Innovative Approaches to Overcome the Blood-Brain Barrier: AI-Guided Design of Dual HER2/VEGFR2 Inhibitors for Effective Brain Metastases Therapy

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Abstract:

Brain metastases (BMs), particularly those stemming from HER2-positive and triple-negative breast cancers (TNBC), remain a formidable clinical challenge due to the impermeability of the blood-brain barrier (BBB), the presence of resistance-driving mutations (e.g., HER2L755S and HER2T798I), and the upregulation of angiogenic drivers such as VEGFR2. Towards addressing these hurdles, our research employs a multimodal strategy that integrates medicinal chemistry, artificial intelligence (AI)-guided drug discovery, and pharmacokinetic modeling to develop BBB-penetrant tyrosine kinase inhibitors (TKIs) for central nervous system (CNS) tumors and BMs.

We synthesized and optimized novel quinazoline and pyrrolotriazine derivatives targeting HER2 and VEGFR2. Compounds such as HA17 and HA149 demonstrated strong antiproliferative activity against TNBC cells and HER2+ breast cancer models. HA47 and HA46 significantly inhibited VEGFR2 with IC_{50} values in the sub-nanomolar range and exhibited antiangiogenic effects in vitro and tumor growth suppression in vivo. Notably, HA46 combined with sorafenib reduced tumor growth by 58.2% in HepG2 xenografts without overt toxicity.

AI-enhanced approaches accelerated the hit-to-lead progression through structure-based design, in silico prediction of ADME/Tox properties, and virtual screening for BBB permeability and efflux liability. In vitro PAMPA-BBB assays and computational modeling confirmed high CNS penetration potential for key candidates like HA149 and HA19. To optimize these promising compounds for CNS applications, in silico PK modeling was employed, focusing on molecular properties: lipophilicity, Mol.Wt, and HB donors.

Collectively, our findings represent a significant advance in CNS oncology, offering a pipeline of dual HER2/VEGFR2 inhibitors with demonstrated brain penetrance, low systemic toxicity, and potential applicability beyond oncology. By harnessing AI and rational drug design, this approach paves the way for more effective, targeted therapies for brain metastases and sets a foundation for future translational success.