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Study of Marine Natural Products as Anti-SARS-CoV-2 Agents Using Molecular Modeling

Priyanka Samanta
University of Mississippi, psamanta@go.olemiss.edu

Sushil K. Mishra
University of Mississippi

Rohini Dwivedi
University of Mississippi

Seon Beom Kim
University of Mississippi

AyoOluwa O. Aderibigbe
University of Mississippi

See next page for additional authors

Authors

Priyanka Samanta, Sushil K. Mishra, Rohini Dwivedi, Seon Beom Kim, AyoOluwa O. Aderibigbe, Poonam Sharma, Fuming Zhang, Pavel Kucheryavy, Mary Zoepfl, Ke Xia, Reena Thara, Robert J. Linhardt, Michael A. McVoy, Ritesh Tandon, Vitor H. Pomin, and Robert J. Doerksen

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Priyanka Samanta[1], Sushil K. Mishra[1], Rohini Dwivedi[1], Seon Beom Kim[1], AyoOluwa O. Aderibigbe[1], Poonam Sharma[2], Fuming Zhang[3], Pavel Kucheryavy[1], Mary Zoepfl[4], Ke Xia[3], Reena Thara[1], Robert J. Linhardt[3], Michael A. McVoy[4], Ritesh Tandon[2], Vitor H. Pomin[1,5], Robert J. Doerksen[1,5*]

[1] Department of BioMolecular Sciences, University of Mississippi, University, MS, USA. [2] Department of Microbiology and Immunology, University of Mississippi Medical Center, Jackson, MS, USA. [3] Center for Biotechnology and Interdisciplinary Studies, Rensselaer Polytechnic Institute, Troy, NY, USA. [4] Department of Pediatrics, Virginia Commonwealth University, Richmond, VA, USA. [5] Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, University, MS, USA.

Introduction & Significance

- The outbreak of severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) has created a global pandemic.
- The entry of SARS-CoV-2 inside the host cell is mediated by binding of S-protein (SGP) to heparan sulfate (HS) proteoglycans present on host cell surfaces.
- Primary interaction of the SGP receptor binding domain (RBD) with surface HS causes its subsequent binding to its secondary receptor, host angiotensin converting enzyme 2 (ACE-2).
- This event is followed by virus endocytosis and eventual infection.

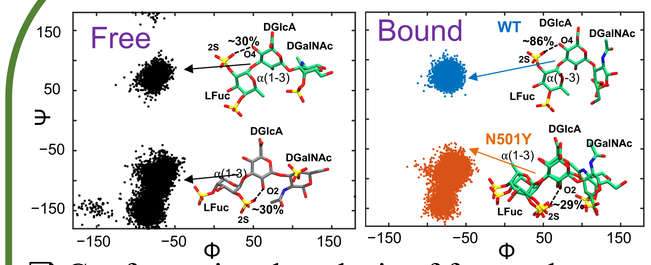
Current Work

- Here, we report a collection of computational studies conducted as part of a collaborative effort to investigate the effects of marine natural products (NPs) on wild-type (WT) and N501Y mutant SGP RBD [1,2].
- Marine NPs isolated from *P. pygmaea*, *I. badionotus* and *B. occidentalis* showed anti-SARS-CoV-2 activity.
- Computational modeling techniques were used to investigate all NP binding sites in SGP RBD using the isolated NPs and their interactions with the RBD (WT and N501Y) investigated.

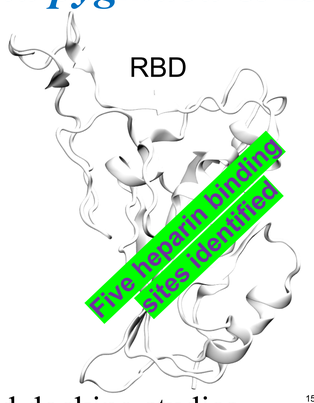
Methods

- SGP RBD models (WT and N501Y mutant) were built based on PDB ID: 6M0J[3].
- Blind docking studies were performed using multiple docking programs: Glide[4], AutoDock Vina[5] and ClusPro[6].
- Site-targeted docking studies were performed at each identified binding site using Glide[4] and AutoDock Vina[5].
- All-atom molecular dynamics (MD) studies were done using multiple force fields (ffs) for the NPs (GLYCAM06[7] or CHARMM36[8]), using AMBER software package.

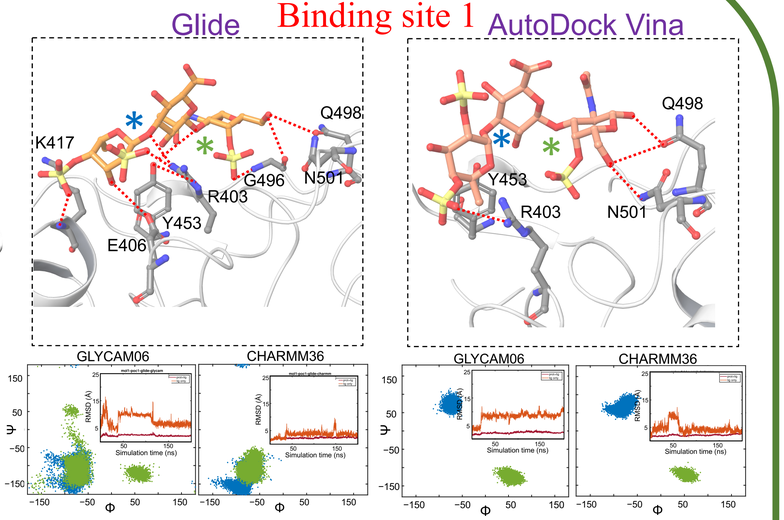
Results (NPs from *Pentacta pygmaea & Isostichopus badionotus)*



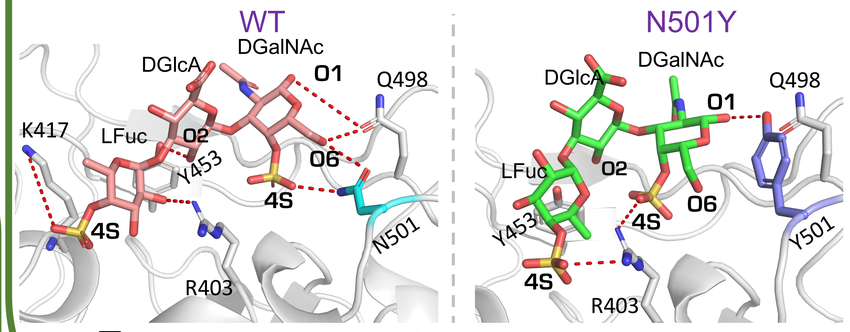
- Conformational analysis of free and protein bound (WT & N501Y) NPs was performed.



- Blind docking studies identified 5 binding sites.



- Both docking programs predicted similar binding poses at Site 1.



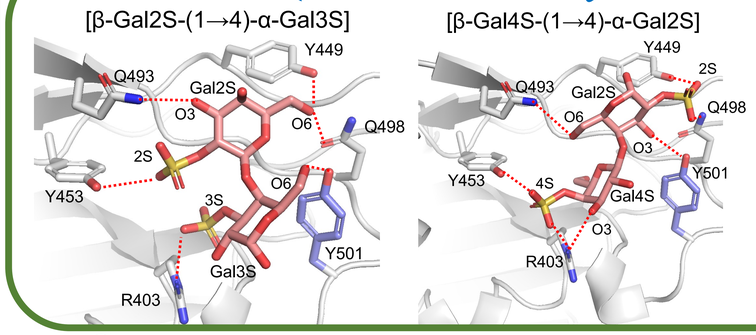
- Molecular docking shows that all molecules bind to SGP RBD WT and N501Y mutant in a similar binding mode.

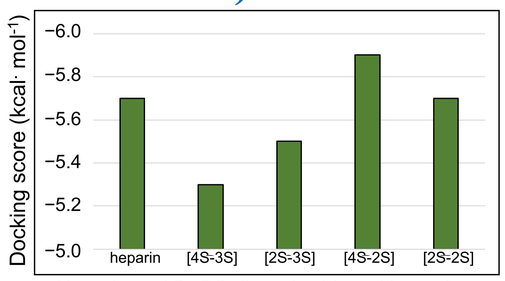
	ADVina	Glide
Site 1	100	100
Site 2	25	37.5
Site 3	25	12.5
Site 4	0	0
Site 5	n/a	100

Heat-map showing stability (%) of protein–NP complexes, with green/red for most/least stable.

- Sites 1 and 5 showed strongest interactions. GAG–protein complexes formed at these sites were stable during MD simulations.

Results (NPs from *Botryocladia occidentalis*)





Heparin and BoSG disaccharides with varying sulfation pattern

- Docking poses showed that residues Y501, Y449, Q498, R403, Q493, and Y453 play key roles in binding of NPs from *B. occidentalis* to the N501Y mutant.

Summary

- These results provide insights into key structural features of the marine isolated NPs that help enable them to bind well to SGP RBD (WT and N501Y) and those that could be modified to enhance binding, as the NPs are considered for development as potential therapeutics.

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