Structural activity relationship approach on a novel compound for the treatment of triple negative breast cancer.

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INTRODUCTION

Triple-negative breast cancer (TNBC) is an aggressive breast cancer type lacking the expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) genes. Therefore, it renders hormonal therapy and HER2-based treatment ineffective. TNBC is characterized by higher metastatic and recurrence rates, as approximately 28% of TNBC patients suffer from the brain metastases, leading to decreased survival rates compared to other breast cancer types.

Among breast cancer types, TNBC shows the most response to chemotherapy. Hence, there is a high demand for identification of the novel anticancer agents with the optimized toxicity profile. Recently, we have identified a novel hit molecule with cytotoxicity against MDA-MB231 cell lines, ability to cross the BBB in vitro and in vivo and optimized toxicological profile. Here, we report our work targeting optimization of the hit molecule to advance this class of compounds to preclinical studies.

OBJECTIVE

- To identify the pharmacophore of the hit molecule using SAR approach.
- To evaluate the obtained analogs for their off target activity.

METHOD

Search for hit and optimization of hit to lead: We synthesized a library of compounds to elucidate the key features responsible for the anticancer activity of these analogs. After that, we performed a structure-activity relationship study to identify lead molecules with the desired in vitro and in vivo profile. We selected the following compound as a hit molecule because of its better cytotoxicity profile compared to other compounds.

RESULTS

Synthesis of analogous of selected hit molecule:

CONCLUSION

To understand the pharmacophore requirements, we have designed and synthesized a library of analogs. These analogs were evaluated in vitro. The SAR studies are ongoing, but current result suggests the following trend:

- Phenyl ring of part B requires disubstitution at meta and para positions, with preferred electron withdrawing character of substituents.
- Part A of the hit molecule can tolerate the presence of a diphenyl as well as a monophenyl moiety. Electron withdrawing para substitution is favored.
- The drop in activity of cyclic analogs in alkyl urea linker suggested that unsubstituted alky chain linker is preferred for the observed anticancer activity of the hit molecule.
- Prepared analogs have low, if any, activity at the selected GPCRs suggesting optimized toxicological profile if used in the treatment of secondary tumors.

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