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Discovery of *trans*-*N*-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro-[6-azaisobenzofuran-1(3*H*),1′-cyclohexane]-4′-carboxamide, a potent and orally active neuropeptide Y Y5 receptor antagonist

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ABSTRACT

A series of *trans*-3-oxospiro[(aza)isobenzofuran-1(3*H*),1′-cyclohexane]-4′-carboxamide derivatives were synthesized to identify potent NPY Y5 receptor antagonists. Of the compounds, **21j** showed high Y5 binding affinity, metabolic stability and brain and cerebrospinal fluid (CSF) penetration, and low susceptibility to P-glycoprotein transporters. Oral administration of **21j** significantly inhibited the Y5 agonist-induced food intake in rats with a minimum effective dose of 1 mg/kg. This compound was selected for proof-of-concept studies in human clinical trials.

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] At least 6 receptor subtypes of the NPY family have been characterized based on cloning and/or their pharmacological properties.[5–19] Various pharmacological studies, employing receptor deficient mice and/or subtype-selective agonists and antagonists, have suggested that the Y1 and Y5 receptors are involved in body weight regulation.[14,16,20–33] Thus, antagonism of the Y1 and/or Y5 receptors may have considerable therapeutic benefits for the treatment of obesity. In diet-induced obese (DIO) mice, treatment with Y5 antagonists reduces body weight in a fat mass-selective manner, implying that Y5 receptor antagonists are useful for the treatment of obesity.[33,34] We developed various potent and orally bioavailable Y5 receptor antagonists.[35–39] Of the Y5 antagonists, a spiro[3-oxoisobenzofurane-1(3*H*),4′-piperidine]-urea derivative (**1**, Fig. 1) was potent at the Y5 receptor, orally bioavailable in laboratory animals including rats, dogs and rhesus monkeys, and brain-penetrant in rats and mice. Thus, this compound was a primary candidate for clinical trials. While **1** reduced the body weight of DIO mice in a fat-selective manner, a relatively high dosage of 10 mg/kg was required to show significant efficacy.[34] More potent compounds could be required to produce clearer results in clinical proof-of-concept studies, and we tried to derivatize **1** to obtain more potent compounds in in vivo.

In vivo more potent compounds may exhibit stronger Y5 antagonistic activities as well as better pharmacokinetic profiles and better penetration to the brain and cerebrospinal fluid (CSF). In the spiro[3-oxoisobenzofurane-1(3*H*),4′-piperidine]-urea derivative

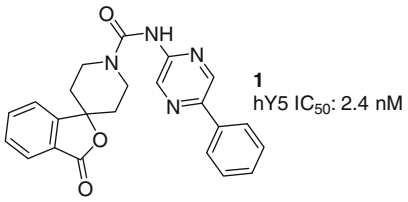

Figure 1. Structure of compound **1**.

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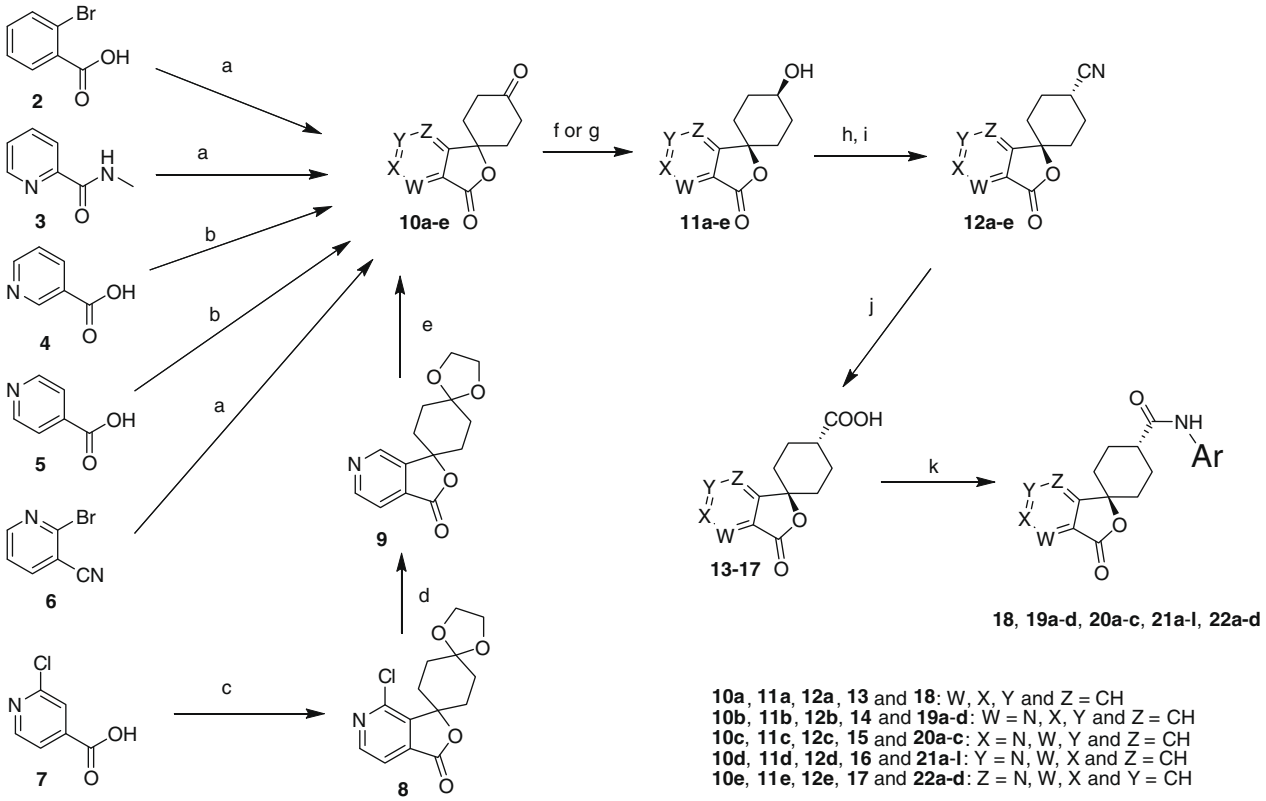
Y5 antagonists, CSF levels were a better indicator to predict in vivo efficacy;[39] hence, CSF levels may be a more important parameter than brain levels. In the course of our structure–activity studies of spiropiperidine-urea NPY Y5 antagonists, we noticed that replacement of the urea linkage with amide produced increased Y5 antagonistic activities. In addition, amide analogs tended to exhibit better brain penetrability compared with the corresponding urea analogs.[38] In contrast, the urea to amide transformation increased the lipophilicity of the compounds. Since higher lipophilic compounds could show less CSF/brain ratios, too lipophilic compounds could not produce very high CSF levels. If amide derivatives of spiro[3-oxoisobenzofurane-1(3*H*),4′-piperidine] can be appropriately designed while maintaining appropriate lipophilicity, such compounds may be highly potent at the Y5 receptor, orally available and well brain- and CSF-penetrant. This working hypothesis prompted us to design and synthesize various 3-oxospiro[(aza)isobenzofuran-1(3*H*),1′-cyclohexane]-4′-carboxamide derivatives. This effort resulted in the discovery of a series of highly potent Y5 antagonists exemplified by **21j**, which was tested in clinical proof-of-concept studies. An oral 1 mg/man dosing of **21j** produced almost complete Y5 receptor occupancy over 24 h and showed statistically significant reduction in body weight although the magnitude of induced weight loss was not clinically meaningful.[40] In this paper, we report discovery of *trans*-*N*-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisoben zofuran-1(3*H*),1′-cyclohexane]-4′-carboxamide (**21j**), a potent and orally active NPY Y5 receptor antagonist.

2. Chemistry

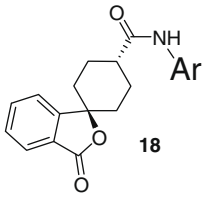
The synthesis of 3-oxospiro[(aza)isobenzofuran-1(3*H*),1′-cyclohexane]-4′-carboxamide derivatives comprises the synthesis of *trans*-3-oxospiro[(aza)isobenzofuran-1(3*H*),1′-cyclohexane]-4′-carboxylic acid portions (**13**–**17**) and subsequent coupling with aromatic amine partners. 2-Bromobenzoic acid (**2**) and *N*-methyl-2-pyridinecarboxamide (**3**) were reacted with *n*-BuLi (2.1 equiv) to generate dianions, which were subsequently reacted with 1,4-cyclohexanedione mono-ethyleneketal followed by acid-mediate hydrolysis to afford spiro[benzofurane-1(3*H*),1′-cyclohexane]-3,4′-dione (**10a**) and spiro[4-azabenzofurane-1(3*H*),1′-cyclohexane]-3,4′-dione (**10b**) in 38% and 62% yields, respectively. 2-Bromo-3-cyanopyridine (**6**) was reacted with 1.1 equiv of *n*-BuLi, and the resulting anion was treated similarly to yield spiro[7-azabenzofurane-1(3*H*),1′-cyclohexane]-3,4′-dione (**10b**, 39%). Pyridine-3-carboxylic acid (**4**) and pyridine-4-carboxylic acid (**5**) were treated with lithium 2,2,6,6-tetramethylpiperidide (2.1 equiv), and the resulting anions were treated similarly to yield spiro[5-azabenzofurane-1(3*H*),1′-cyclohexane]-3,4′-dione (**10c**, 30%) and spiro[6-azabenzofurane-1(3*H*),1′-cyclohexane]-3,4′-dione (**10d**, <27%). In the synthesis of **10d**, the yield was generally low and was not reproducible presumably due to poor solubility of the intermediate dianion, and we developed an alternative method. 2-Chloropyridine-4-carboxylic acid (**7**) was reacted with lithium 2,2,6,6-tetramethylpiperidide (2.1 equiv) followed by 1,4-cyclohexanedione mono-ethyleneketal to afford a spirolactone **8** (49%). Hydrogenolysis of **8** (100%) followed



Scheme 1. Synthesis of 3-oxospiro[(aza)isobenzofuran-1(3*H*),1′-cyclohexane]-4′-carboxamide derivatives. Reagents and conditions: (a) *n*-BuLi, 1,4-cyclohexanedione mono-ethyleneketal, THF, −70 °C; then concd HCl, H_2O, acetone, 80 °C, 38–62%; (b) *n*-BuLi, 2,2,6,6-tetramethylpiperidine, 1,4-cyclohexanedione mono-ethylene ketal, THF, −40 °C; then 6 N HCl, 80 °C, 30% for the step from **4**, 10–27% for the step form **5**; (c) *n*-BuLi, 2,2,6,6-tetramethylpiperidine,4-cyclohexanedione mono-ethyleneketal, THF, −50 °C, 49%; (d) H_2, Pd/C, Et_3N, THF, quant.; (e) TsOH, H_2O, acetone, 80 °C, 91%; (f) $NaBH_4$, THF, H_2O, 0 °C, 76–77% for the step from **10a** and **10d**; (g) $LiAl(OtBu)_3H$, THF, 0 °C, 87–98% for the step from **10b**, **10c** and **10e**; (h) MsCl, Et_3N, 0 °C; (i) Et_4NCN, DMF, 100 °C, 31–70% over all yield for the steps (h) and (i); (j) 30% H_2SO_4, 100 °C, 90–92%; (k) Ar-NH_2, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, pyridine.

by acid-mediate hydrolysis (91%) produced **10d**. Although the total yield was low, this method was practical enough for the medicinal chemistry purpose. The ketones **10a** and **10d** were stereoselectively reduced by $NaBH_4$ to produce *cis* alcohols **11a** and **11d** in 76% and 77% yields, respectively. Stereoselective reduction of the ketones **10b**, **10c** and **10e** was accomplished by using $LiAl(OtBu)_3H$ to afford

Table 1
Human Y5 receptor binding affinities, bioavailability, and plasma, brain and CSF exposure data in rats



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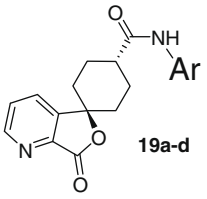
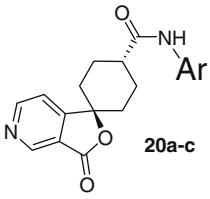
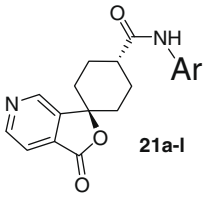


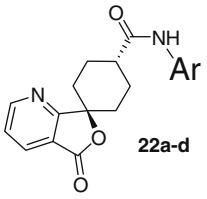
19a-d



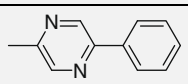
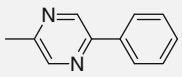
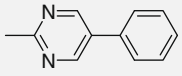
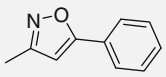
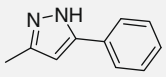
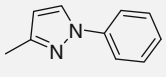
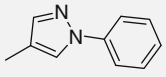
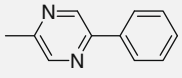
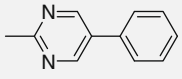
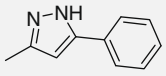
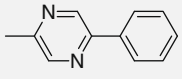
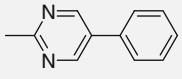
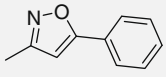
20a-c



21a-l

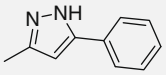
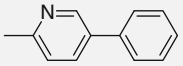
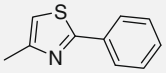
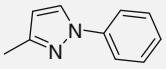
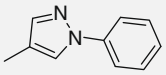
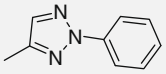
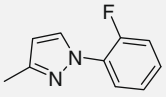
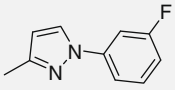
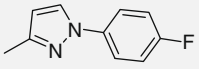
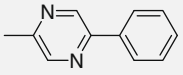
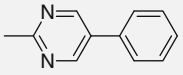
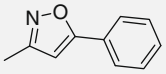
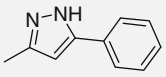


22a-d

Compounds	Ar	hY5 binding IC_{50}[a] (nM)	Metabolic stability in rat hepatocytes, CL_h (mL/min/kg)	Log $D_{7.4}$	Brain, plasma and CSF levels at 2 h after 10 mpk po in rats[b]		
					Plasma level (μM)	Brain level (nmol/g tissue)	CSF level (μM)
18		1.5	35	>4	NT	NT	NT
19a		4.2	18	3.10	3.75	2.50	0.174
19b		2.1	49	2.32	NT	NT	NT
19c		2.8	6	3.30	0.83	0.23	0.016
19d		5.4	2	NT	NT	NT	NT
19e		4.4	4	2.80	6.46	2.79	0.416
19f		1.3	1	2.90	6.68	0.50	0.091
20a		2.4	42	NT	NT	NT	NT
20b		2.0	42	NT	NT	NT	NT
20c		2.9	9	NT	NT	NT	NT
21a		2.2	36	3.39	NT	NT	NT
21b		1.8	39	2.65	NT	NT	NT
21c		2.1	6	NT	(0.29)[c]	NT	NT

(*continued on next page*)

Table 1 (*continued*)

Compounds	Ar	hY5 binding IC_{50}[a] (nM)	Metabolic stability in rat hepatocytes, CL_h (mL/min/kg)	Log $D_{7.4}$	Brain, plasma and CSF levels at 2 h after 10 mpk po in rats[b]		
					Plasma level (μM)	Brain level (nmol/g tissue)	CSF level (μM)
21d		2.7	3	3.16	6.10	0.50	0.059
21e		2.1	14	NT	(0.02)[c]	NT	NT
21f		1.2	12	NT	(0.19)[c]	NT	NT
21g		2.3	20	3.10	2.94	3.13	0.276
21h		2.2	<1	NT	1.52	0.39	0.045
21i		0.89	21	3.40	0.68	1.33	0.042
21j		1.3	9	3.20	1.59	2.15	0.152
21k		2.0	10	3.40	1.09	1.36	0.077
21l		0.92	7	3.20	0.89	1.24	0.081
22a		3.9	39	NT	NT	NT	NT
22b		2.9	49	2.71	NT	NT	NT
22c		2.4	36	3.70	NT	NT	NT
22d		26	NT	NT	NT	NT	NT

NT, not tested. ND, not detected.

[a] In vitro data in nM are the average of at least two experiments.

[b] $n = 3$.

[c] Plasma exposure screening data using 2 animals.

the *cis* alcohols **11b**, **11c** and **11e** in 87%, 94% and 98% yields, respectively. The alcohols **11a–e** were reacted with MsCl in the presence of Et_3N, and the resulting mesylates were reacted with Et_4NCN followed by hydrolysis to produce the desired *trans*-3-oxospiro[(aza)isobenzofuran-1(3*H*),1′-cyclohexane]-4′-carboxylic acids (**13–17**) in 31–70% yields. The carboxylic acids were reacted with aromatic amine partners in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in pyridine to give the desired 3-oxospiro[(aza)isobenzofuran-1(3*H*),1′-cyclohexane]-4′-carboxamide derivatives (Scheme 1).[41]

3. Results and discussion

The synthesized compounds were first evaluated for their human Y5 binding affinities,[42,43] and potent compounds were evaluated for their metabolic stability in rat hepatocytes.[44] Selected compounds were further evaluated for their brain and CSF penetration in rats, and the results are listed in Table 1. Replacement of the urea linkage in **1** with amide produced *trans*-*N*-[5-phenyl-2-pyrazinyl]-3-oxospiro[isobenzofuran-1(3*H*),1′-cyclohexane]-4′-carboxamide (**18**), which showed potent human Y5 binding affinity.

Table 2
Inhibitory effects on D-Trp[34]NPY-induced food intake, rat Y5 receptor binding affinities and plasma, brain and CSF exposure data in rats and susceptibility to P-gp transporters

Compounds	Minimum effective dose[a] (mg/kg po)	rY5 binding IC_{50}[b] (nM)	Susceptibility to P-gp transporters, B-to-A/A-to-B ratio[c]	
			Human L-MDR1[d]	Mouse L-mdr1a[e]
1	3	1.7	0.99	1.36
19e	10	4.7	1.97	6.05
19f	>10	2.2	6.13	21.1
21g	3	2.1	1.05	1.74
21j	1	2.1	1.29	1.57
21l	>10	2.5	1.28	2.41

[a] Inhibitory effect on D-Trp[34]NPY-induced food intake.
[b] In vitro data in nM are the average of at least two experiments.
[c] Transcellular transport across the monolayers of L-MDR1 or L-mdr1a. Values represent the ratio of basal-to-apical (B-to-A) versus apical-to-basal (A-to-B) at 3 h.
[d] Human *MDR1* transfectants.
[e] Mouse *mdr1a* transfectants.

However, this compound was unstable in rat hepatocytes. We conjectured the poor metabolic stability was due to its high lipophilicity (Log $D_{7.4}$ >4), and less lipophilic analogs of **18** may be metabolically more stable. In order to decrease the lipophilicity, a nitrogen atom was incorporated into the benzene ring of the 3-oxoisobenzofurane moiety to produce 4-, 5-, 6- and 7-aza analogs, **19a**, **20a**, **21a** and **22a**, and these compounds showed Y5 binding affinities in the low nM range. As demonstrated by **19a** and **21a**, the incorporation of a nitrogen atom effectively decreased lipophilicity (Log $D_{7.4}$ = 3.10 and 3.39, respectively), and **19a** showed improved metabolic stability as expected. Compound **19a** showed good brain and CSF penetration in rats, and the data encouraged us to further explore this lead. As for the amine partners so far examined, heteroaromatic amines, such as 5-phenyl-2-pyrazinamine, 5-phenyl-2-pyrimidinamine, 5-phenyl-3-isoxazolamine and 5-phenyl-3-pyrazolamine, produced potent Y5 binding inhibitors as shown in Table 1. As for the azaisobenzofuranone part, all isomers produced similar Y5 binding activities if they had the same aromatic amine partners. However, it should be noted that 5-azaisobenzofuranone analogs **20a–c** exhibited unacceptable CYP3A inhibitory activities (>50% at 10 μM), which decreased the usefulness of this scaffold for drug candidates.[45,46] The 7-azaisobenzofuranone analogs **22a–d** were generally less stable in rat hepa- tocytes compared with the other 4-, 5- or 6-aza analogs having the same amine-part structures, so the 7-aza analogs were no longer priorities. Of the remaining 4-aza and 6-aza analogs (**19a–d** vs **21a–d**), the 6-aza analogs tended to show better brain penetration, and further exploration at the amine-part structure was made using the 6-azaisobenzofuranone scaffolds. The 5-phenyl-2-pyridyl and the 2-phenyl-4-thiazolyl analogs (**21e** and **21f**) were potent at the Y5 receptor and stable in rat hepatocytes; however, these compounds exhibited unexpectedly low plasma exposure in rats after 10 mg/kg oral administration. The 1-phenyl-3-pyrazolyl analog **21g** was a potent Y5 binding inhibitor and fairly stable in rat hepatocytes, and this compound was well penetrable to the brain and CSF (brain/plasma ratio = 1.06, CSF/brain ratio = 0.088). A structurally very close isomer, 1-phenyl-4-pyrazolyl analog **21h** was potent at Y5 and metabolically stable; however, **21h** was less brain-penetrant. The 2-phenyl-4-triazolyl analog **21i** was also potent at Y5 and metabolically stable. Although this compound was well penetrant to the brain, its CSF penetration was less than that of **21g** and **21h** (CSF/brain ratio = 0.032 for **21i**, 0.088 for **21g**, 0.115 for **21h**). Finally, we focused on the 1-phenyl-3-pyrazolyl structure for its high binding affinity, good metabolic stability, and good brain and CSF penetration profiles. Introduction of F on the phenyl group in **21g** effectively improved the metabolic stability, and the analogs **21j**, **21k** and **21l** were potent at Y5 and well penetrant to the brain and CSF. The 1-phenyl-3-pyrazolyl and 1-phenyl-4-pyrazolyl structures were combined with the 4-aza-isobenzofuranone structure, and **19e** and **19f** were potent at Y5 and metabolically stable. Compounds **19e** and **19f** were very CSF-penetrant (CSF/brain ratio = 0.15 and 0.18, respectively) although their brain/plasma ratios were less than those of the corresponding 6-azaisobenzofuranone analogs.

Compounds **19e**, **19f**, **21g**, **21j** and **21l** were evaluated for their inhibitory effects on the Y5-agonist [D-Trp[34]]NPY-induced food intake in rats as well as susceptibility to human and mouse P-glycoprotein (P-gp) transporters,[47,48] and the results are listed together with the data of **1** in Table 2. These compounds exhibited equally potent binding affinities to the rat Y5 receptor as well as the human Y5 receptor. A 1-phenyl-4-pyrazolyl analog **19f** was weak in the food intake assay, and its B-to-A/A-to-B ratio in the mouse P-gp transporter assay of 21.1 indicated this compound is a good substrate for the mouse P-gp transporter. Compound **19e** was the corresponding 3-pyrazolyl analog of **19f**, and its susceptibility to

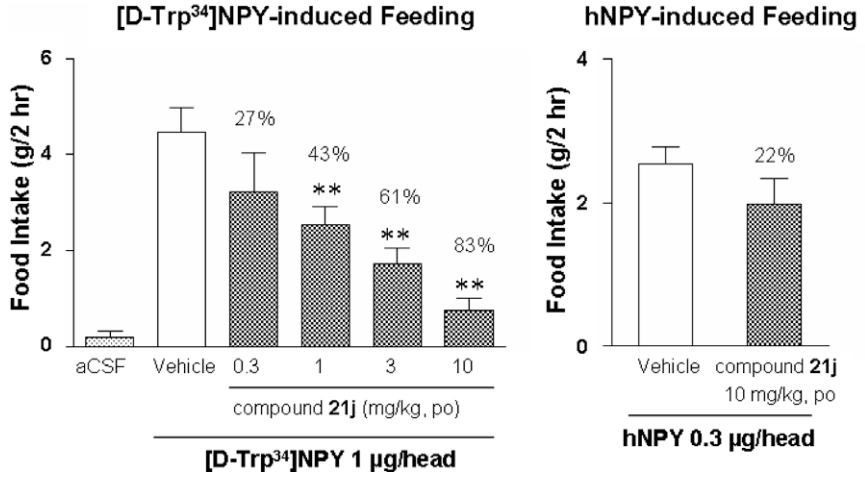


Figure 2. [D-Trp[34]]NPY-induced food intake of compound **21j** in SD rats. Compound **21j** was orally administered 2 h before the 3rdV-injection of the agonists. $^{**}p$ <0.01 versus vehicle-treated group (Dunnett). n = 8–18.

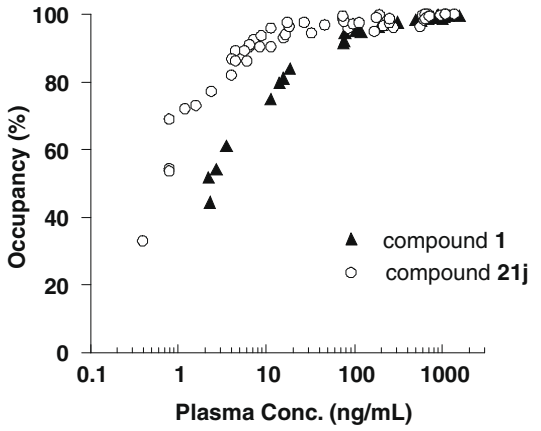


Figure 3. Receptor occupancy and plasma level data of compounds **1** and **21j**.

human and mouse P-gp transporters were very different from those of **19f**. In addition, **21g** was the corresponding 6-aza analog of **19f**, and a large difference in susceptibility to P-gp transporters was observed between **21g** and **19f**. It was interesting that such small structural alterations largely changed the susceptibility to P-gp transporters nevertheless these changes did not largely change their lipophilicity (Log $D_{7.4}$ = 2.80, 2.90 and 3.10 for **19e**, **19f** and **21g**, respectively). Compounds **19e**, **21g**, **21j** and **21l** were not good substrates for the human P-gp transporter. Of the compounds, **21j** most strongly inhibited [D-Trp^{34}]NPY-induced food intake with a minimum effective dose of 1 mg/kg po. In contrast, **21j** was very weak in inhibiting NPY-induced food intake, indicating that the inhibitory effect in [D-Trp^{34}]NPY-induced food intake was brought about by Y5 receptor-selective antagonism (Fig. 2). In the in vitro P-gp transporter assay, **21j** exhibited B-to-A/A-to-B ratios of 1.29 and 1.57 in human and mouse, respectively, indicating that this compound is a very poor substrate for the human and mouse P-gp transporters. Compound **21j** as well as **1** showed a strong inhibitory effect in the [D-Trp^{34}]NPY-induced food intake assay, and these compounds were poor substrates for both human and mouse P-gp transporters. Then, **21j** was compared with **1** in brain Y5 receptor occupancy studies in mice.[33] As shown in Figure 3, **1** and **21j** showed plasma level-dependent brain Y5 receptor occupancy. In order to produce almost complete receptor occupancy, 100–200 ng/mL plasma levels were required for **1** while 10–20 ng/mL plasma levels were required for **21j**. Assuming the plasma levels reflect systemic exposure, and a part of the adverse events, such as liver injury, would result from systemic exposure, **21j** is particularly attractive in that relatively lower plasma levels of 10–20 ng/mL produce almost complete receptor occupancy. Thus, **21j** was selected as a better Y5 antagonist for clinical proof-of-concept studies.

4. Conclusion

A series of *trans*-3-oxospiro[(aza)isobenzofuran-1(3*H*),1′-cyclohexane]-4′-carboxamide derivatives were synthesized. Of the compounds, *trans*-*N*-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro-[6-azaisobenzofuran-1(3*H*),1′-cyclohexane]-4′-carboxamide (**21j**) was very potent at the Y5 receptor, metabolically stable, and well brain- and CSF-penetrant, and oral administration of the compound significantly inhibited the Y5 agonist [D-Trp^{34}]NPY-induced food intake with a minimum effective dose of 1 mg/kg. Compound **21j** was very weak in inhibiting NPY-induced food intake in rats, indicating that the inhibitory effect in [D-Trp^{34}]NPY-induced food intake was attributable to the Y5-selective antagonism. Compound **21j** was a poor substrate for human and mouse P-gp transporters, and 10–20 ng/mL plasma levels of **21j** produced almost perfect brain Y5 receptor occupancy in mice. Compound **21j** was selected as a better Y5 antagonist than compound **1** for clinical proof-of-concept studies.

5. Experimental

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). ^{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) 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.

5.1. 3*H*,4′*H*-Spiro[4-aza-2-benzofuran-1,1′-cyclohexane]-3,4′-dione (10b)

n-Butyllithium (1.5 M in hexane, 500 mL, 750 mmol) was added dropwise to a solution of *N*-methylpyridine-2-carboxamide (**3**, 48.6 g, 357 mmol) in anhydrous tetrahydrofuran (1.5 L) below −50 °C under a nitrogen atmosphere. A solution of 1,4-cyclohexanedione mono-ethylene ketal (55.7 g, 357 mmol) in anhydrous tetrahydrofuran (0.25 L) was added to the solution at −50 to −10 °C. The mixture was poured into water (1 L), which was washed with hexane (1 L) and ether (0.5 L). The aqueous layer was adjusted to pH 3 with concd HCl, and the mixture was stirred for 1 h. The mixture was adjusted to pH 7 with K_2CO_3, and the produced solid was collected by filtration. The solid was taken into a mixture of 2 N HCl and acetone, and the mixture was refluxed for 15 h. After being cooled to room temperature, the mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was crystallized (EtOAc/hexane) to yield 28.3 g (62%) of the desired compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.11–2.22 (m, 2H), 2.37–2.58 (m, 4H), 2.93–3.08 (m, 2H), 7.60 (dd, J = 7.9, 4.7 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 8.97 (d, J = 4.7 Hz, 1H); MS (ESI) m/z = 218 [M+H]$^+$.

5.2. 3*H*,4′*H*-Spiro[2-benzofuran-1,1′-cyclohexane]-3,4′-dione (10a)

Compound **10a** was prepared from the corresponding starting material **2** in a manner similar to that described for **10b** as a yellow solid in 38% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.08–2.21 (m, 2H), 2.34–2.58 (m, 4H), 2.92–3.07 (m, 2H), 7.40 (d, J = 7.1 Hz, 1H), 7.59 (t, J = 7.1 Hz, 1H), 7.72 (t, J = 7.1 Hz, 1H), 7.96 (d, J = 7.1 Hz, 1H); MS (ESI) m/z = 217 [M+H]$^+$.

5.3. 3*H*,4′*H*-Spiro[7-aza-2-benzofuran-1,1′-cyclohexane]-3,4′-dione (10e)

Compound **10e** was prepared from the nitrile **6** in a manner similar to that described for **10b** as a yellow solid in 39% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.09–2.11 (m, 2H), 2.52–2.70 (m, 4H), 2.82–2.98 (m, 2H), 7.53 (dd, J = 7.9, 4.7 Hz, 1H), 8.32 (d, J = 7.9 Hz, 1H), 8.88 (d, J = 4.7 Hz, 1H); MS (ESI) m/z = 218 [M+H]$^+$.

5.4. 3*H*,4′*H*-Spiro[5-aza-2-benzofuran-1,1′-cyclohexane]-3,4′-dione (10c)

n-Butyllithium (1.6 M in hexane, 500 mL, 800 mmol) was added to a solution of 2,2,6,6-tetramethylpiperidine (81 mL, 480 mmol) in anhydrous tetrahydrofuran (1.6 L) at −40 °C under a nitrogen atmosphere, and nicotinic acid (**4**, 39.4 g, 320 mmol) was added to the solution after 5 min. The mixture was stirred at the same temperature for 1 h. To the mixture was added dropwise a solution of 1,4-cyclohexanedione mono-ethylene ketal (50 g, 320 mmol) in anhydrous tetrahydrofuran (370 mL) at −40 °C. After being stirred at −40 °C for 30 min, the mixture was allowed to warm to room temperature and poured into water, which was extracted with diethyl ether. The aqueous layer was acidified (about pH 3) with 6 N hydrochloric acid. The mixture was stirred at room temperature for 15 h to produce precipitate. The precipitate was collected by filtration, taken into satd sodium hydrogencarbonate, which was extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residual solid was washed with ethyl acetate/hexane = 1/1 to afford 28.45 g of crude 3*H*-dispiro[5-aza-2-benzofuran-1,1′-cyclohexane-4′,2″-[1,3]dioxolan]-3-one as a pale brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.77–1.89 (m, 4H), 2.09–2.31 (m, 4H), 3.98–4.08 (m, 4H), 7.42 (d, J = 5.1 Hz, 1H), 8.84 (d, J = 5.1 Hz, 1H), 9.15 (S, 1H); MS (ESI) m/z = 296 $[M+H]^+$.

2 N Hydrochloric acid (109 mL, 218 mmol) was added to a mixture of the ketal (28.45 g, 109 mmol) in acetone (31 mL). The mixture was stirred under reflux for 2 days, cooled to room temperature, neutralized with potassium carbonate, and extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residual solid was washed with ethyl acetate/hexane = 1/1 to afford 21.17 g of the title compound as pale brown solid in 30% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.09–2.23 (m, 2H), 2.31–2.62 (m, 4H), 2.89–3.08 (m, 2H), 7.40 (d, J = 5.1 Hz, 1H), 8.90 (d, J = 5.1 Hz, 1H), 9.21 (s, 1H); MS (ESI) m/z = 218 $[M+H]^+$.

5.5. 7-Chloro-3*H*-dispiro[6-aza-2-benzofuran-1,1′-cyclohexane-4′,2″-[1,3]dioxolane]-3-one (8)

n-Butyllithium (2.46 M in hexane, 427 mL, 1.05 mol) was added to a solution of 2,2,6,6-tetramethylpiperidine (177 mL, 1.05 mol) in anhydrous tetrahydrofuran (1.25 L) at −50 to −45 °C under a nitrogen atmosphere, and 2-chloroisonicotinic acid (**7**, 78.8 g, 0.500 mol) was added to the mixture after 20 min. The mixture was stirred at the same temperature for 3.5 h. To the mixture was added dropwise a solution of 1,4-cyclohexanedione mono-ethylene ketal (78.1 g, 0.500 mol) in anhydrous tetrahydrofuran (0.25 L) at −55 to −50 °C. After being stirred at −50 °C for 10 min, the mixture was allowed to warm to −30 °C, and 2 N hydrochloric acid (525 mL, 1.05 mol) was added dropwise. The mixture was stirred for additional 30 min at 15 °C, poured into water (0.50 L), which was extracted with ethyl acetate (0.75 L × 2). The combined organic layers were washed with 1 N hydrochloric acid (1.2 L), saturated aqueous NaHCO3 (1.0 L) and brine (0.50 L) successively, dried over magnesium sulfate, filtered and concentrated in vacuo. The residual solid was stirred in ethanol/hexane = 1/3 (0.4 L) at room temperature overnight. The solid was collected by filtration and washed with ethanol/hexane = 1/3 (0.4 L) to afford 72.4 g (49%) of the title compound as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.64–1.72 (m, 2H), 1.81–1.89 (m, 2H), 2.14 (dt, J = 13.5, 4.5 Hz, 2H), 2.86 (dt, J = 13.5, 4.5 Hz, 2H), 4.03 (s, 4H), 7.73 (d, J = 4.9 Hz, 1H), 8.62 (d, J = 4.9 Hz, 1H); MS (ESI) m/z = 296 $[M+H]^+$.

5.6. 3*H*-Dispiro[6-aza-2-benzofuran-1,1′-cyclohexane-4′,2″-[1,3]dioxolane]-3-one (9)

To a solution of 7-Chloro-3*H*-dispiro[6-aza-2-benzofuran-1,1′-cyclohexane-4′,2″-[1,3]dioxolane]-3-one (**8**, 72.4 g, 245 mmol) and triethylamine (51 mL, 367 mmol) in tetrahydrfuran (0.5 L) was added 10% palladium on activated carbon (7.2 g, type M, water ~50%, Pd 10%, dry weight basis) under a nitrogen atmosphere. The reaction mixture was stirred for 5.5 h under a hydrogen atmosphere at room temperature, diluted with ethyl acetate (0.5 L) and filtered through a Celite pad to remove the catalyst and triethylammonium chloride. The filtrate was concentrated in vacuo to afford 64.0 g (100%) of the title compound as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.80–1.89 (m, 4H), 2.14 (dt, J = 14.0, 4.0 Hz, 2H), 2.34 (dt, J = 14.0, 4.0 Hz, 2H), 4.00–4.06 (m, 4H), 7.76 (dd, J = 4.9, 1.3 Hz, 1H), 8.85 (d, J = 4.9 Hz, 1H), 8.89 (d, J = 1.3 Hz, 1H); MS (ESI) m/z = 262 $[M+H]^+$.

5.7. 3*H*,4′*H*-Spiro[6-aza-2-benzofuran-1,1′-cyclohexane]-3,4′-dione (10d)

A solution of 3*H*-dispiro[6-aza-2-benzofuran-1,1′-cyclohexane-4′,2″-[1,3]dioxolane]-3-one (**9**, 64.0 g, 245 mmol) and *p*-toluenesulfonic acid monohydrate (9.3 g, 49.0 mmol) in acetone (0.70 L) and water (0.70 L) was heated overnight at 70 °C, and then acetone was removed in vacuo. The residual aqueous solution was neutralized by addition of $NaHCO_3$ (4.2 g, 50 mmol) and extracted with ethyl acetate (0.60 L + 0.30 L × 2). The combined organic layers were washed with brine (0.30 L), dried over magnesium sulfate, filtered and concentrated in vacuo to afford 48.3 g (91%) of the title compound as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.14–2.24 (m, 2H), 2.49 (dt, J = 14.0, 5.0 Hz, 2H), 2.51–2.60 (m, 2H), 2.95 (dt, J = 14.0, 5.0 Hz, 2H), 7.82 (d, J = 5.0 Hz, 1H), 8.88 (s, 1H), 8.91 (d, J = 5.0 Hz, 1H); MS (ESI) m/z = 218 $[M+H]^+$.

5.8. *cis*-4′-Hydroxy-3*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexan]-3-one (11d)

Sodium borohydride (6.73 g, 178 mmol) was added slowly to a suspension of 3*H*,4′*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexane]-3,4′-dione (**10d**, 48.3 g, 222 mmol) in anhydrous ethanol (0.4 L) below −10 °C. The reaction mixture was stirred for 1 h at 0 °C, and then saturated aqueous ammonium chloride (400 mL) was added slowly to the mixture at 0 °C. The mixture was diluted with water and extracted with chloroform (0.80 L + 0.40 L × 2). The combined organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. The residual solid was stirred in ethanol/hexane = 1/2 (0.30 L) overnight at room temperature. The solid was collected by filtration and washed with ethanol/hexane = 1/2 (0.3 L) to afford 37.5 g (77%) of the title compound as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.56 (dq, J = 13.5, 3.6 Hz, 2H), 1.70–1.82 (m, 2H), 1.84–1.94 (m, 2H), 2.15 (dt, J = 13.5, 4.0 Hz, 2H), 3.66 (tt, J = 10.7, 4.3 Hz, 1H), 7.81 (dd, J = 5.0, 1.3 Hz, 1H), 8.84 (d, J = 5.0 Hz, 1H), 9.10 (d, J = 1.3 Hz, 1H); MS (ESI) m/z = 220 $[M+H]^+$.

5.9. *cis*-4′-Hydroxy-3*H*-spiro[2-benzofuran-1,1′-cyclohexan]-3-one (11a)

Compound **11a** was prepared from **10a** in a manner similar to that described for **11d** as a white solid in 76% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.59 (d, J = 6.1 Hz, 1H), 1.78–2.11 (m, 8H), 3.77–3.89 (m, 1H), 7337 (d, J = 7.1 Hz, 1H), 7.52 (t, J = 7.1 Hz, 1H), 7.67 (t, J = 7.1 Hz, 1H), 7.89 (d, J = 7.1 Hz, 1H); MS (ESI) m/z = 219 $[M+H]^+$.

5.10. *cis*-4′-Hydroxy-3*H*-spiro[5-aza-2-benzofuran-1,1′-cyclohexan]-3-one (11c)

Lithium tri-*tert*-butoxyaluminohydride (1.0 M in tetrahydrofuran, 117 mL, 117 mmol) was added dropwise to a suspension of 3*H*,4′*H*-spiro[5-aza-2-benzofuran-1,1′-cyclohexane]-3,4′-dione (**10c**, 21.17 g, 97.4 mmol) in anhydrous tetrahydrofuran (500 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 30 min and quenched with 2 N hydrochloric acid. Tetrahydrofuran was evaporated in vacuo. The residue was adjusted to pH 3 with potassium carbonate and extracted with chloroform. The organic layer was dried over magnesium sulfate. The solvent was evaporated to give 20.20 g (94%) of the title compound as a pale brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.80–2.15 (m, 8H), 3.80–3.90 (m, 1H), 7.38 (d, J = 5.1 Hz, 1H), 8.86 (d, J = 5.1 Hz, 1H), 9.15 (s, 1H); MS (ESI) m/z = 220 $[M+H]^+$.

5.11. *cis*-4′-Hydroxy-3*H*-spiro[4-aza-2-benzofuran-1,1′-cyclohexan]-3-one (11b)

Compound **11b** was prepared from ketone **10b** in a manner similar to that described for **11c** as a yellow solid in 87% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.81–2.11 (m, 8H), 3.78–3.90 (m, 1H), 7.55 (dd, J = 7.8, 4.8 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 8.90 (d, J = 4.8 Hz, 1H); MS (ESI) m/z = 220 $[M+H]^+$.

5.12. *cis*-4′-Hydroxy-3*H*-spiro[7-aza-2-benzofuran-1,1′-cyclohexan]-3-one (11e)

Compound **11e** was prepared from ketone **10e** in a manner similar to that described for **11c** as a yellow solid in 98% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.55–1.62 (m, 2H), 1.80–1.98 (m, 3H), 2.09–2.31 (m, 3H), 3.81–3.96 (m, 1H), 7.49 (dd, J = 7.9, 4.7 Hz, 1H), 8.30 (d, J = 7.9 Hz, 1H), 8.90 (d, J = 4.7 Hz, 1H); MS (ESI) m/z = 220 $[M+H]^+$.

5.13. *trans*-3-Oxo-3*H*-spiro[6-aza-2–2-benzofuran-1,1′-cyclohexane]-4′-carbonitrile (12d)

Methanesulfonyl chloride (16.1 mL, 207 mmol) was added dropwise to a solution of *cis*-4′-hydroxy-3*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexan]-3-one (**11d**, 37.5 g, 171 mmol) and triethylamine (34.1 mL, 244 mmol) in anhydrous dimethylformamide (0.40 L) below 4 °C. The mixture was stirred at 0 °C for 10 min, diluted with ethyl acetate (0.80 L) and washed with water (0.80 L). The aqueous layer was extracted with ethyl acetate (0.40 L + 0.40 L). The combined organic layers were washed with water (0.40 L), saturated aqueous $NaHCO_3$ (0.40 L) and brine (0.30 L) successively, dried over magnesium sulfate and silica gel (40 g, Wakogel C-300, WAKO), filtered and concentrated in vacuo to afford 41.3 g (81%) of *cis*-3-oxo-3*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexan]-4′-yl methanesulfonate as a pale brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.92–2.00 (m, 2H), 2.11 (dt, J = 12.0, 4.3 Hz, 2H), 2.15–2.32 (m, 4H), 3.07 (s, 3H), 4.89 (tt, J = 10.0, 5.0 Hz, 1H), 7.77 (dd, J = 5.0, 1.0 Hz, 1H), 8.84 (d, J = 1.0 Hz, 1H), 8.87 (d, J = 5.0 Hz, 1H); MS (ESI) m/z = 298 $[M+H]^+$.

Tetraethylammmonium cyanide (28.2 g, 180 mmol) was added to a solution of the methanesulfonate (41.3 g, 139 mmol) in anhydrous dioxane (0.30 L). The mixture was heated at 100 °C for 3 h, and then ca. 150 mL of dioxane was removed in vacuo. The mixture was diluted with ethyl acetate (0.60 L) and washed with water (0.60 mL). The aqueous layer was extracted with ethyl acetate (0.30 L × 2). The combined organic layers were washed with water (0.50 L) and brine (0.30 L) successively, dried over magnesium sulfate, filtered through a short pad of silica gel column (40 g, Wakogel C-300, WAKO) and concentrated in vacuo. The residual solid was stirred in methanol (80 mL) overnight at room temperature. The solid was collected by filtration and washed with methanol (80 mL) to afford 18.6 g (59%) of the title compound as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.80–1.88 (m, 2H), 2.08–2.19 (m, 2H), 2.20 (tt, J = 13.5, 3.5 Hz, 2H), 2.37 (dt, J = 13.5, 4.5 Hz, 2H), 3.15–3.21 (m, 1H), 7.78 (dd, J = 5.0, 1.2 Hz, 1H), 8.90 (d, J = 5.0 Hz, 1H), 8.95 (d, J = 1.2 Hz, 1H); MS (ESI) m/z = 229 $[M+H]^+$.

5.14. *trans*-3-Oxo-3*H*-spiro[2-benzofuran-1,1′-cyclohexane]-4′-carbonitrile (12a)

Compound **12a** was prepared from the corresponding alcohol **11a** in a manner similar to that described for **12d** as a white solid in 79% yield.

5.15. *trans*-3-Oxo-3*H*-spiro[4-aza-2–2-benzofuran-1,1′-cyclohexane]-4′-carbonitrile (12b)

Compound **12b** was prepared from the corresponding alcohol **11b** in a manner similar to that described for **12d** as a white solid in 45% yield.

5.16. *trans*-3-Oxo-3*H*-spiro[5-aza-2–2-benzofuran-1,1′-cyclohexane]-4′-carbonitrile (12c)

Compound **12c** was prepared from the corresponding alcohol **11c** in a manner similar to that described for **12d** as a white solid in 58% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.78–1.86 (m, 2H), 2.06–2.36 (m, 6H), 3.15–3.21 (m, 1H), 7.49 (d, J = 5.1 Hz, 1H), 8.91 (d, J = 5.1 Hz, 1H), 9.185 (s, 1H); MS (ESI) m/z = 229 $[M+H]^+$.

5.17. *trans*-3-Oxo-3*H*-spiro[7-aza-2–2-benzofuran-1,1′-cyclohexane]-4′-carbonitrile (12e)

Compound **12e** was prepared from the corresponding alcohol **11e** in a manner similar to that described for **12d** as a white solid in 33% yield.

5.18. *trans*-3-Oxo-3*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxylic acid (16)

A solution of *trans*-3-oxo-3*H*-spiro[2-benzofuran-1,1′-cyclohexane]-4′-carbonitrile (**12d**, 18.5 g, 81.1 mmol) in 47% sulfuric acid (90 mL, 548 mmol) and water (30 mL) was heated at 100 °C for 48 h. After cooling to room temperature, the mixture was adjusted to pH 4 with 5 N sodium hydroxide to produce precipitate. The precipitate was collected by filtration and washed with water to afford 18.4 g (92%) of the title compound as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.76–1.85 (m, 2H), 1.90–2.11 (m, 6H), 2.68–2.74 (m, 1H), 7.84 (dd, J = 5.0, 1.0 Hz, 1H), 8.87 (d, J = 5.0 Hz, 1H), 9.06 (d, J = 1.0 Hz, 1H), 12.35 (br s, 1 H); MS (ESI) m/z = 248 $[M+H]^+$.

5.19. *trans*-3-Oxo-3*H*-spiro[2-benzofuran-1,1′-cyclohexane]-4′-carboxylic acid (13)

Compound **13** was prepared from the corresponding carbonitrile **12a** in a manner similar to that described for **16** as a white solid in 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.68–1.87 (m, 2H), 2.03–2.37 (m, 6H), 3.13–3.20 (m, 1H), 7.49 (d, J = 7.1 Hz, 1H), 7.56 (t, J = 7.1 Hz, 1H), 7.73 (t, J = 7.1 Hz, 1H), 7.91 (d, J = 7.1 Hz, 1H); MS (ESI) m/z = 247 $[M+H]^+$.

5.20. *trans*-3-Oxo-3*H*-spiro[4-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxylic acid (14)

Compound **14** was prepared from the corresponding carbonitrile **12b** in a manner similar to that described for **16** as a white solid in 90% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.64–1.82 (m, 2H), 1.90–2.06 (m, 6H), 2.64–2.74 (m, 1H), 7.72 (dd, J = 7.9, 4.7 Hz, 1H), 8.20 (d, J = 7.9 Hz, 1H), 8.85 (d, J = 4.7 Hz, 1H); MS (ESI) m/z = 248 $[M+H]^+$.

5.21. *trans*-3-Oxo-3*H*-spiro[5-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxylic acid (15)

Compound **15** was prepared from the corresponding carbonitrile **12c** in a manner similar to that described for **16** as a white solid in 92% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.67–1.81 (m, 2H), 1.86–2.10 (m, 6H), 2.68–2.75 (m, 1H), 7.77 (d, J = 5.1 Hz, 1H), 8.86 (d, J = 5.1 Hz, 1H), 9.06 (s, 1H); MS (ESI) m/z = 248 $[M+H]^+$.

5.22. *trans*-3-Oxo-3*H*-spiro[7-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxylic acid (17)

Compound **17** was prepared from the corresponding carbonitrile **12e** in a manner similar to that described for **16** as a white solid in 90% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.73–1.85 (m, 2H), 1.85–1.99 (m, 2H), 1.99–2.13 (m, 2H), 2.14–2.27 (m, 2H), 2.64–2.73 (m, 1H), 7.65 (dd, J = 7.8, 4.8 Hz, 1H), 8.30 (d, J = 7.8 Hz, 1H), 8.90 (d, J = 4.8 Hz, 1H); MS (ESI) m/z = 248 $[M+H]^+$.

5.23. *trans*-*N*-[1-(2-Fluorophenyl)-1*H*-pyrazol-3-yl]-3-oxo-3*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (21j)

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (14.0 g, 0.073 mol) was added to a mixture of *trans*-3-oxo-3*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxylic acid (**16**) (15.9 g, 0.064 mol) and 3-amine-1-(2-fluorophenyl)-1*H*-pyrazole (12.0 g, 0.068 mol) in pyridine (100 mL), and the mixture was stirred overnight. The reaction mixture was poured into a mixture of H_2O (1 L) and EtOAc (250 mL), and the mixture was stirred for 30 min. Precipitate was collected by filtration to yield 17.45 g (67%) of the title compound as a white solid. The filtrate was separated, and the organic layer was washed with 10% citric acid (300 mL + 200 mL), satd $NaHCO_3$ (200 mL) and brine (200 mL), dried over MgSO4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAc/hexane), and crystallized from EtOAc to yield 4.34 g (17%) of the title compound as a white solid. Mp: 238–239 °C (EtOAc); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.8–2.2 (m, 8H), 2.7–2.9 (m, 1H), 6.91 (d, J = 2.6 Hz, 1H), 7.3–7.5 (m, 3H), 7.7–7.8 (m, 1H), 7.87 (dd, J = 4.9, 1.1 Hz, 1H), 8.11 (t, J = 2.6 Hz, 1 H), 8.89 (d, J = 4.9 Hz, 1H), 9.13 (d, J = 1.1 Hz, 1H), 10.82 (br s, 1H); HRMS (ESI) m/z = 407.1517 $[M+H]^+$ ($C_{22}H_{19}FN_4O_3$ requires: 407.1519). Elemental Anal. Calcd: C, 65.02; H, 4.71; N, 13.79. Found: C, 64.88; H, 4.59; N, 13.70.

5.24. *trans*-3-Oxo-*N*-(5-phenylpyrazin-2-yl)-3*H*-spiro[2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (18)

Compound **18** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 73% yield. Mp: 223–225 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.75–2.30 (m, 8H), 2.93–2.95 (m, 1H), 7.30–7.90 (m, 9H), 8.20–8.60 (m, 3H), 9.05 (d, J = 1.2 Hz, 1H), 9.46 (d, J = 1.2, 1H), 10.93 (s, 1H); HRMS (ESI) m/z = 400.1655 $[M+H]^+$ ($C_{24}H_{21}N_3O_3$ requires: 400.1661).

5.25. *trans*-3-Oxo-*N*-(5-phenylpyrazin-2-yl)-3*H*-spiro[4-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (19a)

Compound **19a** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 58% yield. Mp: 237–239 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.84–1.92 (m, 2H), 2.12–2.20 (m, 6H), 2.93–2.97 (m, 1H), 7.45–7.55 (m, 3H), 7.76 (dd, J = 7.9, 4.7 Hz, 1H), 8.09 (dd, J = 8.0, 1.3 Hz, 2H), 8.25 (dd, J = 8.0, 1.3 Hz, 1H), 8.89 (dd, J = 4.6, 1.3 Hz, 1H), 9.01(d, J = 1.5 Hz, 1H), 9.46 (d, J = 1.5 Hz, 1H), 10.94 (s, 1H); HRMS (ESI) m/z = 401.1607 $[M+H]^+$ ($C_{23}H_{20}N_4O_3$ requires: 401.1614).

5.26. *trans*-3-Oxo-*N*-(5-phenylpyrimidin-2-yl)-3*H*-spiro[4-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (19b)

Compound **19b** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 35% yield. Mp: 237–239 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.82–1.89 (m, 2H), 1.97–2.06 (m, 4H), 2.12–2.19 (m, 2H), 2.99–3.04 (m, 1H), 7.43–7.54 (m, 3H), 7.73–7.80 (m, 3H), 8.21 (dd, J = 7.9, 1.2 Hz, 1H), 8.88 (dd, J = 4.7, 1.2 Hz, 1H), 9.00 (s, 2H), 10.77 (s, 1H); HRMS (ESI) m/z = 401.1610 $[M+H]^+$ ($C_{23}H_{20}N_4O_3$ requires: 401.1614).

5.27. *trans*-3-Oxo-*N*-(5-phenylisoxazol-3-yl)-3*H*-spiro[4-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (19c)

Compound **19c** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 84% yield. Mp: 260–262 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.87–2.00 (m, 2H), 2.19–2.50 (m, 6H), 2.96–3.08 (m, 1H), 7.37 (s, 1H), 7.48–7.64 (m, 4H), 7.78–7.88 (m, 2H), 8.01 (d, J = 7.2 Hz, 1H), 8.91 (dd, J = 4.8, 1.5 Hz, 1H), 10.00 (br s, 1H); HRMS (ESI) m/z = 390.1460 $[M+H]^+$ ($C_{22}H_{19}N_3O_4$ requires: 390.1454).

5.28. *trans*-3-Oxo-*N*-(3-phenyl-1*H*-pyrazol-5-yl)-3*H*-spiro[4-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (19d)

Compound **19d** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white amorphous solid in 24% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.83–1.90 (m, 2H), 1.97–2.02 (m, 4H), 2.10–2.17 (m, 2H), 2.78–2.79 (m, 1H), 6.97 (d, J = 1.7 Hz, 1H), 7.33–7.37 (m, 1H), 7.42–7.48 (m, 2H), 8.22 (d, J = 7.3 Hz, 1H), 8.87–8.90 (m, 1H), 10.50 (s, 1H); HRMS (ESI) m/z = 401.1610 $[M+H]^+$ ($C_{23}H_{20}N_4O_3$ requires: 401.1614).

5.29. *trans*-3-Oxo-*N*-(1-phenyl-1*H*-pyrazol-3-yl)-3*H*-spiro[4-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (19e)

Compound **19e** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 71% yield. Mp: 204–206 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.8–2.2 (m, 8H), 2.75–2.85 (m, 1H), 6.86 (d, J = 2.4 Hz, 1H), 7.2–7.3 (m, 1H), 7.4–7.55 (m, 2H), 7.7–7.8 (m, 3H), 8.23 (d, J = 8.0 Hz, 1H), 8.41 (d, J = 2.4 Hz, 1H), 8.85–8.9 (m, 1H), 10.78 (br s, 1H); HRMS (ESI) m/z = 389.1609 $[M+H]^+$ ($C_{22}H_{20}N_4O_3$ requires: 389.1614).

5.30. *trans*-3-Oxo-*N*-(1-phenyl-1*H*-pyrazol-4-yl)-3*H*-spiro[4-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (19f)

Compound **19f** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 63% yield. Mp: 225–227 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.8–2.2 (m, 8H), 2.7–2.8 (m, 1H), 7.25–7.3 (m, 1H), 7.4–7.55

(m, 2H), 7.7–7.8 (m, 3H), 8.21 (d, J = 7.2 Hz, 1H), 8.56 (s, 1H), 8.88 (d, J = 4.6 Hz, 1H), 10.22 (br s, 1H); HRMS (ESI) m/z = 389.1611 $[M+H]^+$ ($C_{22}H_{20}N_4O_3$ requires: 389.1614).

5.31. *trans*-3-Oxo-*N*-(5-phenylpyrazin-2-yl)-3*H*-spiro[5-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (20a)

Compound **20a** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a pale yellow solid in 43% yield. Mp: 269–271 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.80–1.96 (m, 2H), 1.98–2.22 (m, 6H), 2.95 (m, 1H), 7.40–7.56 (m, 3H), 7.82 (dd, J = 5.2, 1.0 Hz, 1H), 8.06–8.13 (m, 2H), 8.91 (d, J = 5.2 Hz, 1H), 9.00 (d, J = 1.5 Hz, 1H), 9.09 (d, J = 1.0 Hz, 1H), 9.46 (d, J = 1.5 Hz, 1H), 10.93 (s, 1H); HRMS (ESI) m/z = 401.1609 $[M+H]^+$ ($C_{23}H_{20}N_4O_3$ requires: 401.1614).

5.32. *trans*-3-Oxo-*N*-(5-phenylpyrimidin-2-yl)-3*H*-spiro[5-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (20b)

Compound **20b** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 20% yield. Mp: 219–221 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.80–1.92 (m, 2H), 1.93–2.22 (m, 6H), 3.02 (m, 1H), 7.40–7.56 (m, 3H), 7.72–7.81 (m, 3H), 8.90 (d, J = 5.2 Hz, 1H), 9.00 (s, 2H), 9.08 (d, J = 1.0 Hz, 1H), 10.77 (s, 1H); HRMS (ESI) m/z = 401.1607 $[M+H]^+$ ($C_{23}H_{20}N_4O_3$ requires: 401.1614).

5.33. *trans*-3-Oxo-*N*-(3-phenyl-1*H*-pyrazol-5-yl)-3*H*-spiro[5-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (20c)

Compound **20c** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white amorphous solid in 24% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.80–2.20 (m, 8H), 2.79 (m, 1H), 6.97 (br s, 1H), 7.34 (m, 1H), 7.40–7.50 (m, 2H), 7.72 (d, J = 7.3 Hz, 2H), 7.78 (dd, J = 5.2, 1.0 Hz, 1H), 8.91 (d, J = 5.2 Hz, 1H), 9.09 (d, J = 1.0 Hz, 1H), 10.49 (br s, 1H), 12.82 (br s, 1H); HRMS (ESI) m/z = 401.1608 $[M+H]^+$ ($C_{23}H_{20}N_4O_3$ requires: 401.1614).

5.34. *trans*-3-Oxo-*N*-(5-phenylpyrazin-2-yl)-3*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (21a)

Compound **21a** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 44% yield. Mp: 239–241 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.88–1.94 (m, 2H), 2.25–2.45 (m, 6H), 2.84–2.88 (m, 1H), 7.46–7.54 (m, 3H), 7.78 (dd, J = 5.0, 1.1 Hz, 1H), 7.99–8.01 (m, 3H), 8.70 (d, J = 1.5 Hz, 1H), 8.89 (d, J = 4.9 Hz, 1H), 9.05 (d, J = 0.8 Hz, 1H), 9.63 (s, 1H); HRMS (ESI) m/z = 401.1621 $[M+H]^+$ ($C_{23}H_{20}N_4O_3$ requires: 401.1614).

5.35. *trans*-3-Oxo-*N*-(5-phenylpyrimidin-2-yl)-3*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (21b)

Compound **21b** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 13% yield. Mp: 193–195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.81–1.90 (m, 2H), 2.04–2.30 (m, 4H), 2.47–2.58 (m, 2H), 3.22 (m, 1H), 7.45–7.58 (m, 5H), 7.77 (dd, J = 5.0, 1.3 Hz, 1H), 8.18 (br s, 1H), 8.85 (s, 2H), 8.87 (d, J = 5.0 Hz, 1H), 9.03 (d, J = 1.3 Hz, 1H); HRMS (ESI) m/z = 401.1615 $[M+H]^+$ ($C_{23}H_{20}N_4O_3$ requires: 401.1614).

5.36. *trans*-3-Oxo-*N*-(5-phenylisoxazol-3-yl)-3*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (21c)

Compound **21c** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 76% yield. Mp: 262–264 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.89–1.99 (m, 2H), 2.23–2.49 (m, 6H), 2.95–3.03 (m, 1H), 7.40 (s, 1H), 7.50–7.58 (m, 3H), 7.78–7.88 (m, 3H), 8.88 (d, J = 5.1 Hz, 1H), 9.04 (d, J = 0.9 Hz, 1H), 9.86 (br s, 1H); HRMS (ESI) m/z = 390.1456 $[M+H]^+$ ($C_{22}H_{19}N_3O_4$ requires: 390.1454).

5.37. *trans*-3-Oxo-*N*-(3-phenyl-1*H*-pyrazol-5-yl)-3*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (21d)

Compound **21d** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 33% yield. Mp: 196–198 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.87–2.26 (m, 8H), 2.72–2.79 (m, 1H), 6.98 (s, 1H), 7.34–7.36 (m, 1H), 7.42–7.48 (m, 2H), 7.71–7.73 (m, 2H), 7.87 (dd, J = 5.0, 1.1 Hz, 1H), 8.89 (d, J = 5.0 Hz, 1H), 9.12 (s, 1H), 10.50 (br s, 1H), 12.82 (br s, 1H); HRMS (ESI) m/z = 401.1609 $[M+H]^+$ ($C_{23}H_{20}N_4O_3$ requires: 401.1614).

5.38. *trans*-3-Oxo-*N*-(5-phenylpyridin-2-yl)-3*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (21e)

Compound **21e** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 54% yield. Mp: 238–239 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.80–1.98 (m, 2H), 2.14–2.51 (m, 6H), 2.73–2.88 (m, 1H), 7.41 (d, J = 6.9 Hz, 1H), 7.48 (dd, J = 7.5, 6.9 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.77 (dd, J = 5.1, 0.9 Hz, 1H), 7.97 (dd, J = 8.8, 2.4 Hz, 1H), 8.15 (br s, 1H), 8.33 (d, J = 8.7 Hz, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.88 (d, J = 5.1 Hz, 1H), 9.04 (d, J = 0.9 Hz, 1H); HRMS (ESI) m/z = 400.1664 $[M+H]^+$ ($C_{24}H_{21}N_3O_3$ requires: 400.1661).

5.39. *trans*-3-Oxo-*N*-(2-phenyl-1,3-thiazol-4-yl)-3*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (21f)

Compound **21f** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a pale yellow solid in 65% yield. Mp: 288–289 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.82–2.23 (m, 8H), 2.80–2.91 (m, 1H), 7.44–7.56 (m, 3H), 7.71 (s, 1H), 7.83–7.97 (m, 3H), 8.88 (d, J = 5.0 Hz, 1H), 9,12 (s, 1H), 11.2 (s, 1H); HRMS (ESI) m/z = 406.1232 $[M+H]^+$ ($C_{22}H_{19}N_3O_3S$ requires: 406.1225).

5.40. *trans*-3-Oxo-*N*-(1-phenyl-1*H*-pyrazol-3-yl)-3*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (21g)

Compound **21g** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 86% yield. Mp: 249–250 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.85–2.2 (m, 8H), 2.75–2.85 (m, 1H), 6.86 (d, J = 2.5 Hz, 1H), 7.2–7.3 (m, 1H), 7.4–7.55 (m, 2H), 7.7–7.8 (m, 2H), 7.87 (dd, J = 4.9, 1.0 Hz, 1H), 8.42 (d, J = 2.5 Hz, 1H), 8.89 (d, J = 4.9 Hz, 1H), 9.13 (s, 1H), 10.79 (br s, 1H); HRMS (ESI) m/z = 389.1612 $[M+H]^+$ ($C_{22}H_{20}N_4O_3$ requires: 389.1614).

5.41. *trans*-3-Oxo-*N*-(1-phenyl-1*H*-pyrazol-4-yl)-3*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (21h)

Compound **21h** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white amorphous solid in 98% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.85–2.2 (m, 8H), 2.8–2.9 (m, 1H), 7.28 (t, J = 7.3 Hz, 1H),

7.45–7.50 (m, 2H), 7.75–7.85 (m, 3H), 7.87 (d, J = 5.1 Hz, 1H), 8.59 (s, 1H), 8.89 (d, J = 5.1 Hz, 1H), 9.11 (s, 1H), 10.23 (s, 1H); HRMS (ESI) m/z = 389.1606 $[M+H]^+$ ($C_{22}H_{20}N_4O_3$ requires: 389.1614).

5.42. *trans*-3-Oxo-*N*-(2-phenyl-2*H*-1,2,3-triazol-4-yl)-3*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (21i)

Compound **21i** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 89% yield. Mp: 231–232 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.80–1.90 (m, 2H), 2.15–2.50 (m, 6H), 2.80–2.90 (m, 1H), 7.30–7.40 (m, 1H), 7.45–7.55 (m, 2H), 7.78 (dd, J = 1.2 Hz, 4.9 Hz, 1H), 7.95–8.00 (m, 2H), 8.07 (br s, 1H), 8.30 (s, 1H), 8.88 (d, J = 4.9 Hz, 1H), 9.03 (d, J = 1.0 Hz, 1H); HRMS (ESI) m/z = 390.1554 $[M+H]^+$ ($C_{21}H_{19}N_5O_3$ requires: 390.1566).

5.43. *trans*-*N*-[1-(4-Fluorophenyl)-1*H*-pyrazol-3-yl]-3-oxo-3*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (21k)

Compound **21k** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 60% yield. Mp: 257–259 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.80–2.25 (m, 8H), 2.70–2.90 (m, 1H), 6.86 (d, J = 2.5 Hz, 1H), 7.33 (t, J = 8.8 Hz, 2H), 7.71–7.83 (m, 2H), 7.88 (dd, J = 10.5, 4.9 Hz, 1H), 8.38 (d, J = 2.5 Hz, 1H), 8.88 (d, J = 4.9 Hz, 1H), 9.13 (s, 1H), 10.8 (s, 1H); HRMS (ESI) m/z = 407.1516 $[M+H]^+$ ($C_{22}H_{19}FN_4O_3$ requires: 407.1519).

5.44. *trans*-*N*-[1-(3-Fluorophenyl)-1*H*-pyrazol-3-yl]-3-oxo-3*H*-spiro[6-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (21l)

Compound **21l** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 75% yield. Mp: 247–249 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.78–2.25 (m, 8H), 2.70–2.90 (m, 1H), 6.90 (d, J = 2.6 Hz, 1H), 7.03–7.18 (m, 1H), 7.43–7.59 (m, 1H), 7.59–7.70 (m, 2H), 7.87 (dd, J = 5.0, 1.1 Hz, 1H), 8.49 (d, J = 2.6 Hz, 1H), 8.83 (d, J = 5.0 Hz, 1H), 9.13 (d, J = 1.1 Hz, 1H), 10.81 (s, 1H); HRMS (ESI) m/z = 407.1514 $[M+H]^+$ ($C_{22}H_{19}FN_4O_3$ requires: 407.1519).

5.45. *trans*-3-Oxo-*N*-(5-phenylpyrazin-2-yl)-3*H*-spiro[7-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (22a)

Compound **22a** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a pale yellow solid in 7% yield. Mp: 246–248 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.93–2.01 (m, 2H), 2.20–2.37 (m, 4H), 2.47–2.58 (m, 2H), 2.76–2.80 (m, 1H), 7.45–7.54 (m, 4H), 7.98–8.05 (m, 3H), 8.19 (dd, J = 7.8, 1.6 Hz, 1H), 8.68 (d, J = 1.6 Hz, 1H), 8.88 (dd, J = 4.9, 1.6 Hz, 1H), 9.66 (d, J = 1.5 Hz, 1H); HRMS (ESI) m/z = 401.1614 $[M+H]^+$ ($C_{23}H_{20}N_4O_3$ requires: 401.1614).

5.46. *trans*-3-Oxo-*N*-(5-phenylpyrimidin-2-yl)-3*H*-spiro[7-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (22b)

Compound **22b** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 45% yield. Mp: 201–203 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.80–2.01 (m, 4H), 2.10–2.22 (m, 2H), 2.23–2.37 (m, 2H), 2.96 (m, 1H), 7.43 (m, 1H), 7.47–7.55 (m, 2H), 7.65 (dd, J = 7.8, 4.9 Hz, 1H), 7.75–7.80 (m, 2H), 8.29 (dd, J = 7.8, 1.6 Hz, 1H), 8.92 (dd, J = 4.9, 1.6 Hz, 1H), 9.00 (s, 2H), 10.71 (s, 1H); HRMS (ESI) m/z = 401.1607 $[M+H]^+$ ($C_{23}H_{20}N_4O_3$ requires: 401.1614).

5.47. *trans*-3-Oxo-*N*-(5-phenylisoxazol-3-yl)-3*H*-spiro[7-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (22c)

Compound **22c** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a white solid in 86% yield. Mp: 253–255 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.90–2.02 (m, 2H), 2.20–2.44 (m, 4H), 2.46–2.60 (m, 2H), 2.86–2.96 (m, 1H), 7.40–7.59 (m, 5H), 7.78–7.83 (m, 2H), 8.19 (dd, J = 7.5, 1.5 Hz, 1H), 8.87 (dd, J = 4.8, 1.5 Hz, 1H), 9.60–9.70 (m, 1H); HRMS (ESI) m/z = 390.1458 $[M+H]^+$ ($C_{22}H_{19}N_3O_4$ requires: 390.1454).

5.48. *trans*-3-Oxo-*N*-(3-phenyl-1*H*-pyrazol-5-yl)-3*H*-spiro[7-aza-2-benzofuran-1,1′-cyclohexane]-4′-carboxamide (22d)

Compound **22d** was prepared from the corresponding acid and amine in a manner similar to that described for **21j** as a pale white solid in 2.7% yield. Mp: 245–247 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.18–1.96 (m, 4H), 2.15–2.34 (m, 4H), 2.71–2.75 (m, 1H), 6.89 (s, 1H), 7.30–7.35 (m, 1H), 7.41–7.46 (m, 2H), 7.64 (dd, J = 7.8, 4.9 Hz, 1H), 7.72–7.74 (m, 2H), 8.29 (dd, J = 7.8, 1.5 Hz, 1H), 8.91 (dd, J = 4.9, 1.5 Hz, 1H); HRMS (ESI) m/z = 401.1609 $[M+H]^+$ ($C_{23}H_{20}N_4O_3$ requires: 401.1614).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.08.019.

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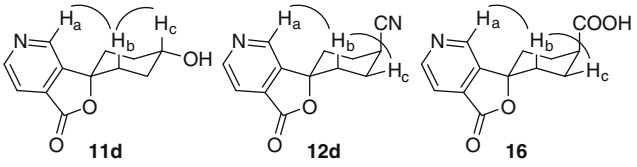

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