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Synthesis and NK_1 Receptor Antagonistic Activity of (±)-1-Acyl-3-(3,4-dichlorophenyl)-3-[2-(spiro-substituted piperidin-1'-yl)ethyl]piperidines

Hirokazu Kubota,* Yoshinori Okamoto, Masahiro Fujii, Ken Ikeda, Makoto Takeuchi, Tadao Shibanuma and Yasuo Isomura

Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., 21, Miyukigaoka, Tsukuba, Ibaraki 305-8585 JAPAN

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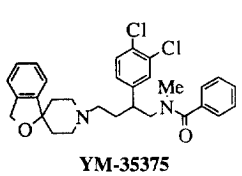
Abstract: (±)-1-Acyl-3-(3,4-dichlorophenyl)-3-[2-(spiro-substituted piperidin-1'-yl)ethyl]piperidines and their quaternary ammonium salts were prepared and evaluated for their NK_1 receptor antagonistic activity. Some of these inhibited SP-induced contraction in guinea pig ileum with IC_{50} values at a level of 10^{-9} M and showed potent inhibitory activity against selective NK_1 receptor agonist-induced bronchoconstriction in guinea pigs.

Keywords: Tachykinin; Antagonists; Antiinflammatories, Analgesics

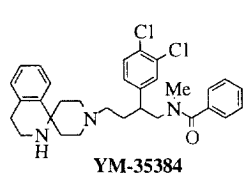
Substance P (SP)[1] is known to exhibit a wide variety of biological responses, including smooth muscle contraction, pain transmission, vasodilatation, salivary secretion, neurogenic inflammation and activation of the immune system, which are mediated through the NK_1 receptor. Because inhibition of the binding between SP and the NK_1 receptor may be efficient for the treatment of these diseases, a number of potent and selective non-peptide NK_1 receptor antagonists have been reported[2-8] and evaluated for their clinical efficacy.

We have already reported that the spiro[isobenzofuran-1(3H),4'-piperidine] derivative, 'YM-35375', exhibited weak affinity for the NK_1 receptor.[9] The studies of its structure–activity relationships revealed that the 3,4-dihydrospiro[isoquinoline-1(2H),4'-piperidine] derivative, 'YM-35384', was 12-fold more potent than



YM-35375

NK_1 binding: IC_{50} = 710 nM[9]

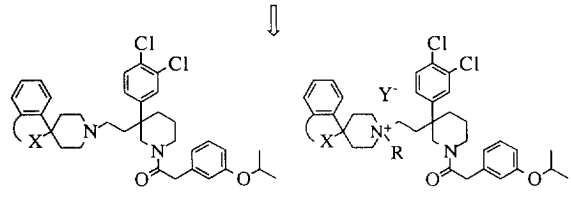


YM-35384

NK_1 binding: IC_{50} = 58 nM[10]

SR140333

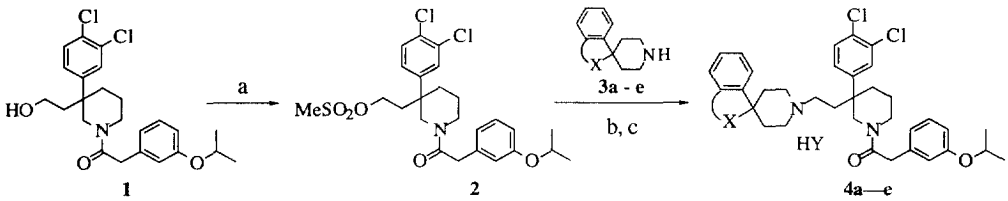
NK_1 binding: IC_{50} = 0.019 nM[3]



PII: S0960-894X(98)00260-1

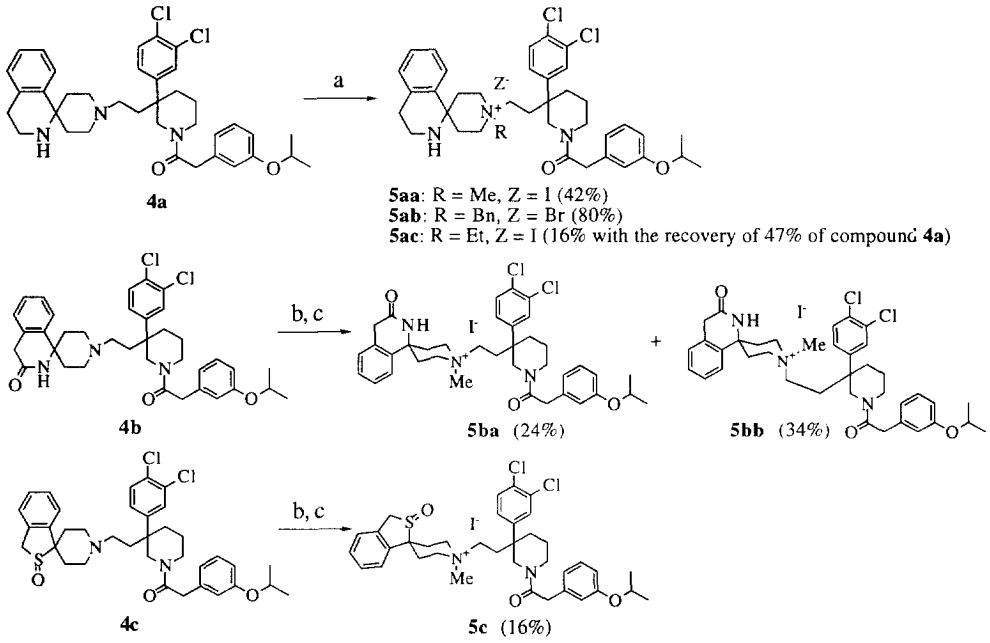
YM-35375.[10] These results encouraged us to find a potent NK_1 receptor antagonist by structural modifications of the spiro-substituted piperidines. In 1993, it was reported that the 1-acyl-3-(3,4-dichlorophenyl)piperidine, SR140333[3], exhibited high affinity for the NK_1 receptor with an IC_{50} value of 0.019 nM in binding assay. This compound is one of the most potent NK_1 receptor antagonists to our knowledge. In order to find a novel NK_1 receptor antagonist, we introduced the spiro-substituted piperidines and their quaternary ammonium salts instead of the quinuclidine moiety. Here we report the synthesis and the evaluation of the spiro-substituted piperidines as NK_1 receptor antagonists.

The (±)-1-acyl-3-(3,4-dichlorophenyl)-3-[2-(spiro-substituted piperidin-1'-yl)ethyl]piperidines **4a—e** were prepared as the racemates except for compound **4c**, which was the diastereomeric mixture, and the synthetic method is shown in Scheme 1. The alcohol **1**[11] was converted to the mesylate **2** with methanesulfonyl chloride in the presence of Et_3N. Substitution of the mesylate with the spiro-substituted piperidines **3a—e** provided the desired compounds **4a—e** after purification by silica gel chromatography and conversion to the salts (hydrochlorides **4a** and **e**, fumarate **4b** and **c** or oxalate **4d**).



1 **2** **4a—e**

Scheme 1. (a) methanesulfonyl chloride, Et_3N / CH_2Cl_2, r.t.; (b) Et_3N / DMF, 70°C; (c) HY (15—56% from **1**)



4a

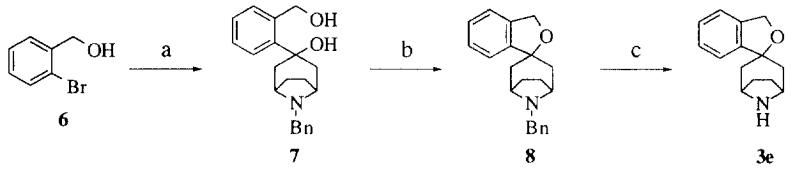
5aa: R = Me, Z = I (42%)
5ab: R = Bn, Z = Br (80%)
5ac: R = Et, Z = I (16% with the recovery of 47% of compound **4a**)

4b **5ba** (24%) **5bb** (34%)

4c **5c** (16%)

Scheme 2. (a) R-Z / MeCN, r.t.—reflux, (16—80%); (b) MeI / MeCN, r.t.; (c) silica gel chromatogaphy

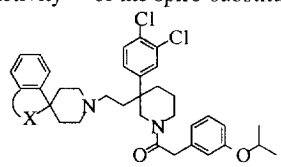
The syntheses of the quaternary ammonium salts **5** are outlined in Scheme 2. The spiro-substituted piperidines **4a—c** were treated with MeI, BnBr or EtI in MeCN to give the corresponding quaternary ammonium salts. In the case of MeI or BnBr, the reactions were proceeded at room temperature; EtI was reacted under reflux condition. Although these alkylations gave the sole products **5aa—ac**, respectively, the stereochemistries around the piperidinium nitrogens of these compounds could not be identified. On the contrary, methylation of compound **4b** gave the two isomers **5ba** and **bb** which were separated by silica gel chromatography. ^{13}C-NMR spectra of these compounds revealed that the methyl group on the piperidinium nitrogen of the less polar compound **5ba** (δ 44.48) shifted to up-field relative to the more polar compound **5bb** (δ 52.87).[12] In general, axial methyl groups on aliphatic ring systems are known to resonate more up-field than the equatorial ones. From these results, we identified that compound **5ba** possessed an axial methyl group on the piperidinium nitrogen and

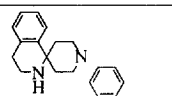
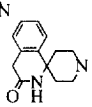
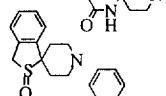
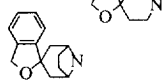
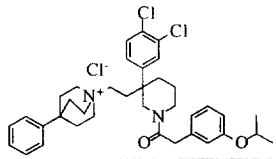


6 7 8 3e

Scheme 3. (a) 2 equiv *n*-BuLi / THF – Et_2O – *n*-hexane, –78°C then 8-benzyl-3-tropinone, –78°C, (49%); (b) *p*-TsCl, pyridine / CH_2Cl_2, r.t., (36%); (c) HCl then 20% $Pd(OH)_2$ – C, H_2 / MeOH, r.t., (85%)

Table 1. NK_1 antagonistic activity[14] of the spiro-substituted piperidines **4a—e**



Compd. No.		salt	NK_1 antagonistic activity IC_{50} (nM)[a]	
4a		2HCl	31	(27—35)
4b		fumarate	54	(46—63)
4c		fumarate	18	(11—29)
4d		oxalate	16	(13—21)
4e		HCl	105	(94—116)
(±)-**SR140333**			0.31	(0.29—0.33)

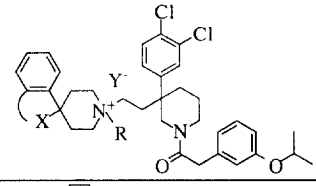
a) Numbers in parentheses represent 95% confidence limits.

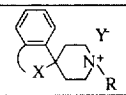
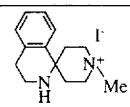
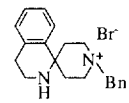
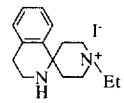
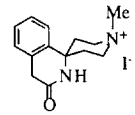
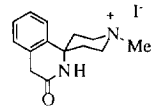
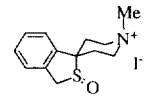
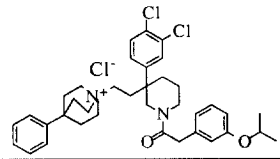
that the methyl group of compound **5bb** occupied the equatorial position.[12] Methylation of compound **4c** also gave the two isomers, and only the less polar product **5c** was isolated by silica gel chromatography. This compound was also the diastereomeric mixture, and the chemical shift (δ 42.77) of the methyl group on the piperidinium nitrogen indicated that this methyl group occupied the axial position.

The spiro-substituted piperidines **3a—d** were prepared according to the methods described in the literature.[9,10] Spiro[isobenzofuran-1(3H),3'-(8'-azabicyclo[3.2.1]octane)] **3e** was synthesized from 2-bromo-benzyl alcohol **6** as shown in Scheme 3. Compound **6** was converted to a dianion with *n*-BuLi in THF–Et_2O and treated with 8-benzyl-3-tropanone to give 8-benzyl-3-hydroxy-3-(2-hydroxymethyl-phenyl)-8-aza-bicyclo[3.2.1]octane **7**. The primary hydroxyl group of compound **7** was selectively tosylated by treatment with *p*-toluenesulfonyl chloride, and the resultant tosylate was cyclized in the presence of pyridine to give the protected spiro-substituted piperidine **8**. Compound **8** was converted to the hydrochloride, followed by the hydrogenation in the presence of palladium hydroxide on carbon to give compound **3e**.[13]

Thus the obtained compounds **4** and **5** were evaluated for their inhibitory activity against SP-induced contraction in guinea pig ileum ,[14] and the results are summarized in Tables 1 and 2. In our assay, (±)-SR140333[11,15] exhibited potent NK_1 antagonistic activity with an IC_{50} value of 0.31 nM. Compound **4a** possessing 3,4-dihydrospiro[isoquinoline-1(2H),4'-piperidine] instead of 4-phenylquinuclidinium of SR140333

Table 2. NK_1 antagonistic activity[14] of the spiro-substituted piperidinium salts **5**



Compd. No.		NK_1 antagonistic activity IC_{50} (nM)[a]	
5aa		2.0	(1.7—2.4)
5ab		16	(9.9—25)
5ac		4.8	(4.1—5.7)
5ba		1.9	(1.2—3.1)
5bb		35	(32—38)
5c		6.3	(5.1—7.7)
(±)-SR140333		0.31	(0.29—0.33)

a) Numbers in parentheses represent 95% confidence limits.

exhibited moderate potency (IC_{50} value of 31 nM), and the 3-isoquinolone derivative **4b** was slightly less potent than compound **4a** (Table 1). Substitution of 5-membered spiro-substituted piperidines (**4c**, **4d**) for 3,4-dihydrospiro[isoquinoline-1(2H),4'-piperidine] resulted in an almost 2-fold increase in the potency. The tropine derivative **4e** which was expected to possess almost the same bulkiness as quinuclidine was 10-fold less potent than the piperidine derivative **4d**. Among these compounds, the 5-membered spiro-substituted piperidines may be favorable for showing potent NK_1 receptor antagonistic activity.

As shown in Table 2, the conversion of compound **4a** to the corresponding *N*-methylpiperidinium salt **5aa** resulted in a 15-fold increase in the potency. The bulky substituents on the quaternary ammonium nitrogen were unfavorable for showing potent NK_1 receptor antagonistic activity (**5aa** *vs.* **5ab**, **5ac**). The sulfoxide derivative **5c** was 3-fold less potent than compound **5aa**. Among the isoquinolone derivatives, the axial methyl group (**5ba**) was more favorable for exhibiting potent activity than the equatorial group (**5bb**), and compound **5ba** was equipotent to compound **5aa**. The conformation of the compounds induced by the axial methyl group may be important to show potent NK_1 receptor antagonistic activity. Unfortunately, compounds **5aa** and **5ba** were less potent than (±)-SR140333 [P] in this assay, but these *N*-methylpiperidinium derivatives were more than 15 times as potent as the corresponding piperidines (**4a**, **4b**). From these results, we considered that the quaternary ammonium nitrogen may be crucial to show potent inhibitory activity against the NK_1 receptor.

Some potent compounds (**5aa**, **5ba**) were evaluated for their inhibitory activity against selective NK_1 receptor agonist-induced bronchoconstriction in guinea pigs,[16] and the results are shown in Table 3. The isoquinoline derivative **5aa** was not as potent as (±)-SR140333. In contrast, the isoquinolone derivative **5ba** was almost equipotent to (±)-SR140333 (ID_{50} values of 24 and 19 μg/kg (i.v.), respectively) in spite of its 6-fold lower potency *in vitro*. This result suggests that 3-oxo-3,4-dihydrospiro[isoquinoline-1(2H),4'-piperidinium] group may be favorable to exhibit NK_1 receptor antagonistic activity *in vivo*.

Table 3. Inhibitory activity of the spiro-substituted piperidinium salts **5aa** and **5ba** against [Sar^9, $Met(O_2)^{11}$]-SP-induced bronchoconstriction in guinea pigs.[16]

Compd. No.	inhibitory activity ID_{50}[a] (μg / kg, i.v.)
5aa	49 (42—58)
5ba (YM-49244)	24 (19—30)
(±)-**SR140333**	19 (8.6—41)

a) Numbers in parentheses represent 95% confidence limits.

In conclusion, we synthesized the spiro-substituted piperidines and their quaternary ammonium salts in order to find a novel NK_1 receptor antagonist. Among the compounds, 3-oxo-3,4-dihydrospiro[isoquinoline-1(2H),4'-piperidinium] derivative **5ba**, 'YM-49244', was the most potent not only in the isolated tissue but also in the selective NK_1 receptor agonist-induced bronchoconstriction model. This compound was almost as potent as (±)-SR140333 *in vivo* and may be useful for the treatment of the diseases caused by NK_1 receptor activation.

Acknowledgement: 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. We are also grateful to Ms. A. Orita for measurements of the biological activities.

References and Notes

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11. Emonds-Alt X., Gueule P., Proietto V., Van Broeck D., Eur. Pat. Appl. 591040 (1994) [*Chem. Abstr.*, **120**, 323276*k* (1994)].
12. the less polar product: ^{1}H-NMR ($CDCl_3$) δ 1.22—1.38 (8H, m), 1.95—2.16 (4H, m), 2.30—2.54 (4H, m), 3.16—3.28 (4H, m), 3.40—3.54 (5H, m), 3.63—3.78 (4H, m), 3.82—4.09 (4H, m), 4.44—4.49 (1H, m), 6.66—6.72 (3H, m), 7.13 (1H, t, *J* = 7.9 Hz), 7.22—7.31 (3H, m), 7.40 (2H, t, *J* = 7.9 Hz), 7.41 (1H, d, *J* = 8.5 Hz), 7.53 (1H, d, *J* = 1.8 Hz), 8.96 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ 44.48 [N+-Me(ax.)]. FAB-MS *m/z*: 662 [(M-I)+]. *Anal.* Calcd for $C_{38}H_{46}Cl_2IN_3O_3 \cdot H_2O$: C, 56.44; H, 5.98; N, 5.20; Cl, 8.77; I, 15.69. Found: C, 56.58; H, 5.81; N, 5.17; Cl, 8.63; I, 15.69.
the more polar product: ^{1}H-NMR ($CDCl_3$) δ 1.23—1.48 (7H, m), 1.79—2.02 (7H, m), 2.20—2.35 (3H, m), 2.99—3.34 (5H, m), 3.50—3.75 (7H, m), 3.87—3.88 (1H, m), 4.04—4.20 (3H, m), 4.47—4.52 (1H, m), 6.69—6.74 (4H, m), 7.06 (1H, d, *J* = 7.3 Hz), 7.14—7.17 (1H, m), 7.23 (1H,t, *J* = 7.3 Hz), 7.31 (1H, t, *J* = 7.3 Hz), 7.49—7.55 (2H, m), 7.58 (1H, s), 8.84 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ 52.87 [N+-Me(eq.)]. FAB-MS *m/z*: 662 [(M-I)+]. *Anal.* Calcd for $C_{38}H_{46}Cl_2IN_3O_3 \cdot 1.5\ H_2O$: C, 55.82; H, 6.04; N, 5.14; Cl, 8.67; I, 15.52. Found: C, 55.76; H, 5.85; N, 5.16; Cl, 8.77; I, 15.81.
13. ^{1}H-NMR ($CDCl_3$) δ 2.06 (2H, d, *J* = 19 Hz), 2.24—2.26 (2H, m), 2.58—2.60 (2H, m), 2.77 (2H, dd, *J* = 19, 3.5 Hz), 4.18 (2H, br s), 5.07 (2H, s), 7.18—7.55 (4H, m). EI-MS *m/z*: 215 (M+).
14. Guinea pig ileal strips were suspended with an initial tension of 1.0 g in the organ baths filled with oxygenated Tyrode's solution, containing atropine (5 mM), mepyramine (5 mM) and indomethacin (5 mM), at 37 °C. After obtaining three reproducible contractions evoked by SP (1 nM), a compound was added to the bath. The contraction was induced by the agonist again 15 min after the addition of the compound, and reduction of the peak-contraction was determined. The IC_{50} values were determined by log-logit linear regression.
15. (±)-SR140333 was prepared according to the method described in reference 11 in our laboratory.
16. Bronchoconstriction was induced by [Sar^9, Met(O_2)^{11}]-SP in urethane-anesthetized guinea pigs under mechanical ventilation. Inhibitory activities of the compounds were determined by measuring the reduction in the agonist-induced maximal responses after administration. Test compounds were given 15min before challenge with the agonist, and lung resistance was measured using a whole-body plethysmogram. The responses were measured by the Konzett–Rossler method. The doses required to reduce the responses by 50% (ID_{50}) were determined by probit analysis.