Cyclin-dependent Kinase Inhibitors

Docking Phthalimides

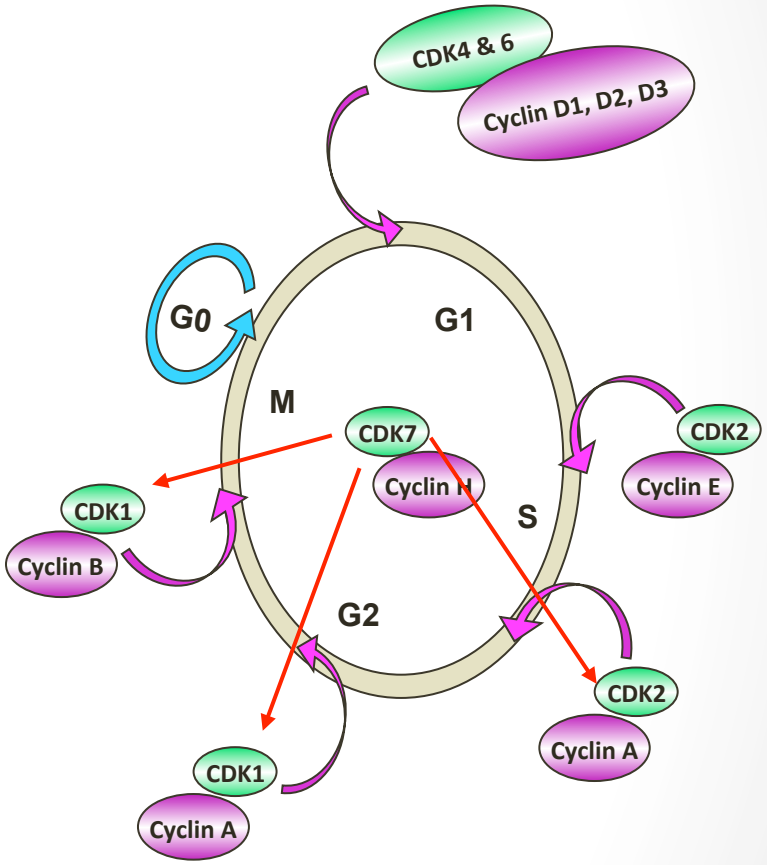
The Cell Cycle

What are CDK's?

- CDK's are proteins that are activated by cyclin.
- CDK's regulate the cell cycle.

Inhibiting a CDK Protein

- Inhibiting a CDK protein can stop the cell cycle from progressing.
- Prevent a defective cell from proliferating.

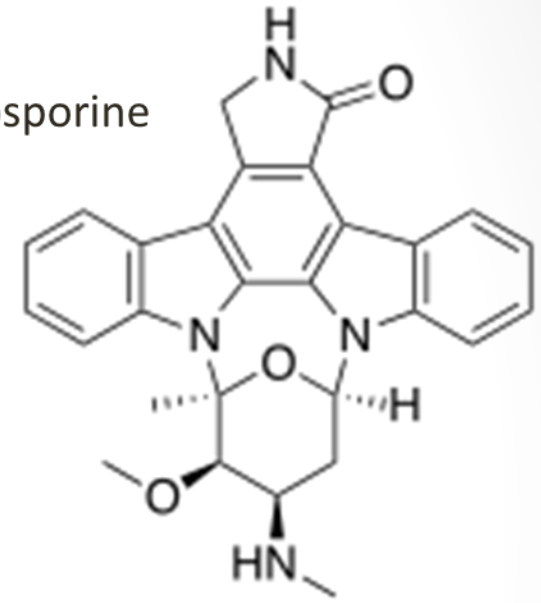


Inhibitor

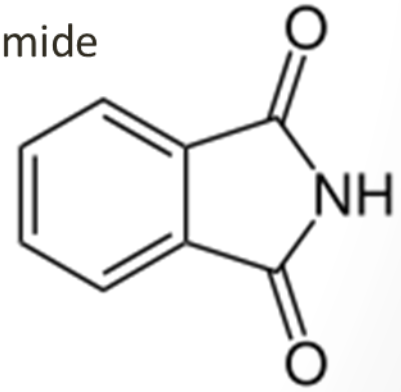
- Over 200 4-amidophthalimides and 5-amidophthalimdes are used in the simulations.

- Phthalimides are used for two reasons:
  1. They are commercially available.
  2. They have similarities to staurosporine.

Staurosporine

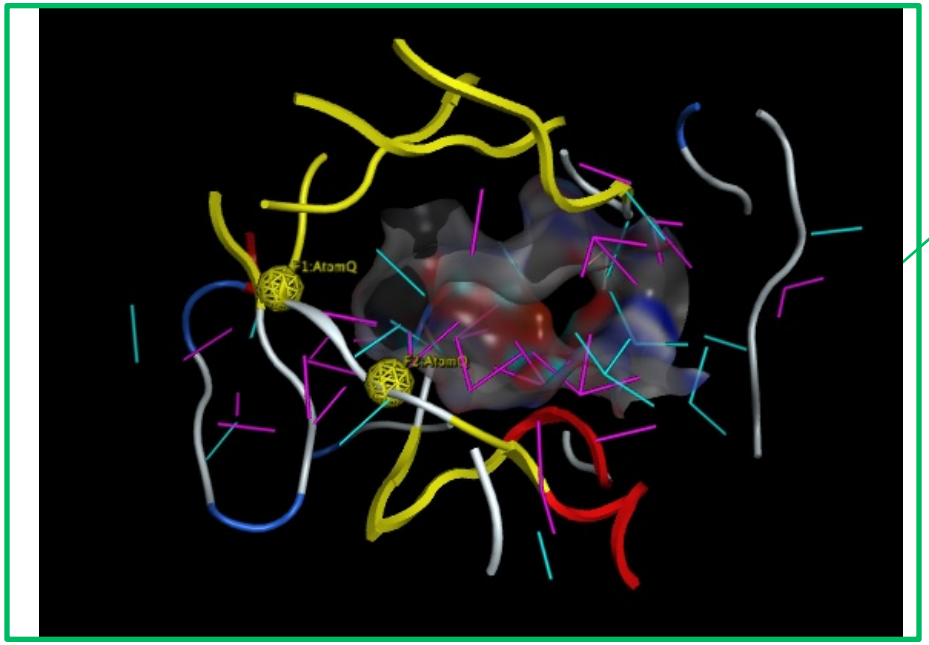


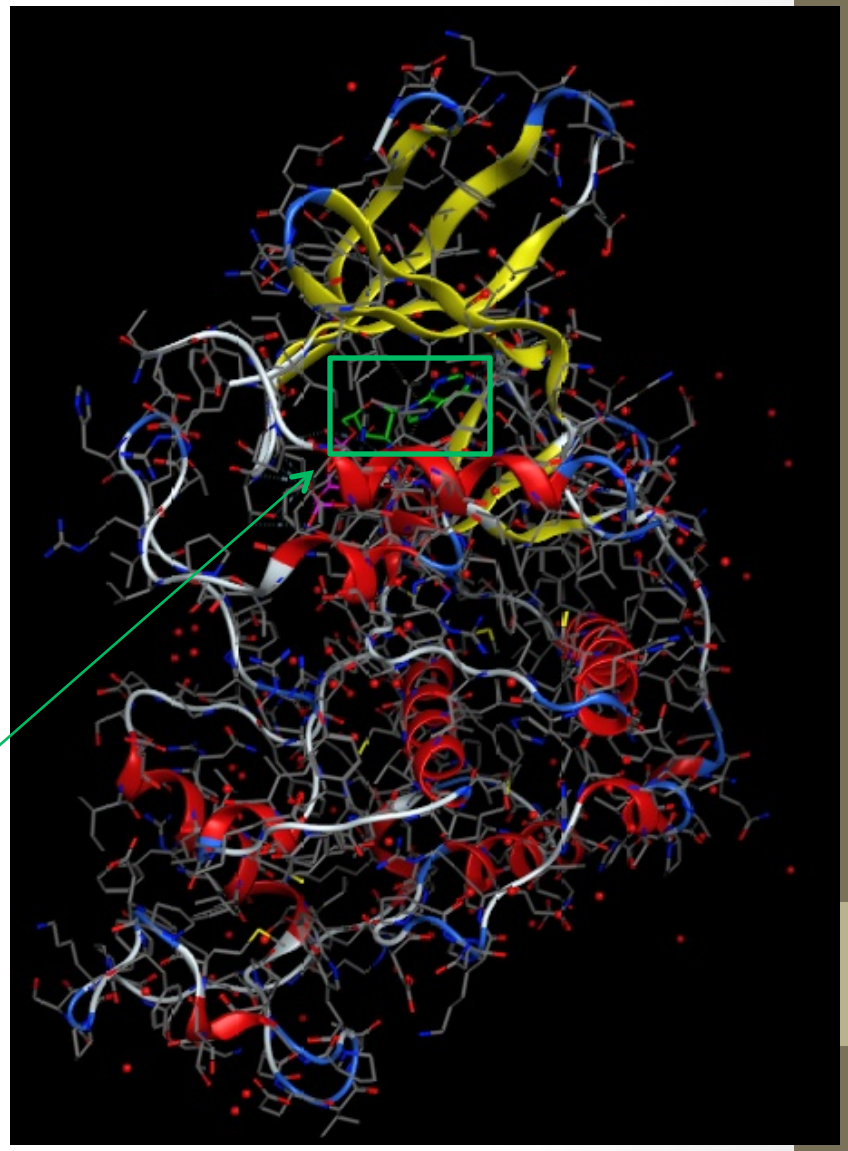
Phthalimide



CDK 2

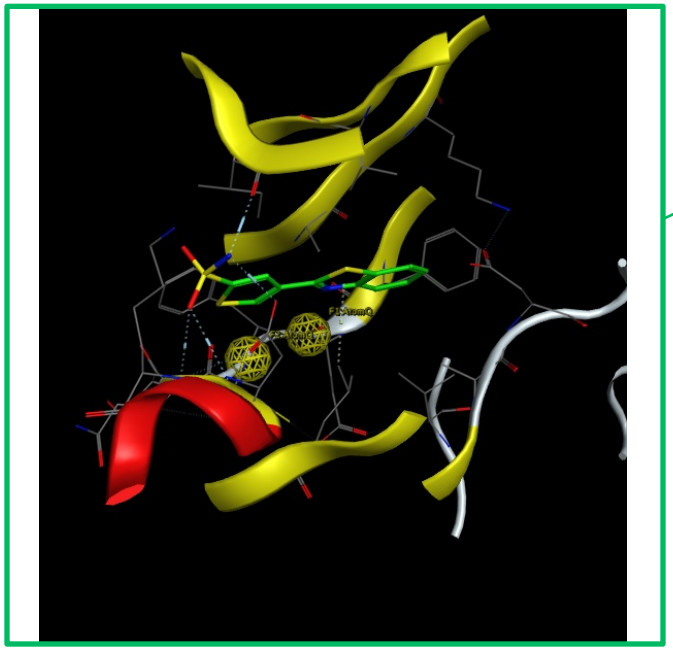
- Has ATP as ligand.
- Inhibitors must be ATP competitive.

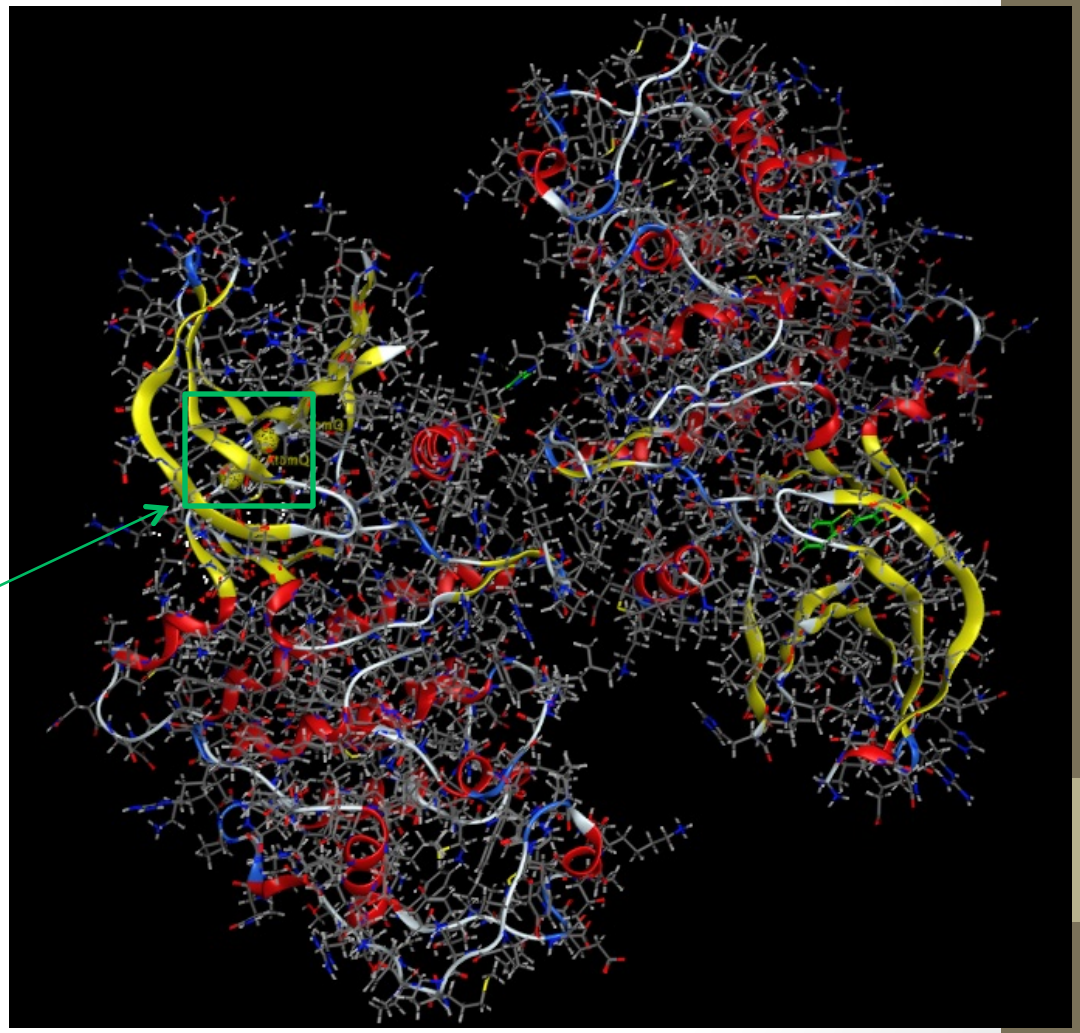




CDK 5

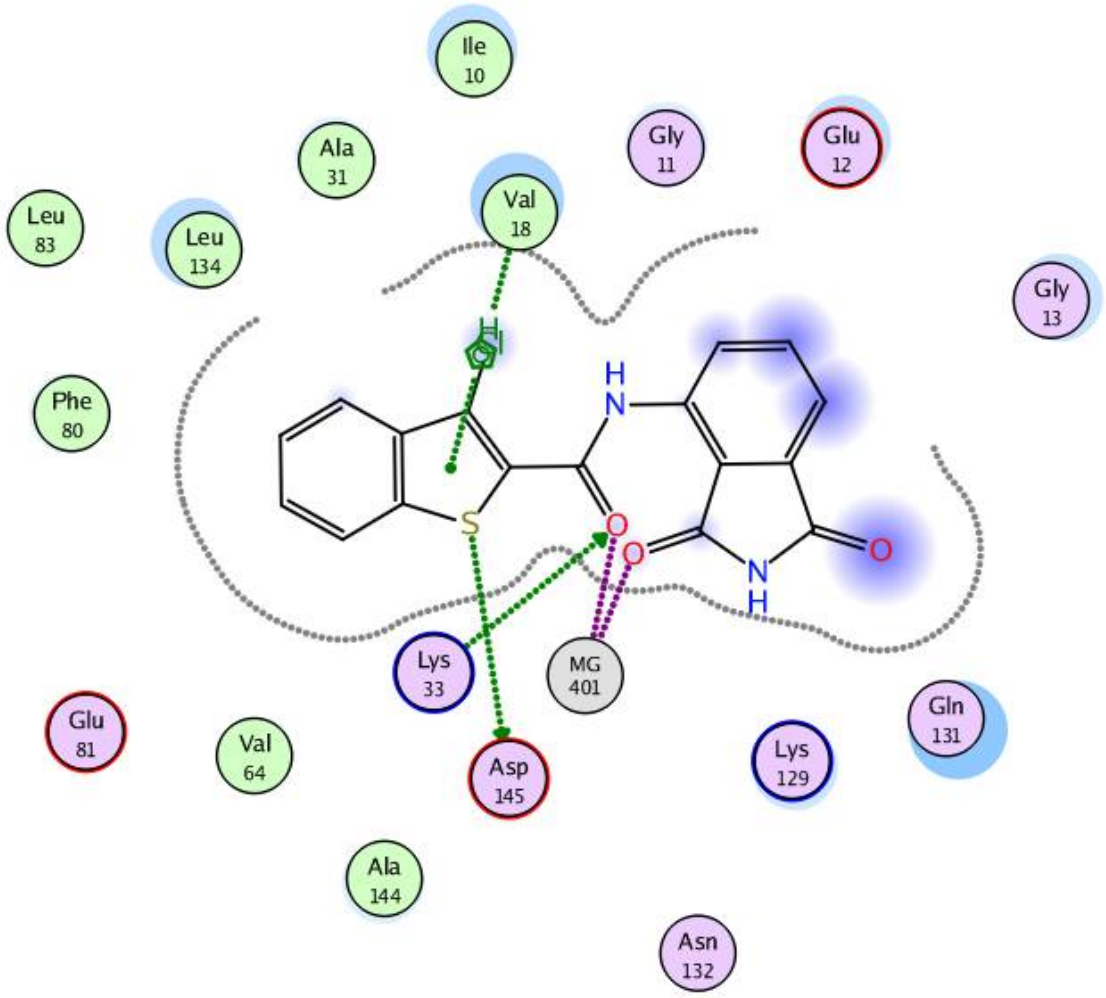
- Contains 3 different ligands.
- Only one of them needs to be replaced.





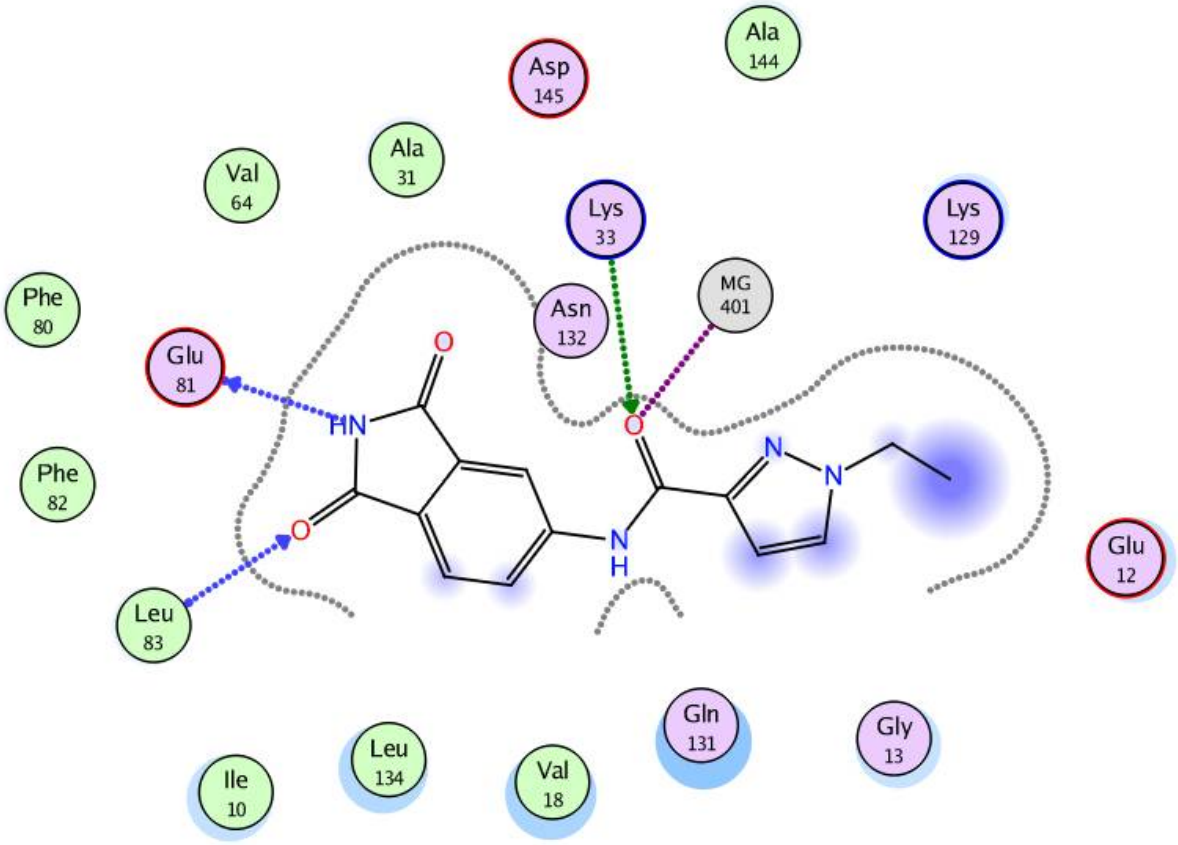
4-amidophthalimide (CDK 2)

- High binding score of -0.9650.
- Could be ATP-competitive.
- No hydrogen bonds to Glu81 or Leu83.



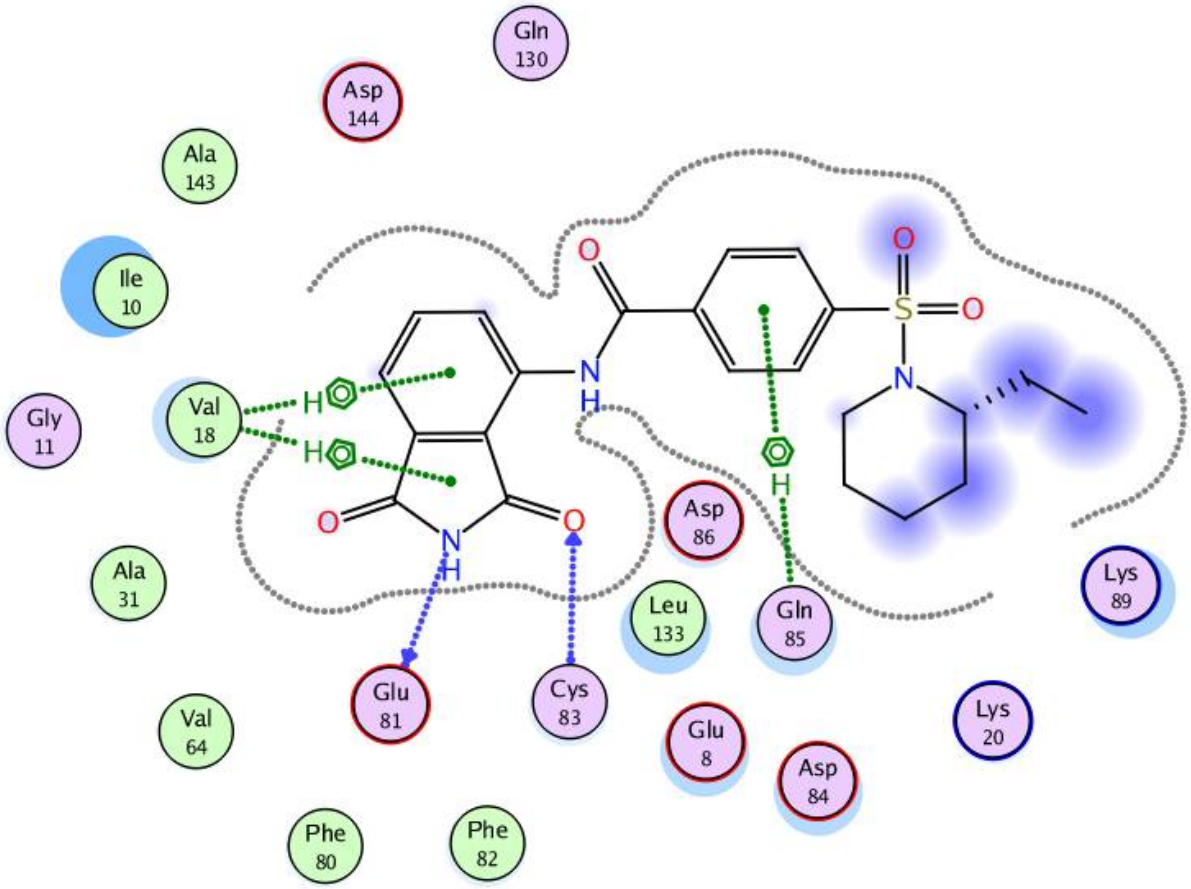
5-amidophthalimide (CDK2)

- Low binding score of -6.5204.
- ATP-competitive.
- Hydrogen bond to Glu81 and Leu83.
- Favorable.



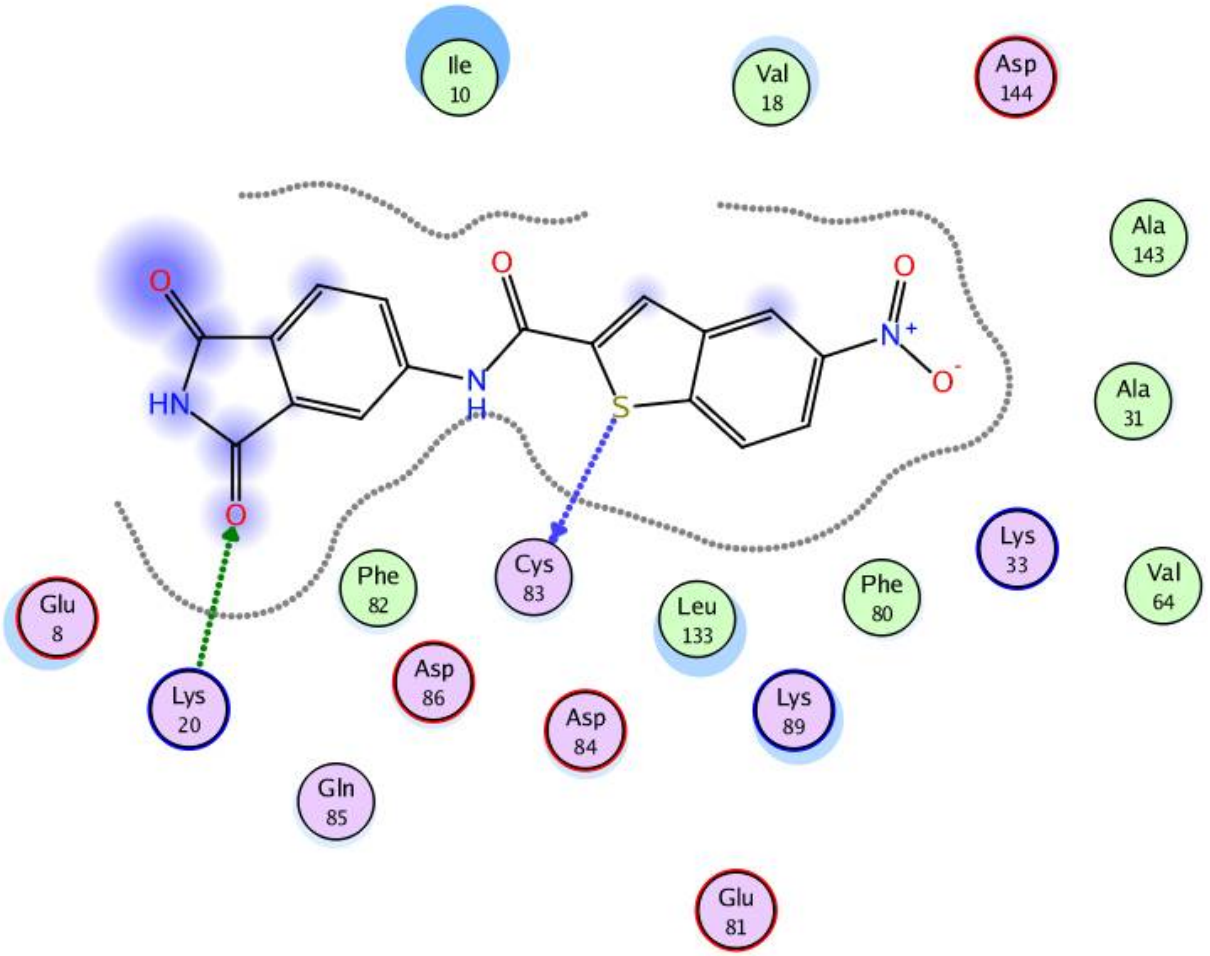
4-amidophthalimide (CDK 5)

- Low binding score of -7.5125.
- ATP-competitive.
- Hydrogen bonds with Glu81 and Cys83.
- Favorable.



5-amidophthalimide (CDK 5)

- Binding score of –6.7852.
- Somewhat ATP-Competitive.
- Hydrogen bond to Cys83.
- Somewhat favorable.



Future Work

- Residues to be targeted for CDK subtype selectivity:-
  - CDK2
    - Glutamic acid 8.
    - Glutamine 85.
    - Lysine 89.
    - Glutamine 131
    - Threonine 137.
  - CDK5
    - Glutamic acid 8.
    - Glutamine 85.
    - Lysine 89.
    - Glutamine 130.
    - Arginine 136.
- Residues to be targeted for increasing potency of CDK inhibitors:-
  - Glutamic acid 8.
  - Lysine 9.
  - Isoleucine 10.
  - Lysine 33.
  - Glutamic acid 51.
  - Phenylalanine 80.
  - Glutamic acid 81.
  - Leucine 83.
  - Histidine 84.
  - Glutamine 85.
  - Aspartic acid 86.
  - Lysine 89.
  - Glutamic acid 131.
  - Asparagine 132.
  - Aspartic acid 145.

Acknowledgements

- I would like to thank Dr. Jayalakshmi Sridhar for her mentorship and assistance.
- I would also like to thank Dr. Riley for his assistance.
- I would also like to thank the La-sigma program and Xavier University for granting me this opportunity.

References

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