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IDENTIFICATION AND CHEMICAL SYNTHESIS OF MDL 105,212, A NON-PEPTIDE TACHYKININ ANTAGONIST WITH HIGH AFFINITY FOR NK_1 AND NK_2 RECEPTORS.

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Abstract: We have synthesized and identified MDL 105,212, a non-peptide tachykinin receptor antagonist that has high affinity for human NK_1 (IC_{50}=3.11 nM) and NK_2 (IC_{50}=8.40 nM) receptors. The chemical synthesis of MDL 105,212 and the SAR of a series of racemic amide analogs are described. Copyright © 1996 Elsevier Science Ltd

In the airways, sensory neuropeptides, including substance P (SP) and neurokinin A (NKA), are localized primarily in capsaicin-sensitive primary afferent nerves.[1] They are co-released by a variety of chemical, physical, and pharmacological stimuli. These peptides regulate vascular and bronchial tone, vascular permeability, mucus secretion, cell proliferation, and immune responses through action at their preferred receptors.[2] The NK_1 receptors are activated preferentially by SP, the NK_2 receptors by NKA, and the NK_3 receptors by NKB.[1] Recognition of the similarities between tachykinin-mediated effects and asthmatic symptoms has led to the postulation that SP and NKA participate in the inflammatory processes in the airways of asthmatics.[3] Based on the complementary nature of the airway effects of SP and NKA and since both are released upon sensory nerve stimulation, we felt an agent that simultaneously inhibits the receptors for both tachykinins would potentially be of greater benefit in the treatment of asthma than a receptor-selective antagonist. We report here the identification and chemical synthesis of MDL 105,212, a non-peptide tachykinin antagonist with high affinity for human NK_1 and NK_2 receptors.

The first reported non-peptide antagonists selective for NK_1 and NK_2 receptors were CP 96,345[4] and SR 48,968,[5] respectively. SR 48,968 has high affinity for the NK_2 receptor and, in addition, has low but significant affinity for the NK_1 receptor. Examination of low energy conformations of SR 48,968 suggested that constraining the 3,4-dichlorophenylbutylbenzamide side chain in a pyrrolidine ring would mimic the low energy conformations and give a good overlap of the 3,4-dichlorophenyl and benzamide rings in the two compounds. MDL 103,220 was synthesized and found to have good affinity for the NK_2 receptor (IC_{50}=2.25 ± 0.20 nM) and slightly improved affinity for the NK_1 receptor (IC_{50}=161 ± 34.9 nM) compared to SR 48,968 (see Table 2).

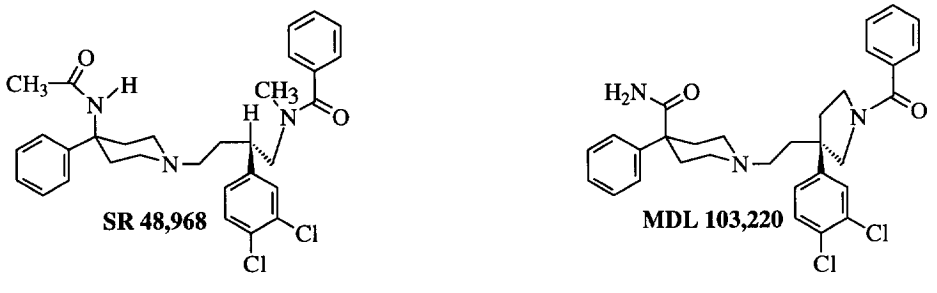
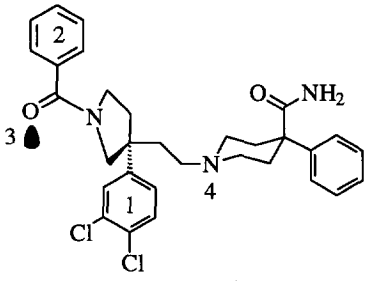


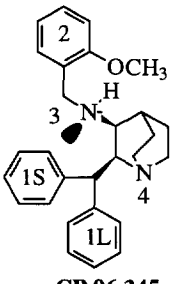
Figure 1. SR 48,968 and MDL 103,220.

Molecular modeling studies,[6] using low energy conformations of MDL 103,220 and CP 96,345, revealed two conformations that had good overlap of four pharmacophore points: (1) the 3,4-dichlorophenyl ring and one of the aromatic rings of the diphenylmethyl moiety; (2) the aromatic ring of the benzamide and the aromatic ring of the benzyl

amine; (3) a hydrogen bond acceptor; and (4) the tertiary amine (Figure 1). In addition, MDL 103,220 has a 4-phenylpiperidine moiety, like SR 48,968, that enhances NK_2 affinity.



MDL 103,220



CP 96,345

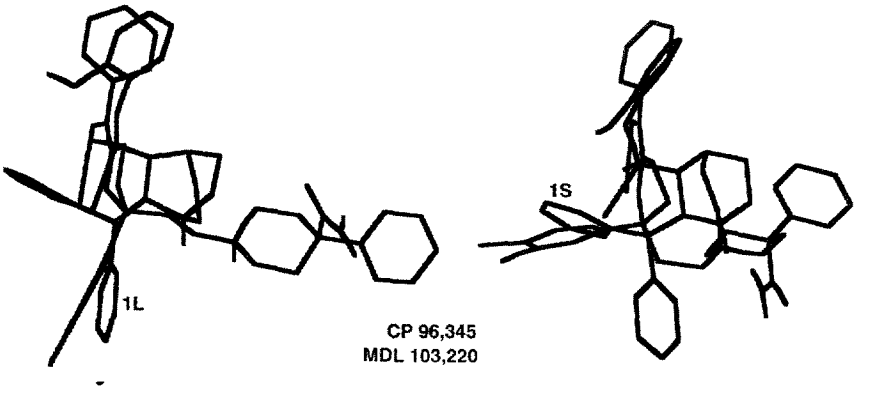


Figure 2. Potential common pharmacophore and two overlaps of low energy conformations for CP 96,345 and MDL 103,220.

The overlaps of MDL 103,220 and CP 96,345 (Figure 2[7]) suggested that substitution on the benzamide ring with a methoxyl group might lead to pyrrolidine compounds with enhanced NK_1 receptor affinity. We found that the 2-methoxy and 3-methoxy benzamide analogs (**2** and **3**, respectively) had improved NK-1 receptor affinity relative to racemic MDL 103,220 (**1**). The 4-methoxy benzamide analog (**4**) had diminished affinity for the NK_1 receptor. The 2,6-dimethoxy benzamide analog (**5**) showed an additional improvement relative to the 2-methoxy benzamide analog (**2**), however, the NK_2 receptor affinity decreased. The 3,5-dimethoxy benzamide analog (**7**) had improved NK_1 receptor affinity relative to the 3-methoxy benzamide analog (**3**) while maintaining NK_2 receptor affinity. The 3,4,5-trimethoxy benzamide analog, MDL 103,392, was found to have the best dual NK_1/NK_2 receptor affinity from this series (Table 1).[8] Other 3,4,5-trisubstituted benzamide analogs **8-12** and phenacetylamide analogs **13-15** had lower affinity for both receptors. The difference in SAR with regards to aryl ring 2 (Figure 2) between CP 96,345 and the substituted pyrrolidines may result in part from the difference in the nature of the H-bond acceptor (pharmacophore point 3 in Figure 2). Further molecular modeling studies regarding NK_1 and NK_2 receptor affinities will be reported in due course.

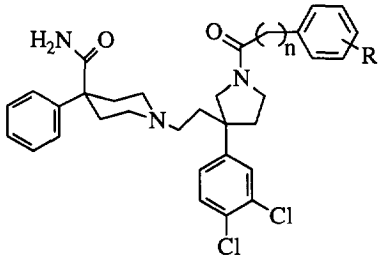


Table 1. Receptor binding affinities for pyrrolidine amide derivatives (racemic).[9]

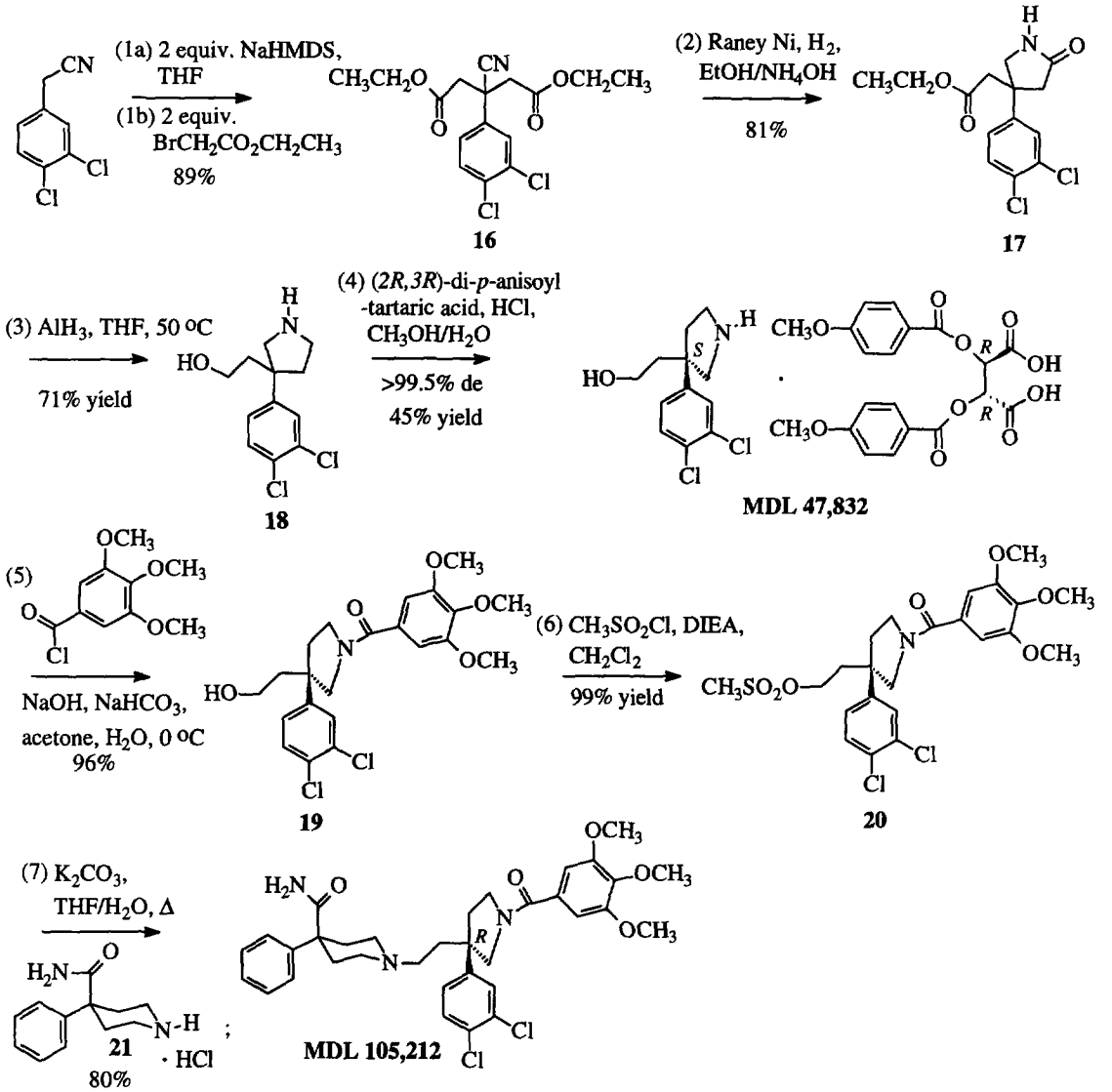
Compound	R	n	NK_1 IC_{50} (nM)	NK_2 IC_{50} (nM)
1	H	0	271 ± 23.6	7.02 ± 0.91
2	2-methoxy	0	73.6 ± 1.24	16.7 ± 2.15
3	3-methoxy	0	107 ± 16.1	12.0 ± 0.95
4	4-methoxy	0	634 ± 57.3	11.8 ± 1.28
5	2,6-dimethoxy	0	22.8 ± 2.34	53.2 ± 2.94
6	2,4-dimethoxy	0	127 ± 17.6	34.2 ± 2.90
7	3,5-dimethoxy	0	69.9 ± 5.09	19.1 ± 0.46
MDL 103,392	3,4,5-trimethoxy	0	6.19 ± 0.85	18.8 ± 2.23
8	3,5-dimethoxy-4-methyl	0	64.1 ± 9.96	13.4 ± 4.01
9	3,5-dimethoxy-4-isopropoxy	0	65.9 ± 13.7	42.4 ± 3.22
10	3,5-dimethyl-4-methoxy	0	168 ± 8.82	6.94 ± 2.57
11	3,5-dimethoxy-4-ethoxycarbonyloxy	0	252 ± 14	96.3 ± 9.91
12	3,5-dibromo-4-methoxy	0	313 ± 57.9	4.04 ± 1.61
13	2-methoxy	1	48.2 ± 9.08	74.0 ± 6.11
14	3-isopropoxy	1	138 ± 31.6	548 ± 62.7
15	3,4,5-trimethoxy	1	66.2 ± 7.96	55.5 ± 4.74

Chemical Synthesis of MDL 105,212

The synthesis of MDL 105,212, the (*R*)-enantiomer of MDL 103,392 (see Table 2), is outlined in Scheme 1. Treatment of 3,4-dichlorophenylacetonitrile with two equivalents of sodium bis(trimethylsilyl)amide and alkylation of the resulting dianion with two equivalents of ethylbromoacetate afforded nitrile diester **16** in 89% yield. Hydrogenation of the nitrile with H_2/Raney nickel and spontaneous cyclization of the intermediate amine gave lactam ester **17** in 81% yield. The lactam ester was reduced with alane[10] in THF at 50 °C to produce amino alcohol **18** in 71% yield, which was resolved using 0.5 equivalents of (*2R,3R*)-di-*p*-anisoyl tartaric acid[11] and 0.5 equivalents of hydrochloric acid. The salt was recrystallized from methanol/water to yield the desired diastereomer, MDL 47,832, in 45% yield (>99.5% diastereomeric excess, de). The absolute configuration of the chiral center was determined by single crystal X-ray crystallography of MDL 47,832.[12]

The salt was selectively *N*-acylated using 3,4,5-trimethoxybenzoyl chloride under Schotten-Baumann type conditions (1 equiv. NaOH, 5 equiv. $NaHCO_3$, acetone/water) to afford the desired benzamide **19** in 96% yield. Amide alcohol **19** was converted to the methanesulfonate **20** (CH_3SO_2Cl, DIEA, CH_2Cl_2, 99% yield), which was displaced with

4-phenylpiperidine carboxamide hydrochloride[13] **21** in THF/H_2O at reflux in the presence of K_2CO_3 to provide MDL 105,212 in 80% yield.



Scheme 1. Synthesis of MDL 105,212.

MDL 105,212 has high affinity for human NK_1 and NK_2 receptors (Table 2). In addition, it has significant affinity for the guinea pig NK_3 receptor. MDL 104,335, the (*S*)-enantiomer of MDL 103,392, was synthesized from the (*R,R,R*)-enantiomer of MDL 47,832 by an analogous route. This compound had poor binding affinity for NK_1, NK_2, and NK_3 receptors (Table 2).

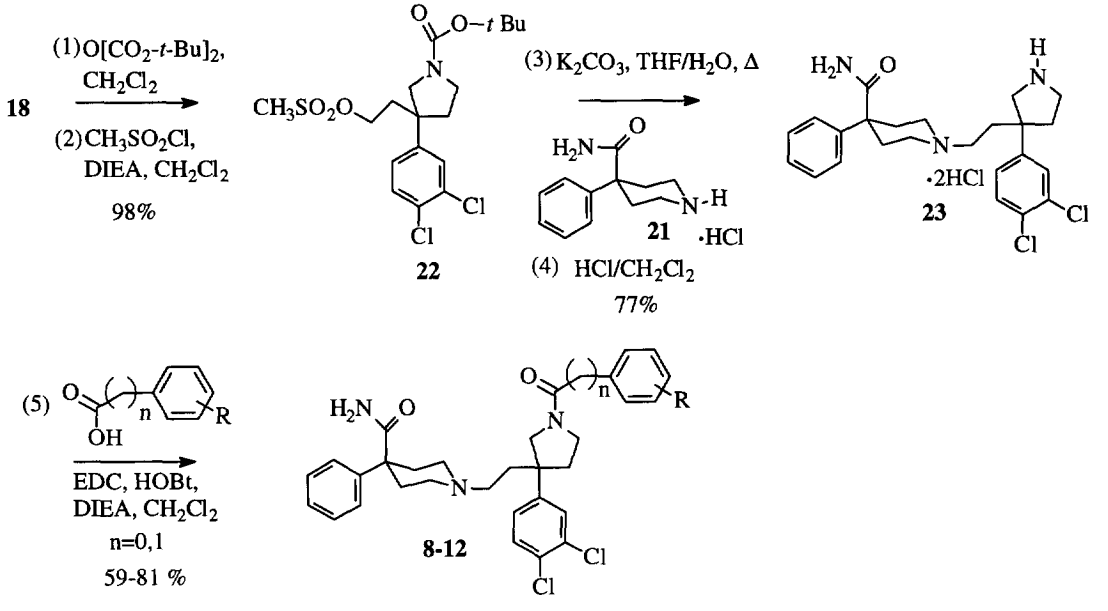
Table 2. Summary of Tachykinin Receptor Binding Affinity.[14]

Antagonist	NK_1 IC_{50} (nM)	NK_2 IC_{50} (nM)	NK_3 IC_{50} (nM)
CP 96,345	0.33 ± 0.03	>10,000	>10,000
SR 48,968	593 ± 59.0	0.44± 0.04	208± 19.2
MDL 105,212 (*R*)-enantiomer	3.11 ± 0.31	8.40 ± 1.54	21.0 ± 3.59
MDL 104,335 (*S*)-enantiomer	160 ± 15.6	760 ± 63.7	2,307 ± 121

Chemical Synthesis of racemic amide analogs

Substituted racemic amide analogs of MDL 103,392 (Table 1) were synthesized using the sequence outlined in Scheme 1 without the resolution step. Amino alcohol **18** was *N*-acylated with the appropriate acid chloride and the resulting amide alcohol was allowed to react with methanesulfonyl chloride to give the corresponding mesylate. The mesylates were displaced with 4-phenyl-piperidine carboxamide hydrochloride **21** to afford the analogs **1-7** and **13-15**.

Alternatively, amino alcohol **18** was allowed to react with di-*tert*-butyl dicarbonate to give the *t*-Boc derivative which was treated with methanesulfonyl chloride to provide mesylate **22** in 98% yield. The mesylate was stirred with 4-phenylpiperidine carboxamide hydrochloride **21** in THF/H_2O at reflux in the presence of K_2CO_3 to afford the *t*-Boc intermediate which was treated with HCl to give amine dihydrochloride **23** in 77% yield. This amine was *N*-acylated with the appropriate carboxylic acid under EDC[15] coupling conditions to give the racemic substituted amide derivatives **8-12** (Scheme 2).



Scheme 2. Alternative synthesis of racemic amide analogs.

In summary, a synthetic route for the large-scale synthesis of substituted pyrrolidin-3-yl-alkyl-piperidines has been developed. MDL 105,212 is the most potent, non-peptide tachykinin receptor antagonist[16] reported to date, with relatively equivalent affinity for human NK_1 and NK_2 receptors. In addition, it has significant affinity for guinea pig NK_3 receptors. If the hypothesis that neurogenic inflammation plays a role in asthma is correct, then tachykinin receptor antagonists with dual NK_1/NK_2 receptor affinity should offer an advantage over tachykinin receptor selective agents in the treatment of this disease. Further in vitro and in vivo characterization of MDL 105,212 is reported elsewhere.[16]

Acknowledgment

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