2(*S*)-((3,5-Bis(trifluoromethyl)benzyl)-oxy)-3(*S*)-phenyl-4-((3-oxo-1,2,4-triazol-5-yl)methyl)morpholine (1): A Potent, Orally Active, Morpholine-Based Human Neurokinin-1 Receptor Antagonist

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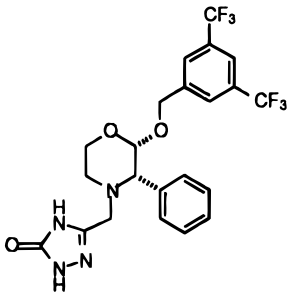
The pharmacologic actions of the mammalian tachykinin substance P (SP) have been implicated in the pathogenesis of a variety of inflammatory diseases, including migraine,[1] rheumatoid arthritis,[2] asthma,[3] and inflammatory bowel disease.[4] This profile has stimulated a great deal of interest in the identification of antagonists of the neurokinin-1 (NK-1) receptor (to which SP preferentially binds[5]), since the clinical application of such compounds could result in substantial therapeutic advantages over existing treatment modalities. Since the disclosure[6] of the first nonpeptide human NK-1 receptor antagonist, CP-96,345 (**2**), numerous reports of antagonists encompassing a variety of structure types have appeared in the literature.[7] We wish to report herein our initial efforts toward the preparation and characterization of a series of novel, orally active, morpholine-based human NK-1 antagonists exemplified by **1** (2(*S*)-((3,5-bis(trifluoromethyl)benzyl)-oxy)-3(*S*)-phenyl-4-((3-oxo-1,2,4-triazol-5-yl)methyl)morpholine, L-742,694).



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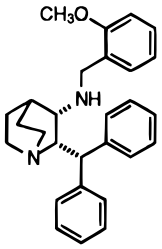
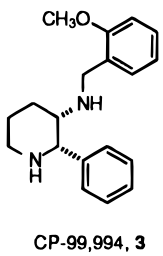
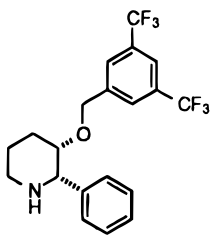
The affinity of the quinuclidine **2** for the L-type calcium channel has been implicated as a possible source of the antinociceptive and antiinflammatory activities of compounds in this structure class.[8] Structural changes in several classes of compounds, including the piperidine amines[9] (such as CP-99,994, **3**) and piperidine ethers[10] (such as L-733,060, **4**), that were aimed at lowering basicity have been reported to reduce this nonspecific interaction. Substitution on the nitrogen of the piperidine ethers with electron-withdrawing groups such as $-CH_2CO_2Me$ and $-CH_2CONH_2$ led to compounds with minimal basicity and markedly decreased L-type calcium channel affinity in which affinity for the human NK-1 receptor was maintained at nanomolar levels.[11a] Recently, it has been demonstrated that



CP-96,345, **2**



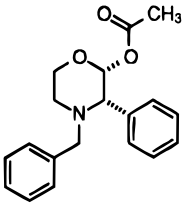
CP-99,994, **3**



L-733,060, **4**

when small heterocycles are linked to the piperidine nitrogen by a methylene spacer, subnanomolar antagonists with good oral activity can be identified.[11b] These observations prompted us to execute a study of potential human NK-1 receptor antagonists featuring the weakly basic morpholine core which employs a side-chain ether linkage established to have activity as well as potency-enhancing substituents on the morpholine nitrogen.[11b]

The synthesis of 2-alkoxy-3-phenylmorpholines (which are known in other contexts[12]) has not been the subject of any systematic study. The chemistry that was developed to diastereoselectively prepare either of the 2,3-disubstituted morpholine core structures is shown in Scheme 1. Partial reduction of 3(*S*)-phenyl-2-morpholinone (**5**; prepared from *N*-benzyl-(*S*)-phenylglycine[13] using a modification of the literature procedure[14]) could be carried out with a variety of reducing agents (DIBALH, Red-Al, L-Selectride) to afford lactol **6** which was obtained as an 8:1 *trans*/*cis* mixture of C2 epimers. Attempts to convert **6** to a morpholine having the desired 2,3-*cis* configuration were unsuccessful as conventional alkylation,[15] glycosidation,[16] or acetal exchange[12] conditions afforded mainly the 2,3-*trans*-morpholine. A control experiment was carried out in which the reaction of **5** with 1.1 equiv of L-Selectride at −78 °C was quenched with acetic anhydride. This afforded the 2,3-*cis*-acyl acetal **7** as the major product and showed that isomerization of the 2,3-*cis*-lactol alkoxide was minimized in the absence of moisture at low temperature. Alkylation of the L-Selectride reduction intermediate proved to be more difficult than acylation but was possible using 3,5-bis(trifluoromethyl)benzyl trifluoromethanesulfonate (**8**); this gave **9** as the major product. Catalytic reduction of **9** afforded morpholine **10**, which has 2(*S*),3(*S*) stereochemistry, making it configurationally analogous to **3**.



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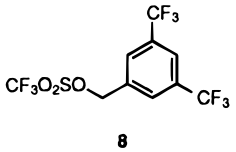

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The 2,3-*trans*-morpholine diastereomer was prepared via a Williamson etherification[15] of lactol **6** to afford **11** as the sole product in excellent yield. Catalytic reduction of **11** gave morpholine **12**. The enantiomers of compounds **10** and **12** (**13** and **14**, respectively) were prepared starting from *N*-benzyl-(*R*)-phenylglycine. Analysis by chiral HPLC showed that all four diastereomers had >98.0% ee.

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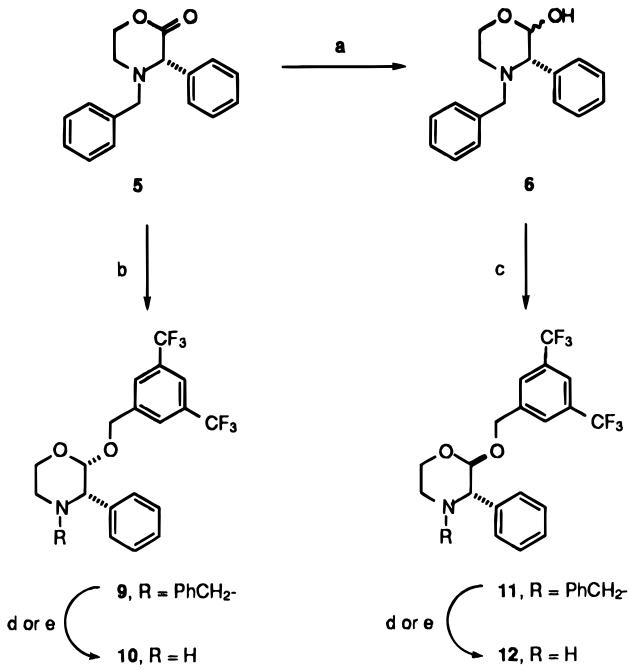
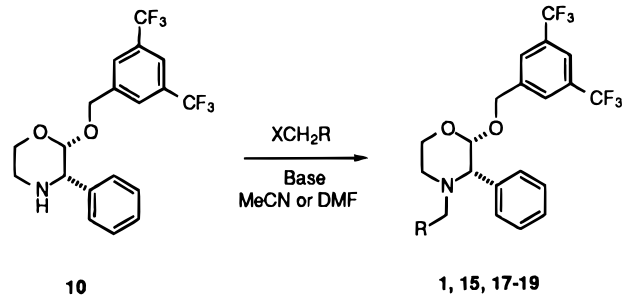
Scheme 1[a]



[a] Reagents: (a) DIBALH, CH_2Cl_2/toluene, −78 °C (94%); (b) L-Selectride, THF, −78 °C, then **8**, −50 °C (73%); (c) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, cat. $Bu_4N^+I^-$, THF, 0 °C to room temperature (93%); (d) H_2, 10% Pd/C, 95% EtOH; (e) ammonium formate, 10% Pd/C, MeOH/H_2O, 65 °C.

Scheme 2[a]

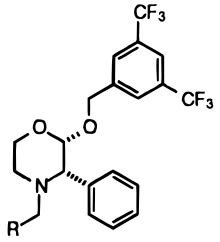


[a] See text and Supporting Information for details.

Several N-substituted derivatives of morpholine **10** were prepared (Scheme 2). Carboxylic ester **15** and carboxamide **17** were prepared by *N*,*N*-diisopropylethylamine-mediated alkylation of **10** with methyl bromoacetate and iodoacetamide, respectively, while saponification of **15** afforded carboxylic acid **16**. Heterocyclic carboxamide replacements were introduced by alkylating **10** with either *N*-formyl- or *N*-(methoxycarbonyl)-2-chloroacetamidrazone[17] followed by thermal ring closure to afford the corresponding 1,2,4-triazole (**19**) and 1,2,4-triazol-3-one (**1**) derivatives. The three stereoisomers of **1** were also prepared from the appropriate intermediate morpholine (**12** → **20**, **13** → **21**, **14** → **22**) and obtained with high enantiomeric purity (≥99.8% ee) after recrystallization.[18]

Binding affinities were determined by measuring the displacement of ^{125}I-labeled SP from the human NK-1 receptor stably expressed in CHO cells[19] (Table 1). Data for the four possible N-unsubstituted morpholine isomers **10** and **12**−**14** confirmed that the 2(*S*),3(*S*) stereochemistry is preferred. Modest enhancement in potency was seen in the compounds N-alkylated with neutral, electron-withdrawing head groups (**15** and **17**), while introduction of a carboxylic acid (**16**) substantially

Table 1. Human NK-1 Receptor Binding



compd	R	IC_{50} (nM)[a]
2		0.4 ± 0.1
3		0.5 ± 0.1
4		0.87 ± 0.51 (n = 7)
10		2.4 ± 2.2
12		376 ± 105
13		287 ± 58
14		59 ± 19
15	CO_2CH_3	1.6 ± 1.1
16	CO_2H	66 ± 14
17	$CONH_2$	1.1 ± 0.4
19	1,2,4-triazolyl	0.13 ± 0.04
1	3-oxo-1,2,4-triazolyl	0.09 ± 0.03 (n = 6)
20		21 ± 2
21		116 ± 34
22		19 ± 3

[a] Displacement of ^{125}I-labeled SP from the human NK-1 receptor expressed in CHO cells. Data are reported as the mean ± SD for n = 3 determinations unless otherwise noted.

Table 2. L-Type Calcium Channel Binding and SPIDER

compd	Ca^{2+} channel (IC_{50}, μM)[a]	SPIDER (ID_{50}, mpk)[b]
3	4 ± 1	1.6
1	11 ± 4	0.009

[a] Inhibition of [^{3}H]diltiazem binding to the L-type calcium channel in rabbit skeletal muscle. Data are reported as the mean ± SD for n = 2 determinations. [b] SP-induced dermal inflammation (SPIDER) assay in the guinea pig. Antagonist was administered po followed by SP challenge id after 1 h. Dose−response data was determined for n = 5−12 animals/data point.

decreased human NK-1 binding affinity. A more dramatic increase in potency occurred when the carboxamide was replaced by either a 1,2,4-triazole (**19**) or a 3-oxo-1,2,4-triazole (**1**), the latter being >25 times more potent than the parent morpholine **10**. Interestingly, a more modest increase was seen with the isomers of **1** (**20**−**22**) as compared to their corresponding parent morpholines. These results nicely parallel observations with the piperidine ethers.[11]

Screening of **1** against cloned human NK-2 and NK-3 receptors expressed in CHO cells using [^{125}I]neurokinin A and [^{125}I]Bolton-Hunter-labeled eledoisin as radioligands, respectively, was also carried out.[20] The measured binding constants (human NK-2, IC_{50} = 7 μM; human NK-3, IC_{50} = 150 nM) indicate that **1** is highly selective for the human NK-1 receptor. Measurement of the inhibition of [^{3}H]diltiazem binding to the L-type calcium channel in rabbit skeletal muscle[21] by **1** showed it to have about a 3-fold lower affinity than **3** (Table 2).

The unique structure of **1** prompted an examination of some of its physicochemical properties. The pK_a of the morpholine nitrogen of **1** was determined to be <3 in 1:1 (v/v) methanol/water. Coupled with the potency of **1**, this shows that the strategy, employed by others,[11,22] of minimizing the pK_a of basic NK-1 antagonists in order to lessen L-type calcium channel binding can be extended to this family of compounds. (The pK_a's of the benzyl and piperidine amines of **3** in 1:1 (v/v) methanol/water were 4.0 and 8.7, respectively.) The

stability of **1** toward acid was also examined. Incubation of **1** in simulated gastric fluid[23] at 37 °C for 4 h resulted in no acetal hydrolysis (no generation of 3,5-bis(trifluoromethyl)benzyl alcohol occurred) or isomerization to a 2,3-*trans* diastereomer.[24] This stability, an obviously desirable property of a compound that would be administered po, was further evidenced by the high oral potency of **1** in the SP-induced plasma extravasation (SPIDER) assay[25] (Table 2). The ID_{50} of **1** in this assay is 170 times less than that of **3**; this marked difference may be attributed at least in part to the poor oral bioavailability of **3**.[26]

In conclusion, the morpholine compounds described herein represent a novel class of human NK-1 receptor antagonists. Further, **1** is a potent, orally active member of this class that should prove to be an important tool in the study of neurokinin pharmacology. Elaboration on the synthetic chemistry required for the preparation of these compounds and detailed structure–activity studies will be the subject of future reports.

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Supporting Information Available: Full descriptions of the preparation of compounds **1** and **5**–**22**, the chiral HPLC assays used to determine the enantiomeric excess of compounds **1**, **5**, **10**, **12**–**14**, and **20**–**22**, the assays used to determine the pK_a and acid stability of **1**, and the dose–response data from the SPIDER assay of **1** and **3** (13 pages). Ordering information is given on any current masthead page.

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