"**The Discovery of Small Molecules for the Selective Inhibition of Pancreatic Cancer Metastasis**"

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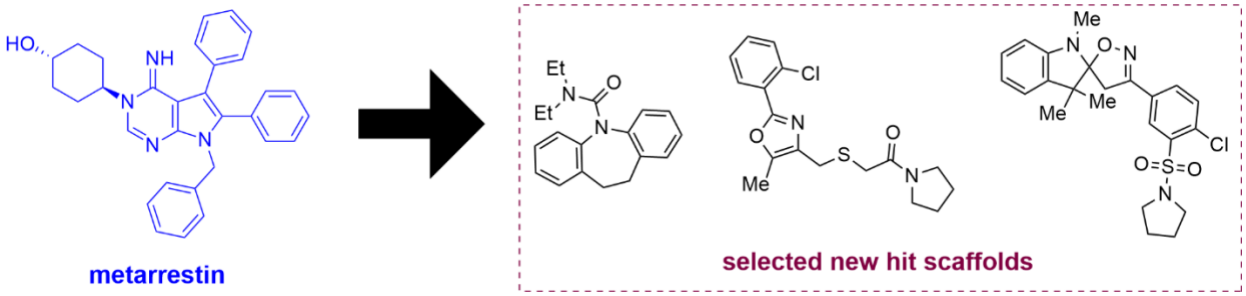
ABSTRACT:

Metastasis remains a significant challenge in cancer treatment, necessitating innovative strategies.[1] Collaborating with Sui Huang (Northwestern University) and NCATS (NIH), we identified PNC formation as a key marker for metastatic behavior.[2] Through screening, we discovered metarrestin, disrupting PNC with high efficacy (IC50 ≈ 300 nM), and inhibiting metastasis in murine models of pancreatic, prostate, and breast cancers.[2] Metarrestin is now in a Phase I clinical trial (NCT04222413) for treatment-resistant cancer patients.[3] Our ongoing research aims to elucidate molecular pathways, optimize analogues, and develop chemically distinct PNC modulators. The distinct PNC modulators could offer promising advances in combating cancer metastasis and improving patient outcomes.

We have developed practical synthetic routes to six validated anti-metastasis screening hits that allowed structural variation at multiple sites. Specific analogues were designed to probe the molecular features responsible for activity and follow-up analogues designed based on these preliminary results. In particular, we have begun to focus on the dibenzazepine series by incorporating either a methoxy or chlorine on the para position of the aromatic ring. Current synthetic approaches include using a convergent approach of the starting material to obtain a common intermediate and then exploiting two divergent pathways with either a direct homologation of the amine or a magnesium reduction of the intermediate followed by homologation of the amine. Preliminary analogue efforts have revealed promising PNC disruption and future efforts will be aimed at modifying structures based on analogues with increased potency.



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