Large Scale Docking of Chemical Compounds Against CDK20

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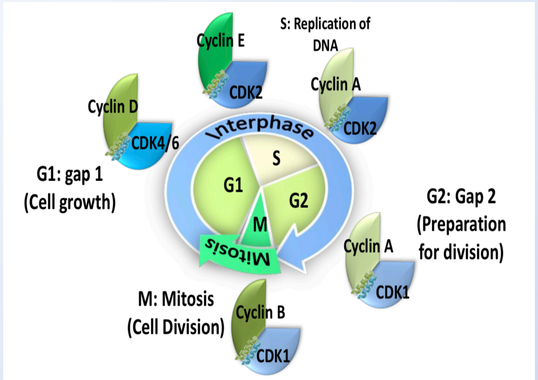
Introduction

Regulation of the eukaryotic cell cycle is directed by the activation of cyclin-dependent kinases (CDKs). CDK's are known to interact with cyclins and are inhibited by enzymes like p27. Literature has identified CDK20 as an interesting target for cancer treatment because a CDK20 knockout causes cell growth reduction and eventually termination. By using CDK2, CDK5, and CDK7 structures a computational homology model for CDK20 was previously generated. I hypothesize that if the computational model of CDK20 is docked against a library of chemical lead-like compounds; then some of those compounds might inhibit the CDK20 complexing with a Cyclin or an Enzyme Inhibitor (like KIP1). I computationally docked molecules from a ZINC database using Autodock-Vina to score CDK20/inhibitor complexes. I mapped protein amino acid side chain interactions with the small molecule in the docked complex and ranked drug leads for analysis. This research has significant impact if one of these drug leads can be matured into a drug candidate and used in a cancer therapy. It also has near term impact by providing small molecule disrupters of CDK20 that can be used in basic research in our function studies of lung cancer using H1437, H2122, and A549 cell lines.



CDK20-1jsu alignment

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         10         20         30         40         50         60
MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAIREISLLKELNHP-NIVKLL
MDQYCILGRIGEGAHGIVFKAKHVETGEIVALKKVALRRLEDGFPNQALREIKALQEMEDNQYVVQLK
*        ****  * * **    *** *****  *     * *  * ***  * *       * *

70         80         90        100        110        120        130
DVIHTENKLYLVFEFLHQDLKKFMDASALTGIPLPLIKSYLFQLLQGLAFCHSHRVLHRDLKPQNLLI
AVFPHGGGFVLAFEFMLSDL-AEVVRHAQRPLAQAQVKSYLQMLLKGVAFCHANNIVHRDLKPANLLI
 *        * ***   **       *         ****  ** * ****     ****** ****

 140        150        160        170        180        190        200
NTEGAIKLADFGLARAFGVP-VRTY-HEVVTLWYRAPEILLGCKYYSTAVDIWSLGCIFAEMVTRRAL
SASGQLKIADFGLARVFSPDGSRLYTHQVATRWYRAPELLYGARQYDQGVDLWSVGCIMGELLNGSPL
   *  * ******* *     * * * * * ****** * *   *   ** ** ***  *      *

   210        220        230        240        250        260        270
FPGDSEIDQLFRIFRTLGTPDEVVWPGVTSMPDY-KPSFPKWARQDFSKVVPPLDEDGRSLLSQMLHY
FPGKNDIEQLCYVLRILGTPNPQVWPELTELPDYNKISFKEQVPMPLEEVLPDVSPQALDLLGQFLLY
***   * **    * ****   ***  *  *** * **          * *        ** * * *

     280        290        300
DPNKRISAKAALAHPFFQDVTKPVPHLRL
PPHQRIAASKALLHQYFFTAPLPAHPSEL
 *  ** *  ** *  *     *     *
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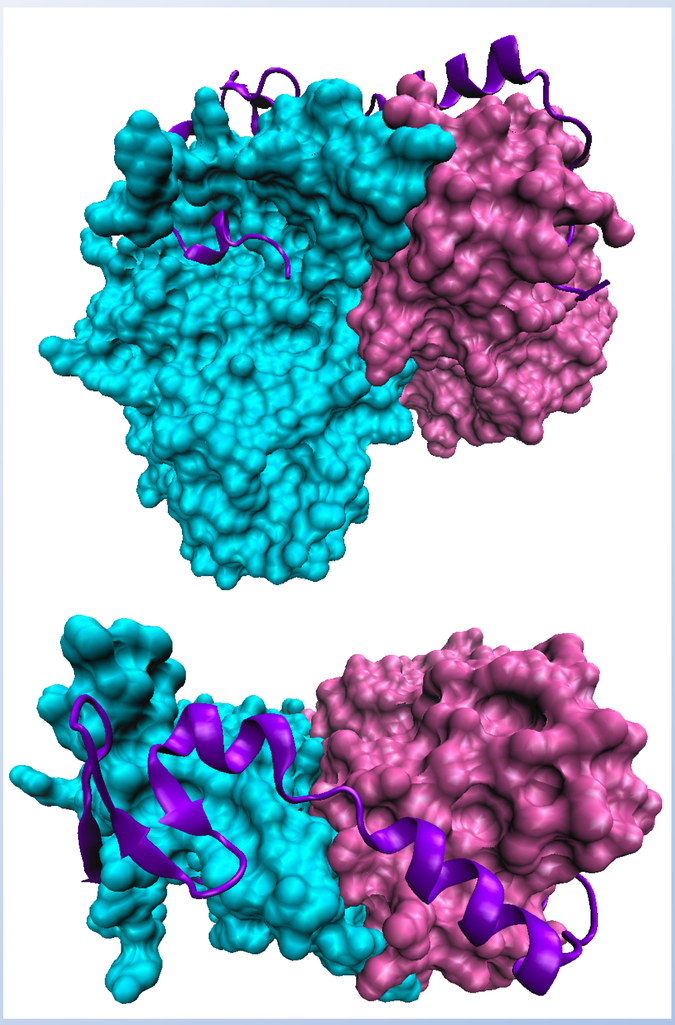
Using the CDK20-1jsu alignment, I was able to find what amino acids that are within 5 angstroms of chain A (CDK2) and chain B (Cyclin A). Using those amino acids, I found the correlating amino acids on the CDK20-1jsu alignment. I also found the distance between the amino acids of CDK2 and Cyclin A that are within 5 angstroms of each other.



Results and Discussion

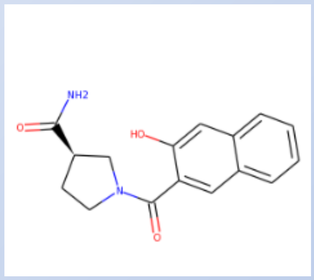
CDK20	CDK2	Cyclin A	Distance
R	T 39	K 289	4.18
L	E 40	K 288	4.38
R	T 40	K 288	4.89
R	E 42	V 275	3.82
F	V 44	K 266	2.85
N	S 46	T 47	2.8
R	R 50	F 267	3.14
I	I 52	F 304	3.66
K	S 53	F 267	3.64
E	E 57	Y 185	3.47
P	H 71	H 296	3.99
H	T 72	G 73	4.2
G	E 73	Q 65	4.93
H	H 119	Y 178	4.1
A	S 120	Y 178	4.98
N	H 121	Y 178	4.81
N	R 122	Y 185	4.61
V	A 151	F 267	3.85
F	F 152	Q 313	5.23
P	V 154	H 179	4.74
D	P 155	L 320	3.73
R	R 157	E 268	3.91
H	H 161	Y 271	4.77
H	N 272	V 175	3.98
A	A 277	Y 178	3.61
A	K 278	D 181	3.55

CDK20 alignment model with ZINC53891773

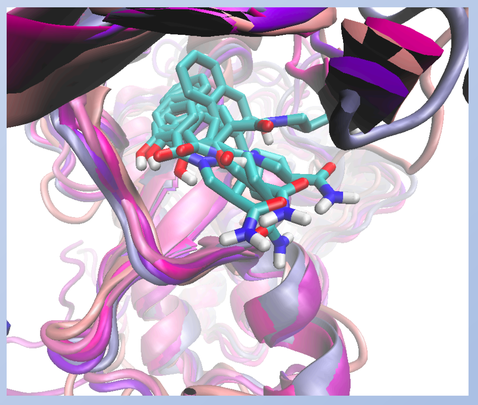
Methodology

Using Opuntia, I analyzed a survey of 434,418 molecules. I am currently looking at the top 10 compounds with the most favoralbe energies that can interact when docking with the protein. Preferably, a good drug lead would bind near to the activation loop or other allosteric pockets.

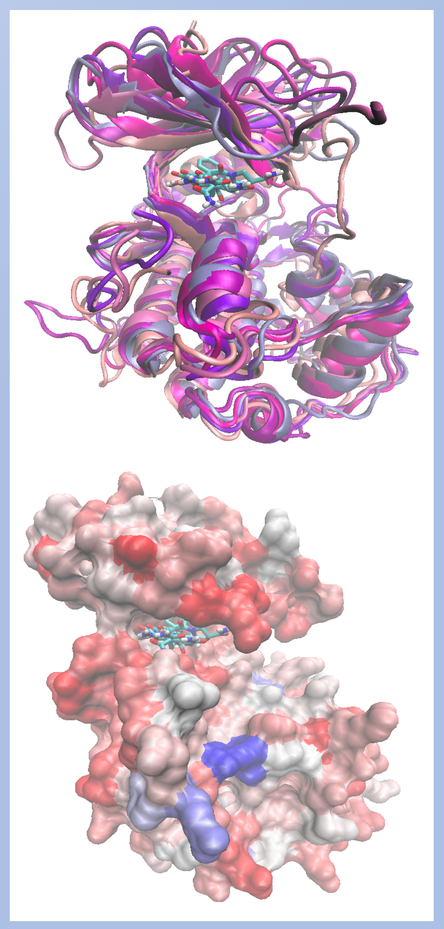
- VMD molecular visualization
- AutoDock Tools
- AutoDock VINA
- ChimeraMolecular visualization
- CACDS Unix Cluster



Compound	Energies
ZINC53891773	-11.1
ZINC318425855	-10.9
ZINC129453234	-10.9
ZINC188306323	-10.9
ZINC237860900	-10.8
ZINC135475080	-10.8
ZINC152573883	-10.8
ZINC263247985	-10.7
ZINC282370983	-10.7
ZINC329148651	-10.7



ZINC53891773 binds in the internal face of the N-terminal beta sheet of CDK20 between the sheet and the alpha helical C-terminal lobe of the structure. If CDK20 binds to known inhibitors similar to other members of the CDK family, it might interfere with the interface of p27.



Conclusion

- The initial screening of CDK20 shows promise to find drug leads for future theraputics.

Future Work

- Be able to interfere with the function of a CDK20 complex to test a phenotype of a drug.

References

1. Liu, Y., Wu, C. & Galaktionov, K. p42, a Novel Cyclin-dependent Kinase-activating Kinase in Mammalian Cells. J. Biol. Chem. 279, 4507–4514 (2004).
2. Wohlbold, L., Larochelle, S., Livshits, G., Singer, J. & Shokat, K. M. CDK- Supports Cell Proliferation but has no Intrinsic CDK-Activating Kinase RIB. Cell Cycle 546–554 (2006).
3. Peyressatre, M., Prével, C., Pellerano, M. & Morris, M. C. Targeting cyclin-dependent kinases in human cancers: From small molecules to peptide inhibitors. Cancers (Basel). 7, 179–237 (2015).
4. Wang, Y. et al. CDK7-Dependent Transcriptional Addiction in Triple-Negative Breast Cancer. Cell 163, 174–186 (2015).
5. An, X. et al. Functional characterisation of cell cycle-related kinase (CCRK) in colorectal cancer carcinogenesis. Eur. J. Cancer 46, 1752–1761 (2010).
6. Marti-Renom, M. A., Madhusudhan, M. S. & Sali, A. Alignment of protein sequences by their profiles. Protein Sci. 13, 1071–1087 (2004).
7. Trott, O. & Olson, A. J. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. J. Comput. Chem. 31, 455–461 (2010).
8. Tarricone, C. et al. Structure and regulation of the CDK5-p25nck5a complex. Mol. Cell 8, 657–669 (2001).
9. Mapelli, M. et al. Mechanism of CDK5/p25 Binding by CDK Inhibitors. J. Med. Chem. 48, 671–679 (2005).
10. Malmström, J. et al. Synthesis and structure-activity relationship of 4-(1,3-benzothiazol-2-yl)-thiophene-2-sulfonamides as cyclin-dependent kinase 5 (cdk5)/p25 inhibitors. Bioorg. Med. Chem. Lett. 22, 5919–5923 (2012).
11. Lolli, G., Lowe, E. D., Brown, N. R. & Johnson, L. N. The crystal structure of human CDK7 and its protein recognition properties. Structure 12, 2067–2079 (2004).
12. Ayaz, P. et al. Conformational Adaption May Explain the Slow Dissociation Kinetics of Roniciclib (BAY 1000394), a Type I CDK Inhibitor with Kinetic Selectivity for CDK2 and CDK9. ACS Chem. Biol. 11, 1710–1719 (2016).
13. Craft, J. W. & Legge, G. B. An AMBER/DYANA/MOLMOL phosphorylated amino acid library set and incorporation into NMR structure calculations. J. Biomol. NMR 33, 15–24 (2005).