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Combined NK_1 and NK_2 Tachykinin Receptor Antagonists: Synthesis and Structure-Activity Relationships of Novel Oxazolidine Analogues

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Abstract: We report herein the synthesis and structure-activity relationships of a series of novel oxazolidine analogues with regards to NK_1 and NK_2 tachykinin receptor binding affinity. Among this series of oxazolidine analogues, some compounds exhibited excellent high binding affinities for both NK_1 and NK_2 receptors. In addition, we describe the inhibitory effect *in vivo* on SP-induced airway vascular hyperpermeability and NKA-induced bronchoconstriction in guinea pigs.

The tachykinins are a family of neuropeptides comprising substance P (SP), neurokinin A (NKA) and neurokinin B (NKB), that share the common C-terminal sequence *Phe-X-Gly-Leu-Met-*NH_2 in 10- or 11-amino acid residue. Based on the different orders of potency of natural tachykinins, three distinct receptor types which belong to the G-protein-coupled 7-transmembrane superfamily have been identified: NK_1 (SP-preferring), NK_2 (NKA-preferring), and NK_3 (NKB-preferring).[1] The presence of the various forms of tachykinin in the mammalian body is associated with a variety of biological actions such as pain transmission, vasodilation, smooth muscle contraction, and neurogenic inflammation. In the airway and lung, SP and NKA play an important role in the pathogeneses of asthma such as airway constriction, plasma extravasation, leukocyte adhesion, and mucus secretion.[2] Therefore, airway inflammation and bronchoconstriction in asthma and chronic airway-obstructive disease continue to be the major foci of clinical interest in tachykinin research. Among several classes of recently reported tachykinin receptor antagonist, there is speculation that a combined NK_1 and NK_2 receptor antagonist might be an effective drug in asthma and chronic airway obstruction.

A number of peptide and non-peptide antagonists selective for NK_1 and NK_2 and NK_3 receptors have been reported respectively, but until recently few potent combined NK_1 and NK_2 receptor antagonists were known.[3] Among these, MDL 105,212 has been known to be one of the potent compounds with a high affinity for both receptors (IC_{50}: NK_1; 3.11 nM, NK_2; 8.40 nM), and it also has been shown to have beneficial effects in an *in vivo* asthma model.[4] Information from MDL 105,212 studies has allowed us to synthesize more potent analogues with oral efficacy and long duration of action. We then applied these strategies for the design of a novel combined antagonist with potential as a therapeutic drug for the treatment of asthma via the action of oxazolidine analogues.

We report herein the design, chemical synthesis, and structure-activity relationships of novel optically active oxazolidine analogues.[5] Preliminary studies indicated that the stereochemistry of the 5-substituents of the oxazolidine ring has great impact on the binding activity to receptor, and the (*R*)-configuration has been shown to be an essential requirement for more potent binding affinity. Therefore, we synthesized compounds in optically active form.

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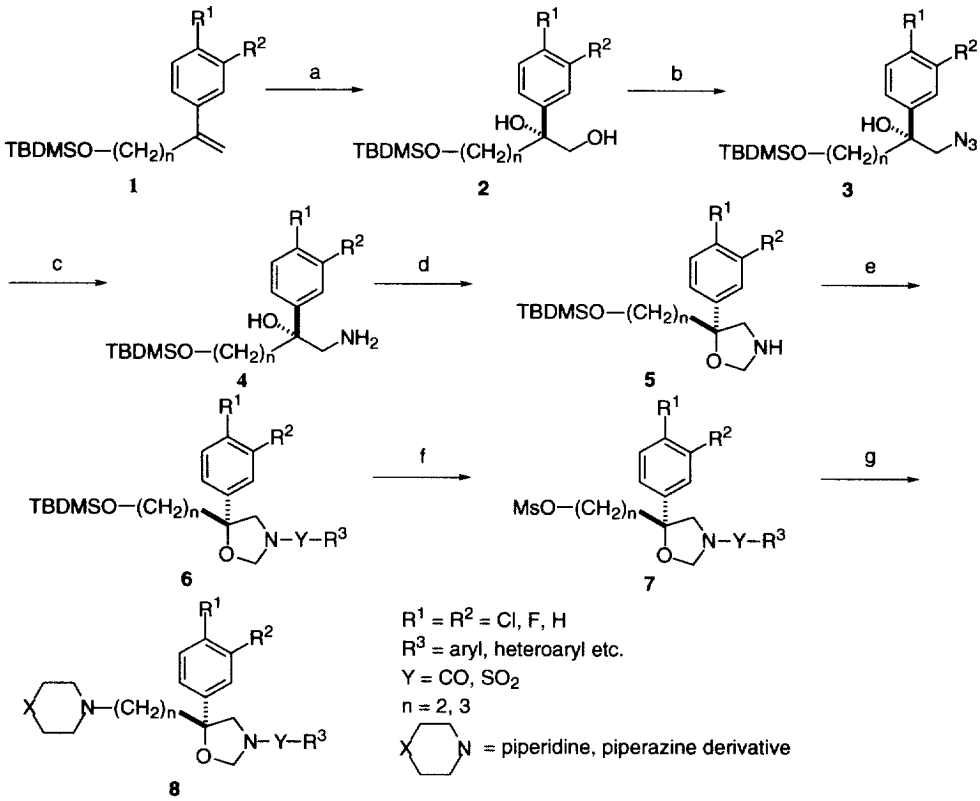
The synthetic route to optically active (5*R*)-oxazolidine analogues is outlined in Scheme 1. Sharpless asymmetric dihydroxylation (AD) of **1** was employed to introduce the required absolute stereochemistry. Olefins **1**[6] were treated with AD-mix-β[7] in *t*-BuOH-H_2O to obtain (*R*)-diols **2** with high enantiomeric purity (>97 %*ee*) as previously described.[8] After selective formation of the primary methanesulfonate of **2**, substitution with sodium azide was performed in DMF at 80 °C, and the reduction of the resulting azide **3** with triphenylphosphine in aqueous THF cleanly provided **4**. In the continued construction of the oxazolidine ring, treatment of **4** with paraformaldehyde in benzene using Dean-Stark apparatus provided oxazolidine derivatives **5** in good yield. Then, oxazolidines **5** were condensed with various kinds of acyl chloride, carboxylic acid or sulfonyl chloride to yield **6**. After deprotection of the *tert*-butyldimethylsilyl (TBDMS) group of **6**, resulting alcohols were converted to the methanesulfonate **7** in quantitative yield. Nucleophilic displacement of the various kinds of piperidine and piperazine derivatives with $NaHCO_3$ and KI in DMF at 80 °C provided the desired compounds **8** in good yield. Thus, a series of novel oxazolidine compounds were prepared, and their binding affinities to guinea pigs lung NK_1 receptor and guinea pigs ileum NK_2 receptor were evaluated.

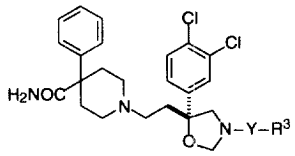


Reagents: a) AD-mix-β, *t*-BuOH-H_2O; b) i) MsCl, cat.DMAP, pyridine; ii) NaN_3, DMF, 120 °C; c) Ph_3P, aq. THF, 60 °C; d) paraformaldehyde, benzene, Dean-Stark, 100 °C; e) R^3COCl, NEt_3, CH_2Cl_2 or R^3CO_2H, WSC, HOBt, NEt_3, CH_2Cl_2 or R^3SO_2Cl, NEt_3, CH_2Cl_2; f) i) AcOH, aq. THF, 50 °C; ii) MsCl, cat.DMAP, pyridine; g) piperidine or piperazine derivative $NaHCO_3$, KI, DMF, 80 °C

Scheme 1

The NK_1 and NK_2 receptor binding affinity data (IC_{50} (ng/ml) or % inhibition at 1 μg/ml) are summarized in Table 1-3.[9] The compounds shown in Table 1 explore the variation of the Y-R^3 (acyl and sulfonyl) group, mainly substituents of the benzene ring. We found that the methoxy substituent on benzamide **10-12** had improved NK_1 receptor affinity. Comparison of substituents on the 4-position of the benzene ring illustrated that compounds bearing methyl **13**, acetylamino **14**, cyano **15**, chloro **16** and carbomethoxy **17** on the 4-position are less potent than the 4-methoxybenzamide derivative **12**. The introduction of 3,5-dimethyl and 3,5-bis(trifluoromethyl) substituent on benzamide (**18** and **19**) led to an increase in the binding potency. Dimethoxy-substituted compounds **20-23** improved NK_1 receptor affinity, and 3,4,5-trimethoxy-substituted compound **24** was found to have the best combined NK_1 and NK_2 receptor affinity from this series. Reduced potency against NK_1 receptor is generally observed for significant changes in benzamide substitution. Replacement of the R^3 group with heterocycles (i.e. 2-pyridyl **25**, 3-pyridyl **26**, 4-pyridyl **27**, 2-pyrazinyl **28**, and 2-thienyl **29**) causes a loss of affinity for the NK_1 receptor while maintaining NK_2 receptor affinity. Replacing the R^3 group with the larger heteroaryl group as in **31-33** was also a detrimental activity against NK_1 receptor, except in the case of compound **30**. Phenylacetyl derivatives (i.e. 3-isopropyloxyphenylacetyl **34** and 3,4,5-trimethoxyphenylacetyl **35**) and 3,4-Dimethoxybenzenesulfonyl derivative **36** all led to reductions in activity and none had activity against NK_2 receptor.

Table 1. Replacement of the Y-R^3 group

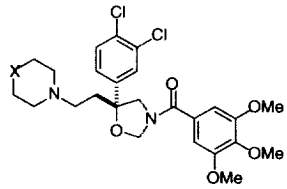


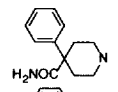
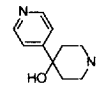
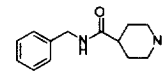
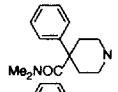
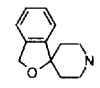
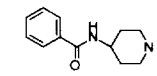
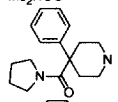
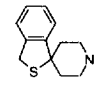
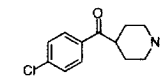
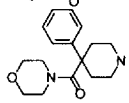
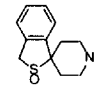
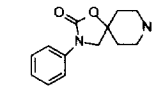
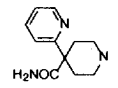
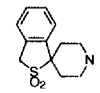
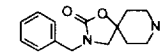
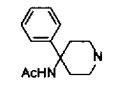
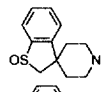
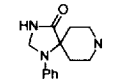
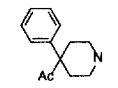
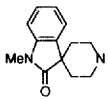
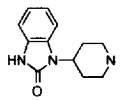
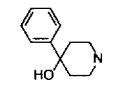
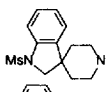
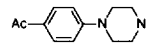
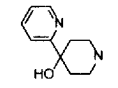
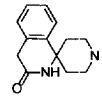
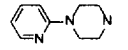
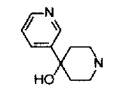
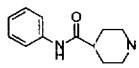
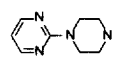
Compound	Y-R^3	IC_{50} (ng/ml) or (% inhibition at 1 μg/ml) NK_1	NK_2	Compound	Y-R^3	IC_{50} (ng/ml) or (% inhibition at 1 μg/ml) NK_1	NK_2
9	benzoyl	(75)	(87)	**23**	3,5-dimethoxybenzoyl	(93)	(97)
10	2-methoxybenzoyl	(100)	(87)	**24**	3,4,5-trimethoxybenzoyl	6.2	91
11	3-methoxybenzoyl	(100)	(82)	**25**	2-pyridinecarbonyl	(39)	(73)
12	4-methoxybenzoyl	65	170	**26**	3-pyridinecarbonyl	(38)	(48)
13	4-methylbenzoyl	(56)	(88)	**27**	4-pyridinecarbonyl	(65)	(57)
14	4-acetylaminobenzoyl	(9)	(85)	**28**	2-pyrazinecarbonyl	(23)	(47)
15	4-cyanobenzoyl	(29)	(79)	**29**	2-thienylcarbonyl	(33)	(83)
16	4-chlorobenzoyl	(50)	(88)	**30**	2-indolecarbonyl	(96)	(26)
17	4-carbomethoxybenzoyl	(36)	(85)	**31**	2-benzofurancarbonyl	NE	(59)
18	3,5-dimethylbenzoyl	(100)	(90)	**32**	2-quinolinecarbonyl	NE	(71)
19	3,5-bis(trifluoromethyl)benzoyl	100	110	**33**	2-quinoxalinecarbonyl	(38)	(71)
20	2,4-dimethoxybenzoyl	(78)	(85)	**34**	3-isopropyloxyphenylacetyl	(59)	(18)
21	2,6-dimethoxybenzoyl	(74)	(83)	**35**	3,4,5-trimethoxyphenylacetyl	(87)	NE
22	3,4-dimethoxybenzoyl	(93)	(88)	**36**	3,4-dimethoxybenzenesulfonyl	(71)	(10)

The compounds shown in Table 2 explore the variation of piperidine and piperazine moiety. The carboxamide derivatives of the 4-phenylpiperidines **24**, **37-39** had balanced binding activities, and incorporation

of the pyridyl moiety **40** was found to reduce the potency. 4-Acetylamino and 4-acetyl derivatives **41-42** were only moderately potent, and 4-hydroxy-4-phenyl and 4-hydroxy-4-pyridyl-substituted piperidine derivatives **43-46** had strong binding affinities with the NK_1 receptor. The introduction of spiro-substituted piperidine had profound effects on binding. Compounds **49**[10], **51**, and **54** had especially strong binding affinities with both receptors in this series. Further modification of the piperidine moiety with 4-amido and 4-acylamino and 4-acyl group **55-58** resulted in loss of activities, and spiroheterocycles **59-62** did not improve the potency. Replacement to piperazine derivatives **63-65** had less of an effect in terms of NK_2 receptor affinity.

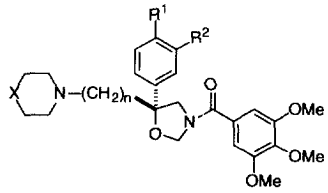
Table 2. Replacement of piperidine and piperazine derivatives

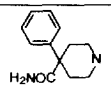
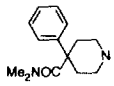


Compound		IC_{50} or (%inhibition) NK_1	NK_2	Compound		IC_{50} or (%inhibition) NK_1	NK_2	Compound		IC_{50} or (%inhibition) NK_1	NK_2
24		6.2	91	**46**		1.9	89	**56**		61	(64)
37		17	5.5	**47**		(98)	(91)	**57**		(89)	(44)
38		7.8	64	**48**		(100)	(89)	**58**		(97)	(54)
39		32	52	**49**		6.7	7.5	**59**		(86)	(12)
40		(95)	(83)	**50**		23	19	**60**		(86)	(44)
41		(100)	(62)	**51**		5.9	7.3	**61**		5.0	160
42		(83)	(57)	**52**		9.2	34	**62**		(100)	(85)
43		(100)	(58)	**53**		(98)	(91)	**63**		18	74
44		(100)	(76)	**54**		12	3.0	**64**		(100)	(42)
45		(100)	(100)	**55**		(44)	(72)	**65**		(100)	(48)

Next, we investigated the effects on substituents of the phenyl ring in the 3,4-dichlorophenyl moiety, and also the effects of alkyl chain length. The representative results are shown in Table 3. Chlorine substitution at the 3- and 4-positions of the aromatic ring causes a significant improvement in affinity. In contrast to case of 3,4-dichlorophenyl derivatives, 4-chlorophenyl derivatives only marginally augmented the affinity and selectivity. 3,4-Difluorophenyl and 4-fluorophenyl derivatives had binding affinities close to the desired levels, but these were clearly less active than the corresponding 3,4-dichlorophenyl and 4-chlorophenyl derivatives. As can be seen in compound **69**, elongated alkyl chain (n = 3) causes a loss of affinity for the NK_2 receptor while maintaining NK_1 receptor affinity. This modification slightly boosted the affinity for NK_1 receptor and decreased the NK_2 receptor affinity.

Table 3. Replacement of R^1, R^2 substituent, and alkyl chain length



Compound	X	n	R^1	R^2	IC_{50} (ng/ml) NK_1	IC_{50} (ng/ml) NK_2	Compound	X	n	R^1	R^2	IC_{50} (ng/ml) NK_1	IC_{50} (ng/ml) NK_2
24		2	Cl	Cl	6.2	91	**49**		2	Cl	Cl	6.7	7.5
66	"	2	Cl	H	27	200	**73**	"	2	Cl	H	12	6.9
67	"	2	F	F	10	200	**74**	"	2	F	F	16	19
68	"	2	F	H	27	440	**75**	"	2	F	H	15	21
69	"	3	Cl	Cl	23	>1000							
37		2	Cl	Cl	17	5.5	**54**		2	Cl	Cl	12	3.0
70	"	2	Cl	H	50	4.7	**76**	"	2	Cl	H	51	3.2
71	"	2	F	F	27	13	**77**	"	2	F	F	28	6.8
72	"	2	F	H	17	9.3	**78**	"	2	F	H	29	6.2

In addition, we evaluated the *in vivo* potency of the potent compound **49**. Compound **49** was evaluated for the inhibitory effect on SP-induced airway vascular hyperpermeability in guinea pigs. We assessed the inhibitory effect based on the amount of leaked evans blue dye as an index of vascular permeability. As can be seen from the results shown in Table 4, compound **49** inhibited SP-induced vascular hyperpermeability, and the inhibitory activity of **49** was at least equal to that of MDL 105,212. Compound **49** was also evaluated for the inhibitory effect on bronchoconstriction induced with [Nle^{10}]-NKA[4-10] in guinea pigs. The assessment of the inhibitory effect was based on airway pressure as an index of bronchoconstriction according to the modified method of Konzett-Rössler, and the results are shown in Table 5. Compound **49** inhibited bronchoconstriction induced with

[Nle^{10}]-NKA[4-10], and the inhibitory activity of **49** was greater than that of MDL 105,212. We assumed this difference might relate to the pharmacologic profile. These results suggest that the novel oxazolidine analogues such as compound **49** are potent combined NK_1 and NK_2 receptor antagonists based on *in vitro* binding activity, and that they have ability to inhibit SP- and NKA-mediated respiratory effects *in vivo*.

Table 4. Inhibitory activity against SP-induced vascular hyperpermeability in guinea pigs

Compound	ID_{50} (μg/kg, *iv*)
49	25
MDL 105,212	19

Table 5. Inhibitory activity against [Nle^{10}]-NKA[4-10]-induced bronchoconstriction in guinea pigs

Compound	ID_{50} (μg/kg, *iv*)
49	74
MDL 105,212	1700

In conclusion, a synthetic route to prepare the novel oxazolidine analogues has been developed. Evaluation of the NK_1 and NK_2 receptor binding affinity revealed that the 1-{2-[(5*R*)-(3,4-dichlorophenyl)-3-(3,4,5-trimethoxybenzoyl)oxazolidin-5-yl]ethyl}piperidine analogues were effective and optimal for binding affinity with both receptors. Their inhibitory effect *in vivo* on SP-induced increases in vascular permeability and on NKA-induced bronchoconstriction in guinea pigs are predicted to have respiratory efficacy for the treatment of asthma.

References and Notes

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6. Synthesis of compound **1** (n = 2); see ref. 8. (n = 3); i) 3,4-dichlorobenzene, succinic anhydride, $AlBr_3$ then c.H_2SO_4, MeOH (41 %). ii) $Ph_3MeP^+Br^-$, *t*-BuOK, benzene (50 %). iii) $LiAlH_4$, THF then TBDMSCl NEt_3, CH_2Cl_2 (60 %).
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10. The absolute stereochemistry of sulfoxide is *S*. Synthesis; Nishi, T.; Nakajima, K.; Iio, Y.; Ishibashi, K.; Fukazawa, T. *Tetrahedron: Asymmetry* **1998**, *9*, 2567.