COMPUTATIONAL PREDICTION OF PYRETHROIDS AS PROMISING AGENTS AGAINST RESPIRATORY SYNCYTIAL VIRUS: A COMPARATIVE STUDY

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ABSTRACT

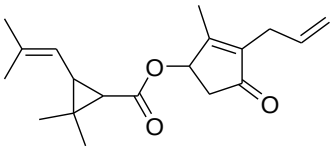
Pyrethrin; derived from natural source (Chrysanthemum cinerariifolium) confirmed as a fundamental nucleus for the development of pyrethroids which ultimately resulted in the outstanding insecticidal activity by targeting the nervous systems of insects. To date, the binding and entry mechanism by which RSV infects respiratory epithelial cells is not still well understood and need to be explored. Notably, pyrethrins have exhibited considerable antiviral potential & thus an effort was made computationally to evaluate the pyrethroids as hopeful inhibitors of Respiratory Syncytial Virus (RSV). Type 1 & type 2 Pyrethroids were subjected to docking simulations by using Maestro 9.2 version (Schrodinger LLC). Cyfluthrin showed better binding interactions against RSV (Glide score: -4.54). Remarkably, it showed two hydrogen bonding interactions with Lys46 (1.82 Å) & Hie151 (2.19 Å) of RSV protein receptor. The decrease in glide score is evidence for greater bond stability with protein. Based on the current findings, these studies in future may act as effective predecessor tool to further validate pyrethroids with wet lab experiments as capable antiviral agents for RSV.

Keywords: Pyrethroids, respiratory syncytial virus, docking

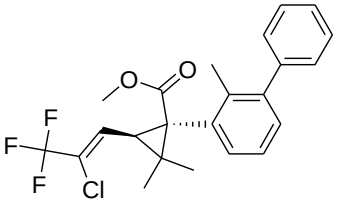
INTRODUCTION

For the infant and young children respiratory syncytial virus (RSV) serves as an important precursor for the development of bronchiolitis. According to WHO, RSV showed accountability alone for more than 60% of acute respiratory infections in children worldwide. More than 80% of infant younger than 1 year suffered from lower tract infection during the peak viral season.[1] Previous studies have indicated that at the age of 2 to 3 month (lowest IgG concentration), the infections happened mostly with no time. The host responses to RSV infection depend on magnitude and intensity of infection.[2] RSV belongs from the family paramyxoviridne which is a single stranded RNA virus. The genome compromises of ten genes that encodes for eleven different proteins. The major antigen F protein and the G glycoprotein these are two surface proteins these are responsible for the virulence of the RSV. Till date, there is no specific drug of choice for the treatment of RSV infection and the drugs which are already available in the market posses certain drawbacks such as binfant suffered from congenital heart disease & chronic lung diseases, respectively.[3] Pyrethin is a chief phytoconstituent of *Chrysanthemum cineraraefolum* which serves as an important predecessor for the development of pyrethroids. Pyrethroids are widely used in home and agriculture as insecticides to control the pest. Human are exposed to pyrethroid by various mode like air, water, vegetables, etc at low concentration and it's safe to humans. Deltamethrin and fenvalerate are chemically type 2 pyrethroids which show α-cyano phenoxy benzyl moiety while the type 1 pyrethroids such as permethrin lack this moiety. The chiral nature of all the synthetic pyrethroids usually exists in different forms of enantiomers.[4-5] Synthetic pyrethroids reported as hemopiosons which act on the axons and in the central nervous system by interfering with sodium channel in mammals or in insects.[6] Hata et al., 2011 demonstrated that at a concentration of 4-12 μM, pyrethrin showed antiplasmodial activity while between 7 to 31 μM showed antitrypanosomal action. On the other hand, the efficacy of pyrethrin analogues formulations were also examined against vector diseases.[7] The literature report has indicated the pyrethrins role as antiviral source & thus an attempt was made to evaluate the pyrethroids as expectant inhibitors of Respiratory Syncytial Virus (RSV).[8] To date, the binding and way in mechanism by which RSV infects respiratory epithelial cells is still

unclear and need to be unlocked. Therefore, the present study was designed to comparatively evaluate the *in-silico* potential of type1 & type 2 pyrethroids against RSV infections.



Allethrin



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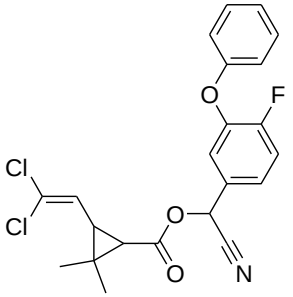
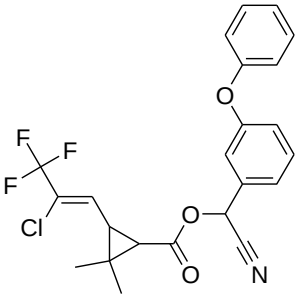
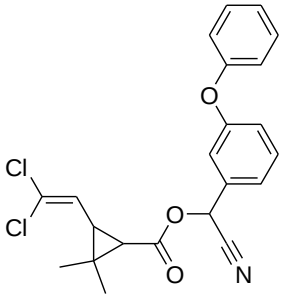


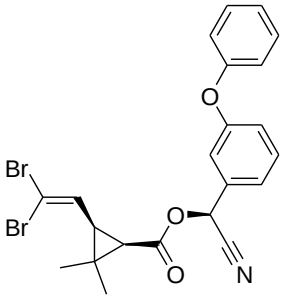
Cyfluthrin



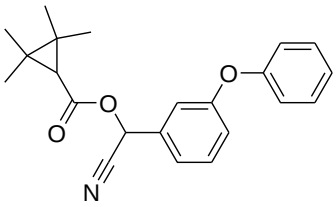
Cyhalothrin



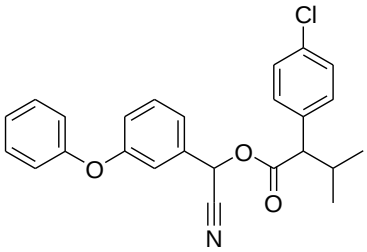
Cypermethrin



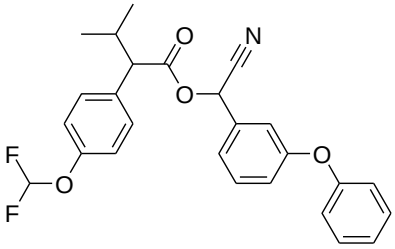
Deltamethrin



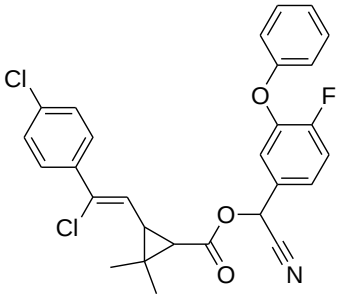
Fenpropathrin



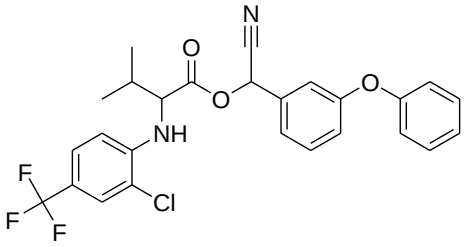
Fenvalerate



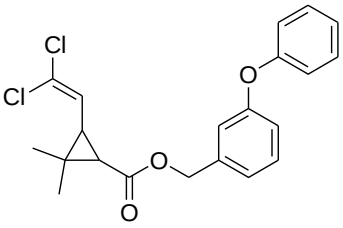
Flucythrinate



Flumethrin



Fluvalinate



Permethrin

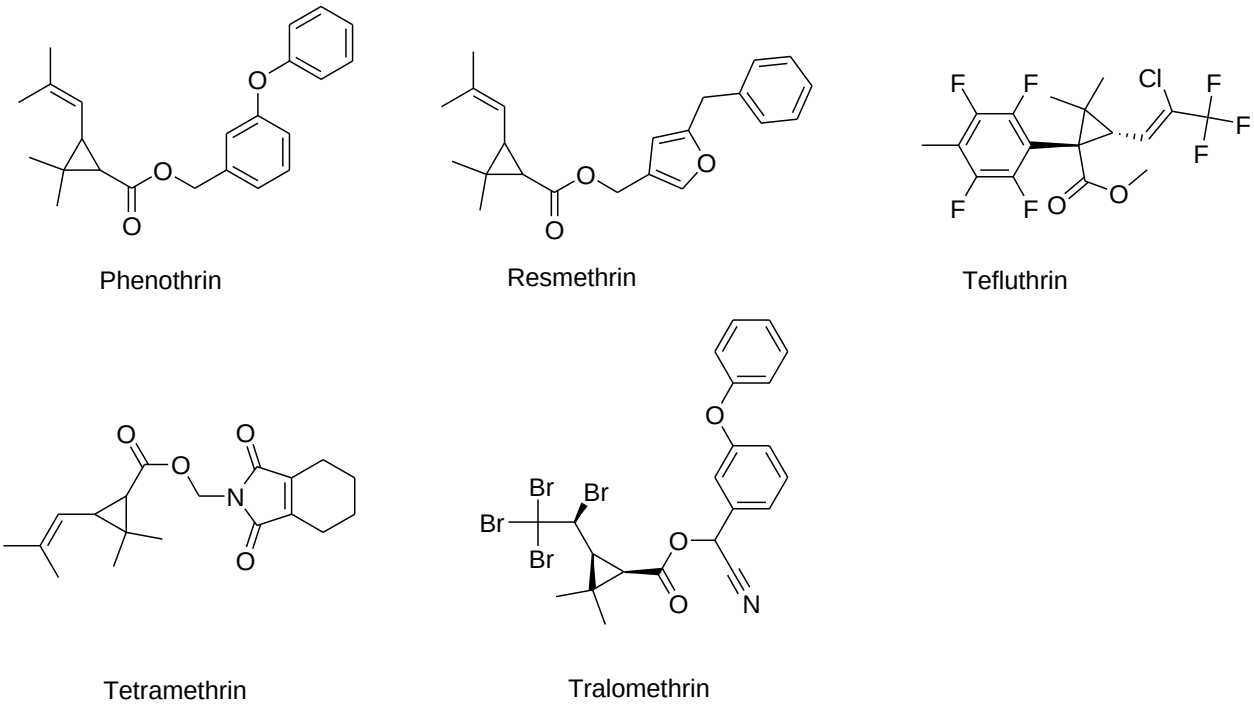


Figure 1: Chemical entities structures of type 1 & 2 Pyrethroids.

MATERIALS & METHODS

Maestro 9.2 version software (Schrodinger LLC suite) was used for carrying out the docking simulations. Molecular docking software was installed in single machine running on core TM processor with 2 GB RAM and 180 GB with centrp linux as operating system.

Protein preparation

The 3-dimensional protein structure (PDB: 4UCC) was retrieved from RCSB protein site in PDB format [9] & exported into Maestro software. Protein pre-processes was done by addition of polar hydrogen and removal of metal ions, cofactor and water molecule outside 5Å. The ionization (PH: 6.7-7.3), optimization of hydrogen bond and restorative energy minimization have executed to receptors molecule, an essential step to the correct geometry of receptors.

Ligand library

With the help of Chem draw ultra 10.0 (Cambridge soft) the structure were drawn and tested compounds were saved in three dimensional structure (.mol format) and then plot into maestro project table. Least square OPLS_2005 force field is used to complete the ligands preparations plus energy minimization. Furthermore, generations of conformers plus energy minima were performed to enhance the stability of ligands with the receptor.

Grid generation & docking assessment

XP visualize was used for the docking pose analysis. The binding pocket having the electrostatic and vander wall's potential was assigned through grid box. The *in-silico* docking results should analysed not only on the basis of glide score but also different type of interactions of tested molecules with the receptor.[10]

RESULTS & DISCUSSION

The reference ligand (1-[(2,4-dichlorophenyl)methyl]pyrazole-3,5- dicarboxylic acid) along with type 1 & type 2 pyrethroids were docked against cancer proteins (PDB: 4UCC). According to the glide score of the test ligands the ranking were evaluated by top HITs. Table 1 reports have revealed that cyfluthrin possess higher binding affinity with estrogen (Glide Score: -4.54) against RSV receptor.

Table 1: Docking results of Pyrethroids for Respiratory Syncytial Virus on Maestro (PDB: 4UCC)

Compounds	Glide Score	No. of H-bonds	H-bond distance (Å)	Amino acid involved
*Ref	-5.44	4	2.06	Arg132
			1.98	Arg132
			1.60	Lys46
			1.90	Hie151
Cyfluthrin	-4.54	2	1.82	Lys46
			2.19	Hie151
Resmethrin	-4.24	1	1.94	Hie151
Permethrin	-4.24	1	2.00	Hie151
Phenothrin	-4.01	1	2.14	Hie151

Compounds	Glide Score	No. of H-bonds	H-bond distance (Å)	Amino acid involved
Flucythrinate	-4.01	1	2.29	Arg132
Fenvalerate	-3.83	1	2.26	Arg132
Cypermethrin	-3.65	1		Hie151
Flumethrin	-3.53	1	2.17	Arg132
Tralomethrin	-3.45	-	-	-
Tetramethrin	-3.38	2	1.89	Arg150
			2.09	Hie151
Tefluthrin	-3.18	1	2.11	Arg150
Deltamethrin	-2.89	2	2.21	Arg150
			2.24	Arg132
Fluvalinate	-2.78	1	2.15	Arg150
Fenpropathrin	-2.03	2	1.87	Arg132
			2.35	Arg132
Cyhalothrin	-	-	-	-
Bifenthrin	-	-	-	-
Allethrin	-	-	-	-

*Ref: 1-[(2,4-dichlorophenyl)methyl]pyrazole-3,5- dicarboxylic acid

Top ranked pyrethroid HITs

Cyfluthrin

Cyfluthrin has resulted in the most powerful hit (first rank) compound against RSV protein. The hydrophobic interactions such as Phe111, Met50, Ile53 & Tyr135 were observed. Additionally, π-π interactions were examined (Hie151 & Tyr135). This compound was too capable of forming H-bonding interactions with Lys46 & Hie151, respectively.

Resmethrin

It was also placed among top ranked hits (second rank) with glide score as indicated in Table 1. Interestingly, hydrophobic interactions with different amino acid residues like Phe111, Met50, Ile53 & Tyr135 correspondingly were reported. The amino acid residues like Arg132 & Hie151 were able of forming H-bonding interactions while Tyr135 showed π-π interaction.

Permethrin

Permethrin was also capable of showing hydrophobic interactions like Phe111, Met50, Ile53 & Tyr135 with RSV proteins. Markedly, H-bonding interaction of Hie151 was observed. Moreover, Tyr135 & Hie151 was also capable of forming π-π interactions.

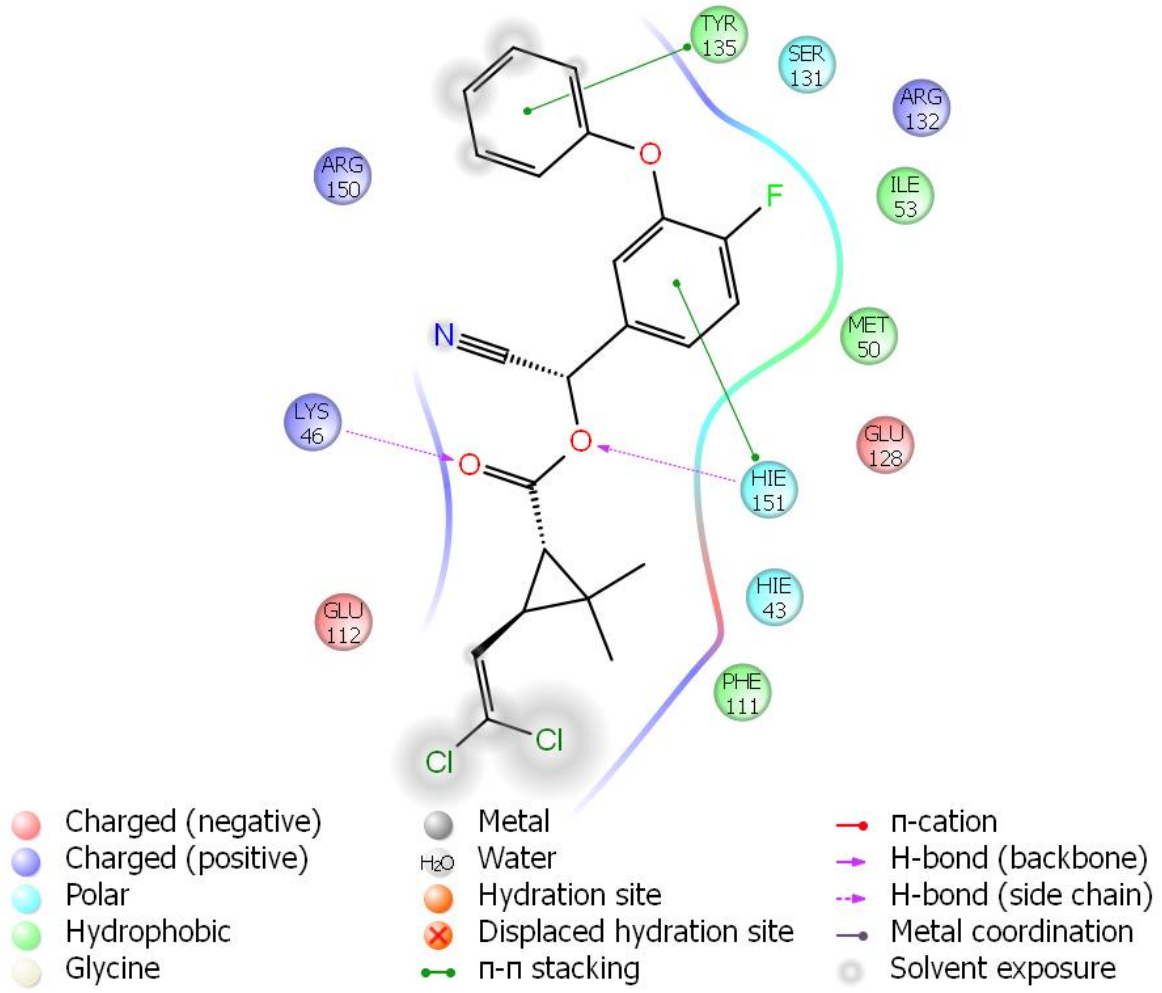


Figure 2: Binding interactions of Cyfluthrin with RSV protein receptor.

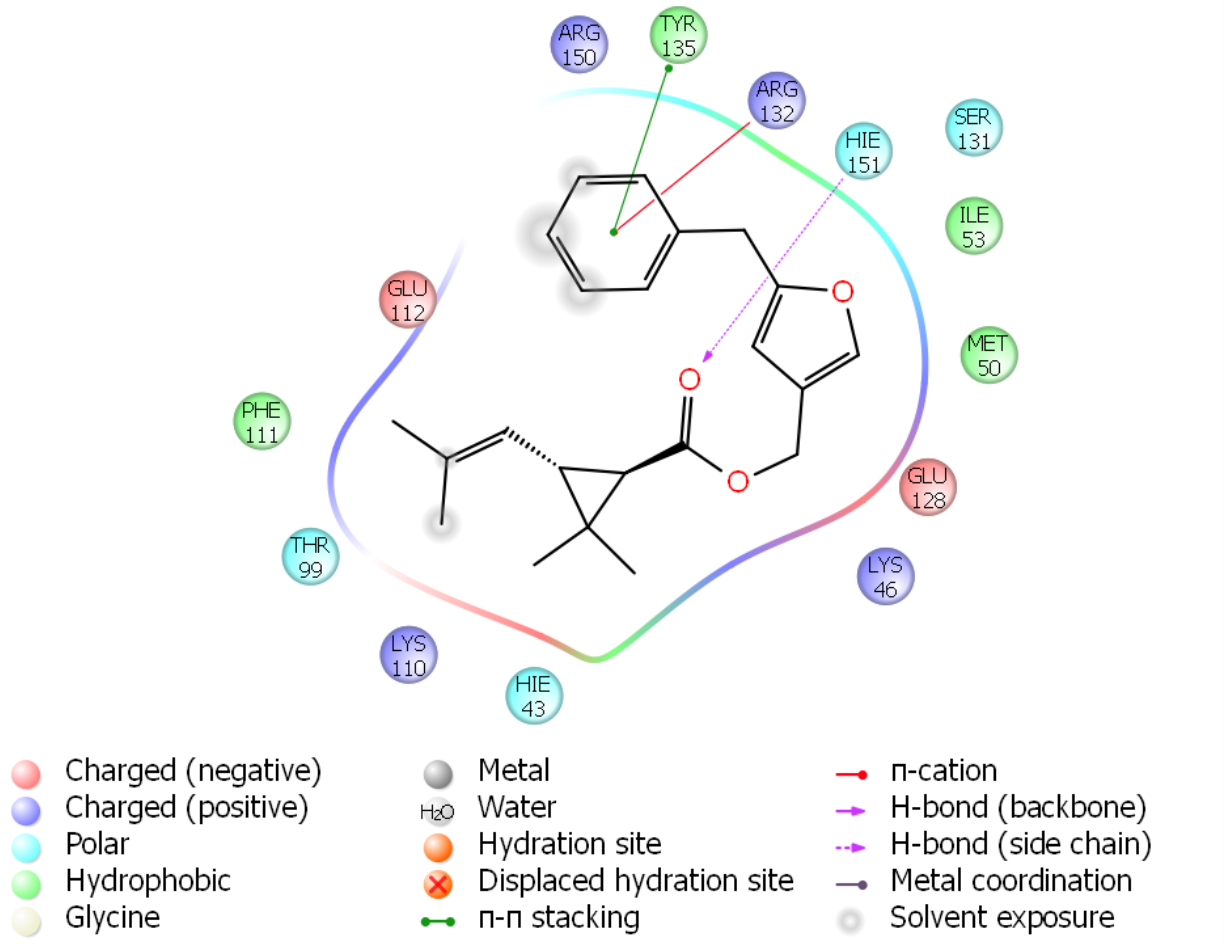


Figure 3: Binding interactions of Resmethrin with RSV protein receptor.

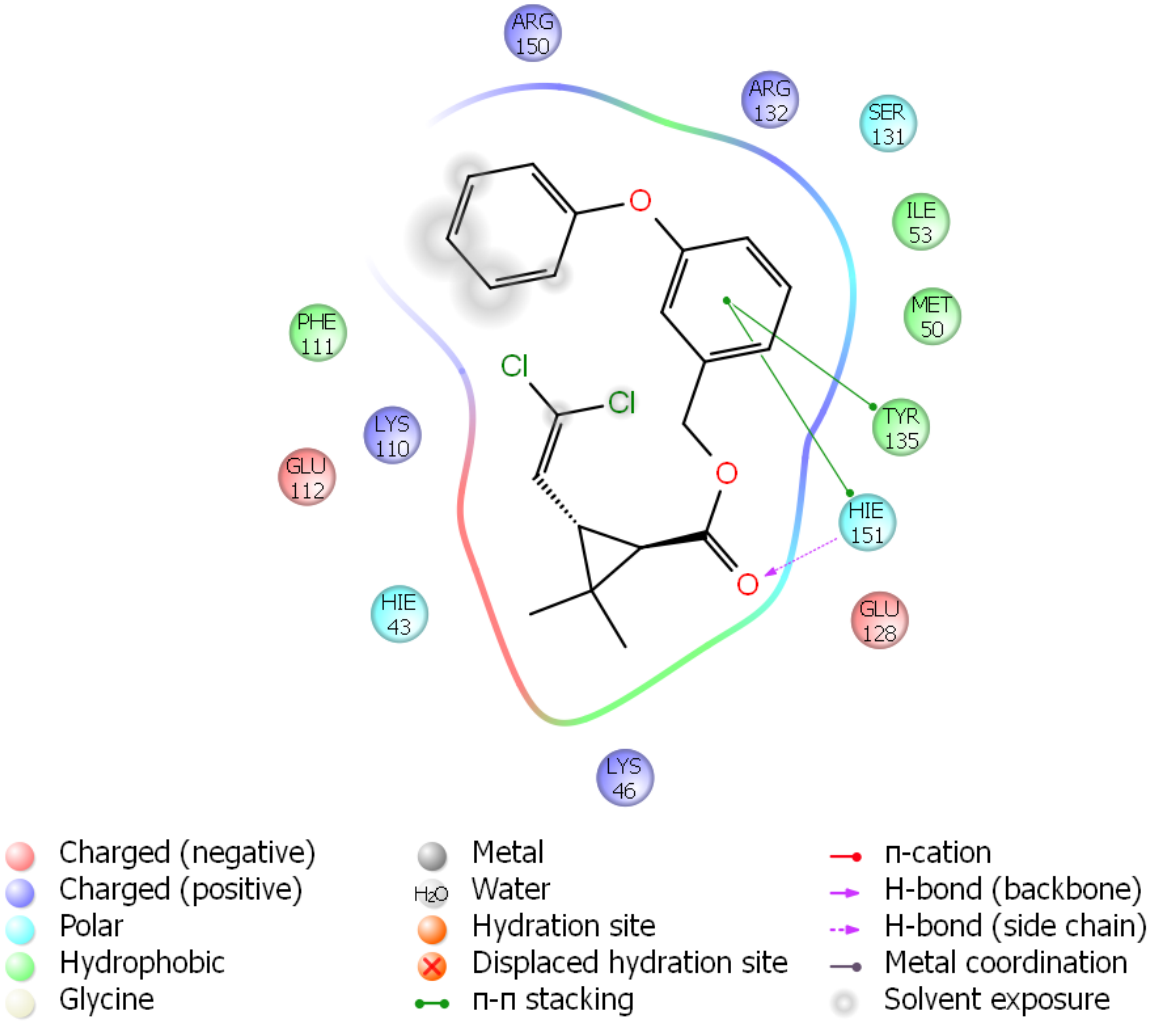


Figure 4: Binding interactions of Permethrin with RSV protein receptor.

CONCLUSION

The glide score of tested pyrethroids were resulted from -4.54 to -2.03 which indicate the strong affinity towards RSV receptor. Top screened pyrethroids like Cyfluthrin, Resmethrin & Permethrin have resulted in most hopeful outbreak to RSV. The present preliminary molecular docking study can serve as an important breakthrough to further experimentally understand its antiviral nature with its clear mechanism. Furthermore, if experimentally results are positively correlated then inclusive efficacy and safety examinations should be judged to initiate a clinical trial for these compounds.

REFERENCES

1. Piedimonte, G., Perez, M.K., Respiratory syncytial virus infection and bronchiolitis. *Pediatr. Rev.*, **2014,** *35*, 519-530.
2. Domachowske, J.B., Rosenberg, H.F. Respiratory syncytial virus infection: immune response, immunopathogenesis, and treatment. *Clin. Microbiol. Rev.*, **1999**, 12, 298-309.
3. Krilov, L.R. Respiratory syncytial virus disease: update on treatment and prevention. *Expert Rev. Anti Infect. Ther.*, **2011**, 9, 27-32.
4. Saillenfait, A. M., Nadiaye, D., Sabate J. P. Pyrethroids : Exposure and health effect-an update. *Int. J. Hyg. Environ. Health*, 2015, 218, 281-292.
5. Kumar, A., Sasmal, D., Sharma, N. An insight into deltamethrin induced apoptotic calcium, p53 and oxidative stress signalling pathways. *Toxicol. Environ. Health Sci.*, **2015**, 7, 25-34.
6. Hata, Y., Zimmermann, S., Quitschau, M., Kaiser, M., Hamburger, M., Adams, M. Antiplasmodial and antitrypanosomal activity of pyrethrins and pyrethroids. *J..Agric. Food Chem.*, **2011**, 59, 9172-9176.
7. Sulaiman, S., Fadhlina, K., Hidayatulfathi, O. Evaluation of pyrethrin formulations on dengue/dengue haemorrhagic fever vectors in the laboratory and sublethal effects. *J. Arthropod Borne Dis.*, **2007**, 1, 1-6.
8. Stanberry, L. R., Bernstein, D. I., Myers, M. G. Evaluation of the herpes simplex virus antiviral activity of pyrethrins. *Antiviral Res.*, **1986**, 6, 95-102.
9. RCSB Protein Data Bank - RCSB PDB. http://www.rcsb.org/pdb/. (Last assessed on 03/08/2016).
10. Kumar, M., Dagar, V., Gupta, V. K., Sharma, A. In silico docking studies of bioactive natural plant products as putative DHFR antagonists. *Med. Chem. Res.*, **2014**, 23, 810-817.