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Discovery of tranylcypromine analogs with an acylhydrazone substituent as LSD1 inactivators: Design, synthesis and their biological evaluation

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ABSTRACT

Lysine specific demethylase 1 (LSD1), the first identified histone demethylase, plays an important role in epigenetic regulation of gene activation and repression, has been reported to be up-regulated and involved in numbers of solid malignant tumors. In this study, we identified a series of phenylalanyl hydrazones based LSD1 inhibitors, and the most potent one, compound **4q**, can inactivate LSD1 with IC_{50} = 91.83 nM. In cellular level, compound **4q** can induce the accumulation of CD86 as well as H3K4me2, and inhibit gastric cancer cell proliferation by inactivating LSD1. Our findings indicated that compound **4q** may serve as a potential leading compound to target LSD1 overexpressed gastric cancer.
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Epigenetic post-transcriptional modifications on histone, including acetylation, methylation, and phosphorylation, modulate gene activation and repression. Among these modifications, methylation and demethylation of lysine are dynamically regulated by a number of histone methyltransferases (HMTs) and histone demethylases (HDMs) including lysine specific demethylase 1 (LSD1). LSD1, the first characterized demethylase in 2004[1] is a highly conserved flavin adenine dinucleotide (FAD)-dependent oxidative enzyme, containing amine oxidase domain. It demethylates mono-, di-methylated K4 and K9 of histone 3, as well as p53, E2F transcription factor 1 (E2F1) and DNA methyltransferases (DNMTs) and further regulates their downstream cellular function.[2–7] It has been reported to be overexpressed in many malignant tumors, including breast, colon, prostate, lung and gastric cancers.[8–16] Its downregulation by RNAi or various kinds of inhibitors has been shown to effectively treat those cancers by inducing re-expression of aberrantly silenced genes.[11,12,17–24] Therefore, LSD1 is considered as an important and promising anticancer target.

Until now, plenty of articles were published about LSD1 inhibitors[25–27] but only several of them can inactivate LSD1 with IC_{50} in the nanomolar range. Several monoamine oxidase (MAO) inhibitors, such as tranylcypromine, are known as irreversible LSD1 inhibitors, and only three tranylcypromine based irreversible inhibitors have entered into clinical trials[28] Acylhydrazone scaffold (—CONHN=) has attracted considerable attention for decades due to their broad applications range from medicinal agents. Many compounds containing this moiety have been reported, and which demonstrated significant biological activity such as antimicrobial[29] anti-virus[30] and antitumor[31] activity in medicinal fields. For example, compound (Fig. 1, SP2509) with a benzo-hydrazone moiety exhibited potent anticancer activity against several tumor cell lines by inhibiting LSD1[31] Compound **I** (Fig. 1), an N-acylhydrazone derivative, was reported as a potent (HDAC) 6/8 dual inhibitor[32] Hence, inspired by the versatility of tranylcypromine skeleton and hydrazone moiety mentioned above, we designed a group of tranylcypromine derivatives (Fig. 2), which resulted in a novel series of LSD1 inhibitors.

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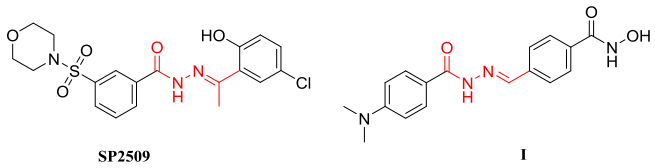


Fig. 1. Hydrazone-contained compounds with anticancer activity.

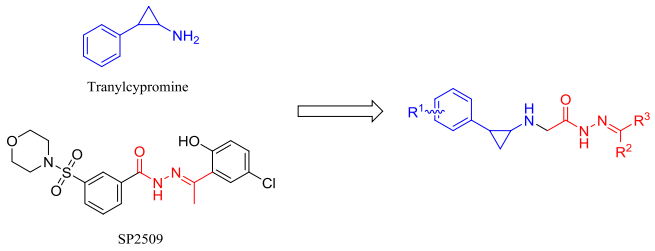


Fig. 2. Novel LSD1 inhibitor designed and synthesized in this work.

In this study, we identified a potent phenylalanyl hydrazone based LSD1 inhibitor, compound **4q**, which can inactivate LSD1 with IC_{50} = 91.83 nM. Meanwhile, several of its derivatives also performed potent LSD1 inhibitory effect. The further cellular study indicated that compound **4q** can induce the accumulation of CD86 and H3K4me2 and inhibit gastric cancer cell proliferation by inactivating LSD1. Our findings indicated that compound **4q** may serve as a potential leading compound for the treatment of LSD1 overexpressed gastric cancer.

The synthesis of compounds **4a–s** is shown in Scheme 1. (*1R,2S*)-2-(3,4-difluorophenyl)-cyclopropan-1-amine **1** reacted with methyl bromoacetate in the presence of *N,N*-Diisopropylethylamine (DIPEA) gave compound **2**, which then reacted with hydrazine hydrate in methanol, afforded compound **3**.[33] Targeted compounds **4a–s** were readily obtained by refluxing **3** with the substituted aromatic aldehyde or ketone in alcohol[34]

All the target compounds were synthesized and initially screened for their inhibitory activities against LSD1 *in vitro*. As presented in Table 1, the limited Structure-activity relationship (SAR) was studied. Hydrazone obtained from acetophenone (**4a**) showed the inhibitory as 201.23 nM. Halogens and nitro group were introduced in the phenyls (**4b–4e**) firstly, showed that the electron-whithdrawing group in 4-position decreased the inhibitory activities. When amino group substituted the meta-hydrogen in phenyl ring, the activity decreased slightly. Inspired by the compound SP2509 (Fig. 1), we think the ortho-hydroxy substituted phenyl group may play an important role, so we also introduced this fragment into the target molecules. (**4h–4l**, **4o–4s**) The activity of compounds **4i** and **4j** decreased by about 4 times, while **4h** enhanced

Table 1
LSD1 inhibitory activities of compounds **4a–t**.

Compound	R^1	R^2	IC_{50} (nM)[a]
4a	CH_3	Ph	201.23 ± 2.30
4b	CH_3	4-Cl-Ph	224.11 ± 2.35
4c	CH_3	4-Br-Ph	223.13 ± 2.35
4d	CH_3	4-F-Ph	631.19 ± 2.74
4e	CH_3	4-NO_2-Ph	350.26 ± 2.54
4f	CH_3	3-NH_3-Ph	423.42 ± 2.63
4g	CH_3	2-OH-Ph	221.97 ± 2.35
4h	CH_3	2,5-diOH-Ph	147.70 ± 2.17
4i	CH_3	2-OH-5-Cl-Ph	881.51 ± 2.95
4j	CH_3	2-OH-5-Br-Ph	828.31 ± 2.92
4k	CH_3	2-OH-5-F-Ph	273.72 ± 2.41
4l	CH_3	2-OH-3-NH_3-Ph	349.06 ± 2.54
4m	H		366.54 ± 2.56
4n	H		273.83 ± 2.44
4o	H	2-OH-5-Cl-Ph	455.51 ± 2.66
4p	H	2-OH-5-Br-Ph	388.08 ± 2.57
4q	H	2-OH-4-diethylamino-Ph	91.83 ± 1.96
4r	H	2-OH-4-MeO-Ph	169.61 ± 2.22
4s	H	2-OH-3-EtO-Ph	110.25 ± 2.04
4t	H	4-diethylamino-Ph	253.60 ± 1.09
SP2509			26.13 ± 1.55

[a] Data are presented as the means ± SDs of three independent experiments.

slightly achieved 147.70 nM. **4o** and **4p** showed better activity than **4j** and **4k**, illustrated the methyl group in hydrazine was not necessary. Also, the phenyl scaffold replaced by furan ring (**4m**) and thiophene ring (**4n**) was helpless. The LSD1 inhibitory activity was improved greatly by introduced the hydrogen bond acceptor in the 2-OH phenyl ring. **4r** and **4s** achieved the inhibitory as 169.61 nM and 110.25 nM, **4q** gave the best 91.83 nM IC_{50} value

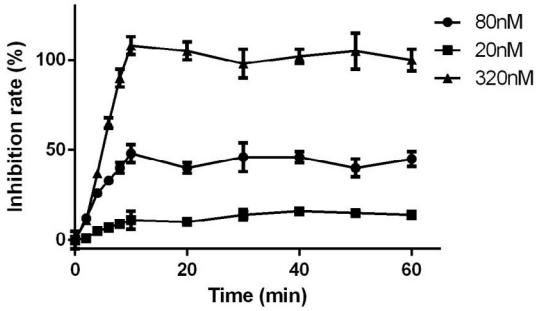
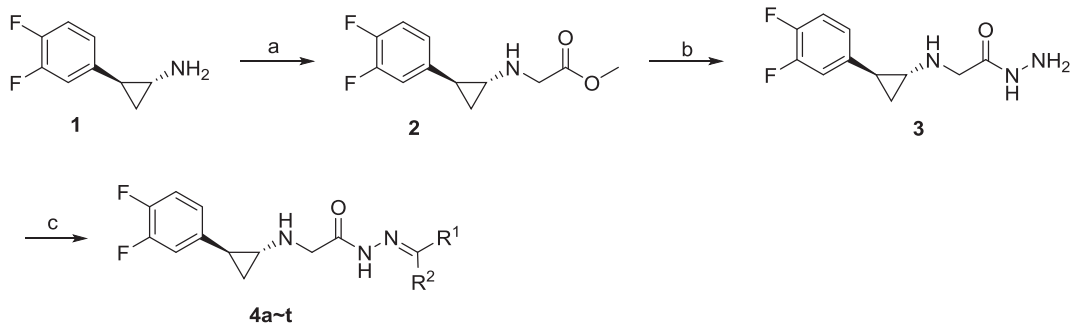


Fig. 3. Time dependent assay of compound **4q** against LSD1. The stable progress curves for the inactivation of LSD1 were obtained by indicated concentrations of compound **4q** treatment. Data are mean ± SD. P < .01 was considered statistically highly significant.



Scheme 1. Reagents and conditions: (a) $BrCH_2COOCH_3$, DIPEA, CH_3CN, 12h, 90%; (b) CH_3OH, $NH_2NH_2{\cdot}H_2O$, RT, 5 h, 85%; (c) Corresponding aldehyde or ketone, EtOH, reflux, 4–8 h, 67–82%.

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