



Study of Interactions of Various Potential Anti-cancer Drugs with Microtubules and Evaluation of Structural Dynamics and Conservation of Function of Kinesin-II Stalk

Angelina Thomas V., Veena Chaudhari, Bajarang Vasant Kumbhar, Arijit Bhaumik and Ambarish Kunwar*

Department of Biosciences and Bioengineering, Indian Institute of Technology Bombay, Powai, Maharashtra- 600076

Abstract

Microtubules play an important role in cell division, cell signaling and intracellular transport thereby making it an important target for designing a new drug. Rhizoxin is a potential anticancer agent that binds at the interface of $\alpha\beta$ tubulin heterodimer and stops microtubule dynamics but its binding mode and interaction with tubulin is not known at the atomic level. Hence, we investigated the binding mode and its interaction using molecular modeling studies.

Intracellular transport is regulated by molecular motors i.e. kinesin which walk on microtubule. Therefore, we also studied how human kinesin motors accomplish their cellular tasks using molecular dynamics simulation.

Methodology

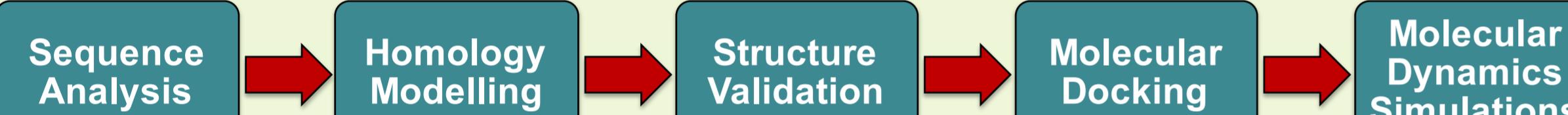


Figure 6: Workflow of Methodology performed.

Sequence Analysis

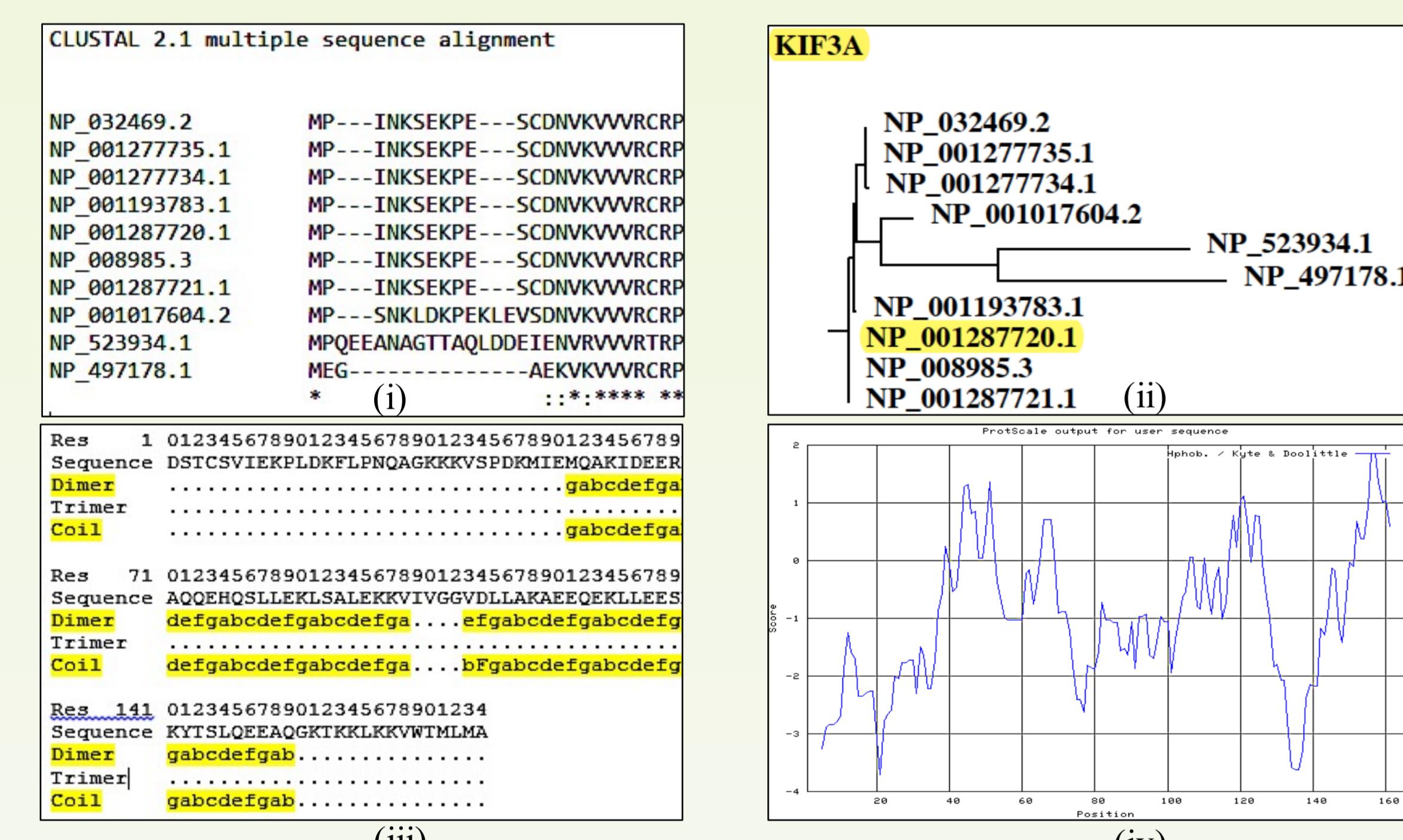


Figure 7: (i) MSA using Clustal, (ii) Phylogeny Analysis, (iii) Multicoil predictions, (iv) Hydrophobicity predictions using ProtScale.

Homology Modelling

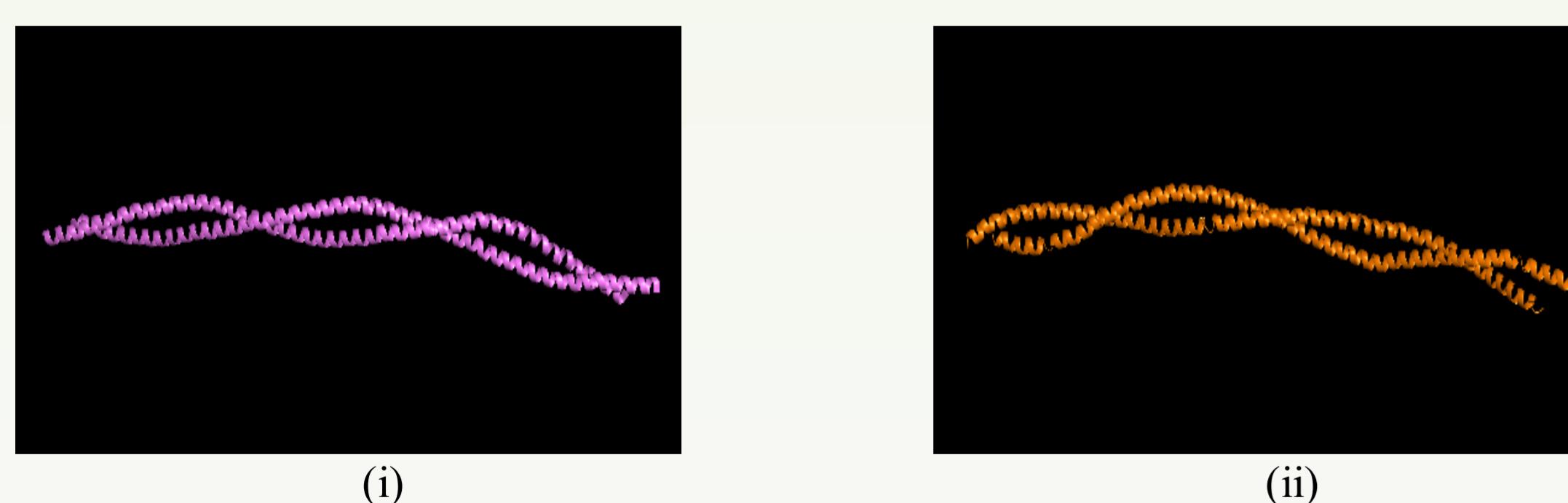


Figure 8: (i) Tropomyosin (Chain A/Chain B) (ii) Homo sapiens (HsKIF3A/HsKIF3B).

Structure Validation

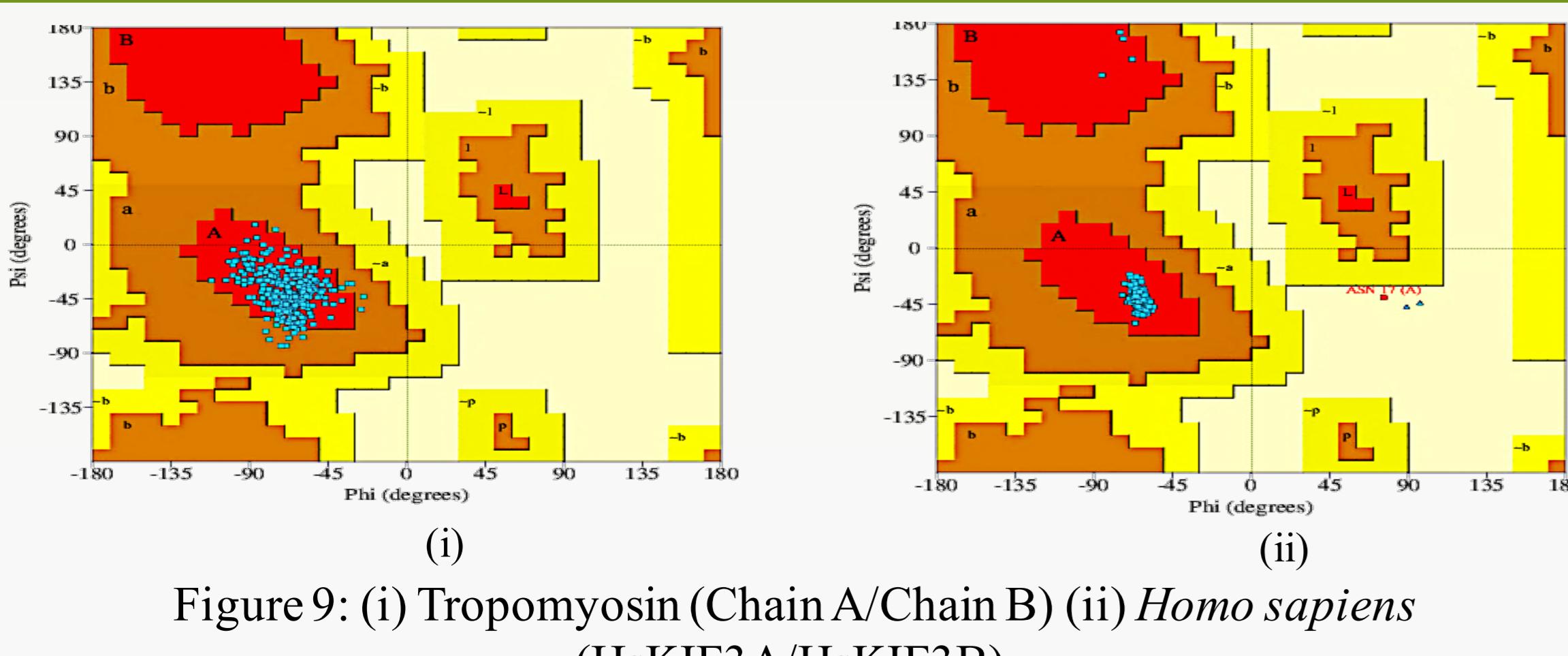


Figure 9: (i) Tropomyosin (Chain A/Chain B) (ii) Homo sapiens (HsKIF3A/HsKIF3B).

Introduction

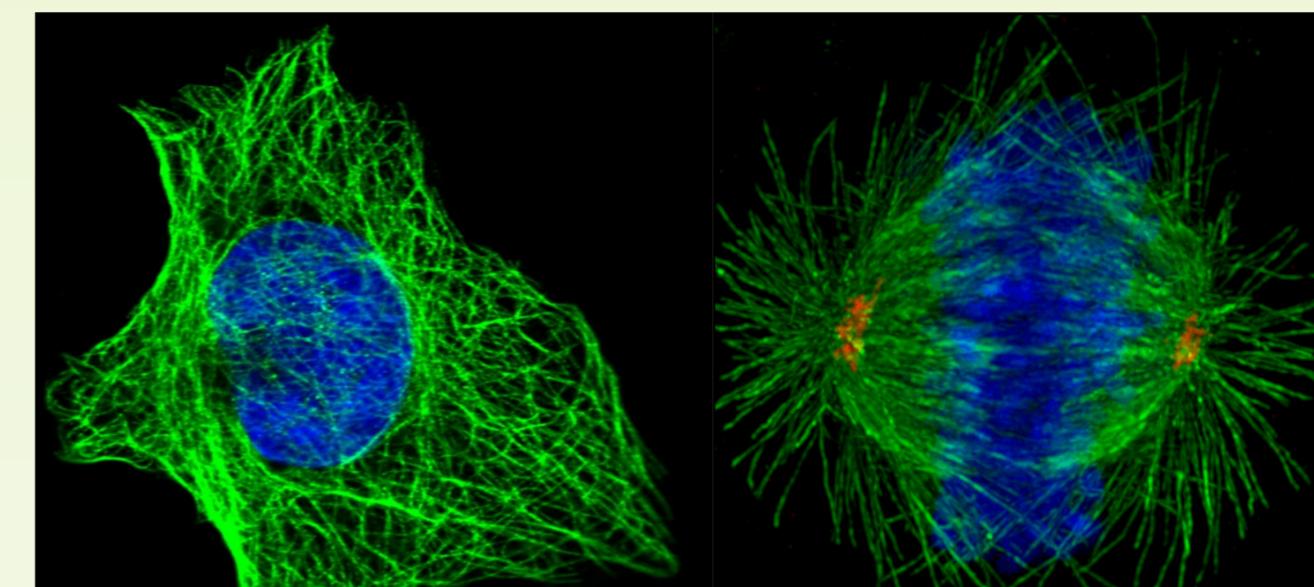


Figure 1: Human cell
Courtesy: <http://www.proteinatlas.org>

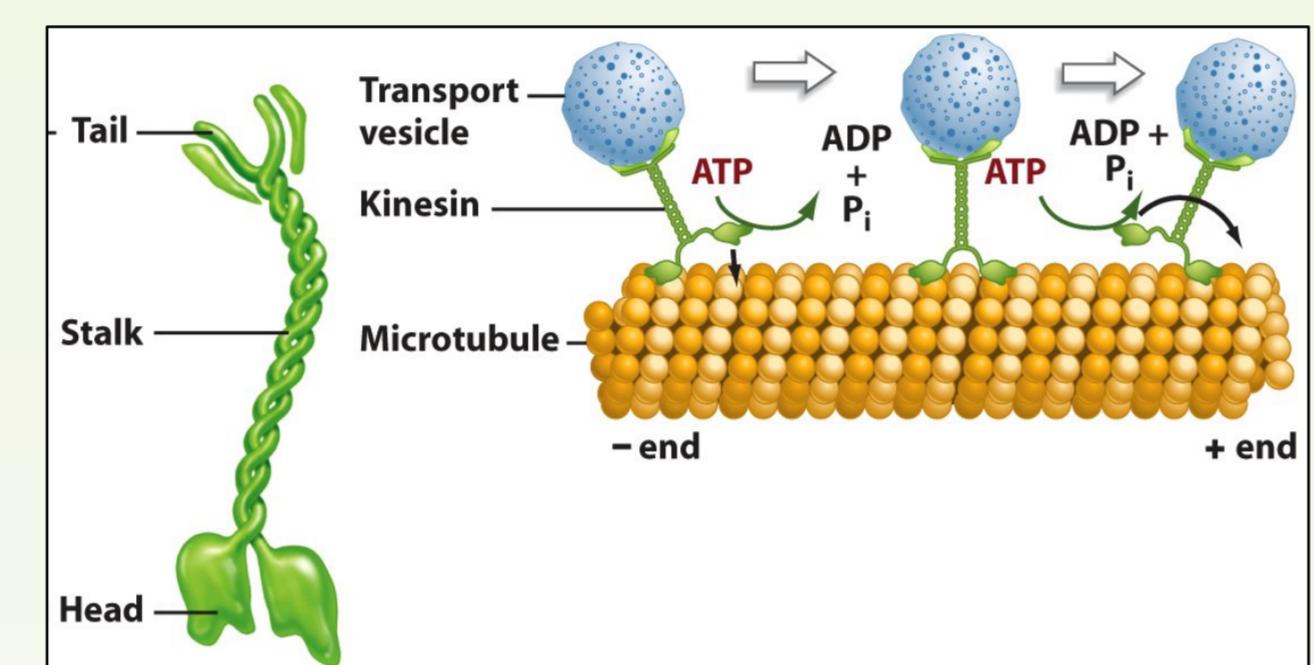


Figure 2: Kinesin across microtubule
Courtesy: Figure 7, Biological Science, 2/e;
Pearson Prentice Hall, Inc. (2005)

Rhizoxin isolated from a plant pathogenic fungus which causes rice seedling blight inhibits mitosis of tumor cells in a manner similar to that of Vinca alkaloids as revealed by morphological study and flow cytometry analysis.

Kinesin-II is a conserved microtubule-based motor involved in the intraflagellar transport, cilia assembly, axonal transport and other intracellular processes. The Kinesin's overall architecture forms a prerequisite to understand how these motors accomplish their cellular tasks and how to efficiently target them in treatment regimens.

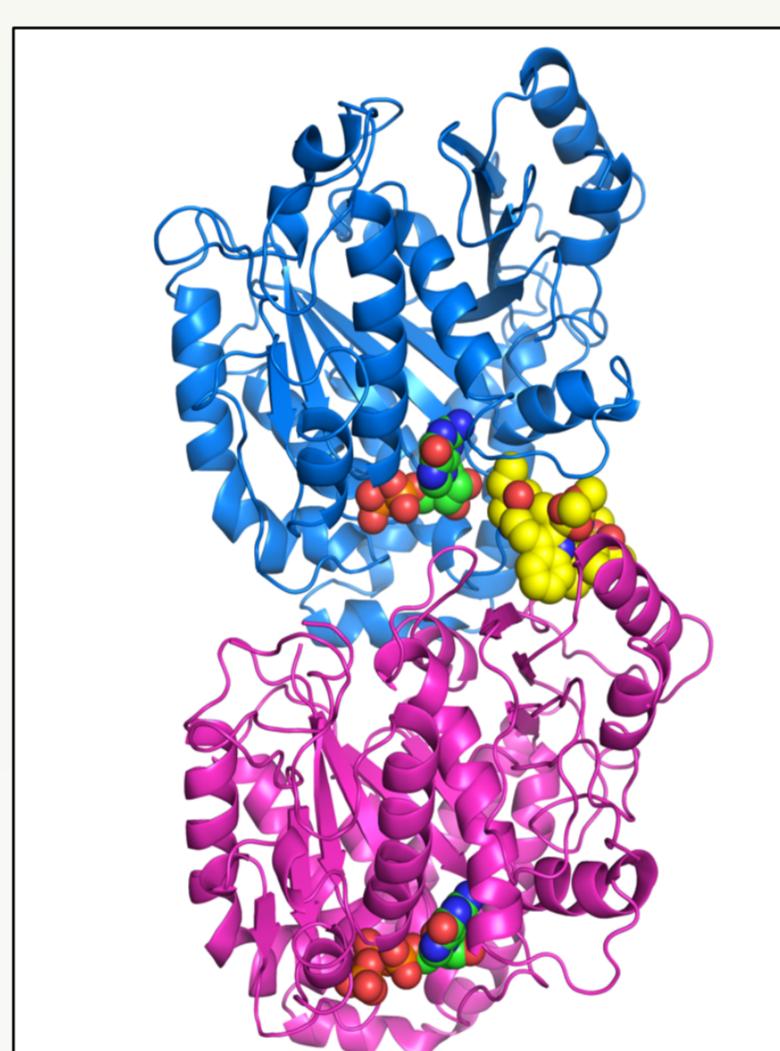


Figure 3: Crystal structure of $\alpha\beta$ Tubulin heterodimer with Vinblastine (1Z2B)

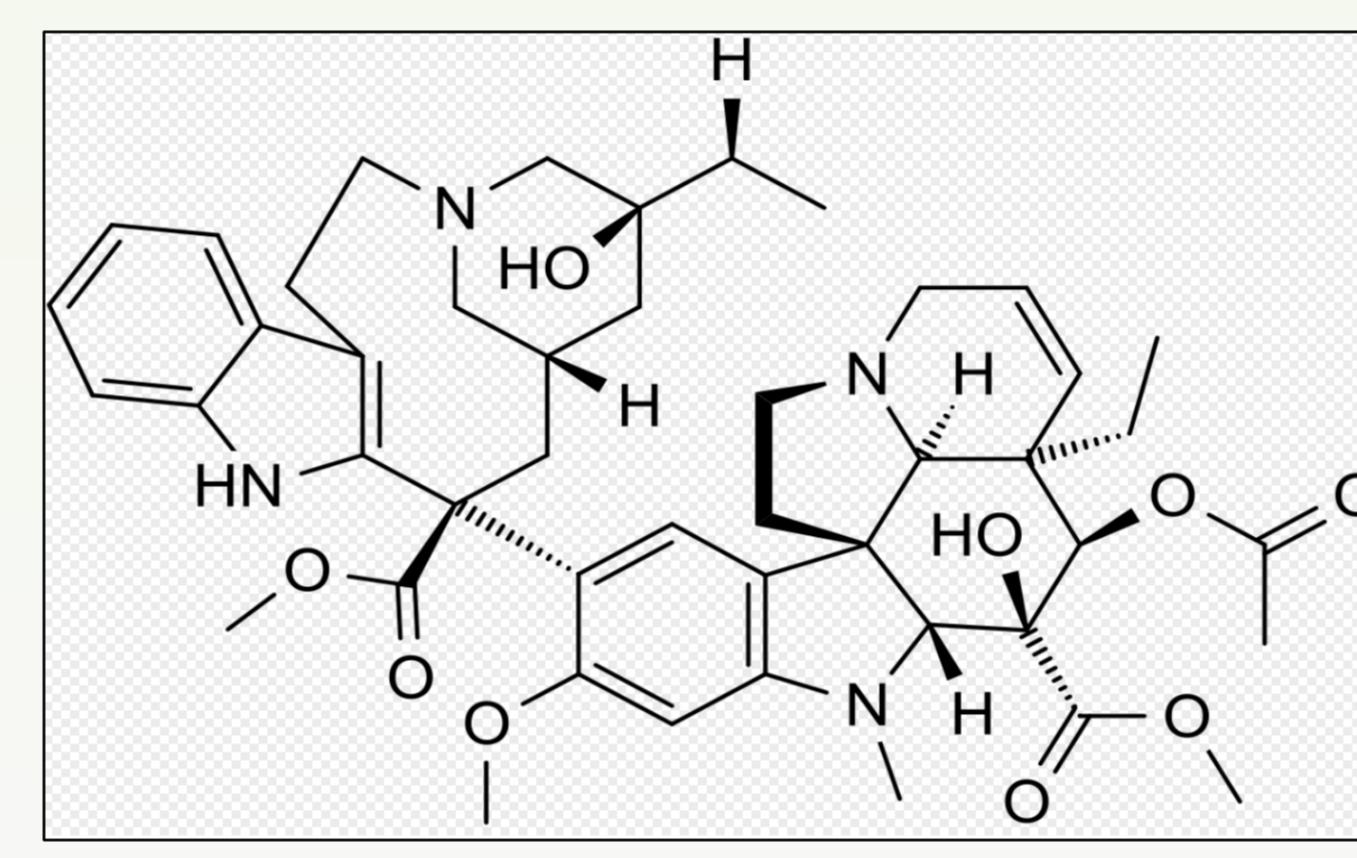


Figure 4: Schematic representation of Vinblastine

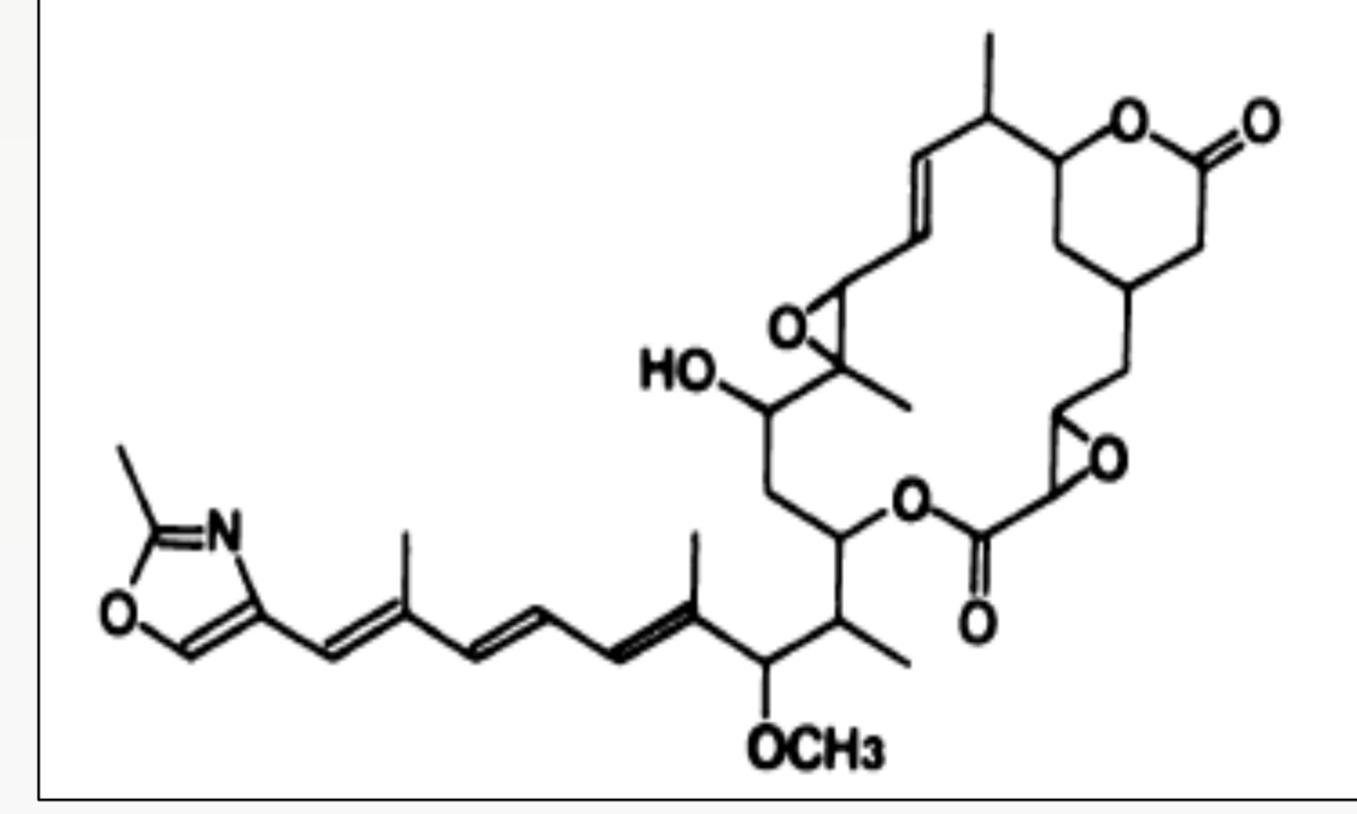


Figure 5: Schematic representation of Rhizoxin

Molecular Docking

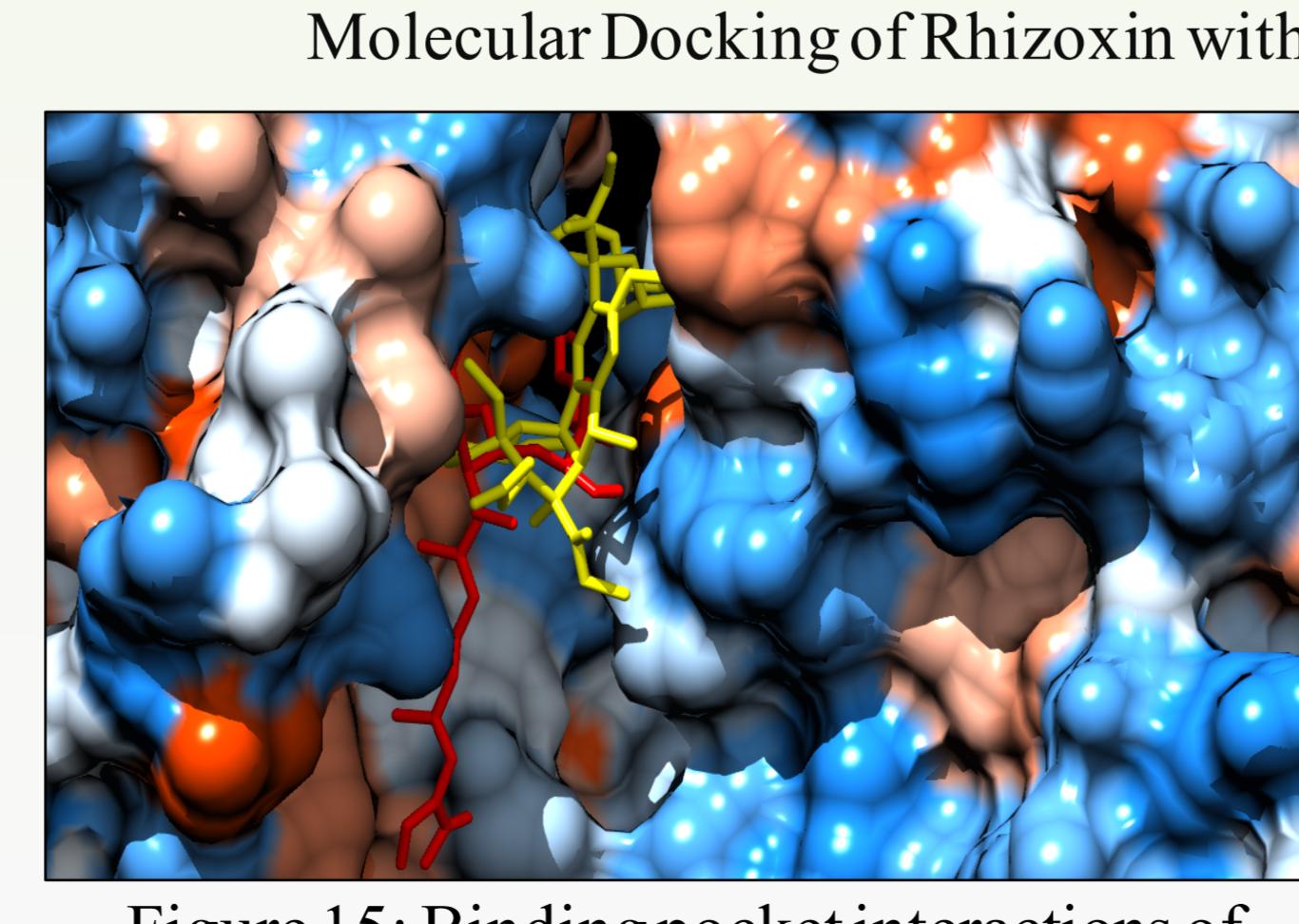
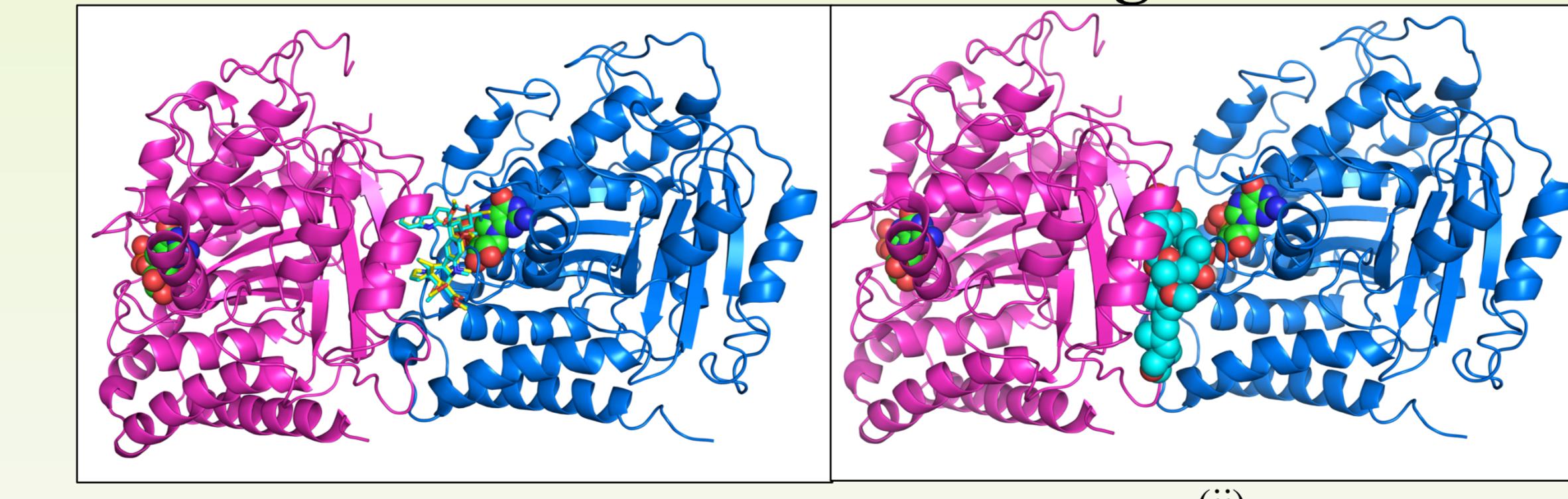


Table 1: RMSD and binding energy of Vinblastine and Rhizoxin with $\alpha\beta$ Tubulin.

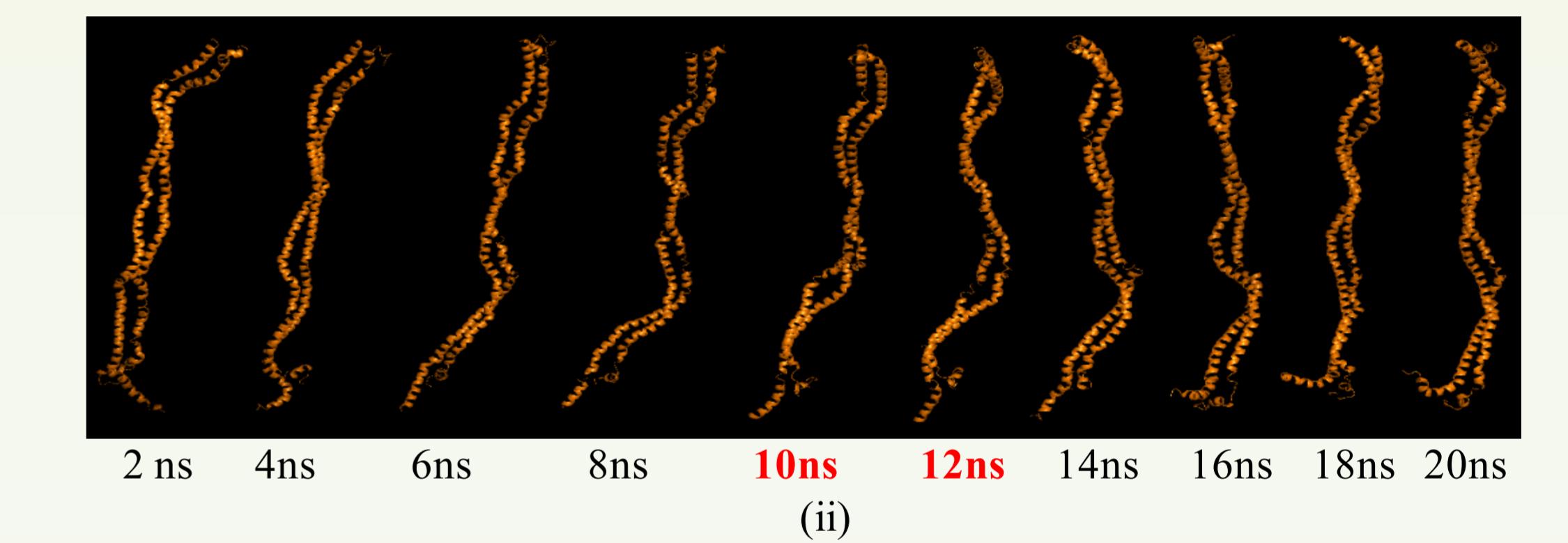
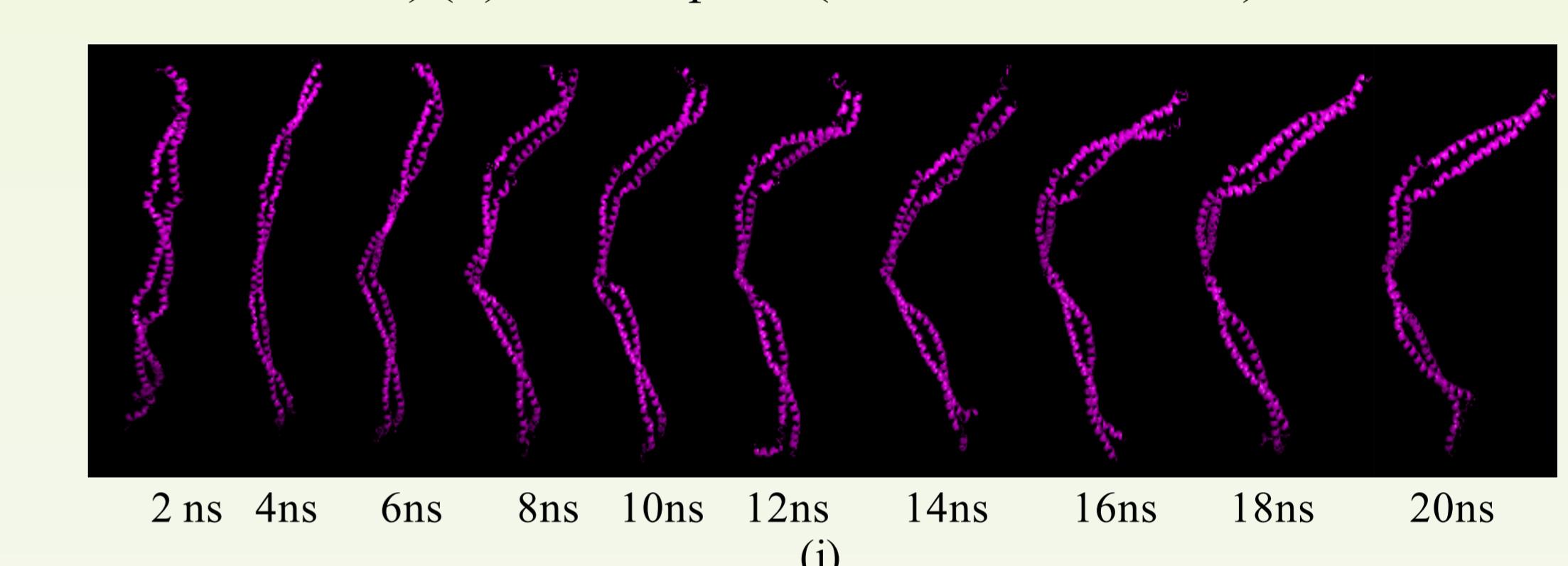
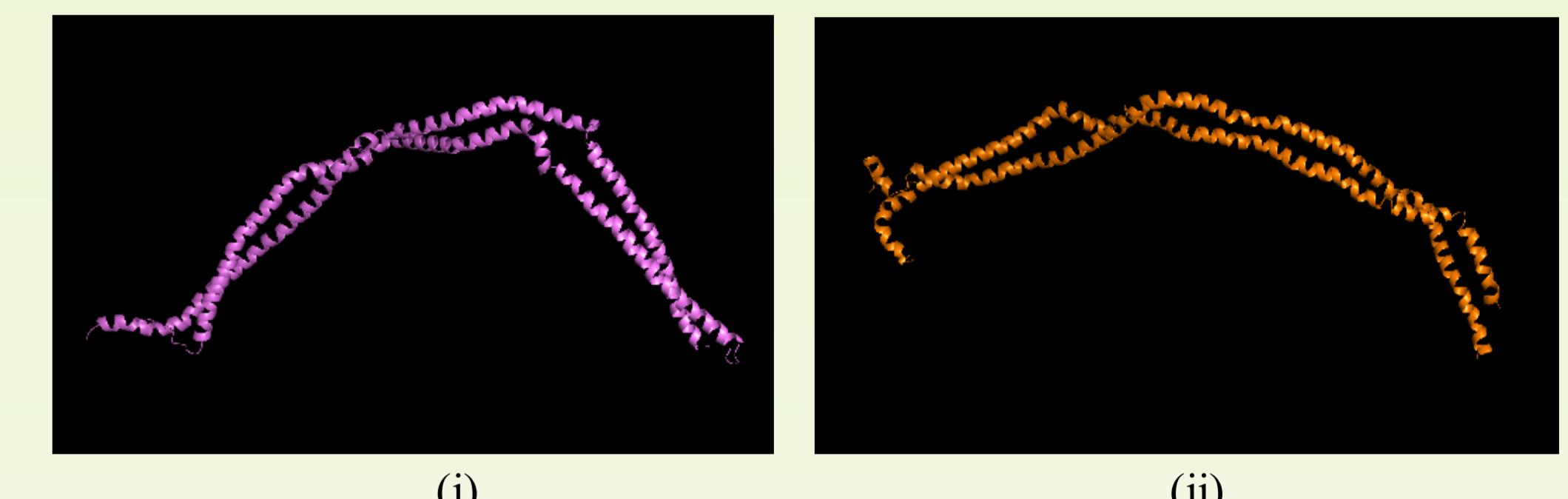
Protein Structures	RMSD in (\AA)	Binding Energy
$\alpha\beta$ -Vinblastine	0.758	-11.61
$\alpha\beta$ -Rhizoxin	-	-9.65

Conclusion

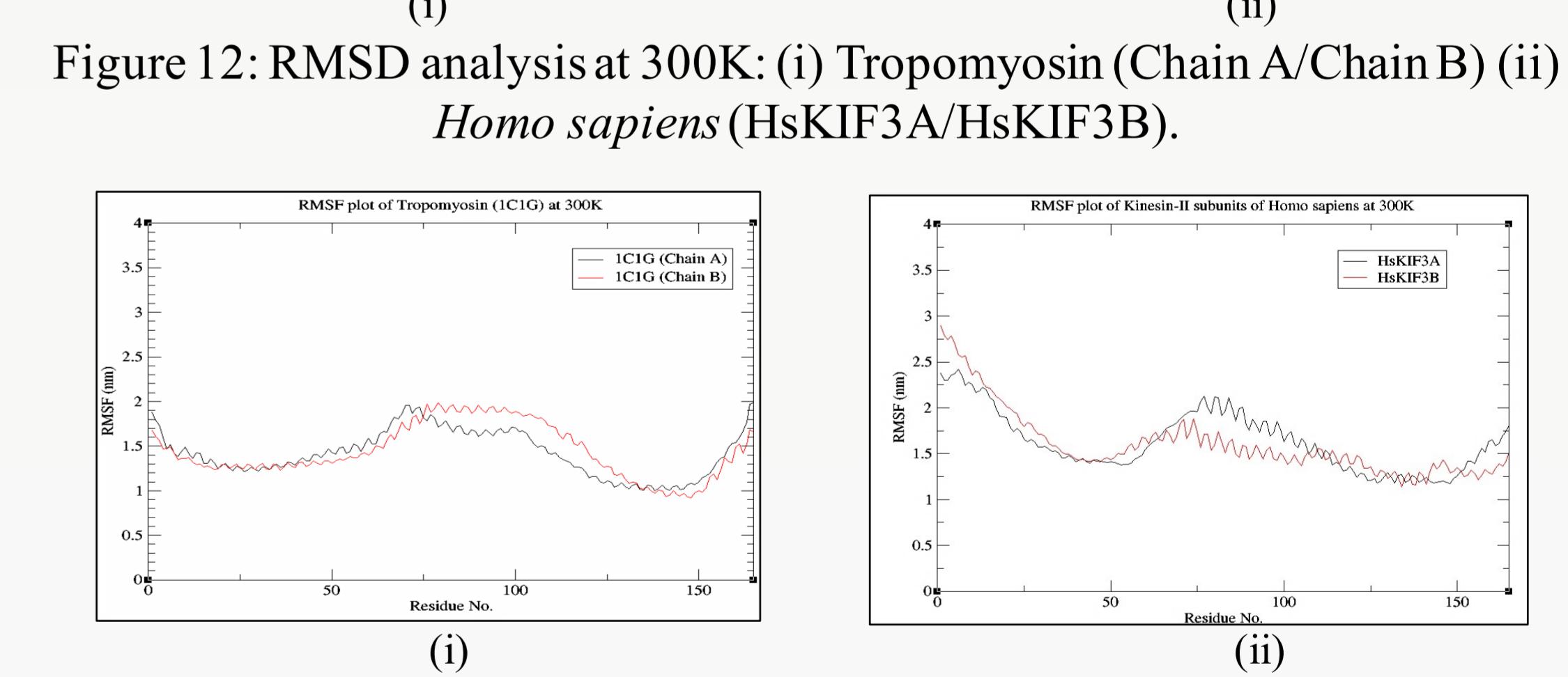
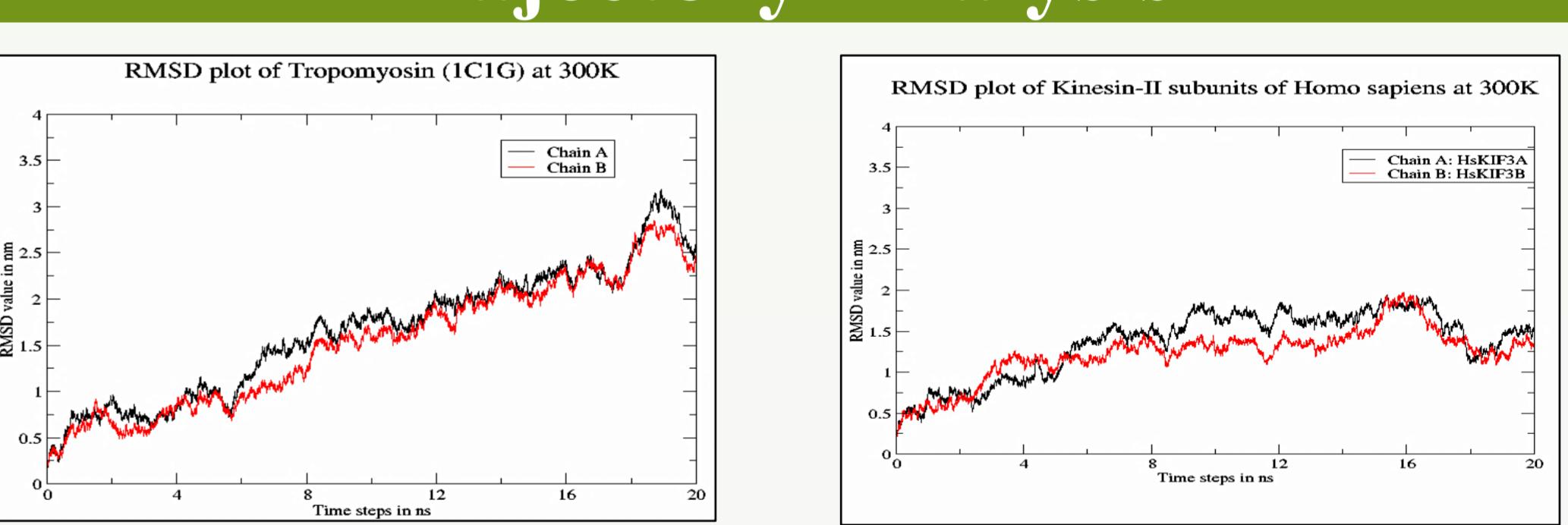
The binding mode of Rhizoxin forms a perfect binding in the pocket region with $\alpha\beta$ tubulin dimer. The N-Terminal coiled-coil regions of the Kinesin-II stalk needs further analysis and investigation using explicit MD simulations.

Results

Molecular Dynamic Simulations



Trajectory Analysis



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References

- Eckhard et al.(2002) "Kinesin motors and disease", Cell Biology, 1-7.
- Wenjun et al.(2015) "Kinesins, Dyneins, and Other Microtubule-based Motors".
- Takashi et al.(1986) "Rhizoxin: A new Anti-Tumour drug".