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Synthesis and NK₁ Receptor Antagonistic Activity of (±)-1-Acyl-3-(3,4-dichlorophenyl)-3-[2-(spiro-substituted piperidin-1'-yl)ethyl]piperidines

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Abstract: (\pm)-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 NK₁ receptor antagonistic activity. Some of these inhibited SP-induced contraction in guinea pig ileum with IC₅₀ values at a level of 10-9 M and showed potent inhibitory activity against selective NK₁ receptor agonist-induced bronchoconstriction in guinea pigs. © 1998 Elsevier Science Ltd. All rights reserved.

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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 NK₁ receptor. Because inhibition of the binding between SP and the NK₁ receptor may be efficient for the treatment of these diseases, a number of potent and selective non-peptide NK₁ receptor antagonists have been reported²⁻⁸ 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 NK₁ 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



0960-894X/98/\$19.00 © 1998 Elsevier Science Ltd. All rights reserved. *PII:* S0960-894X(98)00260-1 YM-35375.¹⁰) These results encouraged us to find a potent NK₁ receptor antagonist by structural modifications of the spiro-substituted piperidines. In 1993, it was reported that the 1-acyl-3-(3,4-dichlorophenyl)piperidine, SR140333³), exhibited high affinity for the NK₁ receptor with an IC₅₀ value of 0.019 nM in binding assay. This compound is one of the most potent NK₁ receptor antagonists to our knowledge. In order to find a novel NK₁ 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 NK₁ receptor antagonists.

The (\pm) -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 Et₃N. 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**).



Scheme 1. (a) methanesulfonyl chloride, Et₃N / CH₂Cl₂, r.t.; (b) Et₃N / DMF, 70°C; (c) HY (15-56% from 1)



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. ¹³C-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



Scheme 3. (a) 2 equiv n-BuLi / THF – Et₂O – n-hexane, -78°C then 8-benzyl-3-tropinone, -78°C, (49%); (b) p-TsCl, pyridine / CH₂Cl₂, r.t., (36%); (c) HCl then 20% Pd(OH)₂ – C, H₂ / MeOH, r.t., (85%)

Compd. No.		salt	NK_1 antagonistic activity $IC_{50} (nM)^{a}$	
4a		2HCI	31	(27—35)
4b	H X	fumarate	54	(46—63)
4c		fumarate	18	(11—29)
4d		oxalate	16	(13—21)
4 e		HCI	105	(94—116)
(±)-SR140333			0.31	(0.290.33)

Table 1. NK₁ antagonistic activity¹⁴⁾ of the spiro-substituted piperidines 4a - e

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-Et₂O 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, (\pm) -SR140333^{11,15}) exhibited potent NK₁ antagonistic activity with an IC₅₀ value of 0.31 nM. Compound 4a possessing 3,4-dihydrospiro[isoquinoline-1(2H),4'-piperidine] instead of 4-phenylquinuclidinium of SR140333



Table 2. NK₁ antagonistic activity¹⁴⁾ of the spiro-substituted piperidinium salts 5

a) Numbers in parentheses represent 95% confidence limits.

exhibited moderate potency (IC₅₀ 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 NK₁ 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 NK₁ 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 NK₁ receptor antagonistic activity. Unfortunately, compounds **5ba** were less potent than (\pm)-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 NK₁ receptor.

Some potent compounds (**5aa**, **5ba**) were evaluated for their inhibitory activity against selective NK₁ 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 (\pm)-SR140333. In contrast, the isoquinolone derivative **5ba** was almost equipotent to (\pm)-SR140333 (ID₅₀ 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 NK₁ receptor antagonistic activity *in vivo*.

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)

Table 3. Inhibitory activity of the spiro-substituted piperidinium salts **5aa** and **5ba** against [Sar⁹, $Met(O_2)^{11}$]-SP-induced bronchoconstriction in guinea pigs.¹⁶

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 NK₁ 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 NK₁ receptor agonist-induced bronchoconstriction model. This compound was almost as potent as (\pm)-SR140333 *in vivo* and may be useful for the treatment of the diseases caused by NK₁ receptor activation.

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- 12. the less polar product: ¹H-NMR (CDCl₃) 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). ¹³C-NMR (CDCl₃) δ 44.48 [N+-Me(ax.)]. FAB-MS *m/z*: 662 [(M-I)+]. *Anal*. Calcd for C₃₈H₄₆Cl₂IN₃O₃·H₂O: 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: ¹H-NMR (CDCl₃) 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). ¹³C-NMR (CDCl₃) δ 52.87 [N+-Me(eq.)]. FAB-MS *m/z*: 662 [(M-I)+]. *Anal*. Calcd for C₃₈H₄₆Cl₂IN₃O₃·1.5 H₂O: 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. ¹H-NMR (CDCl₃) 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 IC₅₀ 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 [Sar⁹, Met(O₂)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% (ID₅₀) were determined by probit analysis.