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MORPHOLINE-BASED SUBSTANCE P ANTAGONISTS: ASSESSMENT OF THE 3-POINT BINDING MODEL

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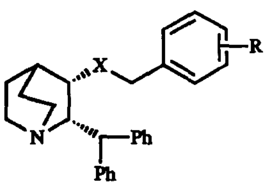
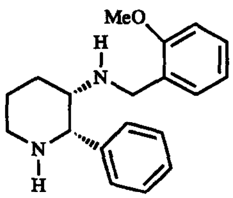
Abstract: The carbon-linked morpholine analogues of the Substance P antagonist CP-99,994 were synthesised. The activities of the resulting compounds suggest that there is a specific interaction between the benzylic heteroatom of these antagonists and the NK_1 receptor.

Substance P, an undecapeptide neurotransmitter that mediates its effects through the neurokinin-1 (NK_1) receptor, has been implicated in a variety of diseases including rheumatoid arthritis and migraine.[1,2] Hence a stable, non-peptide NK_1 antagonist could possibly have powerful clinical implications. Since the revelation of the first such SP antagonist CP-96,345 by Lowe *et.al.* [3] several disclosures have taken place of both analogous [4] and structurally distinct series.[5,6] Lowe has proposed a three point binding model for the antagonist binding site at the SP receptor (**Figure 1**) which consists of a) an ion-pair site that interacts with the basic nitrogen, b) an accessory binding site that binds the benzhydryl of CP-96,345, and c) a specificity site that recognizes the benzylamino side chain.



CP-96,345 : X=NH, R=2- OMe
L- 709,210 : X=O, R=3,5-$(CH_3)_2$



CP-99,994

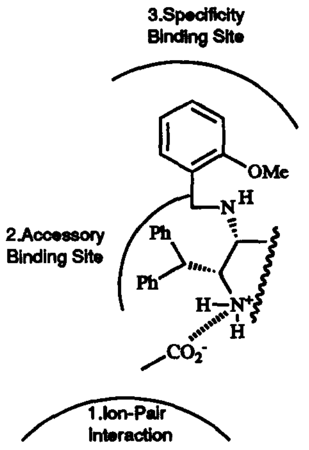
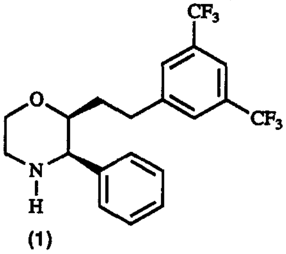
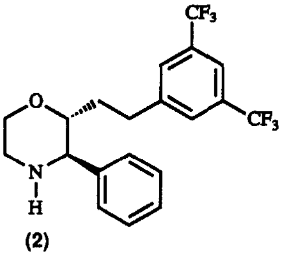


Figure 1

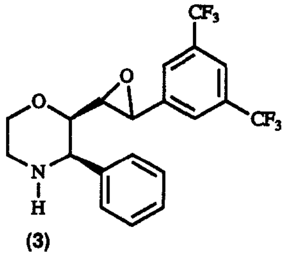
Since the ring nitrogens of CP-96,345 and of the analogous piperidine subsequently reported, CP-99,994, [7] are proposed to participate in an ion-pair interaction at the receptor binding site, it would be expected that in the latter this interaction would be weaker since the ring nitrogen not only is part of a less basic piperidine, but is in addition, benzylic. The affinities of the quinuclidine CP-96,345 and the piperidine CP-99,994 are in fact comparable (Table 1). Hence we sought to make a series of morpholine analogues (1-3) of CP-99,994 where the pK_a of the nitrogen will be even further reduced in order to test the limits of this proposed interaction. In doing so we chose to use a carbon-link for the C-2 side chain in the morpholines instead of the established nitrogen or oxygen in analogous series, and the affinities of the resulting compounds provide further evidence to suggest that the NK_1 receptor interacts specifically with the benzylic heteroatom in the antagonists.[8]



(1)



(2)

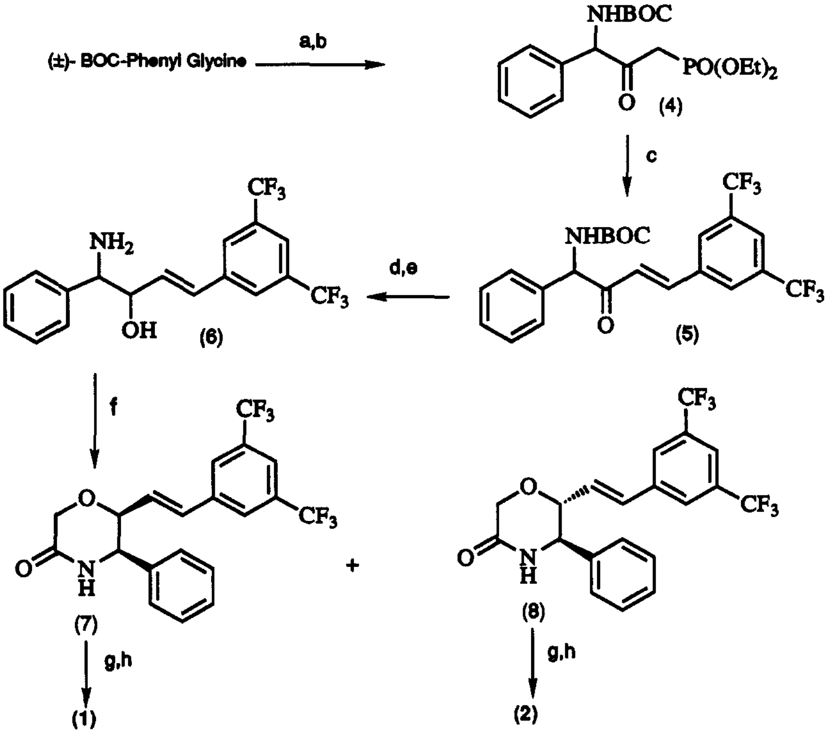


(3)

The synthesis of the carbon-linked morpholines (Scheme 1) began with (±)-BOC-phenyl glycine which was converted to the corresponding Weinreb amide[9], and reacted with the lithium anion of diethyl methyl phosphonate to form the keto-phosphonate 4. The anion of 4 was generated using either sodium hydride in THF or potassium carbonate in CH_3CN and subsequently reacted with 3,5- bis(trifluoromethyl) benzaldehyde to yield the Horner-Emmons product 5. The ketone was reduced with $NaBH_4$ and removal of the *tert*- butoxycarbonyl group with TFA furnished the amino als 1 and 2. cohol 6 as an inseparable mixture of diastereomers. The sodium anion of the alcohol was selectively alkylated with ethylchloroacetate and cyclized in a one-pot procedure to yield the morpholine-amides 7 and 8.[10] The cis and trans isomers were separated by flash chromatography and independently hydrogenated to give the reduced compounds. The amides were subsequently reduced with $BH_3 \cdot SMe_2$ to give the corresponding morpholines 1 and 2.

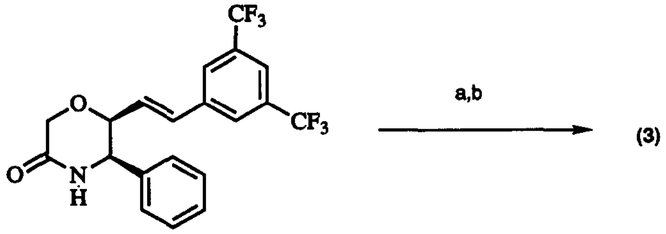
The epoxide 3 was synthesised (Scheme 2) by treating 7 with mCPBA under refluxing conditions and conversion of the resulting intermediate to the morpholine as described before. Interestingly only one diastereomer of the two possible was isolated. Modelling studies on the analogous CP-99,994 have shown that the two phenyl rings of the antagonists exist in a π- stacked conformation and it is plausible that this rigid arrangement of the phenyl rings makes only one face of the double bond accesible to the peracid.

Scheme 1



a) isobutylchloroformate, HN(Me)OMe, EtOAc, 64%; b) $MePO(OEt)_2$, nBuLi,THF, 92%; c) NaH, 3,5-$(CF_3)_2PhCHO$,THF or K_2CO_3, CH_3CN, 56%; d) $NaBH_4$, EtOH, 68%; e) TFA, 80%; f) i) NaH, $ClCH_2CO_2Et$, $PhCH_3$; ii) reflux @ 110°C, 55% g) $Pd(OH)_2$, EtOH, 90%; h) $BH_3 \cdot SMe_2$, 56%.

Scheme 2



a) mCPBA, 2,6-di-*tert*-butyl-4-methylphenol, $ClCH_2CH_2Cl$, reflux, 62%; b) $BH_3 \cdot SMe_2$, 81%.

Table 1 · hNK_1 Receptor Binding

No	IC_{50} (μM)
CP-96,345	0.0005
CP-99,994	0.001
7	2.53 ± 2.45 (n= 3)
1	1.53±1.13 (n= 4)
2	1.13±3.29 (n=3)
3	0.087±12 (n=3)

Displacement of [^{125}I] Substance P Binding from hNK_1 Receptors in CHO Cells

The two carbon-linked morpholines were surprisingly inactive, the cis-isomer **1** being >1000-fold less active than the analogous piperidine CP-99,994. It was interesting to note, however, that the epoxide **3**, where a hydrophilic interaction has been reintroduced, is >10-fold more active than **1**, having an affinity of 87 nM.

Mutagenesis of the NK_1 receptor has identified specific interactions between the benzhydryl group of CP 96,345 and His 197 in helix 5 of the receptor[11], and between the substituted benzyl of the quinuclidine antagonists with His 265 in helix 6.[12] The reduced affinity of **1** therefore may have more to do with the removal of yet another important polar interaction on the C-2 side chain such as that of the nitrogen in CP-96,345 or the oxygen in L-709,210. It is possible that this important interaction can be further optimized and additional work addressing this issue will be reported in due course.

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