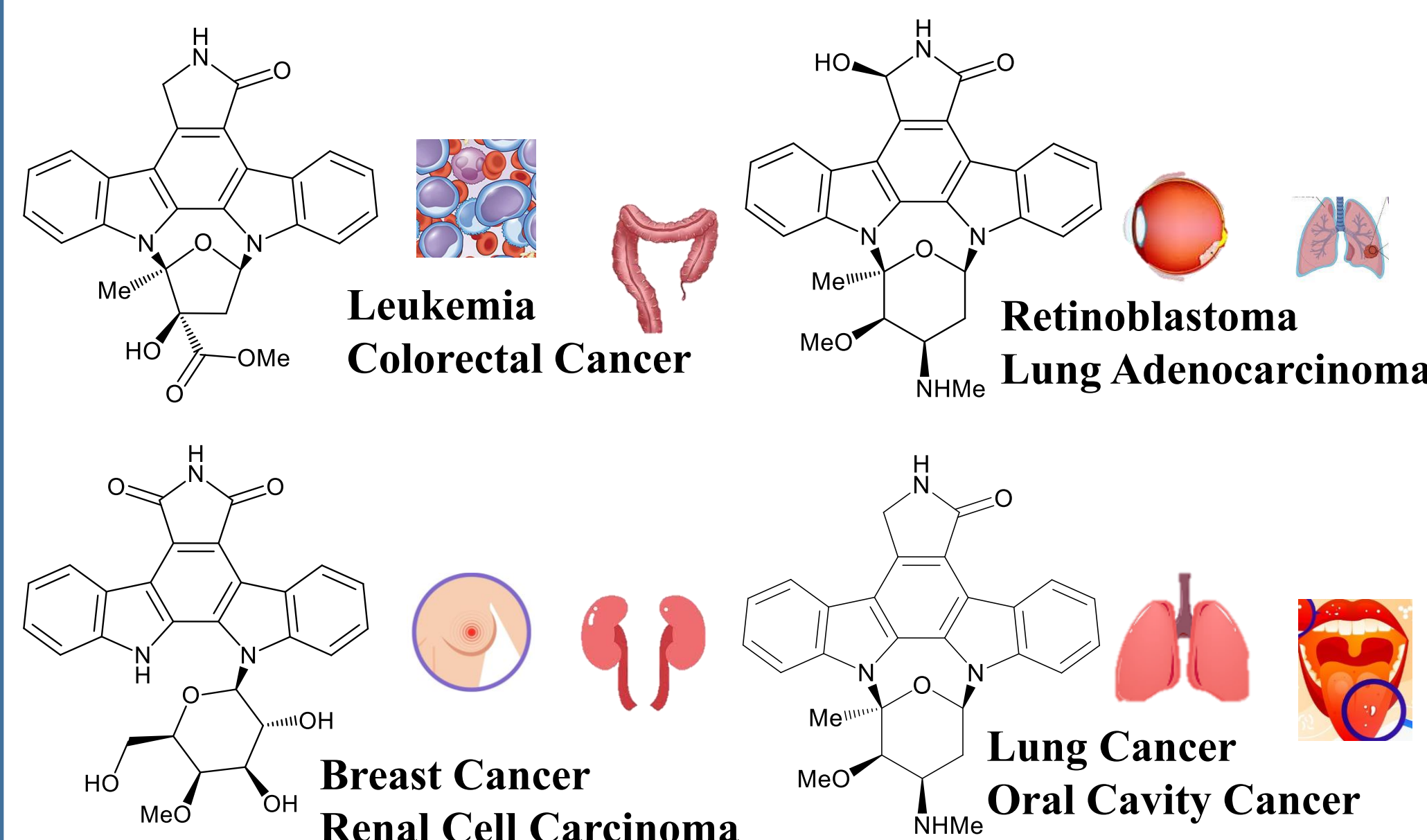
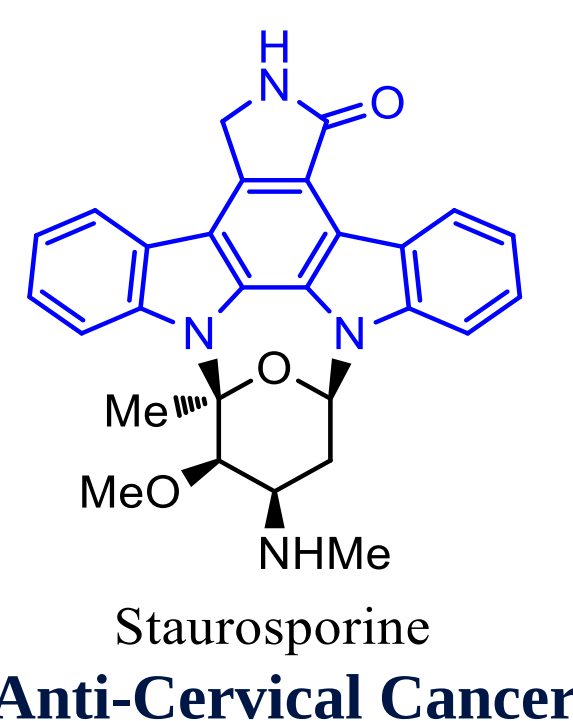


Abstract

Targeted therapy is widely regarded as a pivotal pillar in the future landscape of oncology, offering superior selectivity and attenuated side effects. In this study conducted by Taiwan BT&D² Team, thermodynamic methodologies were deployed to evaluate the binding affinity profiles of diverse molecular targets against a series of M-BIM and MICZ derivatives. The objective was to identify optimal derivative candidates capable of exhibiting high specificity toward downstream kinases within intricate signaling pathways. Furthermore, cell-based assays demonstrated that these novel derivatives possess a significantly milder toxicity profile in comparison with conventional anticancer therapeutics. Following chemical synthesis, the target derivatives were successfully isolated, and their structural integrity and high purity were verified via ¹H NMR spectroscopy, establishing a clean product profile ideal for subsequent cell viability evaluations.

Introduction

Indolocarbazole family of natural products have been shown to exhibit potent anticancer activity. To develop indolocarbazole drugs more specific to particular biological targets with the least off-target side effects has become an important issue.



Material & Method

Synthesis Routes

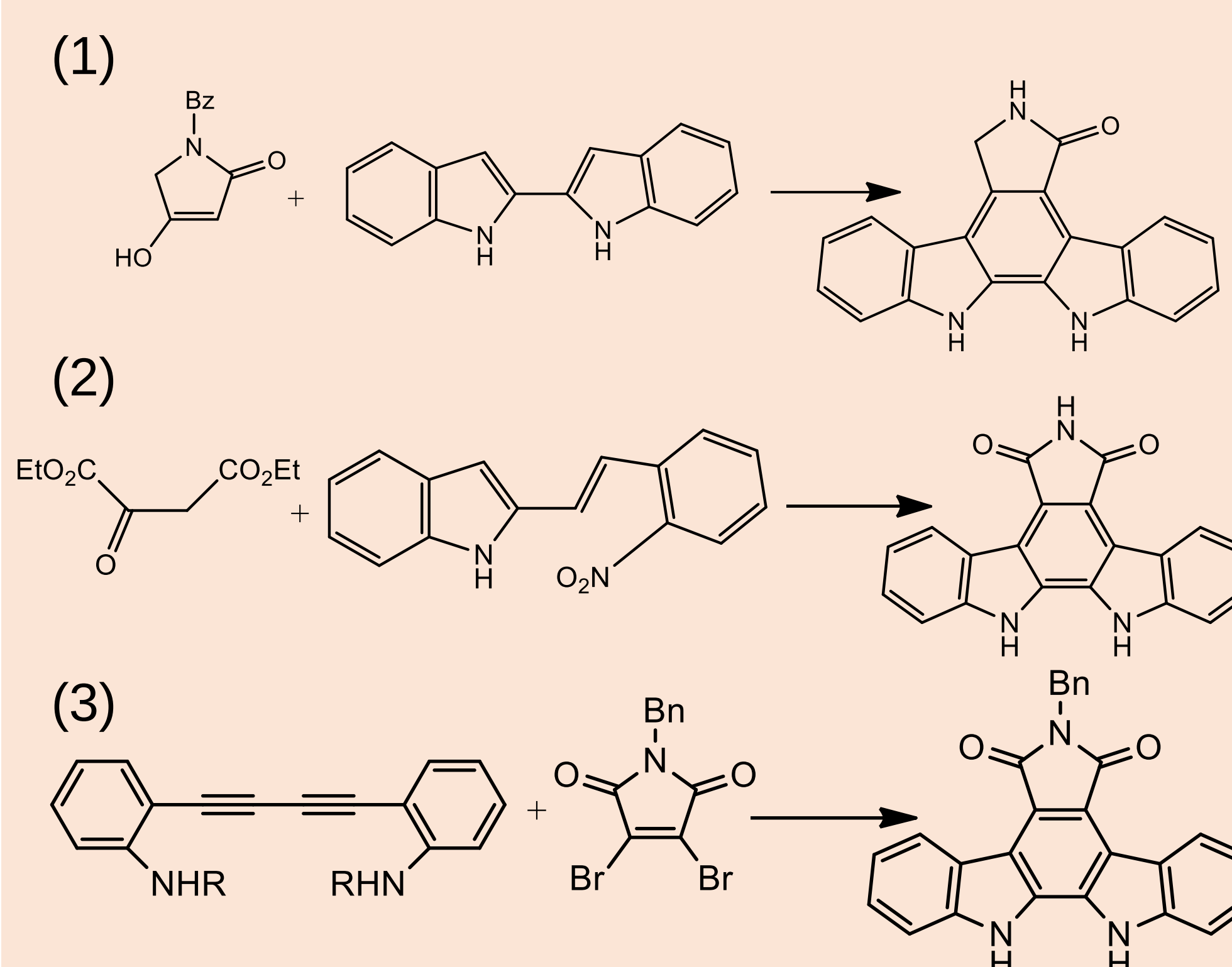


Figure 1. Different synthesis methods of MICZ

Result 1. Chemical Synthesis

Chosen Synthetic Method

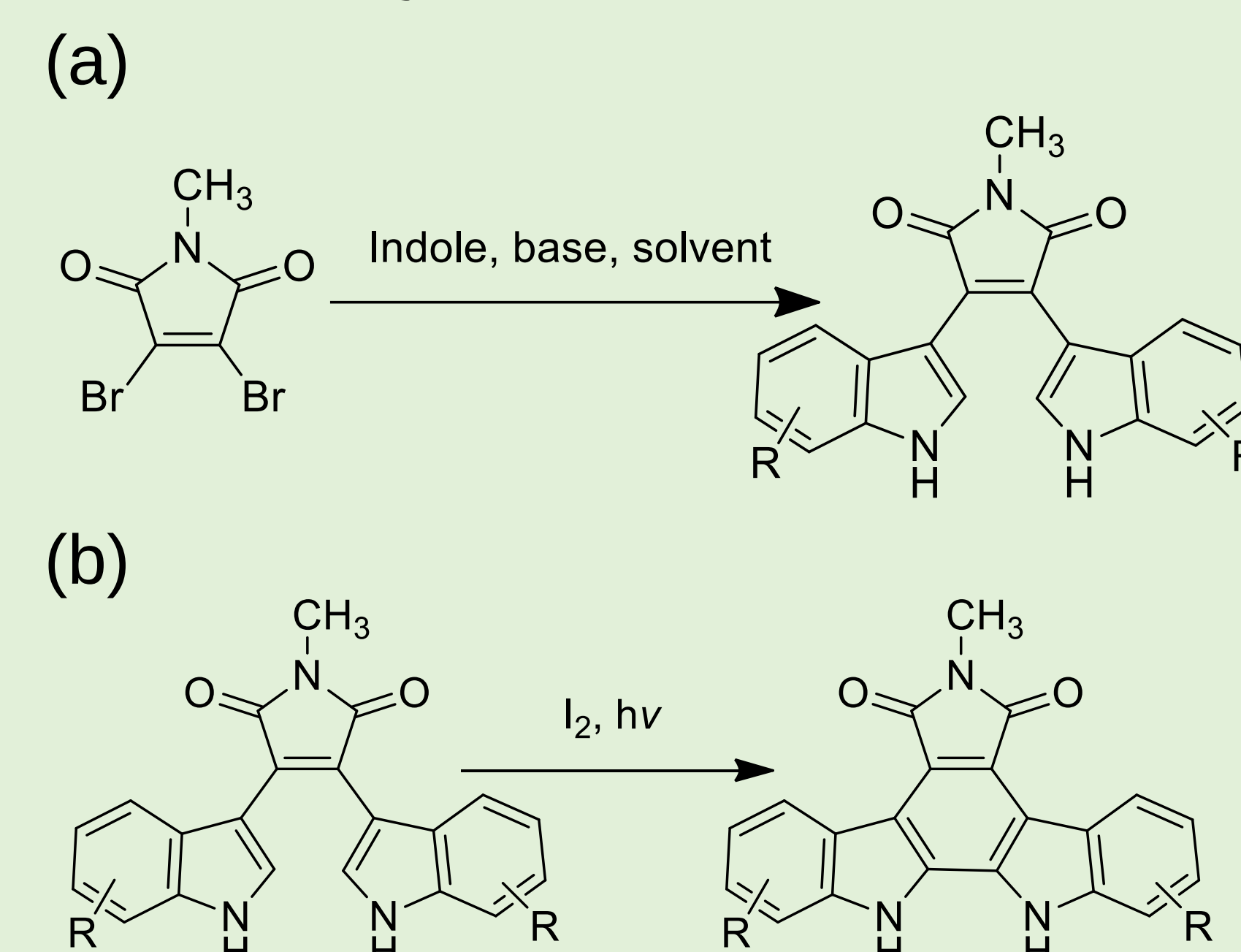


Figure 2. Synthetic routes of (a) M-BIM and (b) MICZ

R = F, Cl, Br, I, OMe

Result 2. Affinity Heat Maps

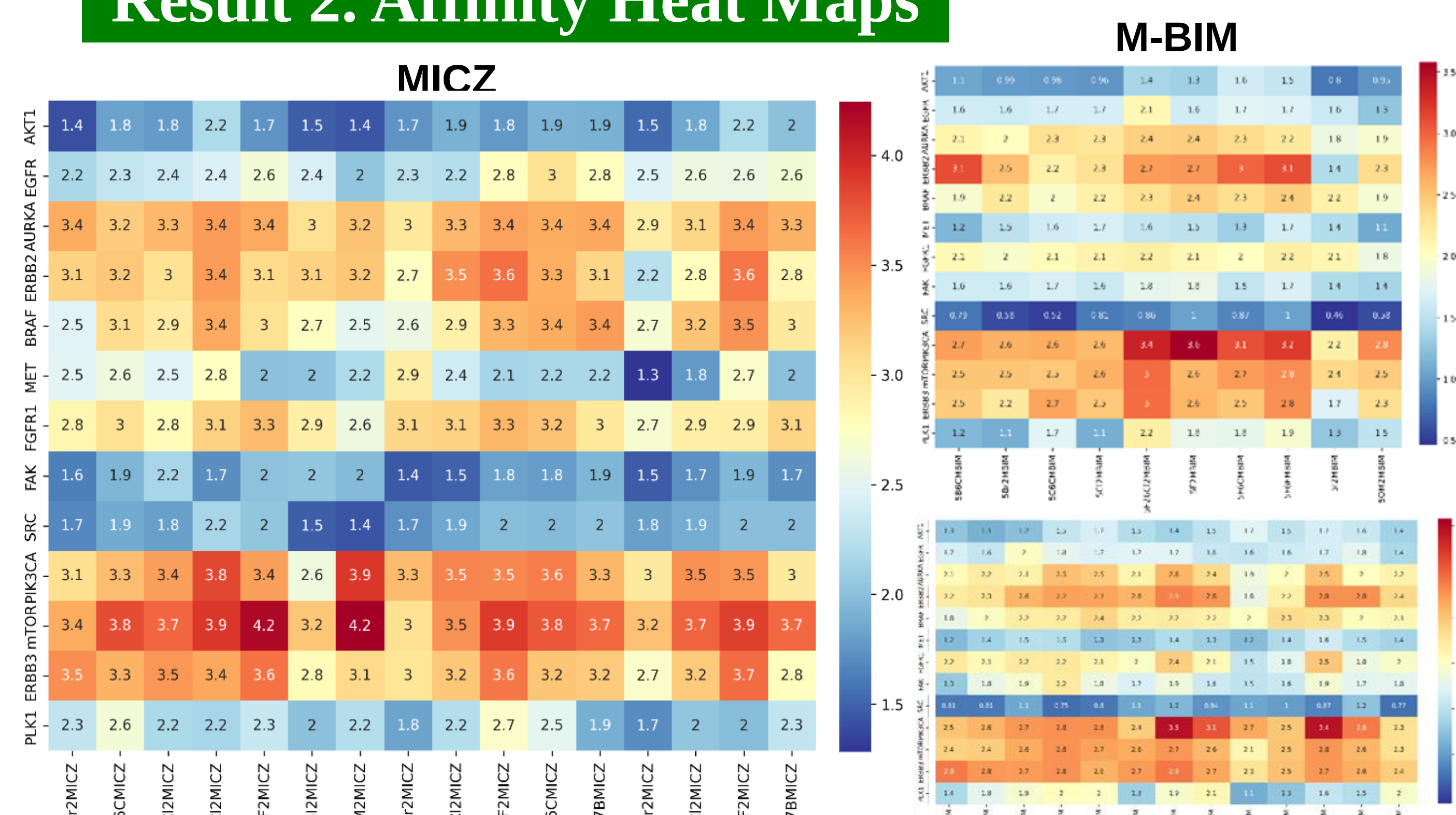
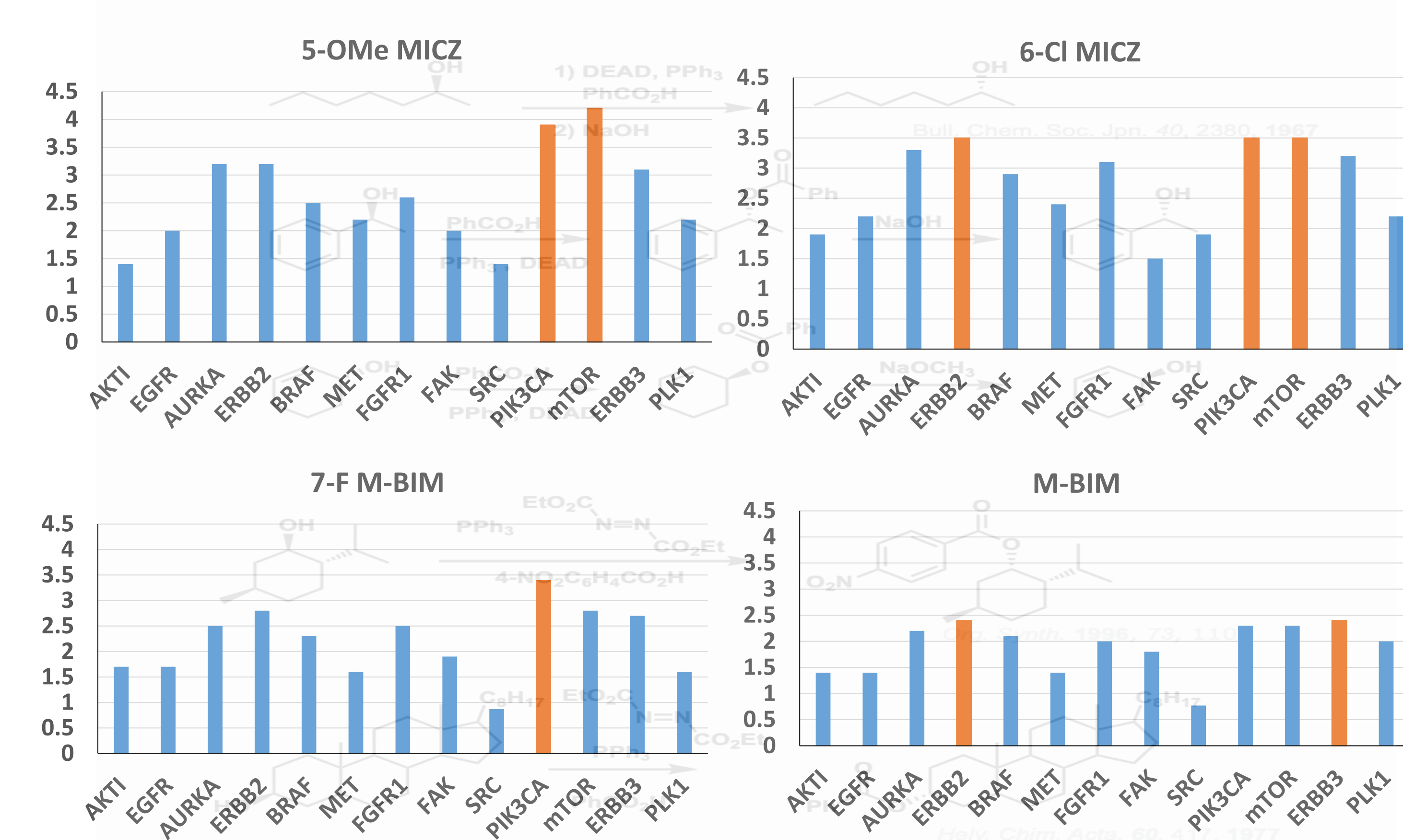


Figure 3. Selectivity and affinity heat maps of M-BIM and MICZ derivatives



Results 3. Product Characterization

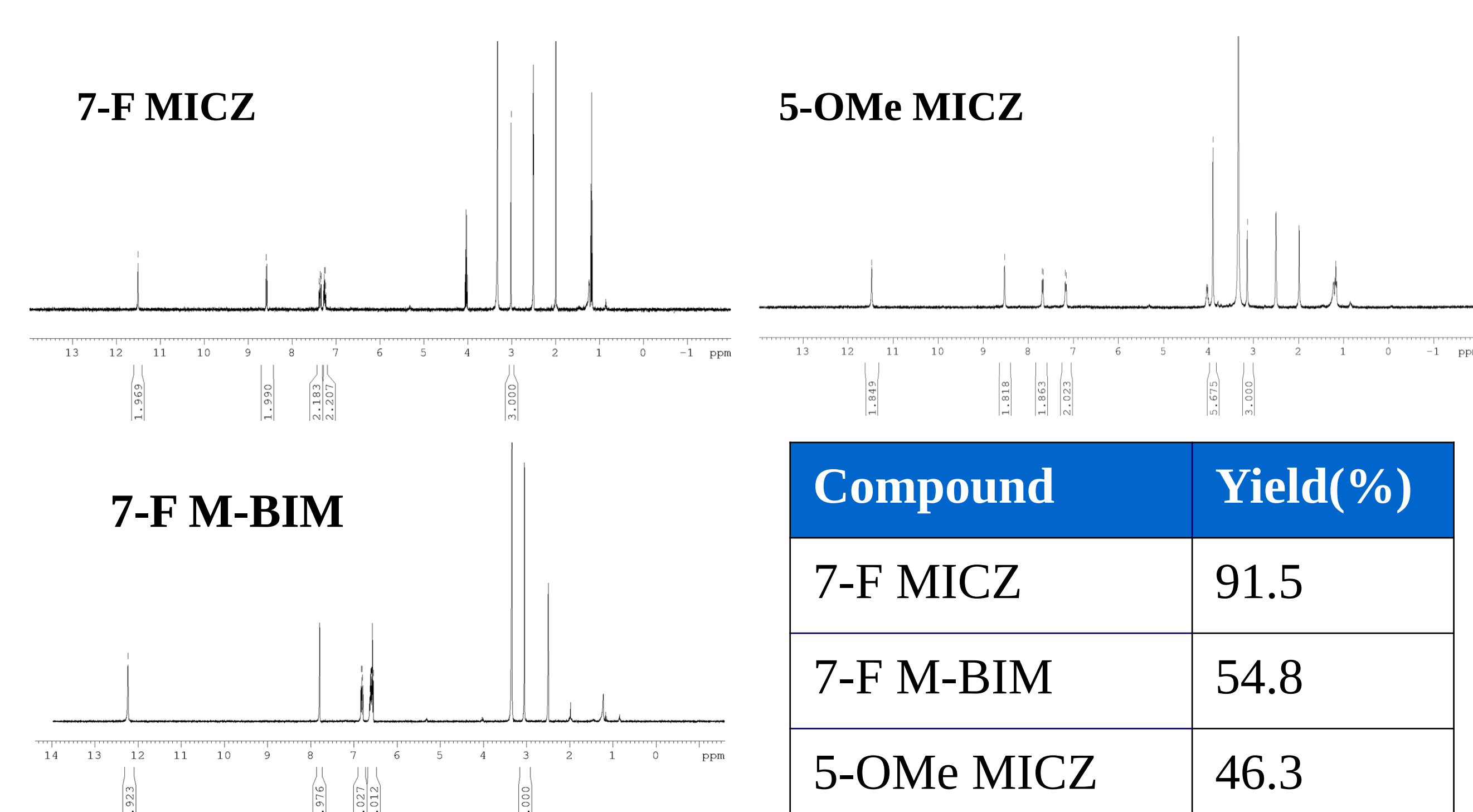


Figure 4. ¹H NMR spectra of synthesized MICZ and M-BIM derivatives

Conclusion

- Computer-aided screening was employed to identify potential derivatives, with the results visualized as a heat map.
- The reaction pathways and conditions for the derivatives were optimized.
- A series of derivatives bearing different substituents were successfully synthesized and purified, yielding products with high purity.
- The binding modes of the derivatives in complexes with members of the protein kinase C (PKC) family were investigated through molecular simulations.

Results 4. Cell Viability & Docking Structures

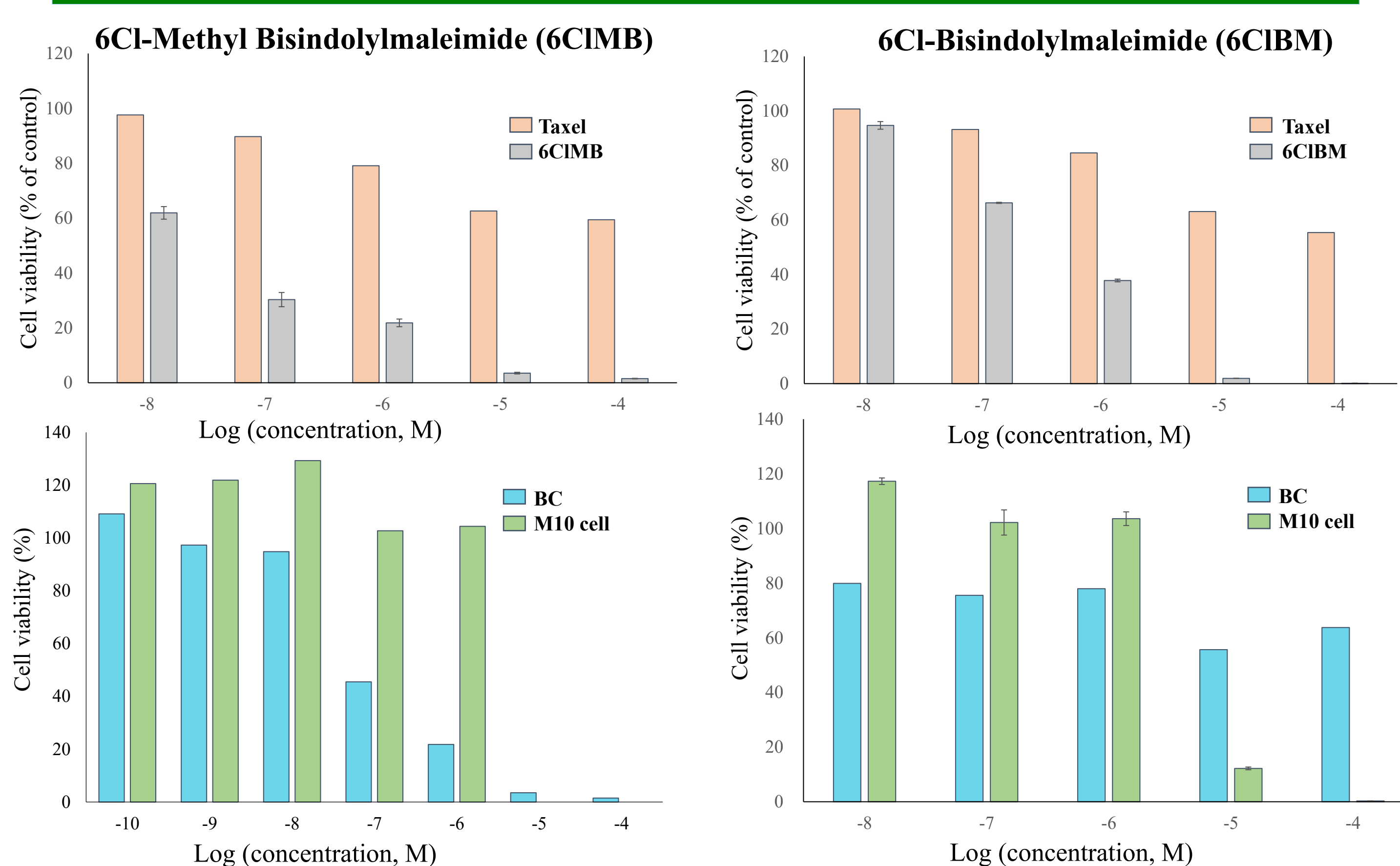


Figure 5. (Upper Panel) M10 cell viability test of MICZ and Taxol.

Figure 6. (Lower Panel) Simulated 3D structure of MICZ complexed with target kinase.

