

# Novel Therapeutic Inhibitors Having Sugar Moiety Targeting HER2/EGFR as Anticancer Agent



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## Background

Several effective small-molecule inhibitors of HER2 or EGFR have been developed to treat metastatic cancer, and some of those drugs are dual HER2/EGFR inhibitors. To investigate the mechanism of the dual inhibition of the receptor tyrosine kinases HER2 and EGFR1, we carried out virtual screening for benzimidazole derivatives having sugar moiety. Based upon virtual screening and HER2/EGFR1 assays data simulation, we confirmed and chosen the benzimidazole skeleton which NO<sub>2</sub> functional groups as a key skeleton for the dual inhibition towards HER2/EGFR1 (8.81 μM, Figure 6) to design novel tyrosine kinases inhibitors. After selection of the core skeleton, we designed our novel inhibitors, targeting both HER2/EGFR1 and having a benzimidazole skeleton including a sugar moiety as aiming to balance their hydrophilic and hydrophobic properties and to increase cell penetration including the pharmacokinetics properties. We are investigating the synthesis of target agent (T-1) and biological properties of these agents against cancer cell line.

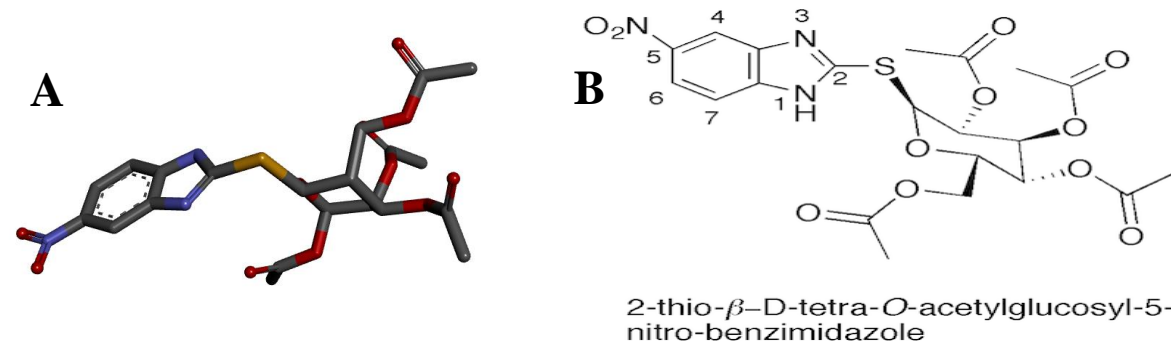


Figure 1: Target ligand T-1 A) Ball and stick model (atom color) and B) Chemical structure

## Molecular Design

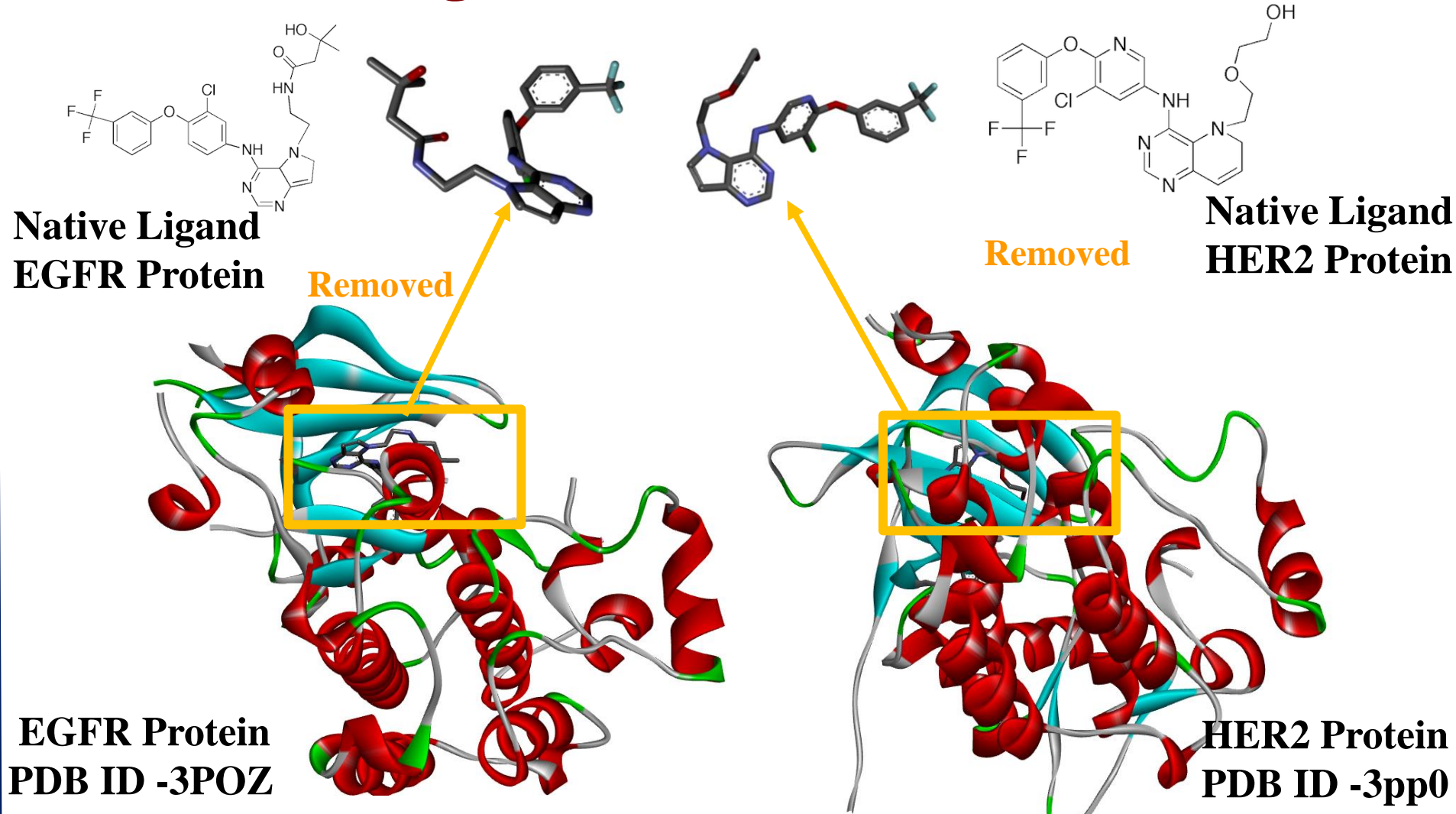


Figure 4: EGFR/HER2 and ligand binding site.

## AutoDock Analysis

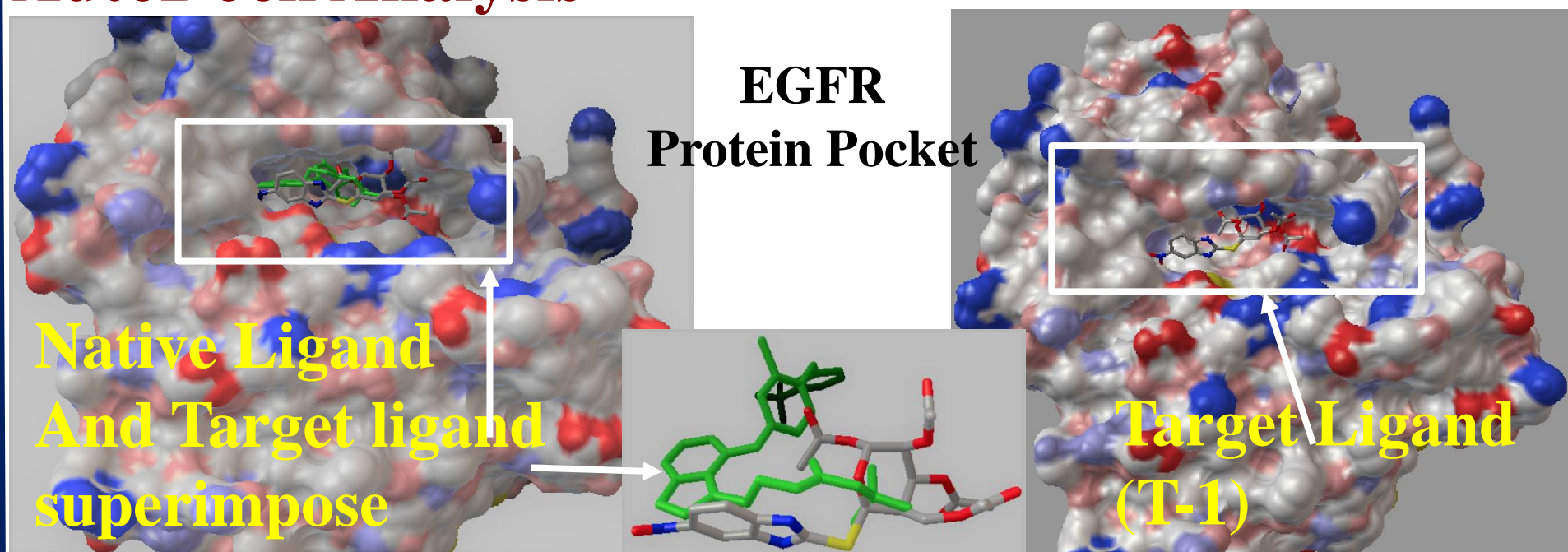


Figure 5: superposition of native ligand (green color) and T-1 (atom color) in the complex with EGFR1 by using the AutoDock 4.0 software tool.

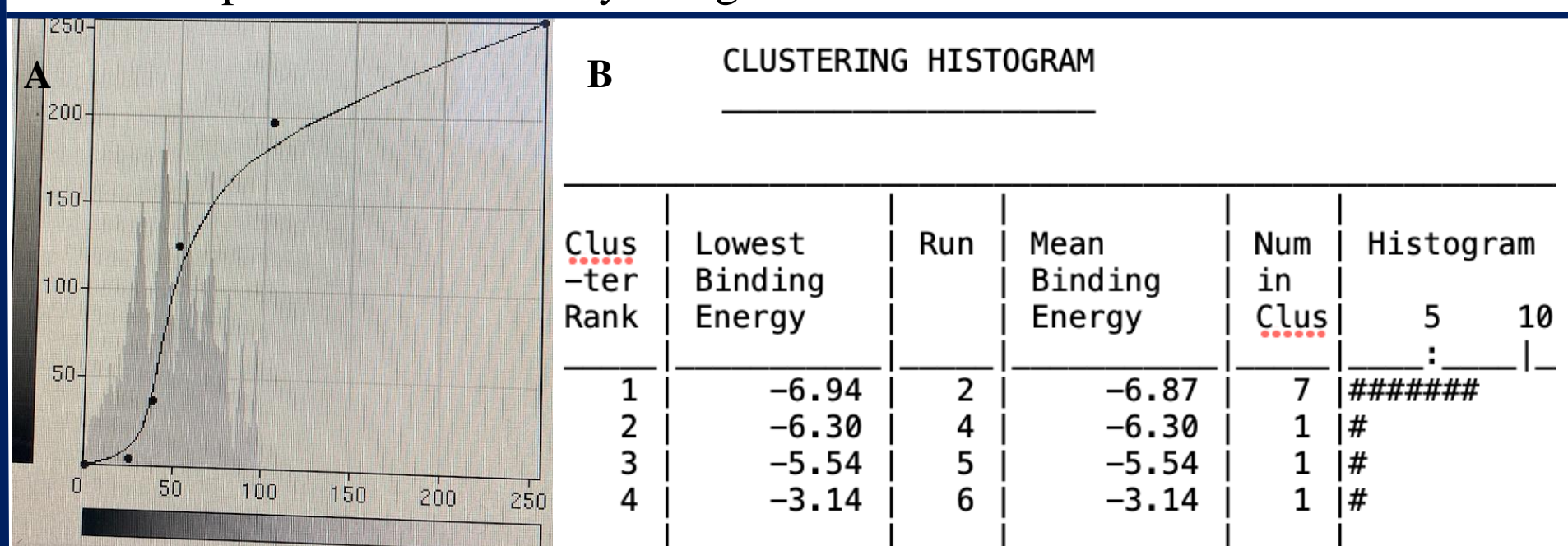


Figure 6: AutoDock modeled binding energy of T-1 inside ATP-binding site of EGFR A) Histogram and B) Binding energy calculation.

## Results

### Spectroscopy Analysis

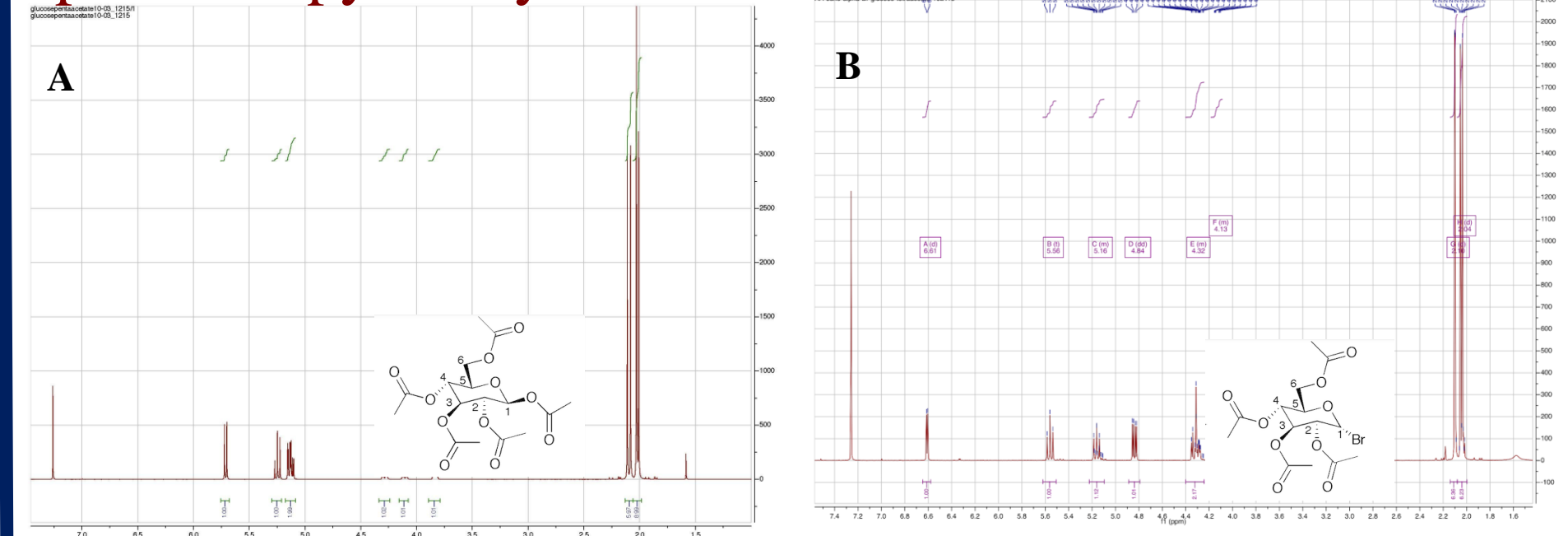


Figure 7: <sup>1</sup>H-NMR: A) 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranosyl B) 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide.

### Physical Properties (m.p.)

**1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranosyl** - 131.5 °C to 132.5 °C (Literature: 130 °C-132 °C, Sigma Aldrich)  
**2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide** - 83.5 °C to 85.5 °C (Literature: 88 °C to 89 °C, *J. Chem. Soc.* 1930, 76, 3224)

### Future Studies

The synthesis of the target product, T-1 is successfully achieved in the lab as shown in Figure 8, solvent system of Ethyl acetate : Hexane : Methanol (1:4:0.5) Target ligand's spectroscopy data including physical properties will be collected, after purification the target ligand, followed by cell apoptosis assays will be performed against cancer cells.

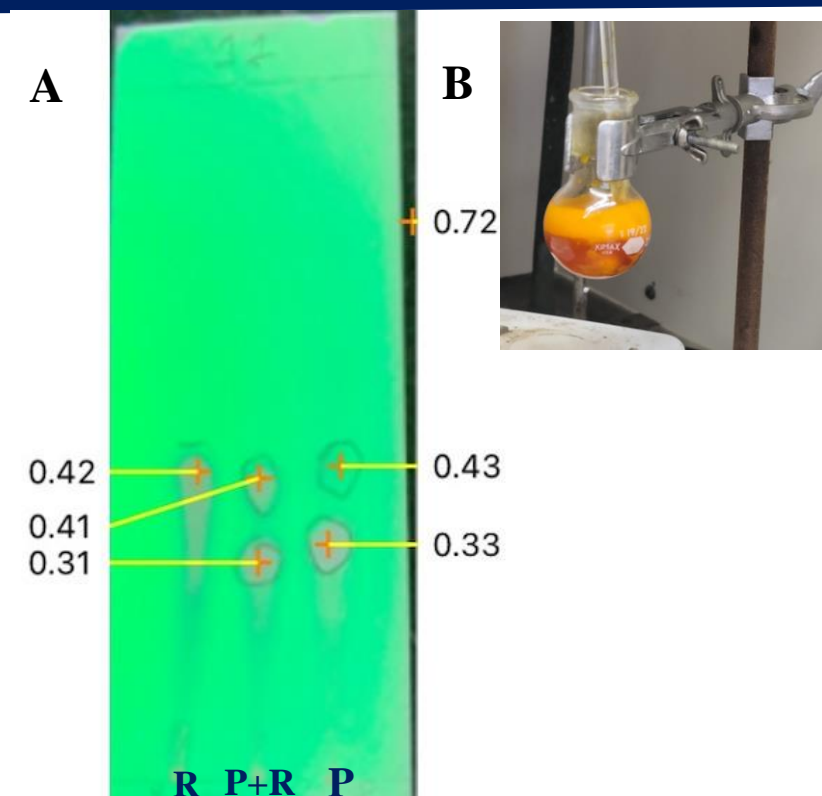


Figure 8: A) TLC results to compare starting material (R), (R+P) and product (P). B) Pictorial view of the Crude (T-1)

## Pathway of tyrosine kinase inhibitors:

An extracellular survival signal activates an RTK, which phosphorylates target proteins. In the presence of growth factors AKT is activated thereby helps activate mTOR in complex 1, which in turn promotes both cell growth and cell survival by stimulating nutrient uptake and metabolism. mTOR complex 2 helps to activate Akt, and it regulates the actin cytoskeleton via Rho family. Two additional parallel intracellular signaling pathways are activated by RTKs: PLCγ which activates PKC which in turn stimulates ELK1 that promotes DNA proliferation. From a drug discovery point of view, inhibition of PK activity can be achieved by a molecule that binds either the ligand or the PK itself to prevent ligand binding, dimerization or catalytic activity.

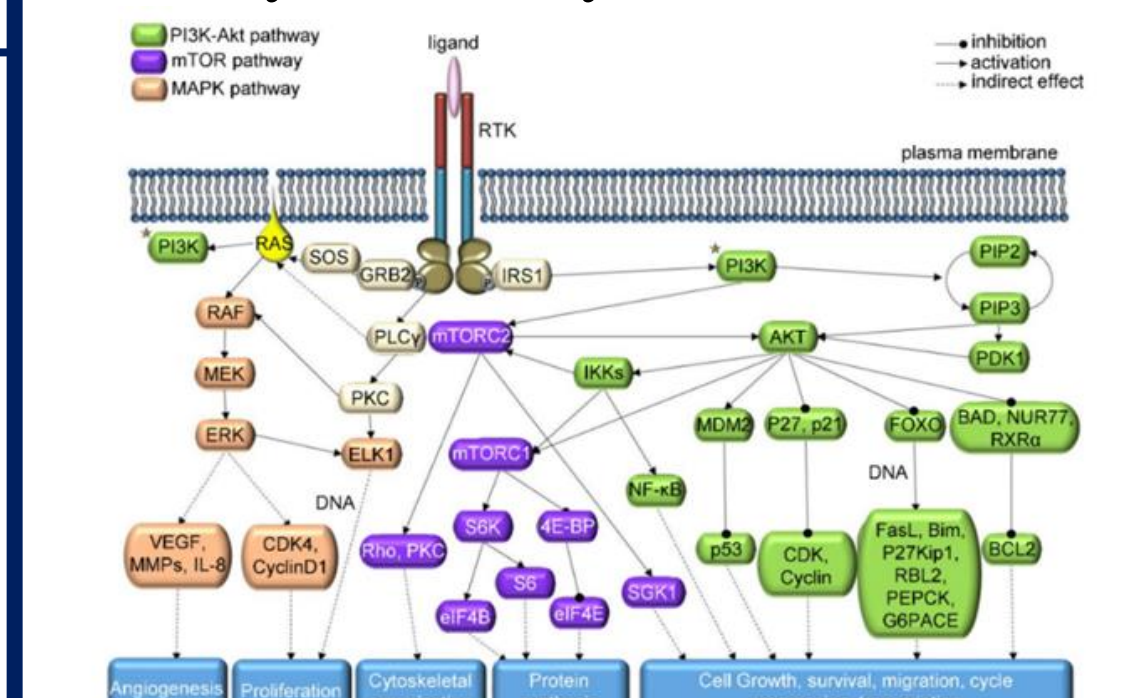


Figure 9: Schematic representation of RTK downstream signaling-modified from Kyoto Encyclopedia of genes and genome. *Theranostics* 2021, Vol. 11, 1546.

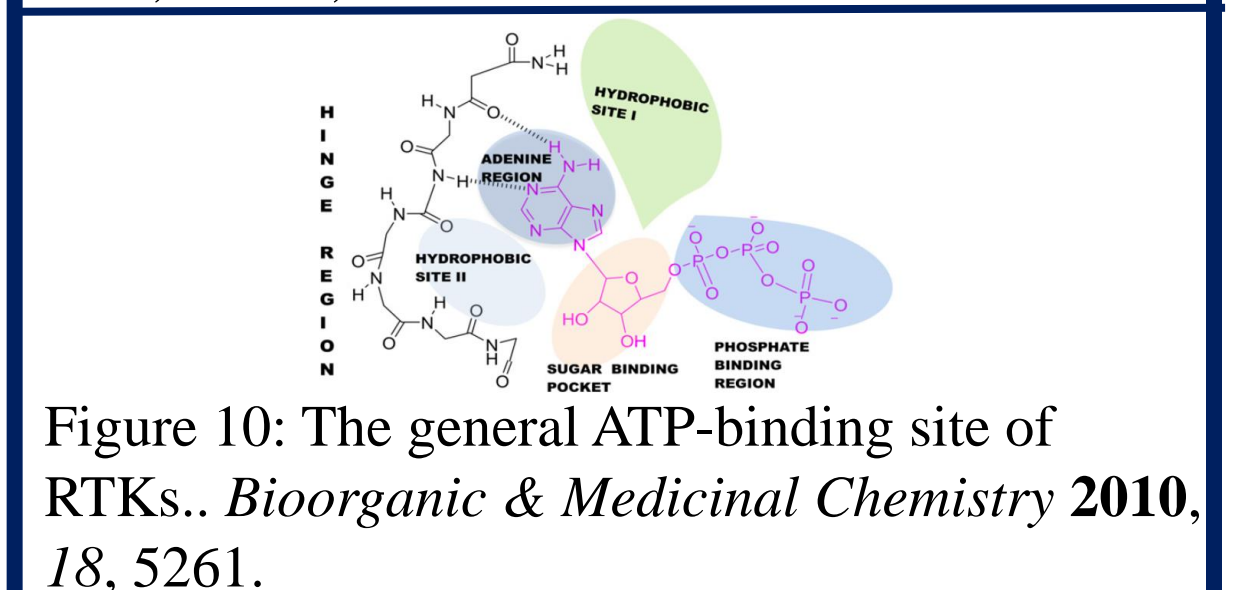


Figure 10: The general ATP-binding site of RTKs. *Bioorganic & Medicinal Chemistry* 2010, 18, 5261.

## Conclusion

With molecular modeling we verified that our designed small inhibitors are suitable to fit inside HER2/EGFR1 receptor binding pockets. In an attempt to prepare the first target ligand (T-1), β-D-Bromoglucose was successfully synthesized, the purity was confirmed from <sup>1</sup>H-NMR spectroscopy and physical properties. Target ligand T-1 preparation underway. After the synthesis of T-1, we will investigate cell apoptosis assay to determine whether the most active of these dual HER2/EGFR1 inhibitors can inhibit growth of Jurkat and cancer cells.

## Acknowledgement

Thanks to University of Bridgeport Chemistry Department for the research opportunity provided for all the help and support

## Chemical Synthesis

### Synthesis of Bromo Sugar derivative:

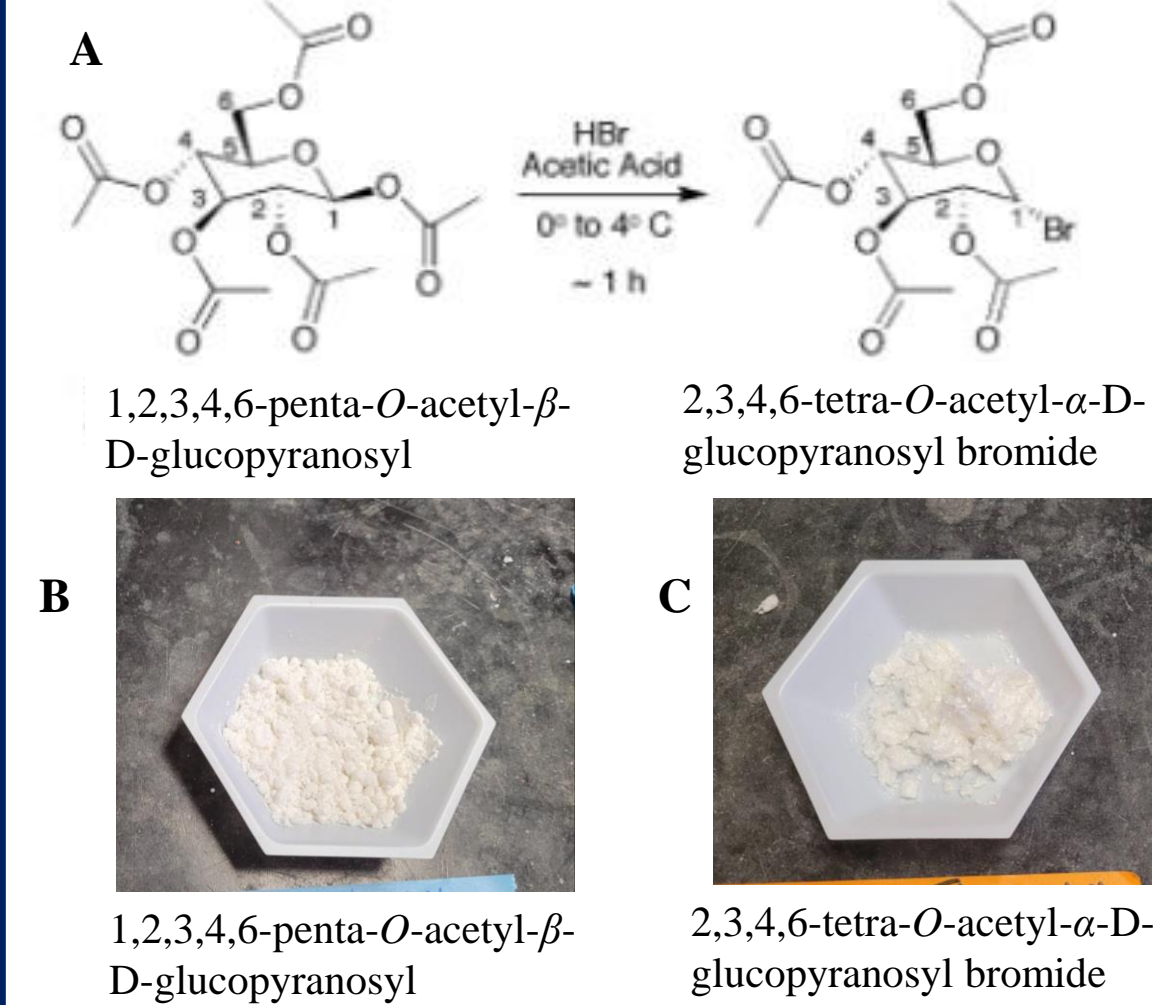


Figure 2: A) Chemical reaction scheme for synthesis of sugar derivative, Pictorial View of B) Starting Material and C) Sugar derivative product.

### Synthesis of Target Ligand T-1

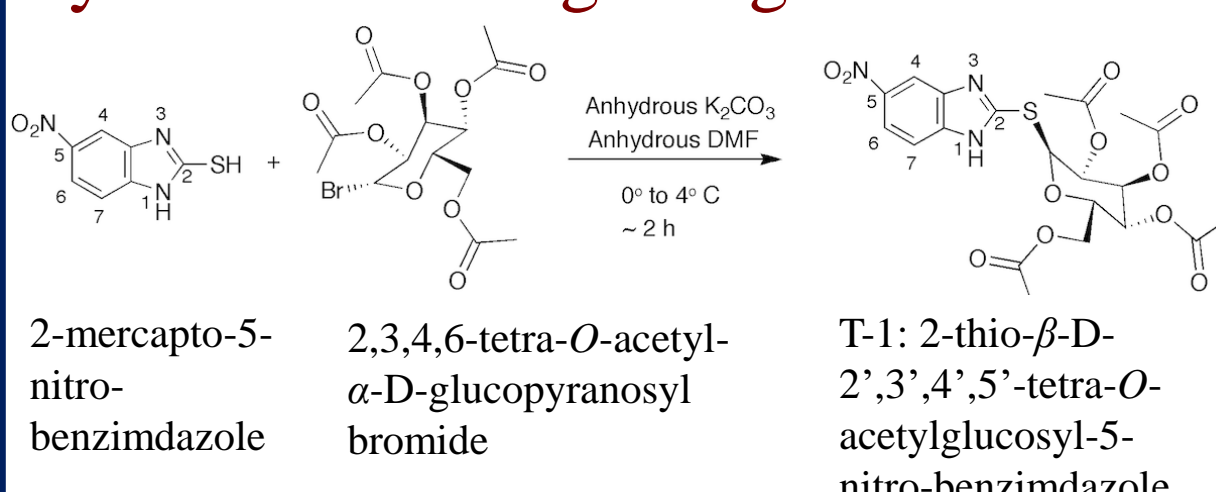


Figure 3: Chemical reaction scheme for synthesis of target T-1, 2-thio-β-D-2',3',4',5'-tetra-*O*-acetylglucosyl-5-nitro-benzimidazole.