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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis and biological activity of *N*-(3-substituted-phenyl) benzenesulfonamides as selective and reversible LSD1 inhibitors

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Abstract Lysine specific demethylase 1 plays a crucial role in regulating histone methylation at residues K4 and K9 on histone H3 and over-expresses in a variety of cancers. Here we designed, synthesized and evaluated a series of *N*-(3-substituted-phenyl)benzenesulfonamides as reversible lysine specific demethylase 1 inhibitors. All the compounds exhibited lysine specific demethylase 1 inhibition with the half maximal inhibitory concentration (IC_{50}) values between 7.5 and 68 μM. Three most active compounds **2a**, **2c** and **2i** displayed only modest effect on flavin adenine dinucleotide-dependent enzymes mono-amine oxidases A and B, and their reversibilities of lysine specific demethylase 1 inhibition were confirmed. Molecular docking was also carried out to predict the binding mode of **2a** into the active site of lysine specific demethylase 1. Taken together, *N*-(3-substituted-phenyl)benzenesulfonamides including **2a** represent a new class of selective and reversible lysine specific demethylase 1 inhibitors with pharmaceutical research.

Keywords LSD1 · Small molecule inhibitors · Selective · Reversible · Molecular modeling

Abbreviations

TEA	Triethylamine
DIPEA	*N,N*-Diisopropylethylamine
EDCI	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
HOBt	*N*-Hydroxybenzotriazole
rt	Room temperature
PyBOP	Benzotriazol-1-yl-oxytripyrrolidinophosphonium
DMAP	4-Dimethylaminopyridine

Introduction

Histone lysine methylation can be dynamically regulated by two counteracting families of enzymes, the histione methyltransferase and the histone demethylase. Histone lysine-specific demethylase 1 (LSD1, also known as KDM1A, AOF2, BHC110 or KIAA0601) was the first histone demethylase discovered in 2004 (Shi et al., 2004), which is a highly conserved flavin adenine dinucleotide

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(FAD)-dependent oxidative enzyme containing a homologous domain to amine oxidase, catalyzing the demethylation reaction. LSD1 plays important roles in normal processes and malignant transformation, mainly as a transcription regulator. It demethylates mono- and dimethylated histone H3 lysine 4 (H3K4me1 and H3K4me2) and H3 lysine 9 (H3K9me1 and H3K9me2) (Shi et al., 2004; Metzger et al., 2005) as well as p53, DNA methyltransferase 1 (DNMT1) and E2F transcription factor 1(E2F1), which further regulates their downstream cellular function (Lynch et al., 2012).

Emerging evidences indicate LSD1 as a potential therapeutic target for the treatment of various cancers. Overexpression of LSD1 in the human malignancies has been observed in a variety of tumors including ER-negative breast cancer, prostate cancer, non-small cell lung cancer, neuroblastoma (Kahl et al., 2006; Lim et al., 2010; Yoshimatsu et al., 2011; Zhao et al., 2012), particularly acute myeloid leukemia (AML) and bladder cancer (Lynch et al., 2012).

To date, a large number of LSD1 inhibitors have been developed. As a member of monoamine oxidase (MAO) family, LSD1 shares high level of sequence homology to MAO-A and MAO-B at the active sites, and requires FAD as its cofactor to catalyze the oxidation, and consequently, the removal of the methyl groups from its substrates (Shi et al., 2004). Therefore, MAO inhibitors were investigated as potential inhibitors of LSD1. Tranylcypromine (TCPA, **A**), a MAO inhibitor originally developed as antidepressant agent in the 1960s, was identified as an irreversible and poor selective LSD1 inhibitor with moderate inhibitory effect. Since then, a variety of TCPA-based compounds have been reported with enhanced level of potency and increased selectivity (Mimasu et al., 2010; Ueda et al., 2009; Binda et al., 2010; Ortega et al., 2011; Guibourt et al., 2010; McCafferty and Pollock, 2013; Liang et al., 2013). OG-L002 (**B**), a TCPA-based compound, shows potent inhibition against LSD1 at 20 nM (https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-002447-29/ES). ORY-1001(**C**), inducing cell differentiation and significantly reducing the clonogenic potential of primary human MLL-AF9 AML cells, was granted orphan drug status by EMA in September 2013 and is currently in phase I/IIa trial study for AML (https://www.oryzon.com/en/therapeutic-programs/our-pipeline). GSK2879552 (**D**) is a selective, mechanism-based irreversible LSD1 inhibitor under the phase I trial studies for the treatment of relapsed/refractory small cell lung carcinoma (http://clinicaltrials.gov/ct2/show/NCT02034123?term=lysine+specific+demethylase&rank=2). Those TCPA based agents are irreversible inhibitors and form covalent bond with the cofactor, FAD, at the LSD1 active site (Ueda et al., 2009; Binda et al., 2010; Mimasu et al., 2008). Although some of the more recently reported compounds belonging to this class have shown significant selectivity towards LSD1 over MAO-A and B, the possibilities to affect other FAD dependent enzymes in vivo has not been fully investigated (Hitchin et al., 2013). Thus it is of great importance for the development of reversible inhibitors. For the reversible LSD1 inhibitors, **E**, **F** and **G** only moderately inhibit LSD1 at micromolar level (Hazeldine et al., 2012; Zheng et al., 2013; Zhou et al., 2015). GSK354 (**H**), disclosed as a potent and reversible inhibitor of LSD1 with high selectivity against MAO-A ($IC_{50} > 200$ mM), yet the further biological data has not been disclosed. Notably, SP2509 (**I**) was a potent and specific LSD1 inhibitor, however, was found to be cytotoxic in THP1 cells dosed for 24 h at concentrations ≥ 2 μM, and such discrepancy was not fully understood yet (Hitchin et al., 2013; Dhanak, 2013). However, the core *N*′-(2-hydroxybenzylidene)hydrazide motif of **I** has been previously identified as a pan-assay interference compound (PAINS), limiting its further clinical potential (Hitchin et al., 2013; Sorna et al., 2013; Baell and Holloway, 2010). Hence, the discovery of drug-like LSD1 inhibitors is necessary for the treatment of LSD1 overexpressing cancer as well as the elucidation of LSD1 function in cancer. (Fig. 1) Reference Dhanak (2015) is cite in the text but not provided in the reference list. Please provide this reference in the list or delete rom the text.

Recently, *N*-(substituted-phenyl)benzenesulfonamides have drawn increasing attention because of their numerous biological activities, especially the anticancer activity (Levin et al., 1999; Kawai et al., 2006; Comess et al., 2004; Sheppard et al., 2006). In this paper, we utilized its core motif to sucessfully design and synthesize a series of *N*-(3-substituted-phenyl)benzenesulfonamides derived LSD1 specific inhibitors. All the compounds exhibited LSD1 inhibition with the IC_{50} values in the range of 7.5–68 μM. Three most active compounds **2a**, **2c** and **2i** displayed only modest effect on the homogulous enzymes MAO-A and MAO-B, indicating good selectivity for LSD1 inhibition. Furthermore, their reversible effects toward LSD1 were further comfirmed experimentally. Molecular docking was also carried out to predict the binding mode of **2a** at the active site of LSD1, providing future opportunities for further optimization. Taken together, our work discovered *N*-(3-substituted-phenyl)benzenesulfonamides as a novel class of selective and reversible LSD1 inhibitors, and particularly, the **2a** represents a lead compound for further research.

Results and discussion

Chemistry

The general route for the synthesis of the *N*-(substituted-phenyl)benzenesulfonamides (**2a**–**2i**) is depicted in

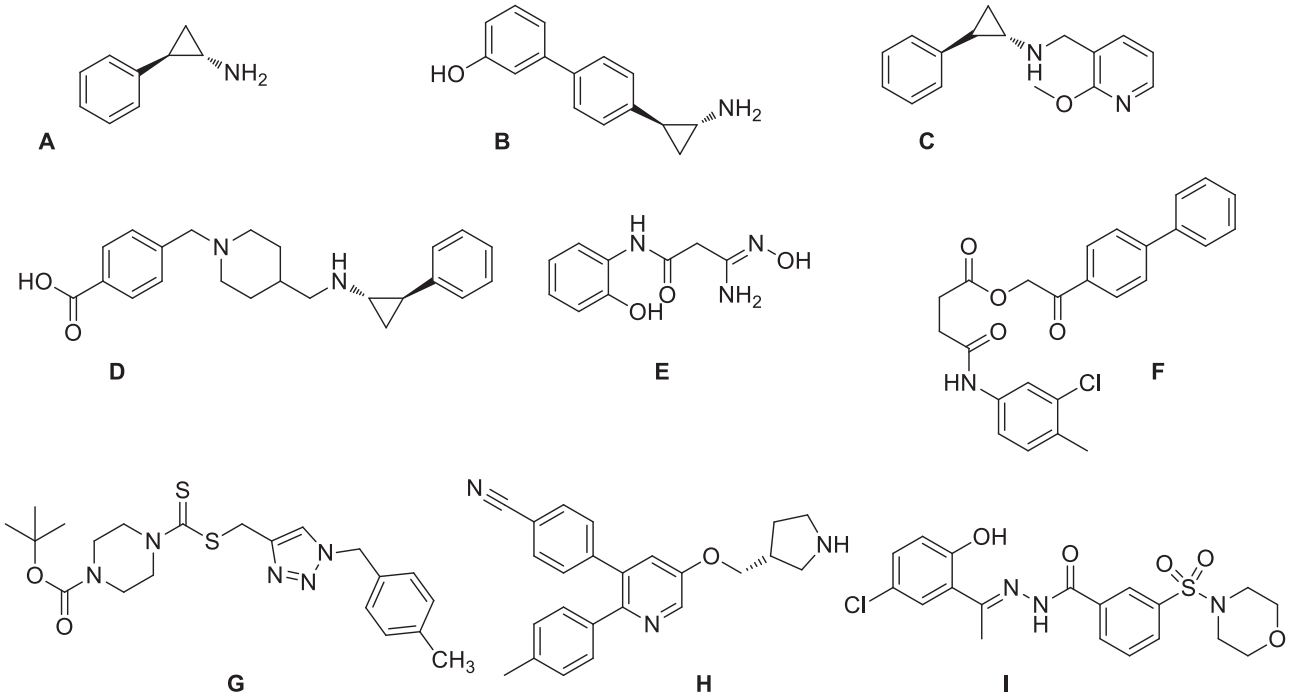
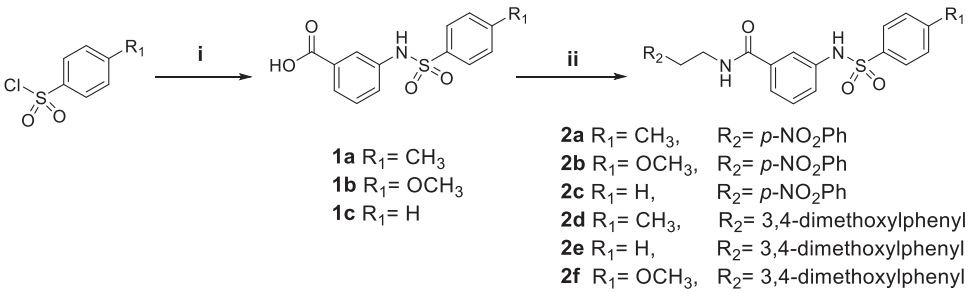


Fig. 1 Representative structures of reported LSD1 inhibitors. **a** Tranylcypromine (TCPA) $IC_{50} = 20.7$ uM, **b OG-L002** $IC_{50} = 20$ nM, **c** ORY-1001 $IC_{50} = 20$ nM, **d** GSK-2879552 $IC_{50} = 20$ nM, **e** $IC_{50} = 16.8$ uM, **f** $IC_{50} = 2.41$ uM, **g** $IC_{50} = 2.11$ uM, **h** GSK-354 $IC_{50} = 90$ nM, **i** SP-2509 $IC_{50} = 13$nM



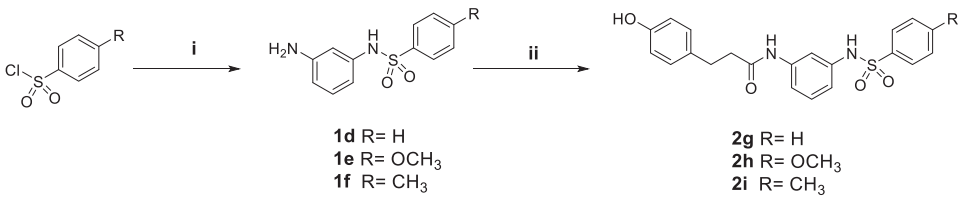
Scheme 1 Synthesis of compounds **2a**–**2f**. Reagents and conditions: *i m*-aminobenzoic acid, Na_2CO_3, H_2O, rt,4 h; *ii* EDCI, HOBt, CH_2Cl_2, rt, 12 h

Schemes 1 and 2. *p*-Benzenesulfonyl chlorides were reacted with *m*-aminobenzoic acid at room temperature to afford the intermediates **1a**–**1c**. Then *p*-phenethylamines were reacted with **1a**–**1c** and EDCI/HOBt[(3-dimethylaminopropyl)ethyl-carbodiimid monohydrochloride/N-Hydroxybenzotriazole] at room temperature to synthesize the target compounds **2a**–**2f**, respectively. Similarly, the reaction of *p*-benzenesulfonyl chlorides with *m*-phenylenediamine in THF was utilized to make the intermediates **1a**–**1c**, and *p*-hydroxyphenylacetic acid was then reacted with **1d**–**1f** using DIPEA (*N*,*N*-Diisopropylethylamine) as the base to give the corresponding target compounds **2g**–**2i**. At this step, we used PyBOP (Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate) as the condensating agent instead of EDCI/HOBt because of its weak condensating effect.

Biochemical evaluation

Biochemical activity of the candidate compounds against LSD1 and the preliminary structure–activity relationship (SAR) analysis

All the compounds synthesized in this study were evaluated for their in vitro inhibitory effect on LSD1, as reported in our previous study (Zhou et al., 2015). A known LSD1 inhibitor, RN-1, was chosen as a positive control (Rivers et al., 2014). The results are summarized in Table 1. All the test compounds showed IC_{50}s at low micromolar range (7.5–68 μM) in vitro. The LSD1 AlphaLISA assay was carried out using recombinant LSD1 protein and H3K4me2 peptide as substrate. Importantly, nitro group in the R_1 postion was the favorable substituent such as compound



Scheme 2 Synthesis of compounds **2g–2i**. Reagents and conditions: *i m*-phenylenediamine, TEA (triethylamine), THF, rt, 9 h; *ii p*-hydroxyphenylacetic acid, PyBoP, DIPEA, DMF, rt, 24 h

2a ($IC_{50} = 7.5$ μM), **2c** ($IC_{50} = 11.4$ μM) and **2i** ($IC_{50} = 8.6$ μM), while the methyloxy and hydroxy groups in the same position decreased the inhibitory effect.

Evaluation of the in vitro inhibitory effect of compounds 2a, 2c and 2i against LSD1's homologies MAO-A and MAO-B

Based on the in vitro results of LSD1 inhibition of the tested compounds (Table 1), the three most potent compounds **2a, 2c** and **2i** were further selected to be evaluated on their potential cross inhibitory effect toward the homologuous enzymes MAO-A and MAO-B. The reuslts are summarized in Table 1. Significantly, **2a**, **2c** and **2i** only exhibited modest inhibition against MAOs with the IC_{50} of 90.0, 63.9 and 109.2 μM for MAO-A, 226.1, 297.5 and 344.4 μM for MAO-B, respectively. Taken together, **2a**, **2c** and **2i** showed around 10 and 30 folds of selective inhibitions for LSD1 over MAO-A and MAO-B, respectively.

Reversiblity of the inhibition by 2a, 2c and 2i toward LSD1

Given that the most potent compounds **2a**, **2c** and **2i** displayed micromolar inhibition against LSD1 ($IC_{50} =$ 7.5–10 μM), we further carried out a jump dilution analysis to investigate the reversibility of the inhibition of these three compounds. The results are summarized in Scheme 3. All three compounds displayed great reversibility at 87, 67 and 84 %, respectively, indicating they were indeed reversible LSD1 inhibitors.

Docking analyses of potential binding modes of compound 2a and 2g binding to LSD1

To understand the initial binding mode and stability of ligand-receptor complexes, molecular modeling studies (CDOCKER docking analysis) were performed utilizing **2a** and **2g** and depicted in Scheme 4. In the case of **2a**, the oxygen atom of sulfonamide formed a hydrogen bond with Arg316 residue and a hydrogen bond was observed between the oxygen of sulfur atom and Ser289 residue. Moreover, it entirely occupied FAD-binding fold region, which could interact with the active site thoroughly with the CDOCKER energy value −46.23 kj/mol. Comparedly, only one oxygen atom of sulfonamide of **2g** interacted with Ser289 via H-bond and it occupied the active site with CDOCKER energy value −44.75 kj/mol. These results may further explain why compound **2a** possesses more potent inhibition against LSD1 than compound **2g**.

Conclusion

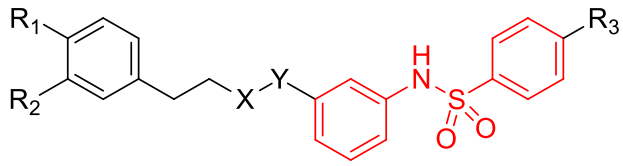
In summary, we synthesized and evaluated a series of *N*-(3-substituted-phenyl)benzenesulfonamides which exhibited low micromolar IC_{50}s of LSD1 inhibition in the range of 7.5–68 μM. Three most active compounds **2a**, **2c** and **2i**, also showed good selectiveties against the homogulous enzymes, MAO-A and MAO-B Furthermore, **2a**, **2c** and **2i** were further confirmed as LSD1 reversible inhibitiors. Docking study was also taken to predict the binding mode of **2a** with LSD1 which shows lower CDOCKER energy and two hypothetic hydrogen bonds. Taken together, we have provided preliminary evidences that *N*-(3-substituted-phenyl)benzenesulfonamides may be a novel class of selective and reversible LSD1 inhibitors that deserve further investigation on their therapeutic potentials.

Experimental section

Chemistry

All chemicals (reagent grade) were purchased from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China). Reactions were followed by thin-layer chromatography (TLC) on silica gel GF_{254} plates (Qingdao Haiyang Chemical Plant, Qingdao, Shandong, China) and the spots were visualized using a UV lamp ($\lambda = 254$ nm). Chromatographic separations were performed on silica gel columns (90–150 μm; Qingdao Marine Chemical Inc., Qingdao, Shandong, China) by flash chromatography. Melting points were measured on an XT-4 micromelting point instrument (Beijing Tech Instrument Corp., Beijing, China) and uncorrected. IR (KBr-disk) spectra were recorded by Bruker Tensor 27 spectrometer (Bruker Corp., Billerica, MA, USA). ^{1}H NMR spectra (300 MHz) and ^{13}C NMR (75 MHz) were acquired on a Bruker ACF-300 spectrometer (Bruker Corp., Billerica, MA, USA) at 25°C and referenced to tetramethylsilane (TMS). Chemical shifts were reported in ppm (δ) using the residue solvent line as internal standard.

Table 1 Structures of compounds **2a–2i** and their in vitro inhibitory effect (IC_{50}) against LSD1

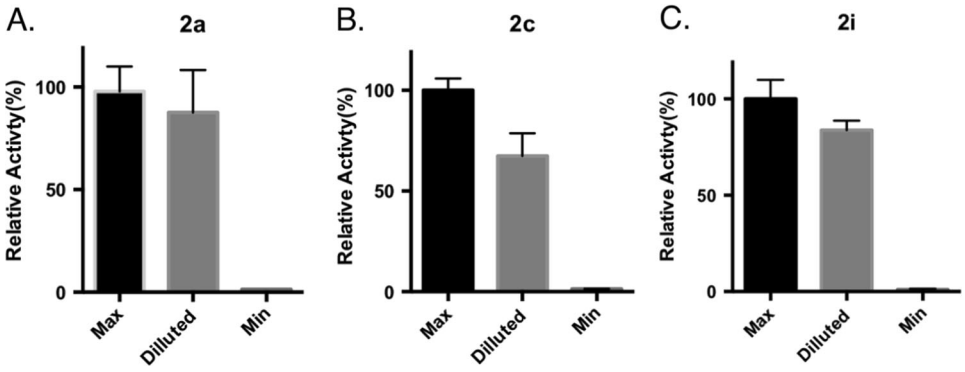


No.	R_1	R_2	X	Y	R_3	IC_{50} (μM)			SI[a]	SI[b]
						LSD1	MAO-A	MAO-B		
2a	NO_2	H	NH	CO	CH_3	7.5	90.0	226.1	12.3	30.1
2b	NO_2	H	NH	CO	OCH_3	11.4	ND[c]	ND	ND	ND
2c	NO_2	H	NH	CO	H	8.6	63.9	297.5	7.4	34.6
2d	OCH_3	OCH_3	NH	CO	CH_3	13.5	ND	ND	ND	ND
2e	OCH_3	OCH_3	NH	CO	H	23.3	ND	ND	ND	ND
2f	OCH_3	OCH_3	NH	CO	OCH_3	22.1	ND	ND	ND	ND
2g	OH	H	CO	NH	H	67.7	ND	ND	ND	ND
2h	OH	H	CO	NH	OCH_3	13.7	ND	ND	ND	ND
2i	OH	H	CO	NH	CH_3	10.0	109.2	344.4	10.9	34.4
RN-1						0.0076				

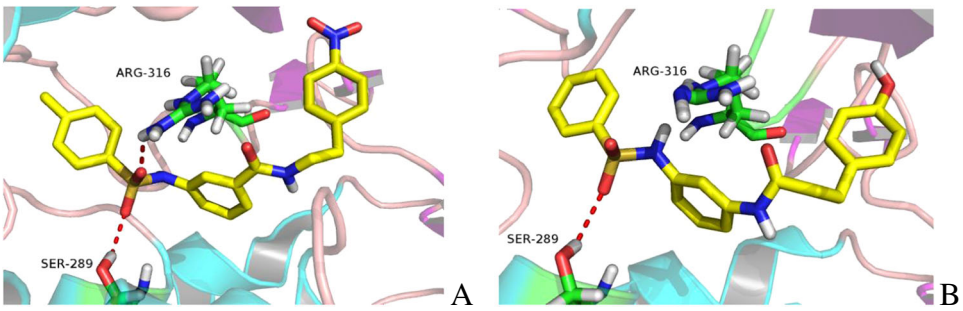
[a] Selectivity index = IC_{50} of MAO-A/IC_{50} of LSD1

[b] Selectivity index = IC_{50} of MAO-B/IC_{50} of LSD1

[c] Not determined



Scheme 3 Compounds **2a**, **2c** and **2i** are reversible LSD1 inhibitors. The reversibility of **a** **2a**, **b** **2c** and **c** **2i**



Scheme 4 Representation of the theoretical binding mode of compounds **2a** **a** and **2g** **b** with LSD1(PDB id: 2Z5U)

Splitting patterns are designed as s, singlet; d, doublet; t, triplet; m, multiplet. The identity of final compounds was confirmed by acquiring mass spectra on an Agilent 1100 Series (Agilent Technologies, Santa Clara, CA, USA) LC/MSD high performance ion trap mass spectrometer and a Mariner ESI-TOF spectrometer. Compound purity was evaluated by reverse phase chromatography using a Shimadzu Shim-Pack VP-ODS (150 × 4.6 mm i.d., 5 µm particle size, Shimadzu Corp., Kyoto, Japan) column and DAD detection. Satisfactory chromatographic analyses were obtained for all new compounds, confirming >95 % purity (see Supporting Information).

*3-((4-Methylphenyl)sulfonamido)benzoic acid (**1a**)*

To a solution of 3-aminobenzoic acid (500 mg, 3.65 mmol) and tosyl chloride (695 mg, 3.65 mmol) in 15 mL H_2O was added with an aqueous solution of 1 mol/L Na_2CO_3 dropwise to adjust the pH to 9. The mixture was stirred at room temperature for about 4 h. After the completion of the reaction monitored by TLC, the mixture was transferred to 100 mL beaker. Then 1 mol/L HCl was added dropwise to adjust the pH to 2 in ice water. The precipitate was collected and the product was afforded as light white solid (0.778 g, 73.4 %) without further purification. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.51 (s, 1H), 7.74 (s, 1H), 7.69 (d, J = 7.4 Hz, 2H), 7.62 (d, J = 5.6 Hz, 1H), 7.38 (m, 4H), 2.36 (s, 3H) (Deng and Mani, 2006).

*3-((4-Methoxyphenyl)sulfonamido)benzoic acid (**1b**)*

According to the preparation procedure of **1a**, **1b** was provided as light white solid (0.815, 72.8 %) without further purification. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 13.01 (s, 1H), 10.37 (s, 1H), 7.72–7.69 (m, 3H), 7.59 (d, J = 6.2 Hz, 1H), 7.40–7.45 (m, 2H), 7.07 (d, J = 8.8 Hz, 2H), 3.80 (s, 3H).

*3-(Phenylsulfonamido)benzoic acid (**1c**)*

According to the preparation procedure of **1a**, **1c** was provided as light white solid as light white solid (0.796 g, 78.8 %) without further purification. ^{1}H NMR (300 MHz, DMSO-d_6 ppm): δ 13.98 (s, 1H), 10.52 (s, 1H), 7.77 (d, J = 7.8 Hz, 2H), 7.70 (s, 1H), 7.61–7.54 (m, 4H), 7.38–7.36 (m, 2H).

*3-((4-Methylphenyl)sulfonamido)-*N*-(4-nitrophenethyl) benzamide (**2a**)*

To a solution of 3-((4-methylphenyl)sulfonamido)benzoic acid (400 mg, 1.37 mmol) , 4-nitrophenethylamine hydrochloride (185.5 mg, 0.92 mmol), EDCI (228 mg,

1.19 mmol) and HOBt (161 mg, 1.18 mmol) in dichloromethane (15 mL) was added with triethylamine (383 μL, 2.75 mmol). The reaction mixture was stirred overnight at room temperature. After completion of the reaction monitored by TLC, the solvent was removed under vacuum and the crude mixture was dissolved by EtOAc (15 mL). The solution was washed by $NaHCO_3$ and saturated NaCl solution (15 mL *3), then dried over anhydrous Na_2SO_4. Purification of the crude product with flash column chromatography (PE:EA = 2:1, *v*:*v*) gave 342 mg of **2a** as a pale yellow solid, yield 85 %. Mp: 167–168 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.37 (s, $SO_2N\underline{H}$, 1H), 8.53–8.51 (m, CON<u>H</u>, 1H), 8.17 (d, $J = 8.0$ Hz, Ar–H, 2H), 7.66 (d, $J = 8.1$ Hz, Ar–H,2H), 7.56 (s, 1H), 7.53 (d, $J = 8.4$ Hz, Ar–H, 2H) 7.52 (s, Ar–H, 1H), 7.41 (d, $J = 7.5$ Hz, Ar–H, 1H), 7.35 (d, $J = 7.7$ Hz, Ar–H, 2H), 7.29 (d, $J = 7.5$ Hz, Ar–H, 1H), 7.22 (d, $J = 8.9$ Hz, Ar–H, 1H), 3.56–3.49 (m, $CH_2C\underline{H_2}NHCO$, 2H), 3.01–2.96 (m, $C\underline{H_2}CH_2NHCO$, 2H), 2.34 (s, Ar–CH_3, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): 168.88 (<u>C</u>ONH), 151.05(Ar–C), 149.13 (Ar–C), 146.39 (Ar–C), 141.08 (Ar–C), 139.63 (Ar–C), 138.68 (Ar–C), 133.09 (Ar–C), 132.74 (Ar–C), 132.08 (Ar–C), 129.71 (Ar–C), 126.40 (Ar–C), 125.25 (Ar–C), 122.15 (Ar–C), 43.14 ($CH_2\underline{C}H_2NH$), 37.77 ($\underline{C}H_2CH_2NH$), 23.97 (Ar–$\underline{C}H_3$). IR (KBr, cm^{-1}): 3408, 3160, 1639, 1541, 1517, 1347, 1161. MS (*m*/*z*): 438.1 ([M–H]$^+$). HRMS (ESI): calcd for $C_{22}H_{21}N_3O_5S$, [M+H]$^+$ *m*/*z*, 440.1275; found, 440.1265. HPLC purity: 99.306 %.

3-((4-Methoxyphenyl)sulfonamido)-N-*(4-nitrophenethyl) benzamide (**2b**)*

According to the preparation procedure of **2a**, **2b** was prepared as a pale yellow solid, yield 85.6 %. Mp: 154–155 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.30 (s, 1H), 8.54–8.50 (m, 1H), 8.17 (d, $J = 8.6$ Hz, 2H), 7.70 (d, $J = 8.8$ Hz, 2H), 7.57 (s, 1H), 7.53 (d, $J = 8.6$ Hz, 2H), 7.43 (d, $J = 7.7$ Hz, 1H), 7.33–7.28 (m ,1H), 7.23 (d, $J = 8.1$ Hz, 1H), 7.07 (d, $J = 8.8$ Hz, 2H), 3.80 (s, 3H), 3.56–3.50 (m, 2H), 3.01–2.97 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.89, 151.03, 149.10, 141.19, 138.66, 134.07, 133.06, 132.05, 131.88, 126.38, 125.22, 125.17, 122.13, 117.42, 58.63, 43.14. IR (KBr, cm^{-1}): 3411, 3187, 1642, 1596, 1545, 1512, 1342, 1157. MS (*m*/*z*): 454.1([M–H]$^+$). HR–MS (ESI): calcd for $C_{22}H_{21}N_3O_6S$, [M+H]$^+$ *m*/*z*, 456.1224; found, 456.1211. HPLC purity: 99.497 %.

N-*(4-nitrophenethyl)-3-(phenylsulfonamido)benzamide (**2c**)*

According to the preparation procedure of **2a**, **2c** was prepared as a pale yellow solid, yield 83 %. Mp: 160–162 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.44 (s, 1H), 8.54–8.51 (m, 1H), 8.17 (d, $J = 8.5$ Hz, 2H), 7.77 (d, $J = 7.0$ Hz, 2H), 7.63–7.52 (m ,6H), 7.43 (d, $J = 7.8$ Hz, 1H), 7.34–7.28 (m, 1H), 7.23 (d, $J = 8.1$ Hz, 1H), 3.56–3.49 (m, 2H), 3.01–2.96 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): 168.88, 151.03, 149.12, 142.48, 140.97, 138.72, 135.99, 133.06, 132.30, 132.10, 129.66, 126.38, 125.51, 125.44, 122.41, 43.15, 37.79. IR (KBr, cm^{-1}): 3384, 3133, 1649, 1547, 1517, 1344, 1158. MS (*m*/*z*): 424.1 ([M–H]). HR–MS (ESI): calcd for $C_{21}H_{19}N_3O_5S$, [M+H]$^+$ *m*/*z*, 426.1118; found, 426.1111. HPLC purity: 99.244 %.

N-*(3,4-dimethoxyphenethyl)-3-((4-methylphenyl) sulfonamido)benzamide (**2d**)*

According to the preparation procedure of **2a**, **2d** was prepared as a pale yellow solid, yield 87.3 %. Mp: 183–185 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.35 (s, 1H), 8.47–8.42 (m, 1H), 7.64 (d, $J = 8.0$ Hz, 2H), 7.57 (s, 1H), 7.43 (d, $J = 7.2$ Hz, 2H), 7.34 (d, $J = 8.3$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 1H), 7.21 (d, $J = 8.6$ Hz, 1H), 6.85 (d, $J = 8.1$ Hz, 1H), 6.80 (s, 1H), 6.72 (d, $J = 9.6$ Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.45–3.38 (m, 2H), 2.77–2.72 (m, 2H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): 168.69, 151.66, 150.28, 146.39, 141.10, 139.65, 138.84, 134.99, 132.75, 132.03, 129.71, 125.23, 123.51, 122.25, 115.57, 114.98, 58.56, 58.38, 44.07, 37.59, 23.29. IR (KBr, cm^{-1}): 3362, 3136, 1638, 1585, 1547, 1515, 1344, 1126. MS (m/z): 477.1 ([M+Na]$^+$). HRMS (ESI): calcd for $C_{24}H_{26}N_2O_5S$, [M+H]$^+$ *m*/*z*, 455.1635; found, 455.1631. HPLC purity: 99.158 %.

N-*(3,4-dimethoxyphenethyl)-3-(phenylsulfonamido) benzamide (**2e**)*

According to the preparation procedure of **2a**, **2e** was prepared as a pale yellow solid, yield 88 %. Mp: 186–187 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.43 (s, 1H), 8.47–8.43 (m, 1H), 7.76 (d, $J = 7.3$ Hz, 2H), 7.63–7.52 (m, 4H), 7.44 (d, $J = 7.7$ Hz, 1H), 7.32–7.27 (m, 1H), 7.21 (d, $J = 9.8$ Hz,3H), 6.87–6.80 (m, 2H), 6.73 (d, $J = 8.0$ Hz,1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.45–3.38 (m, 2H), 2.77–2.72 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): 168.65, 151.66, 150.27, 142.47, 140.96, 138.87, 135.98, 134.99, 132.30, 132.03, 129.65, 125.43, 125.38, 123.50, 122.45, 115.57, 114.97, 58.54, 58.36, 44.08, 37.59, 17.10. IR (KBr, cm^{-1}): 3351, 3134, 1732, 1638, 1586, 1515, 1340, 1167. MS (*m*/*z*): 463.1 ([M+Na]$^+$). HRMS (ESI): calcd for $C_{23}H_{24}N_2O_5S$, [M+H]$^+$ *m*/*z*, 441.1479; found, 441.1474. HPLC purity: 99.303 %.

N-*(3,4-dimethoxyphenethyl)-3-((4-methoxyphenyl) sulfonamido)benzamide (**2f**)*

According to the preparation procedure of **2a**, **2f** was prepared as a pale yellow solid, yield 88 %. Mp: 189–190 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.40 (s, 1H), 8.56–8.58 (m, 1H), 7.80 (d, J = 8.6 Hz, 2H), 7.69 (s, 1H), 7.55 (d, J = 7.6 Hz, 2H), 7.43–7.38 (m, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.17 (d, J = 8.6 Hz, 2H), 6.98–6.91 (m, 2H), 6.84 (d, J = 8.2 Hz, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.58–3.50 (m, 2H), 2.88–2.83 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.71, 151.65, 150.27, 141.21, 138.83, 134.99, 134.09, 132.00, 131.89, 125.19, 125.14, 123.50, 122.21, 117.43, 115.56, 114.96, 58.63, 58.54, 58.36, 44.07, 37.59. IR (KBr, cm^{-1}): 3336, 3133, 1635, 1594, 1542, 1515, 1327, 1157. MS (*m/z*): 493.1 ([M+Na]$^+$). HR–MS (ESI): calcd for $C_{24}H_{26}N_2O_6S$, [M+H]$^+$ *m/z*, 471.1584; found, 471.1574. HPLC purity: 96.882 %.

N-*(3-aminophenyl)benzenesulfonamide (**1d**)*

To a solution of benzenesulfonyl chloride (1.77 g, 10 mmol) in THF (10 mL), a solution of triethylamine (2.79 mL, 20 mmol) in THF (5 mL) and *m*-phenylenediamine (1.08 g, 10 mmol) in THF (5 mL) were added dropwise respectively. The reaction mixture was stirred for 12 h at room temperature. After the completion of the reaction monitored by TLC, the mixture was filtered and condensed under reduced pressure. The crude product can be used for the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): 7.71 (d, J = 7.1 Hz, 2H), 7.65–7.61 (m, 1H), 7.56–7.51 (m, 2H), 7.08 (s, 1H), 7.04–6.99 (m, 1H), 6.69–6.65 (m, 2H).

N-*(3-aminophenyl)-4-methoxybenzenesulfonamide (**1e**)*

According to the preparation procedure of **1d**, **1e** was afforded from 4-methoxybenzenesulfonyl chloride. The crude product can be used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, J = 8.6 Hz, 2H), 7.29 (s, 1H), 7.02–6.97 (m, 1H), 6.92 (d, J = 8.7 Hz, 2H), 6.73 (s, 1H), 6.45 (s, 1H), 6.45–6.39 (m, 2H), 3.85 (s, 3H).

N-*(3-aminophenyl)-4-methylbenzenesulfonamide (**1f**)*

According to the preparation procedure of **1d**, **1f** was afforded from the 4-toluene sulfonyl chloride. The crude product can be used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 7.14–7.08 (m, 1H), 7.02–7.00 (m, 2H), 6.84–6.80 (m, 1H), 2.43 (s, 1H).

3-(4-Hydroxyphenyl)-N-*(3-(phenylsulfonamido)phenyl) propanamide (**2g**)*

1d (600 mg, 2.42 mmol), 3-(4-hydroxyphenyl)propanoic acid (803 mg, 4.83 mmol), PyBOP (3.14 mmol, 1.63 g) were dissolved in DMF (25 mL) in the presence of *N*,*N*-diisopropylethylamine (DIPEA) as a catalyst. The reaction mixture was stirred at room temperature for about 36 h. The reaction was monitored by TLC. After the completion of the reaction, the mixture was transfered to water (50 mL) and stirred for 15 min. The organic layer was washed by saturated brine (15 mL*3) and dried over anhydrous Na_2SO_4. Purification of the crude product with flash column chromatography (CH_2Cl_2:CH_3OH = 40:1 v:v) gave **2g** as a pale white solid (368 mg, 38.6 %). Mp: 142–145 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.25 (s, 1H), 9.82 (s, 1H), 9.11 (s, 1H), 7.75 (d, J = 7.2 Hz, 2H), 7.61–7.49 (m, 3H), 7.44 (s, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.10–7.04 (m, 1H), 6.98 (d, J = 8.1 Hz, 2H), 6.71 (d, J = 7.7 Hz, 1H), 6.4 (d, J = 8.2 Hz, 2H), 2.77–2.72 (m, 2H), 2.51–2.48 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): 170.53, 155.45, 139.87, 139.57, 138.00, 132.78, 131.12, 129.13, 129.00, 126.62, 115.02, 114.66, 114.46, 110.60, 38.38, 29.99. IR (KBr, cm^{-1}): 3143, 2966, 2867, 1663, 1607, 1554, 1516, 1459, 1447, 1243, 1156. MS (*m/z*): 395.1. HR–MS (ESI): calcd for $C_{21}H_{20}N_2O_4S$, [M+H]$^+$ *m/z*, 397.1217; found, 397.1208. HPLC purity: 98.194 %.

3-(4-Hydroxyphenyl)-N-*(3-((4-methoxyphenyl)sulfonamido) phenyl)propanamide (**2h**)*

According to the preparation procedure of **2g**, **2h** was prepared as a pale white solid, yield 37.8 %. Mp: 137–139 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.18 (s, 1H), 9.85 (s, 1H), 9.15 (s, 1H), 7.72 (d, J = 8.80 Hz, 2H), 7.45 (s, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.12–7.01 (m, 5H), 6.74 (d, J = 8.2 Hz, 2H), 6.68 (d, J = 8.3 Hz, 1H), 3.80 (s, 3H), 2.80–2.75 (m, 2H), 2.55–2.52 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): 173.62, 158.56, 142.92, 141.65, 134.50, 134.22, 132.17, 132.11, 131.92, 118.12, 117.38, 117.32, 113.47, 58.63, 41.47, 33.09. IR (KBr, cm^{-1}): 3374, 3299, 1656, 1597, 1610, 1553, 1322, 1155. MS (*m/z*): 425.1 ([M+H]$^+$). HR–MS (ESI): calcd for $C_{22}H_{22}N_2O_5S$, [M+H]$^+$ *m/z*, 427.1322; found, 427.1320. HPLC purity: 99.937 %.

3-(4-Hydroxyphenyl)-N-*(3-((4-methylphenyl)sulfonamido) phenyl)propanamide (**2i**)*

According to the preparation procedure of **2g**, **2i** was prepared as a pale white solid, yield 38.4 %. Mp: 145–147 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.20 (s, 1H), 9.88 (s, 1H), 9.17 (s, 1H), 7.70 (d, J = 7.80 Hz, 2H), 7.49 (s, 1H), 7.37 (d, J = 7.3 Hz, 2H), 7.29 (d, J = 7.2 Hz, 1H), 7.16–7.10 (m, 1H), 7.05 (s, J = 7.8 Hz, 2H), 6.77 (s, J = 8.8 Hz, 1H), 6.70 (d, J = 8.1 Hz, 2H), 2.83–2.78 (m, 2H), 2.55–2.53 (m, 2H). 2.37 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): 173.61, 158.52, 146.20, 142.93, 141.22, 139.78, 134.20, 132.64, 132.20, 132.09, 129.77, 118.10, 117.58, 117.33, 113.44,

41.45, 33.07, 23.99. IR (KBr, cm^{-1}): 3374, 3307, 1655, 1610, 1555, 1496, 1323, 1157. MS (*m/z*): 409.1 ($[M+H]^+$). HR–MS (ESI): calcd for $C_{22}H_{22}N_2O_4S$, $[M+H]^+$ *m/z*, 411.1373; found, 411.1371. HPLC purity: 98.213 %.

Computational methods

Preparation of protein structure

The crystal structure of LSD1 resolved with the FAD-*trans*-2-phenylcyclopropylamine adduct was retrieved from the Protein Data Bank (PDB code: 2Z5U) (Mimasu et al., 2010). The complex was cleaned of all water molecules and the remaining structure was prepared using the Prepare Protein utility in Discovery Studio 3.0 (DS 3.0) to fix missing atoms and adding CHARMm force field in a physiological condition (Studio D, 2010). The dielectric constant was set to 10 and ionic strength was set to 0.145. Based on the protonation state of the titratable residues missing hydrogen atoms were added at a pH of 7.4.

Preparing the ligand database

Compounds were sketched in ChemBioDraw14.0 and converted into 3D structures followed by a local minimization using CHARMm force field. The resulting structures were used for the following docking simulations.

CDOCKER docking procedure

The CDOCKER program was utilized as a grid-based dynamics docking algorithm. Ten replicas for each resulting compound was created as a spherical site with a diameter of 16 Å for molecular docking and centered on the FAD-inhibitor adduct. Using the rigid protein and flexible ligand to perform the simulated annealing. Random conformation was set as 10 and related simulated annealing steps were set as 1000. The remaining parameters were left at default. Finally, ten top hit conformations were saved for further analysis.

Biochemical assays

LSD1 screening assay The LSD1 screening biochemical assay was completed by Shanghai ChemPartner Co. Ltd and the detailed protocol was presented as followed. The AlphaLISA assay of LSD1 (BPS Bioscience) was performed in modified Tris buffer (pH 7.5). Briefly, the compounds in DMSO were transferred to assay plate by Echo 550, and then pre-incubated with enzyme (final concentration is 5 nM) for 15 min at room temperature. The reactions were initiated by adding H3K4me2 peptide solution (final concentration is 100 nM) to the reaction mixtures and incubated for 60 min at room temperature. The reactions were terminated by the addition of the acceptor and donor beads mix (PerkinElmer) and incubated for 60 min at room temperature, and then read on EnSpire (PerkinElmer) in Alpha Mode. The reactions without enzyme but all other component served as background. The data was analyzed in GraphPad Prism 5.

MAO-A and MAO-B assays The MAO-A and MAO-B is purchased from Active Motif (Cat#31502, Cat#31503). Biochemical Kit is purchased from Promega (MAO-Glo Assay, V1402). Inhibition assay were carried out according to the manufacturer's protocol. Luminescence is read on Gen5 BioTek Spectrometer and data is processed using GraphPad Prism 5.

Reversibility assay Reversibility was determined using jump dilution analysis. Briefly, Compounds **2a**, **2c** and **2i** at the concentrations of 10× their biochemical IC_{50}s were pre-incuabted with high concentration of LSD1 protein (500 nM) for 15 min, and then diluted 100-fold by H3K4me2 peptide solution. The data was plotted in GraphPad Prism 5.

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Compliance with ethical standards

Conflict of interest F. L. is a shareholder of Constellation Pharmaceuticals Inc. as well as a consultant of Active Motif. The remaining authors declare that they have no conflict of interests.

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