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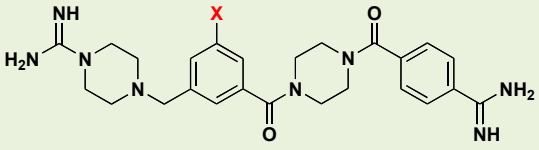
Chicago Discovery Solutions

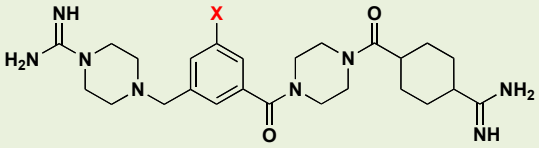
Synthesis of Histone Lysine Demethylase 1 (LSD1) Inhibitor Library and Reference Compounds.

The methylation of histones is not just a covalent modification, but is an external influence that alters gene expression. The recently discovered enzyme lysine-specific demethylase 1 (LSD1) plays an important role in the epigenetic control of gene expression and aberrant gene silencing by removing methyl moieties off of histone H3.

Facilitating the demethylation of histone H3 (H3K4) through amine oxidation is LSD1's main purpose. Overexpression of LSD1 is thought to contribute to the development of cancer. Wang et al (1) developed a new class of specific bioactive small molecule inhibitors of LSD1 that enhanced H3K4 methylation and depresses epigenetically suppressed genes in *vivo*. A small library of 9 molecules was synthesized and each compound's activity was tested. A few of these compounds inhibited histone methylase LSD1. (Figure 1)



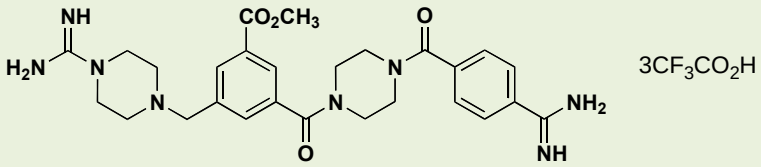
CBB 1001; X = H
CBB 1002; X = CH_3
CBB 1003; X = NO_2
CBB 1004; X = $SO_2N(CH_3)SO_2CH_3$
CBB 1005; X = $SO_2N(CH_3)_2$
CBB 1006; X = $CONH(CH_3)$
CBB 1007; X = CO_2Me
CBB 1009; X = CO_2H



CBB 1008; X = NO_2

Figure 1. Nine molecules of potential histone methylase LSD1 inhibitors.

Wang et al found the amidino-guanidinium compound CBB 1007 particularly interesting. It was shown to act as a potent, reversible LSD1 selective inhibitor (IC_{50} = 5.27 μM for hLSD1). CBB 1007 efficiently blocked LSD1-mediated demethylation of H3K4Me2 and H3K4Me (IC_{50} ≤ 5 μM) with no effect on the activities of H3K4Me3 and H3K9Me2, and LSD2 and JARID1A. It increased the contents of H3K4Me2 and H3K4Me (IC_{50} ≤ 5 μM), and caused activation of epigenetically suppressed *CHRM4/M4-ArchR* and *SCN3A* genes in F9 cells (IC_{50} ≤ 3.74 μM). It was shown to preferentially arrest the growth of pluripotent tumors with minimal effect on non-pluripotent cancer or normal somatic cells (IC_{50} ≥ 100 μM).



$3CF_3CO_2H$

CBB 1007

A comprehensive review on histone lysine demethylase provides an insight into its roles in multiple aspects of development across various species (1). These roles include germline maintenance and meiosis, early embryonic development and differentiation, and hormone receptor-mediated transcriptional regulation.

Compounds CBB 1001, CBB 1002, CBB 1003, CBB 1004, CBB 1005, CBB 1006, CBB 1007, CBB 1008 and CBB 1009 can be synthesized by Chicago Discovery Solutions in an estimated time of 3-6 weeks for R&D purposes (see note below on usage).

Chicago Discovery Solutions provides high quality medicinal chemistry services from hit identification through lead optimization, to effective drug candidates. Our medicinal chemists have extensive experience in developing drug candidates from screening hits.

With our computational chemistry expertise, CDS can design and provide a medicinal chemistry program tailored to your specific requirements. Our “every compound counts” philosophy means that we take into account all of the relevant properties including biological activity, selectivity, pharmacokinetic (i.e. ADME) and toxicology properties, as well as patentability, in the design of your compounds. Please contact sales@chicagodiscoverysolutions.com for more information.

Usage Statement for CBB compounds, CBB1 – CBB9

Unless otherwise stated in our catalog or other company documentation accompanying the product(s), our products are intended for research use only and are not to be used for any other purpose, which includes but is not limited to, unauthorized commercial uses, in vitro diagnostic uses, ex vivo or in vivo therapeutic uses or any type of consumption or application to humans or animals.

References:

(1) Wang et al. Cancer Research, 2011, 71, 7238-7249.
(2) Nottke, Colaiacovo, and Shi. Development, 2009, 136, 879-889.