Spiro-Substituted Piperidines as Neurokinin Receptor Antagonists. II.[1] Syntheses and NK_2 Receptor-Antagonistic Activities of *N*-[2-Aryl-4-(spiro-substituted piperidin-1′-yl)butyl]carboxamides

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In the course of our research on spiro-compounds as neurokinin receptor antagonists, *N*-[2-aryl-4-(spiro-substituted piperidin-1′-yl)butyl]carboxamides were designed, based on YM-35375 (3) as a lead compound, and evaluated for NK_2 receptor-antagonistic activities. Some derivatives inhibited the binding of radio-labeled neurokinin A to the NK_2 receptor with IC_{50} values at the level of 10^{-9} M. Among these compounds, (±)-1′-[4-(*N*-benzoyl-*N*-methylamino)-3-(3,4-dichlorophenyl)butyl]spiro[benzo[*c*]thiophene-1(3*H*), 4′-piperidine] 2-oxide (58, YM-38336) showed 10 times more potent NK_2 receptor binding affinity than compound 3 (IC_{50} values of 8.9 and 84 nM, respectively). It showed more potent inhibitory activity (ID_{50} 20 μg/kg (i.v.)) against [β-Ala^8]-NKA(4—10)-induced bronchoconstriction in guinea pigs than compound 3 (ID_{50} 41 μg/kg (i.v.)). This compound was also effective intraduodenally in the same model, exhibiting an ID_{50} value of 0.41 μg/kg.

Key words spiro-substituted piperidine; NK_2 receptor antagonist; neurokinin A; YM-38336; YM-35375; NK_1–NK_2 dual antagonist

Neurokinin A[2] (NKA), a ten-amino-acid peptide, is one of a class of naturally occurring neurokinins which also includes substance P[3] (SP) and neurokinin B[2] (NKB). SP, NKA and NKB elicit a wide variety of biological responses,[4] including smooth muscle contraction, anxiety, pain transmission, vasodilatation, salivary secretion, neurogenic inflammation and activation of the immune system, which are mediated through three distinct receptors termed NK_1, NK_2 and NK_3, respectively.[5] In particular, NKA induces bronchoconstriction more potently than SP[6] and also causes smooth muscle contraction in the urinary and gastrointestinal systems.[4] It is presumed that NKA participates in the pathogenesis of diseases caused by these contractions, such as asthma, urinary incontinence and irritable bowel syndrome. Thus, a selective NK_2 receptor antagonist may be of clinical benefit for treatment of these diseases.

Recently, highly potent and selective non-peptide NK_2 receptor antagonists, SR48968[7] (**1**) and GR 159897[8] (**2**), have been reported (Fig. 1). In our previous research, we found that the 4-phenyl group of the piperidine of SR48968, but not the acetamide group, was crucial for binding to the NK_2 receptor.[1] Energy calculation of the piperidine moiety of SR 48968 suggested that the phenyl group and the acetamide group occupied an equatorial position and an axial position, respectively.[1] It appeared that the equatorial phenyl group may be crucial for binding to the NK_2 receptor and we hypothesized that a compound with a more restricted equatorial phenyl group might show higher affinity for the NK_2 receptor. Unfortunately, YM-35375 (**3**, Fig. 1) which was designed as a derivative with a conformationally rigid spiro[isobenzofuran-1(3*H*), 4′-piperidine] was found to bind to the NK_2 receptor with an IC_{50} value of 84 nM, being 20-fold less potent than (±)-SR48968. However, YM-35375 was more potent than (±)-SR48968 in an NK_2 receptor agonist-induced bronchoconstriction model, with ID_{50} values of 41 μg/kg (i.v.) and 68 μg/kg (i.v.), respectively.[1] These facts suggested that YM-35375 would be suitable as a lead compound for novel NK_2 receptor antagonists. Therefore, we conducted a study on the structure–activity relationships of YM-35375 derivatives. Namely, we modified the *N*-methylbenzamide moiety, 3,4-dichlorophenyl moiety and spiro[isobenzofuran-1(3*H*), 4′-piperidine] moiety of YM-35375. We will describe here the syntheses, structure–activity relationships and pharmacological properties of these novel spiro-substituted piperidines (**31**—**65**).

Chemistry

As shown in Chart 1, 3,4-dihydrospiro[1*H*-2-benzopyran-1,4′-piperidine] (**8**) was synthesized from 2-(2- bromophenyl)ethanol (**4**) by the method reported previously.[1] Compound **4** was converted to a dianion with *n*-butyllithium (*n*-BuLi) in tetrahydrofuran (THF)–diethyl ether (Et_2O) and treated with 1-ethoxycarbonyl-4-piperidone (**5**) to give ethyl 4-hydroxy-4-[2-(2-hydroxyethyl)phenyl]piperidine-1-carboxylate (**6**). The primary hydroxyl group of compound **6** was selectively tosylated by treatment with *p*-toluenesulfonyl chloride (TsCl), and the resultant tosylate was cyclized in the presence of pyridine to give the protected spiro-substituted piperidine (**7**). Compound **7**

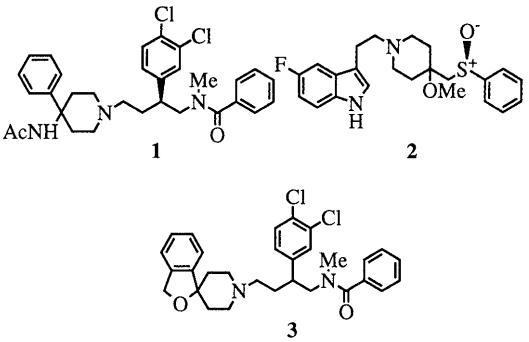

Fig. 1. Structures of SR48968 (**1**), GR159897 (**2**) and YM-35375 (**3**)

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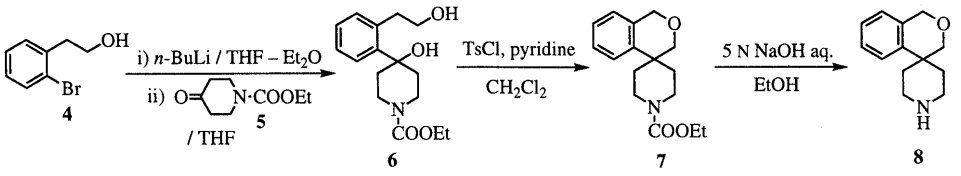


Chart 1

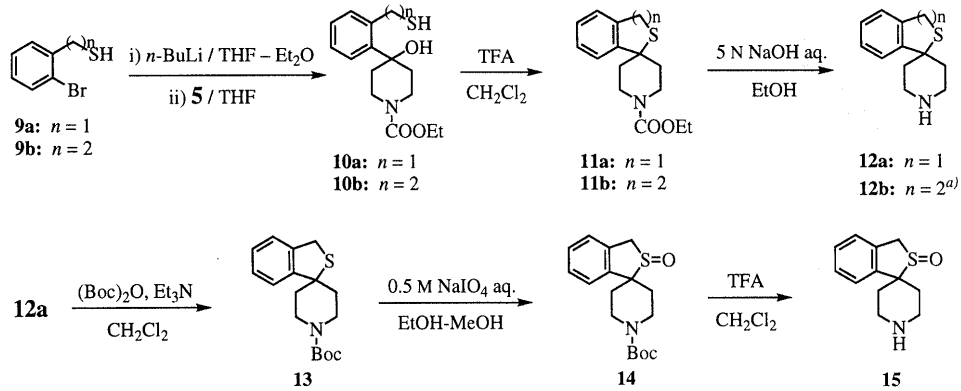


Chart 2

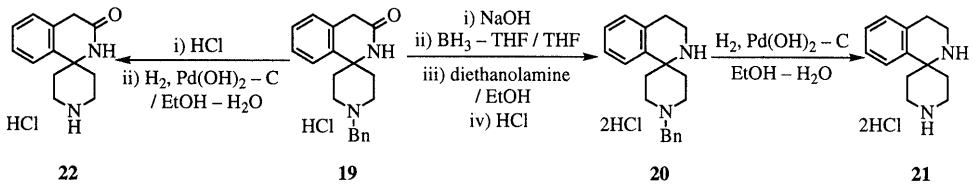


Chart 3

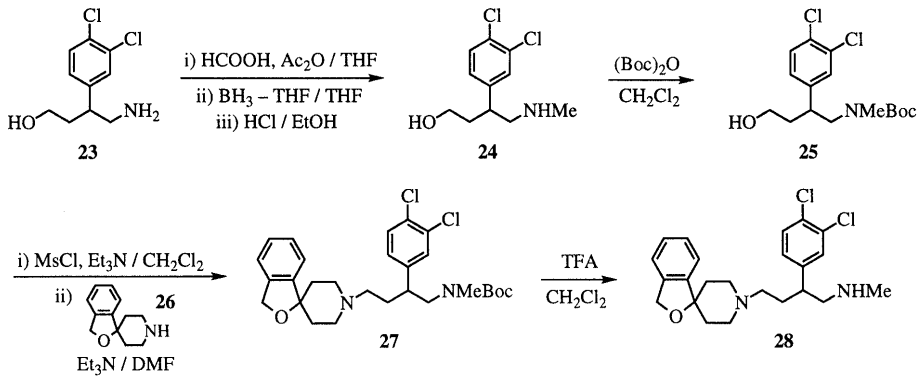


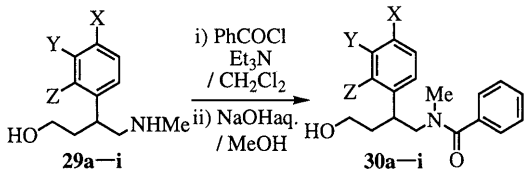
Chart 4

was treated with NaOH to give compound **8**.

Syntheses of the spiro-substituted piperidines containing sulfur atoms are shown in Chart 2. 2-Bromobenzylthiol (**9a**) was converted to a dianion with *n*-BuLi in THF–Et_2O at $-100\,°C$, and this was treated with compound **5** at the same temperature to give ethyl 4-hydroxy-4-(2-mercaptomethylphenyl)piperidine-1-carboxylate (**10a**). Treatment of compound **10a** with trifluoroacetic acid (TFA) gave ethyl spiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine]-1′-carboxylate (**11a**), followed by deprotection of the ethoxycarbonyl group with NaOH to give spiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine] (**12a**). 3,4-Dihydrospiro[1*H*-2-benzothiopyran-1,4′-piperidine] (**12b**) was synthesized from 2-(2-bromophenyl)ethanethiol (**9b**) in the same manner as described for the preparation of compound **12a**. Treatment of compound **12a** with di-*tert*-butoxycarbonyldicarbonate ($(Boc)_2O$) gave the 1′-*tert*-butoxycarbonyl (Boc) derivative (**13**) followed by oxidation with sodium periodate to give 1′-*tert*-butoxycarbonylspiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine] 2-oxide (**14**). Compound **14** was treated with TFA to give spiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine] 2-oxide (**15**). Spiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine] 2,2-dioxide (**17**) was prepared by oxidation of compound **11a** with hydrogen peroxide, followed by deprotection of the ethoxycarbonyl group with NaOH. Oxidation of compound **12b** with sodium periodate in MeOH–H_2O gave 3,4-dihydrospiro[1*H*-2-benzothiopyran-1,4′-piperidine] 2-oxide (**18**).

The isoquinoline and the 3-isoquinolone derivatives (**21**, **22**) were synthesized according to the method shown in Chart 3. Treatment of 1-benzyl-3-oxo-3,4-dihydrospiro[isoquinoline-1(2*H*),4′-piperidine] hydrochloride[9] (**19**) with borane–THF complex, followed by treatment with diethanolamine in EtOH gave 1′-benzyl-3,4-dihydrospiro[isoquinoline-1(2*H*),4′-piperidine] (**20**), which was isolated as the dihydrochloride. Hydrogenation of compound **20** under 4 kg/cm^2 of hydrogen in the presence of palladium hydroxide gave 3,4-dihydrospiro[isoquinoline-1(2*H*),4′-piperidine] dihydrochloride (**21**). Compound **19** was hydrogenated under atmospheric pressure of hydrogen in the presence of palladium hydroxide to afford 3-oxo-3,4-dihydrospiro[isoquinoline-1(2*H*),4′-piperidine] hydrochloride (**22**).

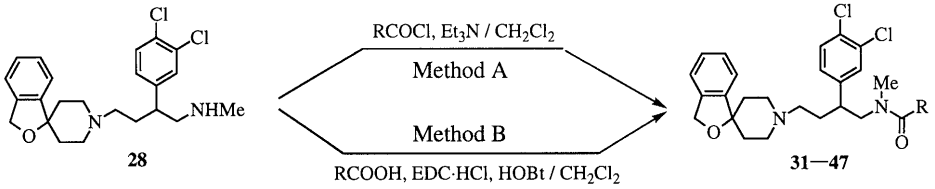
(±)-1′-[3-(3,4-Dichlorophenyl)-4-methylaminobutyl]-spiro[isobenzofuran-1(3*H*),4′-piperidine] (**28**) and (±)-*N*-(2-aryl-4-hydroxybutyl)-*N*-methylbenzamides (**30a**—**j**) were chosen as key intermediates to prepare the designed spiro-substituted piperidines (**31**—**65**) and were synthesized according to the procedures depicted in Charts 4 and 5, respectively, except for compound **30j**, which was prepared by a similar method to that described in the literature.[8,10] (±)-4-Amino-3-(3,4-dichlorophenyl)butanol (**23**) was prepared according to the literature.[11] Compound **23** was treated with a mixture of formic acid and acetic anhydride (Ac_2O), followed by reduction with borane–THF complex to give the *N*-methyl derivative (**24**). Compound **24** was converted to the *N*-*tert*-butoxycarbonyl derivative (**25**) with $(Boc)_2O$, and treatment of compound **25** with methanesulfonyl chloride (MsCl) followed by substitution with spiro[isobenzofuran-1(3*H*),4′-piperi-



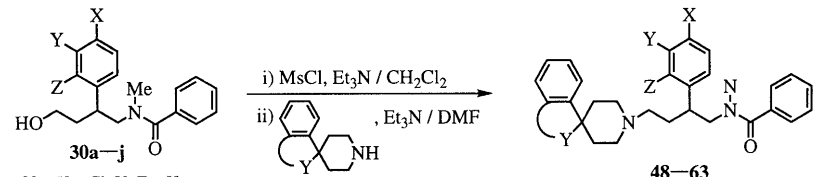
29a: X = Cl; Y, Z = H
29b: Y = Cl; X, Z = H
29c: Z = Cl; X, Y = H
29d: X = F; Y, Z = H
29e: X = Br; Y, Z = H
29f: X = CF_3; Y, Z = H
29g: X = Me; Y, Z = H
29h: X = OMe; Y, Z = H
29i: X, Y = CH:CHCH:CH; Z = H

30a: X = Cl; Y, Z = H
30b: Y = Cl; X, Z = H
30c: Z = Cl; X, Y = H
30d: X = F; Y, Z = H
30e: X = Br; Y, Z = H
30f: X = CF_3; Y, Z = H
30g: X = Me; Y, Z = H
30h: X = OMe; Y, Z = H
30i: X, Y = CH:CHCH:CH; Z = H

Chart 5

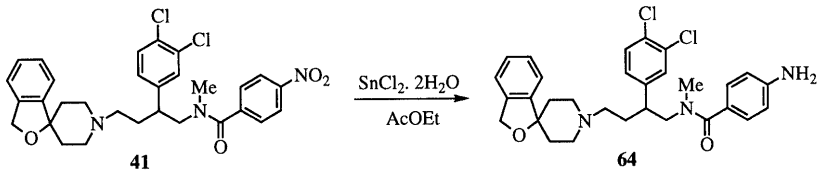


Method C



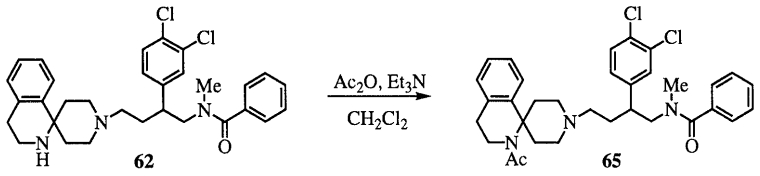
30a: X = Cl; Y, Z = H
30b: Y = Cl; X, Z = H
30c: Z = Cl; X, Y = H
30d: X = F; Y, Z = H
30e: X = Br; Y, Z = H
30f: X = CF_3; Y, Z = H
30g: X = Me; Y, Z = H
30h: X = OMe; Y, Z = H
30i: X, Y = CH:CHCH:CH; Z = H
30j: X, Y = Cl; Z = H

Chart 6



41 64

Chart 7



62 65

Chart 8

dine][8] (**26**) in the presence of triethylamine (Et_3N) gave the *N*-protected spiro-substituted piperidine (**27**). The key intermediate **28** was prepared by treatment of compound **27** with TFA in dichloromethane (Chart 4).

N-(2-Aryl-4-hydroxybutyl)-*N*-methylamines (**29a—i**) were prepared by a similar method to that described in the literature.[8,10] Treatment of compounds **29a—i** with benzoyl chloride in the presence of Et_3N followed by hydrolysis with NaOH gave *N*-(2-aryl-4-hydroxybutyl)-*N*-methylbenzamides (**30a—i**, Chart 5).

The designed spiro-substituted piperidines (**31—65**) were prepared according to the methods shown in Charts 6, 7 and 8. Treatment of compound **28** with acid chlorides in the presence of Et_3N in dichloromethane gave compounds **31—37** and **40—46** (method A in Chart 6). Compound **28** was also converted to compounds **38**, **39**, and **47** with carboxylic acids in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) and 1-hydroxybenzotriazole (HOBt) in dichloromethane (method B in Chart 6). Treatment of compound **30** with MsCl followed by substitution with the spiro-substituted piperidines (**8**, **12**, **15**, **17**, **18**, **21**, **22**, **26**) in the presence of Et_3N gave compounds **48—63** (method C in Chart 6). The 4-aminobenzamide derivative (**64**) was prepared by reduction of the corresponding nitro derivative (**41**) with stannous chloride (Chart 7).[12] Acetylation of compound **62** with Ac_2O in the presence of Et_3N gave (±)-*N*-[4-(2-acetyl-3,4-dihydrospiro[isoquinoline-1(2*H*),4′-piperidin]-1′-yl)-2-(3,4-dichlorophenyl)butyl]-*N*-methylbenzamide (**65**, Chart 8). The synthetic details and physical properties of compounds **31** to **65** are summarized in Tables 1—4 and 7.

Results and Discussion

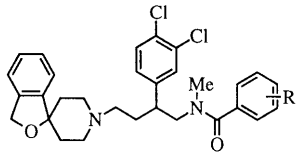
The binding affinities for hamster urinary bladder NK_2 receptor[13] of YM-35375 and compounds **31—65** are also summarized in Tables 1—4.

We first examined the effects of substituents of the phenyl group in the *N*-methylbenzamide moiety, and the results for (±)-*N*-[2-(3,4-dichlorophenyl)-4-(spiro[isobenzofuran-1(3*H*),4′-piperidin]-1′-yl)butyl]-*N*-methylbenzamides are shown in Table 1. Among the compounds bearing methyl groups (**31—33**), the 4-methyl derivative (**31**) tended to show more potent affinity for the NK_2 receptor than YM-35375. The derivatives halogenated at the 4-position (**34—36**) were almost as potent as YM-35375 and were equipotent regardless of the size of the substituents. Among the electron-donating groups at the 4-position of the phenyl group (**37—39**, **64**), methoxy and dimethylamino groups (**37**, **38**) did not influence or slightly decreased the potency. On the other hand, amino and acetamido groups, which could act as both electron-donating and hydrogen-donating groups (**39**, **64**), increased the affinity for the NK_2 receptor. The derivatives with an electron-withdrawing group at the 4-position of the phenyl group (**40**, **41**) were as potent as YM-35375.

Secondly, we introduced aliphatic or other aromatic groups instead of the phenyl group in the *N*-methylbenzamide moiety, and the results are shown in Table 2. Since the introduction of the aliphatic groups (**42**, **43**) instead of the phenyl group decreased the potency, it was suggested that an aromatic ring in this moiety may be necessary for high affinity for the NK_2 receptor. The pyridyl, thienyl and naphthyl derivatives (**44—46**) were as potent as YM-35375 and were almost equipotent regardless of the size of the substituents. A benzimidazole derivative (**47**), possessing a hydrogen-donating moiety at the 4-position of the phenyl group, was 5 times more potent than YM-35375. In the series of compounds prepared in this study, the *N*-methylbenzamide moiety may have interacted with a pocket of the NK_2 receptor through a hydrogen bond, and the size of the substituents may not interfere with this interaction.

Next, we examined the effects of substituents of the phenyl group in the 3,4-dichlorophenyl moiety, and the results are shown in Table 3. In the series of compounds which possess a monochlorinated phenyl group (**48—50**) instead of the 3,4-dichlorophenyl group, the *ortho*-substituted derivative (**50**) showed dramatically decreased potency. We speculated that substitution of 2-chlorophenyl for 3,4-dichlorophenyl may result in an unfavorable conformation for binding to the NK_2 receptor. The compound with a chloro group at the 3-position (**49**) was less potent than YM-35375, in contrast to the 4-chloro derivative (**48**) which showed a 2-fold increase in potency. Other compounds halogenated at the 4-position (**51**, **52**) were also more potent than YM-35375. On the other hand, an electron-withdrawing group (**53**), electron-donating groups (**54**, **55**) and a sterically bulky group (**56**) in this moiety caused a 5- to 7-fold decrease in potency. In the

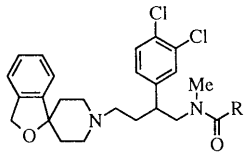
Table 1. Physical and Biological Properties of (±)-*N*-[2-(3,4-Dichlorophenyl)-4-(spiro[isobenzofuran-1(3*H*),4′-piperidin]-1′-yl)butyl]-*N*-methylbenzamides



Compd. No.	R	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	Method[a]	Yield (%)	Recrystn. solvent[b]	NK_2 binding[c] IC_{50} (nM)
3	H									84
31	4-Me	Amorphous	$C_{31}H_{34}Cl_2N_2O_2 \cdot HCl \cdot 0.5H_2O$	63.87 (63.54	6.22 6.36	4.81 4.61)	A	72	—	57
32	3-Me	Amorphous	$C_{31}H_{34}Cl_2N_2O_2 \cdot HCl \cdot 0.75H_2O$	63.37 (63.39	6.26 6.45	4.77 4.56)	A	83	—	170
33	2-Me	Amorphous	$C_{31}H_{34}Cl_2N_2O_2 \cdot HCl \cdot H_2O$	62.90 (63.18	6.30 6.47	4.73 4.48)	A	81	—	120
34	4-F	162—164	$C_{30}H_{31}Cl_2FN_2O_2 \cdot C_4H_4O_4$	62.10 (62.20	5.36 5.35	4.26 4.29)	A	60	A	110
35	4-Cl	Amorphous	$C_{30}H_{31}Cl_3N_2O_2 \cdot HCl \cdot 0.5H_2O$	59.71 (59.36	5.51 5.51	4.64 4.48)	A	79	—	120
36	4-Br	192—194	$C_{30}H_{31}BrCl_2N_2O_2 \cdot C_4H_4O_4$	56.84 (56.96	4.91 4.94	3.90 3.92)	A	50	M–A	120
37	4-OMe	190—192	$C_{31}H_{34}Cl_2N_2O_3 \cdot C_4H_4O_4$	62.78 (62.97	5.72 5.74	4.18 4.19)	A	48	A	79
38	4-NMe_2	172—174	$C_{32}H_{37}Cl_2N_3O_2$	67.84 (67.70	6.58 6.49	7.42 7.40)	B	44	M	240
39	4-NHAc	182—184	$C_{32}H_{35}Cl_2N_3O_3 \cdot C_4H_4O_4 \cdot 0.25H_2O$	61.67 (61.59	5.68 5.64	5.99 5.97)	B	45	M–A	24
40	4-CN	160—161	$C_{31}H_{31}Cl_2N_3O_2 \cdot C_4H_4O_4$	63.26 (63.41	5.31 5.33	6.32 6.27)	A	53	A	65
41	4-NO_2	167—168	$C_{30}H_{31}Cl_2N_3O_4 \cdot C_4H_4O_4$	59.65 (59.75	5.15 5.15	6.14 6.08)	A	50	M–A	95
64	4-NH_2	Amorphous	$C_{30}H_{33}Cl_2N_3O_2 \cdot 0.5H_2O$	65.81 (65.62	6.26 6.14	7.67 7.56)	—[d]	62	—	38

a) See Chart 6. *b*) A = acetonitrile, M = methanol. *c*) The binding affinities for hamster urinary bladder NK_2 receptor. See experimental section. *d*) See Chart 7.

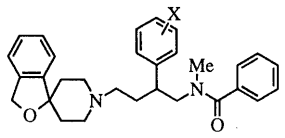
Table 2. Physical and Biological Properties of (±)-*N*-[2-(3,4-Dichlorophenyl)-4-(spiro[isobenzofuran-1(3*H*),4′-piperidin]-1′-yl)butyl]-*N*-methylcarboxamides

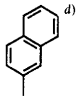


Compd. No.	R	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	Method[a]	Yield (%)	Recrystn. solvent[b]	NK_2 binding[c] IC_{50} (nM)
3	Ph									84
42	Et	167—168	$C_{26}H_{32}Cl_2N_2O_2 \cdot C_4H_4O_4$	60.91 (60.92	6.13 6.12	4.74 4.73)	A	37	M	670
43		Amorphous	$C_{30}H_{38}Cl_2N_2O_2 \cdot HCl \cdot 0.5H_2O$	62.66 (62.56	7.01 7.14	4.87 4.65)	A	83	—	280
44		Amorphous	$C_{29}H_{31}Cl_2N_3O_2 \cdot 2HCl \cdot 0.5H_2O$	57.44 (57.79	5.65 6.05	6.93 6.63)	A	57	—	38
45		Amorphous	$C_{28}H_{30}Cl_2N_2O_2S \cdot HCl \cdot 1.5H_2O$	56.71 (56.59	5.78 5.76	4.72 4.58)	A	80	—	46
46		202—203	$C_{34}H_{34}Cl_2N_2O_2 \cdot C_4H_4O_4$	66.18 (66.34	5.55 5.59	4.06 4.06)	A	57	M–A	57
47		Amorphous	$C_{31}H_{32}Cl_2N_4O_2 \cdot H_2O$	64.03 (64.03	5.60 5.89	9.68 9.63)	B	47	—	17

a—*c*) See the corresponding footnotes in Table 1.

Table 3. Physical and Biological Properties of (±)-*N*-[2-Aryl-4-(spiro[isobenzofuran-1(3*H*),4′-piperidin]-1′-yl)butyl]-*N*-methylbenzamides



Compd. No.	X	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	Method[a]	Yield (%)	Recrystn. solvent[b]	NK_2 binding[c] IC_{50} (nM)
3	3,4-Cl_2									84
48	4-Cl	Amorphous	$C_{30}H_{33}ClN_2O_2 \cdot HCl \cdot 0.5H_2O$	67.41 (67.59	6.60 6.84	5.24 5.11)	C	76	—	32
49	3-Cl	Amorphous	$C_{30}H_{33}ClN_2O_2 \cdot HCl \cdot 0.75H_2O$	66.85 (67.02	6.64 6.80	5.20 5.11)	C	68	—	210
50	2-Cl	Amorphous	$C_{30}H_{33}ClN_2O_2 \cdot HCl \cdot 0.75H_2O$	66.85 (66.87	6.64 7.01	5.20 5.05)	C	34	—	1400
51	4-F	182—184	$C_{30}H_{33}FN_2O_2 \cdot C_4H_4O_4$	69.37 (69.43	6.34 6.37	4.76 4.85)	C	70	P	48
52	4-Br	118—119	$C_{30}H_{33}BrN_2O_2 \cdot C_4H_4O_4$	62.87 (62.74	5.74 5.87	4.31 4.31)	C	78	P–E	44
53	4-CF_3	179	$C_{31}H_{33}F_3N_2O_2 \cdot C_4H_4O_4$	65.82 (65.76	5.84 5.87	4.39 4.38)	C	73	P–E	510
54	4-Me	145	$C_{31}H_{36}N_2O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	70.87 (70.58	6.88 6.72	4.72 4.65)	C	56	A	430
55	4-OMe	132—133	$C_{31}H_{36}N_2O_3 \cdot C_4H_4O_4 \cdot 0.5H_2O$	69.00 (68.66	6.70 6.79	4.60 4.53)	C	72	P–E	560
56	 [d]	164—165	$C_{34}H_{36}N_2O_2 \cdot C_4H_4O_4$	73.53 (73.31	6.50 6.62	4.51 4.44)	C	72	P–E	500

a, *c*) See the corresponding footnotes in Table 1. *b*) A = acetonitrile, E = diethyl ether, M = methanol, P = 2-propanol. *d*) Compound **56** possesses 2-naphthyl group instead of the 3,4-dichlorophenyl group of compound **3**.

series of compounds prepared in this study, only the 4-halogenated phenyl group seems to be favorable for binding to the NK_2 receptor.

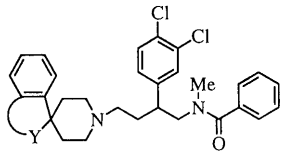
The structure–activity relationships observed in the series of compounds possessing a spiro[isobenzofuran-1(3*H*),4′-piperidine] moiety are summarized below. A hydrogen-donating group at the 4-position of the phenyl group in the *N*-methylbenzamide moiety was favorable to generate high affinity for the NK_2 receptor. In the 3,4-dichlorophenyl moiety, introduction of a 4-halogenated phenyl group instead of the 3,4-dichlorophenyl group did not decrease the potency.

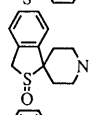
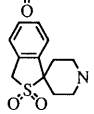
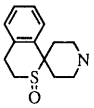
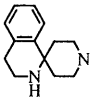
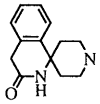
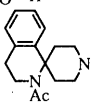
Finally, we attempted to optimize the spiro[isobenzofuran-1(3*H*),4′-piperidine] moiety of YM-35375, and the results are shown in Table 4. Substitution of benzo[*c*]thiophene (**57**) for isobenzofuran resulted in a 3-fold decrease in potency, and the sulfone derivative (**59**) was also less potent than YM-35375. Surprisingly, the sulfoxide derivative (**58**) exhibited nearly 10 times higher affinity for the NK_2 receptor (IC_{50} value of 8.9 nM) than YM-35375. Ring expansion (**60** *vs.* YM-35375 and **61** *vs.* **58**) gave almost the same potency, and the isoquinoline derivative (**62**) was also equipotent to compounds **60** and **61**. The isoquinolone derivative (**63**) and *N*-acetylisoquinoline derivative (**65**), which possess carbonyl groups in this moiety, showed dramatically increased potency, with IC_{50} values of 4.0 and 9.1 nM, respectively. This result implies that a hydrogen bond exists between the carbonyl group in this moiety of the compound and a hydrogen-donating group of the NK_2 receptor. This speculation was supported by the fact that the sulfoxide derivative (**58**), which could also act as a hydrogen acceptor, showed potent affinity for the NK_2 receptor.

Selected compounds (**58**, **62**, **65**) were evaluated for binding affinity[13] to guinea pig urinary bladder NK_1 receptor, and the results and their NK_2 receptor selectivity indexes are summarized in Table 5. The conversion of isobenzofuran of YM-35375 to benzo[*c*]thiophene 2-oxide and *N*-acetyl-1,2,3,4-tetrahydroisoquinoline (**58** and **65**, respectively) retained the affinity for the NK_1 receptor and dramatically improved the NK_2 receptor selectivity, with indexes of 76 and 68, respectively. On the other hand, the 1,2,3,4-tetrahydroisoquinoline derivative (**62**) showed potent affinity not only for the NK_2 receptor, but also for the NK_1 receptor with IC_{50} values of 13 and 58 nM, respectively. Thus, further structural modifications of a series of 2-aryl-4-(spiro-substituted piperidin-1′-yl)butylcarboxamides may generate an increase in NK_1 receptor-antagonistic activity and may also lead to novel NK_1–NK_2 dual antagonists.

Some potent compounds (**48**, **52**, **58**, **62**, **65**) were evaluated for inhibitory activity against [β-Ala[8]]-NKA(4-10)-induced bronchoconstriction in guinea pigs,[14,15] and the results are summarized in Table 6. In the series of compounds with a modified 3,4-dichlorophenyl moiety, the 4-chloro derivative (**48**) was equipotent to YM-35375 when intravenously injected, and the 4-bromo derivative (**52**) was slightly less potent than YM-35375. Compound

Table 4. Physical and Biological Properties of (±)-*N*-[2-(3,4-Dichlorophenyl)-4-(spiro-substituted-4′-piperidin-1′-yl)butyl]-*N*-methylbenzamides



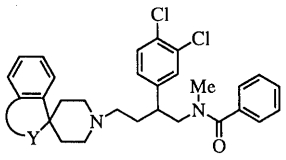
Compd. No.		mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	Method[a]	Yield (%)	Recrystn. solvent[b]	NK_2 binding[c] IC_{50} (nM)
3										84
57		196	$C_{30}H_{32}Cl_2N_2OS \cdot C_4H_4O_4$	62.29 (62.22)	5.53 5.57	4.27 4.27)	C	20	M–A	250
58		Amorphous	$C_{30}H_{32}Cl_2N_2O_2S \cdot H_2O$	62.82 (62.66	5.97 5.70	4.88 4.79)	C	79	—	8.9
59		165—167	$C_{30}H_{32}Cl_2N_2O_3S \cdot C_4H_4O_4 \cdot 0.25H_2O$	59.00 (58.90	5.32 5.28	4.05 4.04)	C	35	M–EA–E	270
60		199—201	$C_{31}H_{34}Cl_2N_2O_2 \cdot C_4H_4O_4$	64.32 (64.31	5.86 5.80	4.29 4.30)	C	43	A	30
61		161—163	$C_{31}H_{34}Cl_2N_2O_2S \cdot C_4H_4O_4 \cdot 0.5H_2O$	60.52 (60.73	5.66 5.59	4.03 4.00)	C	52	P–E	12
62		225 (dec.)	$C_{31}H_{35}Cl_2N_3O \cdot 2HCl$	61.06 (60.87	6.12 6.09	6.89 6.87)	C	47	M	13
63		209 (dec.)	$C_{31}H_{33}Cl_2N_3O_2 \cdot C_4H_4O_4$	63.06 (63.16	5.59 5.49	6.30 6.31)	C	45	M–A–EA	4.0
65		177—178	$C_{33}H_{37}Cl_2N_3O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	63.56 (63.51	5.98 5.82	6.01 6.05)	—[d]	39	M–A	9.1

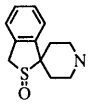
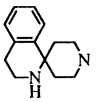
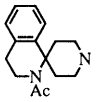
a, *c*) See the corresponding footnotes in Table 1. *b*) A = acetonitrile, E = diethyl ether, EA = ethyl acetate, M = methanol, P = 2-propanol. *d*) See Chart 8.

48 was also effective when intraduodenally administered, but compound **52** showed only weak potency. We speculated that minor change in the 3,4-dichlorophenyl moiety of YM-35375 may influence the ability of the compounds to penetrate the intestinal membrane. In the series of compounds with a modified spiro[isobenzofuran-1(3*H*),4′-piperidine] moiety, compounds **62** and **65** showed decreased potency after intravenous injection, but compound **58** showed 2-fold greater potency. Compounds **58** and **65** showed more potent inhibitory activity on bronchoconstriction after intraduodenal administration than YM-35375. These results suggested that compounds **58** and **65** permeated well through the intestinal membrane. The spiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine] 2-oxide derivative (**58**, YM-38336) was the most potent of the compounds prepared in this study after intravenous injection (ID_{50} 20 μg/kg). Furthermore, YM-38336 was also effective after intraduodenal administration, producing with 85% inhibition at the dose of 3 mg/kg. The time course of the inhibitory activities of YM-38336 and (±)-SR48968 after intraduodenal administration was investigated, and the results are shown in Fig. 2. At 60 min after administration of the compounds, both YM-38336 and (±)-SR48968 showed dose-dependent inhibitory activity (Fig. 2A and 2B, respectively) and were equipotent with ID_{50} values of 0.41 and 0.48 mg/kg, respectively. However, at 30 min after administration of the compounds, YM-38336 inhibited the bronchoconstriction completely (Fig. 2A, 1.0 mg/kg i.d.), whereas (±)-SR48968 inhibited the contraction by about 50% (Fig. 2B, 1.0 mg/kg i.d.).

In summary, we designed novel spiro-substituted piperidine derivatives from the lead compound, YM-35375, and evaluated them for NK_2 receptor-antagonistic activity. This study revealed that hydrogen-donating groups at the 4-position of the phenyl group in the *N*-methylbenzamide moiety, halogens at the 4-position in the 3,4-dichlorophenyl moiety and hydrogen-accepting groups in the spiro[isobenzofuran-1(3*H*),4′-piperidine] moiety significantly enhanced binding affinity for the NK_2

Table 5. NK_2 Receptor Selectivities of Compounds **3**, **58**, **62** and **65**



Compd. No.		NK_1 binding[a] IC_{50} (nM)	NK_2 binding[b] IC_{50} (nM)	NK_2 selectivity index[c]
3		710	84	8.5
58		680	8.9	76
62		58	13	4.5
65		620	9.1	68

a) The binding affinities for guinea pig urinary bladder NK_1 receptor. See experimental section. *b*) The binding affinities for hamster urinary bladder NK_2 receptor. See experimental section. *c*) IC_{50} to NK_1 receptor/IC_{50} to NK_2 receptor.

Table 6. NK_2 Receptor Antagonist Activities of *N*-[2-Aryl-4-(spiro-substituted piperidin-1′-yl)butyl]carboxamides *in Vivo*

Compd. No.	Bronchoconstriction in guinea pigs[a]	
	ID_{50} (μg/kg i.v.)	% inhibition at 3 mg/kg i.d.
3	41	36± 6
48	35	81± 5
52	62	19± 6
58 (YM-38336)	20	85±11
62	272	N.T.[b]
65	115	72±22

a) See experimental section. *b*) Not tested.

receptor. Among these compounds, YM-38336 was the most potent in an NK_2 receptor agonist-induced bronchoconstriction model when intravenously injected. YM-38336 also showed dose-dependent inhibitory activity when intraduodenally administered. From these results, YM-38336 may be of benefit clinically for the diseases caused by NK_2 receptor activation. Furthermore, compound **62** exhibited potent binding affinity not only for the NK_2 receptor, but also for the NK_1 receptor, and it may be possible to find novel NK_1–NK_2 dual antagonists[16] by modifying 2-aryl-4-(spiro-substituted piperidin-1′-yl)butylcarboxamides. We are working in this approach, utilizing YM-35375 as a lead compound.

Experimental

All melting points were determined on a Yanagimoto MP-3 melting point apparatus and without correction. ^{1}H-NMR spectra were taken on a JEOL JNM-EX400 spectrometer or a JEOL JNM-A500 spectrometer. Chemical shifts are given in ppm relative to that of Me_4Si ($\delta=0$) in $CDCl_3$ or dimethylsulfoxide-d_6 (DMSO-d_6) as an internal standard. The abbreviations of signal patterns are as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; dd, double doublet; dt, double triplet; m, multiplet. Column chromatography was carried out on silica gel (Wakogel C-200 or Merck Silica gel 60). FAB-MS were obtained with a JEOL JMS-DX300 mass spectrometer, and electron impact (EI)-MS with a Hitachi M-80 mass spectrometer or a Hewlett-Packard 5890 GC-5970 MSD.

Ethyl 4-Hydroxy-4-[2-(2-hydroxyethyl)phenyl]-1-piperidinecarboxylate (6) A 1.6 M solution of *n*-BuLi (13 ml, 21 mol) in hexane was added dropwise to a solution of 2-(2-bromophenyl)ethanol (**4**) (2.01 g, 10.0 mmol) in THF (10 ml) and Et_2O (10 ml) at −78 °C under an argon atmosphere. The mixture was stirred for 1 h at −78 °C, then 1-ethoxycarbonyl-4-piperidone (**5**) (1.88 g, 11.0 mmol) and Et_2O (10 ml) were added at the same temperature. The mixture was stirred for 6 h at room temperature, H_2O was added and the whole was extracted with ethyl acetate (AcOEt). The extract was washed with saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : AcOEt = 1 : 1) and recrystallized from Et_2O–hexane to give the diol (**6**, 1.34 g, 46%) as a colorless powder. mp 138—140 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.3 Hz), 1.85 (2H, d, J=13.2 Hz), 1.91—2.04 (2H, m), 2.66 (1H, br s), 3.30 (4H, m), 3.91 (2H, m), 4.02 (2H, m), 4.11 (2H, q, J=7.3 Hz), 4.26 (1H, br s), 7.15—7.30 (4H, m). FAB-MS *m/z*: 294 [(M+H)$^+$]. *Anal.* Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.38; H, 7.88; N, 4.74.

Ethyl 3,4-Dihydrospiro[1*H*-2-benzopyran-1,4′-piperidine]-1′-carboxyl-

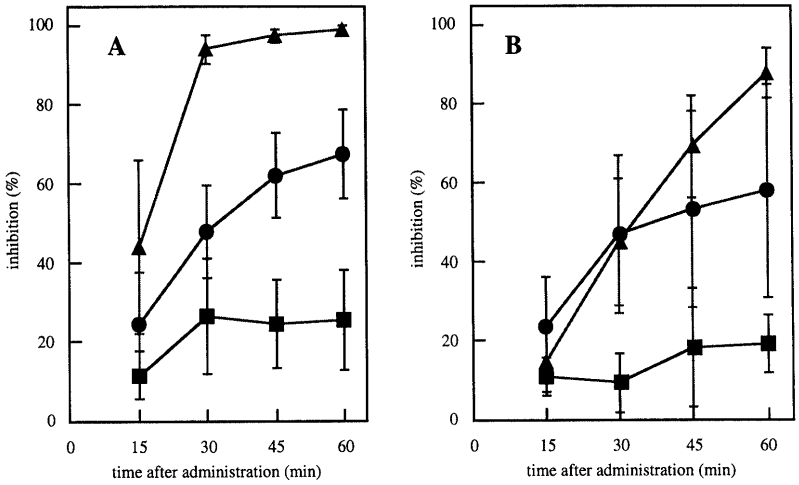


Fig. 2. Inhibitory Activity of YM-38336 (**58**, A) and (±)-SR48968 (B) to [β-Ala^8]-NKA(4-10)-Induced Bronchoconstriction in Guinea Pig after Intraduodenal Administration

Doses of the compounds were 1.0 mg/kg (▲), 0.5 mg/kg (●) and 0.3 mg/kg (■).

ate (7) TsCl (214 mg, 1.12 mmol) was added to a solution of compound **6** (300 mg, 1.02 mmol), pyridine (0.182 ml, 2.25 mmol) and CH_2Cl_2 (5 ml) at 0 °C. The mixture was stirred for 16 h at room temperature, then pyridine (0.082 ml, 1.0 mmol) and TsCl (194 mg, 1.02 mmol) were added at 0 °C. The whole was stirred for 22 h at room temperature, diluted with $CHCl_3$, and washed with H_2O, saturated aqueous $NaHCO_3$, 10% aqueous citric acid and saturated brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : AcOEt = 4 : 1) to give the carboxylate (**7**, 206 mg, 73%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J = 9.0 Hz), 1.85—1.94 (4H, m), 2.84 (2H, t, J = 5.4 Hz), 3.20 (2H, br s), 3.91 (2H, t, J = 5.4 Hz), 4.06 (2H, br s), 4.17 (2H, q, J = 7.1 Hz), 7.07—7.11 (2H, m), 7.13—7.21 (2H, m). EI-MS m/z: 275 (M^+).

3,4-Dihydrospiro[1*H*-2-benzopyran-1,4′-piperidine] Monohydrochloride (8) A mixture of compound **7** (190 mg, 0.690 mmol), 5 N NaOH (2 ml) and EtOH (2 ml) was heated to reflux for 24 h, then concentrated *in vacuo*. The residue was diluted with brine and extracted with AcOEt. The organic layer was washed with saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was diluted with MeOH–AcOEt, 4 N HCl–1,4-dioxane was added and the mixture was concentrated *in vacuo*. The residual colorless powder was recrystallized from MeOH–AcOEt to give the hydrochloride (**8**, 78 mg, 47%) as a colorless powder. mp 229—230 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.89—1.96 (2H, m), 2.34 (2H, dt, J = 13.8, 4.4 Hz), 2.77 (2H, t, J = 5.2 Hz), 3.01—3.11 (2H, m), 3.15—3.21 (2H, m), 3.86 (2H, t, J = 5.6 Hz), 7.13—7.28 (4H, m). EI-MS m/z: 203 (M^+). *Anal.* Calcd for $C_{13}H_{17}NO \cdot HCl$: C, 65.13; H, 7.57; N, 5.84. Found: C, 65.16; H, 7.53; N, 5.87.

Ethyl 4-Hydroxy-4-(2-mercaptomethylphenyl)-1-piperidinecarboxylate (10a) A 1.6 M solution of *n*-BuLi (100 ml, 160 mmol) in hexane was added dropwise to a solution of 2-bromobenzylthiol (**9a**) (15.5 g, 76.2 mmol) in THF (75 ml) and Et_2O (150 ml) at −100 °C under an argon atmosphere. The mixture was stirred for 1 h at −100 °C; then 1-ethoxycarbonyl-4-piperidone (**5**) (101 g, 591 mmol) and THF (50 ml) were added to the solution at the same temperature. The mixture was stirred for 4 h at −100 °C, poured into 1 N HCl and extracted with AcOEt. The extract was washed with H_2O and saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : AcOEt = 4 : 1) to give the mercaptoalcohol (**10a**, 17.5 g, 78%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.21—1.38 (7H, m), 2.40—2.48 (2H, m), 3.72—3.75 (4H, m), 4.09—4.21 (2H, m), 7.19—7.36 (7H, m). FAB-MS m/z: 296 [$(M+H)^+$].

Ethyl Spiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine]-1′-carboxylate (11a) TFA (100 ml) was added to a solution of compound **10a** (17.5 g, 59.2 mmol) in CH_2Cl_2 (200 ml) at 0 °C. The mixture was stirred for 2 h at room temperature, then poured into H_2O. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : AcOEt = 9 : 1) to give the carboxylate (**11a**, 9.14 g, 56%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J = 7.0 Hz), 1.88—1.91 (2H, m), 2.04—2.12 (2H, m), 3.03—3.11 (2H, m), 4.09—4.28 (6H, m), 7.15—7.18 (1H, m), 7.25—7.33 (3H, m). EI-MS m/z: 277 (M^+).

The following compound was similarly prepared from 2-(2-bromophenyl)mercaptoethanol (**9b**).

Ethyl 3,4-Dihydrospiro[1*H*-2-benzothiopyran-1,4′-piperidine]-1′-carboxylate (**11b**): ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J = 7.3 Hz), 1.86—1.95 (2H, m), 2.18 (2H, dt, J = 13.5, 4.3 Hz), 2.82 (2H, t, J = 6.0 Hz), 3.13 (2H, t, J = 6.0 Hz), 3.30—3.38 (2H, m), 4.00—4.21 (4H, m), 7.11—7.17 (2H, m), 7.20—7.24 (1H, m), 7.34 (1H, d, J = 8.0 Hz). FAB-MS m/z: 292 [$(M+H)^+$].

Spiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine] (12a) A 5 N NaOH solution (120 ml) was added to a solution of compound **11a** (12.4 g, 44.7 mmol) in EtOH (120 ml) at 0 °C. The mixture was heated to reflux for 22 h, then concentrated *in vacuo*. The residue was diluted with H_2O and extracted with $CHCl_3$. The organic layer was washed with saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give the piperidine (**12a**, 9.08 g, 99%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.78 (1H, br s), 1.88—1.94 (2H, m), 2.10 (2H, dt, J = 14.8, 4.0 Hz), 2.94 (2H, dt, J = 12.5, 2.3 Hz), 3.10—3.16 (2H, m), 4.17 (2H, s), 7.18—7.28 (4H, m). EI-MS m/z: 205 (M^+).

3,4-Dihydrospiro[1*H*-2-benzothiopyran-1,4′-piperidine] Monohydrochloride (12b) A mixture of compound **11b** (398 mg, 1.37 mmol), 5 N NaOH (5 ml) and EtOH (5 ml) was heated to reflux for 13 h, then concentrated *in vacuo*. The residue was diluted with brine and extracted with $CHCl_3$. The organic layer was washed with saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was diluted with MeOH, 4 N HCl–1,4-dioxane was added and the mixture was concentrated *in vacuo*. The residue was crystallized from AcOEt to give the hydrochloride (**12b**, 281 mg, 80%) as a colorless powder. ^{1}H-NMR (DMSO-d_6) δ: 1.97 (2H, d, J = 14.5 Hz), 2.59 (2H, dt, J = 13.8, 3.8 Hz), 2.84 (2H, t, J = 5.8 Hz), 3.06 (2H, t, J = 6.0 Hz), 3.04—3.30 (4H, m), 7.14—7.20 (2H, m), 7.28 (1H, t, J = 7.5 Hz), 7.47 (1H, t, J = 8.0 Hz), 8.98 (1H, br s), 9.33 (1H, br s). EI-MS m/z: 219 (M^+).

***tert*-Butyl Spiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine]-1′-carboxylate (13)** $(Boc)_2O$ (2.14 g, 9.82 mmol) was added to a mixture of compound **12a** (1.68 g, 8.18 mmol), Et_3N (1.71 ml, 12.3 mmol) and CH_2Cl_2 (40 ml) at 0 °C. The mixture was stirred at room temperature overnight, diluted with AcOEt, and washed with H_2O, 10% aqueous citric acid and saturated brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : AcOEt = 4 : 1) to give the carboxylate (**13**, 1.25 g, 63%) as colorless crystals. mp 126—129 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (9H, s), 1.87 (2H, d, J = 12.2 Hz), 2.06 (2H, dt, J = 12.5, 4.3 Hz), 3.02 (2H, s), 4.12—4.31 (4H, m), 7.15 (1H, d, J = 6.1 Hz), 7.22—7.27 (3H, m). EI-MS m/z: 305 (M^+). *Anal.* Calcd for $C_{17}H_{23}NO_2S$: C, 66.85; H, 7.59; N, 4.59. Found: C, 66.82; H, 7.63; N, 4.51.

1′-*tert*-Butoxycarbonylspiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine] 2-Oxide (14) A 0.50 M aqueous $NaIO_4$ solution (6.8 ml, 3.4 mmol) was added to a solution of compound **13** (1.00 g, 3.27 mmol) in MeOH (20 ml) and EtOH (10 ml) at 0 °C. The mixture was stirred at room temperature overnight and concentrated *in vacuo*. The residue was diluted with H_2O and the mixture was extracted with $CHCl_3$. The extract was washed with saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give the sulfoxide (**14**) as a colorless oil containing impurities (3.94 g). FAB-MS m/z: 322 [$(M+H)^+$].

Spiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine] 2-Oxide (15) TFA (36 ml) was added to a solution of compound **14** (3.91 g, containing impurities) in CH_2Cl_2 (90 ml) at 0 °C. The mixture was stirred for 2 h at the same temperature, then concentrated *in vacuo*. The residue was taken up in H_2O, and the mixture was washed with $CHCl_3$. The aqueous layer was alkalized with 1 N NaOH and extracted with $CHCl_3$. The extract was washed with saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give the piperidine (**15**, 2.18 g, 92% from **13**) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.55—1.62 (2H, m), 1.86—1.92 (2H, m), 2.25 (2H, dt, J = 13.3, 4.5 Hz), 2.38—2.44 (2H, m), 4.01 (1H, d, J = 16.5 Hz), 4.34 (1H, d, J = 17.0 Hz), 7.28—7.38 (4H, m). EI-MS m/z: 221 (M^+).

1′-Ethoxycarbonylspiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine] 2,2-Dioxide (16) A solution of compound **11a** (1.00 g, 3.61 mmol) in 31% aqueous H_2O_2 (0.800 ml, 8.09 mmol) was stirred for 4 h at room temperature and then heated for 2 h at 80 °C. The reaction mixture was diluted with AcOEt, and washed with H_2O and saturated brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$) to give the dioxide (**16**, 931 mg, 83%) as a colorless powder. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J = 7.0 Hz), 1.96—2.06 (2H, m), 2.39 (2H, d, J = 15.9 Hz), 3.42—3.56 (2H, m), 4.07—4.25 (4H, m), 4.37 (2H, s), 7.20—7.23 (1H, m), 7.25—7.29 (1H, m), 7.32—7.42 (2H, m). FAB-MS m/z: 310 [$(M+H)^+$].

The following compound was prepared by the same method as described for compound **12a**.

Spiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine] 2,2-Dioxide (**17**): ^{1}H-NMR ($CDCl_3$) δ: 1.72 (1H, br s), 1.97—2.06 (2H, m), 2.38 (2H, d, J = 14.0 Hz), 3.03—3.11 (2H, m), 3.28 (2H, dt, J = 24.4, 2.5 Hz), 4.34 (2H, s), 7.25—7.29 (1H, m), 7.30—7.35 (2H, m), 7.39—7.42 (1H, m). EI-MS m/z: 237 (M^+).

3,4-Dihydrospiro[1*H*-2-benzothiopyran-1,4′-piperidine] 2-Oxide (18) A 0.50 M aqueous $NaIO_4$ solution (2.2 ml, 1.1 mmol) was added to a solution of compound **12b** (260 mg, 1.02 mmol) in MeOH (10 ml) at 0 °C. The mixture was stirred at room temperature overnight and concentrated *in vacuo*. The residue was taken up in H_2O and 1 N NaOH, and the mixture was extracted with $CHCl_3$. The extract was washed with saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give the sulfoxide (**18**, 206 mg, 86%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 1.76—1.82 (1H, m), 2.14—2.34 (2H, m), 2.38—2.52 (1H, m), 2.80—2.92 (2H, m), 2.96—3.02 (1H, m), 3.08—3.12 (1H, m), 3.14—3.22 (1H, m), 3.24—3.44 (2H, m), 3.62—3.74 (1H, m), 7.12—7.20 (2H, m), 7.24—7.34 (1H, m), 7.44—7.55 (1H, m). FAB-MS m/z: 236 [$(M+H)^+$].

1-Benzyl-3,4-dihydrospiro[isoquinoline-1(2*H*),4′-piperidine] Dihydrochloride (20) A 1 N NaOH solution (30 ml) was added to a mixture of 1-benzyl-3-oxo-3,4-dihydrospiro[isoquinoline-1(2*H*),4′-piperidine] hydrochloride (**19**, 6.55 g, 19.1 mmol) and H_2O (100 ml), and the free base of compound **19** was extracted with $CHCl_3$. The extract was washed with saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in THF (120 ml) and BH_3–THF complex (1.0 M solution in THF, 58 ml, 58 mmol) was added at 0 °C. The mixture was heated to reflux for 4 h, then EtOH (100 ml) and diethanolamine (4.02 g, 38.2 mmol) were added at 0 °C, and the mixture was heated again to reflux for 14 h. It was then concentrated *in vacuo*, diluted with brine and extracted with $CHCl_3$. The extract was washed with saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was diluted with AcOEt, 4 N HCl–1,4-dioxane (15 ml) was added and the product was recrystallized from MeOH–AcOEt–Et_2O to give the dihydrochloride (**20**, 4.09 g, 59%) as a colorless powder. ^{1}H-NMR (DMSO-d_6) δ: 2.34—2.43 (2H, m), 3.78—3.88 (2H, m), 3.04—3.12 (2H, m), 3.30—3.48 (4H, m), 3.80—3.92 (2H, m), 4.32—4.38 (2H, m), 7.20—7.24 (1H, m), 7.26—7.36 (2H, m), 7.42—7.52 (4H, m), 7.58—7.68 (2H, m), 10.28 (2H, br s), 11.79 (1H, br s). EI-MS *m/z*: 292 (M^+).

3,4-Dihydrospiro[isoquinoline-1(2*H*),4′-piperidine] Dihydrochloride (21) A mixture of compound **20** (4.09 g, 11.2 mmol), 20% $Pd(OH)_2$ on carbon (2.0 g), EtOH (60 ml) and H_2O (20 ml) was stirred under a hydrogen atmosphere (4 kg/cm^2) for 18 h at room temperature. The catalyst was removed by filtration on Celite and the filtrate was concentrated *in vacuo*. The resultant colorless powder was recrystallized from H_2O–MeOH–AcOEt to give the dihydrochloride (**21**, 2.71 g, 88%) as a colorless powder. ^{1}H-NMR (DMSO-d_6) δ: 2.36 (2H, d, J=15.5 Hz), 2.67 (2H, t, J=29 Hz), 3.10 (2H, t, J=6.0 Hz), 3.30—3.43 (4H, m), 3.64—3.78 (2H, m), 7.23 (1H, d, J=8.0 Hz), 7.29 (1H, t, J=7.3 Hz), 7.35 (1H, t, J=7.5 Hz), 7.51 (1H, d, J=8.0 Hz), 9.26 (1H, br s), 9.95 (1H, br s), 10.31 (2H, br s). EI-MS *m/z*: 202 (M^+).

3-Oxo-3,4-dihydrospiro[isoquinoline-1(2*H*),4′-piperidine] Monohydrochloride (22) A mixture of compound **19** (10.1 g, 33.0 mmol), 20% $Pd(OH)_2$ on carbon (2.0 g), EtOH (500 ml) and H_2O (400 ml) was stirred under atmospheric pressure of hydrogen for 3 h at room temperature. The catalyst was removed by filtration on Celite, and the filtrate was concentrated *in vacuo*. The resultant colorless powder was recrystallized from MeOH–AcOEt to give the hydrochloride (**22**, 7.16 g, 86%) as a pale yellow powder. ^{1}H-NMR (DMSO-d_6) δ: 1.89 (2H, d, J=14.0 Hz), 2.40 (2H, dt, J=14.3, 4.2 Hz), 3.21—3.45 (4H, m), 3.60 (2H, s), 7.22 (1H, d, J=7.5 Hz), 7.26—7.35 (2H, m), 7.39 (1H, d, J=7.5 Hz), 8.37 (1H, s), 9.16 (2H, br s). EI-MS *m/z*: 216 (M^+).

***tert*-Butyl (±)-*N*-[2-(3,4-Dichlorophenyl)-4-hydroxybutyl]-*N*-methylcarbamate (25)** A mixture of Ac_2O (15.0 ml, 168 mmol) and HCOOH (15.0 ml, 398 mmol) was stirred for 1 h at 60 °C, and then a solution of (±)-4-amino-3-(3,4-dichlorophenyl)butan-1-ol (**23**, 7.84 g, 33.5 mmol) in THF (70 ml) was added at 0 °C. The whole was stirred for 2 h at room temperature, poured into H_2O and neutralized with $NaHCO_3$, and the product was extracted with $CHCl_3$. The extract was washed with saturated brine, and the organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. A solution of the residue in THF (80 ml) was treated with BH_3–THF complex (1.0 M solution in THF, 100 ml, 0.10 mol) at 0 °C, and the mixture was heated to reflux for 5 h. EtOH (80 ml) and diethanolamine (6.42 ml, 67.0 mmol) were added at 0 °C, and the whole was heated again to reflux for 14 h and concentrated *in vacuo*. The residue was diluted with H_2O and extracted with AcOEt. The extract was washed with saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was diluted with 1,4-dioxane (100 ml), then Et_3N (7.00 ml, 50.3 mmol) and $(Boc)_2O$ (9.30 g, 42.6 mmol) were added at 0 °C and the reaction mixture was stirred for 30 min at 60 °C. It was concentrated *in vacuo*, and the residue was diluted with H_2O, then extracted with Et_2O. The extract was washed with 5% aqueous $KHSO_4$ and saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give the carbamate (**25**, 12.1 g, quant.) as a colorless oil ^{1}H-NMR ($CDCl_3$) δ: 1.39 (9H, s), 1.73—1.88 (2H, m), 2.64—2.74 (3H, m), 3.11—3.61 (5H, m), 7.07—7.38 (3H, m). FAB-MS *m/z*: 348 [$(M+H)^+$].

***tert*-Butyl (±)-*N*-[2-(3,4-Dichlorophenyl)-4-(spiro[isobenzofuran-1(3*H*),4′-piperidine]-1′-yl)butyl]-*N*-methylcarbamate (27)** MsCl (5.55 ml, 71.8 mmol) was added to a mixture of compound **25** (20.0 g, 57.4 mmol), Et_3N (12.0 ml, 86.1 mmol) and CH_2Cl_2 (200 ml) at 0 °C, and the whole was stirred for 2 h at room temperature, then diluted with H_2O and extracted with $CHCl_3$. The extract was washed with saturated aqueous $NaHCO_3$ and saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Spiro[isobenzofuran-1(3*H*),4′-piperidine] (**26**) (16.3 g, 86.1 mmol), Et_3N (24.0 ml, 172 mmol) and *N*,*N*-dimethylformamide (DMF, 100 ml) were added to the residue, and the mixture was stirred overnight at 70 °C, poured into H_2O and extracted with AcOEt. The extract was washed with H_2O and saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$: MeOH = 24 : 1) to give the carbamate (**27**, 18.7 g, 63%) as a pale brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (9H, s), 1.73—1.77 (4H, m), 1.90—1.98 (3H, m), 2.26—2.38 (4H, m), 2.64—2.83 (5H, m), 2.94—3.49 (3H, m), 5.05 (2H, s), 7.03—7.38 (7H, m). FAB-MS *m/z*: 519 [$(M+H)^+$].

(±)-1′-[3-(3,4-Dichlorophenyl)-4-methylaminobutyl]spiro[isobenzofuran-1(3*H*),4′-piperidine] Dihydrochloride (28) TFA (40 ml) was added to a mixture of compound **27** (18.6 g, 35.8 mmol) and CH_2Cl_2 at 0 °C, and the whole was stirred for 20 min at 0 °C and for 40 min at room temperature, then concentrated *in vacuo*. The residue was diluted with H_2O, alkalized with 0.5 N NaOH and extracted with AcOEt. The extract was washed with saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in AcOEt, then 4 N HCl–1,4-dioxane was added and the mixture was concentrated *in vacuo* to give the dihydrochloride (**28**, 18.2 g, quant.) as a pale yellow amorphous solid. ^{1}H-NMR (DMSO-d_6) δ: 1.81—2.08 (6H, m), 2.45—2.63 (7H, m), 2.81—3.04 (5H, m), 5.06 (2H, s), 7.07—7.41 (7H, m). EI-MS *m/z*: 418 (M^+).

(±)-*N*-[2-(4-Chlorophenyl)-4-hydroxybutyl]-*N*-methylbenzamide (30a) Benzoyl chloride (2.2 ml, 19 mmol) was added to a mixture of (±)-4-amino-3-(4-chlorophenyl)butan-1-ol (**29a**, 1.00 g, 4.68 mmol), Et_3N (3.3 ml, 24 mmol) and CH_2Cl_2 (25 ml) at 0 °C, and the whole was stirred overnight at room temperature. It was diluted with AcOEt and washed with 1 N HCl, saturated $NaHCO_3$ and saturated brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in MeOH (20 ml), and 10% aqueous NaOH (10 ml) was added. The mixture was stirred for 3 h at 60 °C, concentrated *in vacuo*, diluted with H_2O and extracted with AcOEt. The extract was washed with 1 N NaOH, H_2O and saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$: MeOH = 50 : 1) to give the benzamide (**30a**, 876 mg, 59%). ^{1}H-NMR ($CDCl_3$) δ: 1.80—2.03 (2H, m), 2.68, 3.02 (3H, each s), 3.29—3.38 (1H, m), 3.45—3.60 (2H, m), 3.64—3.73 (1H, m), 3.93—4.01 (1H, m), 7.07—7.39 (9H, m). EI-MS *m/z*: 317 (M^+).

The following compounds were similarly prepared.

(±)-*N*-[2-(3-Chlorophenyl)-4-hydroxybutyl]-*N*-methylbenzamide (**30b**): ^{1}H-NMR ($CDCl_3$) δ: 1.71—2.04 (2H, m), 2.68, 3.03 (3H, each s), 3.30—3.38 (1H, m), 3.47—3.61 (2H, m), 3.67—3.72 (1H, m), 4.00—4.07 (1H, m), 6.82—7.40 (9H, m). EI-MS *m/z*: 317 (M^+).

(±)-*N*-[2-(2-Chlorophenyl)-4-hydroxybutyl]-*N*-methylbenzamide (**30c**): ^{1}H-NMR ($CDCl_3$) δ: 1.88—2.10 (2H, m), 2.75, 3.05 (3H, each s), 3.31—4.02 (5H, m), 7.18—7.21 (3H, m), 7.29—7.46 (6H, m). EI-MS *m/z*: 317 (M^+).

(±)-*N*-[2-(4-Fluorophenyl)-4-hydroxybutyl]-*N*-methylbenzamide (**30d**): ^{1}H-NMR ($CDCl_3$) δ: 1.75—2.03 (2H, m), 2.67, 3.02 (3H, each s), 3.29—3.40 (1H, m), 3.49—3.72 (3H, m), 3.91—4.00 (1H, m), 6.86—7.39 (9H, m). EI-MS *m/z*: 301 (M^+).

(±)-*N*-[2-(4-Bromophenyl)-4-hydroxybutyl]-*N*-methylbenzamide (**30e**): ^{1}H-NMR ($CDCl_3$) δ: 1.73—2.04 (2H, m), 2.68, 3.02 (3H, each s), 3.23—3.40 (1H, m), 3.49—3.74 (3H, m), 3.94—4.03 (1H, m), 6.75—7.25 (3H, m), 7.30—7.52 (6H, m). EI-MS *m/z*: 361 (M^+).

(±)-*N*-[4-Hydroxy-2-(4-trifluoromethylphenyl)butyl]-*N*-methylbenzamide (**30f**): ^{1}H-NMR ($CDCl_3$) δ: 1.77—2.06 (2H, m), 2.69, 3.05 (3H, each s), 3.12—3.76 (4H, m), 3.94—4.04 (1H, m), 6.98—7.67 (9H, m). EI-MS *m/z*: 351 (M^+).

(±)-*N*-[4-Hydroxy-2-(4-methylphenyl)butyl]-*N*-methylbenzamide (**30g**): ^{1}H-NMR ($CDCl_3$) δ: 1.71—2.05 (2H, m), 2.33 (3H, s), 2.65, 3.00 (3H, each s), 3.20—3.73 (4H, m), 3.87—4.07 (1H, m), 6.79—7.39 (9H, m). EI-MS *m/z*: 297 (M^+).

(±)-*N*-[4-Hydroxy-2-(4-methoxyphenyl)butyl]-*N*-methylbenzamide (**30h**): ^{1}H-NMR ($CDCl_3$) δ: 1.84—2.01 (2H, m), 2.65, 3.01 (3H, each s), 3.23—3.39 (1H, m), 3.44—3.71 (3H, m), 3.80 (3H, s), 3.97—4.02 (1H, m), 6.76—6.91 (3H, m), 7.09—7.24 (3H, m), 7.31—7.39 (3H, m). FAB-MS *m/z*: 314 [$(M+H)^+$].

(±)-*N*-[4-Hydroxy-2-(2-naphthyl)butyl]-*N*-methylbenzamide (**30i**): ^{1}H-NMR ($CDCl_3$) δ: 1.77—2.13 (2H, m), 2.63, 3.04 (3H, each s), 3.19—3.40 (1H, m), 3.45—3.75 (3H, m), 4.12—4.20 (1H, m), 6.95—7.88

Table 7. ^{1}H-NMR[a] and Mass Spectral Data for Spiro-substituted Piperidines

Compd. No.	NMR (δ)	MS m/z:
32	1.80—1.84 (2H, m), 1.99—2.36 (7H, m), 2.67—3.27 (8H, m), 3.41—3.75 (4H, m), 5.03 (2H, s), 6.59—7.77 (11H, m), 10.78 (1H, br s)	537 [(M+H)$^+$] (FAB)
33	1.76—2.44 (9H, m), 2.54—3.21 (7H, m), 3.29—3.57 (5H, m), 5.01, 5.04 (2H, each s), 7.08—7.70 (11H, m), 10.82 (1H, br s)	537 [(M+H)$^+$] (FAB)
34	1.62—1.70 (3H, m), 1.85—1.97 (3H, m), 2.17—2.51 (4H, m), 2.74—3.21 (6H, m), 3.52—3.75 (2H, m), 4.96 (2H, s), 6.60 (2H, s), 7.09—7.66 (11H, m)	541 [(M+H)$^+$] (FAB)
35	1.80—2.37 (6H, m), 2.71—2.75 (2H, m), 2.86—3.26 (6H, m), 3.45—3.68 (4H, m), 5.03 (2H, s), 6.79—7.95 (11H, m), 10.84 (1H, br s)	556 (M$^+$) (EI)
36	1.61—1.64 (3H, m), 1.85—1.97 (3H, m), 2.13—2.51 (4H, m), 2.67—3.00 (6H, m), 3.51—3.75 (2H, m), 4.96 (2H, s), 6.60 (2H, s), 6.98—7.65 (11H, m)	601 [(M+H)$^+$] (FAB)
37	1.60—1.63 (2H, m), 1.82—1.97 (4H, m), 2.20—2.51 (4H, m), 2.70—2.92 (5H, m), 3.20—3.73 (3H, m), 3.77 (3H, s), 4.96 (2H, s), 6.60 (2H, s), 6.90—7.55 (11H, m)	533 [(M+H)$^+$] (FAB)
39	1.59—1.63 (3H, m), 1.82—1.95 (3H, m), 2.05 (3H, s), 2.20—2.45 (4H, m), 2.70—2.88 (5H, m), 3.05—3.20 (1H, m), 3.55—3.73 (2H, m), 4.95 (2H, s), 6.60 (2H, s), 7.00—7.12 (3H, m), 7.22—7.35 (5H, m), 7.56—7.60 (3H, m), 10.07 (br s)	580 [(M+H)$^+$] (FAB)
40	1.62—1.70 (3H, m), 1.82—1.97 (3H, m), 2.14—2.35 (3H, m), 2.64—2.93 (6H, m), 3.22—3.80 (3H, m), 4.95, 4.97 (2H, each s), 6.60 (2H, s), 7.05—7.64 (9H, m), 7.80—7.90 (2H, m)	548 [(M+H)$^+$] (FAB)
41	1.55—1.65 (3H, m), 1.83—1.93 (3H, m), 2.12—2.45 (3H, m), 2.66—3.00 (6H, m), 3.23—3.81 (3H, m), 4.94, 4.96 (2H, each s), 6.60 (2H, s), 7.06—7.68 (9H, m), 8.18—8.26 (2H, m)	568 [(M+H)$^+$] (FAB)
42	0.85—0.91 (3H, m), 1.62—1.65 (2H, m), 1.80—2.10 (4H, m), 2.15—2.55 (6H, m), 2.69—2.95 (5H, m), 3.01—3.09 (3H, m), 3.41—3.57 (2H, m), 4.96 (2H, s), 6.59 (2H, s), 7.22—7.37 (5H, m), 7.54—7.66 (2H, m)	475 [(M+H)$^+$] (FAB)
43	1.07—1.39 (6H, m), 1.51—1.67 (4H, m), 1.79—1.83 (2H, m), 2.05—2.41 (5H, m), 2.76—2.80 (4H, m), 3.10—3.17 (4H, m), 3.48—3.58 (4H, m), 5.03, 5.04 (2H, each s), 7.14—7.71 (7H, m)	529 [(M+H)$^+$] (FAB)
44	1.77—1.84 (2H, m), 1.99—2.37 (4H, m), 2.73—3.18 (7H, m), 3.29—3.76 (5H, m), 5.02, 5.04 (2H, each s), 6.98—7.94 (10H, m), 8.54—8.58 (1H, m), 10.78, 10.82 (1H, each br s)	524 [(M+H)$^+$] (FAB)
45	1.80—1.83 (2H, m), 1.99—2.39 (4H, m), 2.80—2.92 (4H, m), 2.92—3.25 (4H, m), 3.42—3.45 (2H, m), 3.61—3.67 (2H, m), 5.03 (2H, s), 6.85—7.67 (10H, m), 10.68 (1H br s)	529 [(M+H)$^+$] (FAB)
46	1.58—1.64 (3H, m), 1.83—2.00 (3H, m), 2.13—2.51 (4H, m), 2.68—3.27 (6H, m), 3.60—3.84 (2H, m), 4.97 (2H, s), 6.60 (2H, s), 7.03—7.96 (14H, m)	573 [(M+H)$^+$] (FAB)
47	1.55—1.58 (2H, m), 1.78—1.88 (3H, m), 2.05—2.40 (5H, m), 2.60—3.15 (6H, m), 3.62—3.82 (2H, m), 4.94 (2H, s), 6.91—7.63 (10H, m), 8.30 (1H, d, J=14.2 Hz), 12.57 (1H, br s)	563 [(M+H)$^+$] (FAB)
49	1.73—2.39 (6H, m), 2.59—3.87 (12H, m), 5.03 (2H, s), 6.90—7.53 (13H, m), 10.38, 11.97 (1H, each br s)	489 [(M+H)$^+$] (FAB)
50	1.74—2.40 (6H, m), 2.54—3.95 (12H, m), 5.03 (2H, s), 6.91—7.69 (13H, m), 10.53, 11.98 (1H, each br s)	488 (M$^+$) (EI)
51	1.50—2.03 (6H, m). 2.05—2.46 (4H, m), 2.59—3.24 (6H, m), 3.39—3.72 (2H, m), 4.96 (2H, s), 6.59 (2H, s), 7.00—7.47 (13H, m)	472 (M$^+$) (EI)
52	1.49—2.06 (6H, m), 2.07—3.76 (12H, m), 4.96 (2H, s), 6.59 (2H, s), 6.92—7.60 (13H, m)	533 [(M+H)$^+$] (FAB)
53	1.50—2.07 (6H, m), 2.10—2.47 (3H, m), 2.61—3.84 (9H, m), 4.95 (2H, s), 6.60 (2H, s), 6.96—7.11 (2H, m), 7.20—7.42 (8H, m), 7.56—7.78 (3H, m)	523 [(M+H)$^+$] (FAB)
54	1.46—1.72 (3H, m), 1.88—2.01 (3H, m), 2.05—2.47 (6H, m), 2.58—2.93 (5H, m), 3.06—3.80 (4H, m), 4.96 (2H, s), 6.59 (2H, s), 6.84—7.17 (5H, m), 7.19—7.30 (5H, m), 7.34—7.43 (3H, m)	469 [(M+H)$^+$] (FAB)
55	1.48—1.73 (3H, m), 1.79—2.06 (4H, m), 2.10—2.48 (4H, m), 2.53—3.16 (5H, m), 3.34—3.59 (2H, m), 3.74 (3H, s), 4.97 (2H, s), 6.59 (2H, s), 6.88—6.95 (3H, m), 7.05—7.18 (2H, m), 7.21—7.31 (5H, m), 7.34—7.43 (3H, m)	485 [(M+H)$^+$] (FAB)
56	1.54—2.16 (6H, m), 2.21—2.48 (3H, m), 2.61—2.94 (5H, m), 3.10—3.90 (2H, m), 4.94 (2H, s), 6.60 (2H, s), 6.96—7.42 (9H, m), 7.47—7.59 (3H, m), 7.78—7.95 (4H, m)	505 [(M+H)$^+$] (FAB)
57	1.51—1.99 (4H, m), 2.00—2.45 (6H, m), 2.68—3.09 (6H, m), 3.14—3.25 (1H, m), 3.46—3.66 (2H, m), 3.72—3.82 (1H, m), 4.12 (2H, s), 6.61 (2H, s), 6.98—7.18 (3H, m), 7.22—7.70 (9H, m)	539 [(M+H)$^+$] (FAB)
58	1.57—1.63 (3H, m), 1.83—2.44 (8H, m), 2.70—3.27 (5H, m), 3.54—3.91 (2H, m), 4.00 (1H, d, J=16.4 Hz), 4.32 (1H, d, J=16.4 Hz), 6.80—7.19 (3H, m), 7.30—7.42 (9H, m)	555 [(M+H)$^+$] (FAB)
59	1.50—1.75 (2H, m), 1.81—2.12 (5H, m), 2.15—2.48 (3H, m), 2.65—3.05 (5H, m), 3.16—3.29 (1H, m), 3.45—3.67 (2H, m), 3.76—3.85 (2H, m), 4.58 (2H, s), 6.62 (2H, s), 6.98—7.16 (3H, m), 7.20—7.69 (9H, m)	571 [(M+H)$^+$] (FAB)
60	1.58—1.89 (3H, m), 1.89—2.12 (3H, m), 2.20—3.08 (12H, m), 3.16—3.29 (1H, m), 3.46—3.88 (4H, m), 6.59 (2H, s), 6.97—7.70 (12H, m)	537 [(M+H)$^+$] (FAB)
61	1.54—2.48 (9H, m), 2.53—3.08 (8H, m), 3.14—3.40 (3H, m), 3.47—3.81 (2H, m), 6.12 (2H, s), 7.01—7.30 (6H, m), 7.33—7.68 (6H, m)	569 [(M+H)$^+$] (FAB)
62	1.93—2.48 (4H, m), 2.63—3.29 (10H, m), 3.31—3.87 (8H, m), 6.88—7.77 (12H, m)	536 [(M+H)$^+$] (FAB)
63	1.58—1.82 (3H, m), 1.88—2.21 (4H, m), 2.29—2.41 (1H, m), 2.52—3.27 (10H, m), 3.59—3.81 (2H, m), 6.59 (2H, s), 6.99—7.30 (6H, m), 7.34—7.69 (6H, m), 7.77—7.91 (1H, m)	550 [(M+H)$^+$] (FAB)

a) ^{1}H-NMR spectra were taken in DMSO-d_6 except for compound **58** in $CDCl_3$.

(12H, m). EI-MS *m/z*: 333 (M^+).

(±)-*N*-[2-(3,4-Dichlorophenyl)-4-(spiro[isobenzofuran-1(3*H*),4′-piperidin]-1′-yl)butyl]-4,*N*-dimethylbenzamide Monohydrochloride Hemihydrate (31, Method A) 4-Methylbenzoyl chloride (0.125 ml, 0.948 mmol) was added to a mixture of compound **28** (265 mg, 0.632 mmol), Et_3N (0.176 ml, 1.26 mmol) and CH_2Cl_2 (10 ml) at 0 °C, and the whole was stirred for 36 h at room temperature, diluted with brine and extracted with $CHCl_3$. The extract was washed with saturated $NaHCO_3$ and saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$: MeOH = 49 : 1) and dissolved in AcOEt, then 4 N HCl–1,4-dioxane was added at 0 °C, and the mixture was concentrated *in vacuo* to give the hydrochloride (**31**, 260 mg, 72%) as a pale yellow amorphous solid. ^{1}H-NMR (DMSO-d_6) δ: 1.80—1.83 (2H, m), 1.91—2.37 (7H, m), 2.70—3.57 (10H, m), 5.03 (2H, s), 6.85—7.68 (11H, m), 10.79 (1H, br s). FAB-MS *m/z*: 537 [$(M+H)^+$]. *Anal.* Calcd for $C_{31}H_{34}Cl_2N_2O_2 \cdot HCl \cdot 0.5H_2O$: C, 63.87; H, 6.22; N, 4.81. Found: C, 63.54; H, 6.36; N, 4.61.

(±)-*N*-[2-(3,4-Dichlorophenyl)-4-(spiro[isobenzofuran-1(3*H*),4′-piperidin]-1′-yl)butyl]-4-dimethylamino-*N*-methylbenzamide (38, Method B) EDC·HCl (110 mg, 0.572 mmol) and Et_3N (0.080 ml, 0.57 mmol) were added to a mixture of compound **28** (200 mg, 0.477 mmol), 4-dimethylaminobenzoic acid (95 mg, 0.57 mmol), HOBt (97 mg, 0.72 mmol) and CH_2Cl_2 (5 ml) at 0 °C, and the mixture was stirred for 9 h at room temperature. It was then diluted with brine and extracted with $CHCl_3$. The extract was washed with saturated $NaHCO_3$ and saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$: MeOH = 49 : 1) and recrystallized from MeOH to give the benzamide (**38**, 120 mg, 44%) as a colorless powder. mp 172—174 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.54—1.57 (2H, m), 1.65—1.85 (4H, m), 2.12—2.22 (4H, m), 2.57—2.69 (2H, m), 2.81 (3H, s), 2.92 (3H, s), 3.10—3.16 (1H, m), 3.58 (1H, dd, J = 14.2, 5.9 Hz), 3.70 (1H, dd, J = 13.7, 10.3 Hz), 4.93 (2H, s), 6.64 (2H, d, J = 8.8 Hz), 7.00 (2H, d, J = 8.8 Hz), 7.20—7.28 (5H, m), 7.43—7.54 (2H, m). FAB-MS *m/z*: 566 [$(M+H)^+$]. *Anal.* Calcd for $C_{32}H_{37}Cl_2N_3O_2$: C, 67.84; H, 6.58; N, 7.42. Found: C, 67.70; H, 6.49; N, 7.40.

(±)-*N*-[2-(4-Chlorophenyl)-4-(spiro[isobenzofuran-1(3*H*),4′-piperidin]-1′-yl)butyl]-*N*-methylbenzamide Monohydrochloride Hemihydrate (48, Method C) A mixture of compound **30a** (300 mg, 0.944 mmol), Et_3N (0.260 ml, 1.87 mmol) and CH_2Cl_2 (5 ml) was treated with MsCl (0.088 ml, 1.1 mmol) at 0 °C, and the whole was stirred for 2 h at room temperature. It was diluted with AcOEt, washed with saturated $NaHCO_3$ and saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in DMF (10 ml), then spiro[isobenzofuran-1(3*H*),4′-piperidine] (**26**) (215 mg, 1.14 mmol) and Et_3N (0.390 ml, 2.80 mmol) were added, and the mixture was stirred overnight at 70 °C, diluted with H_2O and extracted with AcOEt. The extract was washed with saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$: MeOH = 49 : 1) and dissolved in AcOEt, then 4 N HCl–1,4-dioxane was added at 0 °C, and the mixture was concentrated *in vacuo* to give the hydrochloride (**48**, 375 mg, 76%) as a colorless amorphous solid. ^{1}H-NMR (DMSO-d_6) δ: 1.73—2.45 (6H, m), 2.57—3.79 (12H, m), 5.03 (2H, s), 6.92—7.55 (13H, m), 10.78, 11.98 (1H, each br s). FAB-MS *m/z*: 489 [$(M+H)^+$]. *Anal.* Calcd for $C_{30}H_{33}ClN_2O_2 \cdot HCl \cdot 0.5H_2O$: C, 67.41; H, 6.60; N, 5.24. Found: C, 67.59; H, 6.84; N, 5.11.

Compounds **32**—**37**, **39**—**47** and **49**—**63** were prepared according to the methods described above (method A—C). Their melting points, elemental analyses and yields are summarized in Tables 1—4, and their NMR and MS data in Table 7.

(±)-4-Amino-*N*-[2-(3,4-dichlorophenyl)-4-(spiro[isobenzofuran-1(3*H*),4′-piperidin]-1′-yl)butyl]-*N*-methylbenzamide Hemihydrate (64) $SnCl_2 \cdot 2H_2O$ (331 mg, 1.47 mmol) was added to a mixture of compound **41** (167 mg, 0.294 mmol) and AcOEt (5 ml), and the whole was heated to reflux for 3 h. It was poured into H_2O, neutralized with aqueous $NaHCO_3$ and filtered on Celite. The filtrate was extracted with AcOEt, and the extract was washed with saturated brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$: MeOH = 24 : 1) to give the hemihydrate (**64**, 98 mg, 62%) as a colorless amorphous solid. ^{1}H-NMR (DMSO-d_6) δ: 1.57—1.63 (2H, m), 1.64—1.90 (4H, m), 2.03—2.30 (4H, m), 2.57—2.80 (5H, m), 3.13 (1H, br s), 3.57 (3H, dd, J = 13.4, 6.1 Hz), 3.67 (1H, dd, J = 13.4, 9.1 Hz), 4.94 (2H, s), 5.42 (1H, d, J = 9.1 Hz), 6.49 (2H, d, J = 7.9 Hz), 6.62—6.93 (3H, m), 7.22—7.26 (4H, m), 7.45—7.55 (2H, m). FAB-MS *m/z*: 538 [$(M+H)^+$]. *Anal.* Calcd for $C_{30}H_{33}Cl_2N_3O_2 \cdot 0.5H_2O$: C, 65.81; H, 6.26; N, 7.67. Found: C, 65.62; H, 6.14; N, 7.56.

(±)-*N*-[4-(2-Acetyl-3,4-dihydrospiro[isoquinoline-1(2*H*),4′-piperidin]-1′-yl)-2-(3,4-dichlorophenyl)butyl]-*N*-methylbenzamide Monofumarate 0.25 Hydrate (65) Acetic anhydride (0.078 ml, 0.82 mmol) was added to a mixture of compound **62** (250 mg, 0.410 mmol), Et_3N (0.240 ml, 0.72 mmol) and CH_2Cl_2 (5 ml) at 0 °C, and the whole was stirred for 8 h at room temperature. Et_3N (0.114 ml, 0.820 mmol) and acetic anhydride (0.078 ml, 0.82 mmol) were added, and the reaction mixture was stirred for 17 h at room temperature. Further Et_3N (0.114 ml, 0.820 mmol) and acetic anhydride (0.078 ml, 0.82 mmol) were added and the whole was stirred for another 22 h at the same temperature, then diluted with AcOEt. The solution was washed with H_2O and saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$: MeOH = 49 : 1), fumaric acid (38 mg, 0.33 mmol) and MeOH were added, and the product was crystallized from 2-propanol–Et_2O. The crude product was recrystallized from acetonitrile (MeCN)–AcOEt to give the fumarate (**65**, 110 mg, 39%) as a colorless powder. mp 177—178 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.60—2.14 (7H, m), 2.18—2.80 (6H, m), 2.80—3.27 (8H, m), 3.42—3.83 (4H, m), 6.60 (2H, s), 6.88—7.30 (6H, m), 7.30—7.68 (6H, m). FAB-MS *m/z*: 578 [$(M+H)^+$]. *Anal.* Calcd for $C_{33}H_{37}Cl_2N_3O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$: C, 63.56; H, 5.98; N, 6.01. Found: C, 63.51; H, 5.82; N, 6.05.

Binding Assays Binding studies were carried out according to the method described by Burcher *et al.*[13] To determine the NK_2 receptor binding affinity of the compounds, ^{125}I-NKA and hamster urinary bladder were used, while ^{125}I-Bolton–Hunter-SP and guinea pig urinary bladder were employed to test the NK_1 binding affinity.

***In Vivo* Assays** Bronchospasm was induced with [β-Ala^8]-NKA(4-10) (1 nmol/kg i.v.) in urethane-anesthetized guinea pigs under mechanical ventilation.[14,15] Inhibitory activities of the compounds were determined by measuring the reduction in the agonist-induced maximal responses after administration. To evaluate the effects of compounds *via* the i.v. route, test compounds were given 15 min before challenge with the agonist, and lung resistance was measured using a whole-body plethysmogram. To test the effects of the compounds *via* the i.d. route, test compounds were given 60 min before challenge with the agonist, and the responses were measured by the Konzett–Rossler method. In some experiments, the effects of the compounds *via* the i.d. route were also determined by recording the tracheal insufflation pressure. The doses required to reduce the responses by 50% (ID_{50}) were determined by probit analysis.

Acknowledgements We are grateful to Drs. K. Murase and T. Mase for their valuable suggestions and encouragement and to the staff of the Molecular Chemistry Research Laboratory for spectral measurements and elemental analyses.

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