Accelerated drug discovery platform yields synthesis of novel stearoyl-CoA desaturase 1 inhibitors that demonstrate anti-tumor efficacy in several models of aggressive cancer.

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**Rationale**

Intra-tumor heterogeneity is the driving force behind disease progression and metastases, drug resistance, and relapse in cancer patients. Defining personalized treatment regimens and increasing the arsenal of targeted therapies available will provide the best chance of prolonging survival and finding curative treatments. Recent work by our group and others has shed light on a novel de novo lipogenesis as a feature of many cancers including kidney, breast, and lung cancer. While there currently are several anti-cancer drugs in the development pipeline designed to inhibit various components of glycolysis and glutaminolysis, the investigation of therapeutics targeting constituents of de novo lipogenesis is minimal, with FASN inhibitors exhibiting promising efficacy against several cancers. Of the other molecules involved in fatty acid metabolism, stearoyl-CoA desaturase 1 (SCD1) is frequently over-expressed in cancer; and targeted inhibition of SCD1 demonstrates a loss of tumor cell viability in a variety of tumor models. While there currently are small molecule inhibitors for SCD1, none are under clinical investigation as anti-cancer therapeutics. In order to evaluate tumor models, we pursued three divergent species of compounds into the top hits. Using this method and diversity of chemical space, we implemented iterative analog generation for the synthesis, we planned to generate unique compounds and test their biological efficacy.

**Methods**

Utilizing an innovative in silico approach, we designed new inhibitors for SCD1 via a scaffold hopping approach while searching for different "core" scaffolds. Critical interaction mistakes from the chemical R-groups were held fixed, while generated cores were rapidly scanned for best-fit criteria (shape, docking, pharmacophore fit (GSPAR)) into our Z-matrix. Following de novo compound generation and synthesis, we implemented iterative analog generation for the top hits. Using this method and diversity of chemical space, we pursued three divergent species of compounds into the top hits. Biological testing of the novel compounds included high-throughput proliferative-based screening, cell acid rescue, and evaluation of the endoplasmic stress response. Preclinical pharmacokinetics was established using a range of doses administered intravenously and orally.

**Results**

A cohort of potential unique small molecule inhibitors against SCD1 were designed and synthesized. Of these, a select group of compounds demonstrated potent and selective enzyme inhibition and reduced tumor growth in vitro. These novel inhibitors weakly reproducibly activated pH 8.5 stress markers, authenticating this biological response as a harbinger for successful abrogation of SCD1 activity. In vivo pharmacokinetic assessment of our novel compounds demonstrate excellent oral bioavailability, with no overt adverse events observed.

**Objectives**

• We have established an effective, expedited, and economical format for in silico modeling of novel agents based on a scaffold-hopping methodology. Our findings provide compelling evidence supporting the therapeutic benefit of SCD1 inhibitors for clinical use as broad-spectrum anti-tumor agents alone or in combination with standard of care.

**Drug Design & Synthesis**


**Biological Validation**


**Clinical Relevance**

**Future Directions**

• While several SCD1 inhibitors have been developed originally designed for use against a number of chronic metabolic disorders, preclinical testing has presented a complicating obstacle: Due to the vast discrepancies between human and rodent SCD isoform expression, tissue distribution, and functional variability, the translational applicability in results achieved in the latter model are limited. Validation in alternative preclinical models may be necessary.

• Given the heterogeneous nature of cancer, preclinical evaluation of our SCD1 inhibitors in models with standard of care or other targeted therapeutics for efficacy and tolerance will be evaluated in a variety of tumor models.

• Clinical assessment of our lead SCD1 inhibitor to establish safety, tolerance, dosing, and evaluate potential adverse effects in patients with advanced malignancy.

**Conclusions**

References