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Novel spirocyclic tranlycypromine derivatives as lysine-specific demethylase 1 (LSD1) inhibitors†

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Herein we describe the design, synthesis, and biological evaluation of a novel series of tranlycypromine-based LSD1 inhibitors *via* conformational restriction using spiro ring systems. A simple, direct spirocyclic analog of tranlycypromine (compounds **8a** and **8b**) was shown to be a 28- to 129-fold more potent inhibitor of LSD1 enzyme compared to tranlycypromine. Further incorporation of various substituted benzyl groups to the amino group resulted in a suite of 2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amines that are potent LSD1 inhibitors with excellent selectivity profiles (e.g. **14a**, **15b**, **16a**, **19a** and **20b**) against closely related enzymes such as MAO-A, MAO-B, and LSD2.

Introduction

Epigenetic modifications of DNA or histone tails, such as methylation and acetylation, provide regulatory mechanisms to influence gene expression. This dynamic process allows for the chromatin uncoiling or compaction, thereby altering the ability of the transcription machineries to access the DNA. Lysine-specific demethylase 1 (LSD1) is now recognized as the first true histone demethylase, originally discovered by the group of Shi Yang in 2004.¹ LSD1 belongs to the flavin adenine dinucleotide (FAD)-dependent amine oxidase superfamily and specifically demethylates mono- and dimethylated histone H3 lysine 4 (H3K4me and H3K4me2).^{1,2} The catalytic cycle is thought to involve the methylated lysine being firstly oxidized by FAD co-factor to form an imine intermediate, followed by hydrolysis to generate formaldehyde and the demethylated lysine. FADH₂, the reduced product of FAD, is then oxidized by O₂ to form FAD and H₂O₂. LSD1 is often present in transcriptional co-repressor complexes such as RE1-silencing transcriptional factor corepressor 1 (CoREST),

which can stabilize and recruit LSD1 after binding to chromatin.³ Alteration of the LSD1 substrate specificity occurs upon association with the androgen receptor, namely from H3K4 to H3K9.⁴ LSD1 is also known for its ability to demethylate non-histone proteins, such as p53, thus inhibiting the apoptosis process mediated by p53.⁵ In addition to LSD1, the LSD family has a homologue known as LSD2 which was first identified in 2009.^{6,7} Both homologues contain the N-terminal SWIRM (Swi3p, Rsc8p and Moira) domain and the C-terminal amine oxidase domain.⁸ However, while LSD1 contains the Tower domain which forms a binding site with CoREST, the LSD2 contains a CW-type zinc finger domain with unknown function.⁶

There are numerous studies reporting that LSD1 is upregulated in various tumor tissue cells and tissues including retinoblastoma,⁹ non-small cell lung cancer,¹⁰ prostate cancer,¹¹ breast cancer,^{12,13} and colon cancer.¹⁴ LSD1 is also overexpressed in MLL-rearranged leukemia as a key regulator to promote the oncogenic potential of MLL-AF9 leukemia stem cell.¹⁵ MLL gene translocation is a major biomarker in acute leukemia which is typically associated with a poor prognosis. The results of RNAi-mediated knockdown or pharmacological inhibition of LSD1 seem to suggest that this enzyme induces re-expression of epigenetically silenced tumor suppressor genes and regulates p53 transcriptional activity or down-regulation of several leukemic-related genes.^{15–17} Overall, LSD1 represents a promising target for the treatment of leukemia as well as other solid tumors.

LSD1 exhibits homology with monoamine oxidases (MAOs) A and B with 17.6% identity.¹⁸ Classic MAO inhibitors such as *trans*-phenylcyclopropylamine (**1**, tPCPA), phenelzine (**2**), and pargyline (**3**) were found to show LSD1 inhibitory activity by forming covalent adduct with FAD (Fig. 1). The (1*R*, 2*S*)-isomer of **1** obtained by chiral resolution of tPCPA reacts with FAD in the active site to produce *N*-(5) adduct A, while the (1*S*, 2*R*)-

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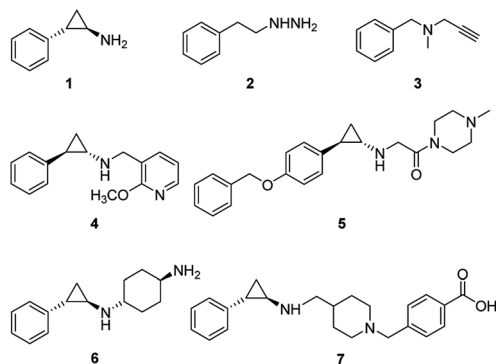


Fig. 1 Structures of irreversible LSD1 inhibitors.

isomer generates *N*-(5) adduct B (Fig. 2).^{18,19} A number of tPCPA-containing inhibitors were developed with the aim to improve the potency at LSD1 as well as the selectivity over MAOs. The catalytic site for LSD1 is larger compared to MAOs,²⁰ with substitutions at the phenyl ring and amino nitrogen atom generally increasing the LSD1 inhibitory activity. Compound 4 is a potent LSD1 inhibitor with an IC_{50} value of 98 nM that has been demonstrated to inhibit colony forming capacity of MLL-AF9 leukemia cells.¹⁵ Compound 5 was reported to be a brain-permeable LSD1 inhibitor that can block memory consolidation in a mouse model.²¹ Other classes of reversible LSD1 inhibitors have also been reported, including peptides, polyamine analogues, pyrimidine-thioureas, 3-(piperidin-4-ylmethoxy)pyridine and 3,5-diamino-1,2,4-triazoles.^{22–27} *N*1-[(1*R*, 2*S*)-2-phenylcyclopropyl]cyclohexane-1,4-diamine dihydrochloride ORY-1001 (6, ORY1001, RG6016, Oryzon Genomics) is an irreversible LSD1 inhibitor that was granted an orphan drug status for the treatment of acute myeloid leukemia (AML) in phase IIA clinical trial.²⁸ GlaxoSmithKline developed a potent LSD1 inhibitor, compound 7 (GSK2879552), which is currently in the phase I trials for treatment of relapsed/refractory small cell lung cancer and AML. More recently, Oryzon Genomics announced tPCPA analogue ORY2001, a dual LSD1/MAO-B inhibitor, that was advanced in phase I studies for Alzheimer's disease in 2016. Other compounds currently in phase I/II clinical trials for oncology include INCB059872, IMG-7289 and CC-90011.²⁹

Although there are numerous medicinal chemistry campaigns on tranlycypromine-related analogues,³⁰ thus far

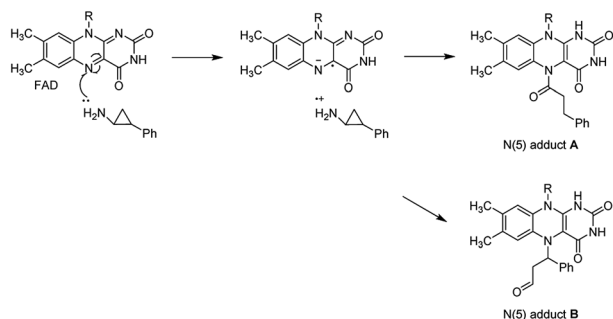


Fig. 2 Proposed mechanism of inactivation of LSD1 by tPCPA.

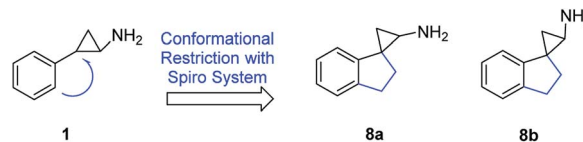
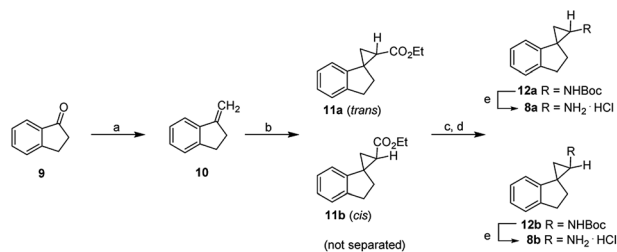


Fig. 3 Conformationally constrained compounds 8a and 8b.

there has been a limited report on the incorporation of spirocycle into the system.^{31,32} Spiro containing system has been increasingly utilized in medicinal chemistry as it introduces not only diverse orientation but also structural novelty.³³ Within this context, the spirocycle constraint may influence the potency and selectivity for LSD1 inhibition over other homologous enzymes, such as LSD2, MAO-A, and MAO-B. In the present study, we report a series of 2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine analogues and their potencies at inhibiting LSD1 and related enzymes (Fig. 3).

Results and discussion

Compounds 8a and 8b were first synthesized as outlined in Scheme 1, starting from the commercially available 2,3-dihydro-1*H*-inden-1-one (9). Terminal olefin 10 was prepared *via* Wittig reaction with methyltriphenylphosphonium bromide. Cyclopropanation with ethyl diazoacetate catalyzed by rhodium(II) acetate dimer resulted in the esters 11a and 11b. Following basic hydrolysis, the corresponding carboxylic acids were in turn converted to the carbamates 12a and 12b *via* Curtius rearrangement using diphenylphosphoryl azide (DPPA), triethylamine and refluxing in anhydrous *tert*-butanol. The resultant enantiomers 12a and 12b were readily separated by flash chromatography and the stereochemical assignments were based collectively on their 1*H*,1*H* COSY and Nuclear Overhauser Effect (NOE) NMR spectra (ESI Table 1†). Briefly, for the aromatic ring of compound 8a, the H-5' proton (δ 7.18–7.12) coupled with H-4' (δ 7.22) and H-6' (δ 7.18–7.12). Similarly, H-6' proton (δ 7.18–7.12) coupled with H-5' (δ 7.18–7.12) and H-7' (δ 6.76). In the aliphatic region, H-3' (δ 3.14) coupled with H-2' (δ 2.35–2.20) and the H-2 (δ 2.88) with H-3 (δ 1.42, 1.29). For compound 8a, NOE correlations were observed between H-7' and H-2. For compound 8b, in the aromatic region, the H-6'



Scheme 1 ^aReagents and conditions: (a) methyltriphenylphosphonium bromide, ^tBuOK, THF, rt; (b) $Rh_2(OAc)_4$ (cat.), N_2CH_2COOEt , CH_2Cl_2 , 45 °C; (c) KOH, EtOH, 80 °C; (d) i. diphenylphosphoryl azide (DPPA), Et_3N , toluene, 0 °C–25 °C; ii. ^tBuOH, reflux; (e) 4 M HCl in ethyl acetate, rt.



proton (δ 7.26–7.21) coupled with H-5' (δ 7.26–7.21) and H-7' (δ 7.08–7.06). Similarly, the H-5' proton (δ 7.26–7.21) coupled with H-4' (δ 7.32) and H-6' (δ 7.26–7.21). In the aliphatic region, the H-3' (δ 3.18–3.10, 2.97) coupled with H-2' (δ 2.38–2.30, 1.97). The H-2 proton (δ 2.88) coupled with H-3 (δ 1.51, 1.43). For compound **8b**, NOE correlations were seen for H-2 and H-2', and therefore supporting the stereochemical assignments of **8a** as the *trans*-isomer and **8b** as the *cis*-isomer. Lastly, deprotection of the Boc group in acidic conditions afforded final compounds **8a** and **8b** as hydrochloride salts.

Following their synthesis, compounds **8a** and **8b** were tested for their inhibitory activities against the purified LSD1 recombinant. As shown in Table 1, compounds **8a** and **8b** drastically improved the inhibitory activity against LSD1 by 129- and 28-fold compared to the control compound tPCPA (**1**), with

the *trans*-isomer **8a** being 5-fold more potent than the *cis*-isomer **8b**. Furthermore, both isomers exhibited very high selectivity of >600- and >120- fold against MAO-A, but only modest selectivity for MAO-B. The observed trend suggested that the conformational restriction imposed by the spirocycle was beneficial for the inhibitory activity against LSD1 and selectivity over MAO-A.

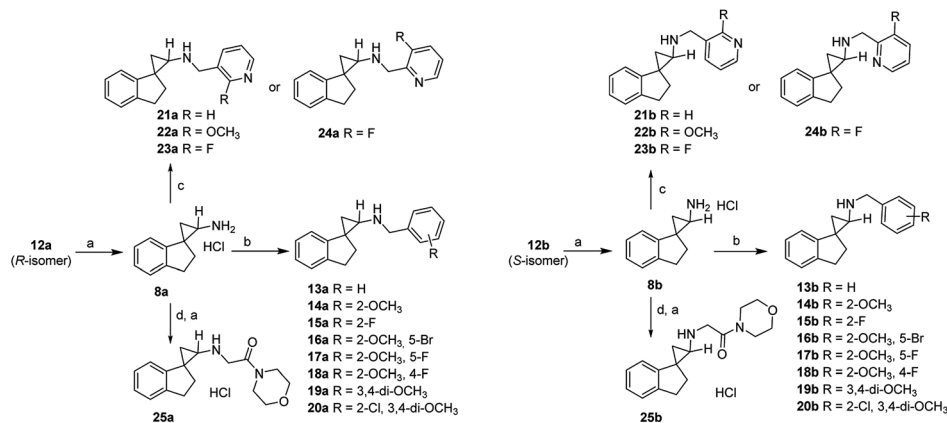
Encouraged by the preliminary *in vitro* results of the spirocycles **8a** and **8b**, we further explored structural extensions on the amino group (**13a–25a**, **13b–25b**). As outlined in Scheme 2, reductive amination of the amines **8a** and **8b** with various substituted benzaldehydes or pyridine aldehydes using NaBH₄ gave the final products **13a–24a** and **13b–25b**. Alkylation of **8a** or **8b** with 2-chloro-1-morpholinoethan-1-one in the presence of sodium hydride in anhydrous dimethylformamide (DMF) provided the amides **25a** and **25b**. Their IC₅₀ values for the

Table 1 *In vitro* inhibitory activities against LSD1, MAO-A, MAO-B, and LSD2^a

Compound	LSD1, IC ₅₀ (μM)	MAO-A, IC ₅₀ (μM)	MAO-B, IC ₅₀ (μM)	LSD2, IC ₅₀ (μM)
1	22	11 ± 4	7.0 ± 0.8	NT ^b
6	0.014 ± 0.003	>100	194 ± 114	NT
8a	0.17 ± 0.01	>100	0.90 ± 0.09	NT
8b	0.78 ± 0.05	>100	7.8 ± 0.7	NT
13a	3.3 ± 0.6	NT	NT	NT
13b	0.11 ± 0.02	0.13 ± 0.01	5.1 ± 0.1	2.0 ± 0.2
14a	0.0022 ± 0.0003	5.9 ± 1.1	12 ± 1	NT
14b	0.0094 ± 0.0027	1.7 ± 0.3	70 ± 35	NT
15a	0.0070 ± 0.0017	4.8 ± 0.5	9.8 ± 2.3	NT
15b	0.0011 ± 0.0001	2.5 ± 0.1	32 ± 3	NT
16a	0.0095 ± 0.0024	3.7 ± 0.8	1.2 ± 0.2	6.8 ± 1.0
16b	0.063 ± 0.008	0.39 ± 0.19	7.7 ± 3.8	4.7 ± 0.8
17a	0.0066 ± 0.0015	0.92 ± 0.18	2.3 ± 0.4	0.80 ± 0.27
17b	0.017 ± 0.003	0.12 ± 0.01	27 ± 4	1.7 ± 0.5
18a	0.0071 ± 0.0013	2.2 ± 0.7	8.7 ± 1.1	0.66 ± 0.06
18b	0.015 ± 0.003	0.090 ± 0.010	31 ± 4	0.49 ± 0.10
19a	0.0030 ± 0.0001	11.7 ± 2.4	15 ± 2	NT
19b	0.012 ± 0.002	3.1 ± 0.2	27 ± 4	NT
20a	0.025 ± 0.007	1.4 ± 0.1	20 ± 1	2.3 ± 0.1
20b	0.0083 ± 0.0019	5.0 ± 1.8	7.0 ± 0.7	1.6 ± 0.2
21a	0.017 ± 0.003	10.8 ± 1.1	15 ± 1	NT
21b	0.020 ± 0.003	6.0 ± 1.1	28 ± 6	NT
22a	0.032 ± 0.006	>100	47 ± 5	NT
22b	0.010 ± 0.005	>100	68 ± 8	NT
23a	0.064 ± 0.001	9.7 ± 1.5	8.2 ± 1.5	13 ± 3
23b	0.070 ± 0.003	9.8 ± 0.8	29 ± 4	8.7 ± 0.8
24a	0.25 ± 0.01	NT	NT	NT
24b	0.47 ± 0.02	NT	NT	NT
25a	1.4 ± 0.1	NT	NT	NT
25b	22 ± 4	NT	NT	NT

^a See Experimental section. Data represent mean values ± SEM of eight-point experiments each performed from three independent experiments. Positive controls: compound **1** and **6**. ^b NT: not tested.





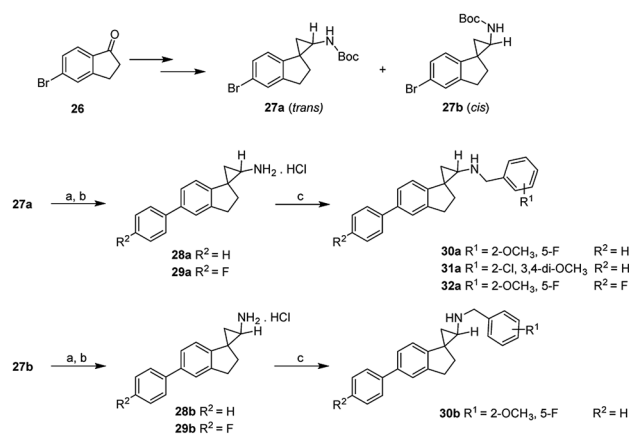
Scheme 2 ^aReagents and conditions: (a) 4 M HCl in ethyl acetate, rt; (c) substituted pyridine aldehyde, NaBH₄, MeOH, rt; (b) substituted benzaldehyde, NaBH₄, MeOH, rt; (d) 2-chloro-1-morpholinoethan-1-one, NaH, DMF, 0 °C–rt.

inhibition of LSD1, MAO-A, MAO-B and LSD2 are summarized in Table 1.

A benzyl substitution on the amino group of **8a** resulted in a 19-fold decrease in the LSD1 inhibitory activity (**13a** vs. **8a**; IC₅₀ = 3.3 μM vs. 0.17 μM), while the reverse trend was observed for **13b** vs. **8b** (IC₅₀ = 0.11 μM vs. 0.78 μM). To our delight, all the other synthesized benzyl and pyridylmethyl derivatives demonstrated potent inhibitory activities at the LSD1 with IC₅₀ values between 1.1 nM and 0.47 μM (**14a–24a**, **14b–24b**). Generally, the *trans*-isomers are more potent LSD1 inhibitors compared to the corresponding *cis*-isomers, with the exceptions of **13a** vs. **13b** (IC₅₀ = 3.3 μM vs. 0.11 μM), **15a** vs. **15b** (IC₅₀ = 7.0 nM vs. 1.1 nM), **20a** vs. **20b** (IC₅₀ = 25 nM vs. 8.3 nM), and **22a** vs. **22b** (IC₅₀ = 32 nM vs. 10 nM). In particular, a 2-methoxybenzyl (**14a**, **14b**) or 2-fluorobenzyl substituents (**15a**, **15b**) on the amino group enhanced the inhibitory potencies to single digit nanomolar levels, indicating that both electron donating and withdrawing groups are tolerated at the 2-position of the aromatic ring. Within the disubstituted benzyl analogues (**16a–19a**, **16b–19b**), all the *trans*-isomers were found to be more potent inhibitors of LSD1 compared to their corresponding *cis*-isomers. Among the 2,5-disubstituted benzyls analogues **16a–17a** and **16b–17b**, while the *trans*-isomers are almost equipotent at LSD1, the additional 5-fluoro substitution gave slightly more potent compounds than the 5-bromo substitution (**17b** vs. **16b**) for the *cis*-isomers, indicating potential steric issues at this region. Moving the fluoro substituent from the 5- to the 4-position of the benzyl group did not elicit significant changes in the IC₅₀ values (**17a**, **17b** vs. **18a**, **18b**). The 3,4-dimethoxy analogues (**19a**, **19b**) were almost as equipotent as the 2-methoxy analogue (**14a**, **14b**). For the trisubstituted benzyl analogue **20**, the *cis*-isomer (**20b**) was found to be 3-fold more potent than the *trans*-isomer (**20a**). Changing a benzyl to a 3-pyridylmethyl group (**21a–23a**, **21b–23b**) resulted in essentially equipotent isomers, with the exception of the 2-methoxy derivative, where the *trans*-isomer **22a** (IC₅₀ = 32 nM) was 3-fold less potent than the *cis*-isomer **22b** (IC₅₀ = 10 nM). The unsubstituted 3-pyridylmethyl analogues **21a** and **21b** were found to be 10-fold and 39-fold more potent than **8a** and **8b**, respectively. The 2-methoxy analogues **22a** and **22b** exhibited similar

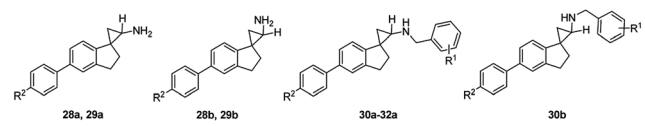
inhibitory activity against LSD1 compared with **21a** and **21b**. However, the 2-fluoro derivatives **23a** and **23b** were approximately 4-fold less potent than the unsubstituted derivatives **21a** and **21b** (IC₅₀ = 64 and 70 nM). Keeping the fluoro group intact, a pyridyl walk from 3- to the 2-position (**24a**, **24b** vs. **23a**, **23b**) resulted in at least a 4-fold reduction in their LSD1 inhibitory potencies. Swapping the aromatic group to an aliphatic morpholinecarbonyl (**25a**, **25b**) showed a further significant reduction in the LSD1 inhibitory activities, with IC₅₀ values of 1.4 and 22 μM, respectively. In terms of selectivity for LSD1 inhibition over other related enzymes LSD2, MAO-A and MAO-B, all of the synthesized target compounds were the most potent at inhibiting LSD1 with selectivity index varying between low (e.g. IC₅₀ values of **13b** and **18b** for LSD1 vs. MAO-A) and excellent (e.g. IC₅₀ values of **14a**, **15b**, **16a**, **19a** and **20b** for LSD1 vs. MAO-A, MAO-B and LSD2).

The subsequent round of structural activity relationship (SAR) investigations involved structural extensions on the aromatic ring of the dihydroindene. As shown in Scheme 3, the commercially available 5-bromo-2,3-dihydro-1H-inden-1-one (**26**) were used as the starting material and subjected to the conditions



Scheme 3 ^aReagents and conditions: (a) Pd(PPh₃)₄ (cat.), boronic acid, Na₂CO₃, DMF, 80 °C; (b) 4 M HCl in EtOAc, rt; (c) substituted benzaldehyde, NaBH₄, MeOH, rt.



Table 2 *In vitro* inhibitory activities of **28a–32a** and **28b–30b** against LSD1^a


Compound	R ¹	R ²	LSD1, IC ₅₀ (μM)
1	—	—	22
8a	—	—	0.17 ± 0.01
8b	—	—	0.78 ± 0.05
28a	—	H	0.10 ± 0.01
28b	—	H	2.7 ± 0.2
29a	—	F	0.30 ± 0.01
29b	—	F	6.0 ± 0.8
30a	2-OCH ₃ , 5-F	H	1.7 ± 0.1
30b	2-OCH ₃ , 5-F	H	4.4 ± 0.3
31a	2-Cl, 3,4-di-OCH ₃	H	8.9 ± 1.2
32a	2-OCH ₃ , 5-F	F	2.6 ± 0.5

^a See Experimental Section. Data represent mean values ± SEM of eight-point experiments each performed from three independent experiments. Positive control: compound **1**.

as previously outlined in Scheme 2. The isomers **27a** and **27b** were separated by flash chromatography and the relative stereochemistry assigned based on a combination of their COSY and NOESY studies. Suzuki coupling of **27a** with aromatic boronic acid in the presence of Pd(PPh₃)₄ at 80 °C in degassed 1 M Na₂CO₃ (aq)/DMF, followed by deprotection of the Boc group afforded the desired compounds **28a** and **29a**. Compounds **28b** and **29b** were synthesized following identical procedures with **27b** as the starting material. The final compounds **30a–32a** and **30b** were readily accessed *via* reductive amination of the corresponding precursors with various substituted benzaldehydes and NaBH₄ as the reducing agent. Their inhibitory activities at LSD1 and related enzymes are shown in Table 2.

As demonstrated in Table 2, an unsubstituted benzene ring extension at the aromatic group of the dihydroindene gave opposite effects depending on the stereochemistry of the cyclopropanamine. For the *trans*-isomers, a very slight increase in potency was observed (**28a** vs. **8a**), whereas an opposite trend was seen for the *cis*-isomers (**28b** vs. **8b**), with **28b** having an IC₅₀ value of 2.7 μM against LSD1. A 4-fluoro substitution on the newly added benzene ring resulted in approximately 3-fold reduction in the LSD1 inhibitory potencies (**29a**, **29b** vs. **28a**, **28b**). The remaining synthesized compounds **30a**, **30b**, **31a** and **32a** all showed IC₅₀ values in the single digit micromolar range, indicating a potentially undesired steric effect at this region. As the most potent LSD1 inhibitor arising from this biphenyl series, compound **28a** was further tested against other enzymes MAO-A, MAO-B and LSD2, with IC₅₀ values of 0.46 μM, 0.17 μM and 94 μM, respectively.

Conclusion

In summary, a novel series of 2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine analogues as potent LSD1 inhibitors have

been developed. In line with the conformational restriction conferred by the spirocycle to the tranlylcypromine system, compounds **8a** and **8b** displayed significant improvements in their LSD1 inhibitory potencies and high selectivities for MAO-A. In order to further explore the SAR, structural modifications on the amino group and the benzene ring of the dihydroindene were found to give more potent compounds. Specifically, the addition of substituted benzyl moieties to the amino group (**13a–25a**, **13b–25b**) showed single digit nanomolar potencies against LSD1 and excellent selectivity profiles against the homologous MAO enzymes and LSD2. While most of the *trans*-isomers were generally found to be more potent than the corresponding *cis*-isomers, there were some exceptions in the SAR data. The additional aromatic moiety at the benzene ring of the dihydroindene (**28a–32a**, **28b–30b**) resulted in a significant drop of the LSD1 inhibitory potencies, indicating an unfavorable steric clash at this region. Overall, these studies warrant the further development of spirocyclic tranlylcypromine derivatives as potent and selective LSD1 inhibitors.

Experimental

Chemistry

Starting materials, reagents, and solvents were purchased from commercial suppliers and used without further purification, unless otherwise stated. Anhydrous tetrahydrofuran (THF) and CH₂Cl₂ were obtained by distillation over sodium wire or CaH₂, respectively. All non-aqueous reactions were run under a nitrogen atmosphere with exclusion of moisture from reagents, and all reaction vessels were oven-dried. The progress of reactions was monitored by TLC on SiO₂. Spots were visualized by their quenching of the fluorescence of an indicator admixed to the SiO₂ layer, or by dipping into phosphomolybdic acid ethanol solution followed by heating. SiO₂ for flash chromatography was of 200–300 mesh particle size, and an EtOAc/PE mixture or gradient was used unless stated otherwise. ¹H NMR spectra were recorded at a spectrometer frequency of 400 MHz, ¹³C NMR spectra at 101 MHz. Chemical shifts are reported in δ (ppm) using the δ 0 signal of tetramethylsilane (TMS) as internal standard. High resolution mass spectra were performed using a Bruker ESI-TOF high-resolution mass spectrometer and Waters Micromass Q-TOF micro Synapt high definition mass spectrometer.

1-Methylene-2,3-dihydro-1H-indene (10). To a solution of 2,3-dihydro-1H-inden-1-one (**9**, 4.00 g, 30.3 mmol) and methyltriphenylphosphonium bromide (12.97 g, 36.32 mmol) in THF (20 mL) was added potassium *tert*-butoxide (4.08 g, 36.32 mmol) in THF (20 mL) *via* an addition funnel over 0.5 h. The resulting mixture was stirred at room temperature for 16 h. The solvent was removed under vacuum and the residue was purified by flash chromatography on silica gel, eluting with PE/EtOAc (100 : 1) to provide the title compound **10**. Colorless oil; yield 87%. ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.47 (m, 1H), 7.25–7.23 (m, 1H), 7.21–7.16 (m, 2H), 5.45–5.43 (m, 1H), 5.02–5.01 (m, 1H), 2.96 (t, *J* = 7.0 Hz, 2H), 2.80–2.77 (m, 2H).

Ethyl 2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-carboxylate (11a and 11b). To a solution of **10** (3.42 g, 26.27



mmol) and rhodium(II) acetate dimer (115 mg, 0.26 mmol) in refluxing CH_2Cl_2 (5 mL) was added ethyl diazoacetate (8.98 g, 78.81 mmol) in CH_2Cl_2 (2 mL) *via* syringe pump over 1 h. After refluxing for 3 h the resulting mixture was stirred at room temperature overnight. The solvent was removed under vacuum and the residue was purified by flash chromatography on silica gel, eluting with PE/EtOAc (100 : 1) to provide the title compounds **11a** and **11b** as a mixture. Colorless oil; total yield 59%. The diastereoisomers **11a** and **11b** were not isolated and used directly in the next reaction.

tert-Butyl ((2*R*)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-yl)carbamate (12a) and tert-butyl ((2*S*)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-yl)carbamate (12b). To a stirred solution of **11a** and **11b** (3.35 g, 15.49 mmol) in EtOH (10 mL) was added KOH (2.61 g, 46.47 mmol). After refluxing for 3 h, the reaction was cooled to rt. EtOAc (20 mL) was added to the reaction mixture, followed by extraction with H_2O (3 $\times$ 30 mL). A 10% aqueous hydrochloric acid solution was added to the combined aqueous layers until pH value dropped to 5–6, which was then extracted with EtOAc (3 $\times$ 30 mL). The combined organic layers were washed with brine (1 $\times$ 30 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford an oil. This residue was then reacted with triethylamine (6.4 mL, 46.47 mmol) and diphenylphosphorylazide (6.7 mL, 30.98 mmol) in anhydrous toluene (20 mL) at 0 $^\circ\text{C}$ while stirring under an argon atmosphere. The reaction mixture was warmed to 25 $^\circ\text{C}$ over 4 h, then washed with water (3 $\times$ 50 mL), brine (1 $\times$ 30 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residual azide was dissolved in anhydrous *tert*-butanol (100 mL) while stirring and heated to reflux for 6 h. After completion, the reaction was cooled to 25 $^\circ\text{C}$ and concentrated *in vacuo* to afford a brown oil. The oil was diluted with EtOAc (50 mL) and washed with saturated sodium bicarbonate (1 $\times$ 50 mL), brine (1 $\times$ 30 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude carbamate was purified by flash chromatography in PE/EtOAc (30 : 1) to yield the pure product **12a** (first elution) and **12b** (second elution). **12a**: white solid, yield 27%. ^1H NMR (400 MHz, CDCl_3) δ 7.18 (d, J = 4.0 Hz, 1H), 7.11–7.10 (m, 2H), 6.65–6.63 (m, 1H), 4.78 (s, 1H), 3.12–2.99 (m, 2H), 2.75 (s, 1H), 2.18–2.02 (m, 2H), 1.44–1.33 (m, 9H), 1.26–0.90 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 156.4, 146.2, 143.7, 126.4, 126.1, 124.3, 118.5, 79.5, 36.2, 32.9, 30.8, 28.9, 28.3, 21.4. **12b**: white solid; yield 19%. ^1H NMR (400 MHz, CDCl_3) δ 7.24–7.20 (m, 1H), 7.15–7.09 (m, 2H), 6.81 (s, 1H), 4.86–4.67 (m, 1H), 3.16–2.92 (m, 2H), 2.76 (s, 1H), 2.28–1.90 (m, 2H), 1.31–1.12 (m, 11H). ^{13}C NMR (101 MHz, CDCl_3) δ 156.3, 145.7, 142.4, 126.2, 125.8, 124.4, 121.2, 79.2, 36.2, 35.1, 33.4, 30.8, 28.2, 19.6.

(2*R*)-2',3'-Dihydrospiro[cyclopropane-1,1'-inden]-2-amine hydrochloride (8a). A solution of **12a** (300 mg, 1.16 mmol) and 4 M HCl in EtOAc (5 mL) was stirred at room temperature overnight. The precipitated solid was filtered, washed with diethyl ether and dried to afford **8a** as hydrochloride salt. Yellow solid; yield 98%. ^1H NMR (400 MHz, CD_3OD) δ 7.23–7.21 (m, 1H), 7.18–7.12 (m, 2H), 6.77–6.75 (m, 1H), 3.14 (t, J = 7.6 Hz, 2H), 2.88 (dd, J = 8.0, 4.8 Hz, 1H), 2.34–2.20 (m, 2H), 1.44–1.27 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 145.4, 144.8, 128.2, 128.0, 125.5, 120.0,

35.3, 31.9, 31.5, 29.4, 19.9. HRMS (ESI): calcd for $\text{C}_{11}\text{H}_{14}\text{N}$ [$\text{M} + \text{H}$] $^+$, 160.1121; found 160.1114.

(2*S*)-2',3'-Dihydrospiro[cyclopropane-1,1'-inden]-2-amine hydrochloride (8b). This compound was synthesized from **12b** according to the methodology described for **12a**. Yellow solid; yield 94%. ^1H NMR (400 MHz, CD_3OD) δ 7.32–7.31 (m, 1H), 7.26–7.21 (m, 2H), 7.08–7.06 (m, 1H), 3.18–2.94 (m, 2H), 2.88 (dd, J = 7.6, 4.8 Hz, 1H), 2.38–1.94 (m, 2H), 1.52–1.41 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 147.5, 140.4, 128.7, 127.7, 126.3, 121.9, 36.6, 35.0, 33.1, 31.5, 15.7. HRMS (ESI): calcd for $\text{C}_{11}\text{H}_{14}\text{N}$ [$\text{M} + \text{H}$] $^+$, 160.1121; found 160.1124.

(2*R*)-*N*-Benzyl-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine (13a). Triethylamine (39 mg, 0.39 mmol) was added to a solution of **8a** (50 mg, 0.26 mmol) in MeOH (2 mL) at rt to produce the free amine. Then benzaldehyde (28 mg, 0.26 mmol) was added and the mixture was stirred at rt for 0.5 h. Molecular sieves type 4 Å (300 mg) were added and the mixture was stirred for another 0.25 h. Sodium borohydride (15 mg, 0.39 mmol) was then added in a single portion. After overnight stirring, the mixture was then filtered and the solvent removed *in vacuo* to give the crude product which was partitioned between saturated NaHCO_3 (20 mL) and EtOAc (20 mL), followed by extraction with EtOAc (3 $\times$ 30 mL). The organic phase was combined, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography in PE/EtOAc (15 : 1) to yield the pure product **13a**. Yellow oil; yield 42%. ^1H NMR (400 MHz, CDCl_3) δ 7.32–7.28 (m, 4H), 7.26–7.23 (m, 1H), 7.20–7.17 (m, 1H), 7.12–7.08 (m, 2H), 6.64–6.60 (m, 1H), 3.86–3.78 (m, 2H), 3.08–2.92 (m, 2H), 2.42–2.34 (m, 2H), 2.17–2.09 (m, 1H), 1.90 (s, 1H), 1.18–0.85 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 147.8, 143.8, 140.4, 128.4, 128.2, 127.0, 126.3, 125.7, 124.2, 118.4, 53.9, 44.8, 33.6, 30.9, 28.4, 22.0. HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{20}\text{N}$ [$\text{M} + \text{H}$] $^+$, 250.1590; found 250.1594.

(2*S*)-*N*-Benzyl-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine (13b). This compound was obtained from **8b** and benzaldehyde according to the methodology described for **13a**. Yellow oil; yield 39%. ^1H NMR (400 MHz, CDCl_3) δ 7.27–7.23 (m, 2H), 7.21–7.17 (m, 2H), 7.15–7.13 (m, 5H), 3.58–3.39 (m, 2H), 3.07–2.91 (m, 2H), 2.44 (dd, J = 7.0, 4.6 Hz, 1H), 2.23–1.82 (m, 2H), 1.08–1.01 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 145.2, 143.9, 140.5, 128.3, 128.2, 126.8, 125.7, 125.6, 124.0, 122.3, 53.5, 44.8, 35.5, 33.8, 30.8, 20.4. HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{20}\text{N}$ [$\text{M} + \text{H}$] $^+$, 250.1590; found 250.1601.

(2*R*)-*N*-(2-Methoxybenzyl)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine (14a). This compound was obtained from **8a** and 2-methoxybenzaldehyde according to the methodology described for **13a**. Yellow oil; yield 65%. ^1H NMR (400 MHz, CDCl_3) δ 7.23–7.17 (m, 3H), 7.11–7.05 (m, 2H), 6.89–6.85 (m, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.60–6.56 (m, 1H), 3.88–3.74 (m, 5H), 3.07–2.93 (m, 2H), 2.43–2.36 (m, 1H), 2.28 (dd, J = 7.4, 4.6 Hz, 1H), 2.15–2.07 (m, 1H), 2.03 (s, 1H), 1.15–0.85 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 157.6, 148.0, 143.8, 129.9, 128.4, 128.2, 126.2, 125.6, 124.1, 120.3, 118.4, 110.2, 55.1, 49.2, 44.7, 33.5, 30.9, 28.3, 22.0. HRMS (ESI): calcd for $\text{C}_{19}\text{H}_{22}\text{NO}$ [$\text{M} + \text{H}$] $^+$, 280.1696; found 280.1676.

(2*S*)-*N*-(2-Methoxybenzyl)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine (14b). This compound was obtained from **8b** and



2-methoxybenzaldehyde according to the methodology described for **13a**. Yellow oil; yield 62%. ^1H NMR (400 MHz, CDCl_3) δ 7.22–7.16 (m, 2H), 7.13–7.10 (m, 3H), 7.04–7.01 (m, 1H), 6.86–6.82 (m, 1H), 6.78 (d, $J = 8.0$ Hz, 1H), 3.76 (s, 3H), 3.61–3.44 (m, 2H), 3.06–2.89 (m, 2H), 2.39 (dd, $J = 6.8, 5.2$ Hz, 1H), 2.18–1.81 (m, 3H), 1.04–1.00 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 157.6, 145.1, 144.2, 130.0, 128.6, 128.0, 125.5, 125.5, 123.9, 122.4, 120.2, 110.0, 55.1, 48.7, 44.7, 35.7, 33.7, 30.8, 20.7. HRMS (ESI): calcd for $\text{C}_{19}\text{H}_{22}\text{NO}$ $[\text{M} + \text{H}]^+$, 280.1696; found 280.1707.

(2R)-N-(2-Fluorobenzyl)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine (15a). This compound was obtained from **8a** and 2-fluorobenzaldehyde according to the methodology described for **13a**. Yellow oil; yield 52%. ^1H NMR (400 MHz, CDCl_3) δ 7.30–7.26 (m, 1H), 7.24–7.16 (m, 2H), 7.12–6.98 (m, 4H), 6.62–6.58 (m, 1H), 3.92–3.81 (m, 2H), 3.07–2.92 (m, 2H), 2.41–2.30 (m, 2H), 2.15–2.10 (m, 1H), 1.80 (s, 1H), 1.17–0.85 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.3 (d, $J_{\text{C-F}} = 246.5$ Hz), 147.8, 143.9, 130.6 (d, $J_{\text{C-F}} = 4.9$ Hz), 128.8 (d, $J_{\text{C-F}} = 8.2$ Hz), 127.4 (d, $J_{\text{C-F}} = 15.3$ Hz), 126.4, 125.9, 124.3, 124.1 (d, $J_{\text{C-F}} = 3.5$ Hz), 118.5, 115.4 (d, $J_{\text{C-F}} = 21.9$ Hz), 47.5 (d, $J_{\text{C-F}} = 2.9$ Hz), 44.7, 33.7, 31.0, 28.4, 22.2. HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{19}\text{FN}$ $[\text{M} + \text{H}]^+$, 268.1496; found 268.1499.

(2S)-N-(2-Fluorobenzyl)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine (15b). This compound was obtained from **8b** and 2-fluorobenzaldehyde according to the methodology described for **13a**. Yellow oil; yield 60%. ^1H NMR (400 MHz, CDCl_3) δ 7.22–7.09 (m, 6H), 7.03–6.93 (m, 2H), 3.66–3.48 (m, 2H), 3.06–2.90 (m, 2H), 2.41 (dd, $J = 7.0, 4.6$ Hz, 1H), 2.20–1.81 (m, 2H), 1.65 (s, 1H), 1.06–1.00 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.3 (d, $J_{\text{C-F}} = 246.4$ Hz), 145.2, 144.0, 130.8 (d, $J_{\text{C-F}} = 5.0$ Hz), 128.6 (d, $J_{\text{C-F}} = 8.1$ Hz), 127.4 (d, $J_{\text{C-F}} = 15.4$ Hz), 125.8, 125.7, 124.1, 123.9 (d, $J_{\text{C-F}} = 3.5$ Hz), 122.5, 115.2 (d, $J_{\text{C-F}} = 22.0$ Hz), 46.8 (d, $J_{\text{C-F}} = 2.8$ Hz), 44.6, 35.6, 33.9, 30.9, 20.8. HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{19}\text{FN}$ $[\text{M} + \text{H}]^+$, 268.1496; found 268.1502.

(2R)-N-(5-Bromo-2-methoxybenzyl)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine (16a). This compound was obtained from **8a** and 5-bromo-2-methoxybenzaldehyde according to the methodology described for **13a**. Yellow oil; yield 57%. ^1H NMR (400 MHz, CDCl_3) δ 7.34–7.29 (m, 2H), 7.20–7.18 (m, 1H), 7.12–7.07 (m, 2H), 6.69 (d, $J = 8.8$ Hz, 1H), 6.62–6.58 (m, 1H), 3.86–3.67 (m, 5H), 3.08–2.93 (m, 2H), 2.40–2.33 (m, 1H), 2.27 (dd, $J = 7.2, 4.8$ Hz, 1H), 2.15–2.08 (m, 1H), 2.03–2.00 (m, 1H), 1.17–0.85 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 156.7, 147.8, 143.8, 132.4, 130.8, 130.7, 126.3, 125.7, 124.2, 118.5, 112.7, 111.9, 55.4, 48.6, 44.6, 33.6, 30.8, 28.3, 22.0. HRMS (ESI): calcd for $\text{C}_{19}\text{H}_{21}\text{BrNO}$ $[\text{M} + \text{H}]^+$, 358.0801; found 358.0768.

(2S)-N-(5-Bromo-2-methoxybenzyl)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine (16b). This compound was obtained from **8b** and 5-bromo-2-methoxybenzaldehyde according to the methodology described for **13a**. Yellow oil; yield 67%. ^1H NMR (400 MHz, CDCl_3) δ 7.26–7.23 (m, 1H), 7.19–7.16 (m, 1H), 7.14–7.07 (m, 4H), 6.61 (d, $J = 8.4$ Hz, 1H), 3.72 (s, 3H), 3.60–3.36 (m, 2H), 3.05–2.89 (m, 2H), 2.36 (dd, $J = 6.8, 4.8$ Hz, 1H), 2.20–1.80 (m, 3H), 1.05–0.98 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 156.5, 145.1, 143.9, 132.6, 130.8, 130.5, 125.6, 125.5, 123.9, 122.3, 112.4, 111.7, 55.3, 48.2, 44.7, 35.5,

33.8, 30.8, 20.5. HRMS (ESI): calcd for $\text{C}_{19}\text{H}_{21}\text{BrNO}$ $[\text{M} + \text{H}]^+$, 358.0801; found 358.0795.

(2R)-N-(5-Fluoro-2-methoxybenzyl)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine (17a). This compound was obtained from **8a** and 5-fluoro-2-methoxybenzaldehyde according to the methodology described for **13a**. Yellow oil; yield 65%. ^1H NMR (400 MHz, CDCl_3) δ 7.21–7.17 (m, 1H), 7.11–7.07 (m, 2H), 6.97 (dd, $J = 8.6, 3.0$ Hz, 1H), 6.91–6.86 (m, 1H), 6.73 (dd, $J = 8.8, 4.4$ Hz, 1H), 6.61–6.57 (m, 1H), 3.88–3.68 (m, 5H), 3.08–2.94 (m, 2H), 2.42–2.35 (m, 1H), 2.28 (dd, $J = 7.4, 4.6$ Hz, 1H), 2.15–2.08 (m, 1H), 1.93 (s, 1H), 1.16–0.85 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 156.9 (d, $J_{\text{C-F}} = 239.3$ Hz), 153.6 (d, $J_{\text{C-F}} = 1.9$ Hz), 147.9, 143.8, 130.3 (d, $J_{\text{C-F}} = 6.7$ Hz), 126.3, 125.7, 124.2, 118.5, 116.5 (d, $J_{\text{C-F}} = 23.2$ Hz), 113.6 (d, $J_{\text{C-F}} = 22.8$ Hz), 110.9 (d, $J_{\text{C-F}} = 8.2$ Hz), 55.6, 48.8 (d, $J_{\text{C-F}} = 0.7$ Hz), 44.6, 33.6, 30.9, 28.3, 22.0. HRMS (ESI): calcd for $\text{C}_{19}\text{H}_{21}\text{FNO}$ $[\text{M} + \text{H}]^+$, 298.1602; found 298.1593.

(2S)-N-(5-Fluoro-2-methoxybenzyl)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine (17b). This compound was obtained from **8b** and 5-fluoro-2-methoxybenzaldehyde according to the methodology described for **13a**. Yellow oil; yield 70%. ^1H NMR (400 MHz, CDCl_3) δ 7.23–7.21 (m, 1H), 7.17–7.14 (m, 3H), 6.90–6.80 (m, 2H), 6.71 (dd, $J = 8.8, 4.4$ Hz, 1H), 3.76 (s, 3H), 3.64–3.42 (m, 2H), 3.09–2.93 (m, 2H), 2.42 (dd, $J = 6.8, 4.8$ Hz, 1H), 2.23–1.84 (m, 3H), 1.09–1.03 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 156.8 (d, $J_{\text{C-F}} = 239.0$ Hz), 153.6 (d, $J_{\text{C-F}} = 2.0$ Hz), 145.1, 144.0, 130.4 (d, $J_{\text{C-F}} = 6.7$ Hz), 125.7, 125.6, 124.0, 122.4, 116.6 (d, $J_{\text{C-F}} = 23.1$ Hz), 113.4 (d, $J_{\text{C-F}} = 22.9$ Hz), 110.7 (d, $J_{\text{C-F}} = 8.3$ Hz), 55.7, 48.3 (d, $J_{\text{C-F}} = 0.8$ Hz), 44.7, 35.6, 33.8, 30.8, 20.7. HRMS (ESI): calcd for $\text{C}_{19}\text{H}_{21}\text{FNO}$ $[\text{M} + \text{H}]^+$, 298.1602; found 298.1584.

(2R)-N-(4-Fluoro-2-methoxybenzyl)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine (18a). This compound was obtained from **8a** and 4-fluoro-2-methoxybenzaldehyde according to the methodology described for **13a**. Yellow oil; yield 71%. ^1H NMR (400 MHz, CDCl_3) δ 7.19–7.17 (m, 1H), 7.14–7.07 (m, 3H), 6.59–6.56 (m, 2H), 6.54–6.53 (m, 1H), 3.83–3.70 (m, 5H), 3.07–2.92 (m, 2H), 2.40–2.33 (m, 1H), 2.25 (dd, $J = 7.6, 4.8$ Hz, 1H), 2.14–2.07 (m, 1H), 1.97 (s, 1H), 1.15–0.84 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.9 (d, $J_{\text{C-F}} = 245.2$ Hz), 157.6 (d, $J_{\text{C-F}} = 9.8$ Hz), 146.9, 142.7, 129.6 (d, $J_{\text{C-F}} = 9.9$ Hz), 125.3, 124.6, 123.2, 123.1 (d, $J_{\text{C-F}} = 3.3$ Hz), 117.4, 105.3 (d, $J_{\text{C-F}} = 21.0$ Hz), 97.7 (d, $J_{\text{C-F}} = 25.9$ Hz), 54.3, 47.6, 43.6, 32.5, 29.8, 27.2, 20.9. HRMS (ESI): calcd for $\text{C}_{19}\text{H}_{21}\text{FNO}$ $[\text{M} + \text{H}]^+$, 298.1602; found 298.1606.

(2S)-N-(4-Fluoro-2-methoxybenzyl)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine (18b). This compound was obtained from **8b** and 4-fluoro-2-methoxybenzaldehyde according to the methodology described for **13a**. Yellow oil; yield 66%. ^1H NMR (400 MHz, CDCl_3) δ 7.19–7.17 (m, 1H), 7.14–7.07 (m, 3H), 6.27 (t, $J = 7.6$ Hz, 1H), 6.54–6.47 (m, 2H), 3.72 (s, 3H), 3.59–3.36 (m, 2H), 3.03–2.88 (m, 2H), 2.37 (dd, $J = 6.8, 4.8$ Hz, 1H), 2.19–2.12 (m, 1H), 1.92 (s, 1H), 1.85–1.79 (m, 1H), 1.05–1.00 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.8 (d, $J_{\text{C-F}} = 244.9$ Hz), 157.5 (d, $J_{\text{C-F}} = 9.7$ Hz), 144.1, 143.0, 129.6 (d, $J_{\text{C-F}} = 9.8$ Hz), 124.6, 124.5, 123.0 (d, $J_{\text{C-F}} = 2.8$ Hz), 122.9, 121.2, 105.1 (d, $J_{\text{C-F}} = 20.9$ Hz), 97.6 (d, $J_{\text{C-F}} = 26.0$ Hz), 54.3,



(400 MHz, CDCl_3) δ 8.03 (d, J = 4.8 Hz, 1H), 7.54–7.49 (m, 1H), 7.19–7.17 (m, 1H), 7.14–7.07 (m, 3H), 7.06–7.02 (m, 1H), 3.69–3.47 (m, 2H), 3.03–2.89 (m, 2H), 2.41 (dd, J = 6.8, 4.8 Hz, 1H), 2.22–2.14 (m, 1H), 1.87–1.81 (m, 1H), 1.76 (s, 1H), 1.08–1.00 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.8 (d, $J_{\text{C-F}}$ = 239.7 Hz), 145.8 (d, $J_{\text{C-F}}$ = 14.8 Hz), 145.1, 143.5, 140.8 (d, $J_{\text{C-F}}$ = 5.9 Hz), 125.8, 125.5, 124.0, 122.4, 122.1 (d, $J_{\text{C-F}}$ = 30.0 Hz), 121.3 (d, $J_{\text{C-F}}$ = 4.2 Hz), 46.4, 44.5, 35.4, 30.7, 29.7, 20.5. HRMS (ESI): calcd for $\text{C}_{17}\text{H}_{18}\text{FN}_2$ $[\text{M} + \text{H}]^+$, 269.1449; found 269.1448.

(2R)-N-((3-Fluoropyridin-2-yl)methyl)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine (24a). This compound was obtained from **8a** and 3-fluoropicolinaldehyde according to the methodology described for **13a**. Yellow oil; yield 47%. ^1H NMR (400 MHz, CDCl_3) δ 8.39–8.37 (m, 1H), 7.37–7.32 (m, 1H), 7.22–7.18 (m, 2H), 7.13–7.08 (m, 2H), 6.64–6.60 (m, 1H), 4.09–4.01 (m, 2H), 3.07–3.03 (m, 2H), 2.47–2.36 (m, 3H), 2.20–2.12 (m, 1H), 1.21–0.92 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 157.5 (d, $J_{\text{C-F}}$ = 257.6 Hz), 147.8 (d, $J_{\text{C-F}}$ = 15.8 Hz), 147.7, 144.9 (d, $J_{\text{C-F}}$ = 5.3 Hz), 143.9, 126.3, 125.8, 124.2, 123.2 (d, $J_{\text{C-F}}$ = 3.7 Hz), 122.6 (d, $J_{\text{C-F}}$ = 19.1 Hz), 118.5, 48.4, 44.7, 33.5, 30.9, 28.3, 22.1. HRMS (ESI): calcd for $\text{C}_{17}\text{H}_{18}\text{FN}_2$ $[\text{M} + \text{H}]^+$, 269.1449; found 269.1431.

(2S)-N-((3-Fluoropyridin-2-yl)methyl)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine (24b). This compound was obtained from **8b** and 3-fluoropicolinaldehyde according to the methodology described for **13a**. Yellow oil; yield 59%. ^1H NMR (400 MHz, CDCl_3) δ 8.30 (d, J = 4.8 Hz, 1H), 7.25–7.21 (m, 1H), 7.16–7.07 (m, 5H), 3.81–3.71 (m, 2H), 3.04–2.87 (m, 2H), 2.45 (dd, J = 6.8, 4.8 Hz, 1H), 2.22 (s, 1H), 2.17–1.82 (m, 2H), 1.07–1.00 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 157.6 (d, $J_{\text{C-F}}$ = 257.6 Hz), 148.1 (d, $J_{\text{C-F}}$ = 15.7 Hz), 145.0, 144.8 (d, $J_{\text{C-F}}$ = 5.4 Hz), 143.9, 125.6, 125.5, 123.9, 123.1 (d, $J_{\text{C-F}}$ = 3.6 Hz), 122.5, 122.4 (d, $J_{\text{C-F}}$ = 19.2 Hz), 48.3, 44.8, 35.6, 33.7, 30.7, 20.8. HRMS (ESI): calcd for $\text{C}_{17}\text{H}_{18}\text{FN}_2$ $[\text{M} + \text{H}]^+$, 269.1449; found 269.1447.

2-(((2R)-2',3'-Dihydrospiro[cyclopropane-1,1'-inden]-2-yl)amino)-1-morpholinoethan-1-one hydrochloride (25a). To a stirred suspension of NaH (28 mg, 50% in mineral oil, 0.59 mmol) in anhydrous DMF (2 mL) at 0 °C was added a solution of **12a** (100 mg, 0.39 mmol). After an additional 0.5 h stirring, 2-chloro-1-morpholinoethan-1-one (77 mg, 0.47 mmol) was added at 0 °C and the mixture was stirred for another 1 h, slowly warming to rt. The reaction mixture was poured into ice-water and extracted with EtOAc (3 $\times$ 30 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered and evaporated. The crude residue was purified by flash chromatography using CH_2Cl_2 : CH_3OH (60 : 1) to afford a yellow solid, which was then immediately treated with 4 M HCl in ethyl acetate (5 mL) and stirred at rt overnight. The precipitated solid was filtered, washed with diethyl ether and dried to afford **25a** as a hydrochloride salt. Yellow solid; yield 48%. ^1H NMR (400 MHz, CD_3OD) δ 7.24–7.16 (m, 3H), 6.77 (d, J = 4.0 Hz, 1H), 4.31 (s, 2H), 3.70–3.60 (m, 6H), 3.48 (s, 2H), 3.17–3.06 (m, 3H), 2.40–2.33 (m, 2H), 1.45 (s, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 164.9, 145.1, 144.8, 128.4, 128.0, 125.5, 120.1, 67.5, 67.4, 50.0, 46.3, 43.5, 42.9, 33.0, 31.7, 29.5, 19.5. HRMS (ESI): calcd for $\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$, 287.1754; found 287.1735.

2-(((2S)-2',3'-Dihydrospiro[cyclopropane-1,1'-inden]-2-yl)amino)-1-morpholinoethan-1-one hydrochloride (25b). This compound

was synthesized from **8b** according to the methodology described for **25a**. Yellow solid; yield 45%. ^1H NMR (400 MHz, CD_3OD) δ 7.36 (d, J = 6.4 Hz, 1H), 7.30–7.20 (m, 3H), 4.16–3.78 (m, 2H), 3.66–3.59 (m, 4H), 3.57–3.54 (m, 2H), 3.31–3.30 (m, 2H), 3.22–3.13 (m, 1H), 3.07 (dd, J = 7.8, 4.6 Hz, 1H), 3.02–2.96 (m, 1H), 2.40–1.94 (m, 2H), 1.75–1.45 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 164.6, 147.6, 140.1, 129.0, 128.0, 126.5, 121.7, 67.5, 67.3, 46.2, 43.6, 42.7, 36.7, 34.0, 31.5, 15.1. HRMS (ESI): calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{NaO}_2$ $[\text{M} + \text{Na}]^+$, 309.1573; found 309.1550.

tert-Butyl ((2R)-5'-bromo-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-yl)carbamate (27a). This compound was obtained from 5-bromo-2,3-dihydro-1H-inden-1-one (**26**) as starting material and prepared according to the methodology described for **12a**. White solid; yield 24%. ^1H NMR (400 MHz, CDCl_3) δ 7.31 (s, 1H), 7.21 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 4.73 (s, 1H), 3.11–2.95 (m, 2H), 2.69 (s, 1H), 2.14–2.04 (m, 2H), 1.43 (s, 9H), 1.35–1.32 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 156.4, 146.2, 145.4, 129.4, 127.4, 119.9, 119.6, 79.7, 36.5, 32.8, 30.6, 28.9, 28.3, 21.0.

tert-Butyl ((2S)-5'-bromo-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-yl)carbamate (27b). This compound was obtained from 5-bromo-2,3-dihydro-1H-inden-1-one (**26**) as starting material and prepared according to the methodology described for **12b**. White solid; yield 22%. ^1H NMR (400 MHz, CDCl_3) δ 7.35 (s, 1H), 7.24 (d, J = 8.4 Hz, 1H), 6.68 (s, 1H), 4.56 (s, 1H), 3.17–2.91 (m, 2H), 2.75 (s, 1H), 2.30–1.91 (m, 2H), 1.31–1.22 (m, 9H), 1.14 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 156.1, 148.0, 141.6, 128.6, 127.5, 122.5, 119.9, 79.4, 37.2, 36.1, 34.9, 30.6, 28.2, 19.3.

General procedure for the synthesis of (2R)-5'-phenyl-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine hydrochloride (28a)

To a mixture of **27a** (150 mg, 0.44 mmol) and tetrakis(triphenylphosphine)palladium (25 mg, 0.022 mmol) in DMF (2.5 mL) was added phenylboronic acid (65 mg, 0.53 mmol) immediately followed by aqueous Na_2CO_3 solution (2 M, 0.4 mL H_2O). The mixture was stirred at 80 °C for 16 h under an argon atmosphere. After cooling, the reaction mixture was filtered and the filtrate was extracted with EtOAc (3 $\times$ 30 mL). The combined organic layers were washed with water, dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography in PE/EtOAc (25 : 1) to yield the pure product as a white solid. A solution of HCl in ethyl acetate (4 M, 5 mL) was then added to the white solid. After stirring at room temperature overnight, the precipitated solid was filtered off, washed with diethyl ether and dried to afford **28a** as a hydrochloride salt. Yellow solid; yield 63%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.73 (s, 2H), 7.63–7.61 (m, 2H), 7.51 (s, 1H), 7.46–7.42 (m, 3H), 7.36–7.32 (m, 1H), 6.93 (d, J = 8.0 Hz, 1H), 3.18–3.04 (m, 2H), 2.85–2.82 (m, 1H), 2.37–2.17 (m, 2H), 1.38–1.35 (m, 2H). ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 144.4, 144.3, 140.4, 139.0, 128.9, 127.2, 126.7, 125.4, 122.5, 119.8, 33.6, 30.3, 30.1, 28.3, 18.8. HRMS (ESI): calcd for $\text{C}_{17}\text{H}_{18}\text{N}$ $[\text{M} + \text{H}]^+$, 236.1439; found 236.1425.

(2S)-5'-Phenyl-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-amine hydrochloride (28b). This compound was obtained from



MAO-A and MAO-B inhibition assay

MAO-A and MAO-B enzymes were purchased from Sigma-Aldrich and the inhibition assay was tested with Promega MAO-Glo™ Assay kit according to the manufacturer's protocol. The luminescent signals were detected using Envision (PerkinElmer). The test was carried out in triplicate. And the IC₅₀ data was calculated using the software GraphPad Prism 5, and chosen the equation "sigmoidal dose-response (variable slope)" for curve fitting.

Conflicts of interest

There are no conflicts of interest to declare.

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