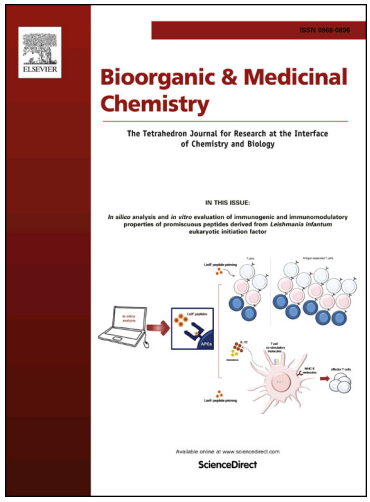

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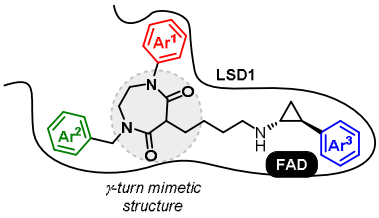

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Design, synthesis and evaluation of γ-turn mimetics as LSD1-selective inhibitors

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ABSTRACT

Lysine-specific demethylase 1 (LSD1) is an attractive molecular target for cancer therapy. We have previously reported potent LSD1-selective inhibitors (i.e., NCD18, NCD38, and their analogs) consisting of *trans*-2-phenylcyclopropylamine (PCPA) or *trans*-2-arylcyclopropylamine (ACPA) and a lysine moiety that could form a γ-turn structure in the active site of LSD1. Herein we report the design, synthesis and evaluation of γ-turn mimetic compounds for further improvement of LSD1 inhibitory activity and anticancer activity. Among a series of γ-turn mimetic compounds synthesized by a Mitsunobu-reaction-based amination strategy, we identified **1n** as a potent and selective LSD1 inhibitor. Compound **1n** induced cell cycle arrest and apoptosis through histone methylation in human lung cancer cells. The γ-turn mimetics approach should offer new insights into drug design for LSD1-selective inhibitors.

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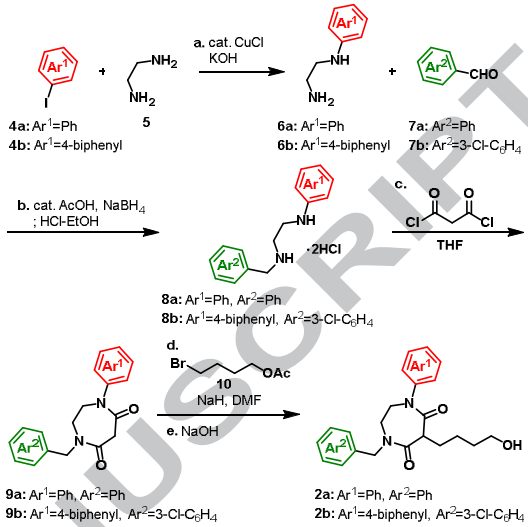
1. Introduction

Lysine-specific demethylase 1 (LSD1) catalyzes the demethylation at position 4 of the monomethyl/dimethyl lysine residue on histone H3 (H3K4me1/2) by flavin adenine dinucleotide (FAD)-dependent amine oxidation.[1] LSD1 binds to nuclear proteins (e.g., histone deacetylases,[2] histone methyltransferases,[3] and nuclear receptors[4]) via CoREST as the corepressor to epigenetically regulate the expression of genes associated with tumorigenesis,[5] globin synthesis,[6] neuron development,[7] and so on. Thus, LSD1 is an attractive molecular target for the therapy of cancer, globin disorders, and neurodegenerative disorders. A number of LSD1 inhibitors have been reported so far[8–10] and they are categorized into two types (i.e., irreversible and reversible inhibitors). Most of the previously reported LSD1 inhibitors are irreversible ones that react with FAD in the active site of LSD1.[8–10] A representative example of irreversible LSD1 inhibitors is *trans*-2-phenylcyclopropylamine (PCPA),[11] which is a non-selective LSD1 inhibitor that also inhibits strongly other FAD-dependent oxidases, such as monoamine oxidases (MAOs). Currently, PCPA analogs, such as ORY-1001[12] and GSK2879552,[13] are being evaluated in clinical trials for the treatment of acute myeloid leukemia and small lung cancer.

In 2007, Cole, Yu, and co-workers reported the co-crystal structure of LSD1 with a suicide substrate consisting of *N*-methylpropargylamine and histone H3 peptide; the substrate forms a γ-turn structure in the active pocket of LSD1,[14] in which two individual amides form a hydrogen bond, as shown in **Figure 1A**.[15] It suggested that the γ-turn structure is important for the substrate binding to the active pocket of LSD1.

We previously reported irreversible LSD1-selective inhibitors, including peptide- or small-molecule-based PCPA analogs.[16–23] We were able to identify histone H3 peptide based LSD1 inhibitors that bear a PCPA moiety at position 4 of the lysine residue on histone H3 peptides, which potently and selectively inhibit LSD1 activity.[18] These previous studies also suggested the importance of the γ-turn structure for potent LSD1 inhibition.

Although H3 peptides bearing PCPA exhibit potent and selective LSD1 inhibitory activities, they were not cell-active due to their low cell membrane permeability.[18] Therefore, we also developed small-molecule-based LSD1 inhibitors consisting of a PCPA moiety and a lysine moiety, such as NCD18 and NCD38, as novel LSD1-selective inhibitors (**Figure 1B**).[18] In particular, NCD38 was found to have unique anticancer activities in both *in cellulo* and *in vivo* studies.[24,25] Recently, we performed a structure–activity relationship study of NCD38 analogs in which



Scheme 1. Synthesis of γ-turn units **2**.

the PCPA moiety of NCD38 was replaced with various *trans*-2-arylcyclopropylamines (ACPAs) to improve the LSD1 inhibitory activity and anticancer activity of NCD38 (**Figure 1B**).[26] Herein we report the design, synthesis, and evaluation of γ-turn mimetics **1** of NCD18, NCD38, and their ACPA derivatives, with an eye to further improving LSD1 inhibitory activity and anticancer activity.

2. Results and discussion

2.1. Design of γ-turn mimetics

The amide moiety of the lysine structure of NCD38 and its derivatives was also considered to have a γ-turn structure in the active site of LSD1 (**Figure 1B**). We hypothesized that the immobilization of the γ-turn structure would improve LSD1 inhibitory activity as well as anticancer activity. Therefore, we designed novel γ-turn mimetic compounds **1** with a rigid 1,4-diazepine-5,7-dione framework in which the γ-turn structure is locked by an ethylene unit between the two nitrogen atoms of a

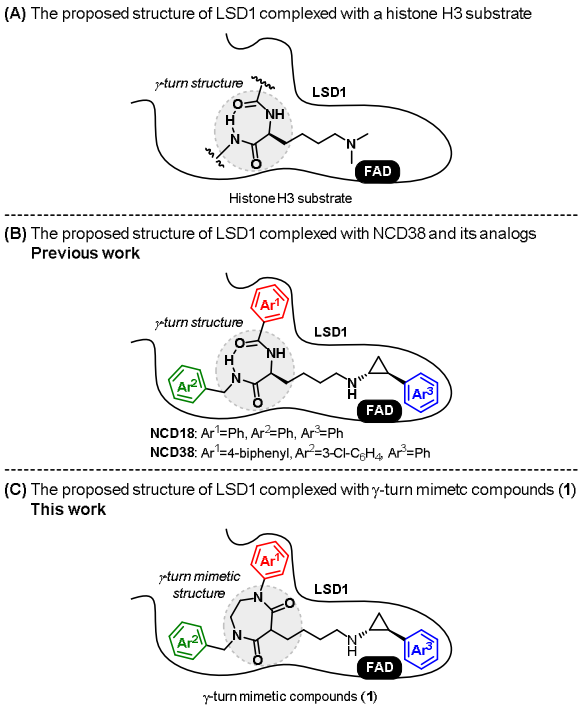


Figure 1. (A) The proposed structure of LSD1 complexed with a histone H3 substrate. (B) The proposed structure of LSD1 complexed with NCD18, NCD38 and their analogs. (C) The proposed structure of LSD1 complexed with γ-mimetic compounds (**1**).

malonamide (**Figure 1C**).[27]

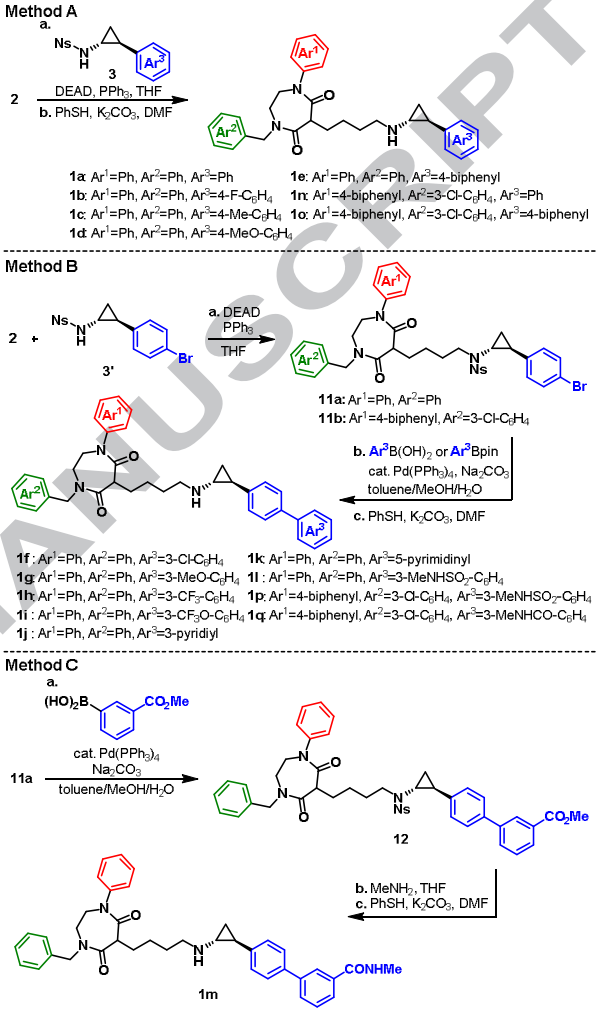
2.2. Synthesis

We began the synthesis by targeting γ-turn units **2**, which could be coupled to PCPA and ACPAs through a Mitsunobu-reaction-based amination strategy.[28] First, monophenyl amines **6** were synthesized by a copper-catalyzed Ullmann coupling of ethylenediamine (**5**) and iodoarenes **4** (**Scheme 1**).[29] Resulting compounds **6** were reacted with aldehydes **7** in a reductive amination to afford diphenylamines **8**. Next, condensation of **8** with malonyl chloride led to 7-membered cyclic compounds **9**.[30] Finally, alkylation of **9** with **10** followed by removal of the acetyl group for the reaction with **10** under basic conditions gave γ-turn units **2**.

Nosyl-ACPAs **3** were previously synthesized by our group through the C–H borylation/Suzuki–Miyaura coupling of cyclopropylamines (**Scheme 2**).[31] The coupling of γ-turn units **2** and ACPAs **3** was accomplished by using one of three methods (Methods A–C). In Method A, a Mitsunobu reaction of **2** with nosyl-ACPAs **3**, followed by removal of the nosyl group afforded desired γ-turn mimetics **1**. In Method B, a Mitsunobu reaction of **2** and bromide-containing ACPA **3'** to give **11**, followed by cross-coupling with arylboronic acids and nosyl group removal afforded corresponding biphenyl products **1**. For the specific synthesis of **1m**, Method C was employed: bromoarene **11a** was coupled with [3-(methoxycarbonyl)phenyl]boronic acid, followed by amidation and nosyl group removal.

2.3. Enzymatic assays and cell proliferation assays

We initially evaluated the LSD1 inhibitory activities of NCD18,[18] which has a simple lysine structure bearing benzoyl



Scheme 2. Synthesis of γ-turn mimetics **1** using one of three methods.

and *N*-benzyl moieties (**Figure 1B**), and its γ-turn mimetics **1a**–**1e** (**Table 1**). γ-Turn mimetic compound **1e** (Ar = 4-biphenyl) inhibited LSD1 activity with a potency similar to NCD18 at the concentration of 10 μM. However, γ-turn mimetics **1a**–**1d** caused significant loss of LSD1 inhibitory activities compared with NCD18. To explain why compounds **1a**–**1d** showed lower potency than NCD18, we performed a docking study with a crystal structure of LSD1 (PDB code: 2UXN). Although we tried to dock compound **1a**, a simple γ-turn mimetic compound of NCD18, into the active pocket of LSD1, proper docking poses of **1a** with LSD1 were not obtained (data not shown). We also calculated the binding mode of **1e** (Ar = 4-biphenyl), which improved the LSD1 inhibitory activity of **1a** (Ar = Ph), in the active pocket of LSD1. As shown in **Supplementary Figure S1**, the biphenyl group of **1e** occupied a part of the active site of LSD1. Thus, the introduction of biphenyl group to the γ-turn mimetics could bring efficient interaction with LSD1. In addition, this docking result suggests that acidic amino acid

residues (i.e., Asp555, Asp556 and Glu559) in the active site of LSD1 are located around the *m*-position of the biphenyl group of **1e** (**Supplementary Figure S1**). Thus, the introduction of various substituents to the *m*-position of the biphenyl group of **1e** or the conversion of the biphenyl group of **1e** into a heteroarylphenyl group was expected to further improve the LSD1 inhibitory activity of **1e**.

Table 1. LSD1 inhibitory activities of NCD18 and its γ-turn mimetics **1a**–**1e**.

Compound	Ar	% inhibition of enzyme activity @ 10 μM[a]
		LSD1
NCD18	-	100
1a	Ph	no inhibition
1b	4-F-C_6H_4	16.3
1c	4-Me-C_6H_4	24.7
1d	4-MeO-C_6H_4	61.7
1e	4-biphenyl	97.7

[a] Values are means of at least three experiments.

Based on these results, we next examined the LSD1 inhibitory activities of NCD18-based γ-turn mimetic compounds **1f**–**1m** in which the biphenyl group of **1e** is replaced with various substituted biphenyl groups (**1f**–**1i**, **1l**, and **1m**) or heteroarylphenyl groups (**1j** and **1k**). We expected improvements in the LSD1 inhibitory activities of the biaryl derivatives because NCD38 derivatives with various ACPAs showed high LSD1 inhibitory activities compared with NCD38 in our previous work.[26] As shown in **Table 2**, most of the derivatives inhibited LSD1 activity at the concentration of 10 μM. In particular, **1g**, **1l**, and **1m** inhibited LSD1 activity completely at the concentration of 10 μM. We also investigated the cell growth inhibitory activities of selected biphenyl derivatives **1g**, **1l**, and **1m**. Biphenyl derivatives **1g**, **1l**, and **1m** weakly inhibited the proliferation of human lung cancer A549 cells like NCD18, whereas NCD38 completely inhibited the proliferation of A549 cells at the concentration of 10 μM.

Table 2. LSD1 inhibitory activities and antiproliferative activities in human lung cancer A549 cells of biphenyl derivatives **1e**–**1m**, NCD18 and NCD38.

Compound	Ar	% inhibition of enzyme activity @ 10 μM[a]	% inhibition of cell growth @10 μM[b]
		LSD1	A549
1e	Ph	97.7	-
1f	3-Cl-C_6H_4	80.1	-
1g	3-MeO-C_6H_4	100	16
1h	3-CF_3-C_6H_4	76.0	-
1i	3-CF_3O-C_6H_4	86.8	-
1j	3-pyridiyl	95.9	-
1k	5-pyrimidinyl	75.7	-
1l	3-$MeNHSO_2$-C_6H_4	100	16
1m	3-MeNHCO-C_6H_4	100	26
NCD18	-	100	no inhibition
NCD38	-	98.3	100

[a] Values are means of at least three experiments.
[b] Values are means of at least four experiments.

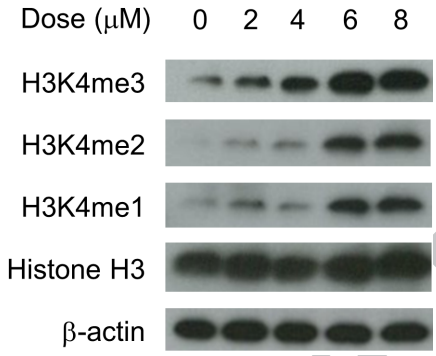
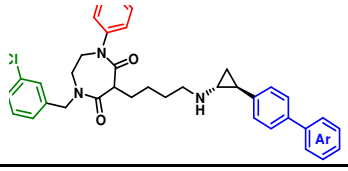


Figure 2. Accumulation of methylated histone H3K4 in lung cancer A549 cells by **1n**. Western blotting for tri-methylated histone H3K4 (H3K4me3), di-methylated histone H3K4 (H3K4me2), mono-methylated histone H3K4 (H3K4me1), and total histone H3 was performed with lysates of the cells treated for 24 hours with the indicated concentration of **1n**. β-actin was used as a loading control.

To improve the antiproliferative activity of γ-turn mimetics, we designed NCD38-based γ-turn mimetics **1n**–**1q** in which the phenyl group and the benzyl group of **1a**, **1e**, **1l**, and **1m** were replaced with a biphenyl group and a 3-chlorobenzyl group, respectively. NCD38-based γ-turn mimetic compound **1n** inhibited LSD1 activity and showed potent antiproliferative activity toward A549 cells (**Table 3**). On the other hand, biphenyl derivatives **1o** and **1p** but not **1q** showed weak or almost no LSD1 inhibitory activity and were not cell-active. Among a series of γ-turn mimetics prepared for this study, compound **1n** was the best in terms of LSD1 inhibitory activity and antiproliferative activity.

Next, we determined the IC_{50} value of γ-turn mimetic compound **1n** for LSD1 and MAO inhibition and the GI_{50} value of **1n** for A549 cell growth inhibition, and compared them with the values of PCPA and NCD38 (**Table 4**). γ-Turn mimetic compound **1n** inhibited LSD1 much more potently than PCPA (PCPA: IC_{50} = 80.7 μM, **1n**: IC_{50} = 0.622 μM). In addition, similar to NCD38, **1n** did not inhibit MAO A or MAO B even at the concentration of 100 μM, showing much higher LSD1 selectivity than PCPA. Moreover, whereas **1n** showed attenuated LSD1 inhibitory activity compared with NCD38 (NCD38: IC_{50} = 0.132 μM, **1n**: IC_{50} = 0.622 μM), its antiproliferative activity toward A549 cells was higher than that of NCD38 (NCD38: GI_{50} = 8.60 μM, **1n**: GI_{50} = 5.80 μM). The reason for the higher antiproliferative activity of **1n** is unclear, but it may be because the γ-turn mimetic structure is more hydrophobic than the amino acid moiety of NCD38 and so **1n** can penetrate the cell membrane and interact with LSD1 efficiently.[27]

Table 3. LSD1 inhibitory activities and antiproliferative activities in human lung cancer A549 cells of NCD38 and its γ-turn mimetics **1n**–**1q**.



Compound	Ar	% inhibition of enzyme activity @ 10 μM[a]	% inhibition of cell growth @ 10 μM[b]
		LSD1	A549
NCD38	-	98.3	100
1n	H	81.7	100
1o	Ph	15.3	-
1p	3-MeNHSO$_2$-C$_6$H$_4$	49.3	-
1q	3-MeNHCO-C$_6$H$_4$	99.4	26

[a] Values are means of at least three experiments.
[b] Values are means of at least four experiments.

Table 4. LSD1 and MAOs inhibitory activities and antiproliferative activities in human lung cancer A549 cells of PCPA, NCD38 and its γ-turn mimetic **1n**.

Compound	IC$_{50}$ (μM)[a]			GI$_{50}$ (μM)[c]
	LSD1	MAO A	MAO B	A549
PCPA	80.7	2.5[b]	2.4[b]	1108
NCD38	0.132	>100[b]	>100[b]	8.60
1n	0.622	>100	>100	5.80

[a] Values are means of at least three experiments.
[b] Data were taken from literature (ref 18).
[c] Values are means of at least four experiments.

*2.4. Mechanism analysis of antiproliferative activity of γ-turn mimetic compound **1n** toward lung cancer A549 cells*

As mentioned above, γ-turn mimetic compound **1n** is a potent and selective LSD1 inhibitor with high antiproliferative activity toward lung cancer A549 cells in which LSD1 is overexpressed.[32,33] In this study, we analyzed the mechanism of the antiproliferative activity of **1n** toward A549 cells. First, we examined whether γ-turn mimetic compound **1n** inhibits LSD1 in A549 cells. We performed western blot analysis to evaluate the level of histone H3K4 methylation in A549 cells because LSD1 demethylates monomethylated histone H3K4 (H3K4me1) and dimethylated histone H3K4 (H3K4me2),[1] and LSD1 inhibitors induce the accumulation of histone H3K4me1 and H3K4me2 in cancer cells.[8–10] As shown in **Figure 2**, γ-turn mimetic compound **1n** induced the accumulation of histones H3K4me1 and H3K4me2 in a dose-dependent manner in A549 cells. In addition, the accumulation of trimethylated histone H3K4 (H3K4me3) was also induced by **1n**. This result is reasonable because LSD1 has been reported to regulate the levels of histone H3K4me2 and H3K4me1 directly and then subsequently regulate the level of histone H3K4me3.[34,35] These results indicate that γ-turn mimetic compound **1n** inhibits LSD1 in A549 cells.

Next, we investigated the antiproliferative activity of γ-turn mimetic compound **1n** toward A549 cells by fluorescence activated cell sorting (FACS) analysis. As shown in **Figure 3A**, compound **1n** at 2 μM or more for 24 hour incubation increased the population of the G1 phase with a decrease of the S phase, indicating that **1n** arrested the cell cycle at the G1 phase. Furthermore, 6 and 8 μM of **1n** increased the cell population at sub-G1 phase in a time-dependent manner, suggesting that compound **1n** induced apoptosis (**Figure 3B**). These results suggest that the antiproliferative activity of **1n** toward A549 cells is mainly due to the induction of cell cycle arrest and apoptosis through histone H3K4 methylation by LSD1 inhibition.

3. Conclusion

We have described the design, synthesis, and evaluation of γ-turn mimetic compounds with an eye to further improving LSD1 inhibitory activity and anticancer activity. A series of γ-turn mimetic compounds were synthesized by a Mitsunobu-reaction-based amination strategy for coupling γ-turn units with PCPA or ACPAs. We identified **1n** as a potent and selective LSD1 inhibitor. Compound **1n** significantly induced cell cycle arrest and apoptosis through histone H3K4 methylation in human lung cancer cells. As a result, γ-turn mimetic compound **1n** improved the cellular activity of NCD38. We believe that this γ-turn

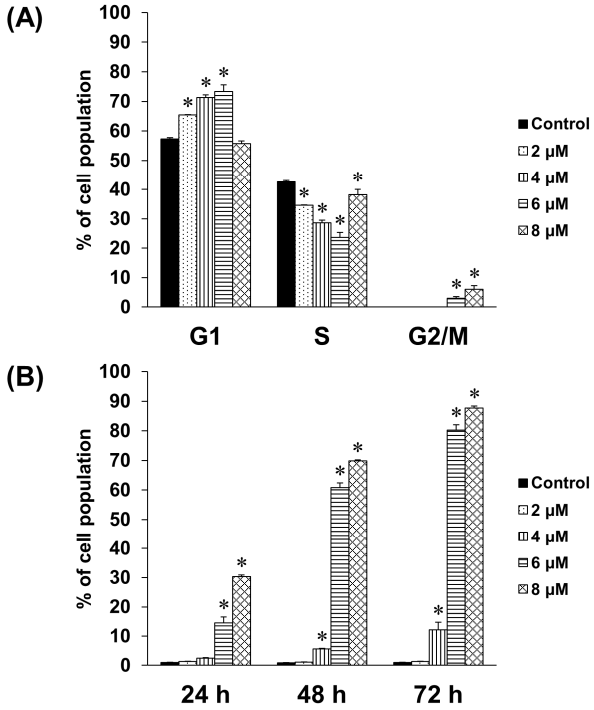


Figure 3. Induction of G1 phase arrest and apoptosis in lung cancer A549 cells by **1n**. A549 cells were treated with the indicated concentration and time point of **1n**. The population of each cell cycle at 24 hours (A) and apoptosis at 24, 48 and 72 hours (B) was determined using FACS analysis. Data represent as the means ± S.D. (n = 3), $^*P < 0.01$ *vs.* control.

mimetics approach should offer new insights into drug design for LSD1-selective inhibitors.[36]

In this study, we utilized the structure of retro-amide C$_7$ mimetics (**Figure 1C**)[27] because this structure is simple and readily available to access various derivatives without multi-step asymmetric synthesis. However, it is also possible to use other γ-turn mimetic structures (e.g., *trans*-olefins, lactams, 3-morpholinones, benzodiazepines, dihydroisoquinolinones, and 1,3,5-trisubstituted benzenes)[37–43] to improve the biological activities of NCD38 and its analogs. Further studies of γ-turn mimetic LSD1 inhibitors are under way.

4. Experimental

4.1. Synthesis

Unless otherwise noted, all reactants or reagents including dry solvents were obtained from commercial suppliers and used as received. Unless otherwise noted, all reactions were performed with dry solvents under an atmosphere of nitrogen in dried glassware using standard vacuum-line techniques. All Suzuki–Miyaura coupling reactions were performed in 20-mL glass vessel tubes equipped with J. Young® O-ring tap and heated in a heating block. All work-up and purification procedures were carried out with reagent-grade solvents in air.

Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). The developed chromatogram was analyzed by UV lamp (254 nm) or phosphomolybdic acid/sulfuric acid solution. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh). Medium pressure liquid chromatography (MPLC) was performed using Yamazen W-prep 2XY. Preparative thin-layer chromatography (PTLC) was performed using Wakogel B5-F silica coated plates (0.75 mm) prepared in our laboratory. The high-resolution mass spectra were conducted on Thermo Fisher Scientific Exactive. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECA-600 spectrometer (^{1}H 600 MHz, ^{13}C 150 MHz) and a JEOL JNM-ECA-500 spectrometer (^{1}H 500 MHz, ^{13}C 125 MHz). Chemical shifts for ^{1}H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.00 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm) or DMSO-d_6 (δ 39.5 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplets, td = triplet of doublets, q = quartet, m = multiplet, brs = broad singlet), coupling constant (Hz), and integration.

*4.1.1. Synthesis of γ-turn units (**2**)*

*4.1.1.1. N^1-Phenylethane-1,2-diamine (**6a**)*[44]

To a suspension of CuCl (265 mg, 2.7 mmol), KOH (3.01 g, 53 mmol) and iodobenzene (**4a**: 3.00 mL, 27 mmol) was slowly added ethylenediamine (**5**: 5.38 mL, 80 mmol) at 0 ºC. After being stirred overnight at room temperature, the reaction mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (20 mL x 5). The combined organic layers were dried over Na_2SO_4, filtered off and concentrated *in vacuo* to give **6a** (3.63 g, 99% yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.6 Hz, 2H), 6.71 (t, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 2H), 4.01 (brs, 1H), 3.19 (t, *J* = 5.6 Hz, 2H), 2.95 (t, *J* = 6.4 Hz, 2H), 1.50 (brs, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.4, 129.3, 117.4, 113.0, 46.5, 41.2.

*4.1.1.2. N^1-(4-biphenyl)ethane-1,2-diamine (**6b**)*

To a suspension of CuCl (106 mg, 1.1 mmol), KOH (1.20 g, 21 mmol) and 4-iodobiphenyl (**4b**: 3.00 g, 11 mmol) was added ethylenediamine (**5**, 2.0 mL, 90 mmol). The reaction mixture was stirred at 50 ºC for 3 h. The reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (20 mL x 5). The combined organic layers were dried over Na_2SO_4, filtered off and concentrated *in vacuo* to give **6b** (2.27 g, quant.) as a pink solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55–7.53 (m, 2H), 7.46–7.43 (m, 2H), 7.40–7.37 (m, 2H), 7.27–7.24 (m, 1H), 6.73–6.70 (m, 2H), 4.13 (brs, 1H), 3.24 (t, *J* = 6.0 Hz, 2H), 2.99 (t, *J* = 6.0 Hz, 2H), 1.24 (brs, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.9, 141.3, 130.4, 128.6, 127.9, 126.3, 126.0, 113.2, 46.6, 41.2; HRMS (ESI) *m/z* calcd for $C_{14}H_{17}N_2$ $[M+H]^+$: 213.1386 found 213.1380.

*4.1.1.3. N^1-Benzyl-N^2-phenylethane-1,2-diamine dihydrochloride (**8a**)*[45]

To a solution of 1,2-diamine **6a** (670 mg, 4.9 mmol), benzaldehyde (**7a**: 552 μL, 5.4 mmol) in MeOH (10 mL) was added AcOH (3 drops). After being stirred for 1 h at room temperature, sodium borohydride (186 mg, 4.9 mmol) was slowly added to the mixture at 0 ºC. The reaction mixture was stirred for 1 h at room temperature. The volatiles were evaporated *in vacuo*. Saturated $NaHCO_3$ aq. (10 mL) was added to the residue and extracted with CH_2Cl_2 (10 mL x 2). The combined organic layers were washed with brine (20 mL x 1), dried over Na_2SO_4, filtered off and concentrated *in vacuo*. The resultant residue was purified by MPLC (CH_2Cl_2/MeOH = 99:1 to 93:7) to give a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 7.15 (t, *J* = 8.4 Hz, 2H), 6.69 (t, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 2H), 3.33 (t, *J* = 6.0 Hz, 2H), 2.95 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.7, 135.9, 129.3, 128.9, 128.8, 128.1, 117.6, 112.9, 52.4, 46.7, 41.9.

The obtained oil was dissolved in EtOH and excess amount of 0.5 M HCl–EtOH was added to the solution. EtOH was evaporated *in vacuo*. The resultant residue was washed with AcOEt to give dihydrochloride **8a** (1.08 g, 73 % yield).

*4.1.1.4. N^1-(4-biphenyl)-N^2-(3-chlorobenzyl)ethane-1,2-diamine dihydrochloride (**8b**)*

To a solution of 1,2-diamine (**6b**: 2.27 g, 11 mmol) and 3-chlorobenzaldehyde (**7b**: 1.33 mL, 12 mmol) in MeOH (30 mL) was added AcOH (cat.). The reaction mixture was stirred for 1 h at room temperature. Sodium borohydride (404.5 mg, 11 mmol) was carefully added to the mixture and stirred for 30 min. at room temperature. The volatiles were evaporated *in vacuo*. Sat.$NaHCO_3$ aq. (20 mL) was added to the residue and extracted with CH_2Cl_2 (30 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered off and concentrated *in vacuo*. The resultant residue was purified by MPLC (CH_2Cl_2/MeOH = 97:3) to give **8b** (2.96 g) as a brown oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.44 (dd, *J* = 7.2, 2.4 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.33 (s, 1H), 7.26–7.22 (m, 3H), 7.19 (d, *J* = 7.2 Hz, 1H), 6.70 (dd, *J* = 7.2, 2.4 Hz, 2H), 4.17 (brs, 1H), 3.78 (s, 2H), 3.25 (t, *J* = 6.0 Hz, 2H), 2.89 (t, *J* = 6.0 Hz, 2H), 1.44 (brs, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.8, 142.3, 141.2, 134.3, 130.3, 129.7, 128.6, 128.1, 127.9, 127.2, 126.2, 126.1, 126.0, 113.2, 53.0, 47.9, 43.5; HRMS (ESI) *m/z* calcd for $C_{21}H_{22}{}^{35}ClN_2$ $[M+H]^+$: 337.1466 found 337.1462

This free base was dissolved in EtOH (5 mL) and 0.5 M HCl–EtOH (50 mL). The volatiles were evaporated *in vacuo*. The resultant residue was washed with AcOEt to give dihydrochloride **8b** (3.40 g, 78% yield) as a light yellow powder.

*4.1.1.5. Benzyl-4-phenyl-1,4-diazepane-5,7-dione (**9a**)*

To a suspension of dihydrochloride **8a** (3.10 g, 10 mmol) in THF (100 mL) was slowly added a solution of malonyl chloride (2.01 mL, 21 mmol) in THF (50 mL). The reaction mixture was stirred for 3 h at room temperature. The reaction mixture was basified with saturated $NaHCO_3$ aq. and extracted with AcOEt (50 mL x 2). The combined organic layers were washed with brine (100 mL x 1), dried over Na_2SO_4, filtered off and concentrated *in vacuo*. The resultant residue was purified by MPLC (ethyl acetate/MeOH = 99:1 to 93:7) to give **9a** (2.67 g, 87% yield) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 8H), 7.16 (d, *J* = 7.2 Hz, 2H), 4.69 (s, 2H), 3.99 (s, 2H), 3.91–3.88 (m, 2H), 3.62–3.59 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 164.8, 142.2, 136.6, 129.4, 128.8, 128.1, 127.8, 127.2, 126.2, 51.0, 50.4, 47.9, 46.7.

*4.1.1.6. 1-(4-biphenyl)-4-(3-chlorobenzyl)-1,4-diazepane-5,7-dione (**9b**)*

To a suspension of dihydrochloride **8b** (1.70 g, 4.2 mmol) in THF (50 mL) was slowly added a solution of malonyl chloride (1.21 mL, 13 mmol) in THF (20 mL). The reaction mixture was stirred overnight at room temperature. Malonyl chloride (0.30 mL, 3.1 mmol) in THF (10 mL) was added to the reaction mixture and stirred overnight again. The reaction mixture was diluted with water (100 mL) and extracted with AcOEt (70 mL x 2). The combined organic layers were washed with brine (50 mL x 1), dried over Na_2SO_4, filtered off and concentrated in vacuo. The resultant residue was purified by MPLC (ethyl acetate/MeOH = 99:1 to 93:7) to give **9b** (875 mg, 52% yield) as an orange amorphous. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60–7.57 (m, 2H), 7.55–7.53 (m, 2H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.35 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.29–7.24 (m, 5H), 7.19–7.18 (m, 1H), 4.66 (s, 2H), 3.99 (s, 2H), 3.97–3.96 (m, 2H), 3.62–3.60 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 164.8, 141.1, 140.3, 140.1, 138.6, 134.7, 130.1, 128.8, 128.12, 128.07, 127.5, 127.1, 126.4, 126.2, (1 aromatic carbon peak overlapped somewhere) 50.7, 50.3, 48.2, 46.6; HRMS (ESI) *m/z* calcd for $C_{24}H_{21}{}^{35}ClN_2NaO_2$ $[M+Na]^+$: 427.1184 found 427.1177.

*4.1.1.7. 4-(1-benzyl-5,7-dioxo-4-phenyl-1,4-diazepan-6-yl)butyl acetate (**2a-OAc**)*

To a solution of dione (**9a**: 400 mg, 1.4 mmol) in DMF/THF (5+5 mL) was slowly added NaH (70.7 mg, 1.8 mmol). After being stirred for 30 min. at room temperature, 4-bromobutyl acetate (**10**: 255.6 µL, 1.8 mmol) was added to the mixture. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with water (20 mL) and extracted with AcOEt (10 mL x 3). The combined organic layers were washed with water (20 mL x 1) and brine (20 mL x 1), dried over Na_2SO_4, filtered off and concentrated *in vacuo*. The resultant residue was purified by MPLC (hexane/ethyl acetate = 3:1 to 0:1) to give **2a-OAc** (315.1 mg, 57 % yield) as a colorless oil and recovered starting material **9a** (135.6 mg, 34 % yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32–7.25 (m, 7H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.04–7.02 (m, 2H), 4.90 (d, *J* = 15.0 Hz, 1H), 4.41 (d, *J* = 15.0 Hz, 1H), 4.42–4.19 (m, 1H), 4.07 (t, *J* = 6.6 Hz, 2H), 4.02 (t, *J* = 6.6 Hz, 1H), 3.80–3.75 (m, 1H), 3.54–3.46 (m, 2H), 2.12–2.05 (m, 2H), 2.02 (s, 3H), 1.73–1.68 (m, 2H), 1.47–1.42 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 167.6, 167.1, 142.2, 136.8, 129.0, 128.5, 127.9, 127.5, 126.8, 126.1, 64.2, 51.0, 49.9, 49.7, 47.0, 28.6, 26.0, 24.2, 20.8; HRMS (ESI) *m/z* calcd for $C_{24}H_{28}N_2NaO_4$ $[M+Na]^+$: 431.1941 found 431.1906.

*4.1.1.8. benzyl-6-(4-hydroxybutyl)-4-phenyl-1,4-diazepane-5,7-dione (**2a**)*

To a solution of acetate (**2a-OAc**: 315.0 mg, 0.77 mmol) in EtOH (10 mL) was added 1M NaOH (1 mL). The reaction mixture was stirred for 2 h at r.t. The volatiles were removed *in vacuo*. 1M HCl (2 mL) and water (10 mL) was added to the residue and extracted with AcOEt (10 mL x 2). The combined organic layers were washed with brine (10 mL x 1) and dried over Na_2SO_4, filtered off and concentrated *in vacuo* to give **2** (282.0 mg, quant.) as a pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32–7.24 (m, 7H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.02–7.00 (m, 2H), 4.91 (d, *J* = 15.0 Hz, 1H), 4.37 (d, *J* = 15.0 Hz, 1H), 4.22–4.17 (m, 1H), 4.04 (t, *J* = 6.6 Hz, 1H), 3.78–3.74 (m, 1H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.47–3.42 (m, 2H), 2.09–2.00 (m, 2H), 1.62–1.58 (m, 2H), 1.46–1.41 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 167.4, 142.4, 136.8, 129.0, 128.6, 127.9, 127.5, 126.8, 126.2, 61.7, 51.0, 49.9, 49.6, 46.9, 32.1, 25.5, 23.6; HRMS (ESI) *m/z* calcd for $C_{22}H_{25}N_2O_3$ $[M-H]^-$: 365.1871 found 365.1855.

*4.1.1.9. 1-(4-biphenyl)-4-(3-chlorobenzyl)-6-(4-hydroxybutyl)-1,4-diazepane-5,7-dione (**2b**)*

To a solution of **9b** (2.21 g, 5.5 mmol) in DMF/THF (15 + 15 mL) was slowly added NaH (437 mg, 11 mmol). After being stirred for 1 h at room temperature, 4-bromobutyl acetate (**10**: 1.58 mL, 11 mmol) was added to the mixture. The reaction mixture was stirred for 4 h at room temperature. The reaction mixture was diluted with water (30 mL) and extracted with AcOEt (20 mL x 3). The combined organic layers were washed with water (30 mL x 1) and brine (30 mL x 1), dried over Na_2SO_4, filtered off and concentrated *in vacuo*. The resultant residue was purified by MPLC (ethyl acetate/MeOH = 99:1 to 93:7) to give 1.32 g of the crude product (**2b-OAc**) as a light yellow amorphous. This crude compound was used for the next reaction without further purification.

To a suspension of **2b-OAc** (1.42 g, 2.7 mmol) in EtOH (15 mL) was added 2M NaOH (5 mL). The reaction mixture was stirred for 2 h at r.t. The volatiles were removed *in vacuo*. 5M HCl (3 mL) was added to the residue and extracted with AcOEt (10 mL x 2). The combined organic layers were washed with brine (10 mL x 1), dried over Na_2SO_4, filtered off and concentrated *in vacuo*. The resultant residue was purified by MPLC (ethyl acetate/MeOH = 99:1 to 93:1) to give **2b** (1.15 g, 41% yield, 2 steps) as a white amorphous. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55–7.52 (m, 4H), 7.16 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.26–7.23 (m, 3H), 7.17–7.14 (m, 3H), 4.88 (d, *J* = 14.0 Hz, 1H), 4.41 (d, *J* = 15.0 Hz, 1H), 4.32 (ddd, *J* = 15.0, 9.5, 4.5 Hz, 1H), 4.06 (t, *J* = 6.5 Hz, 1H), 3.78 (dt, *J* = 14.5, 4.5 Hz, 1H), 3.68 (t, *J* = 6.5 Hz, 2H), 3.61 (dt, *J* = 15.0, 5.5 Hz, 1H), 3.52–3.46 (m, 1H), 2.23 (brs, 1H), 2.13–2.07 (m, 2H), 1.67–1.62 (m, 2H), 1.50–1.44 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 167.5, 141.5, 140.1, 140.0, 139.0, 134.6, 130.1, 128.7, 127.9, 127.5, 127.0, 126.5, 126.2, (2 aromatic carbon peaks overlapped somewhere) 62.0, 50.8, 50.0, 49.9, 47.5, 32.2, 25.6, 23.7; HRMS (ESI) *m/z* calcd for $C_{28}H_{30}{}^{35}ClN_2O_3$ $[M+H]^+$: 477.1939 found 477.1919.

*4.1.2. Synthesis of γ-turn mimetics **1** (Method A)*

General Procedure: To a solution of alcohol **2** (1.0 equiv), nosylate **3** (1.1 equiv) and PPh_3 (3.0 equiv) in THF was slowly added 40 % DEAD in toluene (3.0 equiv). The reaction mixture was stirred overnight at room temperature. The volatiles were evaporated *in vacuo*. The resultant residue was purified by MPLC to give the crude nosylate (often including diethyl hydrazinedicrboxylate). Then, to a suspension of the obtained crude nosylate (1.0 equiv) and K_2CO_3 (4.0 equiv) in CH_3CN was added thiophenol (3.0 equiv). The reaction mixture was stirred overnight at 60 ºC. After cooling to room temperature, the reaction mixture was diluted with water and extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered off and concentrated *in vacuo*. The resultant residue was purified by NH-MPLC to give **1**.

*4.1.2.1. Benzyl-4-phenyl-6-[4-(trans-2-phenylcyclopropylamino)butyl]-1,4-diazepane-5,7-dione (**1a**)*

Alcohol (**2a**: 50.0 mg) was used to obtain **1a** (16.8 mg, 26% yield) as a light yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35–7.22 (m, 9H), 7.15–7.12 (m, 1H), 7.06–7.03 (m, 5H), 4.91 (d, *J* = 15.0 Hz, 1H), 4.46 (dd, *J* = 15.0, 3.0 Hz, 1H), 4.25–4.20 (m, 1H), 3.99 (t, *J* = 6.6 Hz, 1H), 3.79–3.75 (m, 1H), 3.57–3.48 (m, 2H), 2.78 (t, *J* = 7.2 Hz, 2H), 2.34 (ddd, *J* = 7.2, 4.2, 3.0 Hz, 1H), 2.12–2.08 (m, 2H), 1.91–1.88 (m, 1H), 1.63–1.58 (m, 2H), 1.45–

1.40 (m, 2H), 1.06 (ddd, J = 9.0, 4.8, 4.2 Hz, 1H), 0.98–0.95 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 167.4, 142.7, 142.1, 137.0, 129.2, 128.8, 128.2, 128.1, 127.7, 127.0, 126.4, 125.8, 125.4, 51.3, 50.1, 50.0, 49.1, 47.2, 41.4, 30.0, 26.2, 25.5, 24.8, 16.7; HRMS (ESI) *m/z* calcd for $C_{31}H_{36}N_3O_2$ $[M+H]^+$: 482.2802 found 482.2795.

*4.1.2.2. Benzyl-6-{4-[trans-2-(4-fluorophenyl)cyclopropylamino]butyl}-4-phenyl-1,4-diazepane-5,7-dione (**1b**)*

Alcohol (**2a**: 50.0 mg) was used to obtain **1b** (38.6 mg, 68% yield) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.21 (m, 8H), 7.05 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.00–6.97 (m, 2H), 6.94–6.90 (m, 2H), 4.91 (d, *J* = 14.4 Hz, 1H), 4.44 (dd, *J* = 14.4, 3.0 Hz, 1H), 4.24–4.19 (m, 1H), 3.99 (t, *J* = 7.2 Hz, 1H), 3.79–3.75 (m, 1H), 3.56–3.47 (m, 2H), 2.77 (t, *J* = 7.2 Hz, 2H), 2.27 (ddd, *J* = 7.2, 4.8, 3.6 Hz, 1H), 2.13–2.06 (m, 2H), 1.89–1.85 (m, 1H), 1.62–1.57 (m, 2H), 1.45–1.40 (m, 2H), 1.04 (ddd, *J* = 9.0, 4.8, 4.2 Hz, 1H), 0.92–0.89 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 167.4, 161.0 (d, J_{CF} = 241.2 Hz), 142.6, 138.0 (d, J_{CF} = 2.9 Hz), 137.0, 129.2, 128.8, 128.1, 127.7, 127.2 (d, J_{CF} = 8.7 Hz), 127.0, 126.3, 114.9 (d, J_{CF} = 20.1 Hz), 51.2, 50.1 (2 peaks overlapped), 49.1, 47.2, 41.4, 30.0, 26.3, 25.6, 24.3, 16.7; HRMS (ESI) *m/z* calcd for $C_{31}H_{35}FN_3O_2$ $[M+H]^+$: 500.2708 found 500.2691.

*4.1.2.3. Benzyl-4-phenyl-6-{4-[trans-2-(p-tolyl)cyclopropylamino]butyl}-1,4-diazepane-5,7-dione (**1c**)*

Alcohol (**2a**: 39.0 mg) was used to obtain **1c** (15.8 mg, 30% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.22 (m, 8H), 7.06–7.04 (m, 4H), 6.94 (d, *J* = 7.0 Hz, 2H), 4.91 (d, *J* = 14.5, 1H), 4.45 (dd, J = 14.5, 3.0 Hz, 1H), 4.25–4.19 (m, 1H), 3.99 (t, *J* = 6.8 Hz, 1H), 3.80–3.75 (m, 1H), 3.57–3.47 (m, 2H), 2.77 (t, *J* = 7.3 Hz, 2H), 2.31–2.28 (m, 4H), 2.12–2.06 (m, 2H), 1.88–1.84 (m, 1H), 1.63–1.57 (m, 2H), 1.45–1.39 (m, 2H), 1.04–1.00 (m, 1H), 0.94–0.90 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 167.4, 142.6, 139.3, 137.0, 134.8, 129.3, 128.9, 128.8, 128.2, 127.8, 127.1, 126.4, 125.8, 51.3, 50.1, 50.0, 49.2, 47.3, 41.4, 30.0, 26.3, 25.7, 24.7, 20.9, 16.7; HRMS (ESI) *m/z* calcd for $C_{32}H_{38}N_3O_2$ $[M+H]^+$: 496.2959 found 496.2931.

*4.1.2.4. Benzyl-6-{4-[trans-2-(4-methoxyphenyl)cyclopropylamino]butyl}-4-phenyl-1,4-diazepane-5,7-dione (**1d**)*

Alcohol (**2a**: 50.0 mg) was used to obtain **1d** (37.5 mg, 54% yield) as a white amorphous. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.26 (m, 7H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.97 (dd, *J* = 9.0, 1.8 Hz, 2H), 6.79 (dd, *J* = 9.0, 1.8 Hz, 2H), 4.91 (d, *J* = 15.0, 1H), 4.44 (dd, *J* = 15.0, 3.0 Hz, 1H), 4.24–4.19 (m, 1H), 3.99 (t, *J* = 6.6 Hz, 1H), 3.78–3.74 (m, 4H), 3.56–3.47 (m, 2H), 2.77 (t, *J* = 7.2 Hz, 2H), 2.27–2.24 (m, 1H), 2.12–2.07 (m, 2H), 1.86–1.83 (m, 1H), 1.62–1.57 (m, 2H), 1.45–1.40 (m, 2H), 1.01–0.98 (m, 1H), 0.90–0.87 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 167.3, 157.5, 142.6, 137.0, 134.4, 129.2, 128.8, 128.1, 127.7, 127.0, 126.9, 126.3, 113.7, 55.2, 51.2, 50.1, 50.0, 49.2, 47.2, 41.1, 30.0, 26.3, 25.7, 24.2, 16.4; HRMS (ESI) *m/z* calcd for $C_{32}H_{38}N_3O_2$ $[M+H]^+$: 512.2908 found 512.2906.

*4.1.2.5. 6-{4-[trans-2-(4-biphenyl)cyclopropylamino]butyl}-1-benzyl-4-phenyl-1,4-diazepane-5,7-dione (**1e**)*

Alcohol (**2a**: 50.0 mg) was used to obtain **1e** (34.4 mg, 47% yield) as a white amorphous. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.47 (dd, *J* = 8.4, 1.8 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.34–7.26 (m, 8H), 7.22 (td, *J* = 7.8, 1.8 Hz, 1H), 7.11 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.05 (dd, *J* = 8.4, 1.2 Hz, 2H), 4.90 (dd, *J* = 14.4, 3.0 Hz, 1H), 4.44 (dd, *J* = 14.4, 2.4 Hz, 1H), 4.22–4.18 (m, 1H), 3.98 (td, *J* = 7.2, 1.8 Hz, 1H), 3.76–3.72 (m, 1H), 3.54–3.45 (m, 2H), 2.79 (t, *J* = 7.2 Hz, 2H), 2.39–2.37 (m, 1H), 2.13–2.08 (m, 2H), 1.94–1.92 (m, 1H), 1.63–1.58 (m, 2H), 1.46–1.41 (m, 2H), 1.12–1.08 (m, 1H), 1.02–0.99 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 167.3, 142.6, 141.0, 138.3, 137.0, 129.2, 128.8, 128.7, 128.2, 127.7, 127.0, 126.9, 126.8, 126.3, 126.2, (2 aromatic carbon peaks overlapped somewhere) 51.3, 50.1, 50.0, 49.2, 47.2, 41.8, 30.0, 26.3, 25.7, 24.8, 17.1; HRMS (ESI) *m/z* calcd for $C_{37}H_{40}N_3O_2$ $[M+H]^+$: 558.3115 found 558.3103.

*4.1.2.6. 1-(4-biphenyl)-4-(3-chlorobenzyl)-6-[4-(trans-2-phenylcyclopropylamino)butyl]-1,4-diazepane-5,7-dione (**1n**)*

Alcohol (**2b**: 10.0 mg) was used to obtain **1n** (5.8 mg, 47% yield) as a white amorphous. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.53 (m, 4H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.28–7.23 (m, 5H), 7.19–7.12 (m, 4H), 7.04 (d, *J* = 8.0 Hz, 2H), 4.88 (d, *J* = 15.0 Hz, 1H), 4.46 (d, *J* = 15.0 Hz, 1H), 4.36–4.29 (m, 1H), 4.02 (t, *J* = 6.5 Hz, 1H), 3.81–3.76 (m, 1H), 3.65 (td, *J* = 15.0, 6.0 Hz, 1H), 3.55–3.49 (m, 1H), 2.79 (t, *J* = 7.0 Hz, 2H), 2.35–2.33 (m, 1H), 2.14–2.09 (m, 2H), 1.92–1.86 (m, 1H), 1.64–1.58 (m, 2H), 1.46–1.42 (m, 2H), 1.09–1.05 (m, 1H), 0.99–0.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 167.3, 142.3, 141.5, 140.1, 139.9, 139.0, 134.5, 130.0, 128.7, 128.1, 127.92, 127.86, 127.4, 126.9, 126.5, 126.1, 125.7, 125.2, (1 aromatic carbon peak overlapped somewhere) 50.7, 49.9, 49.8, 49.0, 47.4, 41.5, 29.9, 26.2, 25.5, 25.0, 16.9; HRMS (ESI) *m/z* calcd for $C_{37}H_{39}{}^{35}ClN_3O_2$ [M+H]+: 592.2725 found 592.2717.

*4.1.2.7. 1-(4-biphenyl)-6-{4-[trans-2-(4-biphenyl)cyclopropylamino]butyl}-4-(3-chlorobenzyl)-1,4-diazepane-5,7-dione (**1o**)*

Alcohol (**2b**: 50.0 mg) was used to obtain **1o** (27.8 mg, 40%) as a white amorphous. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56–7.53 (m, 6H), 7.47 (dd, *J* = 8.4, 1.8 Hz, 2H), 7.44–7.40 (m, 4H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.27–7.24 (m, 3H), 7.18–7.14 (m, 3H), 7.11 (d, *J* = 7.2 Hz, 2H), 4.86 (dd, *J* = 15.0, 2.4 Hz, 1H), 4.44 (d, *J* = 14.4 Hz, 1H), 4.32–4.27 (m, 1H), 4.02 (td, *J* = 6.6, 1.8 Hz, 1H), 3.77–3.72 (m, 1H), 3.64–3.59 (m, 1H), 3.52–3.47 (m, 1H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.39–2.37 (m, 1H), 2.12 (q, *J* = 7.2 Hz, 2H), 1.95–1.92 (m, 1H), 1.64–1.59 (m, 2H), 1.47–1.42 (m, 2H), 1.12–1.09 (m, 1H), 1.02–0.99 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 167.4, 141.7, 141.6, 141.0, 140.2, 140.1, 139.0, 138.3, 134.7, 130.1, 128.8, 128.7, 128.1, 128.0, 127.4, 127.1, 126.9, 126.8, 126.5, 126.22, 126.17 (2 aromatic carbon peaks overlapped), 50.9, 50.0, 49.9, 49.1, 47.5, 41.7, 30.0, 26.3, 25.6, 24.8, 17.1; HRMS (ESI) m/z calcd for $C_{43}H_{43}{}^{35}ClN_3O_2$ $[M+H]^+$: 668.3038 found 668.3016.

*4.1.3. Synthesis of γ-turn mimetics **1** (Method B)*

*4.1.3.1. N-[4-(1-benzyl-5,7-dioxo-4-phenyl-1,4-diazepan-6-yl)butyl]-N-[trans-2-(4-bromophenyl)cyclopropyl]-2-nitrobenzenesulfonamide (**11a**)*

To a solution of 1-benzyl-6-(4-hydroxybutyl)-4 -phenyl-1,4-diazepane-5,7-dione (**2a**: 50.0 mg, 0.14 mmol), *N*-[*trans*-2-(4-bromophenyl)cyclopropyl]-2-nitrobenzenesulfonamide (**3'**; 59.6 mg, 0.15 mmol) and PPh_3 (107 mg, 0.41 mmol) in THF (3 mL) was slowly added 40 % DEAD in toluene (186.4 µL, 0.41 mmol). The reaction mixture was stirred overnight at room temperature. The volatiles were evaporated in vacuo. The resultant residue was purified by MPLC (hexane/ethyl acetate = 3:1 to 1:3) to give **11a** (82.4 mg, 81% yield) as a white amorphous. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.60–7.75 (m, 2H), 7.37–7.21 (m, 10H), 7.06 (dd, *J* = 7.2, 4.8 Hz, 2H), 6.89–6.86 (m, 2H), 4.93 (dd, *J* = 14.4, 10.2 Hz, 1H), 4.43 (dd, *J* = 14.4, 5.4 Hz, 1H), 4.27–4.20 (m, 1H), 4.02 (ddd, *J* = 6.6,

6.6, 4.2 Hz, 1H), 3.83–3.78 (m, 1H), 3.55–3.45 (m, 3H), 3.35–3.29 (m, 1H), 2.63–2.60 (m, 1H), 2.14–2.05 (m, 3H), 1.76–1.71 (m, 2H), 1.47–1.42 (m, 2H), 1.37 (ddd, *J* = 10.2, 6.0, 4.8 Hz, 1H), 1.21–1.17 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 167.3, 148.0, 142.6, 138.5, 137.0, 133.7, 132.7, 131.5, 131.4, 131.3, 129.2, 128.8, 128.1, 127.8, 127.7, 127.0, 126.4, 124.0, 120.1, 51.2, 50.2, 50.1, 49.6, 47.2, 38.6, 28.4, 26.0, 24.9, 24.7, 16.1; HRMS (ESI) *m/z* calcd for $C_{37}H_{37}{}^{79}BrN_4NaO_6S$ $[M+Na]^+$: 767.1509 found 767.1499.

*4.1.3.2. N-{4-[1-(4-biphenyl)-4-(3-chlorobenzyl)-5,7-dioxo-1,4-diazepan-6-yl]butyl}-N-[trans-2-(4-bromophenyl)cyclopropyl]-2-nitrobenzenesulfonamide (**11b**)*

To a solution of **2b** (1.0 equiv), *N*-[*trans*-2-(4-bromophenyl)cyclopropyl]-2-nitrobenzenesulfonamide (**3'**, 1.1 equiv) and PPh_3 (3.0 equiv) in THF was slowly added 40 % DEAD in toluene (3.0 equiv). The reaction mixture was stirred overnight at room temperature. The volatiles were evaporated *in vacuo*. The resultant residue was purified by MPLC to give crude **11b** including diethyl hydrazinedicrboxylate. The obtained crude **11b** was used for the next reaction without further purification.

*4.1.3.3. General procedure: Suzuki coupling with arylboronic acid and bromide (**11**)*

A suspension of **11** (1.0 equiv), arylboronic acid (3.0 equiv), Na_2CO_3 (3.0 equiv) and $Pd(PPh_3)_4$ (10 mol%) in toluene/MeOH/H_2O (25:5:1) was heated at 70 ºC overnight under N_2 atmosphere. After cooling to room temperature, the reaction mixture was diluted with water and extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered off and concentrated *in vacuo*. The resultant residue was purified by MPLC to give the crude product. Then, to a suspension of the obtained crude nosylate (1.0 equiv) and K_2CO_3 (4.0 equiv) in CH_3CN was added thiophenol (3.0 equiv). The reaction mixture was stirred overnight at 60 ºC. After cooling to room temperature, the reaction mixture was diluted with water and extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered off and concentrated *in vacuo*. The resultant residue was purified by NH-MPLC to give **1**.

*4.1.3.3.1. Benzyl-6-{4-[trans-2-(3'-chlorobiphenyl-4-yl)cyclopropylamino]butyl}-4-phenyl-1,4-diazepane-5,7-dione (**1f**)*

Bromide (**11a**: 80.0 mg) was used to obtain **1f** (40.0 mg, 63% yield) as a white amorphous. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (t, *J* = 1.5 Hz, 1H), 7.44–7.42 (m, 3H), 7.35–7.21 (m, 10H), 7.11 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.05 (dd, *J* = 7.5, 1.0 Hz, 2H), 4.90 (dd, *J* = 15.0, 3.0 Hz, 1H), 4.45 (dd, *J* = 15.0, 3.0 Hz, 1H), 4.24–4.18 (m, 1H), 3.99 (t, *J* = 6.5 Hz, 1H), 3.77–3.73 (m, 1H), 3.56–3.46 (m, 2H), 2.79 (t, *J* = 7.3 Hz, 2H), 2.39–2.36 (m, 1H), 2.13–2.08 (m, 2H), 1.94–1.91 (m, 1H), 1.64–1.58 (m, 2H), 1.46–1.40 (m, 2H), 1.13–1.09 (m, 1H), 1.02–0.99 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 167.3, 142.8, 142.6, 142.5, 137.0, 136.8, 134.5, 129.9, 129.2, 128.8, 128.1, 127.7, 127.0, 126.91, 126.86, 126.8, 126.3, 126.2, 125.0, 51.3, 50.1, 50.0, 49.1, 47.2, 41.9, 30.0, 26.3, 25.7, 24.9, 17.3; HRMS (ESI) *m/z* calcd for $C_{37}H_{39}{}^{35}ClN_3O_2$ $[M+H]^+$: 592.2725 found 592.2719.

*4.1.3.3.2. Benzyl-6-{4-[trans-2-(3'-methoxybiphenyl-4-yl)cyclopropylamino]butyl}-4-phenyl-1,4-diazepane-5,7-dione (**1g**)*

Bromide (**11a**: 70.0 mg) was used to obtain **1g** (27.9 mg, 51% yield) as a white amorphous. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (dq, *J* = 8.4, 1.8 Hz, 2H), 7.34–7.26 (m, 8H), 7.22 (tq, *J* = 7.2, 1.2 Hz, 1H), 7.15–7.13 (m, 1H), 7.10–7.09 (m, 3H), 7.05–7.03 (m, 2H), 6.86 (dd, *J* = 8.4, 1.2 Hz, 1H), 4.90 (dd, *J* = 14.4, 1.8 Hz, 1H), 4.44 (dd, *J* = 15.0, 1.8 Hz, 1H), 4.23–4.18 (m, 1H), 3.98 (t, *J* = 6.6 Hz, 1H), 3.85 (s, 3H), 3.77–3.72 (m, 1H), 3.54–3.46 (m, 2H), 2.79 (t, *J* = 7.2 Hz, 2H), 2.39–2.36 (m, 1H), 2.12–2.07 (m, 2H), 1.94–1.91 (m, 1H), 1.63–1.58 (m, 2H), 1.46–1.41 (m, 2H), 1.12–1.09 (m, 1H), 1.02–0.99 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 167.4, 159.9, 142.7, 142.5, 141.9, 138.2, 137.0, 129.6, 129.2, 128.8, 128.2, 127.7, 127.0, 126.9, 126.3, 126.2, 119.4, 112.6, 112.4, 55.2, 51.3, 50.1 (2 peaks overlapped), 49.1, 47.2, 41.8, 30.0, 26.3, 25.7, 24.9, 17.1; HRMS (ESI) *m/z* calcd for $C_{38}H_{42}N_3O_3$ $[M+H]^+$: 588.3221 found 588.3196.

*4.1.3.3.3. Benzyl-4-phenyl-6-{4-[trans-2-(3'-trifluoromethylbiphenyl-4-yl)cyclopropylamino]butyl}-1,4-diazepane-5,7-dione (**1h**)*

Bromide (**11a**: 50.0 mg) was used to obtain **1h** (3.5 mg, 8.3% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.57–7.51 (m, 2H), 7.47 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.34–7.22 (m, 8H), 7.13 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.06 (dd, *J* = 8.5, 1.0 Hz, 2H), 4.91 (dd, *J* = 14.5, 2.5 Hz, 1H), 4.47 (dd, *J* = 14.5, 2.5 Hz, 1H), 4.26–4.20 (m, 1H), 3.99 (t, *J* = 6.5 Hz, 1H), 3.80–3.75 (m, 1H), 3.58–3.48 (m, 2H), 2.80 (t, *J* = 7.5 Hz, 2H), 2.40–2.37 (m, 1H), 2.14–2.07 (m, 2H), 1.95–1.93 (m, 1H), 1.64–1.59 (m, 2H), 1.47–1.41 (m, 2H), 1.14–1.11 (m, 1H), 1.04–1.00 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 167.4, 142.70, 142.65, 141.8, 137.0, 136.8, 131.1 (q, J_{CF} = 32.1 Hz), 130.1, 129.3, 129.1, 128.8, 128.2, 127.8, 127.1, 127.0, 126.4 (2 peaks overlapped), 124.1 (q, J_{CF} = 271.7 Hz), 123.64 (q, J_{CF} = 4.4 Hz), 123.57 (q, J_{CF} = 2.9 Hz), 51.3, 50.1 (2 peaks overlapped), 49.1, 47.3, 42.0, 30.1, 26.3, 25.7, 24.9, 17.3; HRMS (ESI) *m/z* calcd for $C_{38}H_{39}F_3N_3O_2$ $[M+H]^+$: 626.2989 found 626.2971.

*4.1.3.3.4. Benzyl-4-phenyl-6-{4-[trans-2-(3'-trifluoromethoxybiphenyl-4-yl)cyclopropylamino]butyl}-1,4-diazepane-5,7-dione (**1i**)*

Bromide (**11a**: 50.0 mg) was used to obtain **1i** (17.0 mg, 40% yield) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49–7.39 (m, 5H), 7.35–7.22 (m, 8H), 7.57–7.51 (m, 2H), 7.16 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.12 (dd, *J* = 8.4, 1.5 Hz, 2H), 7.06 (dd, *J* = 9.0, 1.2 Hz, 2H), 4.91 (dd, *J* = 15.0, 3.0 Hz, 1H), 4.46 (dd, *J* = 15.0, 3.0 Hz, 1H), 4.25–4.21 (m, 1H), 3.99 (t, *J* = 6.0 Hz, 1H), 3.78–3.75 (m, 1H), 3.57–3.48 (m, 2H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.38 (ddd, *J* = 7.2, 4.2, 3.0 Hz, 1H), 2.13–2.08 (m, 2H), 1.95–1.92 (m, 1H), 1.63–1.59 (m, 2H), 1.46–1.41 (m, 2H), 1.14–1.11 (m, 1H), 1.04–1.00 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 167.4, 149.6, 143.1, 142.7, 142.6, 137.0, 136.7, 130.0, 129.3, 128.8, 128.2, 127.8, 127.1, 126.9, 126.4, 126.3, 125.2, 120.5 (q, J_{CF} = 255.9 Hz), 119.4, 119.2, 51.3, 50.12, 50.09, 49.2, 47.3, 41.9, 30.0, 26.3, 25.7, 24.9, 17.3; HRMS (ESI) *m/z* calcd for $C_{38}H_{39}F_3N_3O_3$ $[M+H]^+$: 642.2938 found 642.2911.

*4.1.3.3.5. Benzyl-4-phenyl-6-{4-[trans-2-(4-(3-pyridinyl)phenyl)cyclopropylamino]butyl}-1,4-diazepane-5,7-dione (**1j**)*

Bromide (**11a**: 50.0 mg) was used to obtain **1j** (8.3 mg, 22% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (d, *J* = 2.4 Hz, 1H), 8.56 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.47 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.35–7.22 (m, 9H), 7.15 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.66 (dd, *J* = 8.4, 1.2 Hz, 2H), 4.91 (dd, *J* = 14.4, 3.0 Hz, 1H), 4.46 (dd, *J* = 14.4, 3.0 Hz, 1H), 4.26–4.21 (m, 1H), 4.00 (t, *J* = 6.6 Hz, 1H), 3.80–3.75 (m, 1H), 3.57–3.48 (m, 2H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.40–2.38 (m, 1H), 2.13–2.09 (m, 2H), 1.96–1.93 (m, 1H), 1.64–1.59 (m, 2H), 1.46–1.41 (m, 2H), 1.15–1.11 (m, 1H), 1.03–1.00 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 167.4, 148.2, 142.8, 142.7, 137.0, 136.5, 134.9, 134.0, 129.3, 128.8, 128.2, 127.8, 127.1, 126.9, 126.5, 126.4,

123.5 (one aromatic carbon overlapped), 51.4, 50.20, 50.16, 49.2, 47.3, 41.9, 30.1, 26.4, 25.7, 25.0, 17.3; HRMS (ESI) *m/z* calcd for $C_{36}H_{39}N_4O_2$ $[M+H]^+$: 559.3068 found 559.3053.

*4.1.3.3.6. Benzyl-4-phenyl-6-{4-[trans-2-(4-(5-pyrimidinyl)phenyl)cyclopropylamino]butyl}-1,4-diazepane-5,7-dione (**1k**)*

Bromide (**11a**: 50.0 mg) was used to obtain **1k** (6.9 mg, 18% yield) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.92 (s, 2H), 7.46 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.34–7.22 (m, 6H), 7.18 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.15 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.06 (d, *J* = 7.2 Hz, 2H), 4.91 (dd, *J* = 14.4, 3.0 Hz, 1H), 4.47 (dd, *J* = 14.4, 3.6 Hz, 1H), 4.26–4.22 (m, 1H), 4.00 (t, *J* = 6.6 Hz, 1H), 3.80–3.76 (m, 1H), 3.58–3.49 (m, 2H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.41–2.38 (m, 1H), 2.13–2.08 (m, 2H), 1.97–1.94 (m, 1H), 1.64–1.59 (m, 2H), 1.46–1.41 (m, 2H), 1.17–1.14 (m, 1H), 1.05–1.02 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 167.4, 157.2, 154.6, 144.0, 142.7, 137.0, 134.2, 131.2, 129.3, 128.8, 128.2, 127.8, 127.1, 126.83, 126.78, 126.4, 51.4, 50.24, 50.17, 49.1, 47.3, 42.2, 30.1, 26.4, 25.7, 25.0, 17.5; HRMS (ESI) *m/z* calcd for $C_{35}H_{38}N_5O_2$ $[M+H]^+$: 560.3020 found 560.3008.

*4.1.3.3.7. 4'-{trans-2-[4-(1-Benzyl-5,7-dioxo-4-phenyl-1,4-diazepan-6-yl)butyl]cyclopropylamino}-N-methyl-biphenyl-3-sulfonamide (**1l**)*

Bromide (**11a**, 50.0 mg) was used to obtain **1l** (14.8 mg, 34% yield) as a white amorphous. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (t, *J* = 2.0 Hz, 1H), 7.80–7.75 (m, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 6.5 Hz, 2H), 7.34–7.21 (m, 8H), 7.12 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.05 (d, *J* = 7.5 Hz, 2H), 4.91 (dd, *J* = 14.5, 2.5 Hz, 1H), 4.65 (brs, 1H), 4.45 (dd, *J* = 14.5, 3.0 Hz, 1H), 4.26–4.20 (m, 1H), 4.00 (t, *J* = 6.5 Hz, 1H), 3.81–3.76 (m, 1H), 3.57–3.48 (m, 2H), 2.79 (t, *J* = 7.5 Hz, 2H), 2.67 (s, 3H), 2.39–2.36 (m, 1H), 2.12–2.06 (m, 2H), 1.95–1.92 (m, 1H), 1.64–1.58 (m, 2H), 1.46–1.40 (m, 2H), 1.15–1.11 (m, 1H), 1.03–1.00 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 167.4, 142.9, 142.6, 142.2, 139.4, 137.0, 136.2, 130.9, 129.5, 129.3, 128.8, 128.2, 127.8, 127.1, 127.0, 126.42, 126.38, 125.4, 125.3, 51.3, 50.1, 50.0, 49.1, 47.2, 42.0, 30.0, 29.4, 26.3, 25.7, 24.9, 17.3; HRMS (ESI) *m/z* calcd for $C_{38}H_{43}N_4O_4S$ $[M+H]^+$: 651.3000 found 651.2987.

*4.1.3.3.8. 4'-{trans-2-[4-((4-biphenyl)-1-(3-chlorobenzyl)-5,7-dioxo-1,4-diazepan-6-yl)butyl]cyclopropylamino}-N-methyl-biphenyl-3-sulfonamide (**1p**)*

Bromide **11b** (25.0 mg) was used to obtain **1p** (11.7 mg, 13% yield, 3 steps) as a white amorphous. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.80–7.75 (m, 2H), 7.57–7.53 (m, 5H), 7.48 (dd, *J* = 8.4, 1.8 Hz, 2H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.27–7.16 (m, 3H), 7.19–7.16 (m, 3H), 7.12 (dd, *J* = 8.4, 1.2 Hz, 2H), 4.87 (dd, *J* = 15.0, 1.8 Hz, 1H), 4.58 (brs, 1H), 4.46 (dd, *J* = 15.0, 1.8 Hz, 1H), 4.35–4.31 (m, 1H), 4.03 (t, *J* = 6.6 Hz, 1H), 3.81–3.77 (m, 1H), 3.65 (dt, *J* = 15.0, 6.0 Hz, 1H), 3.55–3.50 (m, 1H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.67 (s, 3H), 2.38 (ddd, *J* = 7.2, 4.2, 3.0 Hz, 1H), 2.11 (q, *J* = 7.8 Hz, 2H), 1.96–1.93 (m, 1H), 1.64–1.59 (m, 2H), 1.47–1.42 (m, 2H), 1.15–1.12 (m, 1H), 1.03–1.00 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 167.4, 143.0, 142.2, 141.6, 140.2, 140.2, 139.3, 139.1, 136.3, 134.7, 131.0, 130.2, 129.5, 128.8, 128.08, 128.05, 127.5, 127.1, 127.0, 126.6, 126.4, 126.3, 125.4, 125.3 (1 aromatic carbon peak overlapped somewhere), 50.9, 50.1, 49.9, 49.1, 47.6, 42.0, 30.0, 29.4, 26.3, 25.6, 24.9, 17.3; HRMS (ESI) *m/z* calcd for $C_{44}H_{46}{}^{35}ClN_4O_4S$ $[M+H]^+$: 761.2923 found 761.2911.

*4.1.3.3.9. 4'-{trans-2-[4-((4-biphenyl)-1-(3-chlorobenzyl)-5,7-dioxo-1,4-diazepan-6-yl)butyl]cyclopropylamino}-N-methyl-biphenyl]-3-carboxamide (**1q**)*

Bromide **11b** (25.0 mg) was used to obtain **1q** (10.3 mg, 12% yield, 3 steps) as a white amorphous. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.67 (t, *J* = 7.8 Hz, 2H), 7.56–7.54 (m, 4H), 7.49–7.42 (m, 5H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.27–7.25 (m, 3H), 7.17–7.15 (m, 3H), 7.11 (d, *J* = 7.2 Hz, 2H), 6.30 (brs, 1H), 4.87 (d, *J* = 14.4 Hz, 1H), 4.45 (d, *J* = 15.0 Hz, 1H), 4.34–4.29 (m, 1H), 4.02 (t, *J* = 6.6 Hz, 1H), 3.80–3.76 (m, 1H), 3.64 (dt, *J* = 15.0, 6.0 Hz, 1H), 3.54–3.49 (m, 1H), 3.02 (d, *J* = 4.8 Hz, 3H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.39–2.37 (m, 1H), 2.12 (q, *J* = 7.8 Hz, 2H), 1.95–1.93 (m, 1H), 1.64–1.60 (m, 2H), 1.46–1.42 (m, 2H), 1.14–1.10 (m, 1H), 1.02 (q, *J* = 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.2, 168.0, 167.4, 142.3, 141.6, 141.4, 140.20, 140.17, 139.1, 137.3, 135.2, 134.7, 130.2, 129.7, 128.9, 128.8, 128.09, 128.04, 127.5, 127.1, 126.9, 126.6, 126.29, 126.25, 125.4, 125.2 (1 aromatic carbon peak overlapped somewhere), 50.9, 50.1, 49.9, 49.1, 47.6, 41.9, 30.0, 26.9, 26.3, 25.7, 24.9, 17.2; HRMS (ESI) *m/z* calcd for $C_{45}H_{46}{}^{35}ClN_4O_3$ $[M+H]^+$: 725.3253 found 725.3246.

*4.1.4. Synthesis of γ-turn mimetics **1** (Method C)*

*4.1.4.1. Methyl 4'-{trans-2-[4-(1-benzyl-5,7-dioxo-4-phenyl-1,4-diazepan-6-yl)butyl](2-nitropheny)cyclopropylsulfonamido} bipenyl-3-carboxylate (**12**)*

A suspension of **11a** (70.0 mg, 94 µmol), 3-methoxycarbonylphenylboronic acid (50.7 mg, 0.28 mmol), Na_2CO_3 (29.6 mg, 0.28 mmol) and $Pd(PPh_3)_4$ (10.9 mg, 9.4 µmol) in toluene/MeOH/H_2O (5 mL/1 mL/0.2 mL) was heated at 80 ºC overnight under N_2 atmosphere. After cooling to room temperature, the reaction mixture was diluted with water (5 mL) and extracted with AcOEt (5 mL x 2). The combined organic layers were washed with brine (10 mL x 1) dried over Na_2SO_4, filtered off and concentrated *in vacuo*. The resultant residue was purified by MPLC (hexane/ethyl acetate = 1:1 to 0:1) to give **12** (75.3 mg, quant.) as a white amorphous. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.99 (t, *J* = 7.5 Hz, 2H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 2H), 7.61–7.57 (m, 2H), 7.52–7.47 (m, 3H), 7.34–7.26 (m, 6H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.09–7.05 (m, 4H), 4.93 (dd, *J* = 14.5, 4.0 Hz, 1H), 4.42 (dd, *J* = 14.5, 4.5 Hz, 1H), 4.27–4.20 (m, 1H), 4.05 (ddd, *J* = 7.0, 3.5, 3.5 Hz, 1H), 3.04 (s, 3H), 3.82–3.76 (m, 1H), 3.54–3.45 (m, 3H), 3.40–3.32 (m, 1H), 2.71–2.68 (m, 1H), 2.23–2.19 (m, 1H), 2.15–2.06 (m, 2H), 1.79–1.75 (m, 2H), 1.50–1.38 (m, 3H), 1.29–1.24 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 167.3, 166.9, 147.9, 142.6, 140.8, 139.1, 138.1, 137.0, 133.7, 132.7, 131.4, 131.3, 131.2, 130.6, 129.2, 128.8, 128.7, 128.2, 128.0, 127.9, 127.6, 127.1, 126.9, 126.5, 126.3, 124.0, 52.1, 51.2, 50.2, 50.0, 49.5, 47.1, 38.7, 28.4, 26.0, 24.83, 24.77, 16.2; HRMS (ESI) *m/z* calcd for $C_{45}H_{45}N_4O_8S$ $[M+H]^+$: 801.2953 found 801.2900.

*4.1.4.2. 4'-{trans-2-[4-(1-benzyl-5,7-dioxo-4-phenyl-1,4-diazepan-6-yl)butyl]cyclopropylamino}-N-methyl-bipenyl-3-carboxamide (**1m**)*

A solution of **12** (50.0 mg, 62 µmol) and 40% methylamine solution (1.5 mL, 17 mmol) in THF (1.5 mL) was heated at 80 ºC for 7 h in a reaction vial with a cap. After cooling to room temperature, the volatiles were evaporated *in vacuo*. The resultant residue was purified by MPLC (hexane/ethyl acetate = 1:1 to 0:1) to give the amide (14.7 mg) as a white solid. The obtained crude product was used for the next reaction without further purification.

To a suspension of the crude amide (14.0 mg, 18 µmol) and K_2CO_3 (14.5 mg, 0.11 mmol) in CH_3CN (2 mL) was added thiophenol (8.1 µL, 79 µmol). The reaction mixture was stirred overnight at 60 ºC. After cooling to room temperature, the reaction mixture was diluted with water (5 mL) and extracted

with AcOEt (5 mL x 2). The combined organic layers were washed with brine (10 mL x 1), dried over Na_2SO_4, filtered off and concentrated *in vacuo*. The resultant residue was purified by NH-MPLC (ethyl acetate/MeOH = 99:1 to 93:7) to give **1m** (4.1 mg, 38% yield) as a white amorphous. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (t, *J* = 2.0 Hz, 1H), 7.69–7.67 (m, 2H), 7.52–7.45 (m, 3H), 7.35–7.21 (m, 8H), 7.12 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.26 (d, *J* = 2.5 Hz, 1H), 4.91 (dd, *J* = 14.5, 2.0 Hz, 1H), 4.45 (dd, *J* = 14.5, 2.0 Hz, 1H), 4.25–4.19 (m, 1H), 3.99 (t, *J* = 6.5 Hz, 1H), 3.80–3.75 (m, 1H), 3.57–3.48 (m, 2H), 3.03 (d, *J* = 5.0 Hz, 3H), 2.80 (t, *J* = 7.5 Hz, 2H), 2.40–2.37 (m, 1H), 2.14–2.06 (m, 2H), 1.96–1.91 (m, 1H), 1.64–1.57 (m, 2H), 1.47–1.40 (m, 2H), 1.14–1.10 (m, 1H), 1.03–1.00 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.2, 168.0, 167.4, 142.6, 142.3, 141.5, 137.3, 137.0, 135.2, 129.7, 129.3, 128.9, 128.8, 128.2, 127.8, 127.1, 127.0, 126.4, 126.3, 125.4, 125.2, 51.3, 50.15, 50.08, 49.1, 47.3, 41.9, 30.0, 26.9, 26.3, 25.7, 24.9, 17.2; HRMS (ESI) m/z calcd for $C_{39}H_{43}N_4O_3$ $[M+H]^+$: 615.3330 found 615.3302.

4.2. Enzymatic assays

4.2.1. LSD1 inhibition assay

LSD1 activity assays were performed using an LSD1 fluorescent assay kit (Enzo life science, BML-AK544-0001). Inhibitor candidates were added to an enzyme solution of LSD1 (0.5 μg per well) and HRP on ice, and then reactions were initiated by addition of a substrate solution of the H3K4me2 peptide (4.6 μg per well) and CeLLestial™ Red into all but the blank wells. After incubation (room temperature; 30 min), the fluorescence of the wells was measured on a 2030 ARVO™ X3 multilabel reader (PerkinElmer; excitation: 540 nm; detection: 590 nm) and the % of inhibition was calculated from the fluorescence readings of the inhibited wells relative to those of control wells. The concentration of test compounds that resulted in 50% inhibition was determined by plotting log [ln *h*] against the logit function of the % inhibition. IC_{50} values were determined by regression analysis of the concentration/inhibition data.

4.2.2. MAO inhibition assay

The MAO activity assays were carried out according to the supplier's protocol using a MAO-Glo™ assay system (Promega, V1401). MAOA (18 unit per mL) or MAOB (6 unit per mL) (Sigma-Aldrich; 25 μL per well), 160 μM (for MAOA) or 16 μM (for MAOB), (4*S*)-4,5-dihydro-2-(6-hydroxybenzothiazolyl)-4-thiazolecarboxylic acid (12.5 μL per well), a MAO substrate, and various concentrations of inhibitors (12.5 μL per well) were incubated at room temperature. Reactions were stopped after 60 min by adding a reconstituted Luciferin Detection Reagent (50 μL per well). Then, 20 minutes after addition of this reagent, the chemiluminescence of the wells was measured with a 2030 ARVO™ X3 multilabel reader (PerkinElmer). For the data processing, the same procedure as for LSD1 inhibition activity was used.

4.3. Cellular assays

4.3.1. Cell Proliferation Assay

Lung cancer A549 cells were plated in 96-well plates at the initial density of 1×10^3 cells per well (50 μL per well) and incubated at 37 °C. After 24 h, cells were exposed to test compounds by adding solutions (50 μL per well) of the compounds at various concentrations in a medium at 37 °C under 5% CO_2 in air for 72 h. The mixtures were then treated with 10 μL of AlamarBlue® (AbD Serotec, #BUF012A), and incubation was continued at 37 °C for 3 h. The fluorescence in each well was measured with an ARVO™ X3 microplate reader (excitation at 540 nm, emission, at 590 nm). The percentage cell growth was calculated from the fluorescence readings.

4.3.2. Analysis of cell cycle population and detection of apoptosis

Cells were incubated with the indicated concentrations and time points of **1n**. After washing with PBS, the cells were treated with Triton X-100, and the nuclei were stained with propidium iodide. The DNA content was measured using FACSCalibur (Becton Dickinson). The ModFit software (Verity Software House) and CellQuest (Becton Dickinson) software were used to analyze the data.

4.3.3. Western blotting analysis

Cells were incubated with the indicated concentrations of **1n** for 24 h. After washing with PBS, the cells were lysed in lysis buffer containing 50 mM Tris-HCl [pH 8.0], 150 mM NaCl, 1% NP-40, 0.5% deoxycholic acid, 0.1% SDS, 1 mM EDTA, 1 mM DTT, 0.5 mM PMSF, 2 mg mL^{-1} aprotinin, 2 mg mL^{-1} leupeptin, and phosphatase inhibitor cocktail (1/100 v/v, 07575-51, Nacalai Tesque). The lysate was sonicated and centrifuged, and the supernatant was subjected to SDS-PAGE. Rabbit monoclonal anti-histone H3K4me3 (#9751), histone H3K4me2 (#9725), histone H3K4me1 (#5326), histone H3 (#4499, Cell Signaling Technology), and mouse monoclonal anti-β-actin (A5441, Sigma) antibodies were used as the primary antibodies. The blots were incubated with the appropriate HRP-conjugated secondary antibody (GE Healthcare), and signals were detected with Chemi-Lumi One L (Nacalai Tesque) or Immobilon Western (Millipore).

4.4. Stastical analysis

Statistical analysis was performed using Dunnett's test. $P < 0.01$ was considered significant.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.20XX.XX.XXX.

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