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Combined Tachykinin Receptor Antagonist: Synthesis and Stereochemical Structure–Activity Relationships of Novel Morpholine Analogues

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Abstract—We report herein the synthesis and stereochemical structure–activity relationships of novel morpholine analogues **12** and **13** with regards to NK_1, NK_2 and NK_3 tachykinin receptor binding affinity. An essential requirement for more potent binding affinities was controlled by absolute configuration. (*S,R*)-**12** and (*S,R*)-**13** exhibited high binding affinities for NK_1, NK_2 and NK_3 receptors.

Introduction

The tachykinins are a family of neuropeptides that share the common C-terminal region, Phe-X-Gly-Leu-Met-NH_2. The main members are substance P (SP), neurokinin A (NKA), and neurokinin B (NKB). They are differentially distributed in both the central nervous system and periphery, with a prominent location in the peripheral endings of capsaicin-sensitive primary afferent neurons. Tachykinin actions are mediated by at least three distinct receptors designated as NK_1, NK_2 and NK_3. The endogenous tachykinin ligands interact with all tachykinin receptors, although there is a defined agonist rank order of potency such that SP, NKA and NKB have the highest affinities for NK_1, NK_2 and NK_3 receptors, respectively.[1] SP, NKA and NKB have been linked to several chronic diseases such as asthma, chronic obstructive pulmonary disease, inflammatory bowel disorders, rheumatoid arthritis, pain, migraine, emesis, urinary incontinence, and psychiatric disorders such as anxiety and schizophrenia.[2] It is thus expected that tachykinin receptor antagonists will prove useful in the therapy of a wide variety of disorders. Based on the speculation that combined tachykinin receptor antagonist would be of greater benefit in the treatment of pulmonary diseases than selective antagonist,[3] we have already reported that a series of novel oxazolidine analogues exhibited high binding affinities for both NK_1 and NK_2 receptors.[4]

We report herein the preparation of a series of novel optically active morpholine analogues that possess spiropiperidine moiety. The key steps in the preparation of novel morpholine analogues were Sharpless asymmetric dihydroxylation (AD) and the Mitsunobu reaction. These afforded the intermediate **5** in good yield in which the substituents at 2-position of the morpholine ring were employed to introduce the required stereochemistry. The intermediate **5** was also prepared using iodoetherification and optical resolution. In addition, all stereoisomers were prepared to fully explore the stereochemical preferences of compounds **12** and **13**. Compared to all stereoisomers, (*S,R*)-**12** and (*S,R*)-**13** showed the higher binding affinities to tachykinin receptors. These compounds exhibited excellent high binding affinities for NK_1, NK_2 and NK_3 receptors.

Chemistry

The key intermediate 2-[(2*R*)-(3,4-dichlorophenyl)morpholin-2-yl]ethanol ((*R*)-**5**) was prepared in a straightforward fashion as outlined in Scheme 1.[5] As previously described, olefin **1** was treated with AD-mix-β in *t*-BuOH–H_2O to obtain (*R*)-diol **2** with high enantiomeric

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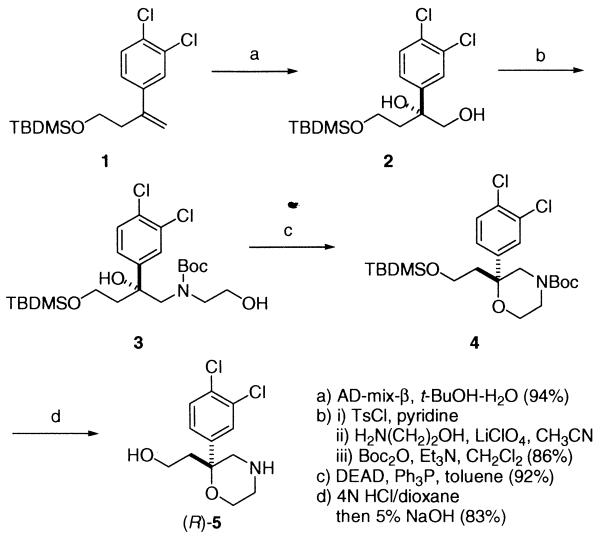
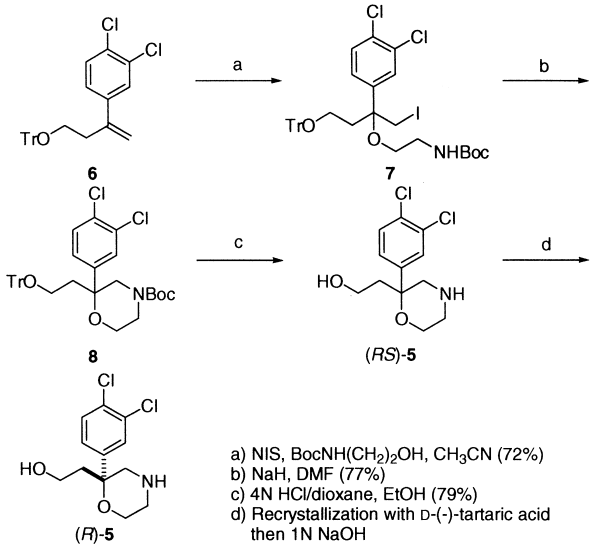


Scheme 1. Synthesis of key intermediate (*R*)-**5** using the Sharpless AD and Mitsunobu reaction.

purity (>97% ee). After selective formation of the primary tosylate, substitution with aminoethanol was performed in the presence of $LiClO_4$ in acetonitrile at 100 °C, and the protection of the resulting secondary amine with Boc_2O and Et_3N cleanly provided **3** in good yield. Next, treatment of **3** with DEAD and Ph_3P in toluene for dehydration provided **4** in good yield. The Boc and TBDMS groups of **4** were deprotected via treatment with 4N HCl/dioxane at 60 °C, and the subsequent base treatment gave the enantiomerically pure (*R*)-**5**. This synthesis also led to the synthesis of 2-[(2*S*)-(3,4-dichlorophenyl)morpholin-2-yl]ethanol ((*S*)-**5**) with the opposite configuration by using AD-mix-α for the Sharpless AD of **1**.

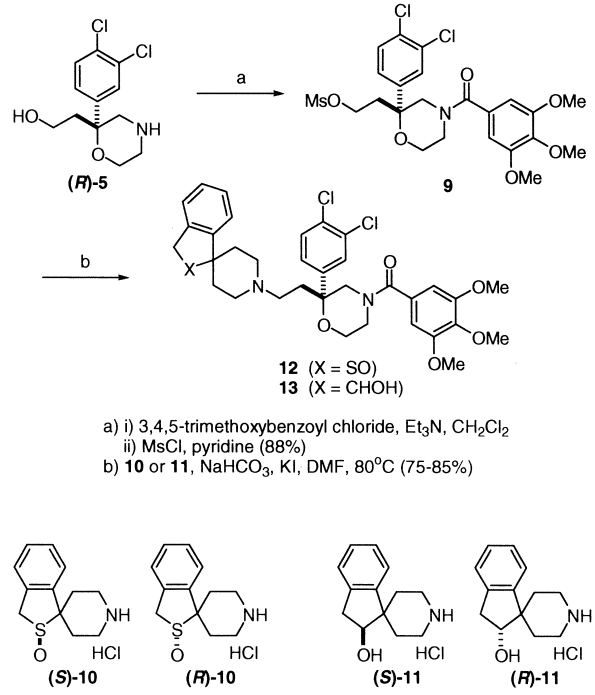
On the other hand, a versatile and short-step synthetic method using iodoetherification has also been achieved (Scheme 2).[6] Styrene derivative **6** was treated with *N*-Boc-aminoethanol and *N*-iodosuccinimide (NIS) in acetonitrile at 70 °C to obtain iodide **7** in good yield. Treatment of **7** with NaH in DMF at 70 °C cleanly provided **8**, and then deprotection of both the triphenylmethyl (Tr) and Boc groups of **8** by 4N HCl proceeded smoothly in good yield. Next, the resulting racemic (*RS*)-**5** was resolved with D-(−)-tartaric acid in EtOH to give (*R*)-**5** with high enantiomeric purity. (*S*)-**5** was also resolved with L-(+)-tartaric acid. This method is useful for the synthesis of a variety of 2,2-disubstituted morpholine derivatives from 1,1-disubstituted olefins.



Scheme 2. Synthesis of key intermediate (*R*)-5 using the iodoetherification and optical resolution.

Next, morpholine **5** was condensed with 3,4,5-trimethoxybenzoyl chloride and the resulting primary alcohol was converted to the methanesulfonate **9** in good yield. In an earlier paper, we described the design rationale that led to the 3,4-dichlorophenyl and 3,4,5-trimethoxybenzoyl groups as the best moiety in terms of combined NK_1 and NK_2 receptor antagonistic activities.[3] Our preliminary studies on the effects of piperidine analogues indicated that compounds possessing spiro-piperidine analogues exhibited higher binding affinities for both receptors compared to structurally related compounds.

Among the series of spiro-piperidine analogues, compounds possessing properties such as spiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine]-2-oxide (**10**) or spiro[(2-hydroxy)indane-1,4′-piperidine] (**11**) moiety were particularly efficacious in increasing the binding affinities. The synthetic methods for the preparation of optically active **10** and **11** have already been reported.[7,8] Heating **9** and spiro-piperidine analogues **10** or **11** in the presence of $NaHCO_3$ and KI at 80 °C in DMF afforded the desired compounds **12** or **13** (Scheme 3).[9] Finally, all of the stereoisomers were prepared to fully explore the stereochemical preferences of compounds **12** and **13**.

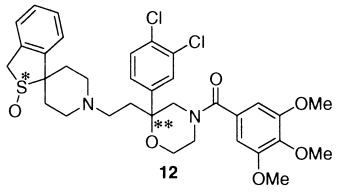


Scheme 3. Synthesis of optically active **12** and **13**.

Results and Discussion

Compounds **12** and **13** were evaluated for their binding affinities, and the NK_1, NK_2 and NK_3 receptor binding affinity data (IC_{50}; nM) are summarized in Tables 1 and 2.[10] As can be seen from the results, the (*R*)-configuration at the 2-position of the morpholine ring was crucial for high affinity (compound (*S,R*)- and (*R,R*)-**12**, **13** versus (*S,S*)- and (*R,S*)-**12**, **13**). (*S,S*)-**12**, **13** and (*R,S*)-**12**, **13** possessing the (*S*)-configuration at the mopholine ring, were both found to be inactive. The data confirmed that the (*R*)-configuration is an essential requirement for high binding affinity. On the other hand, the stereochemistry of the sulfoxide and hydroxy groups also had effects on the activity. When we assessed the sulfoxide-containing spiro-piperidine analogues, we found that (*S,R*)-**12** had 10-fold (NK_1), 20-fold (NK_2), and 15-fold (NK_3) higher levels than (*R,R*)-**12**. As shown in Table 2, the inversion of stereochemistry of the hydroxy group resulted in 7-fold (NK_1), 6-fold (NK_2), and 6-fold (NK_3) decreases in affinity, bringing the affinity down to the same level seen with sulfoxide-containing analogues. These results indicated that the stereochemistry of the sulfoxide of **12** and the hydroxyl group of **13** has great impact on the binding activity to the tachykinin receptor, and thus that the (*S*)-configuration is an essential requirement for more potent binding affinities. These properties clearly appear to form an appropriately positioned pocket in the binding site, probably through their actions as hydrogen bond acceptors or donors, or possibly due to the steric effect.

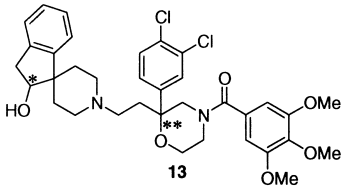
Table 1. In vitro binding affinity of compound **12** to NK_1, NK_2, and NK_3 receptors from the membrane of guinea pigs



Compounds	Absolute configuration		IC_{50} (nM)[a]		
	*	**	NK_1	NK_2	NK_3
(*S,R*)-**12**	*S*	*R*	21	3.1	0.72
(*R,R*)-**12**	*R*	*R*	220	59	11
(*S,S*)-**12**	*S*	*S*	>1000	>1000	520
(*R,S*)-**12**	*R*	*S*	>1000	>1000	660

[a]Each value is the mean of at least three determinations.

Table 2. In vitro binding affinity of compound **13** to NK_1, NK_2, and NK_3 receptors from the membrane of guinea pigs



Compounds	Absolute configuration		IC_{50} (nM)[a]		
	*	**	NK_1	NK_2	NK_3
(*S,R*)-**13**	*S*	*R*	40	6.8	2.7
(*R,R*)-**13**	*R*	*R*	270	45	17
(*S,S*)-**13**	*S*	*S*	>1000	>1000	>1000
(*R,S*)-**13**	*R*	*S*	>1000	>1000	>1000

[a]Each value is the mean of at least three determinations.

We also evaluated the in vivo potency of (*S,R*)-**12** HCl salt and its inhibitory effect on SP-induced tracheal vascular hyperpermeability in anesthetized guinea pigs. (*S,R*)-**12** HCl salt dose-dependently inhibited SP-induced plasma protein extravasation (ID_{50}; 0.1–0.33 mg/kg, iv) mediated by NK_1 receptors in guinea pig airways.[11] It was also evaluated for the inhibitory effects on bronchoconstriction induced by NKA and NKB in anesthetized guinea pigs. It dose-dependently inhibited NKA-induced bronchoconstriction (ID_{50}; 0.040 mg/kg, iv) and NKB-induced bronchoconstriction (ID_{50}; 0.063 mg/kg, iv), respectively.[12]

In conclusion, we have developed a synthetic route for the preparation of the optically active novel morpholine derivatives **12** and **13** and evaluated them as antagonists for tachykinin NK_1, NK_2, and NK_3 receptors. The binding affinity is highly dependent on the stereochemistry of the compounds, showing (*S,R*)-**12** and (*S,R*)-**13** are most potent in the in vitro assay. Furthermore, we also evaluated the in vivo potency of (*S,R*)-**12** HCl salt, and its inhibitory effects on SP-induced tracheal vascular hyperpermeability and NKA- and NKB-induced bronchoconstriction in anesthetized guinea pigs. A more detailed analysis of SAR and further work in elucidating biological activities will be described in future publications.

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9. All new compounds are fully characterized by their spectroscopic and analytical data.
10. NK_1 IC_{50} determined using [^{3}H]-SP and NK_1 receptors from lung membrane of male Hartley guinea pigs. NK_2 IC_{50} determined using [^{3}H]-SR-48968 and NK_2 receptors from

ileum membrane of male Hartley guinea pigs. NK_3 IC_{50} determined using [^{3}H]-senktide and NK_3 receptors from brain membrane of male Hartley guinea pigs. Each value is the mean of at least three determinations.

11. Compounds were administered intravenously just before intravenous injection of SP (1 μg/kg). The amount of Evans blue dye extracted from the trachea was used as the index of plasma protein leakage. The trachea was isolated from the Evans blue-treated animal 15 min after SP injection.

12. The assessment of the inhibitory effect was based on airway pressure as an index of bronchoconstriction according to the modified method of Konzett-Rössler. Compounds were administered intravenously 5 min before intravenous injection of NKA (4 μg/kg) or NKB (4 μg/kg).