

**Abstract:** ERBB4 is a member of the HER/ERBB family of receptors, which are important in the development of breast cancer. ERBB4 has dual roles—it can either promote or suppress tumour growth. As per our objective, we implemented methodologies from systems biology and network pharmacology. Initially, we examined the kinase domain and homologs of ERBB4, followed by a detailed search for ERBB4 inhibitors in publicly available databases. 14 inhibitors of ERBB4 were mined, and associated biological pathways were analyzed using Reactome, KEGG, and BioModels databases followed by Swiss Target Prediction. For all the 14 inhibitors a (PPIN) protein-protein interaction network (PPIN) was reconstructed using STRING, and ensemble of PPIN reconstructed using CytoScape and hub genes were identified. Protein modeling, validation, drug-protein docking and MD simulations were carried out. These hub genes were modeled into an extended network, resulting in the identification of 46 protein kinases and 4 non-kinase proteins as potential therapeutic targets associated with various cancers, including breast carcinoma. Structural data for selected non-kinase targets (MCL1, PTGS2, PLCG1, and HSP90AA1) were done. All the 14 compounds docked 04 target revealed the binding affinity and pharmacophoric interactions with stable conformations. This comprehensive computational framework supports drug repurposing towards non-kinase targets in cancer treatment.

**Keywords:** ERBB4, Kinase, Non-kinase, Systems Biology, and Network Pharmacology.

## Methodology

Target Mining

Protein Network

3D structure

Docking

**Aim:** To apply systems biology and network pharmacology approaches to explore ERBB4-related networks and identify kinase and non-kinase targets for cancer therapy

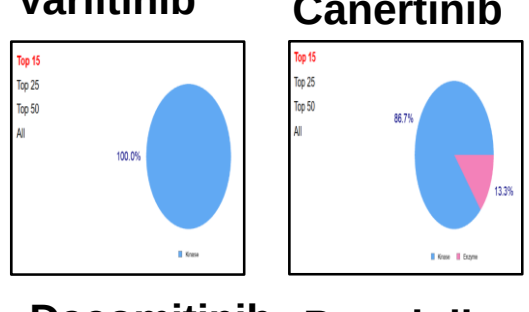
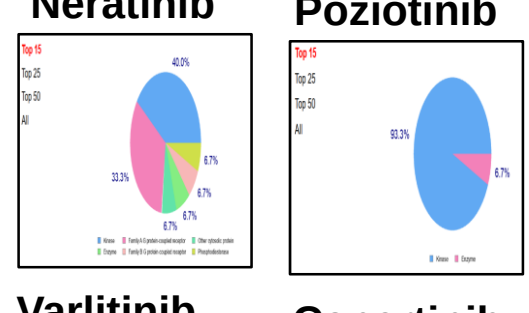
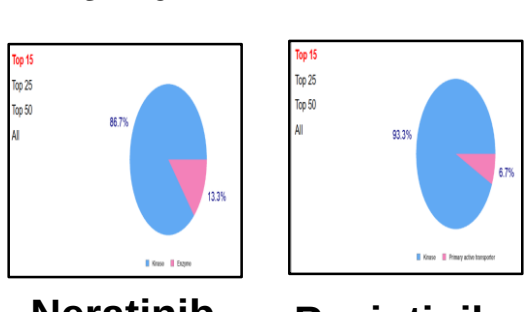
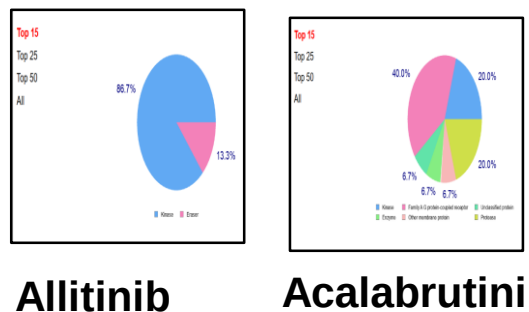
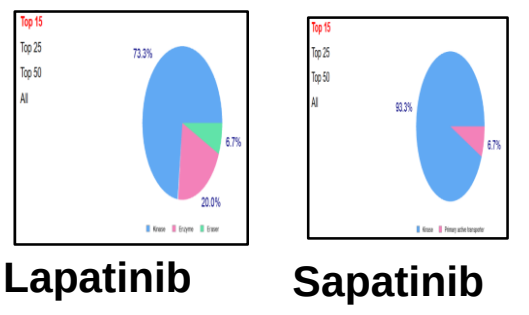
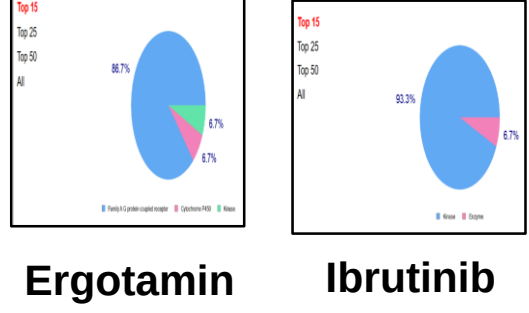
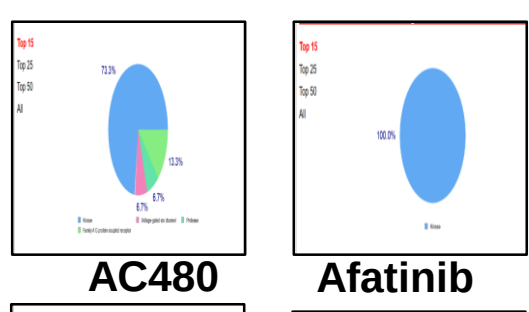
### Objective:

Construct ERBB4-centered protein interaction networks. Identify functional domains, hub genes, and regulatory partners. Predict and validate druggable non-kinase targets using docking and simulation tools.

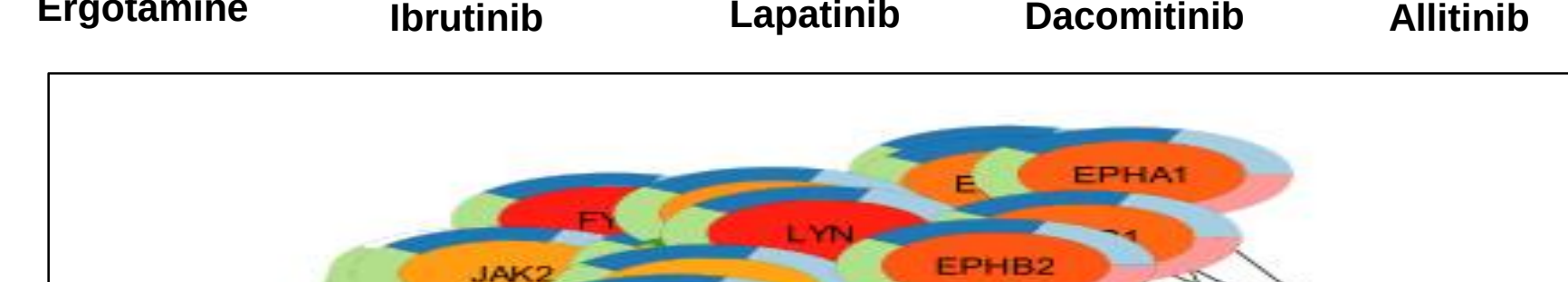
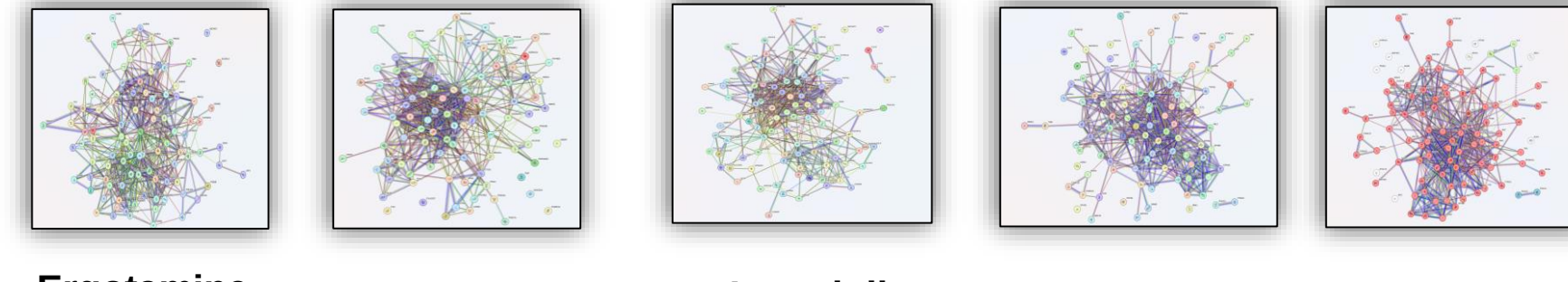
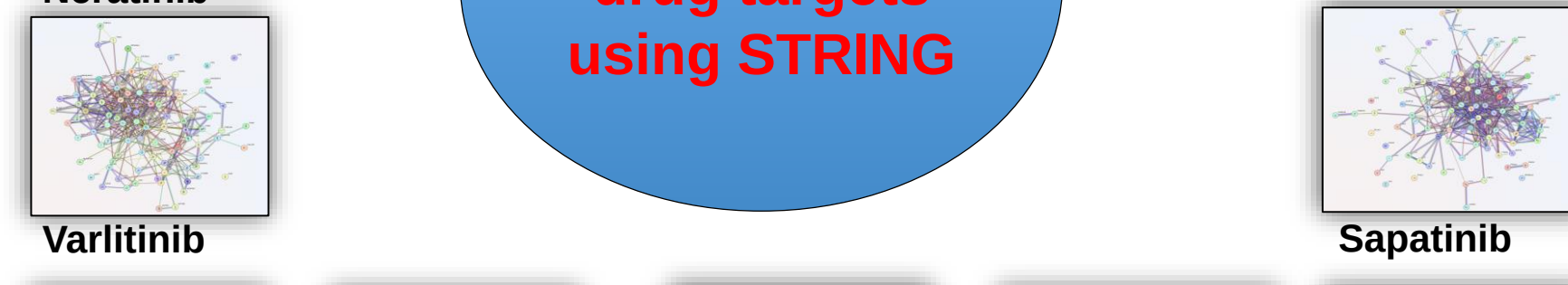
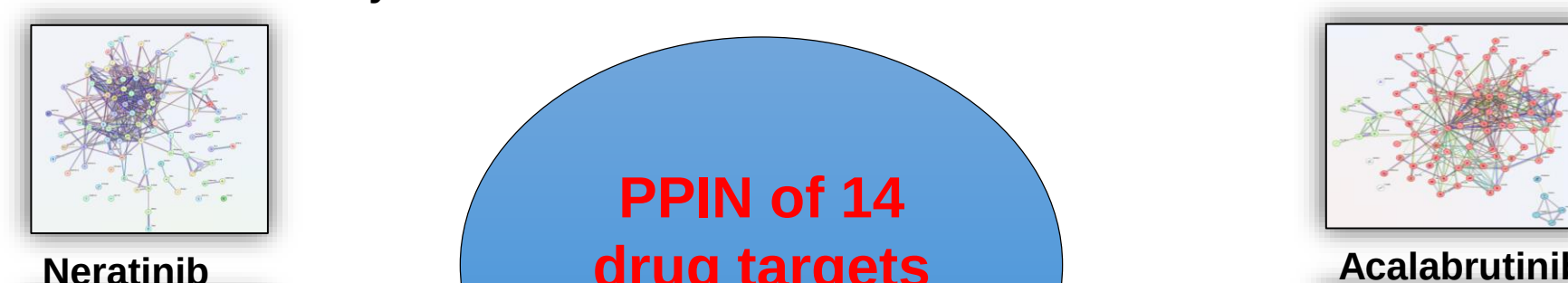
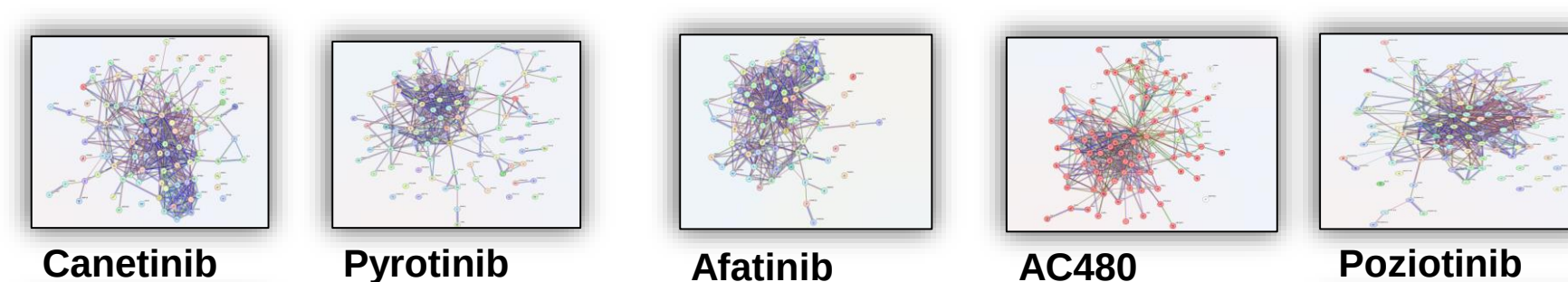
### Problem Statement:

There is a clear gap in understanding ERBB4's interaction networks, drug-binding potential, and influence on downstream pathways. To overcome this, a systems biology and network pharmacology approach is essential for enabling mapping of ERBB4-centered protein-protein interaction networks.

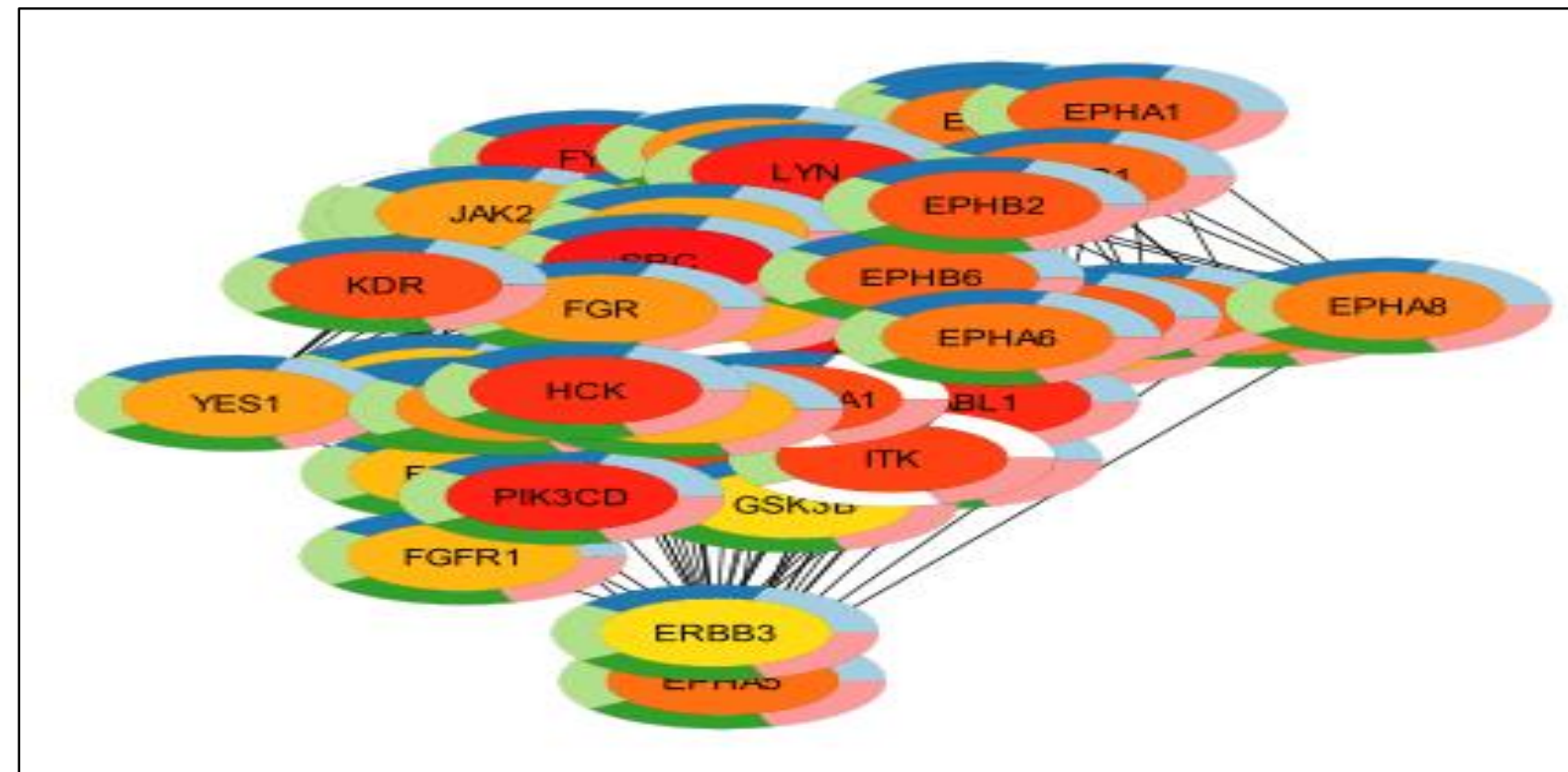
### Target Mining



### Protein-protein Interaction Network

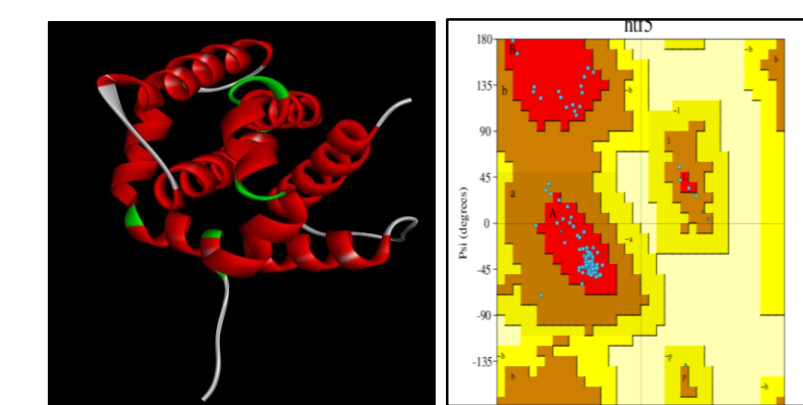


### Hub-Network

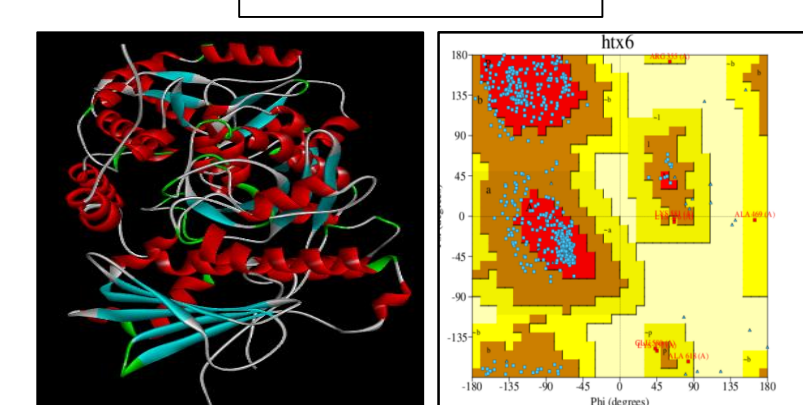


## Results

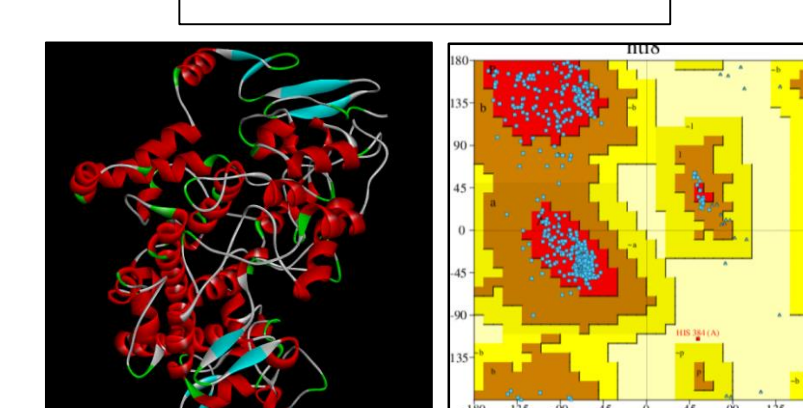
### Protein 3D Model Non Kinase



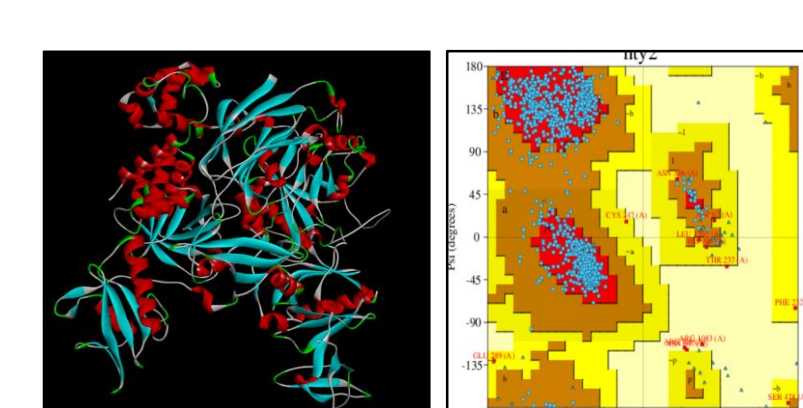
#### MCL1



#### HSP90AA1



#### PTGS2



#### PLCG1

### Non-Kinase Target Molecular Docking Results

| Sr no    | Ligands       | Target-MCL1 Energy Kcal/mol | Ligands       | Target-PTGS2 Energy Kcal/mol | Ligands       | Target-HSP90AA1 Energy Kcal/mol | Ligands       | Target-PLCG1 Energy Kcal/mol |
|----------|---------------|-----------------------------|---------------|------------------------------|---------------|---------------------------------|---------------|------------------------------|
| Standard | LC9           | -6.8                        | TIF           | -3.4                         | PU3           | -5.5                            | NA            | NA                           |
| 1        | Ergotamine    | -8.8                        | Ergotamine    | -9                           | Ergotamine    | -9.5                            | Ergotamine    | -10.8                        |
| 2        | Ibrutinib     | -8.3                        | Dacomotinib   | -8.6                         | AC480         | -8.9                            | Acalabrutinib | -10                          |
| 3        | AC480         | -8.2                        | Varlitinib    | -8.5                         | Poziotinib    | -8.8                            | Ibrutinib     | -10                          |
| 4        | Poziotinib    | -8                          | Acalabrutinib | -8.5                         | Ibrutinib     | -8.7                            | Poziotinib    | -9.8                         |
| 5        | Allitinib     | -7.4                        | Poziotinib    | -8.3                         | Allitinib     | -8.2                            | Varlitinib    | -9.7                         |
| 6        | Varlitinib    | -7.1                        | Ibrutinib     | -8.2                         | Dacomitinib   | -8.1                            | AC480         | -9.5                         |
| 7        | Acalabrutinib | -6.9                        | Allitinib     | -8                           | Sapatinib     | -8                              | Allitinib     | -9.2                         |
| 8        | Lapatinib     | -6.9                        | Ac480         | -7.5                         | Varlitinib    | -7.9                            | Dacomitinib   | -8.3                         |
| 9        | Dacomotinib   | -6.7                        | Afatinib      | -7.5                         | Lapatinib     | -7.6                            | Sapatinib     | -8.3                         |
| 10       | Afatinib      | -6.7                        | Lapatinib     | -7.5                         | Acalabrutinib | -7.4                            | Lapatinib     | -8.2                         |
| 11       | Canertinib    | -6.6                        | Sapatinib     | -7.3                         | Canertinib    | -7.3                            | Pyrotinib     | -8.2                         |
| 12       | Sapatinib     | -6.6                        | Pyrotinib     | -6.9                         | Pyrotinib     | -6.8                            | Neratinib     | -8.1                         |
| 13       | Pyrotinib     | -6.4                        | Canertinib    | -6.6                         | Neratinib     | -6.6                            | Canertinib    | -7.7                         |
| 14       | Neratinib     | -5.7                        | Neratinib     | -6                           | Afatinib      | -6.2                            | Afatinib      | -7.1                         |

**Conclusion:** ERBB4 plays a complex, context-dependent role in cancer, making it a promising yet understudied therapeutic target.

By combining systems biology and network pharmacology, both kinase and non-kinase targets associated with ERBB4 were identified. Network analysis and target prediction highlighted four key non-kinase proteins: MCL1, PTGS2, HSP90AA1, and PLCG1.

**Future work:** Future work will focus on validating MCL1, PTGS2, HSP90AA1, and PLCG1 using MD simulations, followed by in-vitro and in-vivo to confirm their role as actionable, druggable non-kinase targets.