,_D464,_D465,_D466,_D467,_D468,_D469,_D470,_D471,_D472,_D473,_D474,_D475,_D476,_D477,_D478,_D479,_D480,_D481,_D482,_D483,_D484,_D485,_D486,_D487,_D488,_D489,_D490,_D491,_D492,_D493,_D494,_D495,_D496,_D497,_D498,_D499,_D500,_D501,_D502,_D503,_D504,_D505,_D506,_D507,_D508,_D509,_D510,_D511,_D512,_D513,_D514,_D515,_D516,_D517,_D518,_D519,_D520,_D521,_D522,_D523,_D524,_D525,_D526,_D527,_D528,_D529,_D530,_D531,_D532,_D533,_D534,_D535,_D536,_D537,_D538,_D539,_D540,_D541,_D542,_D543,_D544,_D545,_D546,_D547,_D548,_D549,_D550,_D551,_D552,_D553,_D554,_D555,_D556,_D557,_D558,_D559,_D560,_D561,_D562,_D563,_D564,_D565,_D566,_D567,_D568,_D569,_D570,_D571,_D572,_D573,_D574,_D575,_D576,_D577,_D578,_D579,_D580,_D581,_D582,_D583,_D584,_D585,_D586,_D587,_D588,_D589,_D590,_D591,_D592,_D593,_D594,_D595,_D596,_D597,_D598,_D599,_D600,_D601,_D602,_D603,_D604,_D605,_D606,_D607,_D608,_D609,_D610,_D611,_D612,_D613,_D614,_D615,_D616,_D617,_D618,_D619,_D620,_D621,_D622,_D623,_D624,_D625,_D626,_D627,_D628,_D629,_D630,_D631,_D632,_D633,_D634,_D635,_D636,_D637,_D638,_D639,_D640,_D641,_D642,_D643,_D644,_D645,_D646,_D647,_D648,_D649,_D650,_D651,_D652,_D653,_D654,_D655,_D656,_D657,_D658,_D659,_D660,_D661,_D662,_D663,_D664,_D665,_D666,_D667,_D668,_D669,_D670,_D671,_D672,_D673,_D674,_D675,_D676,_D677,_D678,_D679,_D680,_D681,_D682,_D683,_D684,_D685,_D686,_D687,_D688,_D689,_D690,_D691,_D692,_D693,_D694,_D695,_D696,_D697,_D698,_D699,_D700,_D701,_D702,_D703,_D704,_D705,_D706,_D707,_D708,_D709,_D710,_D711,_D712,_D713,_D714,_D715,_D716,_D717,_D718,_D719,_D720,_D721,_D722,_D723,_D724,_D725,_D726,_D727,_D728,_D729,_D730,_D731,_D732,_D733,_D734,_D735,_D736,_D737,_D738,_D739,_D740,_D741,_D742,_D743,_D744,_D745,_D746,_D747,_D748,_D749,_D750,_D751,_D752,_D753,_D754,_D755,_D756,_D757,_D758,_D759,_D760,_D761,_D762,_D763,_D764,_D765,_D766,_D767,_D768,_D769,_D770,_D771,_D772,_D773,_D774,_D775,_D776,_D777,_D778,_D779,_D780,_D781,_D782,_D783,_D784,_D785,_D786,_D787,_D788,_D789,_D790,_D791,_D792,_D793,_D794,_D795,_D796,_D797,_D798,_D799,_D800,_D801,_D802,_D803,_D804,_D805,_D806,_D807,_D808,_D809,_D810,_D811,_D812,_D813,_D814,_D815,_D816,_D817,_D818,_D819,_D820,_D821,_D822,_D823,_D824,_D825,_D826,_D827,_D828,_D829,_D830,_D831,_D832,_D833,_D834,_D835,_D836,_D837,_D838,_D839,_D840,_D841,_D842,_D843,_D844,_D845,_D846,_D847,_D848,_D849,_D850,_D851,_D852,_D853,_D854,_D855,_D856,_D857,_D858,_D859,_D860,_D861,_D862,_D863,_D864,_D865,_D866,_D867,_D868,_D869,_D870,_D871,_D872,_D873,_D874,_D875,_D876,_D877,_D878,_D879,_D880,_D881,_D882,_D883,_D884,_D885,_D886,_D887,_D888,_D889,_D890,_D891,_D892,_D893,_D894,_D895,_D896,_D897,_D898,_D899,_D900,_D901,_D902,_D903,_D904,_D905,_D906,_D907,_D908,_D909,_D910,_D911,_D912,_D913,_D914,_D915,_D916,_D917,_D918,_D919,_D920,_D921,_D922,_D923,_D924,_D925,_D926,_D927,_D928,_D929,_D930,_D931,_D932,_D933,_D934,_D935,_D936,_D937,_D938,_D939,_D940,_D941,_D942,_D943,_D944,_D945,_D946,_D947,_D948,_D949,_D950,_D951,_D952,_D953,_D954,_D955,_D956,_D957,_D958,_D959,_D960,_D961,_D962,_D963,_D964,_D965,_D966,_D967,_D968,_D969,_D970,_D971,_D972,_D973,_D974,_D975,_D976,_D977,_D978,_D979,_D980,_D981,_D982,_D983,_D984,_D985,_D986,_D987,_D988,_D989,_D990,_D991,_D992,_D993,_D994,_D995,_D996,_D997,_D998,_D999,_D1000	100	0.874
18	_H27,_G28,_E29	3	0.885
19	_E33,_C43,_D15,_E44,_Q42,_P444,_L45,_E46,_I47,_L49,_G49,_S49,_K497,_N499,_E51,_Q52,_C52,_E54,_P53,_Q58,_Q57,_V568,_Q500,_E510,_L511,_A512,_P512,_P514,_Q515,_S515,_A517,_K518,_D519,_S520,_E521,_N522,_L523,_R524,_P525,_E526,_P527,_E528,_P529,_E530,_P531,_E532,_P533,_E534,_P535,_E536,_P537,_E538,_P539,_E540,_P541,_E542,_P543,_E544,_P545,_E546,_P547,_E548,_P549,_E550,_P551,_E552,_P553,_E554,_P555,_E556,_P557,_E558,_P559,_E560,_P561,_E562,_P563,_E564,_P565,_E566,_P567,_E568,_P569,_E569,_P570,_E571,_P572,_E573,_P574,_E575,_P576,_E577,_P578,_E579,_P580,_E581,_P582,_E583,_P584,_E585,_P586,_E587,_P588,_E589,_P589,_E590,_P591,_E592,_P593,_E594,_P595,_E596,_P597,_E598,_P599,_E599,_P600,_E601,_P602,_E603,_P604,_E605,_P606,_E607,_P608,_E609,_P609,_E610,_P611,_E612,_P612,_E613,_P613,_E614,_P614,_E615,_P615,_E616,_P616,_E617,_P617,_E618,_P618,_E619,_P619,_E620,_P620,_E621,_P621,_E622,_P622,_E623,_P623,_E624,_P624,_E625,_P625,_E626,_P626,_E627,_P627,_E628,_P628,_E629,_P629,_E630,_P630,_E631,_P631,_E632,_P632,_E633,_P633,_E634,_P634,_E635,_P635,_E636,_P636,_E637,_P637,_E638,_P638,_E639,_P639,_E640,_P640,_E641,_P641,_E642,_P642,_E643,_P643,_E644,_P644,_E645,_P645,_E646,_P646,_E647,_P647,_E648,_P648,_E649,_P649,_E650,_P650,_E651,_P651,_E652,_P652,_E653,_P653,_E654,_P654,_E655,_P655,_E656,_P656,_E657,_P657,_E658,_P658,_E659,_P659,_E660,_P660,_E661,_P661,_E662,_P662,_E663,_P663,_E664,_P664,_E665,_P665,_E666,_P666,_E667,_P667,_E668,_P668,_E669,_P669,_E670,_P670,_E671,_P671,_E672,_P672,_E673,_P673,_E674,_P674,_E675,_P675,_E676,_P676,_E677,_P677,_E678,_P678,_E679,_P679,_E680,_P680,_E681,_P681,_E682,_P682,_E683,_P683,_E684,_P684,_E685,_P685,_E686,_P686,_E687,_P687,_E688,_P688,_E689,_P689,_E690,_P690,_E691,_P691,_E692,_P692,_E693,_P693,_E694,_P694,_E695,_P695,_E696,_P696,_E697,_P697,_E698,_P698,_E699,_P699,_E700,_P700,_E701,_P701,_E702,_P702,_E703,_P703,_E704,_P704,_E705,_P705,_E706,_P706,_E707,_P707,_E708,_P708,_E709,_P709,_E710,_P710,_E711,_P711,_E712,_P712,_E713,_P713,_E714,_P714,_E715,_P715,_E716,_P716,_E717,_P717,_E718,_P718,_E719,_P719,_E720,_P720,_E721,_P721,_E722,_P722,_E723,_P723,_E724,_P724,_E725,_P725,_E726,_P726,_E727,_P727,_E728,_P728,_E729,_P729,_E730,_P730,_E731,_P731,_E732,_P732,_E733,_P733,_E734,_P734,_E735,_P735,_E736,_P736,_E737,_P737,_E738,_P738,_E739,_P739,_E740,_P740,_E741,_P741,_E742,_P742,_E743,_P743,_E744,_P744,_E745,_P745,_E746,_P746,_E747,_P747,_E748,_P748,_E749,_P749,_E750,_P750,_E751,_P751,_E752,_P752,_E753,_P753,_E754,_P754,_E755,_P755,_E756,_P756,_E757,_P757,_E758,_P758,_E759,_P759,_E760,_P760,_E761,_P761,_E762,_P762,_E763,_P763,_E764,_P764,_E765,_P765,_E766,_P766,_E767,_P767,_E768,_P768,_E769,_P769,_E770,_P770,_E771,_P771,_E772,_P772,_E773,_P773,_E774,_P774,_E775,_P775,_E776,_P776,_E777,_P777,_E778,_P778,_E779,_P779,_E780,_P780,_E781,_P781,_E782,_P782,_E783,_P783,_E784,_P784,_E785,_P785,_E786,_P786,_E787,_P787,_E788,_P788,_E789,_P789,_E790,_P790,_E791,_P791,_E792,_P792,_E793,_P793,_E794,_P794,_E795,_P795,_E796,_P796,_E797,_P797,_E798,_P798,_E799,_P799,_E800,_P800,_E801,_P801,_E802,_P802,_E803,_P803,_E804,_P804,_E805,_P805,_E806,_P806,_E807,_P807,_E808,_P808,_E809,_P809,_E810,_P810,_E811,_P811,_E812,_P812,_E813,_P813,_E814,_P814,_E815,_P815,_E816,_P816,_E817,_P817,_E818,_P818,_E819,_P819,_E820,_P820,_E821,_P821,_E822,_P822,_E823,_P823,_E824,_P824,_E825,_P825,_E826,_P826,_E827,_P827,_E828,_P828,_E829,_P829,_E830,_P830,_E831,_P831,_E832,_P832,_E833,_P833,_E834,_P834,_E835,_P835,_E836,_P836,_E837,_P837,_E838,_P838,_E839,_P839,_E840,_P840,_E841,_P841,_E842,_P842,_E843,_P843,_E844,_P844,_E845,_P845,_E846,_P846,_E847,_P847,_E848,_P848,_E849,_P849,_E850,_P850,_E851,_P851,_E852,_P852,_E853,_P853,_E854,_P854,_E855,_P855,_E856,_P856,_E857,_P857,_E858,_P858,_E859,_P859,_E860,_P860,_E861,_P861,_E862,_P862,_E863,_P863,_E864,_P864,_E865,_P865,_E866,_P866,_E867,_P867,_E868,_P868,_E869,_P869,_E870,_P870,_E871,_P871,_E872,_P872,_E873,_P873,_E874,_P874,_E875,_P875,_E876,_P876,_E877,_P877,_E878,_P878,_E879,_P879,_E880,_P880,_E881,_P881,_E882,_P882,_E883,_P883,_E884,_P884,_E885,_P885,_E886,_P886,_E887,_P887,_E888,_P888,_E889,_P889,_E890,_P890,_E891,_P891,_E892,_P892,_E893,_P893,_E894,_P894,_E895,_P895,_E896,_P896,_E897,_P897,_E898,_P898,_E899,_P899,_E900,_P900,_E901,_P901,_E902,_P902,_E903,_P903,_E904,_P904,_E905,_P905,_E906,_P906,_E907,_P907,_E908,_P908,_E909,_P909,_E910,_P910,_E911,_P911,_E912,_P912,_E913,_P913,_E914,_P914,_E915,_P915,_E916,_P916,_E917,_P917,_E918,_P918,_E919,_P919,_E920,_P920,_E921,_P921,_E922,_P922,_E923,_P923,_E924,_P924,_E925,_P925,_E926,_P926,_E927,_P927,_E928,_P928,_E929,_P929,_E930,_P930,_E931,_P931,_E932,_P932,_E933,_P933,_E934,_P934,_E935,_P935,_E936,_P936,_E937,_P937,_E938,_P938,_E939,_P939,_E940,_P940,_E941,_P941,_E942,_P942,_E943,_P943,_E944,_P944,_E945,_P945,_E946,_P946,_E947,_P947,_E948,_P948,_E949,_P949,_E950,_P950,_E951,_P951,_E952,_P952,_E953,_P953,_E954,_P954,_E955,_P955,_E956,_P956,_E957,_P957,_E958,_P958,_E959,_P959,_E960,_P960,_E961,_P961,_E962,_P962,_E963,_P963,_E964,_P964,_E965,_P965,_E966,_P966,_E967,_P967,_E968,_P968,_E969,_P969,_E970,_P970,_E971,_P971,_E972,_P972,_E973,_P973,_E974,_P974,_E975,_P975,_E976,_P976,_E977,_P977,_E978,_P978,_E979,_P979,_E980,_P980,_E981,_P981,_E982,_P982,_E983,_P983,_E984,_P984,_E985,_P985,_E986,_P986,_E987,_P987,_E988,_P988,_E989,_P989,_E990,_P990,_E991,_P991,_E992,_P992,_E993,_P993,_E994,_P994,_E995,_P995,_E996,_P996,_E997,_P997,_E998,_P998,_E999,_P999,_E1000,_P1000	50	0.54
20	_E32,_D33,_E31,_G36,_E36	5	0.800
21	_K452,_Q480,_L438,_Q439,_Q440,_E441	5	0.882
22	_C58,_Q57,_P50,_C59,_C60,_C120,_C124,_Q125,_C126	9	0.588

2.5 Gly m 5.0301:

Predicted Discontinuous Epitope(s):

No.	Residues	Number of residues	Score
1	_Q415,_K420,_C421,_E422,_G423,_G424,_K425,_G425,_R427,_K420,_G428,_P430,_F431,_P432,_G433,_H34,_L430,_Q436,_A437,_L438,_Y438	21	0.503
2	_R3,_V4,_R5,_F3,_F7,_L8,_L9,_V10,_L11,_L12,_G13,_T14,_V15,_F16,_L17,_A18,_S19,_V20,_C21,_V22,_S23,_L24,_K25,_V26,_R27,_E28,_C29,_E30,_N31	29	0.681
3	K317,_Q318,_K319	3	0.863
4	_Q320,_C321,_C322	3	0.704
5	_H48,_Q49,_H53,_K50,_P51,_H52,_G101,_E102,_H103,_P107,_H106,_D109,_H140,_Q141,_H142,_L163,_S164,_S165,_T168,_Q167,_S168,_Q169,_Q170,_S171,_Y172,_L173,_Q174,_G175,_F176,_S177,_H179,_T180,_C181,_E182,_T183,_S184,_F185,_H185,_S187,_E188,_F189,_E190,_E191,_I192,_N193,_R194,_V195,_L196,_F197,_G199,_E199,_E200,_E201,_E202,_Q203,_Q205,_Q206,_E207,_Q208,_V209,_Q210,_V211,_E212	64	0.722
6	H180,_N180,_D111,_D112,_H113,_D114,_Q217,_K218,_H219,_Q220,_L221,_S222,_H223,_I224	14	0.783
7	_A574,_Q375,_E376,_K377,_D378,_N379,_V380,_V381,_D382,_Q383,_I384,_E385,_R386,_Q387,_V388,_Q389,_E590,_L591,_A390,_F393,_P394,_Q395,_E396,_A397,_Q398,_Q399,_V400,_F401,_R402,_L403,_F404,_K405,_K406,_Q407,_R408,_F409,_S410,_Y411	30	0.75
8	_L213,_S214,_K215,_E216	4	0.638
9	E11,_K312,_E313,_Q314,_Q315,_Q316,_E323,_I324,_L325,_E326,_V327	11	0.594
10	_P947,_Q950,_N951,_N952,_P953,_N956,_F981,_Q982,_A987,_T983,_Q984,_K985,_N986,_A987,_Q988,_P989,_Q990,_F991,_I992,_N993,_R994,_V995,_L996,_F997,_G999,_E999,_E200,_E201	17	0.547
11	_A225,_K226,_S227,_S228,_S229,_R230,_K231,_T232,_I233,_S234,_S235,_E236,_D237,_E238,_P239,_F240,_H241,_S244,_R245,_T260,_P261,_E262,_K263,_H264,_P265,_R266,_D271,_A265,_E266,_N267	30	0.524

2.6 Gly m 5.0302:

Predicted Discontinuous Epitope(s):

No.	Residues	Number of residues	Score
1	_M1,_M2,_V4,_R5	4	0.991
2	F431,_F432,_S433,_I434,_L435,_G436,_A437,_L438,_Y439	9	0.956
3	F6,_P7,_L8,_L9,_V10,_L11,_L12,_G13,_T14,_V15,_F16,_L17,_A18,_S19,_V20,_C21,_V22,_S23,_L24	19	0.944
4	_K426,_G429,_P430	3	0.927
5	_E421,_E422,_G423,_S424,_K425,_G426,_R427	7	0.883
6	_L86,_F87,_L163,_S154,_S165,_T166,_O167,_A168,_O169,_Q170,_S171,_V172,_L173,_O174,_G175,_F175,_S177,_F178,_N179,_H180,_L181,_E182,_T183,_S134,_F185,_H136,_S187,_E138,_F185,_E190,_E161,_V192,_N193,_R194,_V195,_L196,_F197,_G198,_E199,_E200,_E201,_E202,_O203,_R204,_O205,_O206,_E207,_G203,_V209	49	0.757
7	_I311,_K312,_C313,_Q314,_Q315,_K317,_Q318,_K319,_Q320,_C321,_C322,_C323,_P324,_L325,_C329	15	0.723
8	_N109,_N110,_D111,_D112,_R113	5	0.672
9	_L373,_A374,_G375,_E376,_K377,_D378,_S379,_V380,_V381,_R382,_Q383,_I384,_E385,_R386,_Q387,_V388,_Q389,_E390,_L391,_A392,_F393,_P394,_G395,_S396,_A397,_Q398,_F399,_V410,_F401,_R402,_I403,_I404,_K406,_O407,_F409,_S410,_V411	57	0.669
10	_N48,_Q49,_V50,_K50,_F61,_H62,_R162,_D114,_S115,_P137,_H138,_D139,_H140,_Q141,_H142,_V211,_E212,_L213,_S214,_K215,_E216,_Q217,_I218,_R219,_Q220,_L221,_S222,_F223,_E224,_N225,_K226,_S227,_S228,_S229,_R230,_K231,_T232,_T233,_S234,_S235,_E236,_D237,_E238,_P239,_P240,_N241,_S244,_R245,_N246,_P247,_S250,_N251,_N252	57	0.593
11	_D414,_A415,_G416,_F417,_G418,_G419	6	0.588
12	_R27,_E28,_D29,_E30,_N31	5	0.516
13	_E67,_N68,_R70,_D91,_V152,_N153,_K154,_P155,_G156,_R157	10	0.519

2.7 Gly m 6.0101:

Predicted Discontinuous Epitope(s):

No.	Residues	Number of Residues	Score
1	_M1 _A2 _K3 _L4 _V5 _F6 _S7 _L8 _C9	9	0.99
2	_K491 _R492 _A493 _V494 _A495	5	0.361
3	_P276 _Q277 _E278	3	0.322
4	_F10 _L11 _I12 _F13 _S14 _G15 _C16 _C17 _F18 _A19 _F20 _S21 _S22 _R23 _E24 _Q25 _P25 _Q27 _Q26 _N28 _E30 _C31 _Q32	23	0.317
5	_Y334 _N335 _P336 _Q337 _A338 _C339 _R365 _K366 _N367 _A368 _M369 _F370 _V371 _P372 _C387 _R423 _S424 _Q425 _S426 _D427 _N428 _T444 _L445 _A446 _C447 _A448 _N449 _S450 _L451 _L452 _N453 _A454 _L455 _F455 _E457 _E453 _V459 _T460 _Q461 _R462 _L463 _F464 _R465 _C466 _K467 _S468 _Q469 _Q470 _A471 _R472 _Q473 _R474 _K475 _N476 _N477 _N479 _P479 _F483 _K481 _F482 _L483 _V484 _P485 _F489 _Q487 _E488 _S489 _Q490	66	0.711
6	_S47 _E48 _G49 _N75 _R76 _N77 _Y104 _P105 _G106 _C107 _P108 _S109 _T110 _F111 _E112 _E113 _P114 _Q115 _Q116 _P117 _Q118 _Q119 _R120 _Q121 _Q122 _S123 _S124 _T125 _P126 _Q127 _D129 _P129 _H30 _Q131 _C152 _D157 _T159 _N173 _Q174 _L175 _D176 _Q177 _M178 _L184 _A195 _G196 _N197 _Q198 _C199 _S199 _T200 _Q201 _Q202 _S203 _F204 _R226 _E227 _T229 _L230 _E230 _H231 _T232 _F235 _S231 _T235 _D236 _K237 _Q238 _L239 _Q240 _K241 _K242 _C243 _Q245 _E246 _N247 _E248 _G249 _E250 _D251 _D252 _G253 _T257 _V258 _K259 _G260 _G261 _L262 _S263 _T264 _P267 _P268 _T269 _D270 _E271 _Q272 _Q273 _Q274 _Q275 _E276 _E296 _E281 _E282 _E283 _E284 _D285 _D287 _P288 _G289 _C290 _K291 _G292 _Q293 _G294 _K295 _H296 _C297 _Q298 _R299 _P300 _R301 _G302 _S303 _Q304 _S305 _K306 _S307 _R308 _R309 _N310 _G311 _I312 _D313 _C314	161	0.364
7	_N395 _C396 _N397 _G398 _E399	5	0.516

2.8 Gly m 6.0201:

Predicted Discontinuous Epitope(s):

No.	Residues	Number of residues	Score
1	_M1, _A2, _K3, _L4, _V5, _L6, _S7, _L8, _C9, _F10, _L11, _L12, _F13, _S14, _G15, _C16, _F17, _A18, _L19	19	0.955
2	_R482, _A493, _V484, _A485	4	0.951
3	_E113, _S114, _G115, _Q116, _R117, _G113, _R119, _S120, _Q121	9	0.878
4	_D271, _F272, _F273, _D274, _N275, _D276, _D277, _F278, _F279	9	0.841
5	_E260, _Q231, _P282, _Q283, _C284, _V285, _E286, _T287, _D238, _K289, _G290, _C291, _Q292, _Q291, _S265, _K236	16	0.815
6	_C21, _Q22, _A23, _Q24	4	0.735
7	_Y124, _N325, _P326, _Q327, _A328, _G329, _R355, _K356, _N357, _A358, _V359, _F360, _V361, _P362, _G377, _R378, _L380, _Q382, _R390, _D395, _G394, _E395, _K413, _S414, _Q415, _S415, _D417, _N413, _N434, _L435, _A433, _Q437, _A438, _N439, _S440, _L441, _L442, _N443, _A444, _L445, _P446, _E447, _E448, _V449, _T450, _G451, _R452, _T453, _F454, _N455, _L456, _K457, _S458, _Q459, _Q463, _A461, _R452, _Q463, _V464, _K463, _N466, _N467, _N468, _F459, _F470, _S471, _F472, _L473, _V474, _F475, _P476, _Q477, _E475, _S478, _C480	75	0.71
8	_R41, _C40, _G44, _C45, _G45, _G47, _N72, _R70, _N74, _N52, _C153, _D154, _T155, _F156, _A102, _G103, _N104, _Q185, _Q197, _Q190, _G199, _S200, _Q201, _S202, _Q233, _K204, _G205, _K205, _Q207, _C208, _E219, _E211, _N212, _E213, _G214, _S215, _N216, _D217, _L218, _S219, _G220, _F221, _A221, _F223, _E224, _F225, _L225, _K227, _E228, _A229, _F230, _G231, _V232, _N233, _M234, _Q235, _Q235, _V337, _R238, _N238, _L240, _Q241, _G242, _E243, _N244, _E245, _E245, _E277, _D248, _S249, _G250, _K251, _V253, _T254, _V255, _K256, _G257, _G258, _L259, _R260, _V261, _T262	80	0.672
9	_P165, _S186, _T187, _V168, _C108, _F110, _P111, _G112, _R122, _P123, _Q124, _D125, _R125, _H127, _Q128, _K129, _P264, _M266, _R267, _K268, _P269, _Q270	22	0.626
10	_E166, _G191, _Q165, _C196	4	0.608
11	_N385, _C303, _N387, _G303, _C309	5	0.555

2.9 Gly m 6.0301:

Predicted Discontinuous Epitope(s):

No.	Residues	Number of residues	Score
1	_M1 _A2 _K3	3	0.995
2	_R478 _V479 _V480 _M481	4	0.943
3	_Q113 _K117 _G118 _Q119 _S120 _S121	6	0.928
4	_I4 _V5 _I6 _S7 _I8 _C9 _F10 _I11 _I12 _F13 _S14 _G15 _C16 _C17 _F18 _A19 _F20 _S21 _F22 _R23	20	0.976
5	_R122 _P123 _Q124 _D125	4	0.756
6	_F323 _N321 _P322 _Q325 _A324 _G325 _P351 _K352 _N353 _A354 _M355 _F356 _V357 _P356 _G373 _R374 _S410 _Q411 _S412 _D415 _N414 _N430 _L431 _A432 _C433 _A454 _N436 _S436 _L437 _L438 _N439 _A440 _A441 _T442 _E443 _E444 _V445 _A45 _Q447 _Q448 _T449 _F450 _N451 _C462 _N464 _Q465 _Q466 _F467 _N468 _Q469 _P461 _N462	67	0.701
7	_Q107 _Q108 _C109 _C200 _T201 _C202 _S203 _Q204 _K205 _C206 _K207 _R208	12	0.585
8	_S47 _F48 _G49 _N75 _R76 _V77 _F104 _P105 _G108 _C107 _P108 _S109 _T110 _F111 _F112 _F113 _P114 _Q115 _P126 _H127 _Q128 _N157 _F153 _D154 _T155 _A187 _G183 _N184 _Q185 _Q187 _E211 _E212 _E213 _I214 _E215 _C215 _C217 _S219 _I219 _L220 _S221 _C222 _F225 _A224 _T225 _E226 _F227 _I228 _E229 _R230 _A231 _F232 _V233 _V234 _D235 _E236 _Q237 _L238 _V239 _R240 _K241 _L242 _Q243 _Q244 _E245 _I245 _E247 _E248 _E249 _E250 _K251 _S252 _L256 _V257 _K259 _G259 _G260 _L261 _S262 _V263 _I264 _S265 _P266 _P267 _L268 _E269 _E270 _Q271 _Q272 _C273 _R274 _P275 _E276 _E277 _E278 _E279 _K280 _P281 _D282 _C283 _D284 _E285 _K286 _D287 _C288 _H289 _C290 _Q291 _S292 _Q293 _G294 _R295 _N296 _S297 _I298 _D299 _C300 _T301 _I302 _C303 _T304 _A305	121	0.68
9	_P194 _Q195 _K196	3	0.549
10	_E24 _Q25 _P26 _Q27 _Q28 _N29 _E30 _C31 _Q32	9	0.561
11	_N381 _C382 _N383 _G384 _E385	5	0.517

2.10 Gly m 6.0401:

1	_E332 _Q333 _D334 _Q335	4	0.99
2	_R325 _P326 _S327 _Q328 _Q329 _K330	6	0.986
3	_R322 _P323 _S324	3	0.973
4	_M1 _G2 _K3 _H4	4	0.968
5	_D313 _E314 _D315 _E316 _D317 _E318 _D319 _K320 _P321	9	0.953
6	_D336 _Q337 _D338 _E339 _D340 _E341 _D342	7	0.952
7	_E343 _D344 _E345 _D346 _Q347 _P348 _R349	7	0.911
8	_V560 _K561 _V562 _A563	4	0.908
9	_R301 _R302 _P303 _S304 _H305 _G306 _K307 _R308	8	0.871
10	_K350 _S351 _R352 _C353 _W354	5	0.867
11	_F5 _T6 _L7 _S8 _L9 _S10 _S11 _L12 _C13 _L14 _L15 _L16 _L17 _S18 _S19 _A20 _C21	17	0.86
12	_Q555 _G556 _S557 _P558 _R559	5	0.85
13	_K208 _S209 _H210 _C211 _C212 _R213 _K214 _Q215 _C216 _Q217 _H218 _Q219 _Q220	13	0.884
14	_S356 _K357 _K358 _T359 _Q360 _P361 _R363 _P364	8	0.875
15	_F22 _A23 _I24 _S25 _S26 _S27 _K28 _L29 _N30 _E31 _C32 _Q35 _L34 _N35 _N36 _L37 _A38 _N105 _F104 _K105 _A106 _Y133 _K431 _N135 _G436 _H137 _S439 _P440 _K458 _R460 _V462 _K463 _C464 _C465 _N467 _A468 _V469 _D471 _G472 _E473 _F486 _V487 _Q491 _A492 _G493 _E494 _G496 _Y512 _I513 _S514 _C515 _V516 _F517 _R518 _A519 _N520 _P521 _S522 _E523 _V524 _T525 _S526 _F527 _S528 _I529 _K530 _F531 _R532 _Q533 _S534 _Q535 _Q536 _S537 _F538 _I539 _R541 _F541 _F542 _R543 _N544 _L546 _P547 _V549 _N550 _P551 _S552 _S553 _O554	89	0.664
16	_Q294 _I295 _P296 _S297 _H298 _P299 _P300	7	0.663
17	_Q202 _Q203 _Q204 _Q205 _Q206 _Q207	6	0.657
18	_S48 _E49 _G50 _N76 _E110 _E113 _E114 _P115 _Q116 _E117 _Q118 _S119 _N120 _R121 _Q123 _S124 _R125 _S126 _Q127 _K128 _Q129 _Q130 _L131 _Q132 _D133 _S134 _H135 _N146 _E147 _I148 _I149 _N150 _P151 _F152 _F153 _F154 _G155 _G156 _F157 _S158 _C159 _S160 _S161 _Q162 _F163 _F164 _Q165 _H166 _F167 _I168 _P169 _D170 _S241 _F242 _N243 _T244 _N245 _E246 _D247 _I248 _Q249 _E250 _K251 _L252 _D253 _S254 _P255 _D256 _E257 _E258 _R259 _K260 _L261 _V265 _E266 _G267 _G268 _L269 _S270 _V271	81	0.638

2.11 Gly m 6.0501:

Predicted Discontinuous Epitope(s):

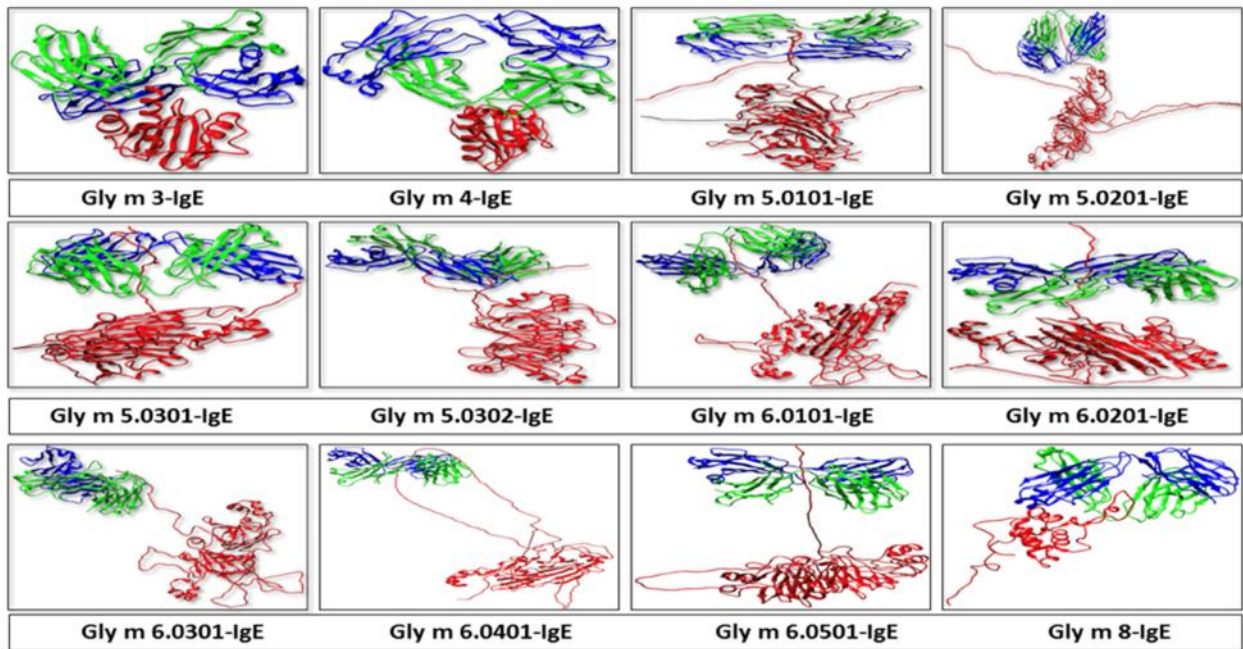
No. ↕	Residues	Number of residues ↕	Score ↕
1	_M1 _G2 _K3 _P4	4	0.956
2	_Y280 _E200 _Q291 _T202 _P203 _S204 _Y205 _P293 _P297 _R298	10	0.346
3	_R299 _P300 _S301 _H302 _G303 _K304 _H305 _E306 _D307 _D308 _E309 _D310 _E311 _D312 _E313 _E314 _E315 _D316 _Q317 _P318	20	0.871
4	_D44 _M201 _Q202 _Q203 _Q204 _Q205 _Q206 _Q207 _K208 _S209 _T210 _G211 _G212 _R213 _K214 _Q215 _G216 _Q217 _T218 _Q219 _Q220 _Q221	22	0.728
5	_F5 _F5 _T7 _L8 _S9 _I10 _S11 _S12 _I13 _C14 _I15 _I16 _I17 _I18 _S19 _S20 _A21 _G22 _F23 _A24 _D5 _T26 _S27 _S28 _K29 _F30 _N31 _F32 _G33 _Q34 _I35 _N36 _H37 _L38 _N39 _A40 _Y368 _N359 _P370 _K371 _A372 _Y380 _R400 _N401 _G402 _A403 _S405 _P406 _N408 _L410 _R422 _Q423 _R424 _R426 _V427 _V428 _I429 _C430 _Q431 _G432 _H433 _A434 _V435 _F436 _D437 _G438 _E439 _H451 _F452 _V453 _G455 _G457 _S458 _G459 _F460 _Q461 _G462 _S477 _Y478 _R479 _K480 _D481 _V482 _F483 _R484 _A485 _H486 _T487 _S488 _E489 _V490 _L491 _S492 _K493 _S494 _Y495 _R495 _L497 _D498 _S499 _S500 _D501 _G502 _R503 _D504 _L505 _K506 _Y507 _D508 _G509 _N510 _S511 _G512 _F513 _L514 _V515 _N516 _F517	118	0.724
6	_Q276 _E275 _D280 _E281 _D282 _E283 _D284 _E285 _D286 _E287 _E288 _G339 _Q340 _Q341 _T342	15	0.339
7	_E48 _S49 _E50 _G51 _N79 _E111 _E114 _K115 _P119 _G117 _G118 _Q119 _S120 _S121 _R122 _R123 _G124 _S125 _R126 _S127 _Q128 _Q129 _Q130 _L131 _Q132 _D133 _S134 _H135 _A190 _G191 _N192 _P193 _D194 _I195 _P198 _E222 _E223 _E224 _G225 _G226 _G227 _V228 _L229 _S230 _G231 _F232 _S233 _Q234 _H235 _F236 _L237 _A258 _Q259 _S270 _F241 _N242 _T243 _N244 _E245 _D246 _T247 _A248 _E249 _K250 _L251 _R252 _S253 _P254 _D255 _D256 _E257 _R258 _K259 _Q260 _T263 _V264 _E265 _G266 _G267 _L268 _S269 _V270	87	0.553
8	_K319 _P320 _D321 _H322	4	0.342

2.12 Gly m 8:

Predicted Discontinuous Epitope(s):

No. ↕	Residues	Number of residues ↕	Score ↕
1	_M1 _T2 _K3	3	0.987
2	_R72 _G73 _R74 _I75 _N76	5	0.884
3	_F4 _T5 _I6 _L7 _L8 _I9 _S10 _L11 _L12 _F13 _C14 _I15 _A16 _H17 _T18 _C19 _S20 _A21 _S22 _K23	20	0.845
4	_Q25 _H26 _Q28 _D29 _S30	5	0.696
5	_Y77 _I78 _R79 _N81 _E82 _G83	6	0.692
6	_Q52 _G53 _R54 _G55 _D56 _D57 _D58 _D59	8	0.665
7	_D60 _D61 _D62 _D63 _D64 _N65 _H66 _I67 _L68 _R69 _T70 _M71	12	0.616
8	_F146 _G147 _P148 _M149 _I150 _Q151 _C152 _D153	8	0.608
9	_E103 _L104 _R105	3	0.563
10	_S122 _E124 _L125 _E126 _E127 _K128	6	0.502

Supplementary Figure 3: The docked pose of different Gly m and HL domain of Fab region of Immunoglobulin E



Supplementary Figure 4: The Multiple Sequence Alignment Analysis and the Sequence Identity Matrix results obtained through Clustal Omega on the identified epitope sites of the *Glycine Max* allergen family.

