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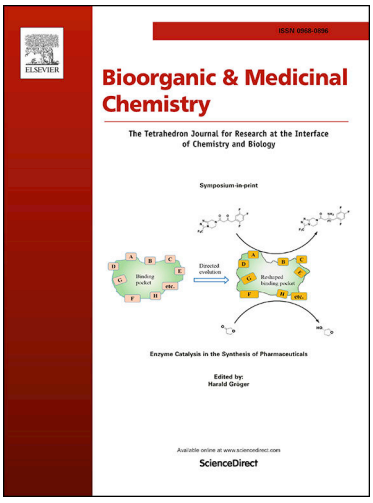

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Discovery and structure-activity relationships of spiroindolines as novel inducers of oligodendrocyte progenitor cell differentiation

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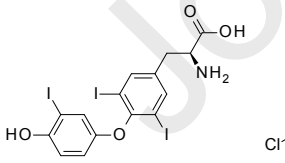
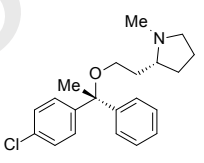
ABSTRACT

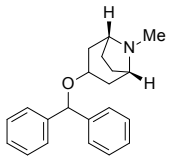
A novel series of spiroindoline derivatives was discovered for use as inducers of oligodendrocyte progenitor cell (OPC) differentiation, resulting from optimization of screening hit **1**. Exploration of structure-activity relationships led to compound **18**, which showed improved potency (rOPC EC_{50} = 0.0032 μM). Furthermore, oral administration of compound **18** significantly decreased clinical severity in an experimental autoimmune encephalomyelitis (EAE) model.

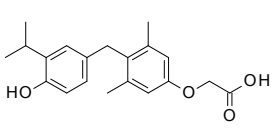
Multiple sclerosis (MS) is one of the most common chronic, autoimmune and inflammatory disorders of the central nervous system (CNS) and affects 2.5 million people worldwide.[1] The onset of MS has been typically observed in individuals aged from 20 to 40 years, with a female to male ratio of 2:1. The pathogenesis of MS is characterized by acute and chronic demyelination, which results in a slowing or block of nerve conduction with subsequent neurologic dysfunction.[2] Thus, identification of multiple foci of demyelination in the CNS is one of the major pathological findings required to confirm MS diagnosis. Several immunomodulatory treatments have been developed since the launch of the first drug for MS in 1993, interferon-β-1b (IFN-β).[3] Glatiramer acetate (GLAT), DNA intercalating drugs such as mitoxantrone,[4] spingosine-1-phosphate (S1P) receptor antagonists such as fingolimod,[5] and dimethyl fumarate[6] induce anti-inflammatory pathways via different mechanisms. Additionally, various monoclonal antibodies, such as natalizumab and ocrelizumab, are able to inhibit the infiltration of immune cells into the CNS. All of these MS drugs target the immune system with mechanisms of action involving general immunosuppression/immunomodulation. Despite their effectiveness in reducing relapse rates and the formation of new lesions, these drugs have very limited effects in preventing the progression of disability. In contrast, progressive phases of multiple sclerosis are associated with inhibited differentiation of the progenitor cell population that generates the mature oligodendrocytes required for remyelination and disease remission.[7] Thus, promoting oligodendrocyte progenitor cell (OPC) differentiation, remyelination of the CNS, and subsequent functional recovery of neurons have been proposed to be the new direction for MS therapy.[8] To date, recent studies have shown that several small molecules, such as triiodothyronine (T3),[9] clemastine,[10] benztropine,[11] sobetirome,[12] PPARδ agonist,[13] 8,9-unsaturated sterols,[14] and κ-opioid receptor agonist,[15] have been reported as inducers of OPC differentiation (**Fig. 1**).

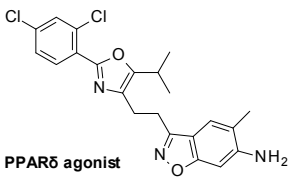
Based on these findings, we aimed to create a novel MS therapeutic agent that produces the differentiation-inducing action of OPC. To identify novel oligodendrocyte differentiation inducers with unique scaffolds, we performed an image-based screen for myelin basic protein (MBP) expression, a differentiation marker for oligodendrocytes, using primary rat OPCs derived from cerebral cortex.[16] As a result, compound **1** was identified as a screening hit with a differentiation-inducing action against OPC. It was derived from rat neonate (hereafter referred to as rOPC). Compound **1** showed submicromolar activity (EC_{50} = 0.16 μM, Emax[17] = 246%) against rOPC, which was comparable to the *in vitro* activity and efficacy of clemastine

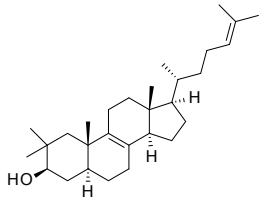


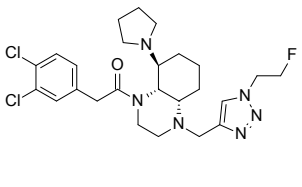


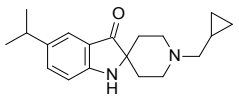












1

rOPC	logD (pH 7.4)	Metabolic stability (h/m)[a]	hERG[b]
EC_{50}; 0.16 μM Emax; 246%	2.9	61%/0%	81%

[a]% original compound remaining after 30 min incubation.

[b]Inhibition at 10 μM.

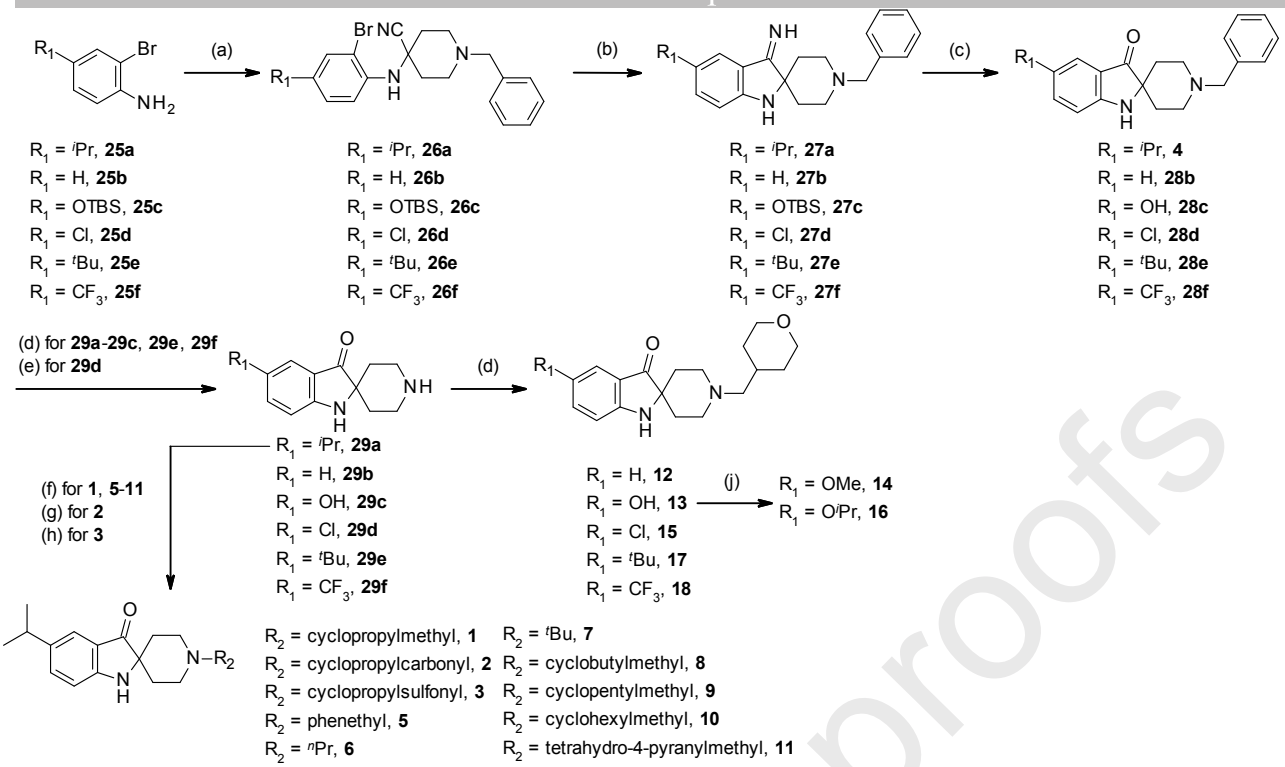
Fig. 2. Chemical structure, activity and ADMET profile of hit compound **1**.

(EC_{50} = 0.12 μM, Emax =191%) and benztropine (EC_{50} = 0.27 μM, Emax = 231%) as evaluated using our in-house functional assay. Compound **1** has structurally unique spiroindoline core. Although nitrogen-containing spirocyclic scaffolds are common structural features in many pharmaceutical candidates and biologically active alkaloid natural products,[18] to the best of our knowledge, there are only a few reports with showing the pharmacological activities of spiroindolin-3-one derivatives, e.g. amoenamide C, a antimicrobial and potent insecticidal activator.[19] Furthermore, compound **1** has high membrane permeability and moderate-to-high human metabolic stability, but poor mouse metabolic stability (**Fig. 2**). Herein, we report on a synthetic development from compound **1** that aimed to produce compounds with high activity and a good ADME profile.

2. Results and discussion

2.1. Chemistry

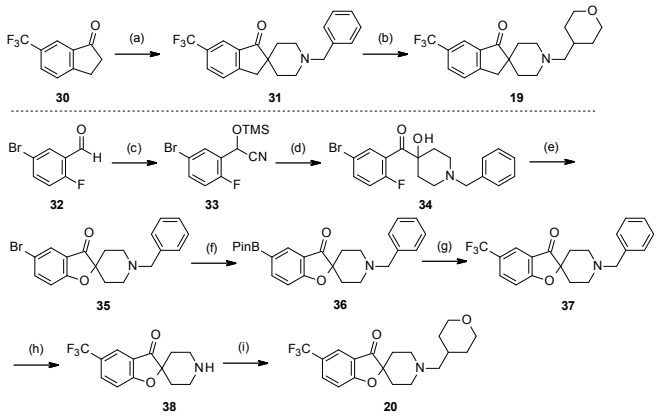
The first of this series, the synthesis of spiro derivatives **1**−**18**, is described in **Scheme 1**. Starting from 2-bromo-4-isopropylaniline **25a**−**25f**, Strecker reaction with *N*-benzyl-4-piperidone afforded **26a**−**26f**, respectively. The indolinone scaffold was then constructed by radical cyclization with **26a**−**26f**, followed by acidic hydrolysis of the resulting **27a**−**27f**, which afforded **4** and **28b**−**28f**, respectively.[20] As for **28c**, the TBS group was also removed simultaneously under acidic hydrolysis. Subsequent removal of the benzyl group in compound **4** by hydrogenolysis afforded **29a**, which was converted to the target compounds **1** and **5**−**11** by reductive amination with corresponding aldehydes. Alternatively, with intermediate amine **29a**, amidation with cyclopropylcarboxylic acid afforded **2**, and sulfonylation with cyclopropylsulfonyl chloride afforded **3**. Removal of the benzyl group in compound



aq. H… …CHO, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, 0 °C to rt, 1 h, 39−94%; (g) cyclopropanecarboxylic acid, EDCI, DMAP, DMF, 0 °C to rt, 18 h, quant.; (h) cyclopropanesulfonyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h, 93%; (i) 4-formyltetrahydropyran, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, 0 °C to rt, 1 h, 29−99%; (j) R-I, NaH, DMF, 0 °C, 30 min, 17−32%.

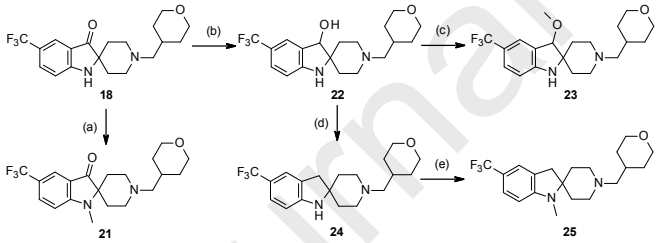
28b−**28f** and subsequent reductive amination with 4-formyltetrahydropyran afforded **12**, **13**, **15**, **17** and **18**, respectively. Further, *O*-alkylation of **13** with methyl iodide or isopropyl iodide afforded compounds **14**, **16**, respectively.

The synthesis of compounds **19** and **20** is described in **Scheme 2**. Starting from commercially-available indanone **30**, dialkylation with *N*-benzylbischloroethylamine, followed by conversion of the benzyl group to a tetrahydropyranylmethyl group afforded compound **19**. Commercially-available **32** was converted to α-hydroxyketone **34** by benzoin condensation using intermediate cyanohydrin **33**, followed by the construction of a benzofuran moiety by S_NAr reaction under basic conditions, which afforded **35**. Compound **35** was converted to borate **36** by Miyaura reaction, followed by trifluoromethylation,[21] which afforded **37**. After deprotection of the benzyl group of compound **37** by hydrogenolysis, reductive amination with 4-formyltetrahydropyran afforded compound **20**.



Scheme 2. *Reagents and conditions*: (a) *N*-benzyl-*N*,*N*-di(2-chloroethyl)amine hydrochloride, NaH, DMF, 0 °C to rt, 20 h, 9%; (b) H_2, Pd/C, 4-formyltetrahydropyran, MeOH, rt, 24 h, 46%; (c) TMSCN, LiCl, CH_2Cl_2, 0 °C to rt, 16 h; (d) **33**, LDA (1 M in THF solution), THF, −78 °C, 1.5 h followed by *N*-benzyl-4-piperidone, −78 °C, 3 h, 34% (2 steps); (e) ^{t}BuOK, THF, 80 °C, 2 h, 74%; (f) $(PinB)_2$, KOAc, $Pd(dppf)Cl_2$, DMSO, rt to 110 °C, 1 h, μW, 34%; (g) Togni's reagent, copper(I) thiophene-2-carboxylate, $LiOH{\cdot}H_2O$, rt to 60 °C, 1 h, μW, 75%; (h) H_2, Pd/C, MeOH, rt, 15 h, 89%; (i) 4-formyltetrahydropyran, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, 0 °C to rt, 1 h, 24%.

The synthesis of compounds **21**−**24** is described in **Scheme 3**. Compound **21** was prepared by *N*-methylation of compound **18**. The reduction of the carbonyl group of **18** with $NaBH_4$ in MeOH afforded compound **22**. Further, *O*-selective methylation of compound **22** afforded compound **23**. Compound **24** was obtained from **22** by reductive removal of the hydroxy group using Et_3SiH and TFA. Further, *N*-methylation of **24** afforded compound **25**.

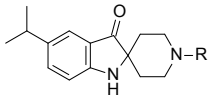


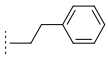
Scheme 3. *Reagents and conditions*: (a) MeI, NaH, DMF, rt, 1 h, 90%; (b) $NaBH_4$, MeOH, 0 °C to rt, 1 h, 73%; (c) MeI, NaH, DMF, 0 °C, 20 min, 34%; (d) Et_3SiH, TFA, CH_2Cl_2, rt, 1 h, 92%; (e) MeI, NaH, DMF, rt, 5 h, 73%

2.2. SAR study

In order to understand the SAR of this chemical series, the results of cyclopropylmethyl moiety modification of compound **1** are summarized in **Table 1**. Replacement of the amine group with an amide (**2**) or sulfonamide group (**3**) decreased the activity. This result indicates that basicity of the piperidine moiety is crucial to the activity of this series of compounds. Replacing the cyclopropylmethyl group with a benzyl (**4**) or phenylethyl (**5**) group resulted in a slight loss in potency versus compound **1**. Compounds with a range of acyclic and cyclic alkyl substituents on the piperidine ring, compounds **6**-**10**, were prepared. The potency of the compound was highly dependent on the size of the substituent. For example, potency increased as the size of the acyclic group increased from propyl (**6**) to *iso*-butyl (**7**). Likewise, for cycloalkyl substituents, potency increased with ring size from cyclopropyl to cyclobutyl (**8**), while cyclopentyl (**9**) and cyclohexyl (**10**) resulted in a slight loss in potency compared to cyclobutyl (**8**). In addition, compound **11**, with a tetrahydropyranylmethyl group, showed significantly improved potency (EC_{50} = 0.0046 μM). This result suggests that the introduction of an oxygen atom is important to the potency.

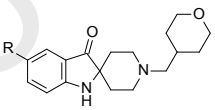
Table 1. SAR of the substituents on the piperidine ring.



Compound	R	rOPC EC_{50} (μM)
1		0.16
2		>10
3		>10
4		0.33
5		0.54
6		0.55
7		0.33
8		0.016
9		0.025
10		0.037
11		0.0046

Based on the results in **Table 1**, the substituent on the piperidine ring was fixed to the tetrahydropyranylmethyl group to elucidate the SAR of the 5-position on the indolinone core (**Table 2**). Deletion of the isopropyl group (**12**) led to a significant loss of potency, and replacement with a hydroxy group (**13**) provided a completely inactive compound, suggesting a beneficial lipophilic interaction in this location. On the basis of this finding, we examined the introduction of lipophilic substituents in place of the phenyl ring. Although the chloro group (**14**), methoxy group (**15**) and isopropoxy group (**16**) had over 10-fold less potency than **11**, *tert*-butyl group (**17**) showed similar potency to **11** (EC_{50}= 0.0099 μM). Eventually, the trifluoromethyl group (**18**) increased potency compared to that of **11** (EC_{50}= 0.0032 μM).

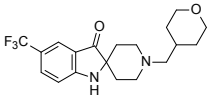
Table 2. SAR of the substituents on piperidine ring.

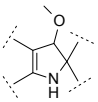
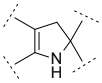


Compound	R	rOPC EC_{50} (μM)
11	^{i}Pr	0.0046
12	H	0.55
13	OH	>10
14	Cl	0.32
15	OMe	0.97
16	O^{i}Pr	0.059
17	^{t}Bu	0.0099
18	CF_3	0.0032

Next, we turned our attention to the spiro core (**Table 3**). Replacing the nitrogen atom of the indolinone core with a carbon atom (**19**) or an oxygen atom (**20**) led to a significant decrease in potency. *N*-methylation of compound **18** led to a slight loss of potency (**21**). Although reduction of the carbonyl group to a hydroxyl group (**22**) reduced potency compared to compound **18**, methylation of the hydroxy group (**23**) led to a robust potency (EC_{50} = 0.0057 μM). Removal of carbonyl group (**24**) and *N*-methylation of compound **24** (**25**) resulted in over 50-fold reductions in potency.

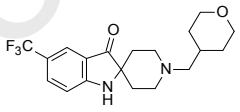
Table 3. SAR of the indolinone core.



Compound	R	rOPC EC_{50} (μM)
18		0.0032
19		0.11
20		0.48
21		0.0093
22		0.52
23		0.0057
24		0.24
25		7.1

2.3. Physical Chemical Properties and Pharmacokinetics (PK)

On the basis of a favorable *in vitro* profile, compound **18** was selected for further evaluation. The metabolic stability of compound **18** in mice was improved as compared to hit **1** (**Fig. 3**). Compound **18** did not exhibit potent inhibition of cytochrome P450 enzymes in human live microsomes (CYP3A4, CYP2C9 IC_{50} > 18 μM) except for CYP2D6 (70% @ 10 μM), and there was no CYP induction issue.



18

rOPC	logD (pH 7.4)	Metabolic stability (h/m)[a]	hERG[b]
EC_{50}; 0.0032 μM Emax; 240%	2.8	35%/68%	94%

[a]% original compound remaining after 30 min incubation.

[b]Inhibition at 10 μM.

Fig. 3. Chemical structure, activity and ADMET profile of compound **18**.

A mouse PK study was performed with compound **18**, as shown in **Table 5**. Plasma concentrations were measured after a single oral dose at 10 mg/kg or single intravenous dose at 1 mg/kg. Although compound **18** showed moderate-to-high plasma clearance (CL: 79.2 mL/min/kg), it displayed high oral bioavailability (F = 116%) and a high brain-to-plasma ratio (25.5 @ 0.5 h). These results indicate that compound **18** is suitable for *in vivo* evaluation.

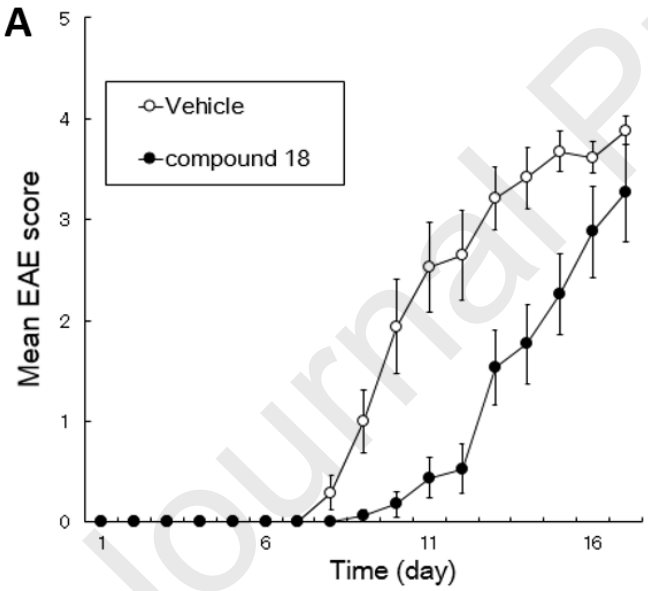
Table 5. Mouse PK profile of compound **18**[a]

CLp (iv[b]; mL/min/kg)	79.2	$T_{1/2}$ (po; h)	6.4
Vd (iv; L/kg)	31.5	F (%)	116
AUC_{last} (po[c]; ng*h/mL)	1775	K_p (brain/plasma)	25.5 (0.5 h) 50.9 (4 h)
C_{max} (po; ng/mL)	308		

[a]Abbreviations: CL: plasma clearance; AUC: area under the concentration-time curve; C_{max}: peak plasma concentration of drug after administration; $T_{1/2}$: elimination half-life; F: bioavailability; p.o.: per oral; iv: intravenous.
[b]IV: 1 mg/kg (n = 2, 10% HP-β-CD dissolved in saline/DMSO = 95/5, v/v)
[c]PO: 10 mg/kg (n = 2, 0.5% HPC dissolved in water)

2.4. Pharmacological evaluation

We evaluated the *in vivo* therapeutic potential of compound **18** in a mouse EAE model, which is one of the most commonly used experimental models for the human inflammatory demyelinating disease MS.[22] EAE was induced by immunization with myelin oligodendrocyte glycoprotein peptide (MOG_{35-55}). Oral administration of compound **18** once daily at a dose of 50 mg/kg from 3 days post-immunization to day 17 significantly reduced the development of clinical symptoms in terms of EAE scores (**Fig. 4A**, **B**). Furthermore, administration of compound **18** delayed disease onset (**Fig. 4C**). These results indicate that the oral administration of compound **18** protected against the development of clinical symptoms caused by immunization with myelin oligodendrocyte glycoprotein (MOG) peptide. Thus, compound **18** might be a promising starting point for further development of optimal remyelinating agents.



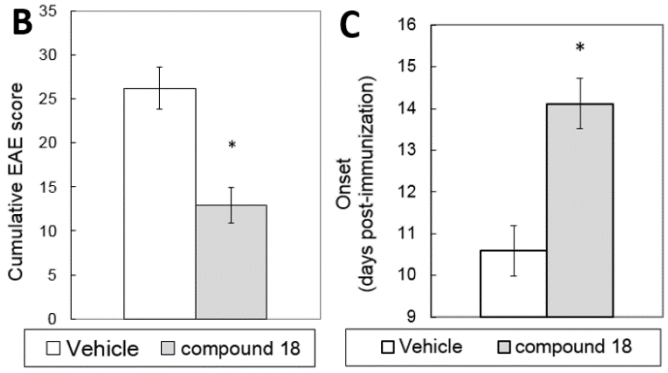


Fig. 4. (A) Effect of compound **18** on MOG-induced EAE model. Compound **2** (50 mg/kg, q.d.) or vehicle (0.5% methylcellulose) was orally administered to mice 3 d post-immunization (n = 13 or 14, mean and SEM): EAE clinical score. (B) Cumulative EAE clinical score, from days 0 to 17. (C) We defined the onset day as the day when the EAE score reached 2 or more (n = 13 or 14), * indicates $p < 0.001$ (t-test).

3. Conclusions

We investigated the structure-activity relationship of spiroindolines for activity in OPC differentiation induction. We found that sidechain replacement of hit compound **1**, from the cyclopropylmethyl group to the tetrahydropyranylmethyl group, led to a significant improvement in potency without increasing lipophilicity. In this transformation, lipophilic efficiency,[23] an important metric in drug discovery programs, increased from 3.9 (for **1**) to 5.6 (for **11**). Further modification for substituents on the phenyl ring led to representative compound **18**, which showed high oral availability and brain exposure in mice. Furthermore, oral administration of **18** at 50 mg/kg daily resulted in a significant decrease in EAE clinical score in the mouse EAE model. Overall, this novel family of compounds forms an attractive base for the development of effective new therapies for MS that complement established immunosuppressive approaches. Further structural optimization of the compound family is currently underway. The results of later work will be reported in due course.

4. Experimental section

4.1. Chemistry

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Brucker Avance III (400 MHz) spectrometer in the indicated solvent. Chemical shifts (δ) are reported in parts per million relative to the internal standard tetramethylsilane. Abbreviations of multiplicity are as follows; s: singlet, d; doublet, t: triplet, q: quartet, m: multiplet, br: broad. Data are presented as follows: chemical shift (multiplicity, integration, coupling constant). Fast atom bombardment (FAB) mass spectra were recorded on a JEOL JMS-700 mass spectrometer. Electrospray ionization (ESI) mass spectra were recorded on an Agilent G1956A MSD spectrometer system. Chemical reagents and solvents were purchased from Aldrich, Tokyo Kasei Kogyo, Wako Pure Chemical Industries Ltd., Kanto Kagaku, and Nacalai Tesque and were used without purification. Flash column chromatography was performed using Purif-Pack® SI 30 µm and Purif-Pack® NH 50 µm supplied by Shoko Scientific, or Chromatorex® SI 30 µm and Chromatorex® NH 60 µm supplied by Fuji Silysia Chemical, or Merck silica gel 60 (230–400 mesh). Conditions of the preparative HPLC purification system were as follows. Column: YMC-Pack Pro C18 ODS, 4.6 mm × 75 mm, mobile phase: solvent A = MeCN–H_2O–trifluoroacetic acid (5:95:0.1), solvent B = MeCN–trifluoroacetic acid (100:0.09), gradient: 0 to 90% solvent B in solvent A with 26%/min, UV detector: 254 nm, flow rate: 1.0 mL/min.

*4.1.1 N-Benzyl-4-[(2-bromo-4-isopropylphenyl)amino]piperidine -4-carbonitrile (**26a**): General procedure A*

A solution of 2-bromo-4-isopropylaniline **25a** (36 g, 170 mmol) and *N*-benzyl-4-piperidone (31 mL, 170 mmol) in AcOH (130 mL) was treated with TMSCN (22 mL, 180 mmol) at room temperature for 5 h. The reaction mixture was neutralized by 8 N aqueous NaOH (380 mL) at 0 °C, and the mixture was extracted with AcOEt (500 mL). The organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt/hexane; 10:90 to 40:60) to afford compound **26a** (55 g, 79%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.38−7.28 (5H, m), 7.28−7.25 (1H, m), 7.14−7.06 (2H, m), 4.27 (1H, s), 3.56 (2H, s), 2.85−2.72 (3H, m), 2.51 (2H, t, J = 10.7 Hz), 2.36 (2H, d, J = 13.3 Hz), 2.00 (2H, s), 1.20 (6H, d, J = 6.8 Hz). ESIMS-LR *m/z* 412, 414 [$(M+H)^+$].

*4.1.2 N-Benzyl-4-((2-bromophenyl)amino)piperidine-4-carbonitrile (**26b**)*

Following general procedure A using compound **25b** (0.64 mL, 5.8 mmol), *N*-benzyl-4-piperidone (0.82 mL, 4.6 mmol), TMSCN (0.94 mL, 7.6 mmol), and AcOH (30 mL), the title compound, **26b** (1.8 g, 81%), was obtained as a brown oil. ^{1}H NMR ($CDCl_3$, 400

MHz) δ: 7.48 (1H, dd, *J* = 8.1, 1.4 Hz), 7.36−7.26 (5H, m), 7.22 (1H, dd, *J* = 7.4, 1.1 Hz), 7.17 (1H, dd, *J* = 8.1, 1.4 Hz), 6.73 (1H, td, *J* = 7.4, 1.2 Hz), 4.41 (1H, s), 3.56 (2H, s), 2.78−2.72 (2H, m), 2.57−2.48 (2H, m), 2.43−2.35 (2H, m), 2.06-1.97 (2H, m). ESIMS-LR *m/z* 370, 372 [(M+H)$^+$].

*4.1.3 N-Benzyl-4-((2-bromo-4-(tert-butyldimethylsilyloxy)phenyl) amino)piperidine-4-carbonitrile (**26c**)*

Step 1. A solution of 4-amino-3-bromo-phenol (1.5 g, 8.0 mmol), imidazole (1.4 g, 21 mmol) in DMF (20 mL) was treated with TBSCl (1.4 g, 9.3 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. The resulting mixture was partitioned between AcOEt (100 mL) and H_2O (50 mL), and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (AcOEt/hexane; 10:90 to 30:70) to afford compound 2-bromo-4-(*tert*-butyldimethylsilyloxy)aniline **25c** (1.4 g, 60%) as a brown oil.

Step 2. Following general procedure A using compound **25c** (1.4 g, 4.6 mmol), *N*-benzyl-4-piperidone (0.82 mL, 4.6 mmol), TMSCN (0.63 mL, 5.1 mmol), and AcOH (10 mL), the title compound, **26c** (2.3 g, 98%), was obtained as a brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.17−7.08 (5H, m), 6.92 (1H, d, *J* = 8.8 Hz), 6.85 (1H, d, *J* = 2.8 Hz), 6.56 (1H, dd, *J* = 8.8, 2.8 Hz), 3.42 (2H, s), 2.68−2.58 (2H, m), 2.33 (2H, t, *J* = 10.0 Hz), 2.13 (2H, dd, *J* = 11.0, 2.5 Hz), 1.88−1.77 (2H, m), 0.80−0.77 (9H, m), 0.01-0.00 (6H, m). ESIMS-LR *m/z* 500, 502 [(M+H)$^+$].

*4.1.4 N-Benzyl-4-((2-bromo-4-chlorophenyl)amino)piperidine-4-carbonitrile (**26d**)*

Following general procedure A using 2-bromo-4-chloroaniline **25d** (3.0 g, 15 mmol), *N*-benzyl-4-piperidone (2.9 mL, 16 mmol), TMSCN (2.3 mL, 19 mmol), and AcOH (20 mL), the title compound, **26d** (3.7 g, 63%), was obtained as a brown amorphous. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.49 (1H, d, *J* = 2.5 Hz), 7.35−7.27 (5H, m), 7.21 (1H, dd, *J* = 8.8, 2.5 Hz), 7.10 (1H, d, *J* = 8.8 Hz), 4.37 (1H, s), 3.56 (2H, s), 2.80−2.69 (2H, m), 2.55−2.47 (2H, m), 2.37 (2H, dd, *J* = 10.9, 2.9 Hz), 1.99 (2H, t, *J* = 9.8 Hz). ESIMS-LR *m/z* 404, 406 [(M+H)$^+$].

*4.1.5 N-Benzyl-4-((2-bromo-4-tert-butylphenyl)amino)piperidine -4-carbonitrile (**26e**)*

Following general procedure A using 2-bromo-4-*tert*-butylaniline **25e** (1.8 g, 7.8 mmol), *N*-benzyl-4-piperidone (2.3 mL, 13 mmol), TMSCN (1.8 mL, 13 mmol), and AcOH (10 mL), the title compound, **26e** (3.1 g, 93%), was obtained as a brown amorphous. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.50 (1H, d, *J* = 2.3 Hz), 7.36−7.29 (5H, m), 7.27−7.23 (1H, m), 7.08 (1H, d, *J* = 8.8 Hz), 4.96 (1H, s), 3.52 (2H, s), 2.74−2.64 (2H, m), 2.39−2.28 (4H, m), 2.03−1.92 (2H, m), 1.24 (9H, s). ESIMS-LR *m/z* 426, 428 [(M+H)$^+$].

*4.1.6 N-Benzyl-4-((2-bromo-3-trifluoromethylphenyl)amino) piperidine-4-carbonitrile (**26f**)*

Following general procedure A using 3-Amino-2-bromobenzotrifluoride **25f** (500 mg, 2.1 mmol), *N*-benzyl-4-piperidone (0.39 mL, 2.2 mmol), TMSCN (0.61 mL, 4.6 mmol), and AcOH (10 mL), the title compound, **26f** (440 mg, 49%), was obtained as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ: 7.36−7.30 (7H, m), 7.19 (1H, dd, *J* = 6.3, 3.0 Hz), 4.83 (1H, s), 3.57 (2H, s), 2.83−2.70 (2H, m), 2.54 (2H, t, *J* = 9.7 Hz), 2.41 (2H, d, *J* = 9.7 Hz), 2.08−2.00 (2H, m). ESIMS-LR *m/z* 438, 440 [(M+H)$^+$].

*4.1.7 N-Benzyl-5-isopropylspiro[indoline-2,4'-piperidin]-3-imine (**27a**) : General procedure B*

A suspension of compound **26a** (2.0 g, 4.9 mmol) and n-Bu_3SnH (1.4 mL, 5.3 mmol) in toluene (40 mL) was treated with AIBN (0.080 g, 0.049 mmol) at room temperature, and the mixture was stirred at 120 °C for 15 h. The reaction was quenched by saturated aqueous KF (15 mL) at room temperature. The whole mixture was partitioned between AcOEt (100 mL) and H_2O (50 mL), and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$; 0:100 to 14:86) to afford compound **27a** (1.1 g, 67%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.48 (1H, d, *J* = 1.5 Hz), 7.39−7.30 (5H, m), 7.28−7.25 (1H, m), 6.83 (1H, d, *J* = 8.5 Hz), 4.79 (1H, s), 3.59 (2H, s), 2.99 (2H, d, *J* = 10.8 Hz), 2.90-2.83 (1H, m), 2.20 (2H, t, *J* = 12.0 Hz), 2.09 (2H, td, *J* = 12.7, 3.9 Hz), 1.42 (2H, d, *J* = 12.0 Hz), 1.22 (6H, d, *J* = 6.8 Hz). ESIMS-LR *m/z* 334 [(M+H)$^+$].

*4.1.8 N-Benzylspiro[indoline-2,4'-piperidin]-3-imine (**27b**)*

Following general procedure B using compound **26b** (1.7 g, 4.6 mmol), n-Bu_3SnH (1.9 mL, 6.9 mmol), AIBN (0.15 g, 0.92 mmol), and toluene (40 mL), the title compound, **27b** (720 mg, 54%), was obtained as a brown amorphous. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.56 (1H, d, *J* = 7.5 Hz), 7.41−7.27 (6H, m), 6.85-6.78 (2H, m), 3.64 (2H, s), 3.49 (1H, s), 3.04 (2H, d, *J* = 10.8 Hz), 2.38−2.21 (2H, m), 2.03 (2H, td, *J* = 12.9, 4.0 Hz), 1.60 (2H, d, *J* = 12.0 Hz). ESIMS-LR *m/z* 292 [(M+H)$^+$].

*4.1.9 N-Benzyl-5-(tert-butyldimethylsilyloxy)spiro[indoline-2,4'-piperidin]-3-imine (**27c**)*

Following general procedure B using compound **26c** (600 mg, 1.2 mmol), n-Bu_3SnH (0.49 mL, 1.8 mmol), AIBN (40 mg, 0.24 mmol), and toluene (20 mL) the title compound, **27c** (160 mg, 31%), was obtained as a pale yellow amorphous. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.22−7.09 (5H, m), 6.83 (1H, s), 6.71 (1H, dd, *J* = 8.5, 2.5 Hz), 6.54 (1H, d, *J* = 8.5 Hz), 4.16 (1H, s), 3.43 (2H, s), 2.91−2.72 (2H, m), 2.16−1.96 (2H, m), 1.82 (2H, td, *J* = 12.9, 3.9 Hz), 1.47−1.28 (2H, m), 0.80 (9H, s), 0.00 (6H, s). ESIMS-LR *m/z* 422 [(M+H)$^+$].

*4.1.10 N-Benzyl-5-chlorospiro[indoline-2,4'-piperidin]-3-imine (**27d**)*

Following general procedure B using compound **26d** (3.9 g, 9.6 mmol), n-Bu_3SnH (3.8 mL, 14 mmol), AIBN (0.32 g, 1.9 mmol), and toluene (30 mL), the title compound, **27d** (720 mg, 33%), was obtained as a yellow amorphous. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.92 (1H, br s), 7.53 (1H, d, *J* = 8.0 Hz), 7.37−7.20 (5H, m), 6.71 (1H, s), 6.62 (1H, d, *J* = 8.0 Hz), 3.54 (2H, s), 2.81 (2H, d, *J* = 11.5 Hz), 2.28 (2H, t, *J* = 11.5 Hz), 1.89−1.80 (2H, m), 1.33 (2H, d, *J* = 12.8 Hz). ESIMS-LR *m/z* 326 [$(M+H)^+$].

*4.1.11 N-Benzyl-5-(tert-butyl)spiro[indoline-2,4'-piperidin]-3-imine (**27e**)*
Following general procedure B using compound **26e** (3.1 g, 7.3 mmol), n-Bu_3SnH (2.1 mL, 8.0 mmol), AIBN (0.11 g, 0.68 mmol), and toluene (30 mL), the title compound, **27e** (1.3 g, 52%), was obtained as a yellow amorphous. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.55 (1H, s), 7.35−7.30 (5H, m), 7.28−7.23 (1H, m), 6.70 (1H, s), 6.68 (1H, d, *J* = 8.5 Hz), 3.53 (2H, s), 2.79 (2H, d, *J* = 11.4 Hz), 2.30 (2H, t, *J* = 11.4 Hz), 1.82 (2H, td, *J* = 12.5, 3.9 Hz), 1.29 (2H, d, *J* = 12.5 Hz), 1.24 (9H, s). ESIMS-LR *m/z* 348 [$(M+H)^+$].

*4.1.12 N-Benzyl-5-(trifluoromethyl)spiro[indoline-2,4'-piperidin]-3-imine (**27f**)*
Following general procedure B using compound **26f** (4.4 g, 10 mmol), n-Bu_3SnH (4.2 mL, 12 mmol), AIBN (0.23 g, 1.4 mmol), and toluene (30 mL), the title compound, **27f** (1.9 g, 53%), was obtained as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.88 (1H, s), 7.65 (1H, dd, *J* = 8.5, 1.8 Hz), 7.40−7.27 (5H, m), 6.92 (1H, d, *J* = 8.5 Hz), 5.30 (1H, s), 3.61 (2H, s), 3.02 (2H, d, *J* = 11.4 Hz), 2.24 (2H, t, *J* = 11.4 Hz), 2.09 (2H, dt, *J* = 17.9, 6.3 Hz), 1.60−1.52 (2H, m). ESIMS-LR *m/z* 360 [$(M+H)^+$].

*4.1.13 N-Benzyl-5-isopropylspiro[indoline-2,4'-piperidin]-3-one (**4**): General procedure C*
A solution of compound **27a** (0.88 g, 2.6 mmol) in MeOH (5.6 mL) was treated with 1 N aqueous HCl (5.6 mL) at room temperature, and the mixture was stirred at 100 °C for 2 h, then cooled to room temperature. The resulting mixture was partitioned between $CHCl_3$ (100 mL × 3) and saturated aqueous $NaHCO_3$ (50 mL), and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was crystalized from Et_2O to afford compound **4** (0.69 g, 77%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.48 (1H, d, *J* = 1.3 Hz), 7.38−7.29 (5H, m), 7.29−7.25 (1H, m), 6.83 (1H, d, *J* = 8.5 Hz), 4.79 (1H, s), 3.59 (2H, s), 2.99 (2H, d, *J* = 11.9 Hz), 2.89−2.83 (1H, m), 2.20 (2H, t, *J* = 11.9 Hz), 2.09 (2H, td, *J* = 12.6, 3.8 Hz), 1.42 (1H, d, *J* = 11.9 Hz), 1.22 (6H, d, *J* = 7.0 Hz). ESIMS-LR *m/z* 335 [$(M+H)^+$]; ESIMS-HR calcd for $C_{22}H_{27}N_2O$ $(M+H)^+$ 335.2118, found 335.2129.

*4.1.14 N-Benzylspiro[indoline-2,4'-piperidin]-3-one (**28b**)*
Following general procedure C using compound **27b** (670 mg, 2.3 mmol), 1 N aqueous HCl (5.0 mL), and MeOH (5.0 mL), the title compound, **28b** (290 mg, 43%), was obtained as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.61 (1H, dd, *J* = 7.9, 0.6 Hz), 7.48−7.42 (1H, m), 7.38−7.29 (4H, m), 7.29−7.25 (1H, m), 6.88 (1H, d, *J* = 7.9 Hz), 6.85−6.81 (1H, m), 4.93 (1H, s), 3.59 (2H, s), 2.99 (2H, dt, *J* = 12.0, 3.6 Hz), 2.20 (2H, td, *J* = 12.0, 2.2 Hz), 2.09 (2H, td, *J* = 12.6, 3.6 Hz), 1.43 (2H, d, *J* = 11.5 Hz). ESIMS-LR *m/z* 293 [$(M+H)^+$].

*4.1.15 N-Benzyl-5-hydroxyspiro[indoline-2,4'-piperidin]-3-one (**28c**)*
Following general procedure C using compound **27c** (2.5 g, 5.9 mmol), 1 N aqueous HCl (7.0 mL), and MeOH (7.0 mL), the title compound, **28c** (1.5 g, 82%), was obtained as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.38−7.30 (4H, m), 7.29−7.26 (1H, m), 7.09 (1H, dd, *J* = 8.6, 2.6 Hz), 7.04−7.01 (1H, m), 6.83 (1H, d, *J* = 8.6 Hz), 4.61 (1H, s), 3.59 (2H, s), 2.99 (2H, d, *J* = 11.9 Hz), 2.20 (2H, t, *J* = 11.9 Hz), 2.07 (2H, td, *J* = 12.6, 3.9 Hz), 1.42 (2H, d, *J* = 12.6 Hz). ESIMS-LR *m/z* 309 [$(M+H)^+$].

*4.1.16 N-Benzyl-5-chlorospiro[indoline-2,4'-piperidin]-3-one (**28d**)*
Following general procedure C using compound **27d** (650 mg, 2.0 mmol), 1 N aqueous HCl (5.0 mL), and MeOH (5.0 mL), the title compound, **28d** (270 mg, 41%), was obtained as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.53 (1H, d, *J* = 8.1 Hz), 7.38−7.30 (4H, m), 7.29−7.26 (1H, m), 6.88−6.85 (1H, m), 6.78 (1H, dd, *J* = 8.1, 1.6 Hz), 5.03 (1H, s), 3.58 (2H, s), 2.99 (2H, dt, *J* = 11.9, 3.6 Hz), 2.18 (2H, td, *J* = 11.9, 2.3 Hz), 2.07 (2H, td, *J* = 12.6, 3.6 Hz), 1.43 (2H, d, *J* = 12.6 Hz). ESIMS-LR *m/z* 327 [$(M+H)^+$].

*4.1.17 N-Benzyl-5-(tert-butyl)spiro[indoline-2,4'-piperidin]-3-one (**28e**)*
Following general procedure C using compound **27e** (3.5 g, 10 mmol), 1 N aqueous HCl (10 mL), and MeOH (10 mL), the title compound, **28e** (2.9 g, 83%), was obtained as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.57 (1H, dd, *J* = 8.8, 2.1 Hz), 7.50 (1H, s), 7.37−7.30 (5H, m), 7.29−7.23 (1H, m), 6.86 (1H, dd, *J* = 8.8, 0.5 Hz), 3.54 (2H, s), 2.85−2.79 (2H, m), 2.29 (2H, td, *J* = 12.0, 2.3 Hz), 1.76 (2H, td, *J* = 12.7, 4.1 Hz), 1.28−1.23 (2H, m), 1.24 (9H, s). ESIMS-LR *m/z* 349 [$(M+H)^+$].

*4.1.18 N-Benzyl-5-(trifluoromethyl)spiro[indoline-2,4'-piperidin]-3-one (**28f**)*
Following general procedure C using compound **27f** (87 mg, 0.24 mmol), 1 N aqueous HCl (1.0 mL), and MeOH (1.0 mL), the title compound, **28f** (68 mg, 78%), was obtained as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.70 (1H, dd, *J* = 8.1, 0.8 Hz), 7.38-7.27 (5H, m), 7.12 (1H, d, *J* = 0.8 Hz), 7.04 (1H, dd, *J* = 8.1, 0.8 Hz), 5.17 (1H, s), 3.59 (2H, s), 3.00 (2H, dt, *J* = 12.0, 3.6 Hz), 2.20 (2H, td, *J* = 12.0, 2.3 Hz), 2.09 (2H, td, *J* = 12.6, 3.6 Hz), 1.46 (2H, d, *J* = 12.0 Hz). ESIMS-LR *m/z* 361 [$(M+H)^+$]; ESIMS-HR calcd for $C_{20}H_{20}F_3N_2O$ $(M+H)^+$ 361.1522, found 361.1521.

*4.1.19 5-Isopropylspiro[indoline-2,4'-piperidin]-3-one (**29a**): General procedure D*

A solution of compound **4** (3.3 g, 1.0 mmol) in MeOH (100 mL) was treated with 10% $Pd(OH)_2/C$ (0.67 g) and the mixture was vigorously stirred under H_2 atmosphere (balloon pressure) at room temperature for 24 h. The catalyst was filtered off through a Celite pad and the filtrate was concentrated *in vacuo* to afford compound **29a** (2.5 g, quant.) as a yellow solid. This material was used in the next reaction without further purification. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.55 (1H, s), 7.39 (1H, dd, J = 8.4, 1.9 Hz), 7.24 (1H, d, J = 1.3 Hz), 6.84 (1H, d, J = 8.5 Hz), 3.17 (1H, s), 3.06−2.97 (2H, m), 2.82 (3H, td, J = 9.7, 4.6 Hz), 1.66 (2H, td, J = 12.7, 4.6 Hz), 1.24−1.17 (2H, m), 1.16 (6H, d, J = 7.0 Hz). ESIMS-LR *m/z* 245 [$(M+H)^+$].

*4.1.20 spiro[indoline-2,4'-piperidin]-3-one (**29b**)*
Following general procedure D using compound **28b** (290 mg, 0.99 mmol), 10% $Pd(OH)_2/C$ (36 mg) and MeOH (1.75 mL), the title compound, **29b** (180 mg, 90%), was obtained as a yellow solid. ESIMS-LR *m/z* 203 [$(M+H)^+$].

*4.1.21 5-hydroxyspiro[indoline-2,4'-piperidin]-3-one (**29c**)*
Following general procedure D using compound **28c** (1.5 g, 0.99 mmol), 10% $Pd(OH)_2/C$ (300 mg) and MeOH (20 mL), the title compound, **29c** (810 mg, 76%), was obtained as a yellow solid. ESIMS-LR *m/z* 219 [$(M+H)^+$].

*4.1.22 5-chlorospiro[indoline-2,4'-piperidin]-3-one (**29d**)*
A solution of compound **28d** (50 mg, 0.15 mmol), triethylamine (0.064 mL, 0.46 mmol) in $CHCl_3$ (1.5 mL) was treated with 1-chloroethyl chloroformate (0.033 mL, 0.30 mmol) at room temperature, and the mixture was stirred at 80 °C for 4 h. The reaction was quenched by MeOH (2.0 mL) at 80 °C for 1 h. The whole mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (NH-SiO_2, MeOH/$CHCl_3$; 1:99 to 10:90) to afford compound **29d** (34 mg, 94%) as a pale yellow solid. ESIMS-LR *m/z* 237 [$(M+H)^+$].

*4.1.23 5-(tert-butyl)spiro[indoline-2,4'-piperidin]-3-one (**29e**)*
Following general procedure D using compound **28e** (2.9 g, 8.4 mmol), 10% $Pd(OH)_2/C$ (0.61 g) and MeOH (200 mL), the title compound, **29e** (1.8 g, 80%), was obtained as a yellow solid. ESIMS-LR *m/z* 259 [$(M+H)^+$].

*4.1.24 5-(trifluoromethyl)spiro[indoline-2,4'-piperidin]-3-one (**29f**)*
Following general procedure D using compound **28f** (10 mg, 0.028 mmol), 10% $Pd(OH)_2/C$ (2.0 mg) and MeOH (0.5 mL), the title compound, **29f** (5.5 mg, 73%), was obtained as a yellow solid. ESIMS-LR *m/z* 271 [$(M+H)^+$].

*4.1.25 N-(Cyclopropylmethyl)-5-isopropylspiro[indoline-2,4'-piperidin]-3-one (**1**): General procedure E*
A solution of compound **29a** (60 mg, 0.25 mmol), cyclopropanecarboxaldehyde (24 μL, 0.37 mmol) and AcOH (56 μL, 0.98 mmol) in CH_2Cl_2 (2.5 mL) was treated with $NaBH(OAc)_3$ (420 mg, 2.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. The resulting mixture was partitioned between AcOEt (50 mL) and saturated aqueous $NaHCO_3$ (30 mL), and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$; 1:99 to 13:87) to afford compound **1** (61 mg, 83%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.47 (1H, s), 7.36 (1H, dd, J = 8.5, 1.8 Hz), 6.83 (1H, t, J = 8.5 Hz), 4.77 (1H, br s), 3.17 (2H, dt, J = 12.1, 3.8 Hz), 2.92−2.81 (1H, m), 2.35 (2H, d, J = 6.4 Hz), 2.26 (2H, t, J = 11.4 Hz), 2.09 (2H, dt, J = 18.1, 6.4 Hz), 1.50 (2H, d, J = 12.8 Hz), 1.23 (6H, d, J = 7.0 Hz), 0.98−0.88 (1H, m), 0.55 (2H, ddd, J = 9.2, 4.6, 3.4 Hz), 0.17−0.11 (2H, m). ESIMS-LR *m/z* 299 [$(M+H)^+$]; ESIMS-HR calcd for $C_{19}H_{27}N_2O$ $(M+H)^+$ 299.2118, found 299.2116.

*4.1.26 N-(Cyclopropanecarbonyl)-5-isopropylspiro[indoline-2,4'-piperidin]-3-one (**2**)*
A solution of compound **29a** (50 mg, 0.21 mmol), EDCI (78 mg, 0.41 mmol) and DMAP (13 mg, 0.10 mmol) in DMF (2.1 mL) was treated with cyclopropanecarboxylic acid (0.016 mL, 0.20 mmol) at 0 °C, and the mixture was stirred at room temperature for 18 h. The resulting mixture was partitioned between AcOEt (50 mL) and H_2O (30 mL), and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$; 1:99 to 10:90) to afford compound **2** (65 mg, quant.) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.50−7.45 (1H, m), 7.39 (1H, dd, J = 8.5, 1.9 Hz), 6.86 (1H, d, J = 8.5 Hz), 4.98 (1H, s), 4.55−4.22 (2H, m), 3.51 (1H, br s), 3.19 (1H, br s), 2.92−2.81 (1H, m), 1.99−1.96 (2H, m), 1.79 (1H, ddd, J = 13.5, 7.1, 3.8 Hz), 1.55−1.52 (2H, m), 1.23 (6H, d, J = 6.8 Hz), 1.03−0.97 (2H, m), 0.79 (2H, dd, J = 8.0, 2.8 Hz). ESIMS-LR *m/z* 313 [$(M+H)^+$]; ESIMS-HR calcd for $C_{19}H_{25}N_2O_2$ $(M+H)^+$ 313.1911, found 313.1913.

*4.1.27 N-(Cyclopropylsulfonyl)-5-isopropylspiro[indoline-2,4'-piperidin]-3-one (**3**)*
A solution of compound **29a** (100 mg, 0.41 mmol), Et_3N (110 μL, 0.82 mmol) in CH_2Cl_2 (2.5 mL) was treated with cyclopropanesulfonyl chloride (54 μL, 0.53 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. The resulting mixture was partitioned between AcOEt (50 mL) and saturated aqueous $NaHCO_3$ (30 mL), and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (Diol, MeOH/$CHCl_3$; 0:100) to afford compound **3** (130 mg, 93%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.47 (1H, d, J = 1.9 Hz), 7.39 (1H, dd, J = 8.4, 1.9 Hz), 6.84 (1H, d, J = 8.4 Hz), 4.59 (1H, s), 3.92−3.86 (2H, m), 3.33−3.27 (2H, m), 2.91−2.84 (1H, m), 2.36 (1H, tt, J = 8.8, 3.5 Hz), 2.08−2.01 (2H, m), 1.68 (2H, ddd, J = 13.8, 6.1, 3.8 Hz), 1.23 (6H, d, J = 6.8 Hz), 1.22−1.18 (2H, m), 1.08−1.02 (2H, m). ESIMS-LR *m/z* 349 [$(M+H)^+$]; ESIMS-HR calcd for $C_{18}H_{25}N_2O_3S$ $(M+H)^+$ 349.1580, found 349.1587.

*4.1.28 5-Isopropyl-N-phenethylspiro[indoline-2,4'-piperidin]-3-one (**5**)*
Following general procedure E using compound **29a** (60 mg, 0.25 mmol), phenylacetaldehyde (40 µL, 0.343 mmol), AcOH (56 µL, 0.98 mmol), $NaBH(OAc)_3$ (420 mg, 2.0 mmol), and CH_2Cl_2 (2.5 mL), the title compound, **5** (47 mg, 55%), was obtained as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.48 (1H, d, *J* = 1.9 Hz), 7.37 (1H, dd, *J* = 8.5, 1.9 Hz), 7.33−7.27 (2H, m), 7.25−7.18 (3H, m), 6.84 (1H, d, *J* = 8.4 Hz), 4.77 (1H, s), 3.10 (2H, d, *J* = 11.8 Hz), 2.91−2.82 (3H, m), 2.71−2.64 (2H, m), 2.26 (2H, t, *J* = 11.8 Hz), 2.09 (2H, td, *J* = 12.7, 4.0 Hz), 1.48 (2H, d, *J* = 12.7 Hz), 1.23 (6H, d, *J* = 6.8 Hz). ESIMS-LR *m/z* 349 [$(M+H)^+$]; ESIMS-HR calcd for $C_{23}H_{29}N_2O$ $(M+H)^+$ 349.2274, found 349.2289.

*4.1.29 5-Isopropyl-N-propylspiro[indoline-2,4'-piperidin]-3-one (**6**)*
Following general procedure E using compound **29a** (30 mg, 0.12 mmol), propionaldehyde (8.8 µL, 0.12 mmol), AcOH (28 µL, 0.49 mmol), $NaBH(OAc)_3$ (210 mg, 0.99 mmol), and CH_2Cl_2 (1.2 mL), the title compound, **6** (22 mg, 62%), was obtained as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.47 (1H, s), 7.38 (1H, dd, *J* = 8.7, 1.8 Hz), 7.23 (1H, d, *J* = 1.8 Hz), 6.85 (1H, d, *J* = 8.7 Hz), 2.90−2.77 (3H, m), 2.32 (2H, t, *J* = 7.3 Hz), 2.24 (2H, t, *J* = 11.5 Hz), 1.74 (2H, td, *J* = 12.8, 4.0 Hz), 1.48 (2H, td, *J* = 14.8, 7.3 Hz), 1.28−1.20 (2H, m), 1.16 (6H, d, *J* = 7.0 Hz), 0.88 (3H, t, *J* = 7.4 Hz). ESIMS-LR *m/z* 287 [$(M+H)^+$]; ESIMS-HR calcd for $C_{18}H_{27}N_2O$ $(M+H)^+$ 287.2118, found 287.2120.

4.1.30 N-Isobutyl-5-isopropylspiro[indoline-2,4'-piperidin]-3-one (7)
Following general procedure E using compound **29a** (30 mg, 0.12 mmol), isobutylaldehyde (11 µL, 0.12 mmol), AcOH (28 µL, 0.49 mmol), $NaBH(OAc)_3$ (210 mg, 0.99 mmol), and CH_2Cl_2 (1.2 mL), the title compound, **7** (27 mg, 73%), was obtained as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.46 (1H, s), 7.38 (1H, dd, *J* = 8.3, 1.8 Hz), 7.23 (1H, s), 6.85 (1H, d, *J* = 8.3 Hz), 2.86−2.75 (3H, m), 2.20 (2H, t, *J* = 11.2 Hz), 2.10 (2H, d, *J* = 7.3 Hz), 1.85-1.69 (3H, m), 1.22 (2H, d, *J* = 9.5 Hz), 1.16 (6H, d, *J* = 7.0 Hz), 0.88 (6H, d, *J* = 6.5 Hz). ESIMS-LR *m/z* 301 [$(M+H)^+$]; ESIMS-HR calcd for $C_{19}H_{29}N_2O$ $(M+H)^+$ 301.2274, found 301.2264.

*4.1.31 N-(Cyclobutylmethyl)-5-isopropylspiro[indoline-2,4'-piperidin]-3-one (**8**)*
Following general procedure E using compound **29a** (30 mg, 0.12 mmol), cyclobutanecarbaldehyde (10 mg, 0.12 mmol), AcOH (28 µL, 0.49 mmol), $NaBH(OAc)_3$ (210 mg, 0.99 mmol), and CH_2Cl_2 (1.2 mL), the title compound, **8** (15 mg, 39%), was obtained as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.43−7.38 (1H, m), 7.34−7.32 (1H, m), 6.88 (1H, d, *J* = 8.5 Hz), 3.04−2.94 (2H, m), 2.87−2.79 (1H, m), 2.69−2.62 (1H, m), 2.57 (2H, d, *J* = 7.0 Hz), 2.41 (2H, td, *J* = 12.2, 2.4 Hz), 2.18−2.07 (2H, m), 2.03−1.88 (3H, m), 1.88−1.71 (3H, m), 1.39 (2H, d, *J* = 12.3 Hz), 1.21 (6H, t, *J* = 6.9 Hz). ESIMS-LR *m/z* 313 [$(M+H)^+$]; ESIMS-HR calcd for $C_{20}H_{29}N_2O$ $(M+H)^+$ 313.2274, found 313.2273.

*4.1.32 N-(Cyclopentylmethyl)-5-isopropylspiro[indoline-2,4'-piperidin]-3-one (**9**)*
Following general procedure E using compound **29a** (30 mg, 0.12 mmol), cyclopentanecarbaldehyde (13 µL, 0.12 mmol), AcOH (28 µL, 0.49 mmol), $NaBH(OAc)_3$ (210 mg, 0.99 mmol), and CH_2Cl_2 (1.2 mL), the title compound, **9** (35 mg, 87%), was obtained as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.46 (1H, s), 7.38 (1H, dd, *J* = 8.5, 1.8 Hz), 7.23 (1H, s), 6.85 (1H, d, *J* = 8.5 Hz), 2.91−2.75 (3H, m), 2.30−2.15 (4H, m), 2.09 (1H, td, *J* = 15.0, 7.4 Hz), 1.80−1.63 (4H, m), 1.60−1.45 (4H, m), 1.27−1.19 (4H, m), 1.16 (6H, d, *J* = 7.0 Hz). ESIMS-LR *m/z* 327 [$(M+H)^+$]; ESIMS-HR calcd for $C_{21}H_{31}N_2O$ $(M+H)^+$ 327.2431, found 327.2432.

*4.1.33 N-(Cyclohexylmethyl)-5-isopropylspiro[indoline-2,4'-piperidin]-3-one (**10**)*
Following general procedure E using compound **29a** (150 mg, 0.61 mmol), cyclohexanecarbaldehyde (0.074 mL, 0.62 mmol), AcOH (0.14 mL, 2.4 mmol), $NaBH(OAc)_3$ (1.0 g, 4.7 mmol), and CH_2Cl_2 (6.1 mL), the title compound, **10** (200 mg, 94%), was obtained as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.45 (1H, s), 7.38 (1H, dd, *J* = 8.5, 1.9 Hz), 7.23 (1H, d, *J* = 1.5 Hz), 6.84 (1H, d, *J* = 8.5 Hz), 2.85−2.75 (3H, m), 2.23−2.12 (3H, m), 1.75 (3H, dd, *J* = 12.8, 3.8 Hz), 1.68 (4H, td, *J* = 8.2, 6.1 Hz), 1.54−1.46 (1H, m), 1.22 (4H, d, *J* = 13.1 Hz), 1.16 (6H, d, *J* = 6.8 Hz), 1.15-1.11 (2H, m), 0.85 (2H, dd, *J* = 21.1, 11.5 Hz). ESIMS-LR *m/z* 341 [$(M+H)^+$]; ESIMS-HR calcd for $C_{22}H_{33}N_2O$ $(M+H)^+$ 341.2587, found 341.2575.

*4.1.34 5-Isopropyl-N-((tetrahydro-2H-pyran-4-yl)methyl)spiro[indoline-2,4'-piperidin]-3-one (**11**)*
Following general procedure E using compound **29a** (50 mg, 0.21 mmol), 4-formyltetrahydropyran (47 mg, 0.41 mmol), AcOH (0.047 mL, 0.82 mmol), $NaBH(OAc)_3$ (350 mg, 1.6 mmol), and CH_2Cl_2 (2.1 mL) the title compound, **11** (57 mg, 81%), was obtained as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.47 (1H, s), 7.38 (1H, d, *J* = 8.5 Hz), 7.23 (1H, s), 6.85 (1H, t, *J* = 8.5 Hz), 3.83 (2H, d, *J* = 8.5 Hz), 3.35−3.22 (4H, m), 2.86−2.78 (3H, m), 2.29−2.18 (3H, m), 1.78−1.72 (2H, m), 1.62 (2H, d, *J* = 11.0 Hz), 1.23 (1H, d, *J* = 8.8 Hz), 1.16 (6H, d, *J* = 6.8 Hz), 1.12 (1H, s). ESIMS-LR *m/z* 343 [$(M+H)^+$]; ESIMS-HR calcd for $C_{21}H_{31}N_2O_2$ $(M+H)^+$ 343.2380, found 343.2371.

*4.1.35 N-(Tetrahydro-2H-pyran-4-ylmethyl)spiro[indoline-2,4'-piperidin]-3-one (**12**)*
Following general procedure E using compound **29b** (170 mg, 0.84 mmol), 4-formyltetrahydropyran (190 mg, 1.7 mmol), AcOH (0.19 mL, 3.3 mmol), $NaBH(OAc)_3$ (1.4 g, 6.6 mmol), and CH_2Cl_2 (10 mL), the title compound, **12** (72 mg, 29%), was obtained as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.61 (1H, d, *J* = 7.8 Hz), 7.48−7.42 (1H, m), 6.88 (1H, dd, *J* = 8.3, 0.8 Hz), 6.84−6.79 (1H, m), 5.11 (1H, s), 4.02−3.92 (2H, m), 3.50 (1H, d, *J* = 6.3 Hz), 3.45−3.34 (2H, m), 2.96 (2H, dt, *J* = 12.0, 3.3 Hz), 2.25 (2H, d, *J*

= 7.3 Hz), 2.17 (2H, td, *J* = 12.3, 2.4 Hz), 2.05 (2H, td, *J* = 12.3, 4.0 Hz), 1.83−1.62 (2H, m), 1.43 (2H, d, *J* = 11.5 Hz), 1.39−1.21 (2H, m). ESIMS-LR *m/z* 301 [(M+H)$^+$]; ESIMS-HR calcd for $C_{18}H_{25}N_2O_2$ (M+H)$^+$ 301.1911, found 301.1913.

*4.1.36 5-Hydroxy-N-(tetrahydro-2H-pyran-4-ylmethyl)spiro [indoline-2,4'-piperidin]-3-one (**13**)*

Following general procedure E using compound **29c** (98 mg, 0.45 mmol), 4-formyltetrahydropyran (110 mg, 0.92 mmol), AcOH (0.10 mL, 1.7 mmol), $NaBH(OAc)_3$ (780 mg, 3.7 mmol), and CH_2Cl_2 (4.5 mL), the title compound, **13** (84 mg, 59%), was obtained as a pale yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.98 (1H, s), 7.02 (1H, dd, *J* = 8.8, 2.6 Hz), 6.96 (1H, s), 6.80 (1H, d, *J* = 8.8 Hz), 6.72 (1H, d, *J* = 2.6 Hz), 3.87−3.79 (2H, m), 3.32−3.25 (3H, m), 2.81 (2H, d, *J* = 11.8 Hz), 2.25−2.14 (4H, m), 1.80-1.67 (3H, m), 1.62 (2H, d, *J* = 13.1 Hz), 1.20 (2H, d, *J* = 13.1 Hz), 1.13 (1H, dd, *J* = 12.7, 4.6 Hz). ESIMS-LR *m/z* 317 [(M+H)$^+$]; ESIMS-HR calcd for $C_{18}H_{25}N_2O_3$ (M+H)$^+$ 317.1860, found 317.1854.

*4.1.37 5-Chloro-1'-(tetrahydro-2H-pyran-4-ylmethyl)spiro[indoline-2,4'-piperidin]-3-one (**15**)*

Following general procedure E using compound **29d** (31 mg, 0.13 mmol), 4-formyltetrahydropyran (30 mg, 0.26 mmol), AcOH (0.03 mL, 0.53 mmol), $NaBH(OAc)_3$ (220 mg, 1.0 mmol), and CH_2Cl_2 (1.3 mL), the title compound, **15** (40 mg, 91%), was obtained as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.15 (1H, dd, *J* = 8.8, 2.8 Hz), 7.05 (1H, d, *J* = 2.8 Hz), 6.86 (1H, d, *J* = 8.8 Hz), 4.64 (1H, s), 3.98 (2H, dd, *J* = 11.3, 3.0 Hz), 3.39 (2H, td, *J* = 11.7, 1.9 Hz), 2.96 (2H, d, *J* = 10.8 Hz), 2.25 (2H, d, *J* = 6.8 Hz), 2.16 (1H, br s), 2.06 (2H, td, *J* = 12.6, 3.6 Hz), 1.84−1.74 (1H, m), 1.70 (2H, d, *J* = 13.6 Hz), 1.41 (1H, br s), 1.36−1.21 (4H, m). ESIMS-LR *m/z* 335 [(M+H)$^+$]; ESIMS-HR calcd for $C_{18}H_{24}ClN_2O_2$ (M+H)$^+$ 335.1521, found 335.1510.

*4.1.38 5-(tert-Butyl)-N-(tetrahydro-2H-pyran-4-ylmethyl)spiro[indoline-2,4'-piperidin]-3-one (**17**)*

Following general procedure E using compound **29e** (50 mg, 0.19 mmol), 4-formyltetrahydropyran (44 mg, 0.39 mmol), AcOH (0.044 mL, 0.77 mmol), $NaBH(OAc)_3$ (330 mg, 1.5 mmol), and CH_2Cl_2 (1.9 mL), the title compound, **17** (67 mg, 97%), was obtained as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ: 7.62 (1H, s), 7.56 (1H, d, *J* = 8.3 Hz), 6.86 (1H, d, *J* = 8.3 Hz), 4.84 (1H, s), 3.98 (2H, d, *J* = 6.4 Hz), 3.39 (2H, t, *J* = 10.9 Hz), 2.96 (2H, d, *J* = 10.9 Hz), 2.24 (2H, d, *J* = 6.4 Hz), 2.20−2.01 (4H, m), 1.82−1.63 (3H, m), 1.42 (2H, d, *J* = 12.0 Hz), 1.35−1.26 (2H, m) 1.30 (9H, s). ESIMS-LR *m/z* 357 [(M+H)$^+$]; ESIMS-HR calcd for $C_{22}H_{33}N_2O_2$ (M+H)$^+$ 357.2537, found 357.2524.

*4.1.39 N-(Tetrahydro-2H-pyran-4-ylmethyl)-5-(trifluoromethyl)spiro[indoline-2,4'-piperidin]-3-one (**18**)*

Following general procedure E using compound **29f** (2.0 g, 7.4 mmol), 4-formyltetrahydropyran (1.7 g, 15 mmol), AcOH (1.7 mL, 30 mmol), $NaBH(OAc)_3$ (12 g, 57 mmol), and CH_2Cl_2 (50 mL), the title compound, **18** (2.7 g, 99%), was obtained as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.86 (1H, d, *J* = 9.3 Hz), 7.65 (1H, dd, *J* = 8.8, 1.8 Hz), 6.95 (1H, d, *J* = 8.8 Hz), 4.00 (2H, dd, *J* = 11.6, 3.4 Hz), 3.41 (2H, td, *J* = 11.6, 2.0 Hz), 3.29 (2H, t, *J* = 6.0 Hz), 2.84 (2H, br s), 2.61 (2H, d, *J* = 6.8 Hz), 2.06−1.91 (5H, m), 1.80 (2H, d, *J* = 13.1 Hz), 1.37 (2H, ddd, *J* = 25.1, 12.0, 4.5 Hz). ESIMS-LR *m/z* 369 [(M+H)$^+$]; ESIMS-HR calcd for $C_{19}H_{24}F_3N_2O_2$ (M+H)$^+$ 369.1784, found 369.1774.

*4.1.40 5-Methoxy-N-(tetrahydro-2H-pyran-4-ylmethyl)spiro [indoline-2,4'-piperidin]-3-one (**14**)*

A suspension of compound **13** (10 mg, 0.032 mmol) and NaH (0.91 mg, 60% dispersion of mineral oil, 0.038 mmol) in DMF (1.0 mL) was treated with MeI (2.0 μL, 0.032 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. The resulting mixture was partitioned between AcOEt (50 mL) and saturated aqueous $NaHCO_3$ (30 mL), and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$; 1:99 to 13:87) to afford compound **14** (3.4 mg, 32%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.15 (1H, dd, *J* = 8.8, 2.8 Hz), 7.05 (1H, d, *J* = 2.8 Hz), 6.86 (1H, d, *J* = 8.8 Hz), 4.64 (1H, s), 3.98 (2H, dd, *J* = 11.3, 3.0 Hz), 3.78 (3H, s), 3.39 (2H, td, *J* = 11.7, 1.9 Hz), 2.96 (2H, d, *J* = 10.8 Hz), 2.25 (2H, d, *J* = 6.8 Hz), 2.16 (1H, br s), 2.06 (2H, td, *J* = 12.6, 3.6 Hz), 1.84−1.74 (1H, m), 1.70 (2H, d, *J* = 13.6 Hz), 1.41 (1H, br s), 1.36−1.21 (4H, m). ESIMS-LR *m/z* 331 [(M+H)$^+$]; ESIMS-HR calcd for $C_{19}H_{27}N_2O_3$ (M+H)$^+$ 331.2016, found 331.2036.

*4.1.41 5-Isopropyloxy-N-(tetrahydro-2H-pyran-4-ylmethyl)spiro[indoline-2,4'-piperidin]-3-one (**16**)*

A suspension of compound **13** (26 mg, 0.082 mmol) and NaH (3.0 mg, 60% dispersion of mineral oil, 0.13 mmol) in DMF (1.0 mL) was treated with 2-iodopropane (8.2 μL, 0.082 mmol) at 0 °C for 30 min. The resulting mixture was partitioned between AcOEt (50 mL) and saturated aqueous $NaHCO_3$ (30 mL), and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$; 1:99 to 15:85) to afford compound **16** (4.9 mg, 17%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.12 (1H, dd, *J* = 8.8, 2.7 Hz), 7.06 (1H, d, *J* = 2.7 Hz), 6.84 (1H, d, *J* = 8.8 Hz), 4.64 (1H, br s), 4.47−4.39 (1H, m), 3.97 (2H, dd, *J* = 11.6, 2.9 Hz), 3.39 (2H, td, *J* = 11.6, 1.8 Hz), 2.97 (2H, d, *J* = 11.0 Hz), 2.26 (2H, d, *J* = 6.8 Hz), 2.18 (2H, br s), 2.05 (2H, td, *J* = 12.6, 3.8 Hz), 1.85−1.71 (3H, m), 1.46 (2H, br s), 1.34−1.28 (2H, m), 1.31 (6H, d, *J* = 6.0 Hz). ESIMS-LR *m/z* 359 [(M+H)$^+$]; ESIMS-HR calcd for $C_{21}H_{31}N_2O_3$ (M+H)$^+$ 359.2329, found 359.2345.

*4.1.42 N-Benzyl-6-(trifluoromethyl)spiro[indene-2,4'-piperidin]-1(3H)-one (**31**)*

A suspension of 6-(trifluoromethyl)-1-indanone **30** (0.38 mL, 2.5 mmol) and NaH (420 mg, 60% dispersion of mineral oil, 10 mmol) in DMF (7.0 mL) was treated with *N*-benzyl-*N*,*N*-di(2-chloroethyl)amine hydrochloride (810 mg, 3.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 20 h. The resulting mixture was partitioned between AcOEt (50 mL) and H_2O (30 mL), and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified by silica gel column chromatography ($CHCl_3$/hexane; 0:100 to 10:90) to afford compound **31** (83 mg, 9.2%) as a pale brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.02 (1H, s), 7.83 (1H, dd, *J* = 8.0, 1.5 Hz), 7.58 (1H, d, *J* = 8.0 Hz), 7.38−7.30 (4H, m), 7.28−7.24 (1H, m), 3.57 (2H, s), 3.09 (2H, s), 2.94 (2H, dt, *J* = 11.6, 3.2 Hz), 2.18 (2H, td, *J* = 11.6, 2.0 Hz), 2.08 (2H, td, *J* = 12.3, 3.2 Hz), 1.39 (2H, d, *J* = 13.1 Hz). ESIMS-LR *m/z* 360 [$(M+H)^+$].

*4.1.43 N-(Tetrahydro-2H-pyran-4-ylmethyl)-6-(trifluoromethyl) spiro[indene-2,4'-piperidin]-1(3H)-one (**19**)*

Following general procedure E using compound **31** (38 mg, 0.11 mmol), 4-formyltetrahydropyran (24 mg, 0.21 mmol), 10% Pd/C (7.6 mg), and MeOH (1.1 mL), the title compound, **19** (18 mg, 46%), was obtained as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.03 (1H, s), 7.83 (1H, dd, *J* = 8.0, 1.3 Hz), 7.58 (1H, d, *J* = 8.0 Hz), 3.98 (2H, dd, *J* = 11.6, 4.1 Hz), 3.39 (2H, td, *J* = 11.6, 2.0 Hz), 3.08 (2H, s), 2.91 (2H, dt, *J* = 11.6, 3.2 Hz), 2.23 (2H, d, *J* = 7.0 Hz), 2.19−2.00 (4H, m), 1.83−1.70 (3H, m), 1.39 (2H, d, *J* = 13.1 Hz), 1.28 (2H, ddd, *J* = 24.4, 12.2, 4.1 Hz). ESIMS-LR *m/z* 368 [$(M+H)^+$]; ESIMS-HR calcd for $C_{20}H_{25}F_3NO_2$ $(M+H)^+$ 368.1832, found 368.1834.

*4.1.44 2-(5-Bromo-2-fluorophenyl)-2-(trimethylsilyloxy)acetonitrile (**33**)*

A suspension of 5-bromo-2-fluorobenzaldehyde **32** (0.80 g, 3.9 mmol), LiCl (0.033 mg, 0.78 μmol) in CH_2Cl_2 (15 mL) was treated with TMSCN (0.49 mL, 3.9 mmol) at 0 °C, and the mixture was stirred at room temperature for 16 h. The resulting mixture was concentrated *in vacuo* to afford compound **33** (1.2 g, quant.) as a colorless oil. This material was used to the next reaction without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.76 (1H, dd, *J* = 6.5, 2.5 Hz), 7.50 (1H, dq, *J* = 8.7, 2.5 Hz), 7.01 (1H, dd, *J* = 17.9, 8.7 Hz), 5.68 (1H, s), 0.26 (9H, s).

*4.1.45 (1-Benzyl-4-hydroxypiperidin-4-yl)(5-bromo-2-fluorophenyl)methanone (**34**)*

A solution of compound **33** (1.0 g, 3.3 mmol) in THF (17 mL) was treated with LDA (1 M in THF solution) (4.7 mL, 4.7 mmol) at −78 °C for 1.5 h. *N*-benzyl-4-piperidone (0.84 mL, 4.7 mmol) was slowly added to the mixture at −78 °C for 3 h. The resulting mixture was partitioned between AcOEt (50 mL) and saturated aqueous $NaHCO_3$ (30 mL), and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified by silica gel column chromatography (AcOEt/hexane; 20:80 to 70:30) to afford compound **34** (520 mg, 34%) as a brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.54 (1H, tt, *J* = 6.8, 2.3 Hz), 7.44 (1H, dd, *J* = 5.6, 2.3 Hz), 7.31 (3H, d, *J* = 4.5 Hz), 7.28−7.22 (2H, m), 7.02 (1H, t, *J* = 9.0 Hz), 3.54 (2H, s), 3.00 (1H, d, *J* = 1.5 Hz), 2.78 (2H, d, *J* = 11.3 Hz), 2.40 (2H, td, *J* = 11.9, 2.4 Hz), 2.12 (2H, td, *J* = 12.9, 4.5 Hz), 1.67 (2H, d, *J* = 11.9 Hz). ESIMS-LR *m/z* 392, 394 [$(M+H)^+$].

*4.1.46 N-Benzyl-5-bromo-3H-spiro[benzofuran-2,4'-piperidin]-3-one (**35**)*

A solution of compound **34** (480 mg, 1.2 mmol) in THF (12 mL) was treated with ^{t}BuOK (150 mg, 1.3 mmol) at room temperature, and the mixture was stirred at 80 °C for 2 h. The resulting mixture was partitioned between AcOEt (50 mL) and saturated aqueous $NaHCO_3$ (30 mL), and the organic phase was washed was saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified by silica gel column chromatography (AcOEt/hexane; 20:80 to 50:50) to afford compound **35** (330 mg, 74%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.77 (1H, d, *J* = 2.2 Hz), 7.68 (1H, dd, *J* = 8.8, 2.2 Hz), 7.38−7.30 (4H, m), 7.28−7.24 (1H, m), 7.03 (1H, d, *J* = 8.8 Hz), 3.60 (2H, s), 2.90 (2H, dt, *J* = 11.5, 3.3 Hz), 2.44 (2H, td, *J* = 11.9, 2.5 Hz), 2.08 (2H, dt, *J* = 18.7, 6.8 Hz), 1.59 (2H, dd, *J* = 14.2, 2.5 Hz). ESIMS-LR *m/z* 372, 374 [$(M+H)^+$].

*4.1.47 1'-benzyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-spiro[benzofuran-2,4'-piperidin]-3-one (**36**)*

A suspension of compound **35** (100 mg, 0.27 mmol), bis(pinacolato)diboron (100 mg, 0.40 mmol) and KOAc (79 mg, 0.81 mmol) in DMSO (2.7 mL) was treated with Pd(dppf)Cl_2 (39 mg, 0.053 mmol) at room temperature, and the mixture was stirred at 110 °C for 1 h with MW irradiation, and then the mixture was cooled to room temperature. The resulting mixture was partitioned between AcOEt (50 mL) and H_2O (30 mL), and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt/hexane; 30:70 to 70:30) to afford compound **36** (38 mg, 34%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.16 (1H, d, *J* = 0.5 Hz), 8.03 (1H, dd, *J* = 8.5, 1.4 Hz), 7.38−7.30 (4H, m), 7.28−7.24 (1H, m), 7.09 (1H, dd, *J* = 8.5, 0.5 Hz), 3.62 (2H, s), 2.95−2.88 (2H, m), 2.47 (2H, td, *J* = 12.1, 2.2 Hz), 2.14−2.05 (2H, m), 1.59 (2H, d, *J* = 12.1 Hz), 1.33 (12H, s). ESIMS-LR *m/z* 420 [$(M+H)^+$].

*4.1.48 N-Benzyl-7-(trifluoromethyl)spiro[indoline-2,4'-piperidin]-3-one (**37**)*

Step 2. A suspension of compound **36** (22 mg, 0.052 mmol), 1,10-phenanthroline (1.9 mg, 11 μmol), Copper(I) thiophene-2-carboxylate (CuTC) (1.0 mg, 5.2 μmol) and $LiOH·H_2O$ (4.4 mg, 0.11 mmol) in CH_2Cl_2 (1.0 mL) was treated with Togni's reagent (1-trifluoromethyl-3,3-dimethyl-1,2-benziodoxole) (19 mg, 0.058 mmol) at room temperature, and the mixture was stirred at 60 °C for 1 h with MW irradiation, and then the mixture was cooled to room temperature. The resulting mixture was partitioned between AcOEt (50 mL) and H_2O (30 mL), and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt/hexane; 10:90 to 40:60) to afford compound **37** (14

mg, 75%) as a brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.98−7.94 (1H, m), 7.87−7.81 (1H, m), 7.39−7.29 (4H, m), 7.29−7.24 (1H, m), 7.22 (1H, d, *J* = 8.8 Hz), 3.61 (2H, d, *J* = 5.5 Hz), 2.91 (2H, dq, *J* = 15.2, 3.9 Hz), 2.45 (2H, ddd, *J* = 22.3, 11.7, 2.6 Hz), 2.10 (2H, ddd, *J* = 26.2, 13.8, 4.6 Hz), 1.67-1.55 (2H, m). ESIMS-LR *m/z* 362 [$(M+H)^+$].

*4.1.49 5-(Trifluoromethyl)-3H-spiro[benzofuran-2,4'-piperidin]-3-one (**38**)*

A solution of compound **37** (21 mg, 0.058 mmol) in MeOH (1.0 mL) was treated with 10% Pd/C (5.0 mg) and the mixture was vigorously stirred under H_2 atmosphere (balloon pressure) at room temperature for 15 h. The catalyst was filtered off through a Celite pad, and the filtrate was concentrated *in vacuo* to afford compound **38** (14 mg, 89%) as a colorless solid. This material was used in the next reaction without further purification. ESIMS-LR *m/z* 272 [$(M+H)^+$].

*4.1.50 N-((Tetrahydro-2H-pyran-4-yl)methyl)-5-(trifluoromethyl) -3H-spiro[benzofuran-2,4'-piperidin]-3-one (**20**)*

Following general procedure A using compound **38** (9.0 mg, 0.033 mmol), 4-formyltetrahydropyran (12 mg, 0.11 mmol), AcOH (12 µL, 0.21 mmol), $NaBH(OAc)_3$ (88 mg, 0.42 mmol), and CH_2Cl_2 (1.0 mL), the title compound, **20** (4.6 mg, 24%), was obtained as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.96 (1H, s), 7.85 (1H, dd, *J* = 8.8, 1.9 Hz), 7.23 (1H, d, *J* = 8.8 Hz), 3.98 (2H, dd, *J* = 11.5, 2.8 Hz), 3.40 (2H, td, *J* = 11.5, 2.0 Hz), 2.91−2.85 (2H, m), 2.42 (2H, td, *J* = 11.9, 2.6 Hz), 2.29 (2H, d, *J* = 7.3 Hz), 2.08 (2H, td, *J* = 13.0, 4.5 Hz), 1.84−1.73 (1H, m), 1.71 (2H, d, *J* = 14.3 Hz), 1.62 (2H, dd, *J* = 14.3, 2.5 Hz), 1.31-1.26 (2H, m). ESIMS-LR *m/z* 370 [$(M+H)^+$]; ESIMS-HR calcd for $C_{19}H_{23}F_3NO_3$ $(M+H)^+$ 370.1625, found 370.1622.

*4.1.51 1-Methyl-N-((tetrahydro-2H-pyran-4-yl)methyl)-5-(trifluoromethyl)spiro[indoline-2,4'-piperidin]-3-one (**21**)*

A suspension of compound **18** (2.9 g, 7.8 mmol) and NaH (0.93 g, 60% dispersion of mineral oil, 23 mmol) in DMF (10 mL) was treated with MeI (1.5 mL, 23 mmol) at 0 °C for 1 h. The resulting mixture was partitioned between AcOEt (100 mL) and saturated aqueous $NaHCO_3$ (50 mL), and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$; 1:99 to 10:90) to afford compound **21** (2.7 g, 90%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.80 (1H, d, *J* = 0.8 Hz), 7.64 (1H, dd, *J* = 8.6, 1.8 Hz), 6.76 (1H, d, *J* = 8.6 Hz), 3.98 (2H, dd, *J* = 10.7, 3.4 Hz), 3.40 (2H, td, *J* = 11.9, 1.9 Hz), 2.97 (3H, s), 2.90 (2H, td, *J* = 11.9, 2.3 Hz), 2.73 (2H, d, *J* = 11.3 Hz), 2.35 (2H, d, *J* = 7.0 Hz), 2.03 (2H, td, *J* = 12.5, 4.3 Hz), 1.85−1.73 (1H, m), 1.70 (2H, d, *J* = 13.3 Hz), 1.50 (2H, dd, *J* = 12.5, 1.5 Hz), 1.30 (2H, ddd, *J* = 24.7, 12.0, 4.5 Hz). ESIMS-LR *m/z* 383 [$(M+H)^+$]; ESIMS-HR calcd for $C_{20}H_{26}F_3N_2O_2$ $(M+H)^+$ 383.1941, found 383.1949.

*4.1.52 N-((Tetrahydro-2H-pyran-4-yl)methyl)-5-(trifluoromethyl) spiro[indoline-2,4'-piperidin]-3-ol (**22**)*

A solution of compound **18** (300 mg, 0.81 mmol) in MeOH (5.0 mL) was treated with $NaBH_4$ (150 mg, 4.1 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. The resulting mixture was partitioned between AcOEt (50 mL) and saturated aqueous $NaHCO_3$ (30 mL), and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$; 1:99 to 15:85) to afford compound **22** (220 mg, 73%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.54 (1H, s), 7.38 (1H, d, *J* = 8.3 Hz), 6.64 (1H, d, *J* = 8.3 Hz), 4.77 (1H, s), 4.28 (1H, s), 3.97 (2H, dd, *J* = 10.9, 3.4 Hz), 3.39 (2H, td, *J* = 11.7, 1.8 Hz), 2.66−2.55 (2H, m), 2.37 (2H, t, *J* = 8.9 Hz), 2.14−2.05 (1H, m), 1.80−1.69 (5H, m), 1.61−1.53 (2H, m), 1.27 (2H, ddd, *J* = 24.5, 12.2, 4.0 Hz). ESIMS-LR *m/z* 371 [$(M+H)^+$]; ESIMS-HR calcd for $C_{19}H_{26}F_3N_2O_2$ $(M+H)^+$ 371.1941, found 371.1926.

*4.1.53 3-Methoxy-N-((tetrahydro-2H-pyran-4-yl)methyl)-5-(trifluoromethyl)spiro[indoline-2,4'-piperidine] (**23**)*

A suspension of compound **22** (30 mg, 0.081 mmol) and NaH (5.8 mg, 60% dispersion of mineral oil, 0.24 mmol) in DMF (1.0 mL) was treated with MeI (7.6 µL, 0.12 mmol) at 0 °C for 20 min. The resulting mixture was partitioned between AcOEt (50 mL) and saturated aqueous $NaHCO_3$ (30 mL), and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified by silica gel column chromatography (NH-SiO_2, AcOEt/hexane; 30:70 to 70:30) to afford compound **23** (11 mg, 34%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.49 (1H, s), 7.39 (1H, dd, *J* = 8.3, 1.3 Hz), 6.66 (1H, d, *J* = 8.3 Hz), 4.32 (1H, s), 3.97 (2H, dd, *J* = 11.7, 2.6 Hz), 3.42 (3H, s), 3.37 (2H, dd, *J* = 11.7, 2.1 Hz), 2.62−2.49 (2H, m), 2.44−2.32 (2H, m), 2.22 (2H, d, *J* = 7.0 Hz), 1.82−1.72 (2H, m), 1.71−1.68 (3H, m), 1.33−1.23 (4H, m). ESIMS-LR *m/z* 385 [$(M+H)^+$]; ESIMS-HR calcd for $C_{20}H_{28}F_3N_2O_2$ $(M+H)^+$ 385.2097, found 385.2079.

*4.1.54 N-((Tetrahydro-2H-pyran-4-yl)methyl)-5-(trifluoromethyl) spiro[indoline-2,4'-piperidine] (**24**)*

A solution of compound **22** (50 mg, 0.14 mmol), Et_3SiH (0.11 mL, 0.68 mmol) in CH_2Cl_2 (2.7 mL) was treated with TFA (0.10 mL, 1.3 mmol) at room temperature for 1 h. The resulting mixture was partitioned between AcOEt (50 mL) and saturated aqueous $NaHCO_3$ (30 mL), and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$; 1:99 to 13:87) to afford compound **24** (44 mg, 92%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26-7.23 (2H, m), 6.53 (1H, d, *J* = 8.8 Hz), 3.96 (2H, dd, *J* = 10.8, 3.5 Hz), 3.38 (2H, td, *J* = 11.7, 1.8 Hz), 2.89 (2H, s), 2.53−2.43 (2H, m), 2.43−2.34 (2H, m), 2.21 (2H, d, *J* = 7.0 Hz), 1.82−1.63 (7H, m), 1.33-1.21 (2H, m). ESIMS-LR *m/z* 355 [$(M+H)^+$]; ESIMS-HR calcd for $C_{19}H_{26}F_3N_2O$ $(M+H)^+$ 355.1992, found 355.1996.

*4.1.55 1-Methyl-N-((tetrahydro-2H-pyran-4-yl)methyl)-5-(trifluoromethyl)spiro[indoline-2,4'-piperidine] (**25**)*
A suspension of compound **24** (30 mg, 0.085 mmol) and NaH (6.8 mg, 60% dispersion of mineral oil, 0.17 mmol) in DMF (1.0 mL) was treated with MeI (7.9 μL, 0.13 mmol) at 0 °C, and the mixture was stirred at room temperature for 5 h. The resulting mixture was partitioned between AcOEt (50 mL) and saturated aqueous $NaHCO_3$ (30 mL), and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (NH-SiO_2, AcOEt/hexane; 10:90 to 50:50) to afford compound **25** (23 mg, 73%) as a colorless oil. ^{1}H NMR ((DMSO-d_6, 400 MHz) δ: 7.29 (1H, d, *J* = 8.3 Hz), 7.24 (1H, s), 6.40 (1H, d, *J* = 8.3 Hz), 3.82 (2H, dd, *J* = 11.3, 2.5 Hz), 3.28 (2H, td, *J* = 11.7, 1.8 Hz), 2.90 (2H, s), 2.80 (2H, d, *J* = 11.3 Hz), 2.69 (3H, s), 2.15 (2H, d, *J* = 7.3 Hz), 1.99 (2H, t, *J* = 11.3 Hz), 1.87 (2H, td, *J* = 12.4, 4.0 Hz), 1.73 (1H, tdd, *J* = 14.8, 7.3, 3.6 Hz), 1.60 (2H, dd, *J* = 13.1, 1.8 Hz), 1.37 (2H, d, *J* = 11.8 Hz), 1.11 (2H, ddd, *J* = 24.8, 11.8, 4.4 Hz). ESIMS-LR *m/z* 369 [$(M+H)^+$]; ESIMS-HR calcd for $C_{20}H_{28}F_3N_2O$ $(M+H)^+$ 369.2148, found 369.2136.

4.2. In vitro and in vivo evaluations

4.2.1. Animals

Prenatal/postnatal Wister rats were purchased from JAPAN SLC, Inc. *In vivo* experiments were performed on female C57BL/6 mice aged 7 weeks. All of the experimental protocols for animal studies were approved by the committee for ethics in animal experiments of Asubio Pharma Co., Ltd.

4.2.2 OPC differentiation assay

Neonatal rats (P4-6) were sacrificed by decapitation. The brains were dissected and the cerebral cortices were collected. Cell dissociation was performed by using a papain dissociation system (Worthington, PDS2). Dissociated cells were seeded on a 10 cm dish and incubated at 36 °C with 5% CO_2. Half the volume of the medium was removed and the same volume of fresh medium was added at 6 DIV (days *in vitro*). At 8 DIV, cells were detached and re-seeded on a 96-well plate. DMSO-dissolved compounds were added to the medium at 10 DIV. Cells were fixed with paraformaldehyde at 13 DIV, and immunostained with anti-MBP and anti-OLIG2 primary antibodies (Santa Cruz Biotechnology, sc-13914 and sc-48817, respectively) and Alexa488- and Alexa555-conjugated secondary antibodies. The MBP-positive area and the number of OLIG2-positive cells were analyzed with OperaLX (Perkin Elmer). The medium used in this study consisted of DMEM/F-12 (Thermo Fisher Scientific, 11320-033), StemPro Neural supplement (Thermo Fisher Scientific, A1050801), Anti-Anti (Thermo Fisher Scientific, 15240-096), 10 ng/mL bFGF (Peprotech, 100-18B) and 10–30 ng/mL PDGF-AA (R&D Systems, 221-AA). All the dishes and plates were coated with polyetheleneimine and laminin.

4.2.3 In vivo evaluation (induction of EAE and grading of disabilities)

Induction of EAE, grading of disabilities, and compound treatment female C57BL/6 mice (7 weeks old) were subcutaneously immunized with 100 μg of myelin oligodendrocyte glycoprotein (MOG) peptide (amino acids 35–55) emulsified with incomplete Freund's adjuvant containing 5 mg/ml of *Mycobacterium tuberculosis* (Day 0), followed by an interperitoneal administration of 200 ng of pertussis toxoid on Days 0 and 2. The animals were examined for disabilities until Day 17 with clinical grading as follows: 0, no signs; 1, limp tail; 2, ataxia and/or paresis of hindlimbs; 3, paralysis of hindlimbs and/or paresis of forelimbs; 4, tetraparalysis; 5, moribund or death. From Day 3, mice were orally administered compound **18** once per day. The control mice were administered with vehicle alone (0.5% methylcellulose).

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Graphical Abstract

Discovery and structure-activity relationships of spiroindolines as novel inducers of oligodendrocyte progenitor cell differentiation

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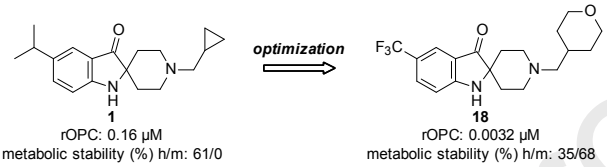

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: