Dr. Derek Cashman

Computational Biophysical Chemistry
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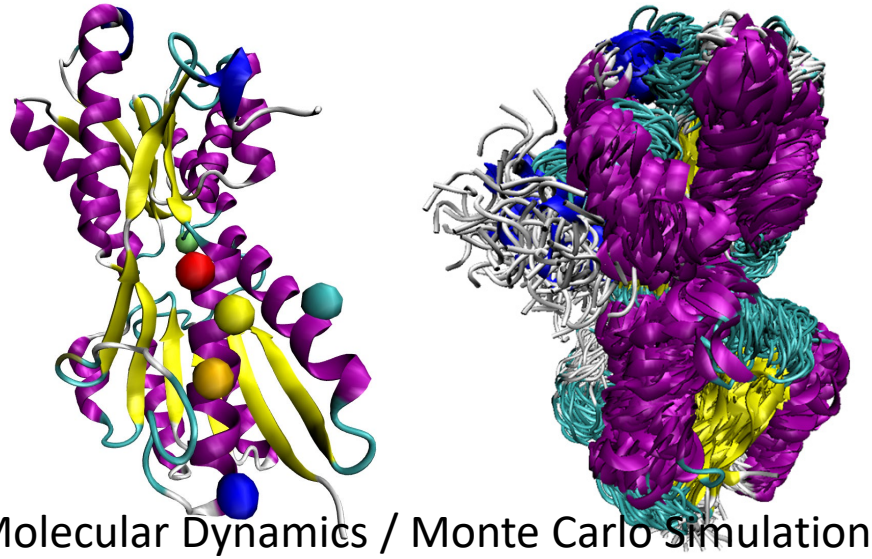
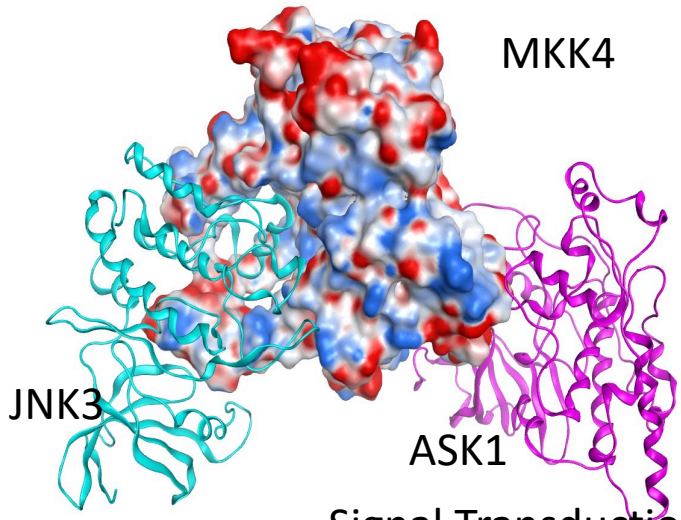


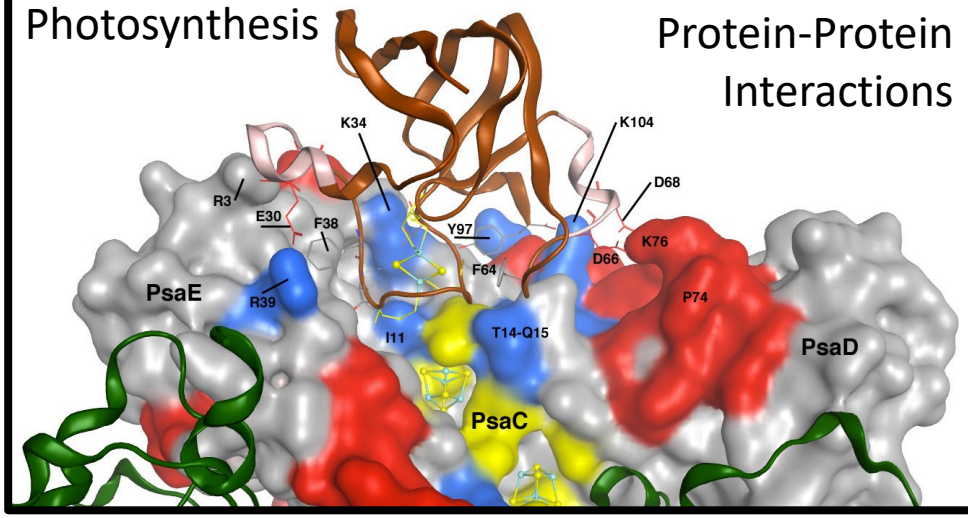
Molecular Dynamics / Monte Carlo Simulations

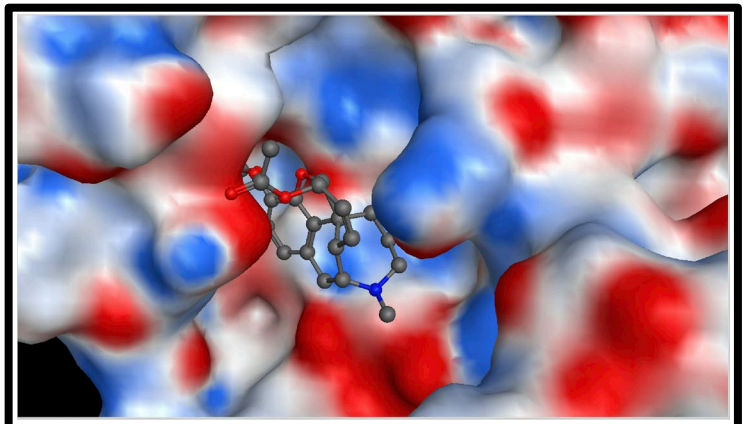


Signal Transduction

Photosynthesis

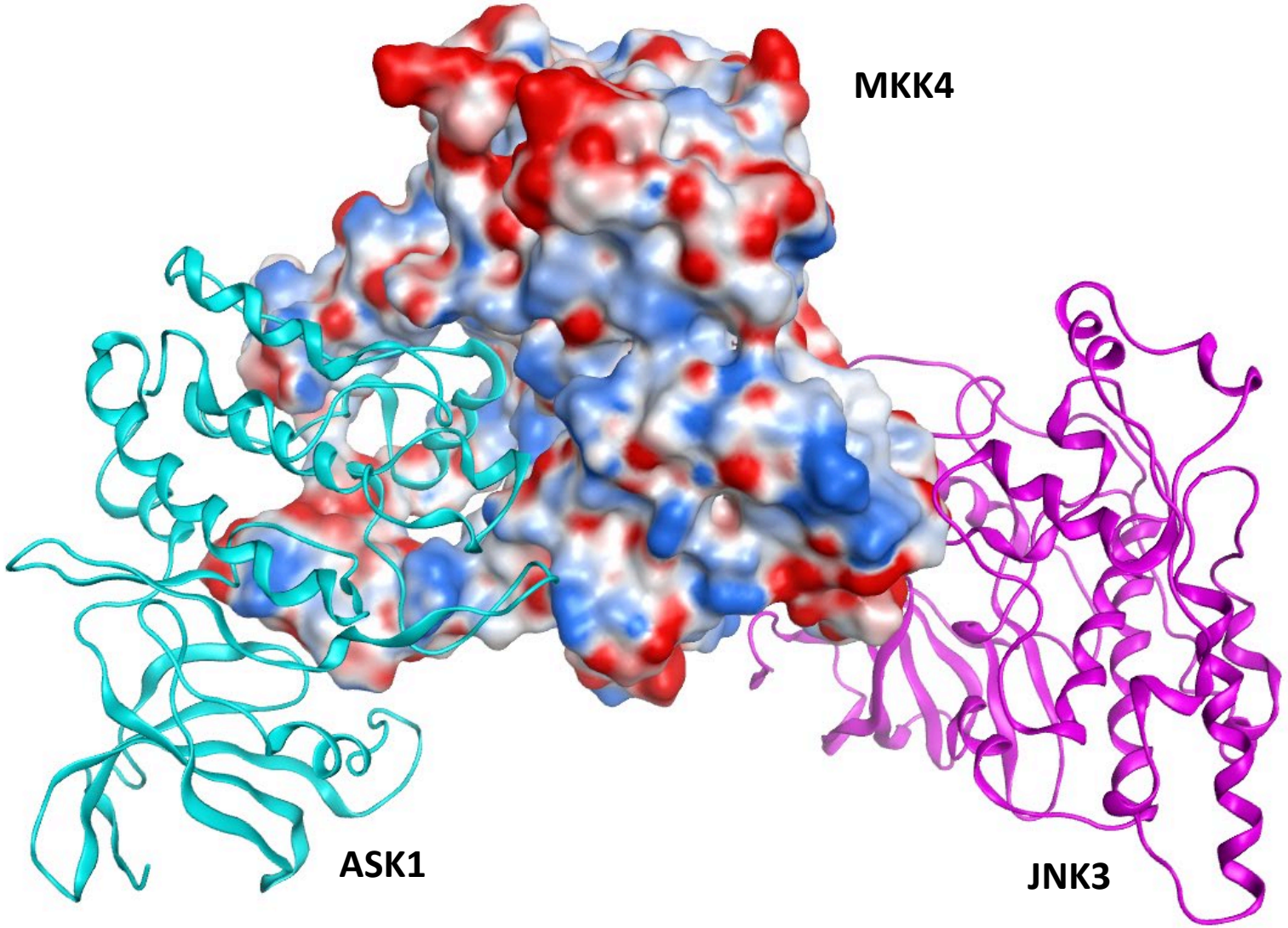
Protein-Protein Interactions





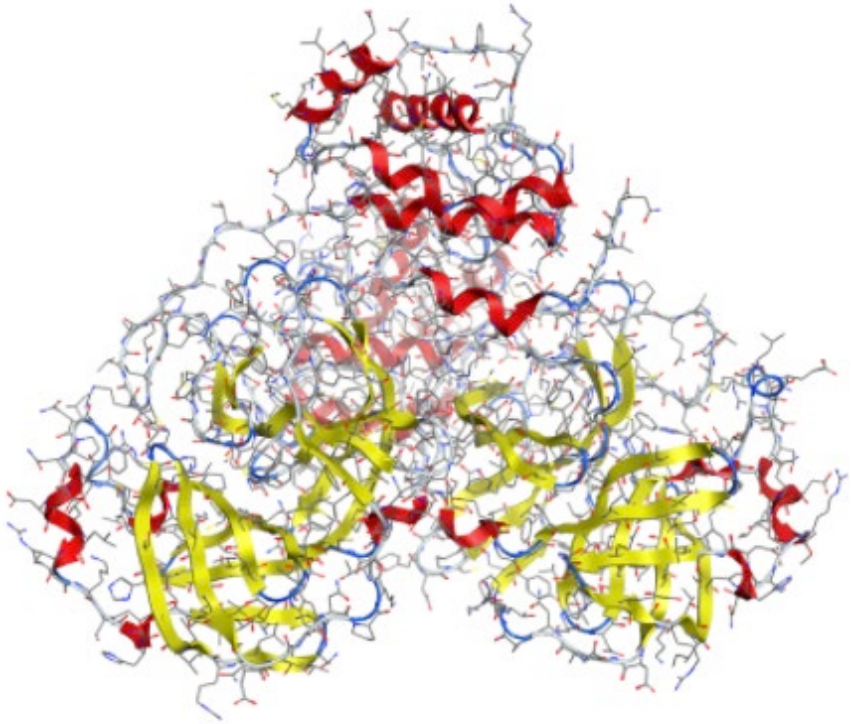
Computer-Based Drug Design

ASK1/MKK4/JNK3 Docking Complex

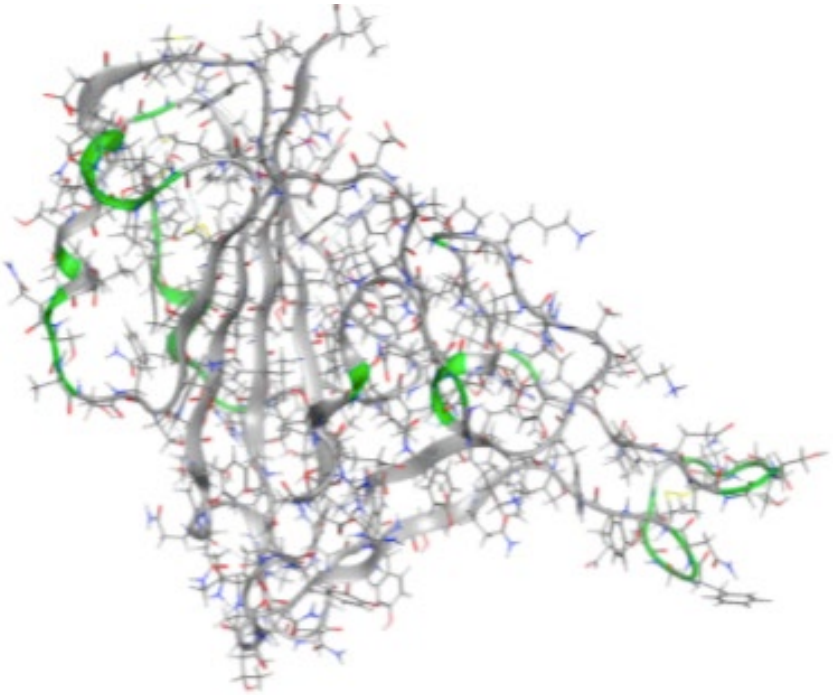


Docking calculations performed on ClusPro Server by Cameron Davis.

2020/2021 Governor's School for Emerging Technologies



SARS-CoV-2 Main Protease

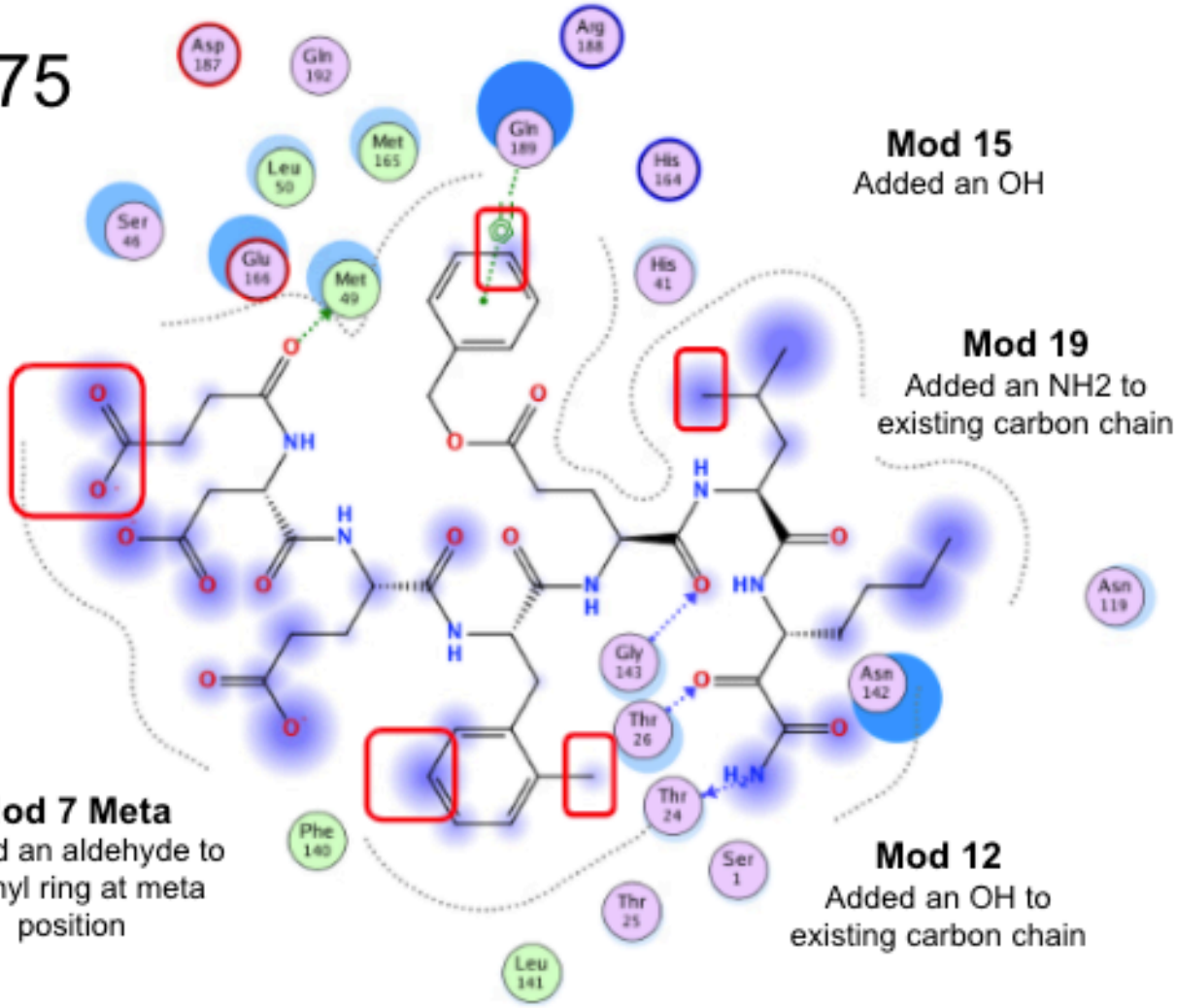


SARS-CoV-2 Receptor-Binding Domain

Thank you to research mentors: Cory Rogers, Rachel Paris and Allison Adams who assisted with this project.

PubChem 88143175

Best Inhibitor Modifications



Mod 15
Added an OH

Mod 19
Added an NH2 to existing carbon chain

Mod 31
Removed a carboxyl group

Mod 7 Meta
Added an aldehyde to phenyl ring at meta position

Mod 12
Added an OH to existing carbon chain

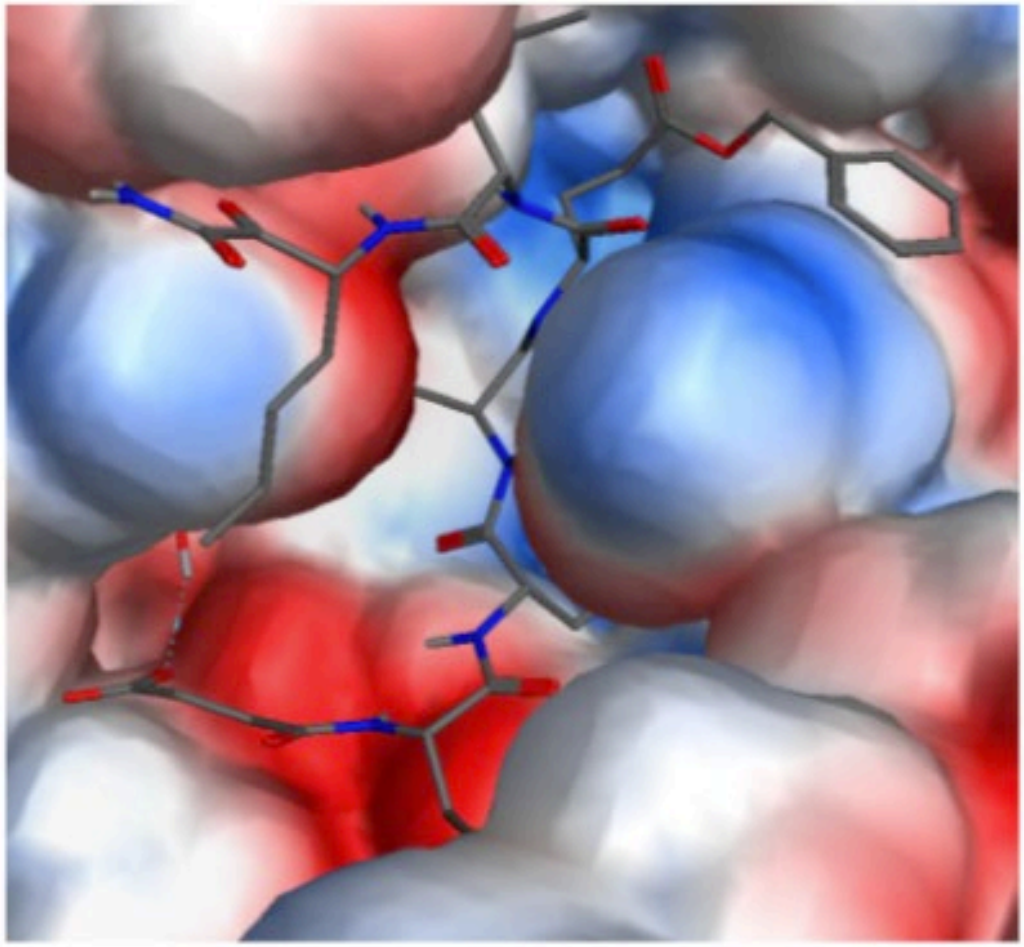
PubChem 88143175

Modification	Change	Grid Score1	Grid VDW Energy	Grid ES Energy	Molec Weight	LogP	No. Rotatable Bonds	H-Bond Donors	H-Bond Acceptors
Mod 12	Moved C + OH meta	-100.07	-95.6	-4.47	1039.08	1.66	45	9	18
Mod 31	Removed a carboxyl	-96.24	-90.86	-5.38	982.054	2.23	42	12	13
Mod 15	Added OH para	-91.17	-90.34	-0.82	1055.08	1.17	46	14	14
Mod 7 Meta	Added OH meta	-90.49	-86.37	-4.13	1021.07	2.85	42	11	15
Mod 19	Replaced C with NH2	-88.85	-86.78	-2.07	1040.07	0.23	47	14	14

1. Grid Energies in kcal/mol; 2. Molec. Weight in g/mol

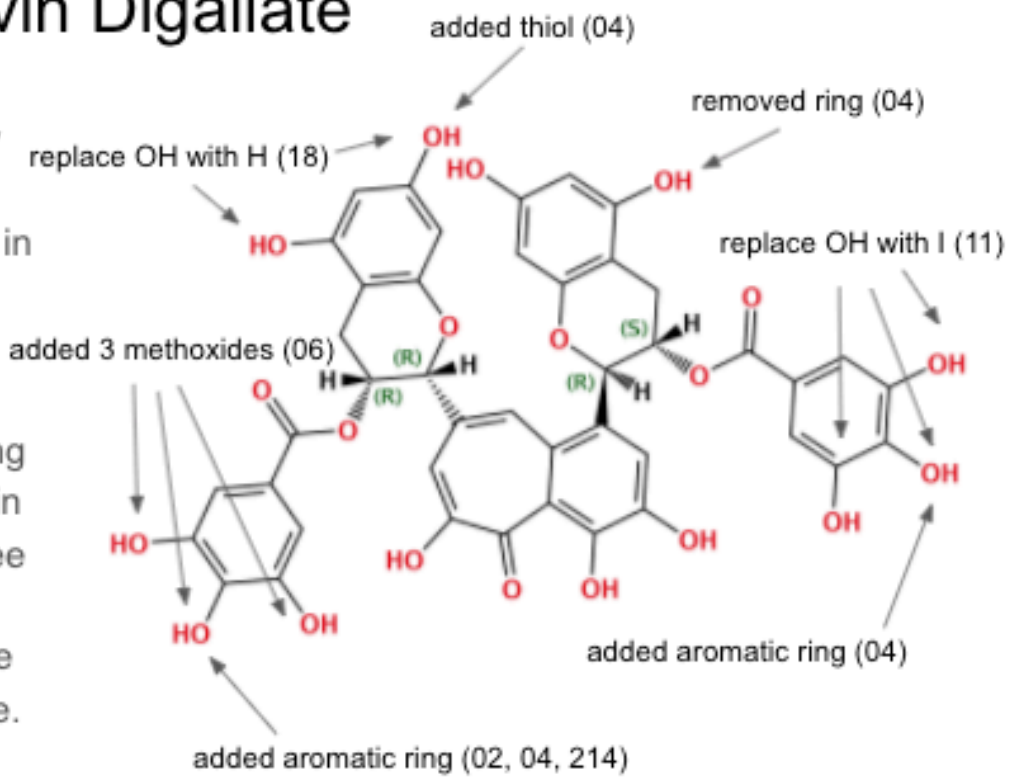
Electrostatic Docking Map of PubChem 88142175 (mod 12)

Modification:	Moved C + OH to Meta
Grid Score:	-100.07 kcal/mol
Grid VDW Energy:	-95.6 kcal/mol
Grid ES Energy :	-4.47 kcal/mol
Molecular Weight:	1059.08 g/mol
LogP:	1.66
Rotatable Bonds:	45
H-Bond Donors:	9
H-Bond Acceptors:	18



Theaflavin Digallate

- Scientists at North Carolina State University found that certain chemical compounds in green tea could inhibit a particular protease in the SARS-CoV-2 virus.
- Researched, analyzed, and docked three compounds from green tea.
- The most successful modification was adding an oxygen and aromatic ring to the theaflavin digallate base, which produced a binding free energy (ΔG_{Bind}) of -8.99 kcal/mol.
- ADME properties of theaflavin digallate were unfavorable regarding Lipinski's Rule of Five.



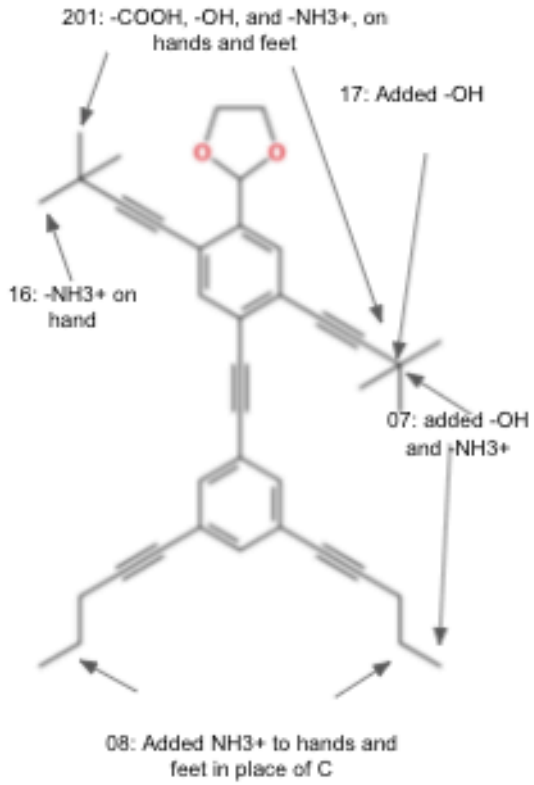
Kulikowski, Mick. Chemical compounds in foods can inhibit a key SARS-CoV-2 enzyme, study finds. November 30, 2020, *Science Daily.* https://www.sciencedaily.com/releases/2020/11/201130131445.htm

Top 7 Theaflavin Digallate Analogs

Molecule	**ΔG Bind** (kcal/mol)	**Log P**	**Mol. Weight** (g/mol)	**H-bond acceptors**	**H-bond donors**	**Toxic?**	**Notes**
TNTECH 2021-02	-8.99	4.59	960.81	18	13	no	Highest overall
TNTECH 2021-04	-8.70	6.02	1052.9	14	10	no	
TNTECH 2021-06	-8.60	4.05	910.79	18	11	no	
TNTECH 2021-11	-8.41	-0.56	1210.36	18	13	no	Extremely high molecular weight
TNTECH 2021-214	-8.07	5.05	944.81	17	12	no	
TNTECH 2021-18	-8.04	8.38	832.81	10	5	no	Lower molecular weight, high logP
TNTECH 2021-31	-7.6	2.97	868.71	18	13	no	Lead compound

Top Five NanoKid Analogs

Compound/ Modification	ΔG_{bind} (kcal/mol)	logP	Molecular Weight (g/mol)	# H-bond acceptors	H-bond donors	Toxic?
TNTECH 2021-07	-8.58	-10.31	718.62	15	10	no
TNTECH 2021-08	-8.48	-17.70	597.6	8	6	no
TNTECH 2021-16	-8.07	-12.53	599.64	8	7	no
TNTECH 2021-17	-8.05	-14.52	721.65	15	11	no
TNTECH 2021-201	-8.05	-18.4	601.64	8	8	no
NanoKid	-7.93	12.18	542.76	2	0	no



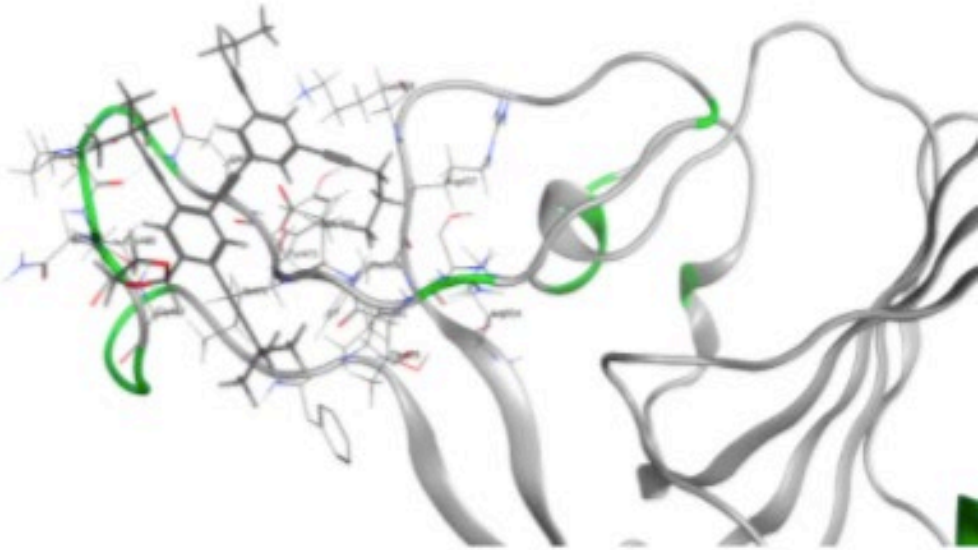
NanoKid Modification Process

Takeaways from lead compound NanoKid:

- Extremely hydrophobic
- Relatively low molecular weight
- Impressive starting binding energy
- Binds to the frustrated area in the SARS-CoV-2 spike protein

Goals and initial thoughts:

- Improve bind and decrease score
- Make hydrophilic
  - Add polar functional groups
- Keep molecular weight low
  - Add to preexisting structures on nanokid
- Avoid toxicity

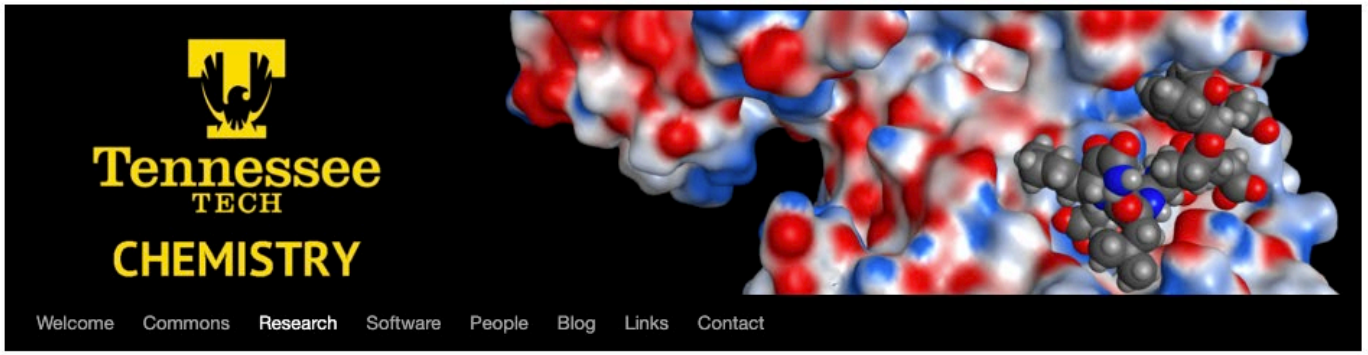


Ligand interactions between SARS-CoV-2 spike protein and lead compound NanoKid

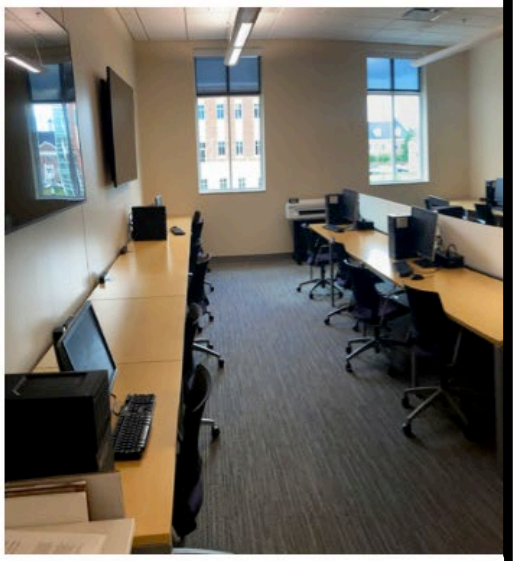
Research Computing | Tennes

sites.tntech.edu/dcashman/research-computing/

Tennessee Tech Chemistry Computer Resources



Research Computing



Computer modeling labora

The computer modeling laboratory in the Labora
eight Linux workstations designed for a variety of scientific computing needs. Each

TTU HPC Cluster

- Approximately 35 teraFLOPS
- 36 non-GPU compute nodes, 3 GPU nodes
- 28 Xeon CPU cores per node (> 1,000 CPUs total)
- 128 GB RAM per compute node
- Each compute node is connected to the campus network via 1 GB ethernet and each node is connected to other nodes via 56 GB InfiniBand
- 200 GB local HD space per node
- 175 TB total HD space

3D Printing With MOE 2020