Spiro-Substituted Piperidines as Neurokinin Receptor Antagonists. I. Design and Synthesis of (±)-*N*-[2-(3,4-Dichlorophenyl)-4-(spiro[isobenzofuran-1(3*H*),4′-piperidin]-1′-yl)butyl]-*N*-methylbenzamide, YM-35375, as a New Lead Compound for Novel Neurokinin Receptor Antagonists

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Analysis of the structural requirements of compound 1 (SR48968), a potent NK_2 receptor antagonist, revealed that the 4-phenyl group of the piperidine is essential for binding with the NK_2 receptor and occupies an equatorial position. Energy calculation of a variety of substituted 4-phenyl piperidines revealed that spiro[isobenzofuran-1(3*H*), 4′-piperidine] possesses a conformationally restricted equatorial phenyl group. Our compound 12 (YM-35375) possessing this spiro-substituted piperidine bound to the NK_2 receptor with an IC_{50} value of 84 nM and to the NK_1 receptor with an IC_{50} value of 710 nM. It showed more potent inhibitory activity (ID_{50} 41 μg/kg (i.v.)) against [β-Ala^8]-NKA(4—10)-induced bronchoconstriction in guinea pigs than (±)-SR48968 (ID_{50} 68 μg/kg (i.v.)). YM-35375 may be a new lead compound for novel NK_2 receptor antagonists or NK_1–NK_2 dual antagonists.

Key words spiro[isobenzofuran-1(3*H*), 4′-piperidine]; NK_2 antagonist; dual antagonist; YM-35375; SR48968

Neurokinins are peptides comprising ten or eleven amino acids and possess in common the sequence –Phe–X–Gly–Leu–Met–NH_2 at their C-termini. Among them, substance P (SP),[1] neurokinin A (NKA)[2] and neurokinin B (NKB),[2] isolated from mammals, exhibit a wide variety of biological responses[3] through their receptors. Neurokinin receptors are now classified into the following three subtypes, NK_1, NK_2 and NK_3, which have high affinity for SP, NKA and NKB, respectively.[4] Recently, Barnes *et al.* proposed that SP and NKA may play important roles in the pathogenesis of asthma.[5] Namely, SP and NKA are released from the endings of sensory nerves by a variety of stimulants and induce the pathological features of asthma, such as microvascular leakage, mucus hypersecretion and bronchoconstriction.[5] In the airway, SP causes microvascular leakage and mucus hypersecretion,[6] and NKA induces bronchoconstriction.[6,7] Based on these mechanisms, NK_1 and NK_2 receptor antagonists could prevent these functions in asthmatic patients and may be of clinical benefit for treatment of asthma.

Recently, various potent and selective non-peptide NK_1 receptor antagonists have been reported[8] and their clinical efficacy has been evaluated. As regards non-peptide NK_2 receptor antagonists, only SR48968[9,10] (**1**, Fig. 1) has been clinically evaluated to our knowledge. SR48968 has a characteristic structure, 4-acetamido-4-phenylpiperidine, which may be important for binding to the NK_2 receptor. In this paper, we report the molecular design, synthesis and pharmacological properties of (±)-*N*-[2-(3,4-dichlorophenyl)-4-(spiro[isobenzofuran-1(3*H*),4′-piperidin]-1′-yl)butyl]-*N*-methylbenzamide (**12**, YM-35375) as a new lead compound for novel antiasthmatic drugs.

Chemistry

(±)-*N*-[2-(3,4-Dichlorophenyl)-4-(4-phenylpiperidino)butyl]-*N*-methylbenzamide (**2**) and (±)-*N*-[4-(4-acetamidopiperidino)-2-(3,4-dichlorophenyl)butyl]-*N*-methylbenzamide (**3**) were synthesized according to the literature.[10]

Spiro[isobenzofuran-1(3*H*),4′-piperidine] (**8**) was synthesized from 2-bromobenzyl alcohol (**4**) as shown in Chart 1. Compound **4** was converted to a dianion with *n*-butyllithium (*n*-BuLi)[11] in tetrahydrofuran (THF)–diethyl ether (Et_2O) and treated with 1-ethoxycarbonyl-4-piperidone (**5**) to give ethyl 4-hydroxy-4-(2-hydroxymethylphenyl)piperidine-1-carboxylate (**6**). The primary hydroxyl group of compound **6** was selectively tosylated by treatment with *p*-toluenesulfonyl chloride (TsCl), and

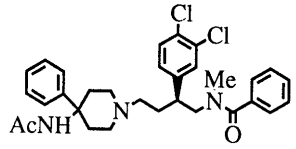

Fig. 1. Structure of SR48968 (**1**)

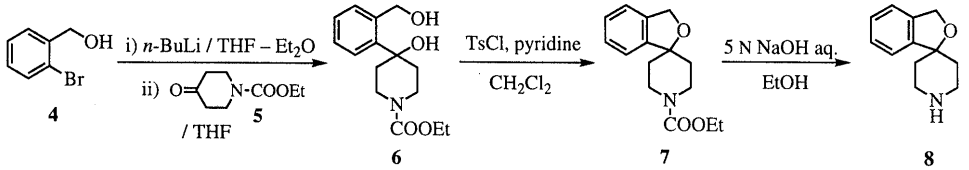

Chart 1

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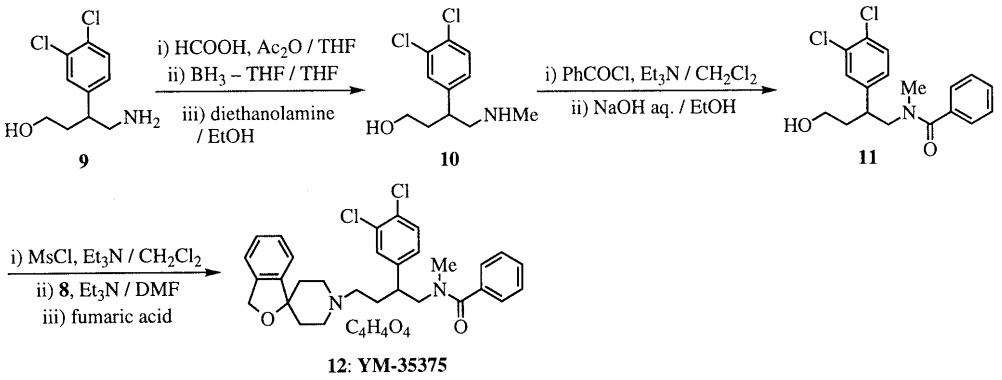
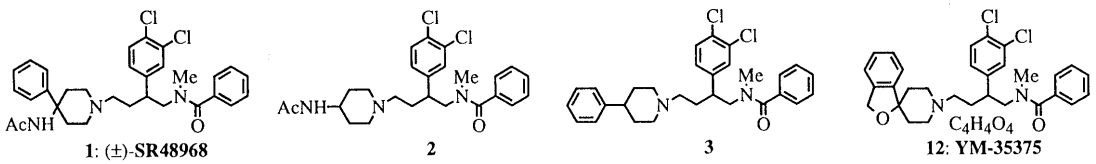


Chart 2

Table 1. NK_2 Receptor Binding Affinities and Antagonistic Activities *in Vivo* of *N*-[2-(3,4-Dichlorophenyl)-4-(4-substituted piperidin-1′-yl)butyl]-*N*-methylbenzamides



	NK_2 binding[a] IC_{50} (nM)	NK_1 binding[b] IC_{50} (nM)	NK_2 selectivity index[c]	Bronchoconstriction in guinea pigs[d] ID_{50} (μg/kg i.v.)
1 [(±)-SR48968]	4.1	>1000	>240	68
2	>1000	N. T.	—	N. T.
3	180	N. T.	—	N. T.
12 (YM-35375)	84	710	8.5	41

a) The binding affinities for hamster urinary bladder NK_2 receptor. See experimental section. *b*) The binding affinities for guinea pig urinary bladder NK_1 receptor. See experimental section. *c*) IC_{50} to NK_1 receptor/IC_{50} to NK_2 receptor. *d*) See experimental section. N. T.: Not tested.

the resultant tosylate was cyclized in the presence of pyridine to give the protected spiro-substituted piperidine (**7**). Compound **7** was treated with sodium hydroxide to give compound **8**. Synthesis of YM-35375 is shown in Chart 2. (±)-4-Amino-3-(3,4-dichlorophenyl)butanol (**9**) was prepared according to the literature.[12] Compound **9** 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 (**10**). Compound **10** was treated with benzoyl chloride in the presence of triethylamine (Et_3N), followed by hydrolysis with sodium hydroxide to give (±)-*N*-[2-(3,4-dichlorophenyl)-4-hydroxybutyl)-*N*-methylbenzamide (**11**). Treatment of compound **11** with methanesulfonyl chloride (MsCl), followed by substitution with compound **8** in the presence of Et_3N gave compound **12** (YM-35375).

Results and Discussion

Thus obtained compounds were evaluated for their binding affinities[13] to hamster urinary bladder NK_2 receptor and guinea pig urinary bladder NK_1 receptor.

As shown in Table 1, (±)-SR48968 exhibited high affinity for the NK_2 receptor with an IC_{50} value of 4.1 nM. The removal of the phenyl group of 4-acetamido-4-phenylpiperidine (**2**) caused complete loss of the potency in contrast to the analog without the acetamido group (**3**), which retained the potency with an IC_{50} value of 180 nM. These facts suggested that the phenyl group at the

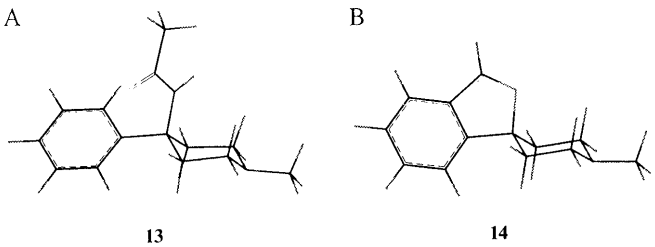


Fig. 2. Putative 3-Dimensional Structures[a] of 4-Acetamido-1-methyl-4-phenylpiperidine (**13**) and 1′-Methylspiro[isobenzofuran-1(3*H*),4′-piperidine] (**14**)

a) The 2-dimensional structures of these molecules were constructed using Sybyl (6.22) and converted to initial 3-dimensional structures with Concord 3.2.1. These initial structures were relaxed using the Tripos force field.

4-position of the piperidine may be crucial to bind to the NK_2 receptor and that the acetamide group may be necessary for increasing the affinity for the NK_2 receptor. To analyze the conformation of the 4-acetamido-4-phenylpiperidine moiety of SR48968, a putative 3-dimensional structure of 4-acetamido-1-methyl-4-phenylpiperidine (**13**), which was adopted as a simplified molecule, was constructed by energy minimization. As shown in Fig. 2A, the phenyl group was placed in an equatorial position and the acetamide group in an axial position. This conformation was 1.68 kcal/mol more stable than the other one with an axial phenyl group and an equatorial acetamide group. We speculated that the phenyl group may be immobilized in the equatorial position by

the axial acetamide group and that compounds with more restricted equatorial phenyl groups may show higher affinity for the NK_2 receptor. We designed 1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidine] (**14**) as a conformationally restricted 4-phenylpiperidine. Conformational analysis of compound **14** suggested that the phenyl group lies in an equatorial position (Fig. 2B). This conformation was 2.51 kcal/mol more stable than the other one with an axial phenyl group. Based on these results, it was expected that YM-35375, which possesses this spiro-substituted piperidine instead of 4-acetamido-4-phenylpiperidine of SR48968, would bind to the NK_2 receptor with high affinity. Unfortunately, it was found that YM-35375 showed affinity for the NK_2 receptor with an IC_{50} value of only 84 nM, which was a 20-fold decrease in potency relative to (±)-SR48968. One of the reasons for this decreased affinity for the NK_2 receptor was considered to be the lack of the acetamide group, which would affect the angle of the equatorial phenyl group and interact with the NK_2 receptor, *e.g.*, through hydrogen bonding.

As shown in Table 1, (±)-SR48968 inhibited [β-Ala^8]-NKA(4—10)-induced bronchoconstriction in guinea pigs[14,15] with an ID_{50} value of 68 μg/kg (i.v.). In contrast to the binding assay, YM-35375 showed more potent inhibitory activity with an ID_{50} value of 41 μg/kg (i.v.) than (±)-SR48968 in this model. These results suggested that the substitution of spiro[isobenzofuran-1(3*H*),4′-piperidine] for 4-acetamido-4-phenylpiperidine was favorable for NK_2 receptor-antagonistic activity *in vivo* and that YM-35375 may be a new lead compound for further research to find a novel NK_2 receptor antagonist. Furthermore, YM-35375 also showed weak NK_1 receptor affinity with an IC_{50} value of 710 nM, and its NK_2 receptor selectivity index was 8.5 in contrast to over 240 of (±)-SR48968. This result suggested that the substitution of spiro[isobenzofuran-1(3*H*),4′-piperidine] for 4-acetamido-4-phenylpiperidine caused a change in selectivity and that the discovery of a novel NK_1–NK_2 dual antagonist[16] might be possible by suitable modifications of YM-35375.

In conclusion, spiro[isobenzofuran-1(3*H*),4′-piperidine] was designed as a conformationally restricted piperidine with an equatorial phenyl group with the aim of obtaining a potent NK_2 receptor antagonist. Although YM-35375 which possessed this spiro-substituted piperidine was less potent than (±)-SR48968 in binding assay, it was more potent than (±)-SR48968 *in vivo*. As YM-35375 also showed weak NK_1 receptor affinity, we anticipate that further structural modifications of this compound may alter the selectivity between the NK_1 and NK_2 receptors and give rise to not only highly selective NK_2 receptor antagonists, but also NK_1–NK_2 dual antagonists. We are currently searching for novel neurokinin antagonists by utilizing YM-35375 as a lead compound. The results will be reported in the near future.

Experimental

All melting points were determined on a Yanagimoto MP-3 melting point apparatus 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 (δ : 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; q, quartet; 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-hydroxymethylphenyl)-1-piperidinecarboxylate (6) A 1.6 M solution of *n*-BuLi (705 ml, 1.13 mol) in hexane was added dropwise to a solution of 2-bromobenzyl alcohol (**4**) (101 g, 537 mmol) in THF (500 ml) and Et_2O (1000 ml) at −78 °C under an argon atmosphere. The mixture was stirred for 1 h at −78 °C, then 1-ethoxycarbonyl-4-piperidone (**5**) (101 g, 591 mmol) and THF (100 ml) were added at the same temperature. The mixture was stirred for 16 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) to give the diol (**6**, 69.3 g, 46%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J = 7.1 Hz), 1.85—1.91 (2H, m), 1.96—2.04 (2H, m), 3.23—3.38 (2H, m), 3.98—4.07 (2H, m), 4.13 (2H, q, J = 7.1 Hz), 4.89 (2H, s), 7.20—7.30 (4H, m). EI-MS m/z : 279 (M^+).

Ethyl Spiro[isobenzofuran-1(3*H*),4′-piperidine]-1′-carboxylate (7) A solution of TsCl (51.6 g, 271 mmol) in CH_2Cl_2 (160 ml) was added to a solution of compound **6** (68.7 g, 246 mmol), pyridine (43.7 ml, 541 mmol) and CH_2Cl_2 (800 ml) at 0 °C. The mixture was stirred for 18 h at room temperature, then pyridine (19.9 ml, 246 mmol) and TsCl (46.9 g, 246 mmol) were added at 0 °C. The whole was stirred for 22 h at room temperature. Further pyridine (19.9 ml, 246 mmol) and TsCl (46.9 g, 246 mmol) was added to the reaction mixture at 0 °C, and stirring was continued for an additional 18 h at room temperature. The mixture was diluted with $CHCl_3$ and washed with H_2O, 5% 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**, 52.2 g, 81%) as a pale yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J = 7.4 Hz), 1.70—1.76 (2H, m), 1.79—1.89 (2H, m), 3.16—3.29 (2H, m), 4.06—4.22 (4H, m), 5.08 (2H, s), 7.07—7.10 (1H, m), 7.20—7.24 (1H, m), 7.26—7.30 (2H, m). EI-MS m/z: 261 (M^+).

Spiro[isobenzofuran-1(3*H*),4′-piperidine] (8) A mixture of compound **7** (51.6 g, 197 mmol), 5 N NaOH (100 ml) and EtOH (500 ml) was heated to reflux for 20 h, then concentrated *in vacuo*. The residue was diluted with brine and extracted with Et_2O. The organic layer was washed with saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give the piperidine (**8**, 33.0 g, 89%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 1.71—1.77 (2H, m), 1.80—1.89 (2H, m), 1.99 (1H, s), 2.99—3.10 (4H, m), 5.07 (2H, s), 7.11—7.16 (1H, m), 7.19—7.22 (1H, m), 7.25—7.30 (2H, m). EI-MS m/z: 189 (M^+).

A 4 N HCl solution in 1,4-dioxane (0.476 ml, 1.90 mmol) was added to a mixture of compound **8** (300 mg, 1.59 mmol), AcOEt (3 ml) and MeOH (0.3 ml) at 0 °C, and the whole was stirred for 20 min at the same temperature. The resulting precipitate was collected by filtration, washed with AcOEt and recrystallized from MeOH–AcOEt to give the hydrochloride of compound **8** (230 mg, 64%) as colorless crystals. mp 191—193 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.74—1.81 (2H, m), 2.16—2.27 (2H, m), 3.04—3.12 (2H, m), 3.27—3.36 (2H, m), 5.04 (2H, s), 7.15—7.20 (1H, m), 7.31—7.37 (3H, m). EI-MS m/z: 189 (M^+).

(±)-*N*-[2-(3,4-Dichlorophenyl)-4-hydroxybutyl]-*N*-methylbenzamide (11) A mixture of Ac_2O (10.0 ml, 112 mmol) and HCOOH (10.0 ml, 265 mmol) was stirred for 30 min at 60 °C, and then a solution of (±)-4-amino-3-(3,4-dichlorophenyl)butan-1-ol (**9**, 2.99 g, 12.8 mmol) in THF (30 ml) was added at 0 °C. The mixture was stirred for 2.5 h at room temperature, poured into H_2O and neutralized with K_2CO_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*. The residue was diluted with THF (30 ml), then added to BH_3–THF complex (1.0 M solution in THF, 38 ml, 0.38 mol) at 0 °C, and the mixture was heated to reflux for 5 h. Next, EtOH (30 ml) and diethanolamine (2.69 g, 25.6 mmol) were added at 0 °C, and the mixture was heated again to reflux for 14 h and concentrated *in vacuo*. The residue was diluted with brine, and extracted with AcOEt. The extract was washed with saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. CH_2Cl_2 (70 ml) and Et_3N (4.46 ml, 32.0 mmol) were added to the residue, and the mixture was cooled to

−30 °C. A solution of benzoyl chloride (3.27 ml, 28.2 mmol) in CH_2Cl_2 (10 ml) was added. The whole was stirred for 5.5 h at room temperature and diluted with $CHCl_3$. This mixture was washed with 0.5 N HCl, saturated $NaHCO_3$ and saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. EtOH (50 ml) and 1 N NaOH (50 ml) were added to the residue, and the mixture was stirred for 14 h at room temperature and concentrated *in vacuo*. The residue was 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 resultant solid was recrystallized from AcOEt–hexane to give the benzamide (**11**, 3.49 g, 77%) as a colorless powder. ^{1}H-NMR (DMSO-d_6) δ: 1.48—2.33 (3H, m), 2.65—3.13 (3H, m), 3.26—4.00 (5H, m), 6.76—7.24 (3H, m), 7.30—7.45 (5H, m). FAB-MS *m/z*: 352 [$(M+H)^+$]. *Anal.* Calcd for $C_{18}H_{19}Cl_2NO_2$: C, 61.37; H, 5.44; N, 3.98. Found: C, 61.33; H, 5.47; N, 3.88.

(±)-*N*-[2-(3,4-Dichlorophenyl)-4-(spiro[isobenzofuran-1(3*H*),4′-piperidin]-1′-yl)butyl]-*N*-methylbenzamide Monofumarate (12) MsCl (0.064 ml, 0.83 mmol) was added to a mixture of compound **11** (233 mg, 0.660 mmol), Et_3N (0.138 ml, 0.991 mmol) and CH_2Cl_2 (10 ml) at 0 °C and the whole was stirred for 50 min at room temperature. It was diluted with AcOEt, washed with H_2O and saturated brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in *N*,*N*-dimethylformamide (DMF, 5 ml), then spiro[isobenzofuran-1(3*H*),4′-piperidine] (**8**) (138 mg, 0.727 mmol) and Et_3N (0.276 ml, 1.98 mmol) were added, and the mixture was stirred for 4 h at 70 °C. It was then diluted with AcOEt, 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) to give the free base of compound **12** (156 mg, 45%) as a pale yellow oil. Fumaric acid (221 mg, 1.91 mmol) and MeOH (8 ml) were added to the free base of compound **12** (1.00 g, 1.91 mmol), and the mixture was concentrated *in vacuo*. The residue was crystallized from 2-butanone–Et_2O and recrystallized from MeOH–MeCN to give the monofumarate (**12**, 767 mg, 63%) as a colorless powder. mp 177—178 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.56—1.75 (3H, m), 1.86—2.04 (4H, m), 2.12—2.60 (3H + DMSO, m), 2.67—3.04 (5H, m), 3.16—3.80 (3H, m), 4.97 (2H, s), 6.60 (2H, s), 6.98—7.18 (2H, m), 7.20—7.44 (8H, m), 7.48—7.69 (2H, m). FAB-MS *m/z*: 523 [$(M+H)^+$]. *Anal.* Calcd for $C_{30}H_{32}Cl_2N_2O_2 \cdot C_4H_4O_4$: C, 63.85; H, 5.67; N, 4.38. Found: C, 63.95; H, 5.72; N, 4.38.

Energy Minimization The 2-dimensional structures of 4-acetamido-1-methyl-4-phenylpiperidine (**13**) and 1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidine] (**14**) were constructed using the molecular modeling program Sybyl (6.22) on an Indigo Elan Workstation (Silicon Graphics, Inc., Mountain View, CA) and converted to initial 3-dimensional structures with Concord 3.2.1. These initial structures were relaxed using the Tripos force field. The total energy of compound **13** was 4.93 kcal/mol with the equatorial phenyl group and 6.61 kcal/mol with the axial phenyl group. The total energy of compound **14** was 10.00 kcal/mol with the equatorial phenyl group and 12.51 kcal/mol with the axial phenyl group.

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

***In Vivo* Assay** 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. Test compounds were given *via* the i.v. route 15 min before challenge with the agonist, and lung resistance was measured using a whole-body plethysmogram. 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, elemental analyses and energy calculations.

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