LSD1 Protein Inhibitors as Cancer Therapeutics

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Technology description

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Researchers at MUSC have identified several potential inhibitors of lysine-specific demethylase 1 (LSD1) utilizing a virtual screen, and found compounds that fit the LSD1 active site in silico. LSD1 is overexposed in a number of human cancers (neuroblastoma, retinoblastoma, prostate, cancer, lung, and bladder), and has emerged as an important target for the development of specific inhibitors as a new class of antitumor drugs. Researchers have synthesized these molecules and evaluated them as LSD1 inhibitors, and several compounds inhibit the enzyme with Ki values in the mid-to upper nanomolar range (Ex on left figure). The series of compounds are new chemical entities and are being developed by structural modification into lead compounds with the goal of developing them as antitumor agents. These compounds are also selective for LSD1 over monoamine oxidase MAO A and B. Preliminary studies have shown that two of the compounds inhibit LSD1 (IC50 1.192 and 2.20 μM) without inhibiting MAO and promote increases in histone lysine methylation at histone 3 lysine 4 (H3K4). Further, to demonstrate the potential for these molecules as cancer therapeutics, researchers tested pancreatic cell line Miapaca-2 and found that the small molecule C1 had similar EC50 values as the current used therapy for pancreatic cancer, Gemcitabine (Right Figure)

Overview

LSD1 is a histone demethlyase that catalyzes the oxidative demethylation of specific histone lysines, which silences genes that code for tumor suppressor proteins important in human cancer. Thus, LSD1 has emerged as an important target for the development of specific LSD1 inhibitors as a new class of antitumor drugs. Investigators in both academia and the pharmaceutical industry are searching for small-molecule scaffolds for the design of specific LSD1 inhibitors. Most of the available inhibitors are based on the tranylcypromine scaffold, and thus there is a potential for off-target effects mediated by MAO which can produce undesirable side effects, and other flavin-dependent amine oxidases. Triazoles C1 and C15 do not contain a tranylcypromine-like core, and do not inhibit monoamine oxidase. Through the discovery of these triazoles, as well as other small molecule scaffolds, our group is among the leaders in the discovery of small-molecule inhibitors of LSD1.

Key Words:Cancer, epigenetics, LSD1, tumor suppressor genes, DNA, histones, enzyme inhibitors.

Publication:Kutz, Craig J., et al. " 3, 5-Diamino-1, 2, 4-triazoles as a novel scaffold for potent, reversible LSD1 (KDM1A) inhibitors. " MedChemComm (2014).

Application area

Therapeutic agents for various cancers as well as diabetes, cardiovascular diseases, and neurological disorders.
Increased specificity for LSD1, which could reduce off-target effects, and improved pharmacokinetic parameters.

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