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Novel orally active NPY Y5 receptor antagonists: Synthesis and structure–activity relationship of spiroindoline class compounds

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ABSTRACT

Spiroindoline urea derivatives, designed to act as NPY Y5 receptor antagonists, were synthesized and their structure–activity relationships were investigated. Of these derivatives, compound **3a** showed good Y5 binding affinity with favorable pharmacokinetic properties. Compound **3a** significantly inhibited bPP Y5 agonist-induced food intake in rats, and suppressed body weight gain in DIO mice.

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1. Introduction

Neuropeptide Y (NPY) is a highly conserved C-terminus amidated peptide consisting of 36 amino acid residues, and has been shown to have potent, centrally-mediated orexigenic effects.[1–4] NPY is abundant in the central nervous system throughout the cerebral cortex, forebrain, hypothalamus, brain stem, and spinal cord. In the periphery, NPY is present in most sympathetic nerve fibers, especially around blood vessels.[5] Reports of NPY activity demonstrate a wide range of potential effects at both central and peripheral targets, acting either alone or in combination with other neurotransmitters such as norepinephrine and glutamate. The effects of the NPY family of peptides are mediated via a family of G-protein coupled receptors (GPCRs), providing opportunities for subtype selective therapeutics. At least six receptor subtypes of the NPY family have been characterized based on cloning and their pharmacological characterization.[6] Various pharmacological studies employing receptor deficient mice and/or subtype-selective agonists and antagonists have suggested that the Y5 receptors are involved in body weight regulation.[7–9] The antagonism of the Y5 receptors may have considerable therapeutic benefits for the treatment of obesity. To date, various structurally diverse NPY Y5 receptor antagonists have been reported by a number of research groups, including ours.[10–23]

Previously, our group reported several types of Y5 antagonists.[18–23] Our first lead compound, **1**, was designed following similarity searching of an MRL compound collection, and had very high potency against Y5 receptor (IC_{50}: 0.85 nM).[23] However, its oral bioavailability was too poor to show in vivo efficacy. In order to improve bioavailability, the incorporation of one or several N atoms into the biphenyl region was conducted. This led to the identification of compound **2c**, which was found to reduce bovine pancreatic polypeptide (bPP)-induced food intake in rats.[24] Moreover, phenyl imidazole **3a** was found to be effective in a chronic obesity model. In this paper, we report detailed SAR studies of this spiroindoline class, as well as the identification of compound **3a** (Fig. 1).

2. Chemistry

The general strategy for the synthesis of the derivatives is described in Scheme 1. Compounds **2a–aj** were prepared by the urea formation between spiroindoline amine **6**, which was previously synthesized and reported by our Process Research group,[25] and phenyl carbamates of the corresponding amines. The phenyl

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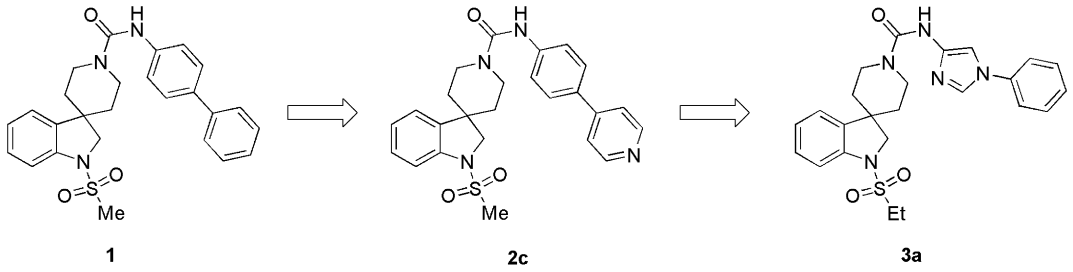
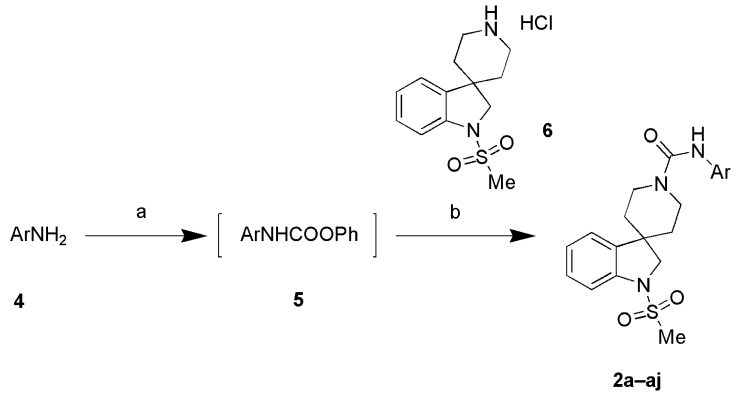


Figure 1. Spiroindoline Y5 antagonists.



Scheme 1. Reagents and conditions: (a) chlorophenylformate, pyridine, rt, or chlorophenylformate, Et_3N, THF, rt; (b) 10 M NaOHaq, DMSO, rt or Et_3N, 1,2-dichloroethane, reflux.

carbamates **5** were generally made from the reaction between biaryl amines **4** and phenyl chloroformate. The aryl amines **4** were either purchased from suppliers as commercially available reagents or prepared using standard synthesis protocols.[26–40]

3. Results and discussion

Previously reported lead compound **1** had high Y5 binding affinity, but unacceptable oral bioavailability (F = 0%). This can be explained by its poor solubility (<0.01 μg/mL at pH 1, 3, 5, and 7) and high lipophilicity (log D at pH 7.4 >4). To address this, we first incorporated one or two nitrogen atoms into the biaryl part of the compound. The binding affinities and bioavailabilities of these derivatives are shown in Figure 2. Introduction of a nitrogen atom on the outer phenyl ring produced *ortho*-, *meta*-, and *para*-pyridyl compounds **2a**, **2b**, and **2c**. While these modifications decreased Y5 binding affinities 2–5-fold, the bioavailability of these compounds was improved. (12%, 47%, and 53%, respectively) Introduction of a pyridine moiety in the inner phenyl ring produced **2d** and **2e**, which retained Y5 affinities. Since incorporation of a nitrogen atom into the inner phenyl ring looked more tolerable in terms of Y5 affinities, heteroaromatics bearing two nitrogen atoms, such as pyridazine, pyrazine, and pyrimidine, were introduced at this position. With the exception of **2f**, all compounds with an inner heteroaromatic ring exhibited high Y5 affinities. The meta-substitution, **2j–l**, was also investigated, but resulted in deceased potency compared to the *para*-substitution. In terms of bioavailability, compounds **2f** and **2i** were the only two compounds among the 6-membered inner heteroaromatic ring analogs to have detectable plasma concentrations after oral administration.

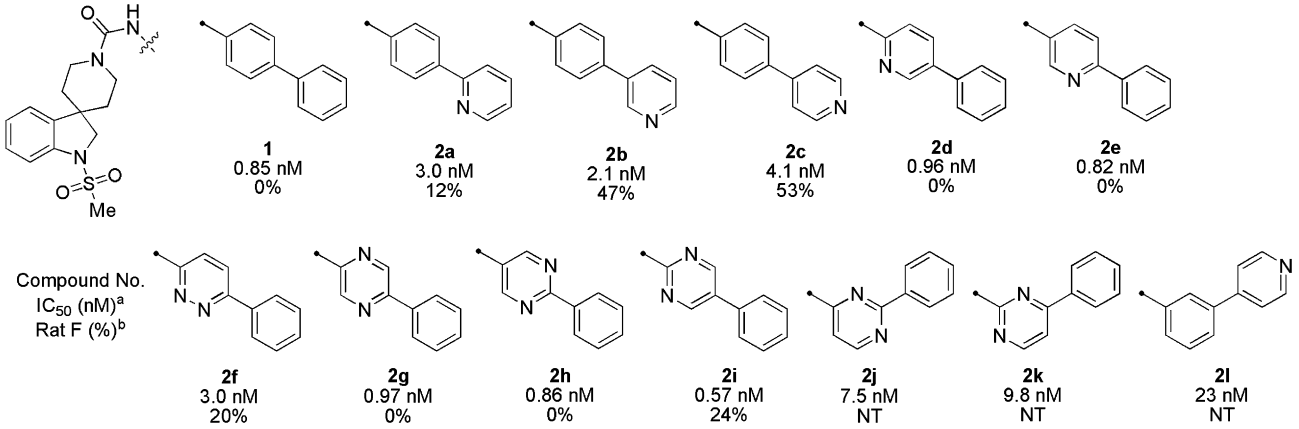
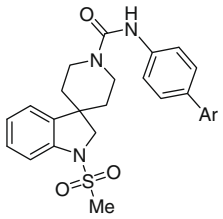
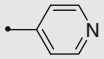


Figure 2. Y5 binding affinities and bioavailability of compounds **1**, **2a–l**. NT, not tested. [a] Values are the mean of two or more independent assays.[41] [b] Bioavailability (F(%)) was calculated from administration at 3 mpk iv and at 10 mpk po dosing in SD rats (n = 2).[43]

Table 1
Profile of compounds **2a–c**



Compound	Ar	IC_{50}[a] (nM)	F[b] (%)	CL_{tot}[c] (mL/min/kg)	C_{max}[c] (μM)	T_{max}[c] (h)	AUC[c] (μM h)	B/P[d]	bPP[e] MED[f] (mg)
2a		3	12	24.4	0.6	0.25	1.8	0.22	>100
2b		2.1	47	13.3	4.7	1	12.7	0.13	100*
2c		4.1	53	17.8	5.5	1	10.8	0.12	10**

[a] Values are the mean of two or more independent assays.[41]
[b] Bioavailability (F(%)) was calculated from administration at 3 mpk iv and at 10 mpk po dosing in SD rats (n = 2).[43]
[c] Other PK parameters were calculated by the trapezoidal method from the plasma concentration at 5 min, 1 h, and 4 h after 3 mpk iv dosing and 0.5 h, 1 h, and 2 h after 10 mpk po dosing.
[d] B/P (brain/plasma) ratio was shown as brain penetration 10 min after 3 mpk iv dosing in rats (n = 2).
[e] bPP inhibition was calculated from the cumulative food intake from 0 h to 2 h after po dosing in SD rats (n = 7 or more).
[f] MED (minimum effective dose; mg) in the bPP assay was shown as statistically-significant (*P < 0.05, **P < 0.01).

Compounds **2a–c**, which incorporate a nitrogen atom in the outer phenyl ring, were evaluated for their brain penetration ability and subsequently for their inhibitory effect on food intake induced by the Y5 agonist, bovine pancreatic polypeptide (bPP) (Table 1). It has been reported that intracerebroventricular (ICV) administration of bPP, which is a Y5 agonist peptide, in SD rats significantly enhances appetite as a Y5 efficacy of bPP. Treatment with Y5 antagonists, such as **2a–c**, competitively suppressed feeding induced by bPP, and **2b** and **2c** showed statistically significant efficacy at doses of 100 mg/kg or lower in this bPP-induced food intake study. Comparison of the pharmacokinetics of compound **2c** and lead compound **1** showed that the oral bioavailability of **2c** was improved dramatically (F = 53%), but its brain penetrability was lower (B/P = 0.12). The pharmacokinetic profiles, including brain penetration, were important for indicating their in vivo efficacy, and their binding efficacies were sufficiently high to show their bPP-induced food intake efficacy. We next evaluated compound **2c** for its suppression effect on body weight in a diet-induced obesity (DIO) model study.[44] DIO mice generally gain weight after eating moderately high fat diets, but the continuous blockade of Y5 receptor suppresses body weight gain. Y5 antagonist **2c** at 100 mg/kg oral dosing did not suppress body weight gain in the DIO model study (data not shown). We speculated that in order to be effective in the DIO model study, the compound must have both better intrinsic potency and a better PK profile, including bioavailability. We therefore further optimized the bi-aryl parts of the spiroindoline skeleton in order to adjust pharmacokinetic properties while maintaining potency.

Extensive exploration of the right biaryl site was conducted, providing compounds such as substituted mono aryl rings **2n–r**, bi-aryl compounds containing a 5-membered ring **2s–ac**, and fused aromatic rings **2ad–ah**. The Y5 affinities of these compounds are summarized in Figure 3. Mono aryl ring compounds **2m–r** demonstrated that substituents at the para position are necessary for potency, since the compound without a substituent, **2m**, showed no Y5 affinity. Benzophenone **2q** was the most potent of these compounds (IC_{50} = 0.68 nM). In the bi-aryl type compounds, various 5-membered heteroaromatics were introduced at either the inner or outer bi-aryl part. The 1,3,4-triazolyl, **2s**, and the 1-methyl-2-imidazolyl, **2x**, had decreased potency. Other biaryl analogues, **2t–w** and **2y–ac** showed slightly decreased potency compared to lead compound **1**. Fused rings, **2ad–ah**, had overall lower potency than the bi-aryl series.

Compounds with acceptable potency were screened using rat PK studies,[43] as shown in Figure 4. Compounds with a 5-membered ring inside tended to have better bioavailability compared to compounds with a 5-membered ring outside. Compounds **2ab**, **2ac**, and **2af** showed greater than 20% bioavailability.

Compounds **2y**, **2ab**, **2ac**, and **2af** were found to have acceptable bioavailability, and so their brain penetration and effect on bPP food intake was assayed (Table 2). The brain penetrability of **2y** and **2af** was too low (B/P = 0.02 and 0.03, respectively) to show efficacy in bPP food intake. Of these four compounds, the isoxazole, **2ab**, had the best B/P ratio, but no efficacy was observed when tested in the bPP food intake assay. Although we were surprised that none of the selected compounds showed efficacy, we further characterized the phenyl imidazole compound, **2ac**. This compound was expected to show some basicity, with the imidazole ring changing the physicochemical properties of the entire compound. Log D value at pH 7.4 of compound **2ac** was lowest among 4 compounds; however, **2ac** had moderate brain penetrability because of the basicity of phenyl imidazole. To our knowledge, basic and lipophilic compounds tend to better penetrate into the brain. The balance of basicity and lipophilicity could lead to a brain penetrable orally active compound.

Adjustment of lipophilicity by modification of the phenyl ring substitution or the spiroindoline moiety was examined. These derivatives were prepared as shown in Schemes 2 and 3. The substituted phenyl imidazoles were obtained using previously reported methods for phenyl imidazole.[40] Derivatives **3**, with an ethanesulfonyl group instead of a methanesulfonyl group on the spiroindoline, were prepared using the same synthetic approach[26] as used for the synthesis of the methanesulfonyl group. Results are summarized in Table 3.

The brain penetrability of compound **3a** was moderately improved (B/P ratio 0.22) compared to compound **2ac**, and showed efficacy in the in vivo bPP assay (MED = 3 mpk). The potential modifications around **3a** led to identify ortho-fluoro derivative **3b**,

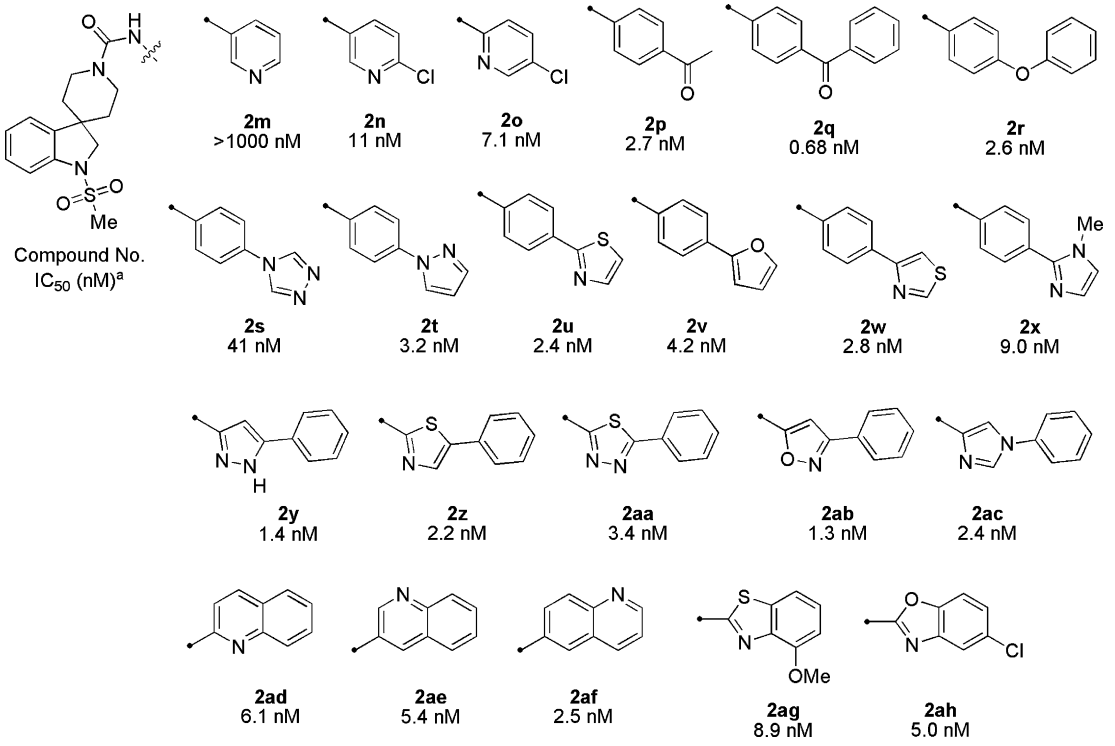


Figure 3. Y5 binding affinities of compounds **2e–ah**. [a] Values are the mean of two or more independent assays.[41]

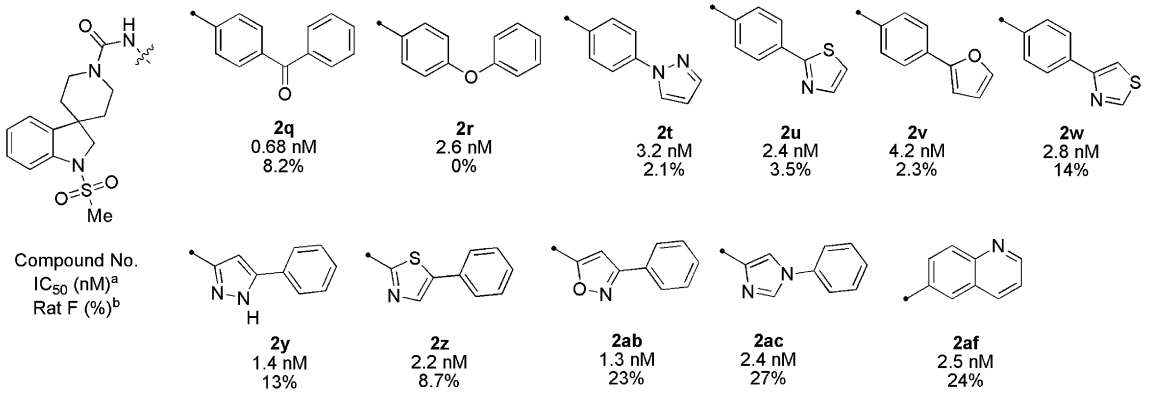


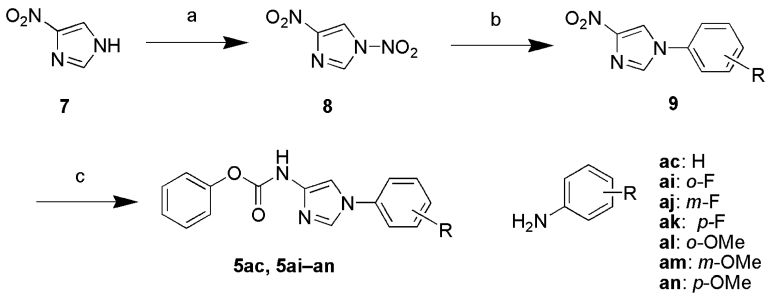
Figure 4. Y5 binding affinities and bioavailability of selected compounds. [a] Values are the mean of two or more independent assays.[41] [b] Bioavailability (F(%)) was calculated from administration at 3 mpk iv and at 10 mpk po dosing in SD rats (n = 2).[43]

Table 2
Results of brain penetrability and bPP food intake assays of compounds **2y**, **2ab**, **2ac**, and **2af**, and their physicochemical properties

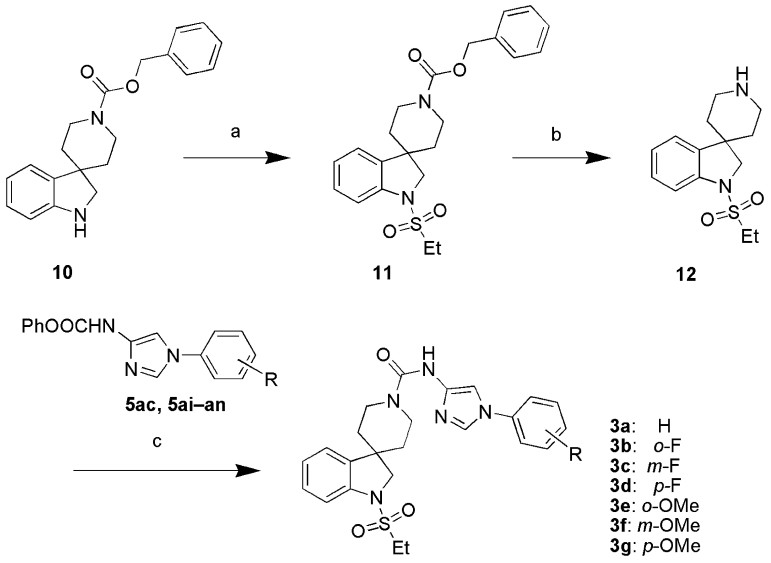
Compound	IC_{50}[a] (nM)	F[b] (%)	B/P ratio[c]	Log D (pH 7.4)[d]	pK_a[e]	MED[f] bPP[g] (mg)
2y	1.4	13	0.02	3.08	NC	>30
2ab	1.3	23	0.22	2.53	NC	>30
2ac	2.4	27	0.10	2.15	6.25	>30
2af	2.5	24	0.03	2.74	5.37	>30

NC, not calculated.
[a] Values are the mean of two or more independent assays.[41]
[b] Bioavailability (F(%)) was calculated from administration at 3 mpk iv and at 10 mpk po dosing in SD rats (n = 2).[43]
[c] B/P (brain/plasma) ratio is shown as brain penetration 10 min after 3 mpk iv dosing in rats (n = 2).
[d] Values of log D at pH 7.4 were calculated by ACD/log D software (ver. 11.01).
[e] Values of pK_a were calculated by ACD/pK_a DB software (ver. 11.01).
[f] bPP inhibition was calculated from the cumulative food intake from 0 h to 2 h after 30 po dosing (n = 7 or more).
[g] MED (minimum effective dose; mg) of bPP assay was shown as being statistically significant. ($^{*}P < 0.05$, $^{**}P < 0.01$).

which was shown to have similar profiles as **3a**, and was effective at 3 mpk in the bPP food intake study. Methanesulfonyl **2ai**, which has *ortho*-fluoro phenyl ring, was also not effective compared to ethanesulfonyl **3b**. *meta*-Methoxy **3f** was effective at 10 mpk in the bPP food intake study. Overall, ethyl substitution on spiroindoline seemed to improve the profile more than phenyl substitution



Scheme 2. Reagents and conditions: (a) HNO_3, H_2SO_4, Ac_2O, rt, 1 h; (b) anilines, MeOH, H_2O, rt, overnight; (c) $Pd(OH)_2$, THF, MeOH, rt, 1 h then phenyl chlorocarbomate.



Scheme 3. Reagents and conditions: (a) ethanesulfonyl chloride, Et_3N, rt, 30 min; b) H_2, $Pd(OH)_2$–C, MeOH, THF, rt, 1 h; (c) Et_3N, $CHCl_3$, reflux.

on the biaryl amine part. Therefore, further investigations focused on compound **3a**. The pharmacokinetics profiles of the representative compounds **2ac** and **3a** are shown in Table 4. Head to head comparison revealed that compound **3a** is superior to **2ac** with respect to PK parameters (F, CL_{tot}, AUC) and brain penetrability.

After ICV administration of bPP, **3a** significantly inhibited bPP-induced food intake (Fig. 5). Oral administration of **3a** (1, 3, and 10 mg/kg) showed moderate dose-dependent efficacy in suppressing feeding induced by bPP. The brain concentration of **3a** in SD rats 2 h after oral administration (10 mg/kg) was 0.64 nmol/g. The result from this artificial food intake study required confirmation with a DIO model study, which is more applicable to the actual disease. Compound **3a** was therefore evaluated in a DIO model study.[44,45] The control mice continuously gained weight over 13 consecutive days, whereas mice treated with **3a** (30 mg/kg) had significantly suppressed weight gain (Fig. 6). Moreover, their cumulative food intake was 8.8% lower than the controls. We also evaluated the effect of **3a** on the body weight change in DIO of Y5 knock-out mice (data not shown), and found that compound **3a** did not suppress weight gain. Taken together, these results indicate that compound **3a** suppresses body weight gain in DIO mice by a Y5 anti-obesity mechanism.

4. Conclusion

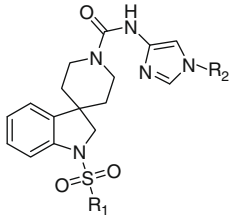
A series of spiroindoline derivatives was synthesized and evaluated as NPY Y5 receptor antagonists. Phenyl imidazole on the right bi-aryl part of the compound was shown to be important for in vivo potency. Compound **3a** had satisfactory pharmacokinetic profiles and brain penetrability in an in vivo animal model. Oral administration of **3a** showed moderate dose–dependent efficacy in suppressing feeding induced by bPP. In a DIO model, **3a** resulted in continuous suppression of weight gain and an 8.8% decrease in cumulative food intake versus the controls.

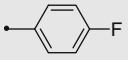
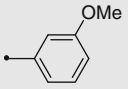
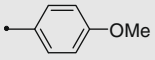
5. Experimental

5.1. Materials and methods

All reagents were obtained from commercial suppliers and used without further purification or drying. TLC was performed with Merck Silica Gel 60 F254 pre-coated plates. Silica gel column chromatography was carried out on Wakogel C-300 (mesh 45–75 μm) or an appropriately sized pre-packed silica cartridge with Moritex NH 60 μM (purchased from Moritex). ^{1}H NMR spectra were recorded on a JEOL JNM-AL 400 spectrometer at 400 MHz, a Varian Gemini 300 spectrometer at 300 MHz, or a Varian Gemini 200 spectrometer at 200 MHz, and are referenced to residual solvent peaks (DMSO-d_6, δ 2.49 ppm; CD_3OD, δ 3.30 ppm) or to an internal standard of tetramethylsilane (TMS, δ 0.00 ppm). Mass spectra were recorded with electronspray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on a Waters micromass ZQ, micromass Quattro II or micromass Q-Tof-2 instrument.

Table 3
Effect of substituents in the phenyl imidazole series



Compound	R1	R2	IC_{50}[a] (nM)	MED[b] bPP[c] (mg)	F[d] (%)	B/P ratio[e]
2ac	Me		2.4	>30	27	0.10
3a	Et		3.4	3**	37	0.22
3b	Et		3.3	3**	23	0.25
3c	Et		3.0	30**	23	0.18
3d	Et		4.1	>30	NT	NT
2ai	Me		3.9	>30	NT	NT
2aj	Me		1.8	>30	NT	NT
3e	Et		4.9	>30	NT	NT
3f	Et		2.0	10*	50.1	0.11
3g	Et		3.2	NT	NT	NT

NT, not tested.
[a] Values are the mean of two or more independent assays.[41]
[b] bPP inhibition was calculated from the cumulative food intake from 0 h to 2 h after 30 po dosing ($n \geqslant 7$).
[c] MED (minimum effective dose; mg) of the bPP assay was shown as being statistically significant. (*$P < 0.05$, **$P < 0.01$).
[d] F(%) was calculated from administration at 3 mpk iv and at 10 mpk po dosing in SD rats.[43]
[e] B/P (brain/plasma) ratio was shown as brain penetration 10 min after 3 mpk iv dosing in rats.

5.2. Chemistry

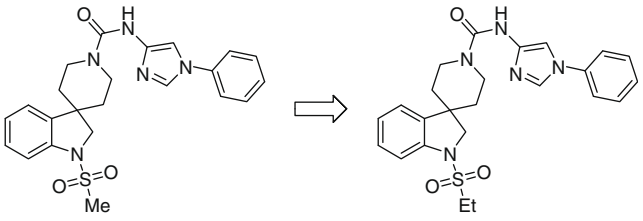
5.2.1. General procedure for the synthesis of phenyl carbamate 5a–ah

The general procedure for the synthesis of phenyl carbamates is described in Ref. 19. To the solution of the corresponding amine **4a–ah** (2.00 mmol) in pyridine (5.00 mL) was added phenyl chloroformate (274 μL, 2.20 mmol) at room temperature. After stirring overnight, AcOEt and 10% aqueous citric acid were added and the mixture was extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure to give crude phenyl carbamates **5a–ah**, which were used in the next reaction without further purification.

5.2.2. Synthesis procedure for compounds, 2a–aj

5.2.2.1. 1-(Methylsulfonyl)-*N*-[4-(pyridin-2-yl)phenyl]-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2a). To the solution of **5a** (130 mg, 0.450 mmol) and **6** (136 mg, 0.490 mmol) in DMSO (2.00 mL) was added aqueous 10 M NaOH (50.0 μL, 0.500 mmol). After stirring vigorously for 2 h, H_2O was added and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure and the residue

Table 4
Profiles of compounds **2ac** and **3a**



2ac **3a**

	2ac	3a
IC_{50}[a]	2.4	3.4
F[b] (%)	27	37
CL_{tot}[b] (mL/min/kg)	3.9	2.5
AUC[b] (μM h)	25.3	58.9
B/P ratio[c]	0.10	0.22
MED in bPP[d,e] (mg)	>30	3**

[a] Values are the mean of two or more independent assays.[41]
[b] PK data (F, CL_{tot}, AUC) are from administration at 3 mpk iv and at 10 mpk po dosing in SD rats ($n = 2$).[43]
[c] B/P (brain/plasma) ratio is shown as brain penetration 10 min after 3 mpk iv dosing in rats.
[d] bPP inhibition was calculated from the cumulative food intake from 0 h to 2 h after po dosing ($n = 6$ for **2ac**; $n \geqslant 10$ for **3a**).
[e] MED (minimum effective dose; mg) of the bPP assay was shown as being statistically significant. (* $P < 0.05$, ** $P < 0.01$).

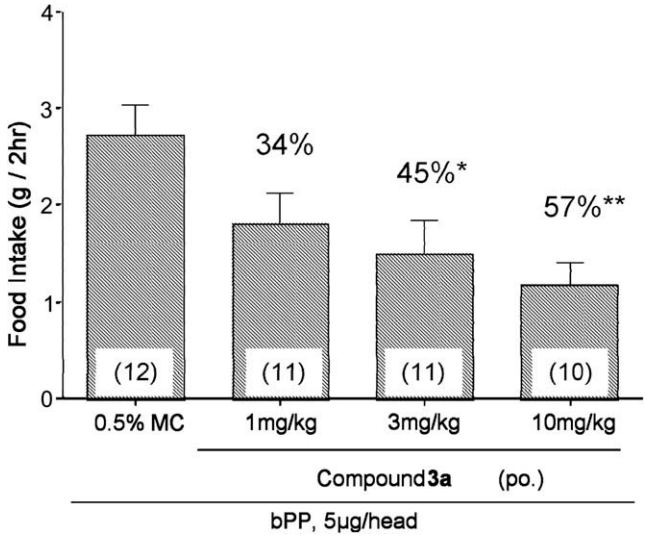


Figure 5. bPP-induced food intake study of compound **3a** (po dosing) in SD rats. Compound **3a** was orally administered 1 h before bPP icv injection. The graphs show the cumulative food intake in SD rats for 2 h after icv injection of bPP. Significant differences with respect to the vechicle treated group are indicated by an asterisk (*$P < 0.05$, **$P < 0.01$). The data shown are expressed as the mean ± SE. $n = 10$–12 rats/group (represented in the bar graph).

was purified by flash chromatography on silica gel (Hexane/EtOAc: 1/2) to give **2a** (123 mg, 70%) as a white solid. **2a** was treated with 4 N HCl in AcOEt to afford **2a** HCl salt: ^{1}H NMR (300 MHz; CD_3OD): δ 8.75 (1H, d, $J = 5.4$ Hz), 8.62 (1H, t, $J = 7.7$ Hz), 8.38 (1H, d, $J = 8.1$ Hz), 7.98–7.93 (1H, m), 7.92 (2H, d, $J = 9.0$ Hz), 7.78 (2H, d, $J = 9.0$ Hz), 7.39 (1H, d, $J = 8.3$ Hz), 7.22–7.29 (2H, m), 7.09 (1H, t, $J = 7.7$ Hz), 4.26 (2H, d, $J = 13.2$ Hz), 3.99 (2H, s), 3.18 (2H, t, $J = 13.0$ Hz), 2.99 (3H, s), 2.05–1.94 (2H, m), 1.83 (2H, d, $J = 13.6$ Hz); HRMS (ESI$^+$) m/z $[M+H]^+$ 463.1806 ($C_{25}H_{27}N_4O_3S$ requires: 463.1804).

5.2.2.2. 1-(Methylsulfonyl)-*N*-[4-(pyridin-3-yl)phenyl]-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2b). To the solution of **5b** (2.94 g, 10.1 mmol) and **6** (3.37 g, 11.1 mmol) in 1,2-dichloroethane (6.00 mL) was added Et_3N (5.70 mL, 40.9 mmol). After reflux for 1.5 h, diluted aqueous NaOH was added and the mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure, and the residue was collected by filtration and washed with EtOH to give **2b** (2.86 g, 61%) as a yellow solid. Compound **2b** was treated with 4 N HCl in AcOEt to afford **2b** HCl salt: ^{1}H NMR (300 MHz; DMSO-d_6): δ 8.86 (1H, d, $J = 1.8$ Hz), 8.51–8.49 (1H, m), 8.05–8.01 (1H, m), 7.64 (4H, s), 7.44 (1H, dd, $J = 7.9$, 4.4 Hz), 7.37–7.21 (3H, m), 7.05 (1H, td, $J = 7.3$, 1.4 Hz), 4.18 (2H, br d, $J = 13.6$ Hz), 3.93 (2H, s), 3.06 (3H, s), 3.06–2.97 (2H, m), 1.85–1.68 (4H, m); HRMS (ESI$^+$) m/z $[M+H]^+$ 463.1795 ($C_{25}H_{27}N_4O_3S$ requires: 463.1804).

5.2.2.3. 1-(Methylsulfonyl)-*N*-[4-(pyridin-4-yl)phenyl]-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2c); 1.65 g (97%). Compound **2c** was treated with 4 N HCl in AcOEt to afford **2c** HCl salt: ^{1}H NMR (300 MHz; DMSO-d_6): δ 8.78 (1H, s), 8.57 (2H, d, $J = 5.3$ Hz), 7.76–7.66 (6H, m), 7.35–7.02 (4H, m), 4.19 (2H, d, $J = 13.5$ Hz), 3.94 (2H, s), 3.07 (3H, s), 3.07–2.99 (2H, m), 1.89–1.73 (4H, m); HRMS (ESI$^+$) m/z $[M+H]^+$ 463.1802 ($C_{25}H_{27}N_4O_3S$ requires: 463.1804).

5.2.2.4. 1-(Methylsulfonyl)-*N*-(5-phenylpyridin-2-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2d); 200 mg (84%). ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.45 (1H, d, $J = 1.8$ Hz), 8.13 (1H, d, $J = 8.2$ Hz), 7.91 (1H, dd, $J = 8.7$, 2.5 Hz), 7.57 (2H, d, $J = 8.6$ Hz), 7.49–7.37 (4H, m), 7.30–7.23 (1H, m), 7.17 (1H, dd, $J = 7.6$, 1.0 Hz), 7.09 (1H, dd, $J = 7.4$, 1.0 Hz), 4.21 (2H, br d, $J = 13.4$ Hz), 3.90 (2H, s), 3.20–3.05 (2H, m), 2.94 (3H, s), 2.05–1.93 (2H, m), 1.82 (2H, br d, $J = 13.8$ Hz); HRMS (ESI$^+$) m/z $[M+H]^+$ 463.1794 ($C_{25}H_{27}N_4O_3S$ requires: 463.1804).

5.2.2.5. 1-(Methylsulfonyl)-*N*-(6-phenylpyridin-3-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2e); 180 mg (87%). ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.52 (1H, d, $J = 2.6$ Hz), 8.15–8.10 (1H, m), 7.95 (2H, dd, $J = 7.6$ Hz), 7.71 (1H, d, $J = 8.6$ Hz), 7.50–7.38 (4H, m), 7.30–7.23 (1H, m), 7.18–7.17 (1H, m), 7.09 (1H, t, $J = 7.5$ Hz), 6.58 (1H, s), 4.20–4.10 (2H, br d), 3.90 (2H, s), 3.20–3.05 (2H, m), 2.95 (3H, s), 2.05–1.93 (2H, m), 1.90–1.80 (2H, m); HRMS (ESI$^+$) m/z $[M+H]^+$ 463.1813 ($C_{25}H_{27}N_4O_3S$ requires: 463.1804).

5.2.2.6. 1-(Methylsulfonyl)-*N*-(6-phenylpyridazin-3-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2f); 177 mg (76%). ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.37 (1H, br s), 8.00 (2H, d, $J = 7.3$ Hz), 7.85 (1H, d, $J = 9.3$ Hz), 7.54–7.45 (4H, m), 7.42 (1H, d, $J = 7.8$ Hz), 7.16 (1H, d, $J = 7.3$ Hz), 7.08 (1H, t, $J = 7.6$ Hz), 4.29 (2H, br s), 3.91 (2H, s), 3.17–3.07 (2H, m), 2.94 (3H, s), 1.99 (2H, td, $J = 13.2$, 4.4 Hz), 1.84 (2H, d, $J = 13.2$ Hz); HRMS (ESI$^+$) m/z $[M+H]^+$ 464.1764 ($C_{24}H_{26}N_5O_3S$ requires: 464.1756).

5.2.2.7. 1-(Methylsulfonyl)-*N*-(5-phenylpyrazin-2-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2g); 202 mg (67%). ^{1}H NMR (300 MHz; DMSO-d_6): δ 9.67 (1H, br s), 9.13 (1H, d, $J = 1.4$ Hz), 8.90 (1H, d, $J = 1.5$ Hz), 8.08 (2H, dd, $J = 8.3$, 1.4 Hz), 7.53–7.39 (6H, m), 7.34 (1H, d, $J = 7.3$ Hz), 7.30–7.19 (2H, m), 7.05 (1H, td, $J = 7.5$, 1.5 Hz), 4.23 (2H, br d, $J = 14.8$ Hz), 3.93 (2H, s), 3.09–3.00 (2H, m), 3.05 (3H, s), 1.84–1.67 (4H, m); HRMS (ESI$^+$) m/z $[M+H]^+$ 464.1750 ($C_{24}H_{26}N_5O_3S$ requires: 464.1756).

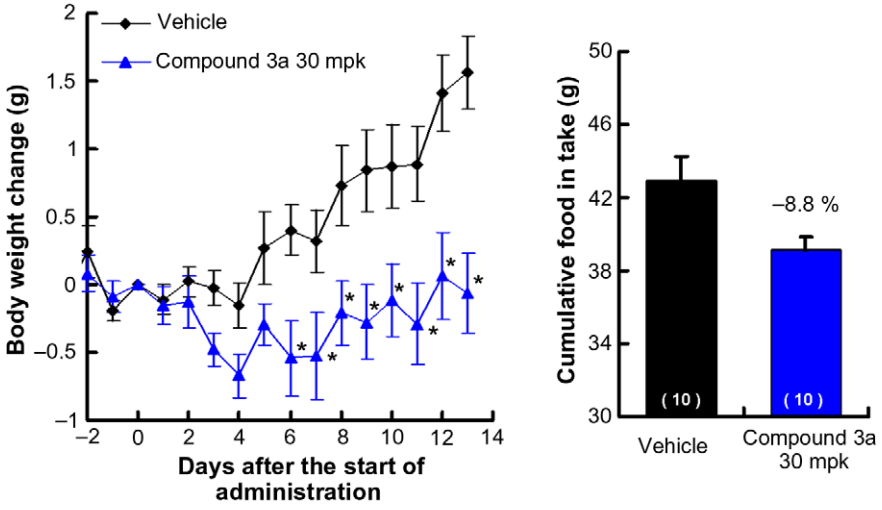


Figure 6. DIO-model study of compound **3a** at 30 mpk po in C57BL/6J mice. Significant differences with respect to vehicle-administered controls are indicated by an asterisk after day 6 (*$P < 0.05$). The DIO model study used C57BL mice, whose weights were between 25.5–31.1 g (vehicle) and 26.0–31.9 g (compound **3a**). $n = 10$ mice/group.

5.2.2.8. 1-(Methylsulfonyl)-*N*-(2-phenylpyrimidin-5-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2h); 161 mg (54%). ^{1}H NMR (300 MHz; DMSO-d_6): δ 9.02 (2H, s), 8.34–8.30 (2H, m), 7.53–7.45 (3H, m), 7.36 (1H, d, J = 7.2 Hz), 7.30–7.20 (2H, m), 7.05 (1H, td, J = 7.1, 1.4 Hz), 4.19 (2H, br d, J = 14.8 Hz), 3.94 (2H, s), 3.12–3.01 (2H, m), 3.06 (3H, s), 1.98–1.70 (4H, m); HRMS (ESI$^+$) m/z [M+H]$^+$ 464.1754 ($C_{24}H_{26}N_5O_3S$ requires: 464.1756).

5.2.2.9. 1-(Methylsulfonyl)-*N*-(5-phenylpyrimidin-2-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2i); 165 mg (80%). ^{1}H NMR (300 MHz; DMSO-d_6): δ 9.68 (1H, br s), 8.88 (2H,s), 7.73 (2H, d, J = 8.1 Hz), 7.49 (2H, d, J = 7.4 Hz), 7.43–7.40 (6H, m), 7.38–7.20 (3H, m), 7.06(1H, td, J = 7.5, 1.5 Hz), 4.11 (2H, br d, J = 13.8 Hz), 3.92 (2H, s), 3.09–2.98 (2H, m), 3.05 (3H, s), 1.87–1.66 (4H, m); HRMS (ESI$^+$) m/z [M+H]$^+$ 464.1745 ($C_{24}H_{26}N_5O_3S$ requires: 464.1756).

5.2.2.10. 1-(Methylsulfonyl)-*N*-(2-phenylpyrimidin-4-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2j); 134 mg (78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 (1H, d, J = 5.9 Hz), 8.36 (2H, td, J = 5.2, 2.6 Hz), 7.92 (1H, d, J = 5.9 Hz), 7.50–7.41 (5H, m), 7.30–7.25 (1H, m), 7.18 (1H, dd, J = 7.8, 1.0 Hz), 7.09 (1H, td, J = 7.6, 1.0 Hz), 4.22 (2H, d, J = 13.7 Hz), 3.91 (2H, s), 3.14 (2H, td, J = 13.3, 2.3 Hz), 2.95 (3H, s), 1.98 (2H, td, J = 13.2, 4.2 Hz), 1.85 (2H, d, J = 13.7 Hz); HRMS (ESI$^+$) m/z [M+H]$^+$ 464.1750 ($C_{24}H_{26}N_5O_3S$ requires: 464.1756).

5.2.2.11. 1-(Methylsulfonyl)-*N*-(4-phenylpyrimidin-2-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2k); 167 mg (75%). ^{1}H NMR (300 MHz; DMSO-d_6): δ 9.53 (1H, s), 8.61 (1H, d, J = 5.2 Hz), 8.18–8.14 (2H, m), 7.59–7.52 (4H, m), 7.29–7.19 (3H, m), 7.07–7.01 (1H, m), 4.12 (1H, br d, J = 13.9 Hz), 3.92 (2H, s), 3.09–3.00 (2H, m), 3.04 (3H, s), 1.88–1.77 (2H, m), 1.71–1.66 (2H, m); HRMS (ESI$^+$) m/z [M+H]$^+$ 464.1764 ($C_{24}H_{26}N_5O_3S$ requires: 464.1756).

5.2.2.12. 1-(Methylsulfonyl)-*N*-[3-(pyridin-4-yl)phenyl]-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2l); 315 mg (99%). Compound **2l** was treated with 4 N HCl in AcOEt to afford **2l** HCl salt (240 mg, 75%): ^{1}H NMR (300 MHz; DMSO-d_6): δ 8.97–8.92 (3H, m), 8.26–8.19 (3H, m), 7.76–7.72 (1H, m), 7.58–7.47 (2H, m), 7.34–7.21 (3H, m), 7.06 (1H, t, J = 7.2 Hz), 4.28–4.20 (2H, m), 3.95 (2H, s), 3.07 (3H, s), 3.10–2.99 (2H, m), 1.88–1.70 (4H, m); HRMS (ESI$^+$) m/z [M+H]$^+$ 463.1811 ($C_{25}H_{27}N_4O_3S$ requires: 463.1804).

5.2.2.13. 1-(Methylsulfonyl)-*N*-(pyridin-3-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2m); 103 mg (81%). ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.2–8.5 (1H, br s), 8.30 (1H, dd, J = 9.1, 1.1 Hz), 8.14 (1H, dd, J = 4.4, 0.9 Hz), 7.87–7.81 (1H, m), 7.42 (1H, d, J = 8.2 Hz), 7.29–7.05 (3H, m), 4.37–4.30 (2H, m), 3.89 (2H, s), 3.16–3.06 (2H, m), 2.94 (3H, s), 2.02–1.91 (2H, m), 1.85–1.80 (2H, m); HRMS (ESI$^+$) m/z [M+H]$^+$ 387.1491 ($C_{19}H_{23}N_4O_3S$ requires: 387.1491).

5.2.2.14. *N*-(6-Chloropyridin-3-yl)-1-(methylsulfonyl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2n); 279 mg (77%). ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.32 (1H, d, J = 1.9 Hz), 8.05 (1H, dd, J = 8.7, 2.9 Hz), 7.41 (1H, d, J = 8.2 Hz), 7.31–7.23 (2H, m), 7.17 (1H, dd, J = 7.7, 1.2 Hz), 7.09 (1H, ddd, J = 7.4, 7.4, 1.0 Hz), 6.73 (1H, s), 4.18–4.11 (2H, m), 3.88 (2H, s), 3.15–3.04 (2H, m), 2.94 (3H, s), 2.02–1.91 (2H, m), 1.84–1.78 (2H, m); HRMS (ESI$^+$) m/z [M+H]$^+$ 421.1110 ($C_{19}H_{22}N_4O_3S$ requires: 421.1101).

5.2.2.15. *N*-(5-Chloropyridin-2-yl)-1-(methylsulfonyl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2o); 71.8 mg (21%). ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.16 (1H, d, J = 2.6 Hz), 8.04 (1H, d, J = 9.0 Hz), 7.64 (1H, dd, J = 9.0, 2.6 Hz), 7.42 (1H, m), 7.31–7.03 (4H, m), 4.20–4.10 (2H, m), 3.89 (2H, s), 3.17–3.01 (2H, m), 2.94 (3H, s), 2.04–1.77 (2H, m), 1.67–1.59 (2H, m); HRMS (ESI$^+$) m/z [M+H]$^+$ 421.1110 ($C_{19}H_{22}N_4O_3S$ requires: 421.1101).

5.2.2.16. *N*-(4-Acetylphenyl)-1-(methylsulfonyl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2p); 175 mg (91%) as a white solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.92 (2H, d, J = 8.7 Hz), 7.51 (2H, d, J = 8.7 Hz), 7.40 (1H, dd, J = 7.8 Hz), 7.29–7.22 (1H, m), 4.20–4.05 (2H, m), 6.87 (1H, s), 4.23–4.10 (2H, m), 3.87 (2H, s), 3.15–3.03 (2H, m), 2.94 (3H, s), 2.56 (3H, s), 2.05–1.90 (2H, m), 1.86–1.74 (2H, m); HRMS (ESI$^+$) m/z [M+H]$^+$ 428.1648 ($C_{22}H_{26}N_3O_4S$ requires: 428.1644).

5.2.2.17. 1-(Methylsulfonyl)-*N*-[4-(phenylcarbonyl)phenyl]-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2q); 163 mg (67%). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.82 (2H, d, J = 8.8 Hz), 7.78 (2H, dd, J = 8.2, 1.3 Hz), 7.58 (1H, tt, J = 7.4, 1.5 Hz), 7.51 (2H, d, J = 8.5 Hz), 7.48 (2H, t, J = 7.1 Hz), 7.42 (1H, d, J = 8.3 Hz), 7.27 (1H, td, J = 7.6, 1.5 Hz), 7.18 (1H, dd, J = 7.7,

1.1 Hz), 7.09 (1H, td, J = 7.4, 1.1 Hz), 6.65 (1H, s), 4.16 (2H, d, J = 13.9 Hz), 3.90 (2H, s), 3.11 (2H, td, J = 13.2, 2.2 Hz), 2.95 (3H, s), 1.99 (2H, dt, J = 18.9, 6.8 Hz), 1.83 (2H, d, J = 13.9 Hz); HRMS (ESI^+) m/z $[M+H]^+$ 490.1809 ($C_{27}H_{28}N_3O_4S$ requires: 490.1801).

5.2.2.18. 1-(Methylsulfonyl)-*N*-(4-phenoxyphenyl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2r); 375 mg (79%). ^1H NMR (300 MHz; $CDCl_3$): δ 7.48–7.25 (6H, m), 7.25–6.95 (7H, m), 6.38 (1H, s), 4.20–4.05 (2H, m), 3.89 (2H, s), 3.17–3.00 (2H, m), 2.94 (3H, s), 2.08–1.88 (2H, m), 1.88–1.72 (2H, m); HRMS (ESI^+) m/z $[M+H]^+$ 178.1809 ($C_{26}H_{28}N_3O_4S$ requires: 478.1801).

5.2.2.19. 1-(Methylsulfonyl)-*N*-[4-(2*H*-1,2,3-triazol-2-yl)phenyl]-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2s); 160 mg (59%). ^1H NMR (300 MHz; DMSO-d_6): δ 8.43(2H, s), 7.60 (1H, d, J = 9.0 Hz), 7.42 (1H, d, J = 8.3 Hz), 7.34–7.25 (3H, m), 7.19 (1H, d, J = 8.1 Hz), 7.10 (1H, t, J = 7.7 Hz), 6.80 (1H, s), 4.20–4.12 (2H, m), 3.90 (2H, s), 3.18–3.08 (2H, m), 2.96 (3H, s), 2.00–1.92 (2H, m), 1.89–1.80 (2H, m); MS(ESI^+) 453 $[M+H]^+$.

5.2.2.20. 1-(Methylsulfonyl)-*N*-[4-(1*H*-pyrazol-1-yl)phenyl]-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2t); 185 mg (82%). ^1H NMR (300 MHz; $CDCl_3$): δ 7.88 (1H, d, J = 2.4 Hz), 7.70 (1H, d, J = 1.5 Hz), 7.62 (2H, d, J = 8.8 Hz), 7.49 (2H, d, J = 9.3 Hz), 7.41 (1H, d, J = 7.8 Hz), 7.18 (1H, d, J = 6.8 Hz), 7.09 (1H, t, J = 7.3 Hz), 6.65 (1H, s), 6.46 (1H, t, J = 2.0 Hz), 4.16 (2H, d, J = 13.7 Hz), 3.89 (2H, s), 3.08–3.04 (2H, m), 2.94 (3H, s), 1.97 (2H, td, J = 13.2, 4.2 Hz), 1.81 (2H, d, J = 13.2 Hz); HRMS (ESI^+) m/z $[M+H]^+$ 452.1748 ($C_{23}H_{26}N_5O_3S$ requires: 452.1756).

5.2.2.21. 1-(Methylsulfonyl)-*N*-[4-(1,3-thiazol-2-yl)phenyl]-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2u); 352 mg (89%). ^1H NMR (300 MHz; $CDCl_3$): δ 7.92 (2H, d, J = 8.7 Hz), 7.83 (1H, d, J = 3.3 Hz), 7.49 (2H, d, J = 8.7 Hz), 7.46–7.30 (1H, m), 7.27 (1H, d, J = 3.3 Hz), 7.30–7.23 (1H, m), 7.23–7.01 (2H, m), 6.53 (1H, s), 4.23–4.07 (2H, m), 3.90 (2H, s), 3.20–3.01 (2H, m), 2.94 (3H, s), 2.10–1.75 (4H, m); HRMS (ESI^+) m/z $[M+H]^+$ 469.1368 ($C_{23}H_{25}N_4O_3S_2$ requires: 469.1368).

5.2.2.22. *N*-[4-(Furan-2-yl)phenyl]-1-(methylsulfonyl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2v); 49.5 mg (84%). ^1H NMR (300 MHz; acetone-d_6): δ 8.11(1H, s), 7.75–7.50 (5H, m), 7.45–7.30 (2H, m), 7.13–7.02 (1H, m), 6.73–6.67 (1H, m), 6.54–6.48 (1H, m), 4.35–4.20 (2H, m), 3.99 (2H, s), 3.22–3.05 (2H, m), 3.00 (3H, s), 2.06–1.70 (4H, m); HRMS (ESI^+) m/z $[M+H]^+$ 452.1648 ($C_{24}H_{26}N_3O_4S$ requires: 452.1644).

5.2.2.23. *N*-[4-(1-Methyl-1*H*-imidazol-2-yl)phenyl]-1-(methylsulfonyl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2w); 143 mg (93%). Compound **2w** was treated with 4 N HCl in AcOEt to afford **2w** HCl salt: ^1H NMR (300 MHz; DMSO-d_6): δ 9.07 (1H, s), 7.82–7.67 (6H, m), 7.33–7.20 (3H, m), 7.08–7.03 (1H, m), 4.25–4.18 (2H, m), 3.95 (2H, s), 3.87 (3H, s), 3.07 (1H, s), 3.10–2.99 (2H, m), 1.88–1.70 (4H, m); HRMS (ESI^+) m/z $[M+H]^+$ 466.1901 ($C_{24}H_{28}N_5O_3S$ requires: 466.1913).

5.2.2.24. 1-(Methylsulfonyl)-*N*-[4-(1,3-thiazol-4-yl)phenyl]-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2x); 120 mg (58%). ^1H NMR (300 MHz; $CDCl_3$): δ 8.86 (1H, d, J = 2.0 Hz), 7.88 (1H, d, J = 8.6 Hz), 7.47 (2H, d, J = 8.6 Hz), 7.47 (1H, s), 7.41 (1H, d, J = 7.7 Hz), 7.27–7.23 (1H, m), 7.20–7.15 (1H, m), 7.08 (1H, t, J = 7.4 Hz), 6.60 (1H, br s), 4.12 (2H, d, J = 7.0 Hz), 3.88 (2H, s), 3.13–3.02 (2H, m), 3.07 (3H, s), 2.04–1.90 (2H, m), 1.82–1.75 (2H, m); HRMS (ESI^+) m/z $[M+H]^+$ 469.1371 ($C_{23}H_{25}N_4O_3S_2$ requires: 469.1368).

5.2.2.25. 1-(Methylsulfonyl)-*N*-(3-phenyl-1*H*-pyrazol-5-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2y); 140 mg (79%). ^1H NMR (300 MHz; $CDCl_3$): δ 7.63 (2H, d, J = 7.8 Hz), 7.50–7.40 (3H, m), 7.40–7.08 (6H, m), 6.72 (1H, s), 4.15–4.10 (2H, m), 3.89 (2H, s), 3.15–3.02 (2H, m), 2.94 (3H, s), 2.00–1.70 (4H, m); HRMS (ESI^+) m/z $[M+H]^+$ 452.1758 ($C_{23}H_{26}N_5O_3S$ requires: 452.1756).

5.2.2.26. 1-(Methylsulfonyl)-*N*-(5-phenyl-1,3-thiazol-2-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2z); 232 mg (72%). ^1H NMR (200 MHz; $CDCl_3$): δ 11.80–11.10 (1H, br s), 7.50–7.30 (6H, m), 7.30–7.00 (4H, m), 4.90–4.38 (2H, br m), 3.90 (2H, s), 3.16–2.80 (2H, m), 2.90 (3H, s), 2.00–1.70 (4H, m); HRMS (ESI^+) m/z $[M+H]^+$ 469.1368 ($C_{23}H_{25}N_4O_3S_2$ requires: 469.1368).

5.2.2.27. 1-(Methylsulfonyl)-*N*-(5-phenyl-1,3,4-thiadiazol-2-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2aa); 387 mg (83%). ^1H NMR (300 MHz; $CDCl_3$): δ 7.85 (2H, d, J = 7.3 Hz), 7.45–7.42 (4H, m), 7.30–7.21 (3H, m), 7.10 (1H, t, J = 6.8 Hz), 4.46 (2H, d, J = 14.6 Hz), 3.93 (2H, s), 3.19 (2H, t, J = 12.2 Hz), 2.93 (3H, s), 2.09 (2H, td, J = 13.7, 4.7 Hz), 1.87 (2H, d, J = 13.7 Hz); HRMS (ESI^+) m/z $[M+H]^+$ 470.1312 ($C_{22}H_{24}N_5O_3S_2$ requires: 470.1321).

5.2.2.28. 1-(Methylsulfonyl)-*N*-(3-phenylisoxazol-5-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2ab); 215 mg (84%) as a white solid. ^1H NMR (300 MHz; $CDCl_3$): δ 7.83–7.77 (3H, m), 7.48–7.39 (4H, m), 7.26 (1H, t, J = 7.5 Hz), 7.15 (1H, d, J = 7.5 Hz), 7.06 (1H, t, J = 7.5 Hz), 6.57 (1H, s), 4.20–4.10 (2H, br m), 3.88 (2H, s), 3.19–3.06 (2H, m), 2.95 (3H, s), 2.01–1.90 (2H, m), 1.87–1.78 (2H, m); HRMS (ESI^+) m/z $[M+H]^+$ 453.1586 ($C_{23}H_{25}N_4O_4S$ requires: 453.1597).

5.2.2.29. 1-(Methylsulfonyl)-*N*-(1-phenyl-1*H*-imidazol-4-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2ac); 244 mg (72%) as a white solid. ^1H NMR (300 MHz; $CDCl_3$): δ 7.61 (1H, s), 7.58 (1H, s), 7.49–7.31 (6H, m), 7.29–7.21 (1H, m), 7.16 (1H, d, J = 7.2 Hz), 7.07 (1H, t, J = 7.2 Hz), 4.21–4.12 (2H, br d), 3.89 (2H, s), 3.15–3.00 (2H, m), 2.93 (3H, s), 2.02–1.90 (2H, m), 1.84–1.70 (2H, m); HRMS (ESI^+) m/z $[M+H]^+$ 452.1752 ($C_{23}H_{26}N_5O_3S$ requires: 452.1756).

5.2.2.30. 1-(Methylsulfonyl)-*N*-(quinolin-2-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2ad); 288 mg (97%) as a colorless amorphous. ^1H NMR (300 MHz; DMSO-d_6): δ 9.63 (1H, s), 8.22 (1H, d, J = 9.0 Hz), 7.99 (1H, d, J = 9.0 Hz), 7.85 (1H, d, J = 7.5 Hz), 7.75 (1H, d, J = 8.6 Hz), 7.64 (1H, m), 7.46–7.18 (4H, m), 7.04 (1H, m), 4.30–4.16 (2H, m), 3.93 (2H, s), 3.14–2.93 (2H, m), 3.05 (3H, s), 1.92–1.60 (4H, m); HRMS (ESI^+) m/z $[M+H]^+$ 437.1656 ($C_{23}H_{25}N_4O_3S$ requires: 437.1647).

5.2.2.31. 1-(Methylsulfonyl)-*N*-(quinolin-3-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2ae); 130 mg (49%) as a colorless solid. ^1H NMR (300 MHz; DMSO-d_6): δ 9.02 (1H, s), 8.97 (1H, d, J = 2.3 Hz), 8.44 (2H, d, J = 2.3 Hz), 7.90 (1H, m), 7.84 (1H, m), 7.61–7.48 (2H, m), 7.38–7.19 (3H, m), 7.05 (1H, m), 4.30–4.18 (2H, m), 3.95 (2H, s), 3.13–3.00 (2H, m), 3.06 (3H, s), 1.90–1.68 (4H, m); HRMS (ESI^+) m/z $[M+H]^+$ 437.1647 ($C_{23}H_{25}N_4O_3S$ requires: 437.1647).

5.2.2.32. 1-(Methylsulfonyl)-*N*-(quinolin-6-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2af); 60 mg (21%) as a pale yellow solid. ^1H NMR (300 MHz; $CDCl_3$): δ 8.89 (1H, d, J = 4.0 Hz), 8.13–8.00 (3H, m), 7.54 (2H, dd, J = 9.5, 2.4 Hz), 7.40–7.05 (5H, m), 6.74 (1H, s), 4.18 (2H, br d, J = 11.0 Hz), 3.88 (2H,

s), 3.11 (2H, t, J = 11.0 Hz), 2.94 (3H, s), 1.98 (2H, td, J = 12.0, 5.0 Hz), 1.85–1.80 (2H, m); HRMS (ESI^+) m/z $[M+H]^+$ 437.1655 ($C_{23}H_{25}N_4O_3S$ requires: 437.1647).

5.2.2.33. *N*-(4-Methoxy-1,3-benzothiazol-2-yl)-1-(methylsulfonyl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2ag); 152 mg (48%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.64 (1H, br s), 7.41 (1H, d, J = 7.8 Hz), 7.33 (1H, d, J = 7.8 Hz), 7.28–7.15 (4H, m), 7.08 (1H, td, J = 7.3, 1.0 Hz), 6.87 (1H, d, J = 8.3 Hz), 4.28 (2H, d, J = 10.7 Hz), 3.99 (3H, s), 3.89 (2H, s), 3.10 (2H, t, J = 12.0 Hz), 2.94 (3H, s), 1.94 (2H, td, J = 13.2, 4.4 Hz), 1.81 (2H, d, J = 14.1 Hz); HRMS (ESI^+) m/z $[M+H]^+$ 473.1324 ($C_{22}H_{25}N_4O_4S_2$ requires: 473.1317).

5.2.2.34. *N*-(5-Chloro-1,3-benzoxazol-2-yl)-1-(methylsulfonyl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2ah); 167 mg (43%). ^1H NMR (300 MHz; $CDCl_3$): δ 7.42–7.40 (1H, m), 7.27–7.20 (2H, m), 7.17–7.13 (3H, m), 7.09–7.06 (1H, m), 4.81–4.46 (2H, m), 3.90 (2H, s), 2.93 (3H, s) 3.16–2.85 (2H, m) 1.96–1.84 (2H, m), 1.82–1.70 (2H, m); HRMS (ESI^+) m/z $[M+H]^+$ 461.1056 ($C_{21}H_{22}ClN_4O_4S$ requires: 461.1050); Analytical HPLC 99.6% pure.

5.2.2.35. 1,4-Dinitro-1*H*-imidazole (8). To a suspension of 1,4-dinitro-1*H*-imidazole **7** (20.0 g, 177 mmol) in acetic acid (360 mL) was slowly added nitric acid (d 1.5, 86 mL) and acetic anhydride (240 mL) while cooling in an ice bath (temperature not to exceed 30 °C). The mixture was stirred at room temperature for 1 h, and then poured onto crushed ice (2 L). AcOEt was added, the organic layer was washed with aqueous K_2CO_3 and brine, then dried with Na_2SO_4. The solvent was evaporated to give **8** (24.5 g, 88%) as a pale yellow solid.

5.2.2.36. 1-(2-Fluorophenyl)-4-nitro-1*H*-imidazole (9ai). To a suspension of **8** (1.58 g, 10 mmol) in water (30 mL) and methanol (30 mL) was added 2-fluoroaniline (1.01 mL, 10.5 mmol) and the mixture was stirred at room temperature for 16 h. The precipitate was collected by filtration and dried in vacuo to give **9ai** (1.91 g, 92%) as a pale yellow solid: ^1H NMR (300 MHz; $CDCl_3$): δ 8.09 (1H, s), 7.75 (1H, s), 7.58–7.31 (4H, m).

5.2.2.37. Phenyl [1-(2-fluorophenyl)-1*H*-imidazol-4-yl]carbamate (5ai). A mixture of **9ai** (1.91 g, 9.22 mmol) and palladium hydroxide (20 wt %, 1.0 g) in tetrahydrofuran (70 mL) and methanol (30 mL) was stirred at rt for 2 h under H_2, filtered through hyflosupercell, then phenyl chlorocarbonate (1.4 mL) was added to the filtrate. The mixture was stirred at room temperature for 10 min, and then saturated aqueous $NaHCO_3$ was added. The mixture was extracted with AcOEt and the organic layer was washed with brine, dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure to give **5ai** (1.95 g, 71%) as a white solid: ^1H NMR (300 MHz; $CDCl_3$): δ 9.45–9.20 (1H, br s), 8.00–7.85 (1H, br s), 7.50–7.35 (5H, m), 7.34–7.18 (5H, m).

5.2.2.38. 1-(3-Fluorophenyl)-4-nitro-1*H*-imidazole (9aj); same as 9ai; 1.23 g (94%). ^1H NMR (300 MHz; $CDCl_3$): δ 8.10 (1H, s), 7.80 (1H, s), 7.62–7.51 (1H, m), 7.30–7.17 (3H, m).

5.2.2.39. 1-(4-Fluorophenyl)-4-nitro-1*H*-imidazole (9ak); same as 9ai; 1.28 g (98%). ^1H NMR (300 MHz; $CDCl_3$): δ 8.60 (1H, s), 8.18 (1H, s), 7.88–7.81 (2H, m), 7.47–7.37 (2H, m).

5.2.2.40. 1-(4-Methoxyphenyl)-4-nitro-1*H*-imidazole (9al); same as 9ai; 1.22 g (88%). ^1H NMR (300 MHz; $CDCl_3$): δ 8.02 (1H, d, J = 1.6 Hz), 7.70 (1H, d, J = 1.6 Hz), 7.36 (2H, d, J = 9.1 Hz), 7.05 (2H, d, J = 9.1 Hz), 3.89 (3H, s).

5.2.2.41. Phenyl [1-(3-fluorophenyl)-1*H*-imidazol-4-yl]carbamate (5aj); same as 5ai; 1.13 g (66%). ^1H NMR (300 MHz; $CDCl_3$): δ 9.60–9.42 (1H, br s), 8.40–8.32 (1H, br s), 7.59 (1H, s), 7.56–7.50 (1H, m), 7.45–7.35 (2H, m), 7.31–7.18 (6H, m).

5.2.2.42. Phenyl [1-(4-fluorophenyl)-1*H*-imidazol-4-yl]carbamate (5ak); same as 5ai; 915 mg (61%). ^1H NMR (300 MHz; $CDCl_3$): δ 9.82–9.70 (1H, br s), 7.89 (1H, s), 7.70–7.64 (2H, m), 7.47–7.37 (3H, m), 7.35–7.20 (5H, m).

5.2.2.43. Phenyl [1-(2-methoxyphenyl)-1*H*-imidazol-4-yl]carbamate (5al); same as 5ai; 599 mg (64%). ^1H NMR (300 MHz; $CDCl_3$): δ 9.8–9.3 (1H, br s), 7.64 (1H, s), 7.42–7.25 (8H, m), 7.06–6.96 (2H, m), 3.83 (3H, s).

5.2.2.44. Phenyl [1-(3-methoxyphenyl)-1*H*-imidazol-4-yl]carbamate (5am); same as 5ai; 869 mg (68%). ^1H NMR (300 MHz; $CDCl_3$): δ 7.70 (1H, s), 7.50 (1H, s), 7.43–7.31 (4H, m), 7.28–7.20 (4H, m), 7.01–6.95 (3H, m), 3.84 (3H, s).

5.2.2.45. Phenyl [1-(4-methoxyphenyl)-1*H*-imidazol-4-yl]carbamate (5an); same as 5ai; 631 mg (37%). ^1H NMR (300 MHz; $CDCl_3$): δ 9.88–9.77(1H, br s), 7.60 (1H, d, J = 1.7 Hz), 7.45–7.20 (8H, s), 6.97 (2H, d, J = 9.0 Hz), 3.84 (3H, s).

5.2.2.46. *N*-[1-(2-Fluorophenyl)-1*H*-imidazol-4-yl]-1-(methylsulfonyl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2ai); 181 mg (77%) as a colorless solid. ^1H NMR (300 MHz; $CDCl_3$): δ 8.66 (1H, br s), 7.91 (1H, d, J = 1.9 Hz), 7.59 (1H, d, J = 1.9 Hz), 7.49–7.22 (6H, m), 7.17–7.07 (2H, m), 4.28–4.22 (2H, m), 3.89 (2H, s), 3.15–3.04 (2H, m), 2.93 (3H, s), 1.97–1.92 (2H, m), 1.84–1.78 (2H, m); HRMS (ESI^+) m/z $[M+H]^+$ 470.1669 ($C_{23}H_{25}FN_5O_3S$ requires: 470.1662).

5.2.2.47. *N*-[1-(3-Fluorophenyl)-1*H*-imidazol-4-yl]-1-(methylsulfonyl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (2aj); 199 mg (84%). ^1H NMR (300 MHz; $CDCl_3$): δ 9.75 (1H, br s), 8.20 (1H, d, J = 1.9 Hz), 7.66 (1H, d, J = 1.9 Hz), 7.51–7.40 (3H, m), 7.31–7.22 (3H, m), 7.17–7.06 (2H, m), 4.35–4.29 (2H, m), 3.89 (2H, s), 3.16–3.05 (2H, m), 2.93 (3H, s), 1.97–1.90 (2H, m), 1.85–1.79 (2H, m); HRMS (ESI^+) m/z $[M+H]^+$ 470.1670 ($C_{23}H_{25}FN_5O_3S$ requires: 470.1662).

5.2.3. Procedure for the synthesis of compound 3a–g

5.2.3.1. Benzyl 1-(ethylsulfonyl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxylate (11). To a solution of **10** (40.0 g, 124 mmol) in $CHCl_3$ (400 mL) was added Et_3N (34.6 mL, 248 mmol) and ethanesulfonyl chloride (23.9 g, 186 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min, poured into water, and extracted with $CHCl_3$. The organic layer was washed with 1 N HCl aq, saturated aqueous $NaHCO_3$, then brine, and dried over Na_2SO_4 Activated carbon was added, then the solution was filtered and concentrated. The crude product was purified by column chromatography (Wakogel C-200, 700 g, Hexane/EtOAc = 3:1–2:1–3:2) to give **11** (47.2 g, 92%) as a yellow foam.

5.2.3.2. 1-(Ethylsulfonyl)-1,2-dihydrospiro[indole-3,4′-piperidine] (12). A mixture of **11** (47.2 g, 114 mmol) and palladium hydroxide (20 wt %, 20.0 g) in THF (75.0 mL) and MeOH (75.0 mL) was stirred at rt for 17 h under H_2, filtered through Celite, and concentrated. The residue was dissolved in THF (50.0 mL) and MeOH (100 mL), and palladium hydroxide (20.0 g) was added. The mixture was stirred at rt for 17 h under H_2, filtered through Celite, and concentrated. To the suspension of the residue in AcOEt (200 mL) and MeOH (20.0 mL) was added 4 N HCl in AcOEt (55.0 mL, 220 mmol). The mixture was stirred at room tempera-

ture for 1 h. The precipitate was collected and washed with ether to give **12** (35.0 g, 96%) as a pale pink solid: ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.90 (2H, s), 7.29–7.21 (2H, m), 7.17 (1H, d, J = 7.3 Hz), 7.07 (1H, td, J = 7.3, 1.5 Hz), 3.97 (2H, s), 3.28 (2H, q, J = 7.3 Hz), 3.05 (2H, t, J = 12.0 Hz), 2.07 (2H, td, J = 13.8, 4.1 Hz), 1.80 (2H, d, J = 14.6 Hz), 1.22 (3H, t, J = 7.6 Hz); MS (ESI$^+$) 281 [M+H]$^+$.

5.2.3.3. 1-(Ethylsulfonyl)-*N*-(1-phenyl-1*H*-imidazol-4-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (3a); 18.6 g (86%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (1H, t, J = 1.6 Hz), 7.58 (3H, t, J = 1.6 Hz) 7.47–7.34 (6H, m), 7.27–7.19 (1H, m), 7.49–7.12 (1H, m), 7.07–7.03 (1H, m), 4.16 (2H, d, J = 14.1 Hz), 3.96 (2H, s), 3.16 (2H, q, J = 7.5 Hz), 3.12–3.01 (2H, m), 1.96–1.89 (2H, m), 1.76–1.70 (2H, m), 1.42 (3H, t, J = 7.5 Hz); HRMS (ESI$^+$) m/z [M+H]$^+$ 466.1905 ($C_{24}H_{28}N_5O_3S$ requires: 466.1913); Analytical HPLC 99.3% pure.

5.2.3.4. 1-(Ethylsulfonyl)-*N*-[1-(2-fluorophenyl)-1*H*-imidazol-4-yl]-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (3b); 166 mg (68%). ^{1}H NMR (300 MHz, acetone-d_6): δ 8.16 (1H, s), 7.69–7.59 (2H, m), 7.50–7.31 (6H, m), 7.25–7.18 (1H, m), 7.08–7.02 (1H, m) 4.35–4.29 (2H, m), 4.05 (2H, s), 3.26 (2H, q, J = 7.4 Hz), 3.18–3.07 (2H, m), 2.01–1.90 (2H, m), 1.83–1.77 (2H, m), 1.35 (3H, t, J = 7.4 Hz); HRMS (ESI$^+$) m/z [M+H]$^+$ 484.1822 ($C_{24}H_{27}FN_5O_3S$ requires: 484.1819).

5.2.3.5. 1-(Ethylsulfonyl)-*N*-[1-(3-fluorophenyl)-1*H*-imidazol-4-yl]-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (3c); 162 mg (67%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.08 (1H, s), 8.14 (1H, d, J = 1.7 Hz), 7.62–7.45 (4H, m), 7.29–7.15 (4H, m), 7.00 (1H, t, J = 7.0 Hz), 4.21–4.16 (2H, m), 3.94 (2H, s), 3.28 (2H, q, J = 7.4 Hz), 2.98–2.89 (2H, m), 1.98–1.62 (4H, m), 1.23 (3H, t, J = 7.4 Hz); HRMS (ESI$^+$) m/z [M+H]$^+$ 484.1822 ($C_{24}H_{27}FN_5O_3S$ requires: 484.1819).

5.2.3.6. 1-(Ethylsulfonyl)-*N*-[1-(4-fluorophenyl)-1*H*-imidazol-4-yl]-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (3d); 216 mg (89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.05 (1H, br s), 8.03 (1H, s), 7.62 (1H, d, J = 1.8 Hz), 7.49–7.43 (2H, m), 7.37 (1H, dd, J = 7.7, 0.7 Hz), 7.28–7.19 (3H, m), 7.14–7.11 (1H, m), 7.07–7.00 (1H, m), 4.30–4.23 (2H, m), 3.96 (2H, s), 3.16 (2H, q, J = 7.4 Hz), 3.17–3.02 (2H, m), 1.96–1.89 (2H, m), 1.84–1.78 (2H, m), 1.43 (3H, t, J = 7.4 Hz); HRMS (ESI$^+$) m/z [M+H]$^+$ 484.1814 ($C_{24}H_{27}FN_5O_3S$ requires: 484.1819).

5.2.3.7. 1-(Ethylsulfonyl)-*N*-[1-(2-methoxyphenyl)-1*H*-imidazol-4-yl]-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (3e); as 3e HCl salt (258 mg, 81%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.40 (1H, s), 8.25 (1H, d, J = 1.8 Hz), 7.58 (1H, d, J = 1.8 Hz), 7.52 (1H, t, J = 7.5 Hz), 7.42–7.35 (2H, m), 7.21 (1H, d, J = 7.5 Hz), 7.17–7.11 (3H, m), 7.03 (1H, t, J = 7.5 Hz), 4.42–4.34 (2H, m), 3.96 (2H, s), 3.91 (3H, s), 3.20–3.03 (4H, m), 2.01–1.89 (2H, m), 1.88–1.79 (2H, m), 1.42 (3H, t, J = 7.5 Hz); HRMS (ESI$^+$) m/z [M+H]$^+$ 496.2017 ($C_{25}H_{30}N_5O_4S$ requires: 496.2019).

5.2.3.8. 1-(Ethylsulfonyl)-*N*-[1-(3-methoxyphenyl)-1*H*-imidazol-4-yl]-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (3f); 248 mg (83%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (1H, s), 7.56 (1H, s), 7.41–7.33 (3H, m), 7.22 (1H, t, J = 7.5 Hz), 7.14 (1H, d, J = 7.5 Hz), 7.07–6.98 (2H, m), 6.95–6.93 (1H, m), 6.90–6.86 (1H, m), 4.20–4.10 (2H, m), 3.96 (2H, s), 3.85 (3H, s), 3.16 (2H, q, J = 7.5 Hz), 3.13–3.01 (2H, m), 2.00–1.89 (2H, m), 1.82–1.75 (2H, m), 1.43 (3H, t, J = 7.5 Hz); HRMS (ESI$^+$) m/z [M+H]$^+$ 496.2012 ($C_{25}H_{30}N_5O_4S$ requires: 496.2019).

5.2.3.9. 1-(Ethylsulfonyl)-*N*-[1-(4-methoxyphenyl)-1*H*-imidazol-4-yl]-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamide (3g); 177 mg (68%) as a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.56 (1H, s), 9.05 (1H, s), 7.69–7.02 (9H, m), 4.14–4.10 (2H, m), 3.97 (2H, s), 3.82 (3H, s), 3.29 (2H, q, J = 7.5 Hz), 3.12–3.05 (2H, m), 1.79–1.73 (4H, m), 1.24 (3H, t, J = 7.5 Hz); HRMS (ESI$^+$) m/z [M+H]$^+$ 496.2014 ($C_{25}H_{30}N_5O_4S$ requires: 496.2019).

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