The Search for Allosteric Inhibitors for Rho Associated Kinases

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Introduction

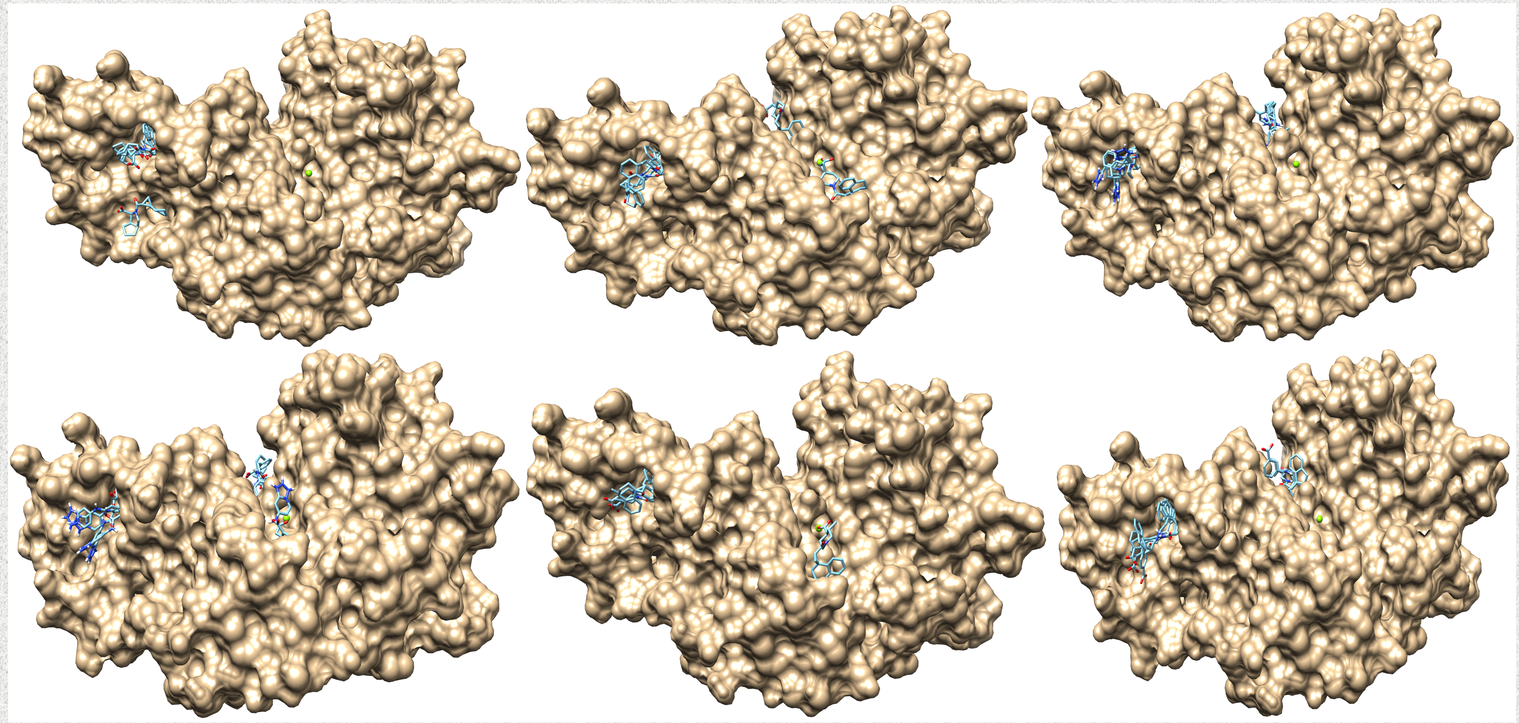
Rho Kinases or ROCKs are multifunctional kinases involved in cell migration, neurite outgrowth, and smooth-muscle migration. ROCK I and ROCK II have been identified as ROCK isoforms. These isoforms share 92% identity in kinase domains and their mRNA's can be found in mouse and rat tissues. The transcripts for ROCKs have high expression levels in the heart, muscle and brain. ROCK has several substrates implicated in cell migration and inhibitors can modulate cell migration and tissue remodeling. ROCK-1 (-/-) null mice do not develop fibrosis and cardiac dysfunction characteristic for ischaemic/reperfusion cardiomyopathy (I/RC); providing a strong rational to pursue drug discovery. During metastasis and tumour-cell invasion, its been discovered that ROCK increases cell migration. Y-27632 and fasudil are ROCK inhibitors can be used to inhibit ROCKs effects on cell migration and reduce tumour-cell dissemination. However Y-27632 and fasudil have off target binding to other kinase family members and severe side effects. I have begun a computation screen of small chemical molecules that might bind ROCKs in an allosteric and specific mechanism looking for effective and save drug leads. This rational approach uses molecular modeling and docking to find compounds that bind near the activation loop or other allosteric pockets.

Methodology

I am analyzing the initial results from a survey of 625,790 molecules run through Opuntia. Currently I'm looking at the top 10 tables of (-) Delta G energies of my directories to see which molecules can interact favorably when docking with the protein. Preferably a good drug lead would bind near the activation loop or other allosteric pockets.

- VMD Molecular visualization
- Chimera Molecular visualization
- AutoDock Tools
- AutoDock VINA
- CACDS Unix Cluster

Results and Discussion



RUN num	Compound	Docking	Energies
VanDusen:results_ef			
55769	ZINC000192909053-dock	VINA	-11.0
77501	ZINC000262065844-dock	VINA	-11.0
92992	ZINC000262920261-dock	VINA	-10.9
96103	ZINC000263007446-dock	VINA	-10.9
100143	ZINC000263103329-dock	VINA	-10.8
16936	ZINC000072425336-dock	VINA	-10.6
99359	ZINC000263085165-dock	VINA	-10.6
118584	ZINC000292660934-dock	VINA	-10.4
133077	ZINC000347111129-dock	VINA	-10.4
50858	ZINC000188326656-dock	VINA	-10.4
VanDusen:results_de			
11111	ZINC000129278447-dock	VINA	-10.6
22222	ZINC000348275313-dock	VINA	-10.4
VanDusen:results_cd			
22654	ZINC000071288115-dock	VINA	-10.2
149183	ZINC000265569321-dock	VINA	-10.1
25055	ZINC000078998529-dock	VINA	-10
56338	ZINC000152573833-dock	VINA	-9.9
43036	ZINC000110788393-dock	VINA	-9.8
50169	ZINC000129479952-dock	VINA	-9.7
65888	ZINC000178264776-dock	VINA	-9.7
87995	ZINC000237818182-dock	VINA	-9.7
90035	ZINC000245204284-dock	VINA	-9.7
108212	ZINC000262511131-dock	VINA	-9.6

Conclusion

Currently my top energies are ZINC000192909053, ZINC000262065844, and ZINC00026290261. We searched about 10% of the Zinc database so far.

Future Work

- I plan to complete docking analysis of about 10 million compounds

References

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