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1,2,3-TRISUBSTITUTED CYCLOHEXYL SUBSTANCE P ANTAGONISTS: SIGNIFICANCE OF THE RING NITROGEN IN PIPERIDINE-BASED NK-1 RECEPTOR ANTAGONISTS

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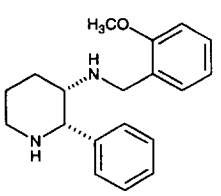
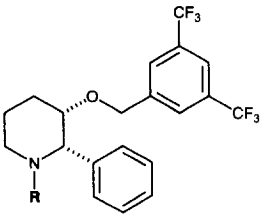
Abstract A stereocontrolled synthesis of 1-benzyloxy-2-phenylcyclohexane derivatives containing polar substituents at C3 is described. These compounds, designed to test the role of the ring nitrogen in a related series of potent piperidine-based substance P antagonists, show similar NK-1 receptor affinity, indicating that the nitrogen may serve a largely structural role in N-substituted piperidine antagonists.

In the last two years a number of papers have reported on piperidine-derived substance P (SP) antagonists which display excellent receptor affinity.[1-4] Of particular note are CP 99,994 (**1**)[2] and the benzyl ethers L-733,060 (**2**)[3] and L-736,281 (**3**)[4], all of which display ≤ 1 nM affinity for the human NK-1 receptor. Implicit in the analyses of the structure-activity relationships for these compounds is the assumption that the ring nitrogen atom plays a critical role in receptor binding. Indeed, in a related series, Lowe and co-workers proposed that a salt bridge may form between the protonated ring nitrogen of the quinuclidine CP 96,345 (**5**) and Glu-78 of the human NK-1 receptor.[5]

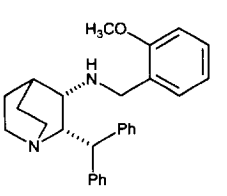
Williams *et. al.* investigated this issue employing acyclic analogs of quinuclidine NK-1 antagonists.[6] They modulated the basicity of the diphenylalaninol ether **6** (IC_{50} = 10.7 nM) to decrease affinity for the L-type calcium channel by preparing the corresponding carboxamidomethyl analog **7** (IC_{50} = 0.85 nM). Since hNK-1 binding was actually increased by this substitution, these authors postulated that a basic nitrogen was not necessary, and showed that alcohol **8** (IC_{50} = 17 nM) and amine **6** displayed fairly similar receptor affinities.[6] Harrison and coworkers employed this strategy in proceeding from **2** (IC_{50} = 1 nM; pK_a = 8.3) to **3** (IC_{50} = 1 nM; pK_a = 5.4), and noted that in their piperidine ethers, receptor affinity and basicity appeared not to be correlated.[4]



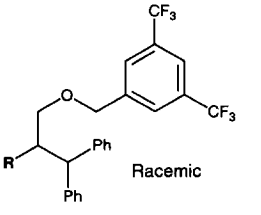
CP 99,994 (1)



R = -H **L-733,060 (2)**
R = -CH_2CONH_2 **L-736,281 (3)**
R = -CH_3 **(4)**



CP 96,345 (5)

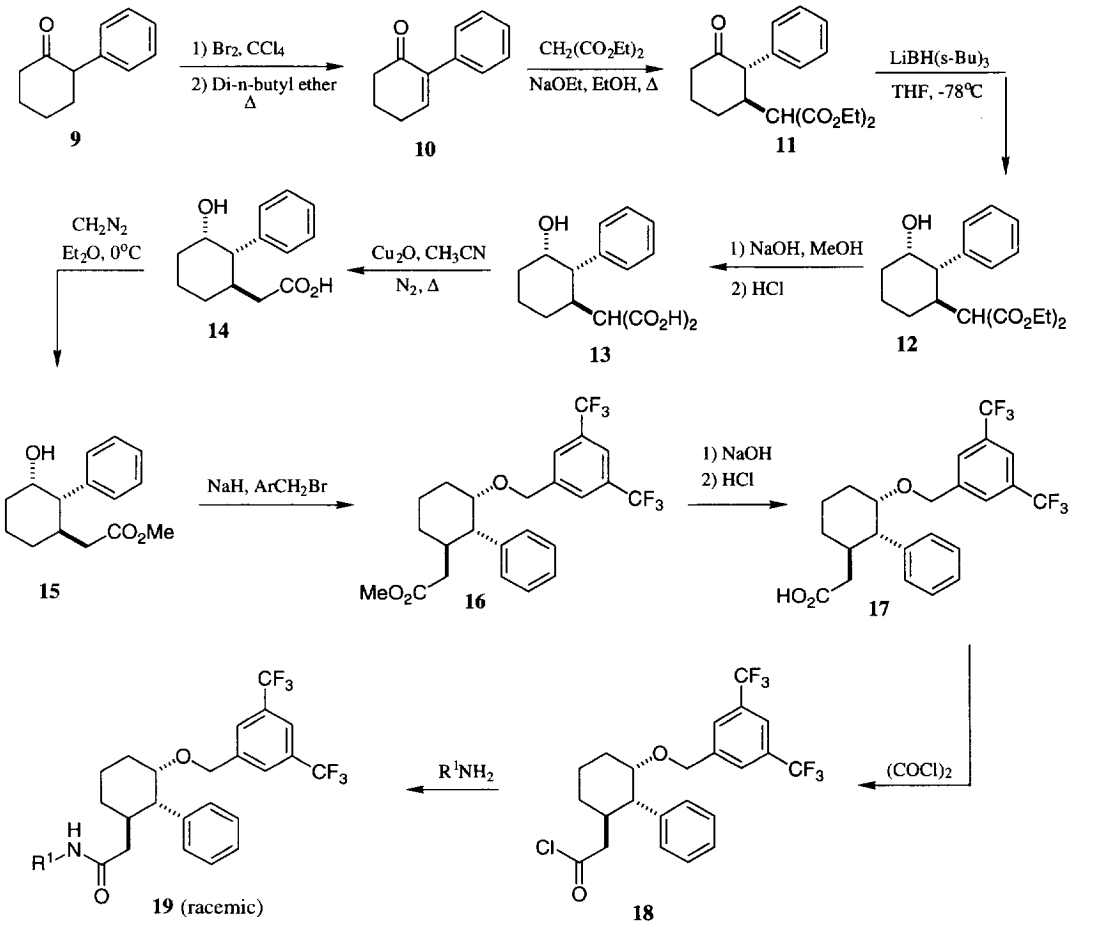


R = H_2N- **(6)**
R = H_2NCOCH_2NH- **(7)**
R = HO- **(8)**

Although the above studies indicate that a cationic group is not required for effective receptor binding, it is still unclear what role the heteroatoms in compounds **3**, **6** and **8** actually play. To address this question we decided to prepare analogs of piperidines **2** and **3** wherein the ring nitrogen has been replaced by carbon or oxygen. In this way we hoped to determine whether the nitrogen interacts specifically with the human NK-1 receptor or if it serves primarily as a scaffold for the presentation of other pharmacophores. Also, it was expected that a carbocyclic framework would be less prone to metabolic degradation than the aliphatic amine core of **3**. In the cyclohexane derivatives described below, we incorporated functionality at the 3-position in an equatorial disposition (*trans* with respect to the 2-phenyl substituent), since it seemed likely that this was the predominant conformer of piperidine **3**.

Preparation of the cyclohexyl amide **19a** (R^1 = H) was carried out according to Scheme 1. The mixture

Scheme 1

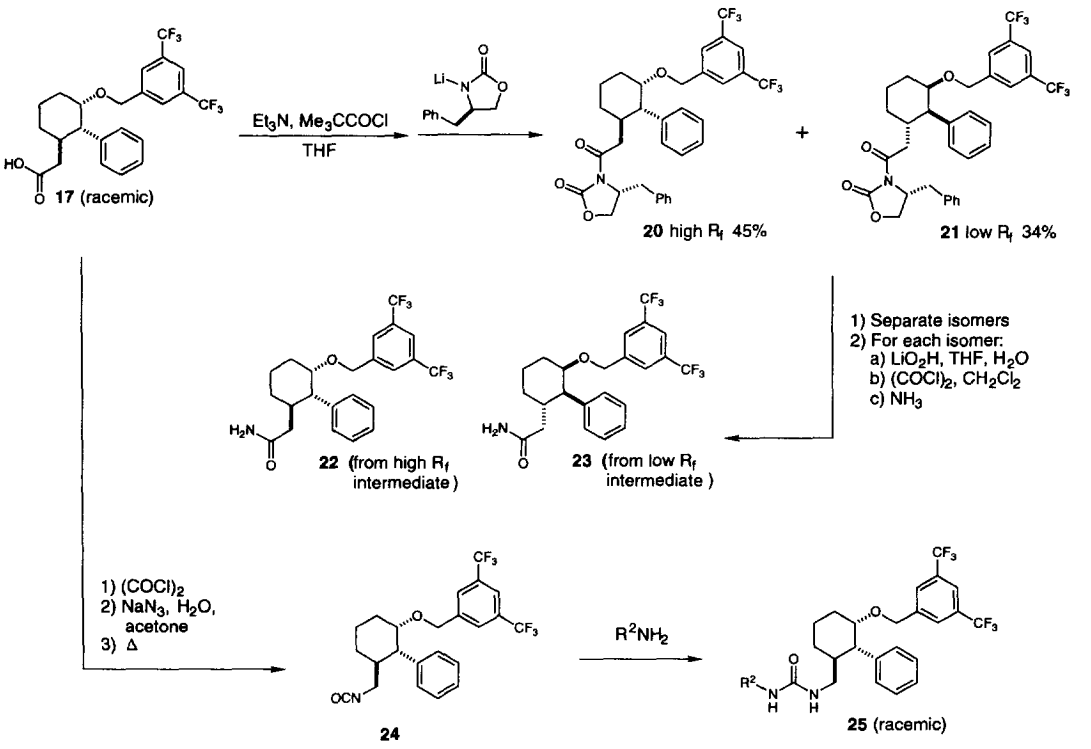


obtained from bromination of 2-phenylcyclohexanone was thermolysed in di-n-butyl ether according to the procedure of Miller and Wong to give enone **10**.[7] Treatment of **10** with the sodium salt of diethyl malonate provided racemic trans isomer **11** as the only detectable Michael addition product.[8] Reduction of ketone **11** with L-Selectride® at -78°C provided exclusively the axial alcohol **12**, which was saponified with sodium hydroxide in methanol to provide the diacid **13** in good yield. Attempted thermal decarboxylation in refluxing xylenes led to a complex mixture. However, reaction with cuprous oxide in warm acetonitrile[9] provided good yields of desired monoacid **14**. Following esterification with diazomethane, the resulting alcohol was treated with sodium hydride and then 3,5-bis(trifluoromethyl)benzyl bromide, to give ether **16**. Basic hydrolysis provided carboxylic acid **17**, which after treatment with oxalyl chloride yielded acid chloride **18**. Treatment with primary amines then gave the desired amides **19a-c**.

Resolution of the enantiomers of carboxamide **19a** was carried out by derivatizing acid **17** with 4-(R)-benzyl-2-oxazolidinone, which produced two diastereomers separable by flash chromatography (Scheme 2). Following cleavage of the chiral auxiliary with lithium hydroperoxide, the enantiomeric amides **22** and **23** were prepared as described above. Additional derivatives were obtained from the isocyanate **24**, which itself was prepared by Curtius rearrangement of the acyl azide derived from acid **17**.

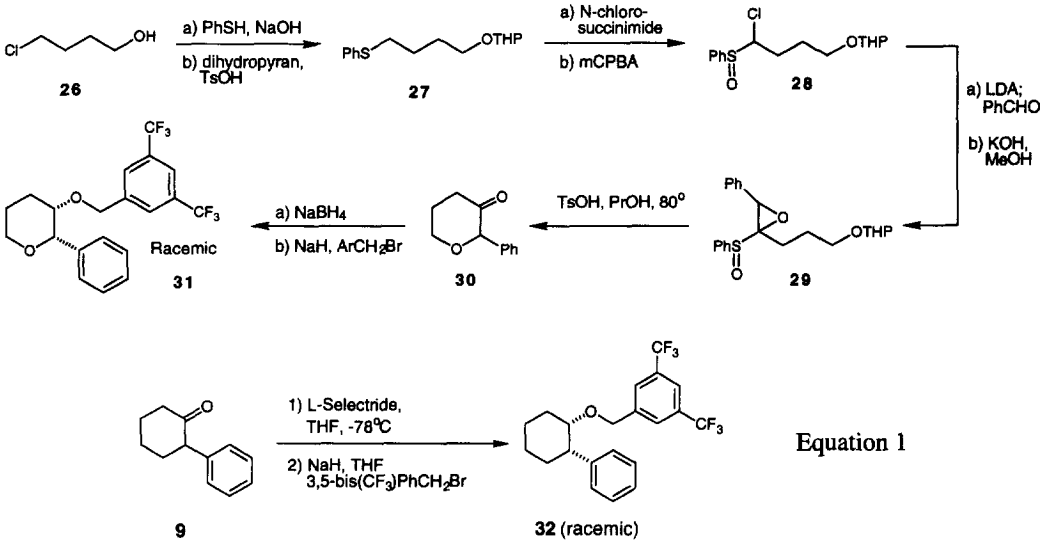
Preparation of the tetrahydropyran derivative **31** was carried out as shown in Scheme 3. The known 3-

Scheme 2



keto-tetrahydropyran **30**[10] was reduced to a mixture of alcohols with sodium borohydride and the cis isomer was alkylated with 3,5-bis(trifluoromethyl)benzyl bromide, to provide pyran derivative **31** as a racemate. The 3-unsubstituted analog **32** was prepared from 2-phenylcyclohexanone by reduction and etherification (Equation 1).

Scheme 3



Equation 1

As shown in Table 1, compound **32**, the simple cyclohexane analog of piperidine **2**, binds to the NK-1 receptor with about 1000-fold poorer affinity.[11] Interestingly, the oxacycle **31** also binds considerably less well than piperidine **2**. Since the tetrahydropyran oxygen is capable of accepting but not donating a hydrogen bond, this comparison would suggest that it is the H-bond donating ability of the nitrogen which is essential. This explanation is also consistent with the 14-fold decrease in activity of the N-methyl piperidine **4** relative to **2**.[4, 12] However, this analysis would not explain the high receptor affinity of piperidine **3**, which possesses no NH group and is too non-basic ($pK_a = 5.4$) to be significantly protonated at physiological pH.

One possibility is that the N-(aminocarbonylmethyl) group, which was originally installed to increase selectivity with respect to L-type calcium channel binding, can substantially increase receptor affinity, over and above the moderate shift observed in going from amine **6** to the substituted amine **7** (see above).[4, 6] Cyclohexane derivative **19a**, the carbocyclic analog of piperidine **3**, was prepared to test this hypothesis. In the event, racemic carboxamide **19a** was found to have an IC_{50} of 3 nM. The separated enantiomers of **19a**, compounds **22** and **23**, displayed affinities of 1.5 and 157 nM, respectively. The former value is essentially identical to that observed for the parent piperidine **3**.

With these data in hand, we examined a few simple analogs of **19a** to determine how well other polar functional groups were tolerated in place of the primary carboxamide. The 3- and 4-aminomethylpyridines **19b** and **19c** also had good affinity for the NK-1 receptor, but showed no advantage over **19a**. We were also interested in compounds which featured a 3-($RNHCH_2$-) ring substituent, since such functionality would not be

expected to be stable in the piperidine series. Ureas **25a** and **25b** did display reasonable IC_{50}'s, although there appeared to be no advantage to this substitution pattern.

Of greater interest is the overall trend observed here, wherein the presence of polar functionality at the 3-position of the cyclohexane ring in a variety of orientations confers a 2 to 3 order of magnitude improvement in receptor binding relative to the 3-unsubstituted compound **32**. This tolerance for substitution may indicate that the 3-position of the cyclohexyl ring (and by extension the nitrogen atom in piperidine-based antagonists) points toward the extracellular space, rather than down into the transmembrane domain, where Glu-78 is located.[5]

Table 1 Inhibition of ^{125}I-Substance P Binding to hNK-1 Receptors in CHO Cells

Compound[a]	hNK-1 (IC_{50}, nM)[b]
19a R^1 =H	3 +/- 1.4 (3)
22 1*S*,2*S*,3*R* isomer	1.5 +/-0.4 (3)
23 1*R*,2*R*,3*S* isomer	≥157 +/-41 (3)[c]
19b $R^1 = NHCH_2$(3-pyridyl)	3.7 +/-0.9 (3)
19c $R^1 = NHCH_2$(4-pyridyl)	7 +/- 5 (3)
25a R^2 = H	6.7 +/- 2.5 (3)
25b $R^2 = CH_2$(3-pyridyl)	34 +/- 19 (3)
31	881 +/- 286 (3)
32	2632 +/- 1998 (3)
1[d]	0.5 +/- 0.1 (4)
2[d]	1
3[d]	1
4[d]	14

[a] compounds are racemates unless otherwise noted
[b] mean +/- SD (number of determinations)
[c] lower limit of detection for active isomer **22** in **23** is ~1%
[d] single enantiomer

In summary, the results presented above have shed light on the role of the endocyclic nitrogen in six-membered ring SP antagonists: it is not necessary for low nanomolar binding to the NK-1 receptor, but it does evidently engage in a specific interaction with the protein when a nitrogen substituent is not present. Thus, the cyclohexane derivatives have proven to be both useful tools for clarifying specific ligand-receptor interactions of heterocyclic SP antagonists and new leads toward selective non-peptide substance P antagonists with unique structural attributes.[13]

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11. Inhibition constants (IC_{50}s) were determined using ^{125}I-Tyr8-substance P at a concentration equivalent to its K_d (0.1 nM) for the human NK-1 receptor expressed in CHO cells as previously described: Cascieri, M. A.; Ber, E.; Fong, T. M.; Sadowski, S.; Bansal, A.; Swain, C. J. ; Seward, E.; Frances, B.; Burns, D.; Strader, C. D. *Mol. Pharmacol.* **1992**, *42*, 458.
12. The greater activity of **4** relative to the pyran **31** could result from binding to the NK-1 receptor by the protonated form of **4**, which is probably the major form present at physiological pH.
13. The cyclohexane series generally shows minimal affinity for the other neurokinin receptors. For example, the NK-2 and NK-3 affinity for compound **19a** is > 1μM. In addition, 5 μM **19a** did not significantly displace ^{3}H-Diltiazem from the L-type calcium channel under standard assay conditions (Reynolds, I.; Snowman, A.M.; Snyder, S.H. *J. Pharmacol. Exp. Therap.* **1986**, *237*, 1731).

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