Computer Simulation of Biosynthetic Modifications to Improve Binding Activity

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Super Bug - Enterococcus Faecium

- Potentially lethal, worldwide infection
- Antibiotic-resistant
- Able to survive for long periods on inanimate objects
- Hospital environments

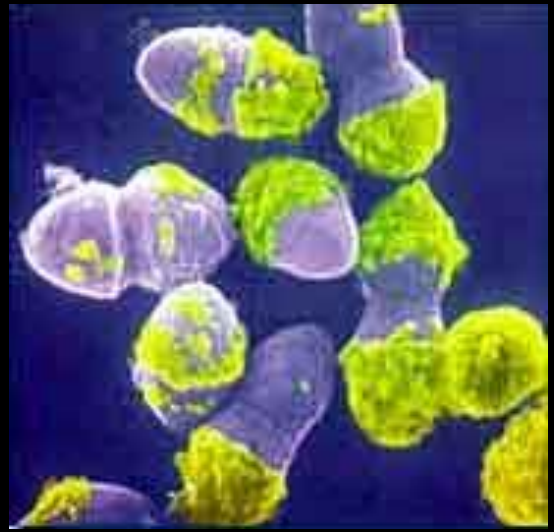
http://efaecium.mlst.net/

Figure 1. Enterococcus Faecium.

Limitations of Existing Drugs

- Vancomycin - resistant
- Penicillin - resistant
- Gentamicin - resistant

- high genome plasticity - Able to acquire numerous other resistances



lbl.gov
Figure 2. Enterococcus Faecium

- Experimental drug development:
  - Expensive
  - Time-consuming
  - Sometimes impossible

- Virtual screening of drugs
  - Fast
  - Cheap
  - Effective
  - Flexible - able to make modifications

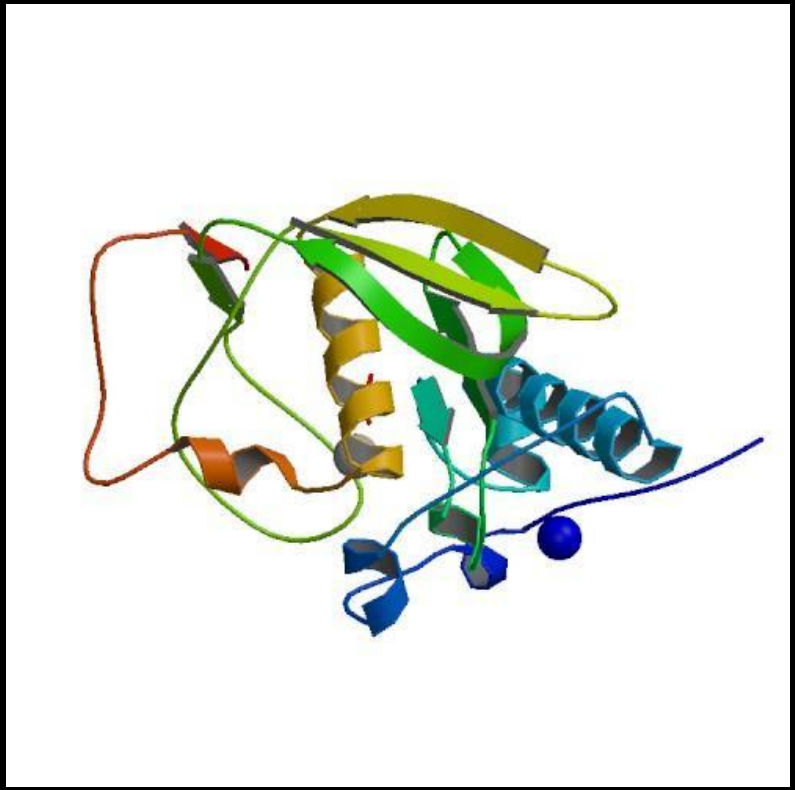
Project Approach

Virtual screening with drug library

Introduce biosynthetic modifications

Test performance of biosynthetic molecules

Protein Target - Peptide Deformylase



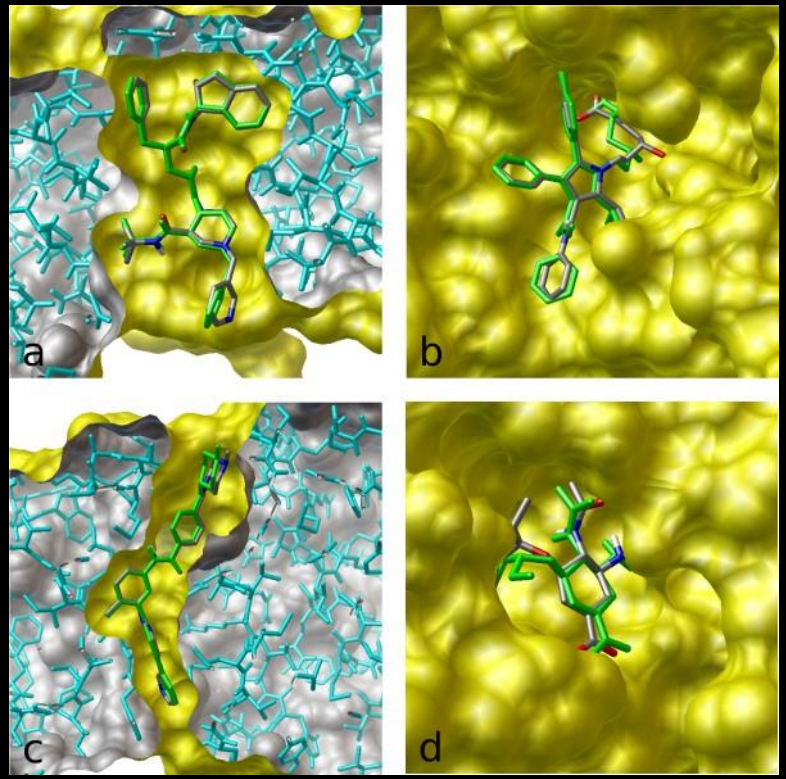
- Production of mature proteins
- Essential for bacterial growth
- Attractive drug target

http://www.rcsb.org/

Figure 3. Crystal structure of Enterococcus Faecium Peptide Deformylase complex with Met-Ala-Ser. PDB ID 3G6N

Virtual Screening

1. Predict binding affinity of drug by docking
    a. estimates the free energy of binding
    b. The more negative the value, the stronger the bond



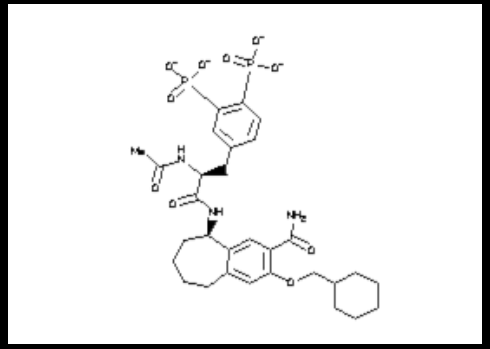
http://vina.scripps.edu/

Figure 4. AutoDock Vina, used to make binding mode predictions and to find binding affinity

Biosynthetic Database

2. Predict possible molecular modifications by finding similar molecules in KEGG database
3. Test binding affinity for predictions

Figure 5a. http://zinc.docking.org/ molecular structure of ZINC53683321



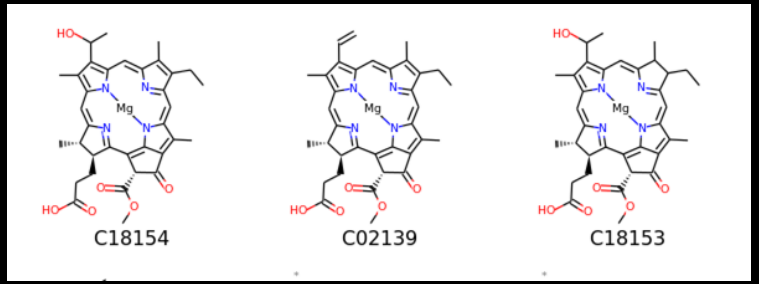
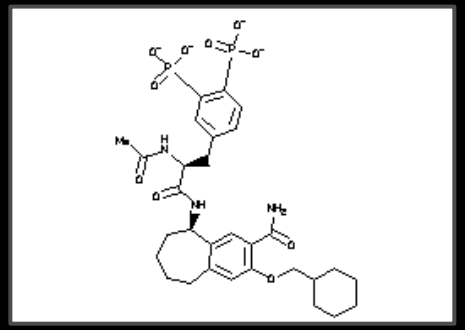


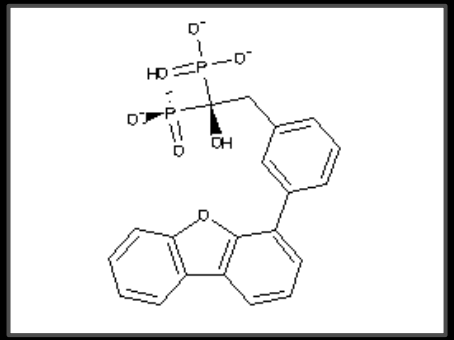
Figure 5b. Molecules found with similar structure

Initial Identification

Drug ID	Known Activity	Predicted Binding Affinity
ZINC53683321	Anti Cancer	-7.8
ZINC16051958	Anti E. Coli	-7.3
ZINC96006023	Antibiotic	-7
ZINC12501002	Coenzyme analog of yeast	-6.5
ZINC58632138	Related to acetyl-CoA synthetase	-6.3



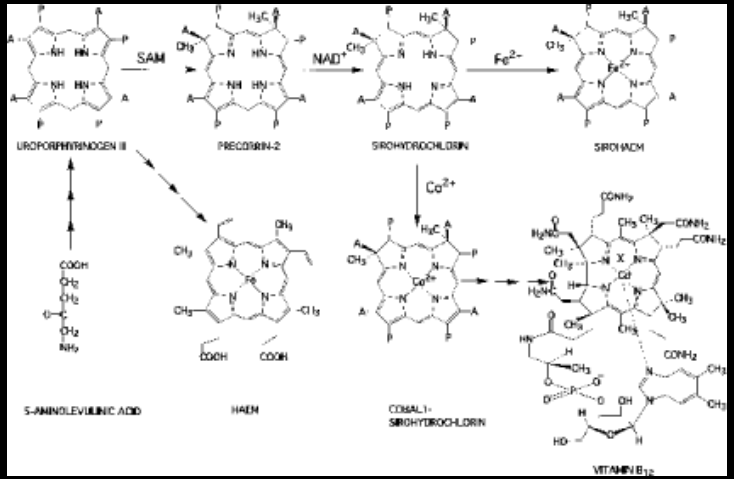
http://zinc.docking.org/
Figure 6a. Structure of ZINC53683321



http://zinc.docking.org/
Figure 6b. Structure of ZINC16051958

Biosynthesis

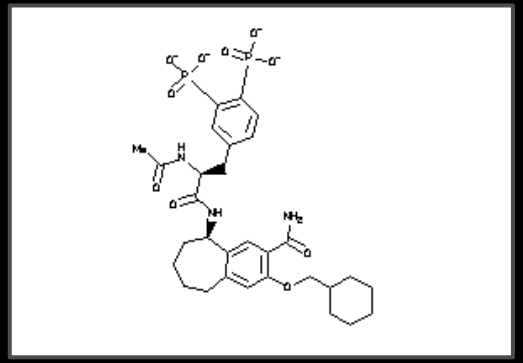
- Enzyme-catalyzed
- Convert substrate to more complex molecules
- Generate molecular features for ligand recognition that are more likely to bind to novel targets



biochemj.org
Figure 7. Branched biosynthetic pathway of the modified tetrapyrroles

Results

Original Drug	Original Predicted Affinity	Molecule ID	Predicted Affinity of Modified Drug
ZINC53683321	-7.8	C01849	-10.1
ZINC16051958	-7.3	C05444	-9.1
~	~	C02807	-8.7
ZINC58632138	-6.3	C00008	-7.3



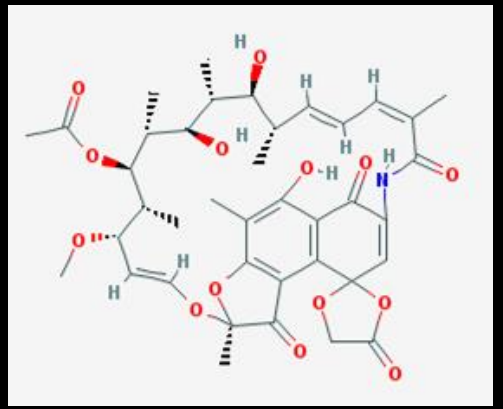


Figure 8. (Top) http://zinc.docking.org/
Original Drug molecule of ZINC53683321
(Bottom) https://pubchem.ncbi.nlm.nih.gov
Similar molecule with better performance C01849

Discussion

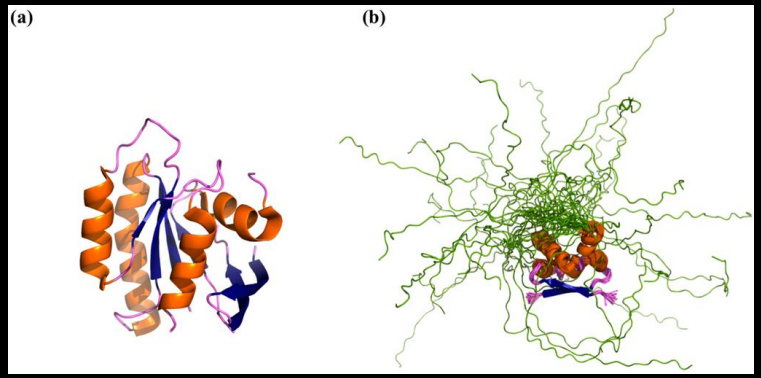
- Improvements for existing drug molecules that target Enterococcus Faecium are found by looking at molecules with similar molecular structures.
- Computer simulations show that drug performance is greatly increased by such modifications.

Future Direction

- Target other organisms in ESKAPE group
- Looking at proteins related to neurological diseases
- Expand drug database and molecule database
- Building new drug molecules using fragment-based design

Intrinsically Disordered Proteins

- Lack a fixed or ordered 3D structure
- Flexible, easy to bind to
- Have close relationships with human diseases such as tumor, Parkinson disease, Alzheimer disease, diabetes, etc.



MDPI

Figure 9. Varied degree of order in proteins. (a) Has well defined three-dimensional coordinates (b) protein with both an ordered region and an IDR

Acknowledgments

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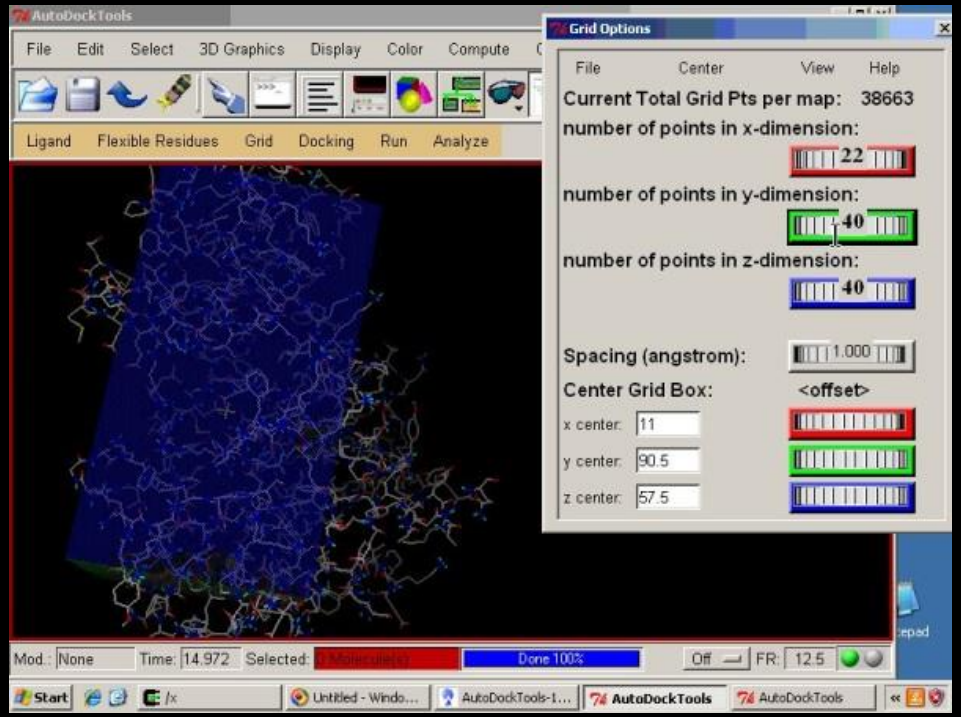
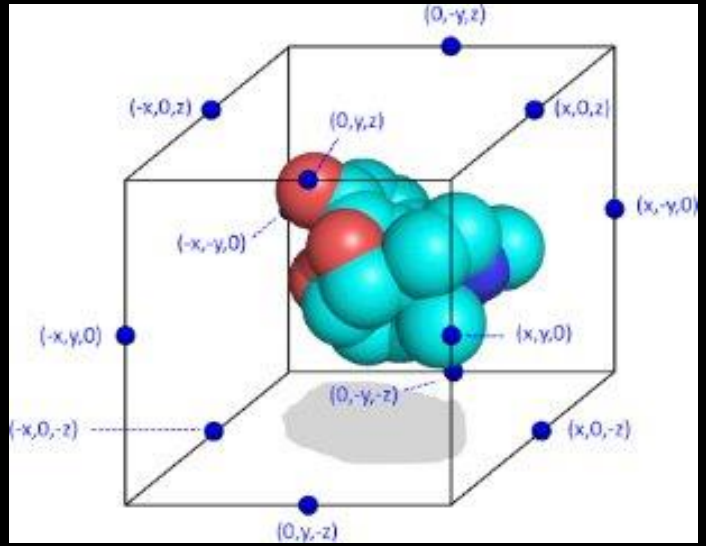
Methods - Binding Affinity

- AutoDock Vina
- Allows running ligand-receptor docking calculation



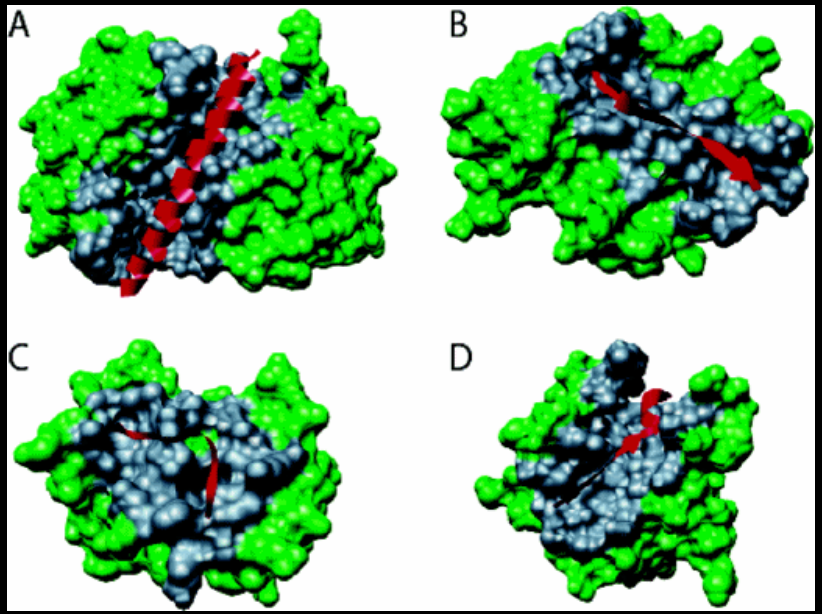
Methods - Binding Probability

- Calculate the spectrophore of the drug molecule and the MoRF
- Binding Probability is calculated from the similarity between the drug molecule and the MoRF



openbabel.org
Demonstration of how spectrophores are calculated

Molecular Recognition Features (MoRFs)



UC Davis
Examples of molecular recognition features (MoRFs)

- Small, intrinsically disordered region of a protein
- Bind to partners, serves as an initial step in molecular recognition