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Synthesis and biological evaluation of novel (*E*)-*N*′-(2,3-dihydro-1*H*-inden-1-ylidene) benzohydrazides as potent LSD1 inhibitors

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ABSTRACT

Lysine specific demethylase 1 (LSD1) plays an important role in regulating histone lysine methylation at residues K4 and K9 on histone H3 and is recognized as an attractive therapeutic target in multiple malignancies. In this study, a series of novel (*E*)-*N*′-(2,3-dihydro-1*H*-inden-1-ylidene) benzohydrazides were synthesized and biologically evaluated for their potential LSD1 inhibitory effect. Among them, compounds **5a** and **5n** showed the most potent LSD1 inhibitory activity with IC_{50} values of 1.4 and 1.7 nM, respectively, which were about 10 times more potent compared with (*E*)-*N*-(1-(5-chloro-2-hydroxyphenyl) ethylidene)-3-(morpholinosulf-only) benzohydrazide (*J. Med. Chem.* **2013**, 56, 9496–9508; as reference compound). Compounds **5a** and **5n** also exhibited marked anti-proliferation activities against cancer cell lines that highly expressed LSD1. These results suggest that these optimized compounds might be served as promising LSD1 inhibitors against cancer, which merit further study.

Epigenetic disregulation contributes to the aberrant gene expression by chromatin modifications, which directly causes oncogenesis and development of cancer.[1] Lysine-specific demethylase (LSD1), a member of the flavin monoamine oxidase family, is the first discovered histone demethylase, which can reversibly catalyze the oxidative demethylation of mono- and dimethylated histone H3 at lysine 4 (H3K4me1 and H3K4me2) and lysine 9 (H3K9me1 and H3K9me2) to mediate changes in gene expression.[2,3] Overexpression of LSD1 is observed in a variety of cancers and is associated with the progression, invasion and recurrence of these cancers including breast cancer, colon cancer, prostate cancer, lung cancer and gastric cancer.[4–8] Knocking down of LSD1 with small-interfering RNAs (siRNAs) resulted in reactivation of tumor suppressor genes through increasing methylation at H3K4, thus suppressed the proliferation and metastasis of cancer cells. Therefore, LSD1 is considered as a promising anticancer drug target.

To date, a handful of small molecule inhibitors of LSD1 have been reported (Fig. 1), such as Monoamine oxidase (MAO) inhibitors tranylcypromine (TCP), pargyline (**A** and **B**) and several derivatives of these scaffolds (**C**–**E**).[9–14] But these small molecule inhibitors presented sorts of drawbacks, like the poor selectivity, low potency and in vivo toxicity.[15] For these reasons, the further contribution of LSD1 in anticancer exploration has been impeded. Recently, a series of *N*′-(1-phenylethylidene)-benzohydrazides had been described as potent LSD1inhibitors with a novel scaffold.[15] Especially, the novel compound (*E*)-*N*-(1-(5-chloro-2-hydroxyphenyl)ethylidene)-3-(morpholinosulf-only) benzohydrazide exerted several advantages of superior selectivity and reversibility.[15] However, its inhibitory activity was still insufficient with the IC_{50} value of 13 nM since the IC_{50} value of the most potent LSD1 inhibitor that had been reported was 5 nM.[9] Therefore, it is needed to optimize this novel compound to improve the inhibitory activity against LSD1. In this study, we set (*E*)-*N*-(1-(5-chloro-2-hydroxyphenyl) ethylidene)-3-(morpholinosulf-only) benzohydrazide as the reference compound and take the optimization as following.

As we know that the use of conformational constraint is a general strategy with which to improve ligand selectivity for a molecular target.[16] We noticed that the conformation of acetophenone moiety of the reference compound could be restricted on one plane if acetophenone moiety was replaced by 2,3-dihydro-1*H*-inden-1-one (Scheme 1). Besides, the previous study had demonstrated the hydroxyl group of the reference compound was essential and the inhibitory activity would be improved slightly with adding the chlorine atom at the o-position of the hydroxyl group.[15] Herein, we designed and synthesized compound **5a** ((*E*)-*N*′-(7-hydroxy-2,3-dihydro-1*H*-inden-1-ylidene)-3-(morpholinosulfonyl) benzohydrazide), **5n** ((*E*)-*N*′-(4-chloro-7-hydroxy-2,3-dihydro-1*H*-inden-1-ylidene)-3-(morpholinosul-fonyl) benzohydrazide) and a series of derivatives (**5b**–**m** and **5o**–**z**) by replacing variety of

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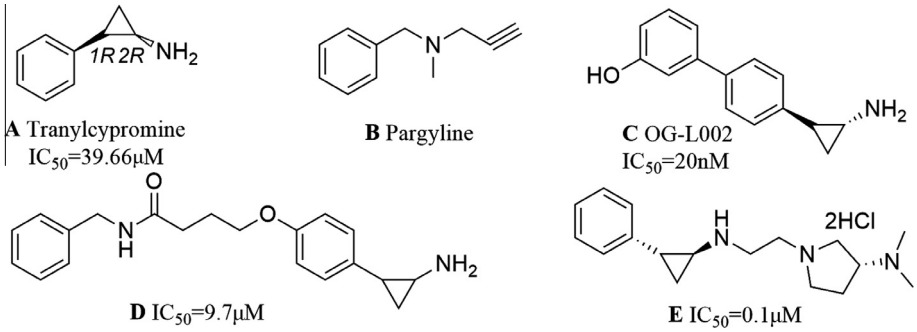
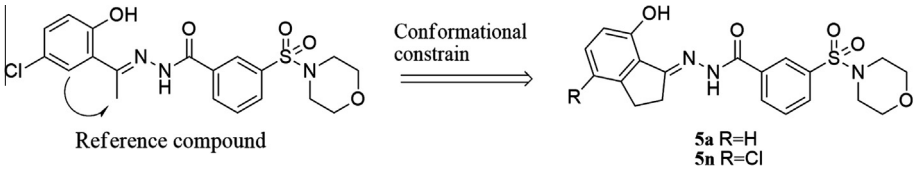
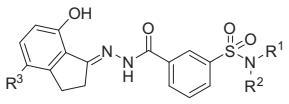


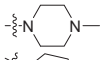
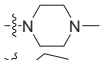
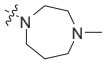
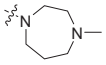
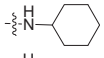
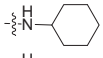
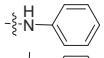
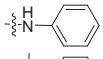
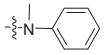
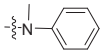
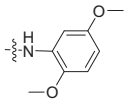
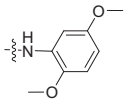
Figure 1. Chemical structures of pargyline, TCP and TCP'S derivatives.



Scheme 1. Initial LSD1 inhibitors.

Table 1
Effect of different sulfamides on LSD1 inhibition



Compd#[a]	R^3	$-NR^1R^2$	Inhibition (%)		IC_{50}[d] (μM)	Compd#	R^3	$-NR^1R^2$	Inhibition (%)		IC_{50}[d] (μM)
			50 μM	10 μM					50 μM	10 μM	
5a	H		99	99	0.0014 ± 0.0003	**5n**	Cl		99	77	0.0017 ± 0.0007
5b	H		100	99	0.0049 ± 0.0011	**5o**	Cl		100	99	0.0092 ± 0.0006
5c	H		99	100	0.0023 ± 0.0003	**5p**	Cl		100	100	0.0046 ± 0.0006
5d	H		N.I.[b]	N.I.	>100	**5q**	Cl		55	31	>10
5e	H		48	33	>50	**5r**	Cl		20	8	>100
5f	H		22	6	>100	**5s**	Cl		28	7	>100
5g	H		9	N.I.	>100	**5t**	Cl		23	N.I.	>100
5h	H		18	4	>100	**5u**	Cl		46	23	>50
5i	H		64	62	>10	**5v**	Cl		38	22	>50
5j	H		1	N.I.	>100	**5w**	Cl		81	47	>10
5k	H		52	17	>10	**5x**	Cl		11	11	>100
5l	H		6	2	>100	**5y**	Cl		N.I.	N.I.	>100
5m	H		92	59	2.9000 ± 0.2000	**5z**	Cl		N.I.	N.I.	>100
RC[c]	-	-	99	99	0.0130 ± 0.0010						

[a] Compd# = compound number.
[b] N.I. = no inhibition.
[c] RC = reference compound.
[d] Values are means of at least three measurements.