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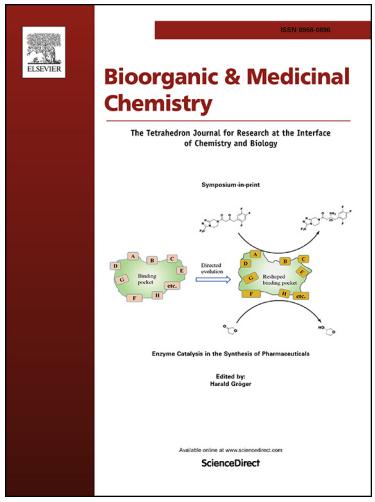

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Design, synthesis and *in vitro* evaluation of stilbene derivatives as novel LSD1 inhibitors for AML therapy

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Abstract

LSD1 is implicated in a number of malignancies and has emerged as an exciting target. As part of our sustained efforts to develop novel reversible LSD1 inhibitors for epigenetic therapy of cancers, in this study, we reported a series of stilbene derivatives and evaluated their LSD1 inhibitory activities, obtaining several compounds as potent LSD1 inhibitors with IC_{50} values in submicromolar range. Enzyme kinetics studies and SPR assay suggested that compound **8c**, the most active LSD1 inhibitor (IC_{50} = 283nM), potently inhibited LSD1 in a reversible and FAD competitive manner. Consistent with the kinetics data, molecular docking showed that compound **8c** can be well docked into the FAD binding site of LSD1. Flow cytometry analysis showed that compound **8c** was capable of up-regulating the expression of the surrogate cellular biomarker CD86 in THP-1 human leukemia cells, suggesting the ability to block LSD1 activity in cells. Compound **8c** showed good inhibition against THP-1 and MOLM-13 cells with IC_{50} values of 5.76 and 8.34 μM, respectively. Moreover, compound **8c** significantly inhibited colony formation of THP-1 cells dose dependently.

Key words: Lysine-specific demethylase 1; AML; stilbene; synthesis

1. Introduction

Lysine-specific histone demethylase 1 (LSD1, also known as KDM1A) was the first histone demethylase identified by the group of Yang Shi in 2004. LSD1 utilizes the flavin adenine dinucleotide (FAD) as a cofactor to specifically demethylate mono- and di-methylated histones H3K4 and H3K9 and serves as a transcriptional repressor or activator depending on the target cell context [1-3]. LSD1 functions as an integral subunit of several protein complexes, such as MLL transcription complex [4, 5], CoREST [3] and NuRD [6], and is involved in a number of cellular processes, including cell proliferation, epithelial-mesenchymal transition (EMT), stem cell biology, and cell differentiation [7, 8]. Furthermore, LSD1 also demethylates several nonhistone substrates including p53 [9], E2F1 [10], DNA methyltransferase1 (DNMT1) [11] and myosin light-chain phosphatase 1 (MYPT1) [12], and further regulates their biological functions and stability. Aberrant expression of LSD1 is believed to be responsible for acute myeloid leukemia (AML) [13, 14], prostate cancer [2, 15], lung cancer [16], estrogen receptor (ER)-negative breast cancer [17], colon cancer [18], and neuroblastoma [19]. Moreover, its high expression is

closely correlated with poor prognosis in several malignancies, such as prostate cancer [15], breast cancer [20] and non-small cell cancer [21]. Notably, more and more evidences support that LSD1 overexpression plays a crucial role in sustaining the self-renewal and oncogenic transcriptional programmes of leukemic stem cells in multiple types of AML [14, 22]. Knockdown of LSD1 or pharmacologic inactivation of LSD1 resulted in induction of differentiation in both murine and primary human MLL-fusion AML cells and inhibited the cell colony growth [14, 23-25]. Co-treatment with LSD1 inhibitors and other agents, including histone deacetylases (HDACs) inhibitor, NEDD8-activating enzyme inhibitor, EZH2 inhibitor and all-trans-retinoic acid, showed promising results and displayed synergistic activity against AML [26-29]. Therefore, inhibition of LSD1 has become an attractive therapeutic target in treating AML as well as other solid tumors [30, 31].

To date, a variety of LSD1 inhibitors with several scaffolds, including tranylcypromine(**1**, **2**) [25, 32], benzohydrazide (**3**) [33, 34], thienopyrrole (**4**) [35], amidoxime (**5**) [36], (4-cyanophenyl)glycine (**6**)[37], pyridine (**7**) [38] and others [39-43], have been reported by different research groups, representatively shown in **Fig. 1**. The most extensively studied and potent LSD1 inhibitors are irreversible, and were mainly derived from tranylcypromine (2-PCPA). Among them, ORY-1001 (**1**) [14, 44, 45], GSK2879552 (**2**) [46], INCB059872 (undisclosed structure) [47] and IMG-7289 (undisclosed structure) [48], four 2-PCPA derivatives, developed by Oryzon Genomics, GSK, Incyte and Imago BioSciences, respectively, are in phase I/II clinical trials for treatment of AML and myelofibrosis. We have previously reported several novel LSD1 inhibitors, including triazole-dithiocarbamate based compounds [49], pyrimidine-thiourea based compounds [41], 2-PCPA based compounds [50] and resveratrol derivatives either [51].

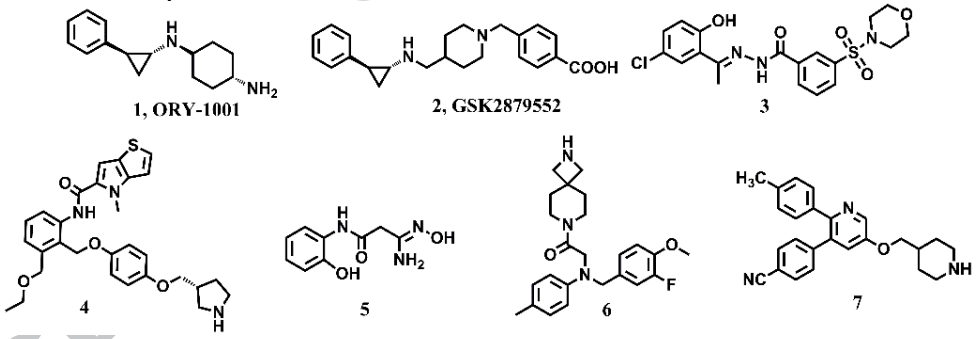


Fig. 1. Representative LSD1 inhibitors described in the literatures

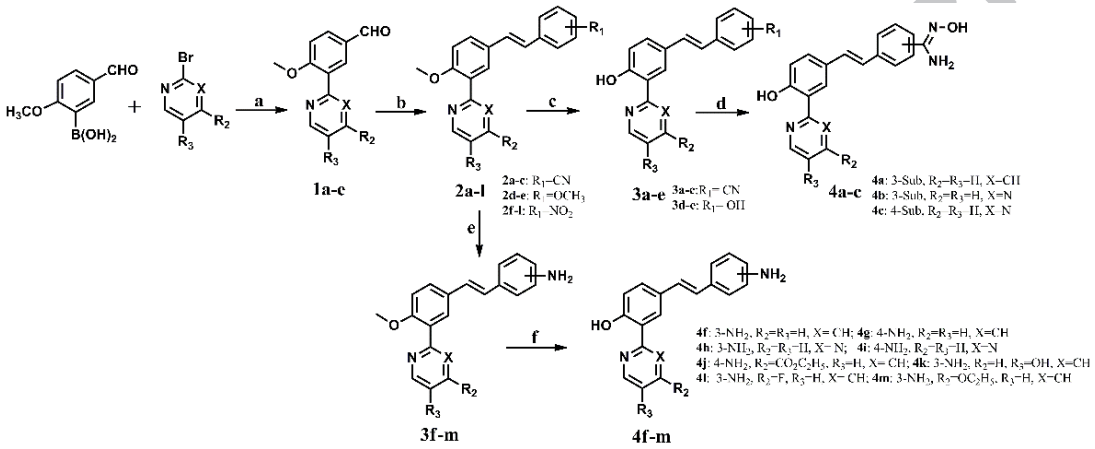
Although several irreversible LSD1 inhibitors have recently entered into clinical trials for the treatment of AML, the development of effective reversible inhibitors has proved more challenging. Extensive interest in the LSD1 in the progression of AML prompted us to identify novel reversible LSD1 inhibitors for AML therapy. Herein, a series of stilbene derivatives designed based on the resveratrol-based LSD1 inhibitors, reported by our group recently [51], were synthesized and evaluated as potent LSD1 inhibitors to treat AML. The results showed that these LSD1 inhibitors possessed moderate to potent activity against AML and deserved further structural modification to find more effective cancer therapeutics.

2. Results and discussion

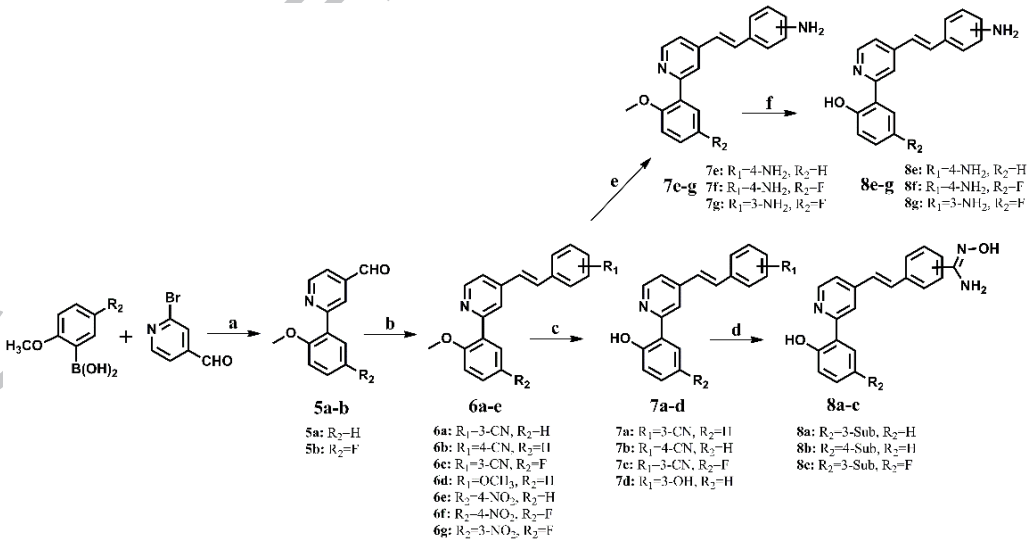
2.1. Chemistry

Compounds **1-4** and **5-8** were synthesized according to the procedures outlined in Schemes 1 and 2. Commercially available boronic acid compounds were reacted with various substituted 2-bromopyridine or 2-bromopyrimidine following Suzuki coupling

reaction procedures, to give compounds **1** and **5**. Compound **1** or **5** was treated with different substituted diethyl benzylphosphonate in dry DMF, in the presence of t-BuOK, to produce the stilbene derivatives **2a-l** and **6a-g**, respectively. Demethylation of **2a-e** or **6a-d** with BBr_3 in dry CH_2Cl_2 provided compounds **3a-e** and **7a-d**, respectively. The reduction of **2f-l** and **6e-g** using stannous chloride in ethyl acetate or ethanol provided amines **3f-m** and **7e-g**, which were then reacted with BBr_3 in dry CH_2Cl_2 to yield **4f-m** and **8e-g**. Compounds **3a-c** and **7a-c** were treated with hydroxylamine in the presence of Et_3N to produce amidoxime compounds **4a-c** and **8a-c**. All of the compounds were confirmed by ^1H NMR, ^{13}C NMR and HRMS (ESI) spectra.



Scheme 1. Synthesis of compounds **1-4**. Reagents and conditions: (a) $Pd(PPh_3)_4$, K_2CO_3, toluene, EtOH, 95℃, 4-6 h; (b) substituted diethyl benzylphosphonate, t-BuOK, dry DMF, 0℃-rt, 0.5-3 h; (c) BBr_3, dry CH_2Cl_2, -35℃-rt, overnight; (d) $NH_2OH{\cdot}HCl$, Et_3N, CH_3OH, reflux, 6h; (e) $SnCl_2$, EtOAc or C_2H_5OH, reflux, 3-6 h; (f) BBr_3, dry CH_2Cl_2, -35℃-rt, overnight.



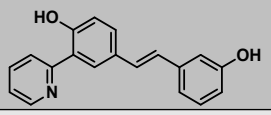
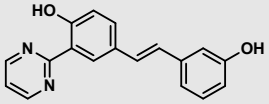
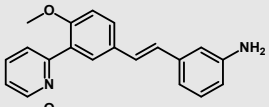
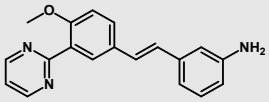
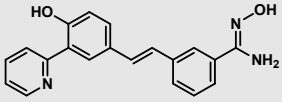
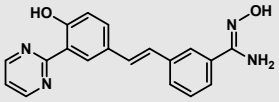
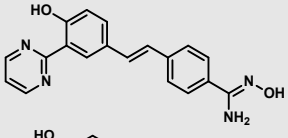
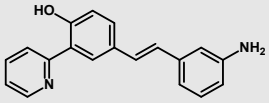
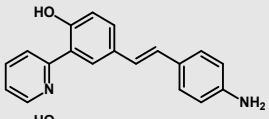
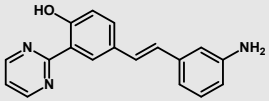
Scheme 2. Synthesis of compounds **5-8**. Reagents and conditions: (a) $Pd(PPh_3)_4$, K_2CO_3, toluene, EtOH, 95℃, 4-6h; (b) substituted diethyl benzylphosphonate, t-BuOK, dry DMF, 0℃-rt, 0.5-3h; (c) BBr_3, dry CH_2Cl_2, -35℃-rt, overnight; (d) $NH_2OH{\cdot}HCl$, Et_3N, CH_3OH, reflux, 6h; (e) $SnCl_2$, C_2H_5OH, reflux, 3-6h; (f) BBr_3, dry CH_2Cl_2, -35℃-rt, overnight.

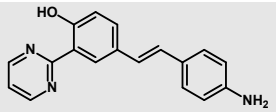
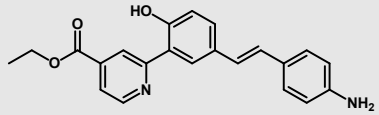
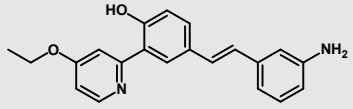
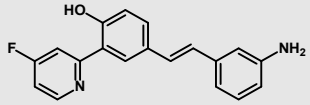
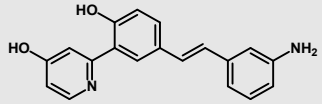
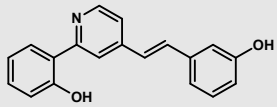
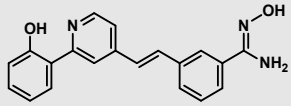
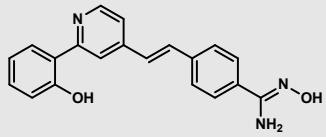
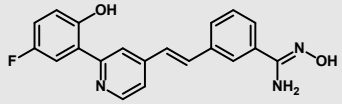
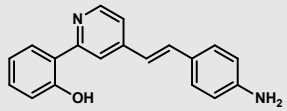
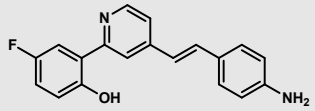
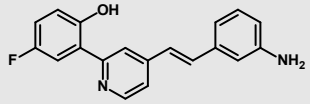
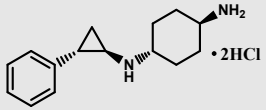
2.2. Enzyme inhibition of target compounds against LSD1

All the target compounds synthesized in this study were investigated for their inhibitory activities against LSD1 in a biochemical *in vitro* assay that was previously

described [51]. **ORY-1001** was used as a positive control. The data are summarized in **Table 1**. Apparently, most of the tested compounds possessed a reasonable inhibitory potency against LSD1 with the exception of compounds **3f, 3h**, **4i** and **8f**. Among them, compounds **4a-4h** and **8a-e** showed single-digit or submicromolar IC_{50} values, and compound **8c** was found most active against LSD1 with an IC_{50} value of 283 nM. These results demonstrated that the target compounds were novel highly potent LSD1 inhibitors. Compounds **4f** and **4h**, with a amino group, retained anti-LSD1 activities comparable to that of **4a** and **4b**, but hydroxy substitution (**3d**, **3e** and **7d)** resulted in a dramatical decrease in activity, thus revealing that the amidoxime or amino moiety in the benzene ring were preferable. Introducing different substituents in pyridine ring (**4j-4m**) generally gave remarkable reduced activity compared with compounds **4f-4g**, showing substituents at this position is not favorable. The amino or amidoxime moiety located at the *meta* position on the benzene ring resulted in the best activity: compounds **4f**, **4h** and **8a** were more potent against LSD1 than the corresponding *para*-substituted derivatives. Compounds bearing a methoxy group at the 2-position of the arylbenzene moiety (**3f** and **3h**) exhibited no activities against LSD1 compared with compounds **4f** and **4h**, indicating the significance of the hydroxy group in retaining their activities.

Table 1 Inhibitory Activity (IC_{50} or percentage of inhibition at 10 μM) against LSD1

Compounds Structures		LSD1 $IC_{50(}\mu M)^a$	Inhibition % at 10μM
3d		4.24 ± 0.89	85.09%
3e		N.T.[b]	20.18%
3f		N.T.	N.I.[c]
3h		N.T.	N.I.
4a		0.72 ± 0.12	97.84%
4b		1.29 ± 0.07	87.50%
4c		0.92 ± 0.04	94.29%
4f		0.301 ± 0.03	98.37%
4g		3.57 ± 0.31	94.32%
4h		0.859 ± 0.07	97.66%

4i		9.55 ± 1.01	51.31%
4j		N.T.	35.43%
4k		N.T.	43.89%
4l		N.T.	30.28%
4m		1.47 ± 0.24	89.30%
7d		N.T.	31.63%
8a		0.364 ± 0.03	97.69%
8b		0.764 ± 0.03	97.57%
8c		0.283 ± 0.02	99.23%
8e		2.96 ± 0.74	94.80%
8f		9.03 ± 0.66	54.14%
8g		11.78 ± 1.09	50.11%
ORY-1001		11.26 ± 0.72 (nM)	N.T.

[a] IC_{50} values are expressed as mean ± SD from at least three independent experiments.
[b] N.T.: Not tested.
[c] N.I.: No Inhibition.

The inhibitory effects of four selected compounds (**4a**, **4f**, **8a** and **8c**) against LSD1's homologies MAO-A and MAO-B were also tested to assess their selectivity, clorgyline and R-(-)-deprenyl were chosen as positive control for MAO-A and MAO-B, respectively. As shown in **Table 2**, the selected four compounds demonstrated excellent selectivity for LSD1 over both MAO-A and MAO-B (IC_{50} >50μM).

Table 2 *In vitro* Inhibition of LSD1, MAO-A and MAO-B of selected compounds

Compounds	IC_{50}(μM)

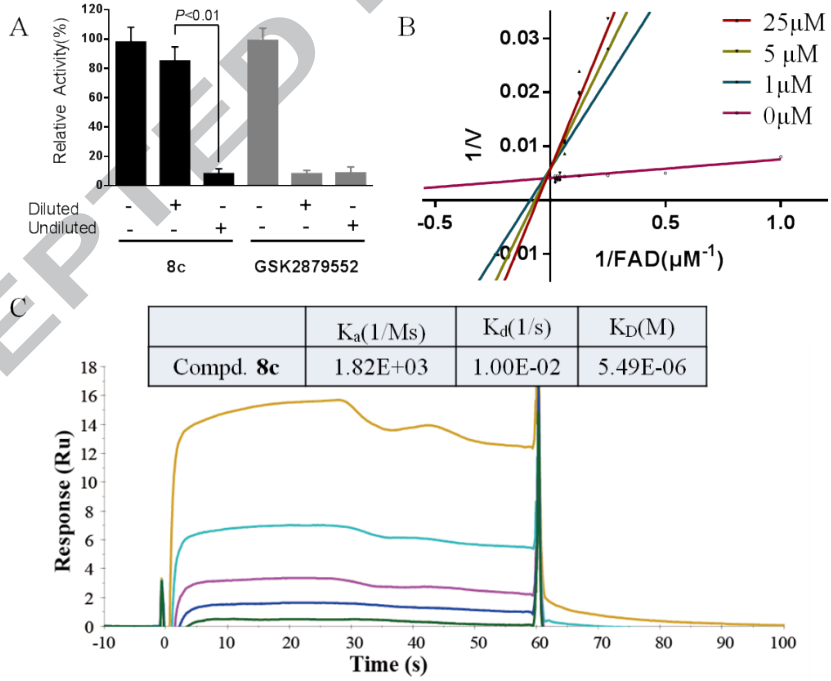
	LSD1	MAO-A	MAO-B
4a	0.72 ± 0.12	>50	>50
4f	0.301 ± 0.03	>50	>50
8a	0.364 ± 0.03	>50	>50
8c	0.283 ± 0.02	>50	>50
Clorgyline	[b]N.D.	[a]0.0031	N.D.
R(-)-deprenyl	N.D.	N.D.	[a]0.071

[a] Values are the mean of two experiments.

[b] N.D.: Not detected

2.3. Enzyme Kinetics Studies

As shown in Table 1, compound **8c** is the most potent LSD1 inhibitor we have obtained. Furthermore, the reversibility of compound **8c** against LSD1 was also investigated using the dilution assay. As shown in **Fig. 2A**, 80-fold dilution of the LSD1/compound **8c** complex resulted in more than 80% recovery of LSD1 activity, while the positive control GSK2879552 failed to recover the activity of LSD1. These results indicated that compound **8c** may interact with LSD1 in a reversible manner. Additionally, with classic Lineweaver-Burk plots, compound **8c** was characterized as a cofactor (FAD) competitive inhibitor over LSD1 (**Fig. 2B**), which suggests that compound **8c** may penetrate into the cavity of LSD1 where FAD stands in order to inactivate LSD1. Compound **8c** was tested by the surface plasmon resonance (SPR), where the binding response increased with the increasing concentration (**Fig. 2C**), suggesting the tight binding between compound **8c** and LSD1 ($K_D = 5.49\times10^{-6}$M) is in a manner of reversible model with fast association ($K_a = 1.82\times10^{3}\ M^{-1}\cdot s^{-1}$) and slow dissociation ($K_d = 1.02\times10^{-2}\ s^{-1}$). Consistent with the dilute assay, these results indicate that compound **8c** is a potent and reversible LSD1inhibitor.



	K_a(1/Ms)	K_d(1/s)	K_D(M)
Compd. **8c**	1.82E+03	1.00E-02	5.49E-06

Fig. 2. Inhibitory effect of compound **8c** on LSD1 activity *in vitro*. (A) The reversibility of compound **8c** toward LSD1 activity was determined by the dilution assay, GSK2879552 was used a control; (B) Lineweaver-Burk plots demonstrated that compound **8c** was competitive with cofactor FAD; (C) SPR based sensorgram of compound **8c**. Bars represent means ± SD of three independent experiments.

2.4. In vitro antiproliferative assay

The synthesized compounds **4a**, **4f**, **8a** and **8c**, with the most potent LSD-

inhibitory activities, were evaluated for antiproliferative activities against three human acute monocytic leukemia cell lines MOLM-13, THP-1 and MV-4-11 *in vitro,* **ORY-1001** was used as a positive control. Data showed that all the four compounds showed medium to good anti-proliferative activity with IC_{50} values ranging from 4.71 μM to 22.59 μM (**Table 3**). Compound **8c** with the highest LSD1 enzyme inhibitory potency exhibited the best antiproliferative activity against MOLM-13 and THP-1 with IC_{50} values of 5.76-8.34 μM. Compound **4a** showed fairly good antiproliferative activity against MV-4-11 with an IC_{50} value of 4.71 μM, which is more potent than compound **8c** (IC_{50} of 7.49 μM). Overall, these antitumor activities suggested that this class of LSD1 inhibitors could be potentially useful cancer therapeutics and further structural modification is therefore warranted.

Table 3 *In vitro* antiproliferative activity of selected compounds in three cancer cell lines

Compounds	IC_{50}(μM)[a]		
	MOLM-13	THP-1	MV-4-11
4a	22.59 ± 2.33	7.89 ± 0.71	4.71 ± 0.89
4f	12.51 ± 1.06	10.51 ± 1.44	10.94 ± 2.03
8a	9.05 ±0.99	13.72 ± 1.08	15.85 ± 1.52
8c	8.34 ± 0.64	5.76 ± 0.55	7.49 ± 1.17
ORY-1001	N.D.[b]	> 20 μM	N.D.

[a] IC_{50} values are expressed as mean ± SD from at least three independent experiments.
[b] N.D.: Not detected

*2.5. Cellular Activity of Compound **8c***

To further evaluate the cellular activity of compound **8c**, we evaluated whether LSD1 inhibitors may alter the colony-forming capacity of THP-1 cells with soft agar assay. As indicated in **Fig. 3A**, treatment of compound **8c** for 14 days significantly inhibited colony formation of THP-1 cells does dependently. As B7-2 (CD86), one of type I transmembrane proteins that was originally identified as a ligand for CD28/CTLA-4, is a bona fide cellular biomarker of LSD1 activity [52], THP-1 cells were treated with compound **8c** at different concentrations to evaluate its effect on membrane expression of CD86 with flow cytometry. As indicated in **Fig. 3B**, increased expression of CD86 was observed, suggesting that compound **8c** may inactivate LSD1 in the cellular level.

To further determine whether target compounds are cell-active LSD1 inhibitors, the effects of selected compound **8c** on the methylation levels of LSD1 substrates H3K4me1 and H3K4me2 were analyzed. After treatment of THP-1 cells for 5 days with compound **8c** at different concentrations (0, 1.25, 2.5 and 5.0 M), the amounts of H3K4me1 and H3K4me2 were dose dependently elevated, which supported the target engagement of compound **8c** in THP-1 cells (**Fig. 3C**).

In addition, hematoxylin and eosin stain (HE stain) was applied to monitor the cellular morphology. After 3 days incubation with compound **8c** at indicated concentrations, characteristic morphological changes were identified by microscope, including blurred cell membrane boundaries and chromatin shrinkage with dose dependently manner (**Fig. 3D**).

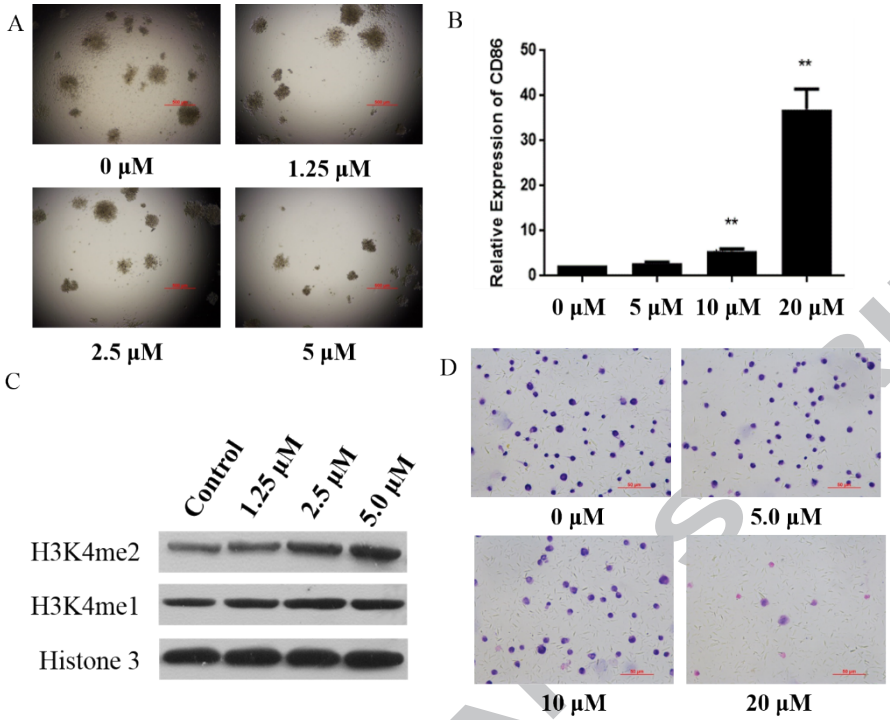


Fig. 3. Cellular activity of compound **8c** in THP-1 cells. (A) Representative images of THP-1 cells after treatment with DMSO and compound **8c** for 14 days; (B) Flow cytometry analysis of the expression of CD86 in THP-1 cells with indicated treatment for 3 days; (C) Western blot analysis of the effect of histone methylation in THP-1 cells with indicated treatment for 5 days; (D) HE staining of THP-1 cells treated as indication for 3 days. Bars represent means ± SD of three independent experiments; $^{**}p < 0.01$, compared to control.

2.6. Molecular docking

To explore the binding mode of compound **8c** and LSD1 and explain the observed biological activity of compound **8c**, molecular docking study was performed using the software MOE 2015.10. In this study, the crystal structure of LSD1 (PDB ID: 2V1D) was selected as the docking receptor, which contains a free cofactor FAD, a substrate of H3K4 mimetic peptide, and a corepressor of CoREST. Based on the structural similarity of compound **8c** with the compounds reported in the literatures[36], [51], the position occupied by the cofactor FAD was selected as the docking site.

As displayed in **Fig. 4**, compound **8c** can well docked into the FAD-binding site of LSD1. The amine of the amidoxime moiety formed a hydrogen bond with the carbonyl group of the backbone of Thr624 and an electrostatic interaction with the O^- of Glu801, respectively, meanwhile its imine nitrogen atom formed a hydrogen bond with the carbonyl group of the backbone of Glu801. Additionally, the phenyl group connecting with the amidoxime formed arene-H interaction with Val288. The phenyl group connecting with the pyridine ring was found to be situated in a hydrophobic cavity surrounded by Gly330, Tyr761, Leu329, Trp751, Lys661, Leu659 and Trp810, and formed arene-H interaction with Trp751. The hydrogen bonds, arene-H, electrostatic and hydrophobic interactions made the compound **8c** bind steadily to LSD1.

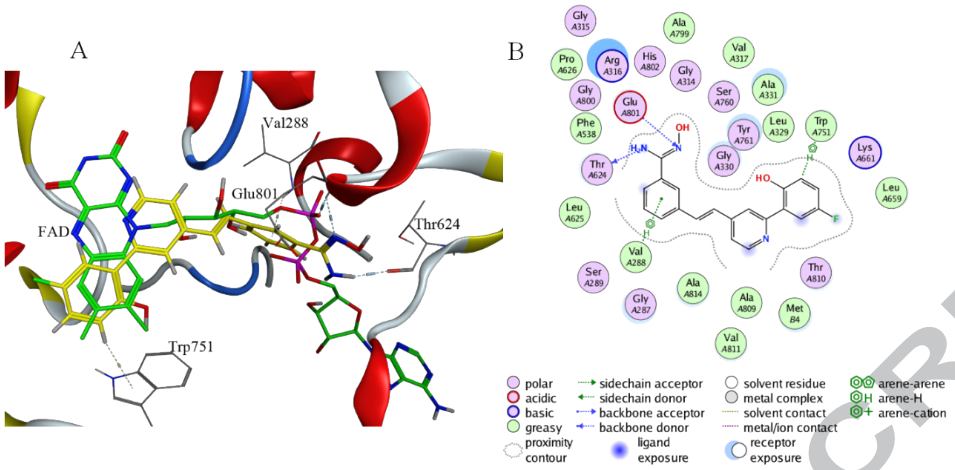


Fig. 4. Docking results of compound **8c** in the FAD-binding site of LSD1 (PDB ID: 2V1D). (A) Interactions between compound **8c** and the residues of LSD1 and FAD. Compound **8c** and FAD are shown as yellow and green sticks, respectively; the associated residues are shown as gray lines, and hydrogen bonds are shown as gray dash lines. (B) Two-dimensional schematics of the protein-ligand interaction of compound **8c** to LSD1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3. Conclusions

In summary, a series of novel stilbene derivatives were synthesized and identified as LSD1 inhibitors. Most of these compounds were evaluated as robust inhibitors against LSD1 recombinant. Especially compound **8c**, the most potent inhibitor, performed excellent LSD1 inhibition activity (IC_{50} = 283 nM). Dilution assay and SPR study indicated that compound **8c** bound to LSD1 in a manner of reversible model with fast association and slow dissociation. Enzyme kinetics study and molecular docking suggested that compound **8c** maybe a competitive inhibitor against the LSD1 cofactor FAD. Treatment of THP-1 cells with compound **8c** lead to the increasing of CD86 dose dependently, showing target engagement activity in cells. Compound **8c** demonstrated good antiproliferative activities against THP-1 and MOLM-13 human leukemia cells with IC_{50} values of 5.76 and 8.34μM, respectively. Furthermore, compound **8c** was able to inhibit the colony formation in THP-1 cells in a concentration-dependent manner. Encouraged by the interesting biological data of this stilbene-based reversible LSD1 inhibitors, further structural optimization is going on.

4. Experimental section

4.1. Chemistry

4.1.1. General procedures

Reagents and solvents were obtained from commercial sources, when necessary, were purified and dried by standard methods. Melting points were determined on an X-5 micromelting apparatus and are uncorrected. All compounds were characterized by ^{1}H NMR and ^{13}C NMR spectra on a Bruker Avance III HD 400 MHz and 100 MHz spectrometer at room temperature respectively, with chemical shifts in parts per million (δ) downfield from TMS, the internal standard. Spin multiplicities were described as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), br (broad signal), or m (multiplet). Coupling constants were reported in hertz (Hz). ESI-HRMS were recorded on a Bruker MicrOTOF-Q III Micro mass spectrometer.

4.1.2. General procedure for synthesis of compounds **1** *and* **5**.

To a 50 mL two-necked flask equipped with magnetic stirrer and condenser was added 2-bromopyridine (1.0 eq), $Pd(PPh_3)_4$ (5mol%), K_2CO_3 solution (2.0 eq) and toluene under N_2 at room temperture. After reacted for 15 minutes, a solution of the boronic acid (1.2 eq) in EtOH was then added. The reaction mixture was then heated to 95℃ and reacted for 4 hours. After cooling to room temperature, to the reaction mixture aqueous NH_4Cl was added and extracted three times with EtOAc. The organic extracts were then combined, washed with brine, dried with $MgSO_4$ and then concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography (Petroleum ether/EtOAc) to give compounds **1** and **5**.

*4.1.2.1. 4-methoxy-3-(pyridin-2-yl)benzaldehyde (***1a***)*

White solid, yield: 87.5%, Mp:52-54℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 8.74-8.72 (m, 1H), 8.31 (d, 1H, J = 2.4 Hz), 7.96 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 7.78-7.87 (m, 1H), 7.75 (td, 1H, J_1 = 1.6 Hz, J_2 = 7.2 Hz), 7.25-7.28 (m, 1H), 7.13 (d, 1H, J = 8.4 Hz), 3.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.99, 161.71, 154.63, 149.58, 135.94, 134.21, 131.15, 130.02, 129.55, 125.03, 122.33, 111.59, 56.05. HRMS (ESI) calcd for $C_{13}H_{12}NO_2$ $[M + H]^+$: 214.0863, Found: 214.0870.

*4.1.2.2. 4-methoxy-3-(pyrimidin-2-yl)benzaldehyde (***1b***)*

White solid, yield: 87.1%, Mp:80-82℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.88 (d, 2H, J = 4.8 Hz), 8.26 (d, 1H, J = 2.4 Hz), 8.00 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.29 (t, 1H, J = 4.8 Hz), 7.16 (d, 1H, J = 8.8 Hz), 3.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.61, 164.71, 162.41, 157.17, 134.47, 132.52, 129.64, 128.77, 119.23, 112.05, 56.44. HRMS (ESI) calcd for $C_{12}H_{10}N_2NaO_2$ $[M + Na]^+$: 237.0634, Found: 237.0639.

*4.1.2.3. 3-(4-fluoropyridin-2-yl)-4-methoxybenzaldehyde(***1c***)*

White solid, yield 77.1%, Mp: 73-75℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 8.70 (dd, 1H, J_1= 5.6 Hz, J_2 = 8.8 Hz), 8.39 (t, 1H, J = 2.0 Hz), 7.98 (dd, 1H, J_1= 1.2 Hz, J_2 = 8.8 Hz), 7.63 (d, 1H, J = 10.4 Hz), 7.16 (d, 1H, J = 8.4 Hz), 7.05-7.01 (m, 1H), 3.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.88, 168.57 (d, $J_{C,F}$ = 259.4 Hz), 161.69, 157.33 (d, $J_{C,F}$ = 8.2 Hz), 151.58 (d, $J_{C,F}$ = 7.4 Hz), 134.23, 131.67, 130.04, 128.12 (d, $J_{C,F}$ = 3.4 Hz), 112.96 (d, $J_{C,F}$ = 18.4 Hz), 111.74, 110.33 (d, $J_{C,F}$ = 16.6 Hz), 56.11. HRMS (ESI) calcd for $C_{13}H_{10}FNNaO_2$ $[M + Na]^+$: 254.0588, Found: 254.0582 .

*4.1.2.4. methyl 2-(5-formyl-2-methoxyphenyl)isonicotinate (***1d***)*

White solid, yield: 70.1%, Mp:117-118℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 8.84 (d, 1H, J = 4.8 Hz), 8.38 (s, 1H), 8.33 (d, 1H, J = 2.4 Hz), 7.97 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 7.80 (dd, 1H, J_1 = 2.0 Hz, J_2 = 4.8 Hz), 7.14 (d, 1H, J = 8.4 Hz), 3.98 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.86, 165.84, 161.79, 155.77, 150.30, 137.39, 134.10, 131.69, 130.08, 128.78, 124.33, 121.41, 111.68, 56.18, 52.79. HRMS (ESI) calcd for $C_{15}H_{13}NNaO_4$ $[M + Na]^+$: 294.0737, Found: 294.0741.

*4.1.2.5. 4-methoxy-3-(5-methoxypyridin-2-yl)benzaldehyde (***1e***)*

White solid, yield: 69.3%, Mp: 91-92℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 8.43 (d, 1H, J = 2.8 Hz), 8.31 (d, 1H, J = 2.0 Hz), 7.93 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.8 Hz), 7.79 (d, 1H, J = 8.8 Hz), 7.29-7.25 (m,1H), 7.12 (d, 1H, J = 8.8 Hz), 3.97 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.12, 161.54, 154.73, 146.94, 137.17, 133.93, 130.57, 130.06, 129.29, 125.22, 120.36, 111.53, 56.03, 55.68. HRMS (ESI) calcd for $C_{15}H_{12}NNaO_2$ $[M + Na]^+$: 266.0788, Found: 266.0790.

*4.1.2.6. 2-(2-methoxyphenyl)isonicotinaldehyde(***5a***)*

White solid, yield: 73.6%, Mp: 51-53℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.93 (d, 1H, J = 4.8 Hz), 8.27 (t, 1H, J_1 = 1.2 Hz), 7.84 (dd, 1H, J_1 = 2.0 Hz, J_2 = 7.6 Hz), 7.61 (dd, 1H, J_1 = 1.2 Hz, J_2 = 4.8 Hz), 7.45-7.39 (m, 1H), 7.11 (td, 1H, J_1 = 1.2

Hz, J_2 = 7.6 Hz), 7.04 (dd, 1H, J_1 = 0.8 Hz, J_2 = 8.4 Hz), 3.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.15, 157.86, 157.07, 150.62, 141.48, 131.16, 130.75, 127.80, 124.57, 121.18, 119.51, 111.41, 55.64. HRMS (ESI) calcd for $C_{13}H_{12}NO_2$ $[M+H]^+$: 214.0863, Found: 214.0866.

*4.1.2.7. 2-(5-fluoro-2-methoxyphenyl)isonicotinaldehyde(***5b***)*

Yellowish solid, yield: 83.4%, Mp: 72-74℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.93 (dd, 1H, J_1 = 1.2 Hz, J_2 = 4.8 Hz), 8.34 (t, 1H, J = 1.2 Hz), 7.67-7.63 (m, 2H), 7.13-7.08 (m, 1H), 6.97 (dd, 1H, J_1 = 4.4 Hz, J_2 = 8.8 Hz), 3.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.88, 156.90 (d, $J_{C,F}$ = 237.6 Hz), 156.47 (d, $J_{C,F}$ = 2.0 Hz), 153.37 (d, $J_{C,F}$ = 2.1 Hz), 150.68, 141.63, 128.84 (d, $J_{C,F}$ = 7.2 Hz), 124.31, 120.07, 117.58 (d, $J_{C,F}$ = 24.5 Hz), 116.73 (d, $J_{C,F}$ = 22.9 Hz), 112.61 (d, $J_{C,F}$ = 8.0 Hz), 56.24. HRMS (ESI) calcd for $C_{13}H_{11}FNO_2$ $[M+H]^+$: 232.0768, Found: 232.0770.

4.1.3. General procedure for synthesis of compounds **2** *and* **6**.

To a solution of t-BuOK (3.0 equiv) in dry DMF was added a substituted diethyl benzylphosphonate (1.1 eq). After the mixture was stirred at 0℃ under nitrogen for 0.5 h, compound **1** or **5** (1.0 eq) in dry DMF was added dropwise to the solution. The reaction mixture was warmed to room temperature and stirred for 0.5-2 h. Ice-water was added, and the precipitate was filtered to afford the crude product. Purification of the crude product by recrystallization from ethyl acetate or by silica gel column chromatography provided the target products **2** and **6**.

*4.1.3.1. (E)-3-(4-methoxy-3-(pyridin-2-yl)styryl)benzonitrile(***2a***)*

Colorless oil, yield: 57.8%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (ddd, 1H, J_1 = 0.8 Hz, J_2 =1.6 Hz, J_3 = 4.8 Hz), 7.99 (d, 1H, J = 2.4 Hz), 7.85 (dt, 1H, J_1 = 1.2 Hz, J_2 =8.0 Hz), 7.75-7.67 (m, 3H), 7.53-7.48 (m, 2H), 7.43 (t, 1H, J = 8.0 Hz), 7.26-7.23 (m, 1H), 7.16 (d, 1H, J = 16.4 Hz),7.04-6.99 (m, 2H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.21, 155.56, 149.51, 138.95, 135.78, 130.61, 130.32, 130.30, 129.65, 129.44, 128.65, 125.22, 124.58, 122.00, 118.93, 112.84, 111.68, 55.80. HRMS (ESI) calcd for $C_{21}H_{16}N_2NaO$ $[M + Na]^+$: 335.1155, Found: 335.1151.

*4.1.3.2. (E)-3-(4-methoxy-3-(pyrimidin-2-yl)styryl)benzonitrile (***2b***)*

Colorless oil, yield: 58.6%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, 2H, J = 4.8 Hz), 7.93 (d, 1H, J = 2.4 Hz), 7.74 (t, 1H, J = 1.6 Hz), 7.69 (dt, 1H, J_1 = 1.6 Hz, J_2 = 8.0 Hz), 7.58 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 7.50 (dt, 1H, J_1 = 1.6 Hz, J_2 = 7.6 Hz), 7.45 (t, 1H, J = 7.6 Hz), 7.27 (t, 1H, J = 4.8 Hz), 7.15 (d, 1H, J = 16.4 Hz), 7.06 (d, 1H, J = 8.8 Hz), 7.02 (d, 1H, J = 16.4 Hz), 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.54, 157.86, 157.09, 138.84, 130.38, 130.36, 130.29, 130.06, 129.71, 129.67, 129.44, 129.14, 128.64, 124.73, 118.92, 118.88, 112.87, 112.22, 56.26. HRMS (ESI) calcd for $C_{20}H_{15}N_3NaO$ $[M + Na]^+$: 336.1107, Found: 336.1100.

*4.1.3.3. (E)-4-(4-methoxy-3-(pyrimidin-2-yl)styryl)benzonitrile (***2c***)*

White solid, yield: 60.3%, Mp:142-144℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, 2H, J = 4.8 Hz), 7.94 (t, 1H, J = 2.0 Hz), 7.63-7.53 (m, 5H), 7.29-7.18 (m, 2H), 7.08-7.00 (m, 2H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.52, 158.04, 157.11, 142.13, 132.49, 131.50, 130.25, 129.85, 129.09, 128.70, 126.63, 125.27, 119.15, 118.94, 112.25, 110.17, 56.26. HRMS (ESI) calcd for $C_{20}H_{15}N_3NaO$ $[M + Na]^+$: 336.1107, Found: 336.1108.

*4.1.3.4. (E)-2-(2-methoxy-5-(3-methoxystyryl)phenyl)pyridine(***2d***)*

Colorless oil, yield: 54.2%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75-8.72 (m, 1H), 7.96 (d, 1H, J = 2.4 Hz), 7.83 (dt, 1H, J_1 = 1.2 Hz, J_2 = 8.0 Hz), 7.72 (td, 1H, J_1 = 2.0 Hz, J_2 = 8.0 Hz), 7.51 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.28-7.21 (m, 2H), 7.13 (d, 1H, J = 16.4 Hz), 7.08-6.98 (m, 4H), 6.79 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.0 Hz), 3.88 (s, 3H), 3.84

(s, 3H) .^{13}C NMR (101 MHz, $CDCl_3$) δ 159.88, 156.68, 155.85, 149.49, 139.15, 135.72, 130.35, 129.61, 129.30, 128.34, 128.17, 127.00, 125.21, 121.88, 119.06, 113.05, 111.65, 111.42, 55.79, 55.24. HRMS (ESI) calcd for $C_{21}H_{19}NNaO_2$ [M + Na]$^+$:340.1308, Found :340.1314.

*4.1.3.5. (E)-2-(2-methoxy-5-(3-methoxystyryl)phenyl)pyrimidine(***2e***)*

Colorless oil, yield: 83.8%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, 2H, J = 4.8 Hz), 7.91 (d, 1H, J = 2.4 Hz), 7.57 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 7.28-7.23 (m, 2H), 7.11 (d, 1H, J = 16.4 Hz), 7.08 (d, 1H, J = 7.2 Hz), 7.05-7.00 (m, 3H), 6.80 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 3.90 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.74, 159.88, 157.33, 157.07, 139.04, 130.06, 129.89, 129.62, 129.32, 128.47, 128.09, 127.17, 119.06, 118.82, 113.06, 112.17, 111.49, 56.23, 55.24. HRMS (ESI) calcd for $C_{20}H_{18}N_2NaO_2$ [M + Na]$^+$: 341.1260, Found: 341.1266.

*4.1.3.6. (E)-2-(2-methoxy-5-(3-nitrostyryl)phenyl)pyridine (***2f***)*

Yellow solid, yield: 67.5%, Mp:108-110℃ .^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76-8.73 (m, 1H), 8.34 (t, 1H, J = 2.0 Hz), 8.08-8.05 (m, 1H), 8.02 (d, 1H, J = 2.0 Hz), 7.86 (dt, 1H, J_1 =1.2 Hz, J_2 = 8.0 Hz), 7.78-7.71 (m, 2H), 7.54 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 7.50 (t, 1H, J = 8.0 Hz), 7.27-7.23 (m, 2H), 7.10 (d, 1H, J =16.4 Hz), 7.03 (d, 1H, J = 8.4 Hz), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.29, 155.55, 149.53, 148.75, 139.54, 135.76, 132.02, 131.07, 129.52, 129.49, 129.46, 129.38, 128.72, 125.19, 124.50, 121.99, 121.63, 120.66, 111.71, 55.81. HRMS (ESI) calcd for $C_{20}H_{17}N_2O_3$ [M + H]$^+$: 333.1234, Found: 333.1242.

*4.1.3.7. (E)-2-(2-methoxy-5-(4-nitrostyryl)phenyl)pyridine (***2g***)*

Yellow solid, yield: 93.3%, Mp: 82-84℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75-8.73 (m, 1H), 8.20 (d, 2H, J = 8.8 Hz), 8.03 (d, 1H, J = 2.0 Hz), 7.86 (dt, 1H, J_1 = 1.2 Hz, J_2 = 8.0 Hz), 7.74 (td, 1H, J_1 = 2.0 Hz, J_2 = 8.0 Hz), 7.60 (d, 2H, J = 8.8 Hz), 7.55 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.31-7.24 (m, 2H), 7.11 (d, 1H, J = 16.4 Hz), 7.03 (d, 1H, J = 8.4 Hz), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.53, 155.42, 149.51, 146.43, 144.29, 135.79, 132.70, 129.75, 129.48, 129.28, 128.94, 126.55, 125.21, 124.66, 124.17, 122.05, 111.71, 55.81. HRMS (ESI) calcd for $C_{20}H_{17}N_2O_3$ [M + H]$^+$: 333.1234, Found: 333.1238.

*4.1.3.8. (E)-2-(2-methoxy-5-(3-nitrostyryl)phenyl)pyrimidine (***2h***)*

Yellow solid, yield: 52.2%, Mp:130-132℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, 2H, J = 4.8 Hz), 8.34 (t, 1H, J = 2.0 Hz), 8.08-8.05 (m, 1H), 7.96 (d, 1H, J = 2.4 Hz), 7.76 (dt, 1H, J_1 = 1.6 Hz, J_2 = 7.6 Hz), 7.60 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.50 (t, 1H, J = 8.0 Hz), 7.27 (t, 1H, J = 4.8 Hz), 7.24 (d, 1H, J = 16.4 Hz), 7.10-7.05 (m, 2H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.55, 157.95, 157.11, 148.75, 139.43, 132.01, 130.82, 130.13, 129.80, 129.53, 129.07, 128.68, 124.65, 121.70, 120.69, 118.93, 112.26, 56.27. HRMS (ESI) calcd for $C_{19}H_{15}N_3NaO_3$ [M + Na]$^+$: 356.1006, Found: 356.1004.

*4.1.3.9. (E)-2-(2-methoxy-5-(4-nitrostyryl)phenyl)pyrimidine(***2i***)*

Yellow solid, yield: 87.1%, Mp:174-176℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, 2H, J = 4.8 Hz), 8.22 (d, 2H, J = 8.8 Hz), 7.98 (d, 1H, J = 2.0 Hz), 7.64-7.60 (m, 3H), 7.31-7.28 (m, 2H), 7.10 (d, 1H, J = 16.8 Hz), 7.09 (d, 1H, J = 8.4 Hz), 3.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.47, 158.21, 157.13, 146.50, 144.18, 132.43, 130.38, 130.02, 128.98, 128.73, 126.59, 124.82, 124.18, 118.97, 112.26, 56.27. HRMS (ESI) calcd for $C_{19}H_{16}N_3O_3$ [M + H]$^+$: 334.1186, Found: 334.1188.

*4.1.3.10. (E)-methyl 2-(2-methoxy-5-(4-nitrostyryl)phenyl)isonicotinate (***2j***)*

Yellow solid, yield: 42.0%, Mp:193-195℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, 1H, J = 4.8 Hz), 8.42 (t, 1H, J = 1.2 Hz), 8.21 (d, 2H, J = 8.8 Hz), 8.04 (d, 1H, J = 2.0 Hz), 7.80 (dd, 1H, J_1 = 1.2 Hz, J_2 = 4.8 Hz), 7.62-7.56 (m, 3H), 7.31-7.27 (m, 1H), 7.11 (d,

1H, *J* = 16.4 Hz), 7.06 (d, 1H, *J* = 8.8 Hz), 3.99 (s, 3H), 3.94 (s, 3H). HRMS (ESI) calcd for $C_{22}H_{18}N_2NaO_5$ $[M + Na]^+$: 413.1108, Found: 413.1111.

*4.1.3.11. (E)-5-methoxy-2-(2-methoxy-5-(3-nitrostyryl)phenyl)pyridine(***2k***)*

Yellow solid, yield: 58.4%, Mp:142-144℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, 1H, *J* = 2.8 Hz), 8.33 (t, 1H, *J* = 2.0 Hz), 8.07-8.04 (m, 1H), 8.00 (d, 1H, *J* =2.4 Hz), 7.82 (dd, 1H, J_1 = 0.8 Hz, J_2 = 8.4 Hz), 7.76 (dt, 1H, J_1 = 1.2 Hz, J_2 = 8.0 Hz), 7.51 -7.47 (m, 2H), 7.27-7.22 (m, 2H), 7.09 (d, 1H, *J* = 16.4 Hz), 7.01 (d, 1H, *J* = 8.4 Hz), 3.92 (s, 3H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.12, 154.54, 148.74, 147.89, 139.58, 137.01, 132.01, 131.19, 129.50, 129.34, 129.19, 129.12, 128.14, 125.36, 124.36, 121.58, 120.64, 120.35, 111.66, 55.80, 55.68. HRMS (ESI) calcd for $C_{21}H_{19}N_2O_4$ $[M + H]^+$: 363.1339, Found: 363.1339.

*4.1.3.12. (E)-4-fluoro-2-(2-methoxy-5-(3-nitrostyryl)phenyl)pyridine(***2l***)*

Yellow solid, yield: 82.8%, Mp:97-98℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (dd, 1H, J_1 = 5.6 Hz, J_2 = 9.2 Hz), 8.36 (t, 1H, *J* = 2.0 Hz), 8.12 (d, 1H, *J* = 2.4 Hz), 8.10-8.06 (m, 1H), 7.78 (dt, 1H, J_1 = 1.2 Hz, J_2 = 8.0 Hz), 7.70 (dd, 1H, J_1 = 2.8 Hz, J_2 = 10.8 Hz), 7.57 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.52 (t, 1H, *J* = 8.0 Hz), 7.24 (d, 1H, *J* = 16.4 Hz), 7.09 (d, 1H, *J* = 16.4 Hz), 7.03 (d, 1H, *J* = 8.8 Hz), 7.01-6.98 (m, 1H), 3.93 (s, 3H). HRMS (ESI) calcd for $C_{20}H_{16}FN_2O_3$ $[M + H]^+$: 351.1139, Found: 351.1142.

*4.1.3.13. (E)-3-(2-(2-(2-methoxyphenyl)pyridin-4-yl)vinyl)benzonitrile(***6a***)*

White solid, yield: 88.3%, Mp: 90-92℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (dd, 1H, J_1 = 0.8 Hz, J_2 = 5.2 Hz), 7.87 (t, 1H, *J* = 1.2 Hz), 7.82 (t, 1H, *J* = 2.0 Hz), 7.77 (d, 1H, *J* = 1.6 Hz), 7.75 (d, 1H, *J* = 1.6 Hz), 7.59 (dt, 1H, J_1 = 1.6 Hz, J_2 = 8.0 Hz), 7.49 (t, 1H, *J* = 8.0 Hz), 7.42-7.37 (m, 1H), 7.32 (dd, 1H, J_1 = 1.6 Hz, J_2 = 5.2 Hz), 7.27 (d, 1H, *J* = 16.4 Hz), 7.15-7.07 (m, 2H), 7.03 (dd, 1H, J_1 = 1.2 Hz, J_2 = 8.0 Hz), 3.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.93, 156.90, 149.81, 143.42, 137.66, 131.62, 131.18, 131.02, 130.33, 130.29, 130.18, 129.68, 129.34, 128.81, 122.90, 121.10, 118.78, 118.56, 113.17, 111.44, 55.74. HRMS (ESI) calcd for $C_{21}H_{17}N_2O$ $[M + H]^+$: 313.1335, Found: 313.1337.

*4.1.3.14. (E)-4-(2-(2-(2-methoxyphenyl)pyridin-4-yl)vinyl)benzonitrile(***6b***)*

White solid, yield: 59.2%, Mp:120-122℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, 1H, J_1 = 0.8 Hz, J_2 = 5.2 Hz), 7.88 (t, 1H, *J* = 0.8 Hz), 7.77 (dd, 1H, J_1 = 1.6 Hz, J_2 = 7.6 Hz), 7.67 (d, 2H, *J* = 8.4 Hz), 7.63 (d, 2H, *J* = 8.4 Hz), 7.42-7.37 (m, 1H), 7.33-7.27 (m, 2H), 7.18 (d, 1H, *J* = 16.4 Hz), 7.10 (td, 1H, J_1 = 1.2 Hz, J_2 = 7.6 Hz), 7.03 (dd, 1H, J_1 = 1.2 Hz, J_2 = 8.4 Hz), 3.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.98, 156.91, 149.91, 143.24, 140.80, 132.60, 131.16, 130.71, 130.38, 130.17, 128.88, 127.39, 122.91, 121.11, 118.79, 111.61, 111.44, 55.75. HRMS (ESI) calcd for $C_{21}H_{17}N_2O$ $[M + H]^+$: 313.1335, Found: 313.1338.

*4.1.3.15. (E)-3-(2-(2-(5-fluoro-2-methoxyphenyl)pyridin-4-yl)vinyl)benzonitrile (***6c***)*

White solid, yield: 80.3%, Mp:185-187℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, 1H, *J* = 5.2 Hz), 7.93 (t, 1H, *J* = 1.2 Hz), 7.83 (t, 1H, *J* = 1.6 Hz), 7.77 (dt, 1H, J_1 = 1.6 Hz, J_2 = 8.0 Hz), 7.61-7.55 (m, 2H), 7.50 (t, 1H, *J* = 7.6 Hz), 7.34 (dd, 1H, J_1 = 2.0 Hz, J_2 = 5.2 Hz), 7.27 (d, 1H, *J* =16.4 Hz), 7.13 (d, 1H, *J* = 16.0 Hz), 7.11-7.05 (m, 1H), 6.96 (dd, 1H, J_1 = 4.4 Hz, J_2 = 8.8 Hz), 3.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.33 (d, $J_{C,F}$ = 237.5 Hz), 155.58 (d, $J_{C,F}$ = 1.9 Hz), 153.20 (d, $J_{C,F}$ = 2.1 Hz), 149.96, 143.56, 137.58, 131.69, 131.04, 130.44, 130.34, 130.04 (d, $J_{C,F}$ = 7.4 Hz), 129.70, 129.18, 122.77, 119.18, 118.55, 117.75 (d, $J_{C,F}$ = 24.1 Hz), 116.08 (d, $J_{C,F}$ = 22.8 Hz), 113.18, 112.68 (d, $J_{C,F}$ = 8.0 Hz), 56.40. HRMS (ESI) calcd for $C_{21}H_{16}FN_2O$ $[M + H]^+$: 331.1241, Found: 331.1241.

*4.1.3.16. (E)-2-(2-methoxyphenyl)-4-(3-methoxystyryl)pyridine (***6d***)*

Colorless oil, yield: 82.5%.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, 1H, *J* = 5.2 Hz),

7.84 (t, 1H, J = 1.2 Hz), 7.75 (dd, 1H, J_1 = 1.6 Hz, J_2 = 7.6 Hz), 7.40-7.35 (m, 1H), 7.32-7.25 (m, 3H), 7.14 (dt, 1H, J_1 = 1.2 Hz, J_2 = 7.6 Hz), 7.11-7.04 (m, 3H), 7.06 (d, 1H, J =8.4 Hz), 6.87 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.0 Hz), 3.87 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 159.96, 156.95, 156.78, 149.73, 144.29, 137.83, 132.70, 131.17, 129.98, 129.83, 129.23, 126.98, 122.69, 121.06, 119.72, 118.75, 114.24, 112.25, 111.44, 55.75, 55.33. HRMS (ESI) calcd for $C_{21}H_{19}NNaO_2$ [M + Na]$^+$: 340.1308, Found: 340.1305.

*4.1.3.17. (E)-2-(2-methoxyphenyl)-4-(4-nitrostyryl)pyridine (***6e***)*

White solid, yield: 70.7%, Mp:116-118℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, 1H, J = 5.2 Hz), 8.25 (d, 2H, J = 8.4 Hz), 7.90 (d, 1H, J = 1.6 Hz), 7.78 (dd, 1H, J_1 = 2.0 Hz, J_2 = 6.4 Hz), 7.69 (d, 2H, J = 8.4 Hz), 7.42-7.33 (m, 3H), 7.24 (d, 1H, J = 16.4 Hz), 7.10 (t, 1H, J = 7.2 Hz), 7.03 (d, 1H, J = 8.0 Hz), 3.90 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 157.05, 156.93, 149.96, 147.40, 143.13, 142.76, 131.23, 131.17, 130.26, 130.21, 128.84, 127.49, 124.22, 122.99, 121.13, 118.83, 111.45, 55.76. HRMS (ESI) calcd for $C_{20}H_{17}N_2O_3$ [M + H] $^+$: 333.1234, Found: 333.1233.

*4.1.3.18. (E)-2-(5-fluoro-2-methoxyphenyl)-4-(4-nitrostyryl)pyridine (***6f***)*

Yellowish solid, yield: 63.1%, Mp:140-142℃.^{1}H NMR (400 MHz,$CDCl_3$) δ 8.71 (d, 1H, J = 5.2 Hz), 8.26 (d, 2H, J = 8.8 Hz), 7.96 (d, 1H, J = 1.6 Hz), 7.70 (d, 2H, J = 8.8 Hz), 7.58 (dd, 1H, J_1 = 3.2 Hz, J_2 = 9.6 Hz), 7.38-7.34 (m, 2H), 7.24 (d, 1H, J = 16.4 Hz), 7.11-7.06 (m, 1H), 6.97 (dd, 1H, J_1 = 4.4 Hz, J_2 = 9.2 Hz), 3.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.36 (d, $J_{C,F}$ = 237.5 Hz), 155.70 (d, $J_{C,F}$ = 1.7 Hz), 153.22 (d, $J_{C,F}$ = 2.1 Hz), 150.01, 147.46, 143.37, 142.65, 131.02, 130.49, 130.00 (d, $J_{C,F}$ = 7.2 Hz), 127.52, 124.23, 122.89, 119.27, 117.67 (d, $J_{C,F}$ = 24.3 Hz), 116.16 (d, $J_{C,F}$ = 22.8 Hz), 112.74 (d, $J_{C,F}$ = 8.0 Hz), 56.42. HRMS (ESI) calcd for $C_{20}H_{15}FN_2NaO_3$ [M + Na]$^+$: 373.0959, Found: 373.0959.

*4.1.3.19. (E)-2-(5-fluoro-2-methoxyphenyl)-4-(3-nitrostyryl)pyridine (***6g***)*

Yellow solid, yield: 52.8%. Mp:133-135℃. ^{1}H NMR (400 MHz,$CDCl_3$) δ 8.70 (d, 1H, J = 5.2 Hz), 8.42 (t, 1H, J = 2.0 Hz), 8.18-8.15 (m, 1H), 7.96 (t, 1H, J = 1.2 Hz), 7.85 (dt, 1H, J_1 = 1.2 Hz, J_2 = 8.0 Hz), 7.60-7.55 (m, 2H), 7.39-7.33 (m, 2H),7.22 (d, 1H, J = 16.4 Hz), 7.11-7.06 (m, 1H), 6.97 (dd, 1H, J_1 = 4.4 Hz, J_2 = 9.2 Hz), 3.89 (s, 3H). HRMS (ESI) calcd for $C_{20}H_{16}FN_2O_3$ [M + H]$^+$: 351.1139, Found: 351.1140.

4.1.4. General procedure for synthesis of compounds **3a-e** *and* **7a-d**.

To a solution of compounds **2a-e** or **6a-d** (1.0 equiv) in dry CH_2Cl_2 was added BBr_3 (6.0 equiv) in dry CH_2Cl_2 dropwise at -35℃ under nitrogen. The resulting mixture was allowed to warm to room temperature and stirred overnight. The solution was poured into ice-water, and a precipitate was formed and collected by filtration to provide the crude product, which was purified by flash column chromatography on silica gel.

*4.1.4.1. (E)-3-(4-hydroxy-3-(pyridin-2-yl)styryl)benzonitrile(***3a***)*

Yellow solid, yield: 56.5%, Mp:116-118℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.36 (s, 1H), 8.67-8.65 (m, 1H), 8.34 (d, 1H, J = 8.4 Hz), 8.30 (d, 1H, J = 2.0 Hz), 8.10 (td, 1H, J_1 = 2.0 Hz, J_2 = 8.0 Hz), 8.04 (t, 1H, J = 2.0 Hz), 7.89 (dt, 1H, J_1 = 1.2 Hz, J_2 = 8.0 Hz), 7.70 (dt, 1H, J_1 = 1.2 Hz, J_2 = 7.6 Hz), 7.62-7.57 (m, 2H), 7.50-7.47 (m, 1H), 7.44 (d, 1H, J = 16.4 Hz), 7.28 (d, 1H, J = 16.4 Hz), 6.98 (d, 1H, J = 8.4 Hz).^{13}C NMR (101MHz, DMSO-d_6) δ 159.92, 156.95, 146.79, 139.43, 139.17, 131.19, 131.12, 130.74, 130.42, 130.22, 129.76, 128.07, 126.25, 124.24, 123.03, 120.46, 119.43, 119.34, 118.92, 112.35. HRMS (ESI) calcd for $C_{20}H_{15}N_2O$ [M + H]$^+$: 299.1179, Found: 299.1179.

*4.1.4.2. (E)-3-(4-hydroxy-3-(pyrimidin-2-yl)styryl)benzonitrile (***3b***)*

Yellow solid, yield: 50.6%, Mp: 141-143℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.42 (s, 1H), 9.02 (d, 2H, J = 5.2 Hz), 8.64 (d, 1H, J = 2.4 Hz), 8.11 (t, 1H, J = 1.6 Hz), 7.94 (dt, 1H, J_1 = 1.6 Hz, J_2 = 8.0 Hz), 7.75 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.68 (dt, 1H, J_1 = 1.2 Hz, J_2 = 7.6 Hz), 7.59-7.54 (m, 2H), 7.51 (d, 1H, J = 16.4 Hz), 7.18 (d, 1H, J = 16.4 Hz), 7.04 (d, 1H, J = 8.4 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.90, 160.66, 157.50, 139.26, 131.64, 131.28, 131.02, 130.80, 130.31, 129.98, 128.24, 128.03, 124.43, 120.15, 119.34, 118.90, 118.83, 112.29. HRMS (ESI) calcd for $C_{19}H_{13}N_3NaO$ $[M + Na]^+$: 322.0951, Found: 322.0952.

*4.1.4.3. (E)-4-(4-hydroxy-3-(pyrimidin-2-yl)styryl)benzonitrile (***3c***)*

Yellow solid, yield: 66.3%, Mp:199-200℃.^{1}H NMR (400 MHz, DMSO-d_6) δ 13.28 (s, 1H), 8.85 (d, 2H, J = 4.8 Hz), 8.69 (d, 1H, J = 2.0 Hz), 7.65-7.57 (m, 5H), 7.31-7.24 (m, 2H), 7.08 (d, 1H, J = 8.4 Hz), 7.07 (d, 1H, J = 16.4 Hz).^{13}C NMR (101 MHz, DMSO-d_6) δ 164.79, 161.21, 156.24, 142.29, 132.49, 131.96, 131.53, 128.17, 127.69, 126.57, 124.54, 119.21, 118.78, 118.76, 118.69, 110.02. HRMS (ESI) calcd for $C_{19}H_{13}N_3NaO$ $[M + Na]^+$: 322.0951, Found: 322.0946.

*4.1.4.4. (E)-4-(3-hydroxystyryl)-2-(pyridin-2-yl)phenol(***3d***)*

Yellow solid, yield: 54.1%, Mp:168-169℃.^{1}H NMR (400 MHz, DMSO-d_6) δ 14.35 (s, 1H), 9.44 (s, 1H), 8.66-8.64 (m, 1H), 8.37 (d, 1H, J = 8.4 Hz), 8.26 (d, 1H, J = 2.0 Hz), 8.08 (td, 1H, J_1 = 1.6 Hz, J_2 = 8.4 Hz), 7.60 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.4 Hz), 7.48 (dd, 1H, J_1 = 5.2 Hz, J_2 = 6.8 Hz), 7.20-7.15 (m, 3H), 7.02 (dt, 1H, J_1 = 1.2 Hz, J_2 = 8.0 Hz), 6.98 (t, 1H, J = 2.0 Hz), 6.96 (d, 1H, J = 8.4 Hz), 6.68 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.0 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.45, 158.09, 157.12, 146.69, 139.30, 139.13, 130.08, 129.88, 128.61, 128.34, 126.67, 125.85, 122.93, 120.52, 119.26, 118.81, 117.65, 114.85, 113.17. HRMS (ESI) calcd for $C_{19}H_{16}NO_2$ $[M + H]^+$: 290.1176, Found: 290.1176.

*4.1.4.5. (E)-4-(3-hydroxystyryl)-2-(pyrimidin-2-yl)phenol (***3e***)*

Yellow solid, yield: 62.7%, Mp: 217-219℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.35 (s, 1H), 9.41 (s, 1H), 9.01 (d, 2H, J = 4.8 Hz), 8.58 (d, 1H, J = 2.4 Hz), 7.74 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 7.57 (t, 1H, J = 4.8 Hz), 7.21(d, 1H, J = 16.4 Hz), 7.16 (t, 1H, J = 8.0 Hz), 7.07-6.98 (m, 4H), 6.68 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.0 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.03, 160.20, 158.06, 157.51, 139.09, 131.50, 130.03, 128.78, 128.16, 127.45, 126.95, 120.08, 118.76, 117.76, 114.93, 113.39. HRMS (ESI) calcd for $C_{18}H_{14}N_2NaO_2$ $[M + Na]^+$: 313.0947, Found : 313.0950.

*4.1.4.6. (E)-3-(2-(2-(2-hydroxyphenyl)pyridin-4-yl)vinyl)benzonitrile (***7a***)*

White solid, yield: 83.8%, Mp:178-179℃.^{1}H NMR (400 MHz, $CDCl_3$) δ 14.27 (s, 1H), 8.49 (d, 1H, J = 5.2 Hz), 7.95 (t, 1H, J = 1.2 Hz), 7.88-7.84 (m, 2H), 7.79 (dt, 1H, J_1 = 1.6 Hz, J_2 = 8.0 Hz), 7.62 (dt, 1H, J_1 = 1.6 Hz, J_2 = 8.0 Hz), 7.53 (t, 1H, J =7.6 Hz), 7.36-7.30 (m, 3H), 7.15 (d, 1H, J = 16.4 Hz), 7.04 (dd, 1H, J_1 = 1.2 Hz, J_2 = 8.4 Hz), 6.96-6.92 (m, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 160.15, 158.51, 146.32, 145.37, 137.23, 132.01, 131.72, 131.49, 131.12, 130.46, 129.80, 128.59, 126.07, 118.85, 118.74, 118.72, 118.45, 116.84, 113.31. HRMS (ESI) calcd for $C_{20}H_{15}N_2O$ $[M + H]^+$: 299.1179, Found: 299.1180.

*4.1.4.7. (E)-4-(2-(2-(2-hydroxyphenyl)pyridin-4-yl)vinyl)benzonitrile(***7b***)*

White solid, yield: 67.1%, Mp:189-190℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.19 (s, 1H), 8.63 (d, 1H, J = 5.2 Hz), 8.43 (s, 1H), 8.13 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.0 Hz), 7.92 (d, 2H, J = 8.4 Hz), 7.88-7.83 (m, 3H), 7.65 (dd, 1H, J_1 = 1.2 Hz, J_2 = 5.2 Hz), 7.57 (d, 1H, J = 16.8 Hz), 7.36-7.31 (m, 1H), 6.99-6.92 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.77, 157.88, 147.14, 146.37, 141.25, 133.29, 133.03, 131.97, 129.94, 128.26,

127.43, 120.10, 119.29, 119.27, 119.24, 118.43, 117.56, 111.20. HRMS (ESI) calcd for $C_{20}H_{14}N_2NaO$ $[M + Na]^+$: 321.0998, Found: 321.0999.

*4.1.4.8. (E)-3-(2-(2-(5-fluoro-2-hydroxyphenyl)pyridin-4-yl)vinyl)benzonitrile(***7c***)*

White solid, yield: 48.3%, Mp:184-185℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.99 (s, 1H), 8.63 (d, 1H, J = 5.2 Hz), 8.44 (s, 1H), 8.16 (t, 1H, J = 1.6 Hz), 8.02-7.97 (m, 2H), 7.86-7.81 (m, 2H), 7.64 (t, 1H, J = 8.0 Hz), 7.61 (dd, 1H, J_1 = 1.2 Hz, J_2 = 5.2 Hz), 7.52 (d, 1H, J = 16.8 Hz), 7.22-7.17 (m, 1H), 6.95 (dd, 1H, J_1 = 5.2 Hz, J_2 = 9.2 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.65 (d, $J_{C,F}$ = 2.8 Hz), 155.97 (d, $J_{C,F}$ = 1.1 Hz), 155.66 (d, $J_{C,F}$ = 231.5 Hz), 147.37, 146.70, 137.90, 132.82, 132.50, 132.24, 130.86, 130.67, 128.62, 120.84, 119.73 (d, $J_{C,F}$ = 7.4 Hz), 119.53 (d, $J_{C,F}$ = 9.9 Hz), 119.07, 118.70 (d, $J_{C,F}$ = 23 Hz), 117.56, 113.16 (d, $J_{C,F}$ = 24.3 Hz), 112.57. HRMS (ESI) calcd for $C_{20}H_{13}FN_2NaO$ $[M + Na]^+$: 339.0904, Found: 339.0903.

*4.1.4.9. (E)-2-(4-(3-hydroxystyryl)pyridin-2-yl)phenol (***7d***)*

Yellow solid, yield: 74.8%, Mp:169-170℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.36 (s, 1H), 9.60 (s, 1H), 8.57 (d, 1H, J = 5.2 Hz), 8.40 (s, 1H), 8.16 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.0 Hz), 7.70 (d, 1H, J = 16.4 Hz), 7.63 (dd, 1H, J_1 = 1.2 Hz, J_2 = 5.6 Hz), 7.35-7.23 (m, 3H), 7.13 (d, 1H, J = 7.6 Hz), 7.08 (t, 1H, J = 2.0 Hz), 6.98-6.92 (m, 2H), 6.79 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.0 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.88, 158.21, 157.79, 147.18, 146.84, 137.89, 135.06, 131.87, 130.34, 127.45, 126.03, 119.76, 119.25, 119.20, 118.67, 118.40, 117.21, 116.61, 114.19. HRMS (ESI) calcd for $C_{19}H_{15}NNaO_2$ $[M + Na]^+$: 312.0995, Found: 312.0998.

4.1.5. General procedure for synthesis of compounds **3f-m** *and* **7e-g**.

To a suspension of compounds **2f-l** or **6e-g** (1.0 equiv) in EtOH or EtOAc was added $SnCl_2{\cdot}2H_2O$ (5.0 eq) and heated to reflux for 4-6 h under N_2. The ethanol was evaporated under vacuum. The residue was dissolved in ethyl acetate, neutralised with $NaHCO_3$ and extracted three times with EtOAc. The organic extracts were then combined, washed with brine, dried with anhydrous Na_2SO_4 and then concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography to give **3f-m** and **7e-g**. Notably, If compound **2l** was reduced in ethanol, the fluorine atom will be substituted by an ethoxyl group to give compound **3m**, while reduced in EtOAC, the fluorine atom will be retained to give compound **3l**.

4.1.5.1. (E)-3-(4-methoxy-3-(pyridin-2-yl)styryl)aniline (**3f**)

Yellow solid, yield: 50.3%, Mp:133-135℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (dt, 1H, J_1 =1.2 Hz, J_2 = 4.8 Hz), 7.90 (d, 1H, J = 2.4 Hz), 7.84-7.82 (m, 2H), 7.62 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.4 Hz), 7.36-7.32 (m, 1H), 7.16 (d, 1H, J = 8.4 Hz), 7.10 (d, 1H, J = 16.4 Hz), 7.00 (t, 1H, J =8.0 Hz), 6.97 (d, 1H, J = 16.4 Hz), 6.77-6.74 (m, 2H), 6.49-6.45 (m, 1H), 5.06 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.73, 155.48, 149.81, 149.28, 138.17, 136.40, 130.31, 129.57, 129.09, 129.03, 128.52, 127.93, 127.24, 125.31, 122.58, 114.90, 113.92, 112.74, 112.02, 56.25. HRMS (ESI) calcd for $C_{20}H_{18}N_2NaO_2$ $[M + Na]^+$: 325.1311, Found: 325.1318.

4.1.5.2. (E)-4-(4-methoxy-3-(pyridin-2-yl)styryl)aniline (**3g**)

Yellow solid, yield: 42.3%, Mp:148-150℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (dt, 1H, J_1 =1.2 Hz, J_2 = 4.8 Hz), 7.92 (d, 1H, J = 2.4 Hz), 7.85 (d, 1H, J = 8.0 Hz), 7.75 (td, 1H, J_1 = 2.0 Hz, J_2 = 7.6 Hz), 7.50 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.34 (d, 2H, J = 8.4Hz,), 7.26 (m, 1H), 7.03-6.99 (m, 2H), 6.95 (d, 1H, J = 16.4 Hz), 6.69 (d, 2H, J = 8.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.10, 155.95, 149.28, 145.82, 135.83, 131.13, 129.02, 128.81, 128.39, 127.69, 127.50, 127.21, 125.23, 124.45, 121.80, 115.24, 111.66, 55.81. HRMS (ESI) calcd for $C_{20}H_{19}N_2O$ $[M + H]^+$: 303.1492, Found: 303.1494.

4.1.5.3. (E)-3-(4-methoxy-3-(pyrimidin-2-yl)styryl)aniline (**3h**)

Yellowish solid, yield: 49.4%, Mp: 160-162℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (d, 2H, J = 4.8 Hz), 7.75 (d, 1H, J = 2.4 Hz), 7.66 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.47 (t, 1H, J = 4.8 Hz), 7.16 (d, 1H, J = 8.8 Hz), 7.08 (d, 1H, J = 16.4 Hz), 7.03-6.96 (m, 2H), 6.76-6.73 (m, 2H), 6.49-6.46 (m, 1H), 5.05 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.53, 157.67, 157.18, 149.28, 138.15, 129.95, 129.57, 129.34, 129.27, 129.23, 128.08, 126.98, 119.91, 114.89, 113.94, 112.95, 112.01, 56.27. HRMS (ESI) calcd for $C_{20}H_{18}N_2NaO_2$ [M + Na]$^+$: 326.1264, Found: 326.1266.

4.1.5.4. (E)-4-(4-methoxy-3-(pyrimidin-2-yl)styryl)aniline (**3i**)

Yellow solid, yield: 69.6%, Mp: 199-200℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (d, 2H, J = 4.8 Hz), 7.68 (d, 1H, J = 2.0 Hz), 7.58 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.8 Hz), 7.46 (t, 1H, J = 4.8 Hz), 7.26 (d, 2H, J = 8.4 Hz), 7.13 (d, 1H, J = 8.8 Hz), 6.97 (d, 1H, J_1 = 16.4 Hz), 6.90 (d, 1H, J_1 = 16.4 Hz), 6.55 (d, 2H, J = 8.4 Hz), 5.26 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.65, 157.65, 156.54, 148.93, 130.77, 129.22, 128.71, 128.49, 127.95, 127.85, 125.44, 122.48, 119.86, 114.37, 112.97, 56.26. HRMS (ESI) calcd for $C_{20}H_{18}N_2NaO_2$ [M + Na]$^+$: 326.1264, Found: 326.1269.

4.1.5.5. (E)-ethyl 2-(5-(4-aminostyryl)-2-methoxyphenyl)isonicotinate (**3j**)

Yellow solid, yield: 40.3%, Mp:123-125℃.^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (d, 1H, J = 4.8 Hz), 8.29 (t, 1H, J = 1.2 Hz), 7.88 (d, 1H, J = 2.4 Hz), 7.76 (dd, 1H, J_1 = 1.6 Hz, J_2 = 5.2 Hz), 7.58 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 7.26 (d, 2H, J = 8.4 Hz), 7.16 (d, 1H, J = 8.4 Hz), 6.96 (d, 1H, J = 16.4 Hz), 6.91 (d, 1H, J = 16.4 Hz), 6.54 (d, 2H, J = 8.4 Hz), 5.26 (s, 2H), 4.37 (q, 2H, J = 7.2 Hz), 3.85 (s, 3H), 1.33 (t, 3H, J = 7.2 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.29, 156.73, 156.12, 150.95, 148.97, 137.48, 131.31, 128.43, 128.38, 128.04, 127.88, 125.40, 123.89, 122.57, 121.13, 114.36, 112.91, 62.08, 56.35, 31.17, 14.49. HRMS (ESI) calcd for $C_{22}H_{20}N_2NaO_3$ [M+Na]$^+$: 397.1523, Found: 397.1528.

4.1.5.6. (E)-3-(4-methoxy-3-(5-methoxypyridin-2-yl)styryl)aniline (**3k**)

Yellowish solid, yield: 64.2%, Mp: 110-112℃.^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, 1H, J = 2.8 Hz), 7.90 (d, 1H, J = 2.4 Hz), 7.83 (d, 1H, J = 8.8 Hz), 7.57 (dd, 1H, J_1= 2.0 Hz, J_2 = 8.4 Hz), 7.44 (dd, 1H, J_1 = 2.8 Hz, J_2 = 8.4 Hz), 7.13 (d, 1H, J = 8.4 Hz), 7.09 (d, 1H, J = 16.4 Hz), 6.98 (t, 1H, J = 8.0 Hz), 6.96 (d, 1H, J = 16.4 Hz), 6.77-6.74 (m, 1H), 6.74 (d, 1H, J = 7.2 Hz), 6.49-6.46 (m, 1H), 5.05 (s, 2H), 3.88 (s, 3H) , 3.85 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.53, 154.70, 149.29, 147.64, 138.19, 137.38, 130.25, 129.57, 128.78, 128.68, 127.88, 127.79, 127.36, 125.59, 120.75, 114.88, 113.89, 112.68, 112.02, 56.22, 56.07. HRMS (ESI) calcd for $C_{21}H_{20}N_2NaO_2$ [M + Na]$^+$: 355.1417, Found: 355.1416.

4.1.5.7. (E)-3-(3-(4-fluoropyridin-2-yl)-4-methoxystyryl)aniline (**3l**)

White solid, yield: 69.4%, Mp:173-174℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (dd, 1H, J_1 =5.6 Hz, J_2 = 9.2 Hz), 7.99 (d, 1H, J = 2.4 Hz), 7.74 (dd, 1H, J_1 = 2.4 Hz, J_2 = 11.2 Hz) , 7.66 (d, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.33-7.28 (m, 1H), 7.19 (d, 1H, J = 8.8 Hz), 7.10 (d, 1H, J = 16.8 Hz), 7.03-6.96 (m, 2H), 6.77-6.74 (m, 2H), 6.49-6.46 (m, 1H), 5.06 (s, 2H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.28 (d, $J_{C,F}$ = 256 Hz), 158.39 (d, $J_{C,F}$ = 7.8 Hz), 156.83, 152.38 (d, $J_{C,F}$ = 7.4 Hz), 149.29, 138.12, 130.35, 129.58, 129.14, 129.02, 128.14, 127.64 (d, $J_{C,F}$ = 3.4 Hz), 127.08, 114.91, 113.97, 112.88, 112.63 (d, $J_{C,F}$ = 17.9 Hz), 112.06, 110.43 (d, $J_{C,F}$ = 16.4 Hz), 56.37. HRMS (ESI) calcd for $C_{20}H_{17}FN_2NaO$ [M + Na]$^+$: 343.1217, Found: 343.1218.

4.1.5.8. (E)-3-(3-(4-ethoxypyridin-2-yl)-4-methoxystyryl)aniline (**3m**)

Yellow solid, yield: 53.6%, Mp: 88-90℃.^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, 1H, J = 5.6 Hz), 7.93 (d, 1H, J = 2.4 Hz), 7.61 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.4 Hz) , 7.37 (d, 1H, J = 2.8 Hz), 7.15 (d, 1H, J = 8.8 Hz), 7.09 (d, 1H, J = 16.4 Hz), 7.00 (t, 1H, J = 7.6 Hz), 6.97 (d, 1H, J = 16.4 Hz), 6.93 (dd, 1H, J_1 = 2.8 Hz, J_2 = 5.6 Hz), 6.77-6.74

(m, 2H), 6.49-6.46 (m, 1H), 5.06 (s, 2H), 4.15 (q, 2H, J = 6.8 Hz), 3.86 (s, 3H), 1.37 (t, 3H, J = 6.8 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.67, 156.81, 156.71, 150.95, 149.29, 138.17, 130.18, 129.57, 129.05, 128.94, 128.47, 127.89, 127.25, 114.88, 113.91, 112.74, 112.02, 111.83, 108.99, 63.80, 56.26, 14.79. HRMS (ESI) calcd for $C_{22}H_{22}N_2NaO_2$ [M + Na] $^+$: 369.1573, Found: 369.1575.

4.1.5.9. (E)-4-(2-(2-(2-methoxyphenyl)pyridin-4-yl)vinyl)aniline(**7e**)

Yellow solid, yield: 68.6%, Mp: 142-144℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, 1H, J = 5.2 Hz), 7.78 (s, 1H), 7.72 (dd, 1H, J_1 = 1.6 Hz, J_2 = 7.6 Hz), 7.40-7.35 (m, 3H), 7.27-7.25 (m, 1H), 7.23 (d, 1H, J = 16.0 Hz), 7.07 (t, 1H, J = 7.6 Hz), 7.01 (d, 1H, J = 8.4 Hz), 6.87 (d, 1H, J = 16.0 Hz), 6.67 (d, 2H, J = 8.4 Hz), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.93, 156.56, 149.52, 147.13, 145.16, 132.90, 131.16, 129.85, 129.40, 128.45, 126.88, 122.69, 122.30, 121.00, 118.45, 115.13, 111.41, 55.75. HRMS (ESI) calcd for $C_{20}H_{19}N_2O$ [M + H]$^+$: 303.1492, Found: 303.1497.

4.1.5.10. (E)-4-(2-(2-(5-fluoro-2-methoxyphenyl)pyridin-4-yl)vinyl)aniline (**7f**)

Yellow solid, yield: 60.3%, Mp: 152-154℃.^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, 1H, J = 5.2 Hz), 7.90 (s, 1H), 7.54 (dd, 1H, J_1 = 3.2 Hz, J_2 = 10.0 Hz), 7.45 (dd, 1H, J_1 = 1.2 Hz, J_2 = 5.2 Hz), 7.38-7.34 (m, 3H), 7.28-7.22 (m, 1H), 7.20-7.16 (m, 1H), 6.93 (d, 1H, J = 16.0 Hz), 6.58 (d, 2H, J = 8.8 Hz), 5.51 (s, 2H), 3.86 (s, 3H) . ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.82 (d, $J_{C,F}$ = 234.5 Hz), 154.72 (d, $J_{C,F}$ = 1.6 Hz), 153.69 (d, $J_{C,F}$ = 1.6 Hz), 150.29, 149.92, 145.87, 134.27, 130.38 (d, $J_{C,F}$ = 7.2 Hz), 129.06, 124.11, 122.02, 120.55, 118.96, 117.11 (d, $J_{C,F}$ = 24 Hz), 116.34 (d, $J_{C,F}$ = 22.7 Hz), 114.24, 113.99 (d, $J_{C,F}$ = 8.1 Hz), 56.76. HRMS (ESI) calcd for $C_{20}H_{17}FN_2NaO$ [M + Na]$^+$: 343.1217, Found: 343.1225.

4.1.5.11 (E)-3-(2-(2-(5-fluoro-2-methoxyphenyl)pyridin-4-yl)vinyl)aniline (**7g**)

Yellow solid, yield: 53.1%, Mp: 109-111℃.^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (d, 1H, J = 5.2 Hz), 7.98 (s, 1H), 7.56-7.52 (m, 2H), 7.40 (d, 1H, J = 16.4 Hz), 7.26 (td, 1H, J_1 = 3.2 Hz, J_2 = 9.2 Hz), 7.19 (dd, 1H, J_1 = 4.4 Hz, J_2 = 9.2 Hz), 7.12 (d, 1H, J = 16.4 Hz), 7.07 (t, 1H, J = 8.0 Hz), 6.85-6.83 (m, 2H), 6.58-6.55 (m, 1H), 5.17 (s, 2H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.82 (d, $J_{C,F}$ = 234.6 Hz), 154.92 (d, $J_{C,F}$ = 1.8 Hz), 153.71 (d, $J_{C,F}$ = 1.7 Hz), 150.10, 149.45, 145.02, 137.06, 134.45, 130.19 (d, $J_{C,F}$ = 7.3 Hz), 129.72, 125.58, 122.62, 119.55, 117.12 (d, $J_{C,F}$ = 24 Hz), 116.48 (d, $J_{C,F}$ = 22.7 Hz), 115.60, 115.15, 114.01 (d, $J_{C,F}$ = 8.1 Hz), 112.65, 56.77. HRMS (ESI) calcd for $C_{20}H_{17}FN_2NaO$ [M + Na]$^+$: 343.1217, Found: 343.1222.

4.1.6. General procedure for synthesis of compounds **4a-c** *and* **8a-c**.

To a solution of compounds **3a-c** or **7a-c** (1.0 eq) in methanol was added Et_3N (3.0 eq) and $NH_2OH{\cdot}HCl$ (3.0 eq), and the reaction mixture was refluxed for 3-8 h. The reaction mixture was concentrated under vacuum, the residue was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by flash column chromatography on silica gel, to afford the pure products **4a-c** and **8a-c**.

*4.1.6.1. N'-hydroxy-3-((E)-4-hydroxy-3-(pyridin-2-yl)styryl)benzimidamide(***4a***)*

White solid, yield: 57.9%, Mp: 195-197℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.34 (s, 1H), 9.65 (s, 1H), 8.66 (d, 1H, J = 4.4 Hz), 8.38 (d, 1H, J = 8.0 Hz), 8.29 (s, 1H), 8.08 (t, 1H, J = 7.2 Hz), 7.91 (s, 1H), 7.63-7.54 (m, 3H), 7.48 (dd, 1H, J_1 = 5.2 Hz, J_2 = 7.6 Hz), 7.38 (t, 1H, J = 7.6 Hz), 7.31 (d, 1H, J = 16.4 Hz), 7.26 (d, 1H, J = 16.4 Hz), 6.97 (d, 1H, J = 8.8 Hz), 5.87 (s, 2H).^{13}C NMR (101 MHz, DMSO-d_6) δ 159.55, 157.09, 151.35, 146.73, 139.14, 137.82, 134.29, 129.95, 128.96, 128.54, 127.16, 126.27,

125.90, 124.72, 123.51, 122.96, 120.54, 119.36, 118.87. HRMS (ESI) calcd for $C_{20}H_{18}N_3O_2$ $[M + H]^+$: 332.1394, Found: 332.1389.

*4.1.6.2. N'-hydroxy-3-((E)-4-hydroxy-3-(pyrimidin-2-yl)styryl)benzimidamide (***4b***)*

Yellowish solid, yield: 42.8%, Mp: 221-222℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.36 (s, 1H), 9.65 (s, 1H), 9.02 (d, 2H, J = 4.8 Hz), 8.62 (d, 1H, J = 2.0 Hz), 7.92 (s, 1H), 7.76 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.4 Hz), 7.62-7.56 (m, 3H), 7.40-7.35 (m, 2H), 7.16 (d, 1H, J = 16.4 Hz), 7.04 (d, 1H, J = 8.8 Hz), 5.88 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.11, 160.31, 157.47, 151.28, 137.73, 134.25, 131.49, 128.93, 128.88, 128.77, 127.62, 127.28, 126.56, 124.78, 123.59, 120.03, 118.93, 118.81. HRMS (ESI) calcd for $C_{19}H_{16}N_4NaO_2$ $[M + Na]^+$: 355.1165, Found: 355.1169.

*4.1.6.3. N'-hydroxy-4-((E)-4-hydroxy-3-(pyrimidin-2-yl)styryl)benzimidamide (***4c***)*

Yellowish solid, yield: 44.3%, Mp: 237-238℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.38 (s, 1H), 9.66 (s, 1H), 9.02 (d, 2H, J = 4.8 Hz), 8.62 (s, 1H), 7.75 (d, 1H, J = 8.0 Hz), 7.68 (d, 2H, J = 8.0 Hz), 7.62 (d, 2H, J = 8.0 Hz), 7.58 (t, 1H, J = 4.8 Hz), 7.37 (d, 1H, J = 16.4 Hz), 7.15 (d, 1H, J = 16.4 Hz), 7.03 (d, 1H, J = 8.4 Hz), 5.82 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.00, 160.32, 157.53, 151.05, 138.33, 132.40, 131.52, 128.89, 128.75, 127.61, 126.41, 126.17, 126.06, 120.11, 118.84, 118.81. HRMS (ESI) calcd for $C_{19}H_{17}N_4O_2$ $[M + H]^+$: 333.1346, Found: 333.1342.

4.1.6.4. N'-hydroxy-3-((E)-2-(2-(2-hydroxyphenyl)pyridin-4-yl)vinyl)benzimidamide (**8a**)

White solid, yield: 69.8%, Mp: 185-187℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.32 (s, 1H), 9.70 (s, 1H), 8.60 (d, 1H, J = 5.2 Hz), 8.42 (s, 1H), 8.17 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.0 Hz), 8.03 (t, 1H, J = 1.6 Hz), 7.82 (d, 1H, J = 16.8 Hz), 7.70-7.66 (m, 2H), 7.64 (dd, 1H, J_1 = 1.6 Hz, J_2 = 5.6 Hz), 7.46 (t, 1H, J = 7.6 Hz), 7.41 (d, 1H, J = 16.8 Hz), 7.35-7.31 (m, 1H), 6.98-6.92 (m, 2H), 5.92 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.86, 157.83, 151.11, 147.07, 146.96, 136.44, 134.68, 134.51, 131.90, 129.20, 128.19, 127.46, 126.61, 126.40, 124.62, 119.84, 119.28, 119.23, 118.42, 117.20. HRMS (ESI) calcd for $C_{20}H_{18}N_3O_2$ $[M + H]^+$: 332.1394, Found: 332.1390.

4.1.6.5. N'-hydroxy-4-((E)-2-(2-(2-hydroxyphenyl)pyridin-4-yl)vinyl)benzimidamide (**8b**)

Yellowish solid, yield: 65.6%, Mp: 205-206℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.32 (s, 1H), 9.75 (s, 1H), 8.59 (d, 1H, J = 5.2 Hz), 8.41 (s, 1H), 8.16 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.0 Hz), 7.82-7.75 (m, 3H), 7.70 (d, 2H, J = 8.0 Hz), 7.63 (dd, 1H, J_1 = 1.6 Hz, J_2 = 5.6 Hz), 7.42 (d, 1H, J = 16.8 Hz), 7.36-7.31 (m, 1H), 6.99-6.93 (m, 2H), 5.88 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.85, 157.81, 150.87, 147.08, 146.95, 137.03, 134.28, 134.02, 131.90, 127.41, 126.64, 126.26, 119.81, 119.27, 119.23, 118.42, 117.20. HRMS (ESI) calcd for $C_{20}H_{17}N_3NaO_2$ $[M + Na]^+$: 354.1213, Found: 354.1211.

4.1.6.6. 3-((E)-2-(2-(5-fluoro-2-hydroxyphenyl)pyridin-4-yl)vinyl)-N'-hydroxy Benzimidamide (**8c**)

White solid, yield: 34.4%, Mp: 220-221℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.13 (s, 1H), 9.70 (s, 1H), 8.62 (d, 1H, J = 5.6 Hz), 8.48 (s, 1H), 8.08-8.02 (m, 2H), 7.89 (d, 1H, J = 16.4 Hz), 7.70-7.64 (m, 3H), 7.46 (t, 1H, J = 7.6 Hz), 7.39 (d, 1H, J = 16.4 Hz), 7.21 (td, 1H, J_1 = 2.8 Hz, J_2 = 8.4 Hz), 6.95 (dd, 1H, J_1 = 4.8 Hz, J_2 = 8.8 Hz), 5.92 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.66 (d, $J_{C,F}$ = 2.8 Hz), 156.06, 155.67 (d, $J_{C,F}$ = 231.4 Hz), 154.51, 151.07, 147.25, 147.16, 136.40, 134.94, 134.52, 129.21, 128.16, 126.42, 124.61, 120.65, 119.71 (d, $J_{C,F}$ = 7.5 Hz), 119.50 (d, $J_{C,F}$ = 8.1 Hz), 118.65 (d, $J_{C,F}$ = 23.0 Hz), 117.38, 113.22 (d, $J_{C,F}$ = 24.4 Hz). HRMS (ESI) calcd for $C_{20}H_{17}FN_3O_2$ $[M + H]^+$: 350.1299, Found: 350.1306.

4.1.7. General procedure for synthesis of compounds **4f-n** *and* **8e-g**.

To a solution of compounds **3f-n** or **7e-g** (1.0 equiv) in dry CH_2Cl_2 was added BBr_3 (6.0 equiv) in dry CH_2Cl_2 dropwise at -35℃ under nitrogen. The resulting solution was slowly warmed to room temperature and stirred overnight. The reaction mixture was added slowly to aqueous $NaHCO_3$, and the precipitate was collected by filtration to provide the crude product, which was purified by flash column chromatography on silica gel.

*4.1.7.1. (E)-4-(3-aminostyryl)-2-(pyridin-2-yl)phenol(***4f***)*

Yellow solid, yield: 39.3%, Mp:133-135℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.31 (s, 1H), 8.65 (dd, 1H, J_1 = 1.6 Hz, J_2 = 5.2 Hz), 8.38 (d, 1H, J = 8.4 Hz), 8.23 (d, 1H, J = 2.4 Hz), 8.07 (td, 1H, J_1 = 2.0 Hz, J_2 = 8.0 Hz), 7.58 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.4 Hz), 7.47 (dd, 1H, J_1 = 5.2 Hz, J_2 = 7.6 Hz), 7.08 (s, 2H), 7.03 (t, 1H, J = 7.6 Hz), 6.94 (d, 1H, J = 8.4 Hz), 6.77-6.74 (m, 2H), 6.48 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.0 Hz), 5.12 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.30, 157.15, 149.22, 146.70, 139.13, 138.40, 129.75, 129.59, 128.78, 127.50, 127.37, 125.70, 122.91, 120.56, 119.27, 118.80, 114.83, 113.85, 111.95. HRMS (ESI) calcd for $C_{19}H_{16}N_2NaO$ $[M + Na]^+$: 311.1155, Found: 311.1158.

*4.1.7.2. (E)-4-(4-aminostyryl)-2-(pyridin-2-yl)phenol(***4g***)*

Yellow solid, yield: 50.2%, Mp: 167-168℃ .^{1}H NMR (400 MHz, DMSO-d_6) δ 14.16 (s, 1H), 8.65-8.63 (m, 1H), 8.34 (d, 1H, J = 8.4 Hz), 8.14 (d, 1H, J = 2.4 Hz), 8.06-8.04 (m, 1H), 7.50 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.4 Hz), 7.48-7.44 (m, 1H), 7.26 (d, 2H, J = 8.4 Hz), 7.04 (d, 1H, J = 16.4 Hz), 6.93-6.88 (m, 2H), 6.57 (d, 2H, J = 8.4 Hz), 5.26 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.57, 157.25, 148.77, 146.71, 139.07, 129.56, 129.17, 127.65, 127.28, 125.67, 124.88, 123.06, 122.81, 120.45, 119.22, 118.70, 114.43. HRMS (ESI) calcd for $C_{19}H_{17}N_2O$ $[M + H]^+$: 289.1335, Found: 289.1332.

*4.1.7.3. (E)-4-(3-aminostyryl)-2-(pyrimidin-2-yl)phenol(***4h***)*

Yellow solid, yield: 62.3%, Mp: 207-208℃.^{1}H NMR (400 MHz, DMSO-d_6) δ 13.32 (s, 1H), 9.01 (d, 2H, J = 4.8 Hz), 8.56 (d, 1H, J = 2.0 Hz), 7.72 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.8 Hz), 7.57 (t, 1H, J = 4.8 Hz), 7.12 (d, 1H, J = 16.4 Hz), 7.04-6.99 (m, 2H), 6.97 (d, 1H, J = 16.4 Hz), 6.79-6.77 (m, 2H), 6.50-6.47 (m, 1H), 5.06 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.03, 160.06, 157.52, 149.27, 138.16, 131.42, 129.58, 128.92, 127.62, 127.29, 127.23, 120.06, 118.75, 114.83, 113.89, 112.12. HRMS (ESI) calcd for $C_{18}H_{15}N_3NaO$ $[M + Na]^+$: 312.1107, Found: 312.1108.

*4.1.7.4. (E)-4-(4-aminostyryl)-2-(pyrimidin-2-yl)phenol(***4i***)*

Yellow solid, yield: 58.8%, Mp:194-196℃.^{1}H NMR (400 MHz, DMSO-d_6) δ 13.22 (s, 1H), 9.00 (d, 2H, J = 4.8 Hz), 8.50 (d, 1H, J = 2.0 Hz),7.64 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.56 (t, 1H, J = 4.8 Hz), 7.29 (d, 2H, J = 8.4 Hz), 6.99-6.94 (m, 3H), 6.56 (d, 2H, J = 8.4 Hz), 5.26 (s, 2H). HRMS (ESI) calcd for $C_{18}H_{15}N_3NaO$ $[M + Na]^+$: 312.1107, Found: 312.1106.

*4.1.7.5. (E)-ethyl 2-(5-(4-aminostyryl)-2-hydroxyphenyl)isonicotinate(***4j***)*

Yellow solid, yield: 48.6%, Mp: 111-112℃ .^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 8.85 (dd, 1H, J_1 = 0.8 Hz, J_2 = 5.2 Hz), 8.61 (t, 1H, J = 1.2 Hz), 8.10 (d, 1H, J = 2.0 Hz), 7.84 (dd, 1H, J_1 = 1.2 Hz, J_2 = 5.2Hz), 7.58 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.4 Hz), 7.27 (d, 2H, J = 8.4 Hz), 6.99-6.94 (m, 3H), 6.56 (d, 2H, J = 8.4 Hz), 5.26 (s, 2H), 4.43 (q, 2H, J = 7.2 Hz), 1.39 (t, 3H, J = 7.2 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.70, 157.73, 157.45, 148.52, 148.37, 139.06, 129.67, 128.64, 127.44, 127.07, 125.90, 125.32, 122.72, 120.90, 119.79, 119.71, 118.37, 114.08, 62.06, 14.23. HRMS (ESI) calcd for $C_{22}H_{20}N_2NaO_3$ $[M + Na]^+$: 383.1366, Found: 383.1370.

*4.1.7.6. (E)-4-(3-aminostyryl)-2-(4-ethoxypyridin-2-yl)phenol (***4k***)*

Yellow solid, yield: 65.4%, Mp: 103-105℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.80 (s, 1H), 8.45 (d, 1H, J = 6.0 Hz), 8.23 (d, 1H, J = 2.0 Hz), 7.83 (d, 1H, J = 2.4 Hz), 7.57 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.4 Hz), 7.08-7.00 (m, 4H), 6.90 (d, 1H, J= 8.4 Hz), 6.77- 6.73 (m, 2H), 6.49-6.45 (m, 1H), 5.07 (s, 2H), 4.30 (q, 2H, J= 6.8 Hz), 1.42 (t, 3H, J = 6.8 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.73, 159.72, 158.97, 149.32, 147.97, 138.47, 129.56, 128.58, 127.59, 127.24, 125.92, 118.92, 118.82, 114.67, 113.73, 111.93, 110.03, 105.86, 64.53, 14.79. HRMS (ESI) calcd for $C_{21}H_{20}N_2NaO_2$ $[M + Na]^+$: 355.1417, Found: 355.1421.

*4.1.7.7. (E)-4-(3-aminostyryl)-2-(4-fluoropyridin-2-yl)phenol (***4l***)*

Yellow solid, yield: 61.7%, Mp:173-174℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.93 (s, 1H), 8.71 (dd, 1H, J_1= 5.6 Hz, J_2 = 8.8 Hz), 8.34 (dd, 1H, J_1= 2.4 Hz, J_2 = 11.6 Hz) , 8.27 (d, 1H, J = 2.0 Hz), 7.59 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.4 Hz), 7.44-7.40 (m, 1H), 7.12 (d, 1H, J = 16.4 Hz), 7.10-7.00 (m, 2H), 6.96 (d, 1H, J = 8.8 Hz), 6.77-6.73 (m, 2H), 6.50-6.46 (m, 1H), 5.10 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.83 (d, $J_{C, F}$ = 258.4 Hz), 160.63 (d, $J_{C, F}$ = 8.4 Hz), 159.07, 150.27 (d, $J_{C, F}$ = 8.6 Hz), 149.31, 138.38, 130.53, 129.60, 129.00, 127.65, 127.26, 126.00, 118.88 (d, $J_{C, F}$ = 3.3 Hz), 118.83, 114.76, 113.86, 111.89, 111.05 (d, $J_{C, F}$ = 18.0 Hz), 108.19 (d, $J_{C, F}$ = 19.2 Hz). HRMS (ESI) calcd for $C_{19}H_{15}FNaN_2O$ $[M + Na]^+$: 329.1061, Found: 329.1065.

*4.1.7.8. (E)-6-(5-(3-aminostyryl)-2-hydroxyphenyl)pyridin-3-ol (***4m***)*

Yellow solid, yield: 63.9%, Mp: 233-234℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.98 (s, 1H), 10.39 (s, 1H), 8.22 (d, 1H, J = 8.8 Hz), 8.19 (d, 1H, J = 3.2 Hz), 8.09 (d, 1H, J = 2.0 Hz), 7.47 (td, 2H, J_1 = 2.0 Hz, J_2 = 8.0 Hz), 7.08-7.00 (m, 3H), 6.89 (d, 1H, J = 8.4 Hz), 6.76-6.71 (m, 2H), 6.47 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.0 Hz), 5.07 (s, 2H). HRMS (ESI) calcd for $C_{19}H_{15}N_2O_2$ $[M - H]^-$: 303.1139, Found: 303.1129.

*4.1.7.9. (E)-2-(4-(4-aminostyryl)pyridin-2-yl)phenol (***8e***)*

Yellow solid, yield: 46.4%, Mp:151-152℃.^{1}H NMR (400 MHz, DMSO-d_6) δ 14.52 (s, 1H), 8.49 (d, 1H, J = 5.2 Hz), 8.27 (s, 1H), 8.13 (dd, 1H, J_1 = 1.2 Hz, J_2 = 8.0 Hz), 7.60 (d, 1H, J = 16.4 Hz), 7.51 (dd, 1H, J_1 = 1.2 Hz, J_2 = 5.6 Hz), 7.39 (d, 2H, J = 8.8 Hz), 7.34-7.29 (m, 1H), 6.98 (d, 1H, J = 16.4 Hz), 6.97-6.90 (m, 2H), 6.61 (d, 2H, J = 8.4 Hz), 5.59 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.97, 157.56, 150.61, 148.26, 146.50, 135.77, 131.72, 129.24, 127.30, 123.97, 120.00, 119.29, 119.11, 119.05, 118.38, 116.23, 114.27. HRMS (ESI) calcd for $C_{19}H_{17}N_2O$ $[M+H]^+$: 289.1335, Found : 289.1338.

*4.1.7.10. (E)-2-(4-(4-aminostyryl)pyridin-2-yl)-4-fluorophenol(***8f***)*

Yellowish solid, yield: 41.2%, Mp:180-181℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.34 (s, 1H), 8.50 (d, 1H, J = 5.6 Hz), 8.32 (s, 1H), 8.03 (dd, 1H, J_1 = 3.2 Hz, J_2 = 10.8 Hz), 7.65 (d, 1H, J = 16.4 Hz), 7.52 (dd, 1H, J_1 = 0.8 Hz, J_2 = 5.2 Hz), 7.38 (d, 2H, J = 8.4 Hz), 7.17 (td, 1H, J_1 = 3.2 Hz, J_2 = 8.8 Hz), 6.97 (d, 1H, J = 16.4 Hz), 6.93 (dd, 1H, J_1 = 5.2 Hz, J_2 = 9.2 Hz), 6.61 (d, 2H, J = 8.4 Hz), 5.60 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.42 (d, $J_{C, F}$ = 2.7 Hz), 156.19 (d, $J_{C, F}$ = 0.9 Hz), 155.63 (d, $J_{C, F}$ = 231.3 Hz), 150.66, 148.48, 146.68, 136.06, 129.24, 123.95, 119.81, 119.73 (d, $J_{C, F}$ = 7.4 Hz), 119.43 (d, $J_{C, F}$ = 7.9 Hz), 118.45 (d, $J_{C, F}$ = 23 Hz), 116.47, 114.28, 113.08 (d, $J_{C, F}$ = 24.2 Hz). HRMS (ESI) calcd for $C_{19}H_{16}FN_2O$ $[M + H]^+$: 307.1241, Found: 307.1237.

*4.1.7.11. (E)-2-(4-(3-aminostyryl)pyridin-2-yl)-4-fluorophenol(***8g***)*

Yellowish solid, yield: 59.2%, Mp:184-185℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.20 (s, 1H), 8.58 (d, 1H, J = 5.6 Hz), 8.43 (s, 1H), 8.07 (dd, 1H, J_1 = 3.2 Hz, J_2 = 10.8 Hz), 7.68 (d, 1H, J = 16.4 Hz), 7.64 (dd, 1H, J_1 = 1.2 Hz, J_2 = 5.2 Hz), 7.22-7.14 (m, 2H),

7.10 (t, 1H, J = 8.0 Hz), 6.94 (dd, 1H, J_1 = 5.2 Hz, J_2 = 8.8 Hz), 6.87-6.84 (m, 2H), 6.61-6.58 (m, 1H), 5.22 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.63 (d, $J_{C,F}$ = 2.8 Hz), 156.11 (d, $J_{C,F}$ = 1.0 Hz), 155.66 (d, $J_{C,F}$ = 231.4 Hz), 149.53, 147.56, 146.96, 137.02, 136.12, 129.82, 124.97, 120.42, 119.71 (d, $J_{C,F}$ = 7.4 Hz), 119.46 (d, $J_{C,F}$ = 8.0 Hz), 118.59 (d, $J_{C,F}$ = 23.0 Hz), 117.37, 115.63, 115.44, 113.24 (d, $J_{C,F}$ = 24.2 Hz), 112.71. HRMS (ESI) calcd for $C_{19}H_{15}FN_2NaO$ $[M + Na]^+$: 329.1061, Found: 329.1066.

4.2. LSD1, MAO-A and MAO-B Enzymatic Assay

Inhibitory effects of the target compounds against LSD1 were evaluated according to our previously reported methods [49]. Full length LSD1 cDNA encoding LSD1 was obtained by RT-PCR and cloned into pET-28b (pET-28b-LSD1). Then the plasmid pET-28b-LSD1 was transfected into BL21 (DE). The recombinant protein was induced with 0.25 mM IPTG at 20 ℃ and purified following affinity chromatography, ion exchange chromatography and gel filtration. Then the compounds were incubated with the 5nM recombinant LSD1 and 25μM H3K4me2 peptide in the present of FAD (50nM), Amplex Red (20nM) and horseradish peroxidase (5.5U/mL) for 30 min. After that, the fluorescence was measured at excitation wavelength 530 nm and emission wavelength 590 nm as reported in order to evaluate the inhibition rate of the candidate compounds. MAO inhibitory activities were determined using a commercialized MAO-Glo assay kit from Promega, according to the manufacturer's protocol.

The dilution assay was done as published [53]. Briefly, an amount of 2.5 μg of recombinant LSD1 was incubated with high concentration of compound **8c**, GSK2879552, or DMSO. After 1 h later, 1.25 μg aliquots were removed from all samples and diluted into HRP-assay solution containing substrate and coupling reagents to a final volume of 100 μL. This represents an 80-fold dilution of the inhibitor concentration, which is expected to yield the same inhibition rate for an irreversible inhibitor or significant difference for a reversible inhibitor.

For the competitive analysis of candidate compound, demethylase activity of LSD1 was assessed in the presence of different concentrations of the compound at a fixed concentration of histone peptide but different concentrations of FAD. Assays were performed triplicate, and kinetics values were obtained using Lineweaver−Burk plots made by GraphPad 6.0.

4.3. Surface plasmon resonance (SPR) experiment

Studies of binding kinetics are performed on a Biacore S200 (GE Healthcare, USA). LSD1 is aimed for an immobilization level of approximately 8000 RU with a CM5 sensor chip, and the running buffer is PBS-P (0.2 M phosphate buffer 0.027 M KCl, 1.37 M NaCl, 0.5%Surfactant P20, PH 7.4). The direct binding assay is tested with buffer and sample in 2% DMSO. Then compounds with twofold dilution series are injected for 60s and dissociated for 300s at a flow rate of 30 μL/min. The data is analyzed by Biacore S200 Evaluation Software 1.0.

4.4 Western blotting

10^6 THP-1 cells/well were incubated with compound **8c** (0, 1.25, 2.5, 5.0 μM) for 5 days. Histone proteins were extracted using EpiQuik total histone extraction kit (Epigentek) according to the manufacturer's protocol. Equivalent amounts of cell

lysates were denatured, separated by SDS-PAGE and transferred onto nitrocellulose membranes. After blocking with PBS containing 5% nonfat milk, the membranes were incubated overnight at 4℃ with specific primary antibodies, followed by incubation with appropriate secondary antibodies. The immunoblots were visualized by enhanced chemiluminescence detection kit from Thermo Fisher.

4.5. Cell Viability Assay

The MTS/PMS method was used to evaluate the inhibition rate of cancer cell proliferation. Cells were treated with various concentrations of the test compounds. After the incubation of 8 days, MTS assay was performed using CellTiter 96® AQueous One Solution Cell Proliferation Assay (Promega, USA) according to the manufacturer's instructions. Each treatment had triplicates and at least three independent experiments were performed for statistics. All data were represented as mean ± SD.

4.6. Colony Formation Assay

THP-1 cells (500 cells/well) were seeded in 24-well plate, 1:1 mixture of RPMI 1640 containing 10% FBS (BI) and Methylcellulose-based medium as the culture medium. Cells were treated with compound **8c** at indicated concentrations for 14 days. Then cells were stained with DAPI (Sigma) according to the manufacturer's instructions and washed with PBS. The colony formation was imaged using microscope (TS-100, Nikon, Japan).

4.*7. Flow-cytometry Analysis*

After the incubation with indicated concentrations of compound **8c** or 0.1% DMSO, 1×10^6 THP-1 cells were treated in the dark with FITC-conjugated CD86 antibody (abcam, ab77131) at 4 °C for 30 minutes. The expression of CD86 was analyzed by FACS BD LSRFortessa flow cytometer (BD Biosciences, San Jose, CA, USA) and the flow cytometry data was analyzed using Flowjo.

4.8. Hematoxylin and Eosin stain

THP-1 cells are seeded in 6-well plate with different concentration of compounds then incubated for 3 days in standard medium. After the incubation period, medium contain cells are centrifuged to gather the cells. Resuspend the cells by PBS and apply them evenly to low-absorbance glass. After followed steps contain staining, dehydration, cleaning with xylene and covered by coverslips upon gum (Solarbio, China), slides are photographed by light microscope (Leica, German)

4.8. Molecular Docking

All molecular modeling studies were performed with MOE (The Molecular Operating Environment) Version 2015.10. The crystal structure for LSD1 (PDB code: 4LXZ) was obtained from the RCSB protein data bank. The docking procedure contained the preparation of protein and ligand and the operation of docking. The preparation of protein structure was performed using the Quickprep module, which contained the deletion of waters, the addition of hydrogen atoms, the protonation and

the repair of missing residues. The geometry optimization of ligand structure mainly was executed by energy minimization and conformation search. Next, compound **8c** was docked into the LSD1. Default triangle matcher method was used for placement of ligand and the final conformation was scored by GBVI/WSA dG. All these above treatments were formed in Amber 10: EHT forcefield.

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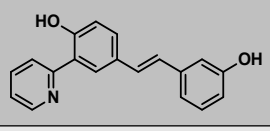
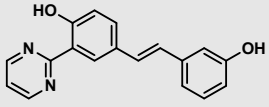
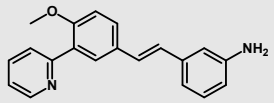
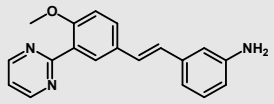
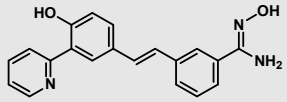
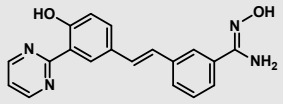
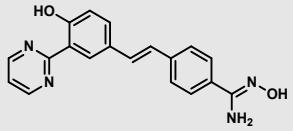
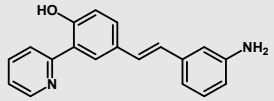
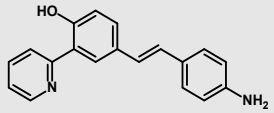
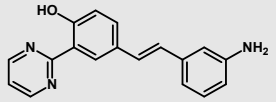
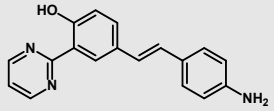
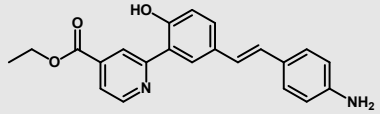
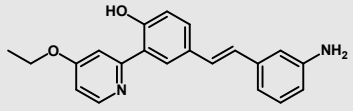
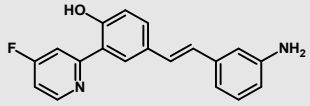
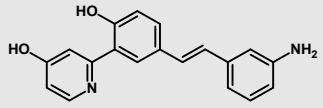
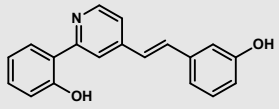
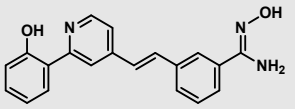
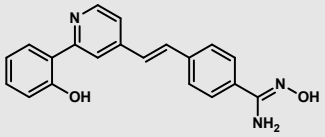
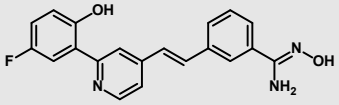
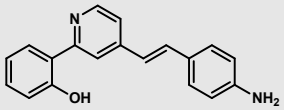
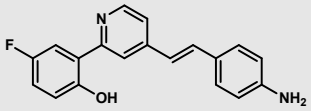
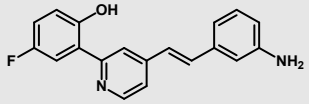
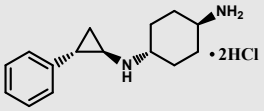
Table 1 Inhibitory Activity (IC_{50} or percentage of inhibition at 10 μM) against LSD1

Compounds Structures		LSD1 $IC_{50}(\mu M)^a$	Inhibition % at 10μM
3d		4.24 ± 0.89	85.09%
3e		N.T.[b]	20.18%

3f		N.T.	N.I.[c]
3h		N.T.	N.I.
4a		0.72 ± 0.12	97.84%
4b		1.29 ± 0.07	87.50%
4c		0.92 ± 0.04	94.29%
4f		0.301 ± 0.03	98.37%
4g		3.57 ± 0.31	94.32%
4h		0.859 ± 0.07	97.66%
4i		9.55 ± 1.01	51.31%
4j		N.T.	35.43%
4k		N.T.	43.89%
4l		N.T.	30.28%
4m		1.47 ± 0.24	89.30%
7d		N.T.	31.63%

8a		0.364 ± 0.03	97.69%
8b		0.764 ± 0.03	97.57%
8c		0.283 ± 0.02	99.23%
8e		2.96 ± 0.74	94.80%
8f		9.03 ± 0.66	54.14%
8g		11.78 ± 1.09	50.11%
ORY-1001		11.26 ± 0.72 (nM)	N.T.

[a] IC_{50} values are expressed as mean ± SD from at least three independent experiments.

[b] N.T.: Not tested.

[c] N.I.: No Inhibition.

Table 2 *In vitro* Inhibition of LSD1, MAO-A and MAO-B of selected compounds

Compounds	IC_{50}(μM) LSD1	MAO-A	MAO-B
4a	0.72 ± 0.12	>50	>50
4f	0.301 ± 0.03	>50	>50
8a	0.364 ± 0.03	>50	>50
8c	0.283 ± 0.02	>50	>50
Clorgyline	[b]N.D.	[a] 0.0031	N.D.
R(-)-deprenyl	N.D.	N.D.	[a]0.071

[a]Values are the mean of two experiments.

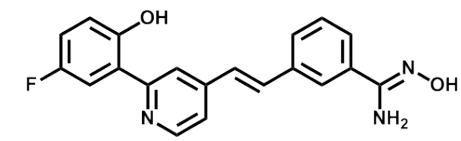
[b]N.D.: Not detected

Table 3 *In vitro* antiproliferative activity of selected compounds in three cancer cell lines

Compounds	IC_{50}(μM)[a] MOLM-13	THP-1	MV-4-11
4a	22.59 ± 2.33	7.89 ± 0.71	4.71 ± 0.89
4f	12.51 ± 1.06	10.51 ± 1.44	10.94 ± 2.03
8a	9.05 ±0.99	13.72 ± 1.08	15.85 ± 1.52
8c	8.34 ± 0.64	5.76 ± 0.55	7.49 ± 1.17
ORY-1001	N.D.[b]	> 20 μM	N.D.

[a] IC_{50} values are expressed as mean ± SD from at least three independent experiments.

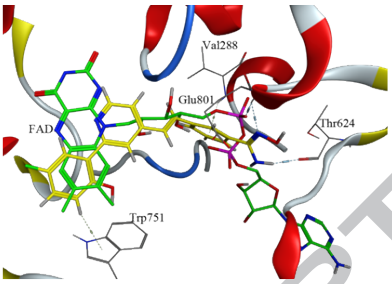
[b] N.D.: Not detected

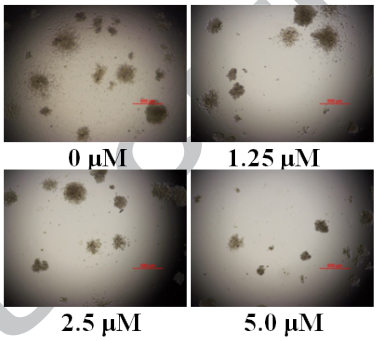


Compound 8c

Potent reversible LSD1 inhibitor

IC_{50} : 283 nM





Highlights

- A series of stilbene derivatives were discovered as novel LSD1 inhibitors.
- Compound **8c** potently inhibited LSD1 in a reversible and FAD competitive manner with an IC_{50} of 283 nM.
- Compound **8c** dose-dependently increased surrogate cellular biomarker CD86 in THP-1 human leukemia cells.
- Compounds **8c** significantly inhibited proliferation and colony formation of THP-1 cells.