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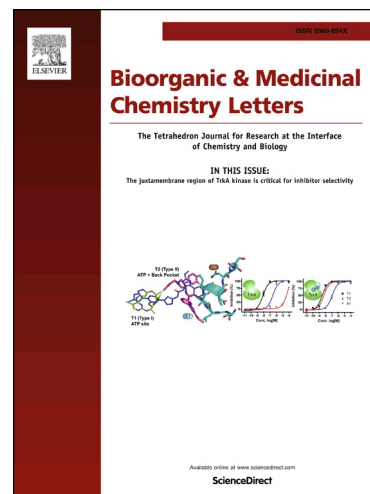
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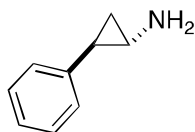


## Graphical Abstract

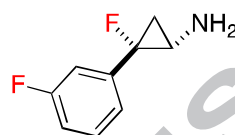
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Tranilcypromine

LSD1 enzyme inhibition  $IC_{50}$  25  $\mu$ MTHP-1 growth inhibition  $IC_{50}$  810  $\mu$ M

Fluorinated analogue

LSD1 enzyme inhibition  $IC_{50}$  6.7  $\mu$ MTHP-1 growth inhibition  $IC_{50}$  1.6  $\mu$ M



## Fluorinated tranlycypromine analogues as inhibitors of lysine-specific demethylase 1 (LSD1, KDM1A)

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### ABSTRACT

We report a series of tranlycypromine analogues containing a fluorine in the cyclopropyl ring. A number of compounds with additional *m*- or *p*- substitution of the aryl ring were micromolar inhibitors of the LSD1 enzyme. In cellular assays, the compounds inhibited the proliferation of acute myeloid leukemia cell lines. Increased levels of the biomarkers H3K4me2 and CD86 were consistent with LSD1 target engagement.

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The methylation of lysine residues is an important post-translational modification that occurs in histone proteins in the nucleosome as well as in non-histone proteins. The process is dynamically reversible through the action of lysine demethylases (KDMs), a family of enzymes that are further subdivided into the lysine-specific demethylases (KDM1, two human isoforms LSD1 and LSD2) and the Jumonji C demethylases (KDM2-7, over twenty human isoforms).<sup>1</sup> Historically, LSD1 was the first demethylase to be discovered and is recruited to the nucleosome as a component of diverse multi-protein complexes. Depending on the context and splice variant, LSD1 can exert either an activating or repressive effect on gene transcription by the demethylation of histone H3K4, H3K9 or H4K20 lysine residues.<sup>2-4</sup>

Although LSD1 is essential for normal function, its dysregulation in cancer, CNS disorders and viral infection has propelled interest in LSD1 as a drug discovery target. LSD1 shares a mechanistic homology with monoamine oxidase (MAO) as both enzymes cleave a substrate C-N bond to give the dealkylated amine and an aldehyde using FAD as an oxidizing cofactor (Fig 1). A number of diverse small molecule leads targeting LSD1 have been reported.<sup>5,6</sup> Some well-established MAO inhibitors also inhibit LSD1 among which the approved antidepressant tranylcypromine **1** (Fig 2) is the best characterized, acting as a suicide substrate that undergoes ring opening to iminium radical **2** that covalently modifies and inactivates the FAD cofactor.

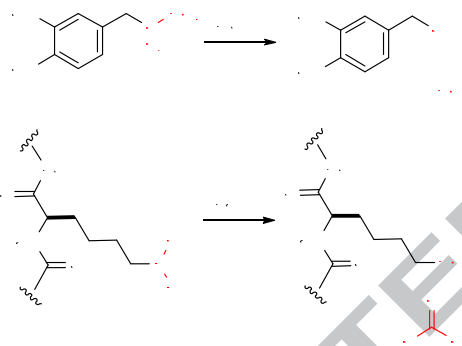


Fig. 1. Oxidative C-N cleavage by MAO and LSD enzymes.

Through LSD1 inhibition, tranylcypromine promotes differentiation in acute myeloid leukemia (AML) cells to overcome their resistance to all-*trans*-retinoic acid (ATRA).<sup>7</sup> Consequently, the drug is undergoing repositioning as an anticancer agent and clinical trials in combination with ATRA are underway. Meanwhile, as tranylcypromine itself is relatively modest in LSD1 inhibition ( $IC_{50} \sim 25 \mu M$ ), medicinal chemistry efforts have focused on second-generation analogues with higher potency.<sup>8-20</sup>

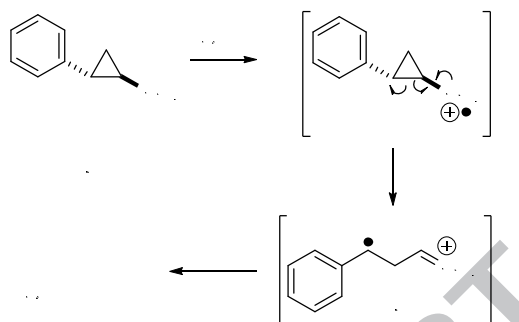


Fig. 2. Mechanism of MAO and LSD inactivation by tranylcypromine.

Despite the mechanistic similarity between amine oxidases, the structure-activity relationships among tranylcypromine analogues is distinct for MAOs versus LSD1. For example, we found that a cyclopropylamine bearing an alkoxy substituent in lieu of the aromatic ring in **1** was a nanomolar MAO inhibitor but inactive against LSD1.<sup>21</sup> In the present study, we were interested in the feasibility of incorporating cyclopropyl ring fluorination in tranylcypromines. While selected examples were previously reported as MAO inhibitors,<sup>22,23</sup> this type of substitution pattern had not been explored for LSD1 inhibition.

In preliminary experiments, we examined the *N*-benzyl derivative **3** (Fig 3) of monofluorinated tranylcypromine and homologated analogues **4** and **5** that contain a spacer between the amine and the cyclopropyl ring. In a fluorescence-based LSD1 enzyme assay that monitors  $H_2O_2$ , the product of FAD turnover, through its reaction with Amplex Red,<sup>12</sup> these compounds did not significantly inhibit LSD1 at a concentration of  $25 \mu M$  (the  $IC_{50}$  of tranylcypromine). The results are consistent with earlier studies by Burger and Haufe where **3-5** or their non-fluorinated congeners were inactive against MAOs.<sup>22,24</sup> Interestingly, the diphenyl analogue **6** was more potent than tranylcypromine with an  $IC_{50}$   $2.1 \pm 0.8 \mu M$ . Moreover, this is an increase by an order of magnitude compared to the activity against MAO A ( $IC_{50}$   $18 \pm 3 \mu M$ ) or MAO B ( $IC_{50}$   $37 \pm 2 \mu M$ ).<sup>23</sup> Overall, the experiments suggested that fluorination can be tolerated in the tranylcypromine scaffold for LSD1 inhibition. Since many analogues with a higher level of activity than the parent drug feature aromatic ring substitution, we next turned to compounds that contained additional functionalization of the benzene ring.

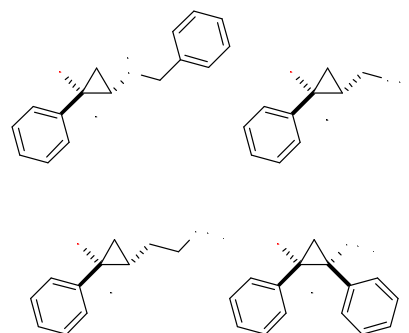
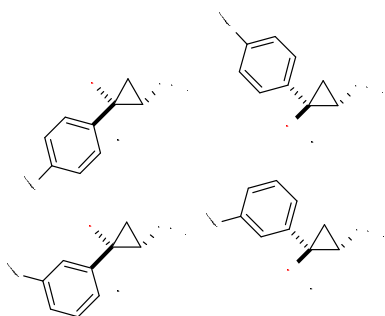


Fig. 3. Structures of initial tranylcypromine analogues investigated. All compounds are racemates.

We investigated a series of twenty-seven fluorinated tranylcypromines **7-10** (Fig 4) in which the phenyl ring contained electron donating or electron withdrawing substituents in the *para* or *meta*-position. Compounds **7-10** were prepared from the corresponding  $\alpha$ -fluorostyrenes through a four step procedure (details in the Supporting Material) involving Cu(I)-catalyzed cyclopropanation with diazoacetates, ester

saponification to the acids, Curtius rearrangement of the acids to Boc-amines and deprotection of the Boc group.<sup>22,23,25</sup> For the majority of compounds, two diastereomers were tested with the phenyl group located in either a *trans* (**7**, **9**) or *cis* (**8**, **10**) relationship with respect to the amine.



**Fig. 4.** Structures of fluorinated transylcypromines with *m*- or *p*-aryl substitution. All compounds are racemates.

After screening at a single concentration in the LSD1 enzyme inhibition assay, dose-response curves were determined for analogues with significant activity (**Table 1**). The simplest analogues **7a** and the *cis* diastereomer **8a** feature the addition of a fluorine without further modifications. Although **7a** and **8a** are respectively three-fold more active or equipotent to transylcypromine in MAO B inhibition,<sup>22</sup> a surprising loss of activity was observed for LSD1 inhibition. Meanwhile, the addition of methoxy, fluoro or trifluoromethyl groups to the phenyl ring of transylcypromine is known to boost LSD1 inhibition.<sup>14,19,24</sup> We found that introduction of these substituents restored the ability to significantly inhibit LSD in the fluorinated analogues **7g**, **9a**, **9c**, **9d** and **10d**. Finally, transylcypromine analogues containing the Cl, NO<sub>2</sub> or SF<sub>5</sub> substituents are undisclosed as LSD1 inhibitors in the literature. Our results indicate all three functional groups are compatible with affinity for this target as **7h**, **7i**, **9b** and **9e** were micromolar inhibitors.

Three of the *meta*-substituted fluorinated analogues **9a-c** together with a *cis* diastereomer **10c** were selected for further evaluation in growth inhibition assays using the acute myeloid

leukemia (AML) cell lines MV4-11 and THP-1 (**Table 2**). The nitro- substituted analogue **9b** was inactive in the tested concentration range whereas the methoxy- analogue **9a** and both fluoro- diastereomers **9c** and **10c** were micromolar in potency. Although **9c** differs from transylcypromine only by the addition of two fluorine atoms, it is >100-fold more potent in the cell assay. We profiled the effects of **9a** on the levels of biomarkers in MV4-11 cells to verify that the antiproliferative effect is due to the pharmacological suppression of LSD1. The compound exhibited a dose-dependent increase in H3K4me2 levels consistent with the inhibition of lysine demethylation (**Fig 5A**). In addition, treatment with **9a** increased the expression levels of CD86 (**Fig 5B**), a cell surface biomarker recently proposed as a surrogate readout for LSD1 inhibition.<sup>26</sup>

In summary, we have studied the effect of cyclopropyl ring fluorination on LSD1 activity within the transylcypromine class of irreversible amine oxidase inhibitors. The addition of a fluorine atom to transylcypromine by itself results in decreased LSD1 inhibition (unlike the increase in MAO inhibition). However, the introduction of an additional substitution in the phenyl ring has yielded a number of fluorinated LSD1 inhibitors that are more active than transylcypromine. Overall, *meta*-substitution is preferred to *para*- as all five *meta*-analogues **9a-e** displayed enhanced activity. Nevertheless, with the CF<sub>3</sub>- or SF<sub>5</sub>-substituents, the *para*-analogue was more active than its *meta*-counterpart. Although the diastereomers that retained transylcypromine's *trans* relationship between the aryl group and the amine (**7** versus **8**, **9** versus **10**) were generally superior, in the case of **9c/10c** and **9d/10d** the differences were negligible. Selected compounds **9a**, **9c** and **10c** inhibited cell proliferation in AML cell lines and increased the levels of the biomarkers H3K4me2 and CD86, supporting a LSD1-dependent cellular mechanism of action.

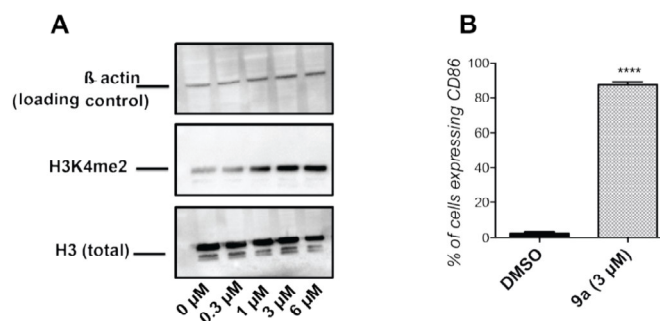
**Table 1:** IC<sub>50</sub> of fluorinated transylcypromines in the LSD1 enzyme assay, ± STD (n=3). The reference compound transylcypromine (**1**) has an IC<sub>50</sub> of 25.0 ± 9.5 μM in the assay.

R	Comp.	IC <sub>50</sub> (μM)	Comp.	IC <sub>50</sub> (μM)	Comp.	IC <sub>50</sub> (μM)	Comp.	IC <sub>50</sub> (μM)
H	<b>7a</b>	>25	<b>8a</b>	>25				
Me	<b>7b</b>	>25	<b>8b</b>	>25				
OMe	<b>7c</b>	>25	<b>8c</b>	>25	<b>9a</b>	1.2 ± 0.1	<b>10a</b>	>50
OEt	<b>7d</b>	>50	<b>8d</b>	>50				
NO <sub>2</sub>	<b>7e</b>	>50	<b>8e</b>	>50	<b>9b</b>	6.8 ± 1.3	<b>10b</b>	>50
F	<b>7f</b>	>25	<b>8f</b>	>25	<b>9c</b>	6.7 ± 1.3	<b>10c</b>	4.1 ± 0.03
CF <sub>3</sub>	<b>7g</b>	2.1 ± 0.2	<b>8g</b>	>25	<b>9d</b>	8.2 ± 0.8	<b>10d</b>	9.2 ± 0.05
SF <sub>5</sub>	<b>7h</b>	0.8 ± 0.2	<b>8h</b>	>25	<b>9e</b>	8.4 ± 0.3	<b>10e</b>	>50
Cl	<b>7i</b>	6.7 ± 0.5						

**Table 2.** IC<sub>50</sub> of fluorinated transylcypromines in cell growth proliferation assays, (72 h incubation) ± STD (n=5) with transylcypromine **1** as a reference.

Compound	MV4-11 IC <sub>50</sub> (μM)	THP-1 IC <sub>50</sub> (μM)
<b>1</b>	630 ± 8.4	810 ± 3.9
<b>9a</b> , R = OMe	1.9 ± 0.1	8.5 ± 0.4

<b>9b</b> , R = NO <sub>2</sub>	>30	>30
<b>9c</b> , R = F	4.9 ± 0.4	1.6 ± 0.3
<b>10c</b> , R = F	8.2 ± 0.4	7.0 ± 0.2



**Fig.3:** (A) Western blot analysis of the methylation state of H3K4 after treatment with compound **9a** for 48 h. Blotting membranes were probed for anti-H3K4me2, H3 (total) and  $\beta$ -actin (loading control). (B) CD86 induction in MV4-11 cells. Bars indicate percentage of cells expressing CD86 upon treatment with 3  $\mu$ M of **9a**. Statistical significance for CD86 expression determined with Student's t-test; values are expressed as means  $\pm$  STD (n=3); \*\*\*\*p < 0.0001.

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### Supplementary Material

Supplementary data associated with this article can be found, in the online version, at