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Pyrrole- and indole-containing tranylcypromine derivatives as novel lysine-specific demethylase 1 inhibitors active on cancer cells

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On the basis of previous researches showing the capability of *N*-carbobenzyloxy- (Z-)amino acid-tranylcypromine (-TCPA) derivatives to inhibit LSD1, we inserted at the 4-amino-TCPA moiety first a Z-Pro (**9**) and a Z-Gly (**10**) residue and then, after the encouraging data of **9**, a pyrrole and indole ring in which the relative N_1 position carried a acetophenone, a N-phenyl/benzylacetamide, or a Z chain (**11a-f** and **12a-f**, respectively). In both series, the Z-pyrrole and indole derivatives **11e,f** and **12e,f** displayed high LSD1 inhibitory activity. The compounds are able to inhibit LSD1 in NB4 cells increasing the expression of two related genes, GFI-1b and ITGAM, and to induce cell growth arrest in the AML MB4-11 and APL NB4 cell lines.

Introduction

Lysine (Lys) residues on histone tails can undergo post-translational methylation and demethylation, and thereby act as important sites for epigenetic control of gene expression. These lysine marks can either activate or deactivate gene expression depending on their position in the histone tail, and their level of methylation (mono-, di- or trimethylated) on their ε-amine group..[1,2] For instance, methylations at Lys4, and methylation at Lys36 and Lys 79 of histone H3 (H3K4, H3K36 and H3K79) are typical activation marks, whereas methylations at H3K9, H3K27 and H4K20 normally lead to gene silencing.[1,2] Moreover, such last lysine marks typically act in concert with DNA methylation at CpG islands near promoters, reinforcing gene repression.

The discovery of the H3K4 demethylase called lysine-specific demethylase 1 (LSD1 or KDM1A) revealed that histone methylation is a reversible process.[3,4] Up to now, a large number of demethylases have been identified, belonging to either the LSD family or the JmJ-containing enzymes.[5,6] As a member of the amine oxidases, LSD1 is able to remove methyl groups from H3K4me1/2 through a FAD-dependent redox process. In specific contexts, LSD1 can catalyze the H3K9me1/2 demethylation changing its role from gene silencer to gene activator.[7] LSD1 is also able to demethylate non-histone substrates, such as the tumor suppressor p53 and the cell cycle and apoptosis regulator E2F1.[8,9] Importantly, aberrant LSD1 expression and/or activity has been associated to several human cancers ranging from neuroblastoma,[10] to prostate,[11] lung,[12] and bladder cancers,[13] sarcomas and hepatocarcinomas.[14] Hence, LSD1 has been considered an attractive target for the treatment of cancer.

To date, a number of small molecules, such as phenelzine **1**, tranylcypromine (TCPA) **2**[15] and related compounds **3**-**5**,[16-18] some polyamines (such as **6**)[19] and amidines (such as **7**),[20] as well as some peptides[21-23] have been described as LSD1 inhibitors (Fig. 1).

Recently, we described some TCPA-based compounds as novel LSD1 inhibitors, by introducing acyl and *N*-(carbobenzyloxy)- (Z-)amino acyl moieties in the aniline NH_2 group of the 4-(2-aminocyclopropyl)aniline.[24] Among them, the Z-phenylalanine (Z-Phe) derivative **8** (Fig. 1) was described as one of the most potent and selective LSD1 inhibitors (K_i = 1.3 μM, IC_{50} = 0.15 μM).[24] Compound **8** also showed relevant biological activities in cellular models, exhibiting antiproliferative and differentiating effects in acute promyelocytic leukemia (APL) cells including primary murine APL blasts.[24] On this basis, pursuing our researches in this field,[23-29] we prepared the Z-Pro and Z-Gly analogues of **8**, compounds **9** and **10**, and after the encouraging results obtained with **9** in term of LSD1 inhibition (see below), we synthesized compounds **11a-f** and **12a-f** in which either a pyrrole or indole ring, carrying a acetophenone, *N*-phenyl/benzylacetylamide or carbobenzyloxy moiety at their N_1 position, was inserted at the 4-(2-aminocyclopropyl)aniline scaffold (Fig. 2).

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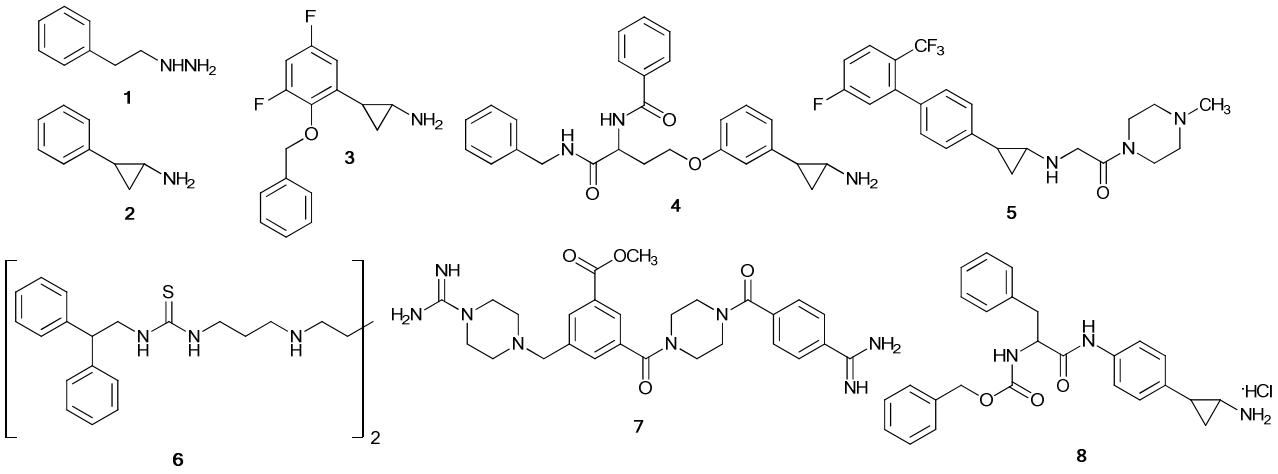


Fig. 1. Known LSD1 inhibitors.

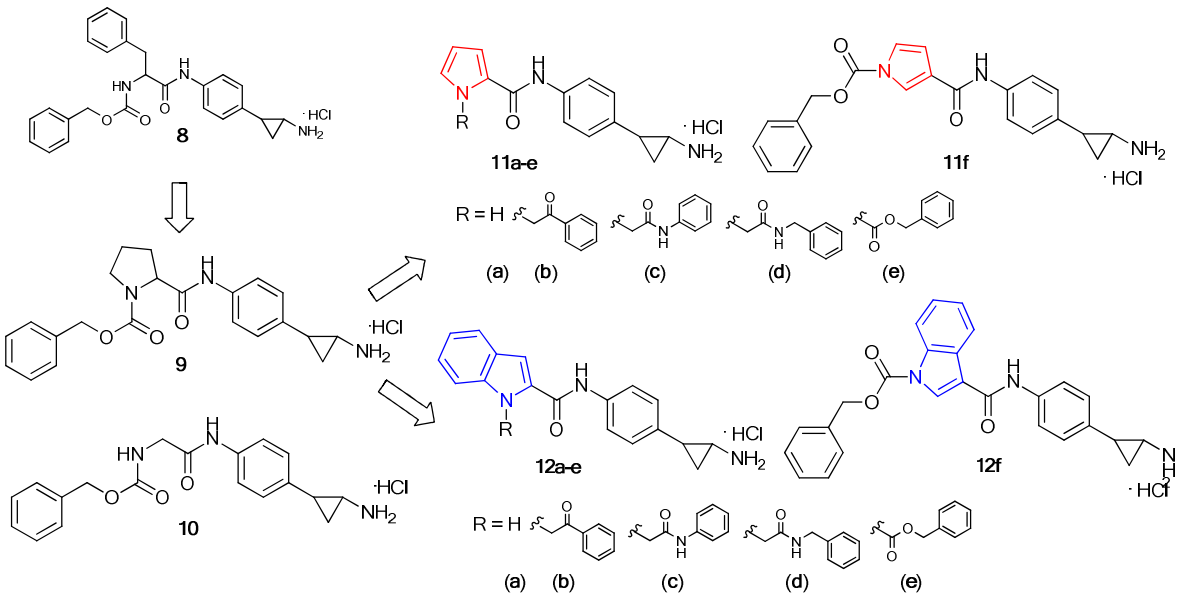
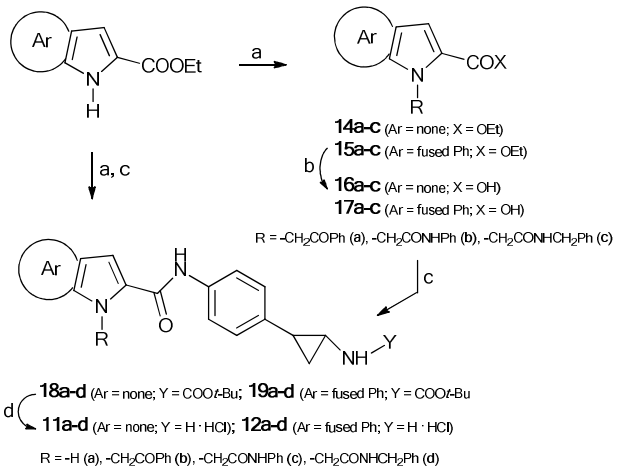


Fig. 2. Novel TCPA analogues based on Z-Pro (**9**), Z-Gly (**10**), pyrrole (**11a-f**) and indole (**12a-f**) structures.

In such compounds, the substituted pyrrole/indole portions could mimic the amino acid portion of our TCPA-based LSD1 inhibitors, without bearing the additional chiral centre, thus simplifying the stereochemistry of such derivatives. The novel pyrrole and indole compounds **11** and **12** were tested against LSD1, in comparison with **8** used as reference drug.

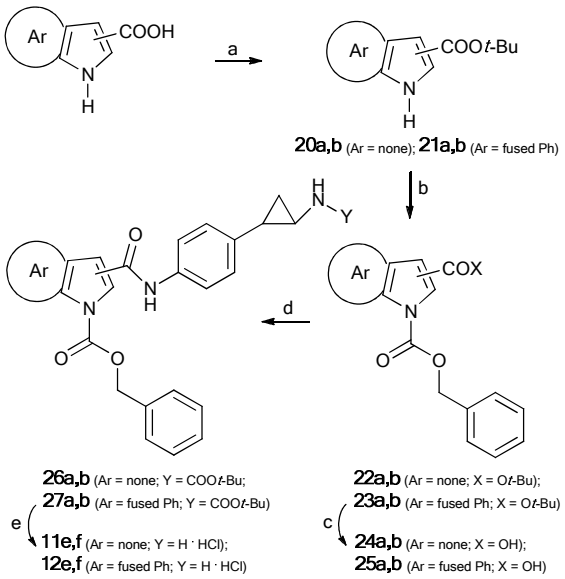
In cellular assays, **11** and **12** were tested to assess their capability to induce mRNA expression of the Growth factor independence 1 (GFI-1b),[25,30-32] a gene that is a direct transcriptional target of LSD1,[30] and Integrin alpha M (ITGAM),[24] a gene related to differentiation, and to affect cell proliferation in leukemia cell lines.

Results and discussion As the first step in our studies, we synthesized two analogues of **8** in which the Z-Phe was replaced by a Z-Pro (**9**) or a Z-Gly (**10**) residue (Scheme S1 in Supplementary information). Particularly, compound **9** exhibited a two-fold improved inhibitory potency against LSD1 (IC_{50} of 0.06 μM; Table 1). Furthermore, the crystal structure



Scheme 1 Synthesis of novel pyrrole and indole derivatives **11a-d** and **12a-d**. Reagents and conditions: (a) 2-bromoacetophenone or 2-bromo-*N*-phenylacetamide or *N*-benzyl-2-bromoacetamide, K_2CO_3, dry CH_3CN, 2 h, 85 °C. (b) 2N LiOH, THF, 4 h, rt. (c) *trans*-*N*-Boc-2-(4-aminophenyl)cyclopropylamine **13**, PyBop, Et_3N, dry DMF, N_2 atmosphere, overnight, rt. (d) 4N HCl, dry dioxane/THF, overnight, rt.

confirmed that the inhibitor binds covalently to the flavin with the same conformation as the parent compound[24] (coordinates deposited in the Protein Data Bank with code 4UXN). These initial results encouraged us in pursuing our goal - the synthesis and analysis of derivatives with substituents (e.g. pyrrole or indole) that restrain the conformation and simplify stereochemistry by lacking the chiral centre of the *Z*-amino acid. The final step required for the synthesis of **9**-**12** is the coupling of the appropriate carboxylic acids with the *trans*-*N*-Boc-2-(4-aminophenyl)cyclopropylamine **13**[24] in the presence of benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluoro phosphate (PyBop) and triethylamine, in dry *N*,*N*-dimethylformamide as a solvent, followed by Boc cleavage with 4N HCl in dioxane and dry THF.[24] To prepare **9**, **10**, **11a** and **12a**, Z-Pro, Z-Gly, 1*H*-pyrrole-2-carboxylic acid and 1*H*-indole-2-carboxylic acid were directly coupled with **13** and cleaved at the Boc moiety as described (Scheme 1). For the synthesis of **11b-d** and **12b-d**, the ethyl 1*H*-pyrrole-2-carboxylate and the ethyl 1*H*-indole-2-carboxylate were treated with 2-bromoacetophenone, 2-bromoacetylanilide, or 2-bromoacetylbenzylamide in anhydrous CH_3CN at 85 °C in the presence of potassium carbonate to provide the N_1-alkylated-pyrrole and -indole ethyl esters **14a-c** and **15a-c**. After alkaline hydrolysis, the corresponding acids **16a-c** and **17a-c** were coupled with **13** giving the Boc-protected derivatives **18a-c** and **19a-c**, after treated with 4N HCl as described (Scheme 1). To prepare compounds **11e,f** and **12e,f**, the 1*H*-pyrrole-2- and -3-carboxylic acids as well as the 1*H*-indole-2- and -3-carboxylic acids, respectively, were treated with *N,N*-dimethylformamide di-*tert*-butyl acetal in dry toluene at 80 °C, to obtain the corresponding *tert*-butyl esters **20a,b** and **21a,b**, commercially available also. Such intermediates were then treated with NaH in dry THF and benzyl chloroformate to furnish the Z-pyrrole



Scheme 2 Synthesis of **11e,f** and **12e,f**. Reagents and conditions: (a) *N,N*-dimethylformamide di-*tert*-butyl acetal, toluene, 1 h, 80 °C; (b) 60% NaH, dry THF, benzyl chloroformate, 1 h, rt; (c) trifluoroacetic acid, dry DCM, 5 h, rt (d) *trans*-*N*-Boc-2-(4-aminophenyl)cyclopropylamine **13**, PyBop, Et_3N, dry DMF, N_2 atmosphere, overnight, rt (e) 4N HCl, dry dioxane/THF, overnight, rt.

and *Z*-indole esters **22a,b** and **23a,b**, which were hydrolyzed with trifluoroacetic acid in dry DCM to furnish the acids **24a,b** and **25a,b**. Such acidic intermediates **24a,b** and **25a,b** were coupled with **13** to give the Boc-protected derivatives **26a,b** and **27a,b**. Further cleavage of their Boc function with 4N HCl yielded the desired compounds **11e,f** and **12e,f** (Scheme 2).

Table 1. LSD1, MAO-A and MAO-B inhibiting activity (IC_{50} values, μM) of compounds **9**, **10**, **11a-f** and **12a-f**. Compound **8** was used for comparison.[a]

Compd	IC_{50}, μM		
	LSD1	MAO-A	MAO-B
8	0.149		
9	0.061		
10	0.304		
11a	0.163		
11b	1.323		
11c	0.125		
11d	0.155		
11e	0.032	0.26	75.8
11f	0.050	0.11	3.9
12a	0.065		
12b	0.853		
12c	0.087		
12d	0.308		
12e	0.040	0.16	>60
12f	0.086	0.46	>70

[a]The IC_{50} values reported are based on two separate curves wherein each data point is the average of two determinations. The resulting IC_{50} values from these curves were then averaged and reported in the table. The error is within ± 10%.

Compounds **9** and **10**, as well as the new pyrrole and indole derivatives **11** and **12** were tested against LSD1 in biochemical assay, and their IC_{50} values were determined. Compound **8** was used for comparison (Table 1). The highly potent compounds **11e,f** and **12e,f** were also assayed against MAO-A and MAO-B, to assess their selectivity profile.

Among the pyrrole derivatives **11a-f**, the N_1-unsubstituted **11a** displayed slightly lower LSD1 inhibition respect to the Z-Phe-TCPA compound **8**, while the analogue with the acetophenone moiety at N_1 **11b** was 10-fold less effective. However, the ability to inhibit LSD1 was fully restored when a N-phenyl/benzylacetamide group was inserted at the pyrrole N_1 position (see IC_{50} values for **11c** and **11d** in Table 1). The introduction of the carbobenzyloxy (Z) substituent at the N_1 position of the pyrrole ring, in either the 2- or the 3-substituted analogue **11e** or **11f**, yielded the highest enzyme inhibition, leading to compounds 5- (**11e**) or 3-fold (**11f**) more potent than **8**, used as reference drug.

In the indole series, the NH analogue **12a** showed improved LSD1 inhibitory activity respect to both **8** and the pyrrole counterpart **11a**, and, similarly to what observed in the pyrrole series, the substitution at the N_1 position with the acetophenone moiety (**12b**) was detrimental for LSD1 inhibition. However, the replacement of this group with the *N*-phenylacetamide portion (**12c**) restored the LSD1 inhibition at a IC_{50} value similar to that of the NH analogue **12a**.

Differently from the pyrrole series, the insertion at the indole N_1 position of the *N*-benzylacetamide chain (**12d**) resulted 3.5-fold lower potency than the *N*-phenyl counterpart (**12c**), likely for steric reasons. Finally, similarly to what seen with pyrroles, also with 2- and 3-substituted indoles the introduction of the Z substituent at the N_1 position gave high LSD1 inhibition, the compounds **12e** and **12f** being 3.7- and 1.7-fold more potent than **8**, respectively. However, by comparing the Z-containing pyrroles **11e,f** and the Z-containing indoles **12e,f** with the corresponding unsubstituted pyrrole (**11a**) and indole (**12a**) analogues, it is clear that the N-substituent is only enhancing activity in the pyrrole serie.

The highly potent LSD1 inhibitors **11e,f** and **12e,f**, when tested against MAOs, exhibited up to 8-fold lower activity against MAO-A, and were practically inactive against MAO-B, with the sole exception of **11f** which showed MAO-B inhibition at low μM range.

To investigate if the compounds were able to inhibit LSD1 in cells, we tested selected pyrrole and indole compounds **11a,c-f** and **12a,c,e,f** for their capability to induce, in human acute promyelocytic leukemia (APL) NB4 cells, the expression of GFI-1b[25,30-32] and ITGAM,[24] two genes related to expression and activity of LSD1 and/or to cell differentiation. Compound **8** was included for comparison purpose. The inhibitors were added to cultures of NB4 cells at a concentration equal to their respective biochemical IC_{50} values, and after 24 hours the GFI-1b and ITGAM mRNA expression levels were measured by quantitative RT-PCR and graphed as fold-induction respect to the control (DMSO). Data depicted in Fig. 3 show that all the selected pyrrole and indole compounds are able to induce GFI-1b and, to a lesser extent, ITGAM gene expression in NB4 cells, thus demonstrating their capability to inhibit LSD1 in cells.

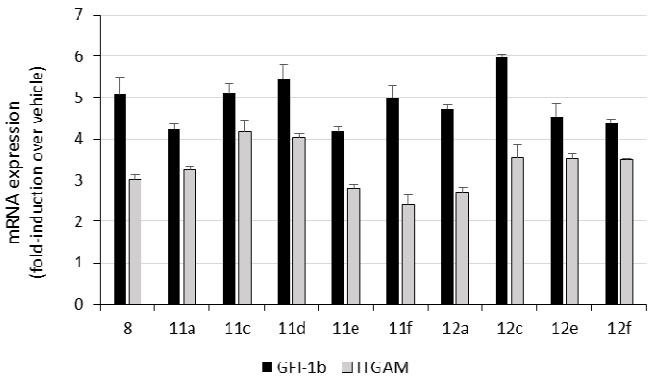


Fig. 3. GFI-1b and ITGAM gene expression induction in NB4 cells by selected **11** and **12** derivatives. The inhibitors were tested at their biochemical anti-LSD1 IC_{50} values. Fold-inductions were calculated respect to DMSO used as a control.

Finally, the Z-pyrrole (**11e,f**) and the Z-indole (**12e,f**) derivatives were tested in two leukemia cell lines, the human acute myelocytic leukemia (AML) MV4-11 and the APL NB4 cell lines, using increasing concentration of the inhibitors for 72 h, to assess their antiproliferative potential (Table 2).

In this assay, the Z-pyrrole derivatives **11e,f** displayed similar or lower antiproliferative activities than **8**, while the Z-indoles **12e,f** were from 2- to 4-fold more potent than **8** in inducing leukemia cell growth arrest, with IC_{50} values in the single-digit μM range.

Table 2. Antiproliferative activities of the Z-pyrrole- and Z-indole-TCPA derivatives **11e,f** and **12e,f** in human AML MV4-11and human APL NB4 cells. Compound **8** was used for comparison.[a]

Compd	IC_{50}, μM	
	MV4-11 cells	NB4 cells
8	10.2	17.4
11e	6.8	56%[b]
11f	15.2	22.3
12e	5.9	6.5
12f	2.5	9.3

[a]The IC_{50} values reported are based on two separate curves wherein each data point is the average of two determinations. The resulting IC_{50} values from these curves were then averaged and reported in the table. The error is within ± 10%. [b]Percentage of inhibition at 100 μM.

Conclusions

Recently we reported a series of Z-amino acid-TCPA derivatives as novel potent LSD1 inhibitors.[24] From this study, the Z-Phe-TCPA derivative **8** emerged as the most potent and selective in enzyme assays as well as in leukemia cells.

Pursuing our researches in this field, we extended our previous work by linking to the 4-amino-TCPA scaffold first a Z-Pro (**9**) and a Z-Gly (**10**) moiety and then, after the encouraging result of **9** in inhibiting LSD1, some pyrrole- and indole-2- and -3-carboxylic acids, in which the N_1 positions were substituted with acetophenone, *N*-phenylacetamide, *N*-benzylacetamide, and benzyloxycarbonyl chains, to mimic the Z-amino acid moiety. The new compounds **11a-f** and **12a-f** have the advantage of lacking the third, additional chiral centre due to the amino acid portion of the previous inhibitors. Tested against LSD1, the pyrroles unsubstituted at N_1 (**11a**) or bearing at the same position a *N*-phenyl/benzylacetamide chain (**11c,d**) displayed similar inhibiting activity as **8**, used as reference drug, and the N_1-carbobenzyloxy-substituted analogues **11e,f** were up to 5-fold more potent than **8**. Among the indole derivatives, the N_1-H (**12a**) as well as the N_1-*N*-phenylacetamide (**12c**) and the two N_1-carbobenzyloxy (**12e,f**) substituted compounds showed 2/3-fold higher potency than **8** in inhibiting LSD1. Such inhibitors were then tested in APL NB4 cells to assess their capability to induce mRNA expression of GFI-1b[25,30-32] and ITGAM,[24] two genes related to LSD1 activity and/or cytodifferentiation. At the concentration equal to their biochemical IC_{50}s, all they induced GFI-1b up to 6-fold, and ITGAM up to 4-fold, with respect to DMSO used as a control. Finally, the N_1-carbobenzyloxy pyrroles and indoles **11e,f** and **12e,f** were tested in APL NB4 and AML MV4-11 cells, to determine their effects on proliferation. In this assay, in particular the indoles **12e,f** displayed single-digit μM cell growth arrest, they being more efficient than **8** tested in the same conditions. Further studies will be undertaken to determine their effective anticancer potential.

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Notes and references

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Electronic Supplementary Information (ESI) available: Synthesis of **11a-f** and **12a-f** and intermediates. LSD1 enzyme inhibition assay. Crystallographic analysis. Gene modulation assays. Cell growth assays. See DOI: 10.1039/b000000x

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Table of Content

A new series of pyrrole- or indole-containing tranylcypromine analogues has been reported as potent and selective LSD1 inhibitors, able to induce gene expression and to arrest proliferation in leukemia cells.