SMART Teams 2014-2015 Qualification Phase

Marquette University High School SMART Team

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Nicotinamide Phosphoribosyltransferase (NAMPT) Inhibition Yields Promising Future Implications

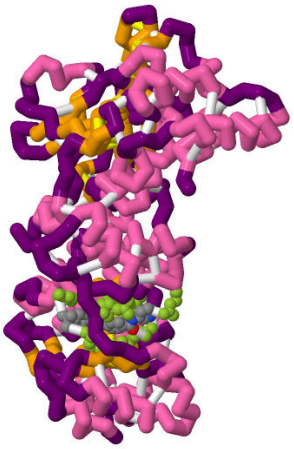
PDB: 4N9D

Primary Citation: Dracovich et al. (2013). Fragment-based design of 3 amino-pyridine-derived amides as potent inhibitors of human nicotinamide phosphoribosyltransferase (NAMPT). *Bioorganic & Medicinal Chemistry Letters* 24: 954-962.

Format: Alpha carbon backbone

RP: Zcorp with plaster

Description:



Human embryonic stems cells (hESC) and induced pluripotent stem cells (hiPSC), collectively termed human pluripotent stem cells (hPSC), differentiate into any cell type. The creation of hPSC free from potentially tumorigenic pluripotent stems is advantageous for research strategies and necessary for future hPSC-based clinical therapies. The STF-31 molecule inhibits an important metabolic enzyme, NAMPT, providing selective toxicity of hPSC in diverse cell culture conditions. This strategy effectively eliminates potentially tumorigenic cells but spares differentiated progeny. The MUHS SMART (Students Modeling A Research Topic) Team has designed a model of NAMPT bound with STF-31 using 3D printing technology. What makes STF-31 unique as a NAMPT inhibitor is its ability to occupy the protein's active site and act as a substrate for the enzyme. The pyridine ring of STF-31 is situated between the F193 and Y188 sidechains of NAMPT. The central phenyl ring of STF-31 occupies the tunnel region of NAMPT. Other binding sites between STF-31 and NAMPT include H191, R196, S241, V242, A244, S275, I309, and R311. NAMPT inhibition research will lead towards the development of clinically safe hPSC progeny for human stem cell based therapies, drug development, and toxicity testing. This is supported by a grant from NIH-CTSA.

Specific Model Information:

The NAMPT model existed as a dimer. One of the two dimers were modeled bounded with STF-31. The following are coloring sequencing for important features on the protein:

1. Backbone: Purple
2. Alpha Helices: Hotpink
3. Beta Sheets: Orange
4. Hydrogen Bonds: Yellow
5. Struts: White

6. Major AA involved in the active site:

Tyr 188
His 191
Phe 193
Arg 196
Asp 219
Ser 241
Val 242
Ala 244
Ser 275
Ile 309
Arg 311

All colored yellowgreen

7. STF-31: CPK

http://cbm.msoe.edu/smartTeams/

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