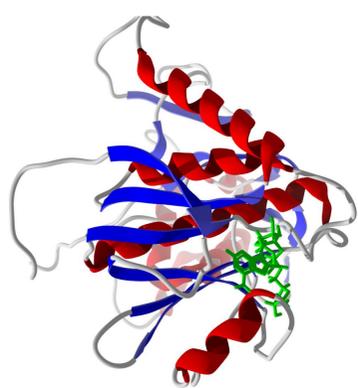


## A Molecular Docking Study on Alphavirus nsP3 Macrodomains

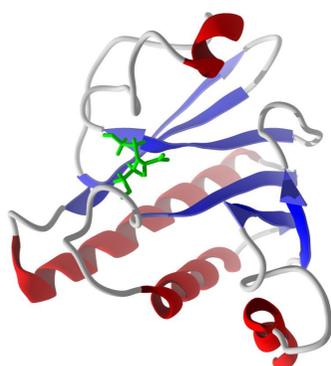
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### Overview

- Alphaviruses are a class of viruses belonging to the family *Togaviridae*. Well-known alphaviruses include Venezuelan Equine Encephalitis virus and Chikungunya virus. These viruses are spread by mosquitoes and have the potential to cause disease in humans. There are no known anti-viral treatments for alphavirus infections.
- The nsP3 macrodomain is a viral replication site. This macrodomain binds ADP-ribose. By using natural products to predict binding at the nsP3 of alphaviruses, potential drug likenesses could be developed.
- The only known crystal structures for the alphavirus nsP3 are that of CHIKV and VEEV. In this study, homology models were created for Aura virus (AURV), Barmah Forest Virus (BFV), and Sindbis virus (SINV) based on each of the two known crystal structures (Figures 1 and 2).



**Figure 1.** This structure is a homology model of the nsP3 macrodomain of Sindbis virus (SINV) based on the crystal structure of Chikungunya virus (CHIKV).



**Figure 2.** The generated homology model of the nsP3 macrodomain of SINV based on the crystal structure of Venezuelan Equine Encephalitis virus (VEEV).

### Methodology

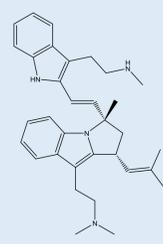
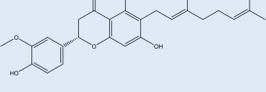
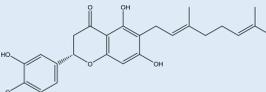
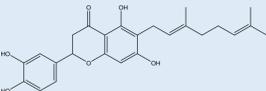
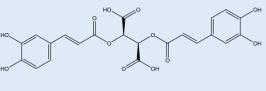
- In this study, modeling software was used to generate a total of six homology models. This was accomplished by use of the NCBI BLAST tool and subsequent sequence alignment of the *known crystal* structures with the sequences of AURV, SINV, and BFV.
- Molegro Virtual Docking was used to record the docking energies of 2,180 natural product ligands with a total of 23 protein structures. The ligands which produced the most exothermic docking energies were then evaluated via Lipinski's Rule of Five to determine potential drug likenesses based on these ligands.

### Acknowledgments

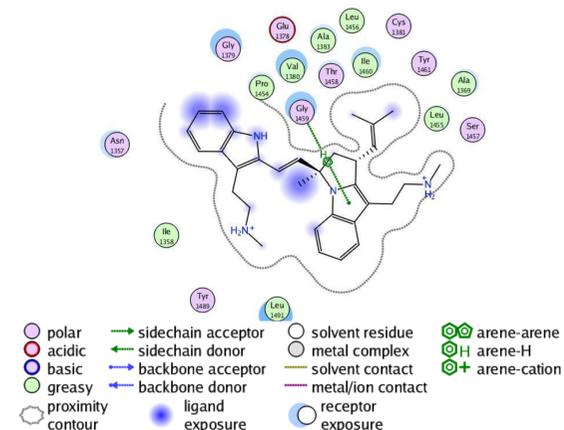
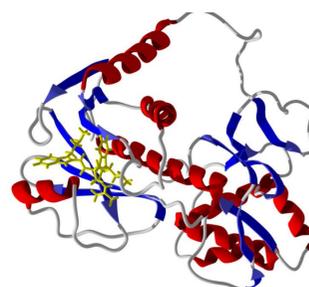
Special thanks to Dr. Kendall Byler at UAH, Dr. Bernhard Vogler, and David Cook. Appreciation is also given to the UAH Office of the Provost, the UAH Office of the Vice President for Research and Economic Development and the Alabama Space Grant Consortium.

### Results

A total of 30 natural product ligands were considered viable for this project. A selection of the top hits are shown below. It is recommended that the 30 natural product ligands be tested further to determine their potential as drug likenesses.

Ligand	Molecular Structure	SINV E <sub>dock</sub>	BFV E <sub>dock</sub>	AURV E <sub>dock</sub>
Flinderole A		-133.7 (CHIKV)	-108.3 (CHIKV)	-127.4 (VEEV)
3'-O-methyldiplacone		-145.4 (CHIKV)	-123.4 (CHIKV)	-126.9 (CHIKV)
4'-O-methyldiplacone		-146.3 (CHIKV)	-125.9 (CHIKV)	-129.4 (CHIKV)
Diplacone		-135.1 (CHIKV)	-113.7 (CHIKV)	-124.8 (CHIKV)
Chicoric acid		-144.3 (CHIKV)	-122.7 (VEEV)	-135.1 (CHIKV)

**Table 1.** A selection of ligands which produced the most exothermic docking energies. The lowest docking score for each alphavirus is shown, along with denotation of whether each particular homology model was based on CHIKV or VEEV.



**Figure 3.** Ribbon structure of SINV docked with Flinderole A (left). Ligand interaction map showing the interaction between the docked Flinderole A ligand and the surrounding amino acid residues of the SINV (CHIKV) protein.