Molecular Modeling in Drug Discovery: From Dual Inhibitors to Stabilized Helical Peptides

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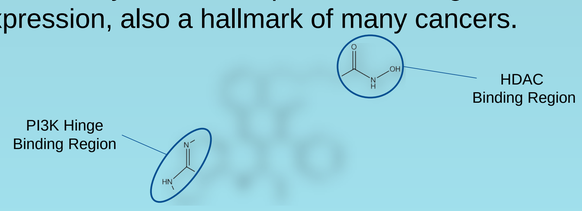
Introduction

Molecular modeling plays a fundamental role in the hit to lead phase of drug discovery. Various computational methods provide a prediction of a compound's efficacy and the determination of a structure-activity relationship. Together these allow for a directed progression from a host of candidate compounds to a single potent molecule.

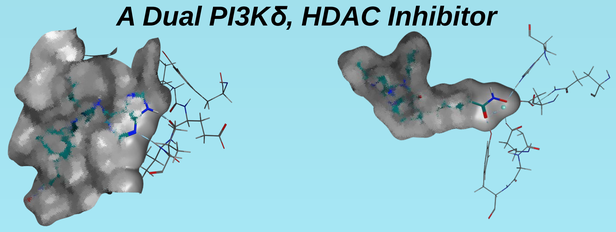
Here molecular modeling was applied to guide the development of two compounds: a small molecule dual inhibitor for rare cancers (DIRC), and a stabilized helical peptide (SHP) to treat a variety of cancers that express the same mutated protein.

Dual Inhibitor for Rare Cancers

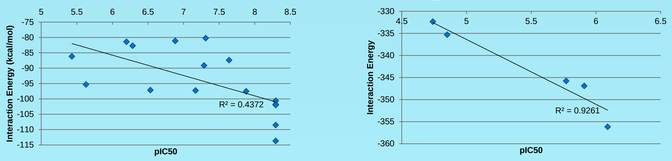
Most small molecule therapeutics have a single target such as a particular enzyme. In some cases tumors may alter their signaling pathways in response to a small molecule inhibitor, rendering the drug inactive. Inhibiting two targets may prove more effective in combating a tumor that mutates to be resistant to a single targeted therapy. Here a dual inhibitor is modeled to inhibit both the PI3Kδ kinase and the HDAC family of enzymes, known cancer targets. The PI3Kδ kinase activates proteins through phosphorylation and its over-expression in cancer cells leads to tumor growth. The HDAC enzymes deacetylate histone proteins leading to increased gene expression, also a hallmark of many cancers.



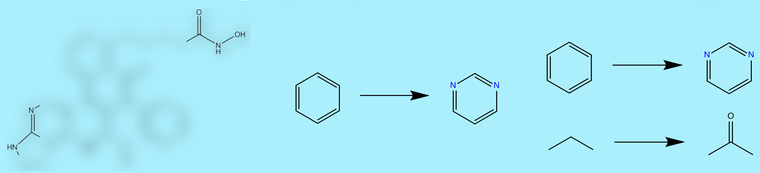
A Dual PI3Kδ, HDAC Inhibitor



An Inhibitor in the PI3Kδ and HDAC$_2$ Binding Pockets



PI3Kδ and HDAC$_2$ Ligand pIC50 and Interaction Energy



PI3K: pIC50 = -0.71, Interaction Energy = -102
HDAC$_2$: pIC50 = -3.1, Interaction Energy = -347

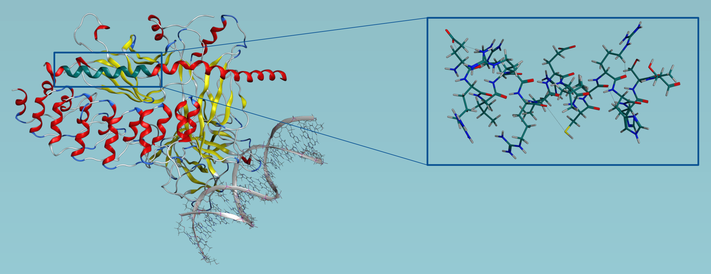
PI3K: Interaction Energy = -105
HDAC$_2$: Interaction Energy = -348

PI3K: Interaction Energy = -123
HDAC$_2$: Interaction Energy = -353

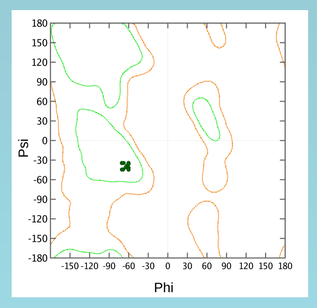
Proposed Changes to DIRC Compounds

Stabilized α-Helical Peptides

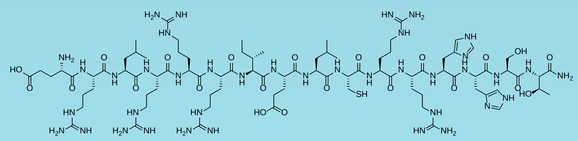
The NOTCH transcription factor complex is responsible for cellular differentiation, proliferation, and death. In healthy cells its activity is regulated by the α-helical domain of the co-activator MAML1 protein family. Up-regulation of the NOTCH signaling pathway is linked to a variety of cancers. Here a stabilized helical peptide is modeled to mimic the wild-type co-activator and with the goal of inhibiting the NOTCH pathway to prevent abnormal cellular proliferation.



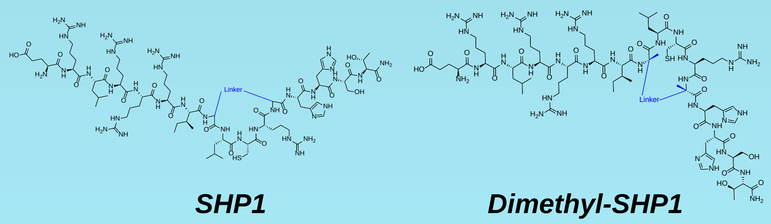
Wild Type NOTCH Transcription Factor Complexed with MAML1



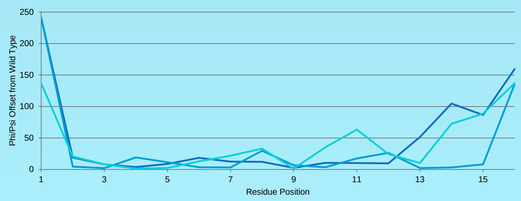
Ramachandran Plot of Wild Type MAML1



Wild Type MAML1 16-Amino-Acid Segment



SHP1 ***Dimethyl-SHP1***



Dihedral Angle Similarity of New SHP Designs to Wild Type MAML1

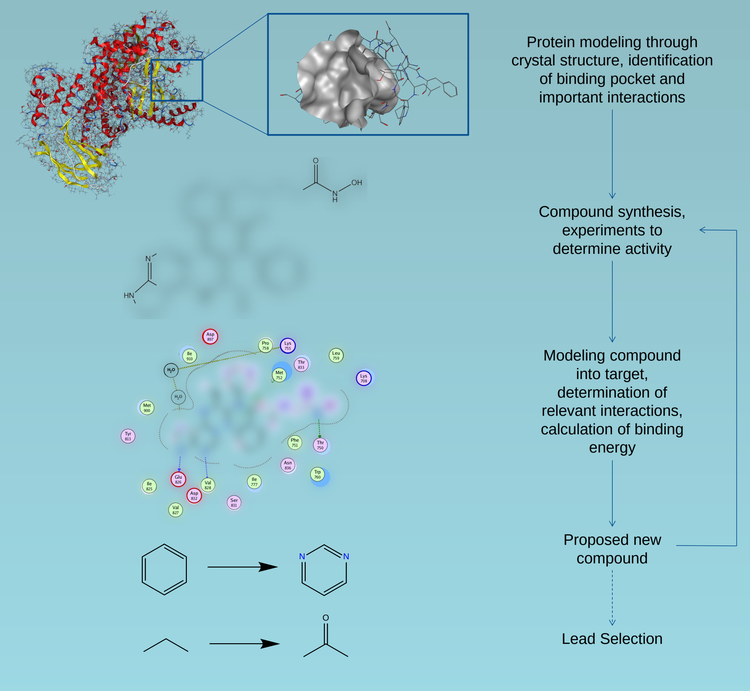
Compound	Average Δ(Phi/Psi)	Helicity
MAML1 (Wild Type Inhibitor)	0.0	87.5%
SHP1	47.44	62.5%
Dimethyl-SHP1	32.38	62.5%
SHP2	41.85	68.8%

Dihedral Angle and Helicity Results for SHP Compounds

Discussion

Drug discovery is subject to a very high preclinical attrition rate due to a lack of compound safety or efficacy. Developing computational models is an important step in translating basic research to an efficacious and potent drug.

The work presented here follows the preclinical hit to lead development pipeline.



Conclusion

Through detailed molecular modeling of specific ligand-protein interactions (DIRC) or ligand geometry arising from self-interaction (SHP), suggestions regarding improvement in potency are made. Next steps include rounds of synthesis, testing, and molecular modeling for new designs to improve potency to desired levels.

Acknowledgments

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References

Molecular Operating Environment (MOE), 2013.08; Chemical Computing Group Inc., 1010 Sherbooke St. West, Suite #910, Montreal, QC, Canada, H3A 2R7, **2016**.