Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 6, pp. 599-604, 1995

0960-894X/95 $9.50+0.00

0960-894X(95)00080-1

1,2,4-TRIACYLPIPERIDINE SUBSTANCE P ANTAGONISTS: SEPARATION OF AFFINITIES FOR THE NK-1 RECEPTOR AND THE L-TYPE CALCIUM CHANNEL

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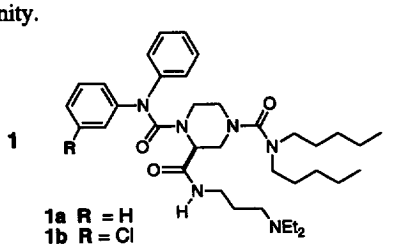
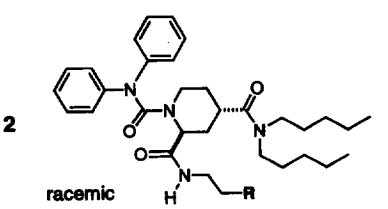
Abstract A series of 1,2,4-triacylpiperidines are shown to be potent antagonists of the NK-1 (Substance P) receptor with significant affinity for the L-type calcium channel as well. The latter property can be diminished by suitable substitution on the terminal nitrogen while maintaining good NK-1 receptor binding.

The endogenous peptide substance P (SP) mediates its biological actions largely through binding to the neurokinin-1 (NK-1) receptor.[1,2] It has been shown that SP elicits a range of physiological responses, particularly transmission of pain to the central nervous system and induction of neurogenic inflammation.[1-3] Several classes of non-peptide NK-1 receptor antagonists have recently been disclosed.[4-6] Such agents may have utility in the clinical application of NK-1 antagonists for disorders such as rheumatoid arthritis,[7] migraine[8] and pain.[9]

A recent publication from this laboratory reported on the discovery of the N,N'-diacylpiperazine class of SP antagonists (for example, piperazine **1a**, R = H).[10] In evaluating these compounds we became interested in the role N-4 played in the conformation and electronic properties of the 4-acylamide subunit. To clarify these issues we prepared a related series of piperidine derivatives (i.e. structure **2**). In the course of this work we have also investigated the structural dependence of binding to the L-type calcium channel, a property seen in the piperazines described earlier, as well as in other classes of SP antagonists.[5,6b,11] These investigations have resulted in the identification of a series of tight-binding NK-1 receptor antagonists displaying minimal calcium channel affinity.

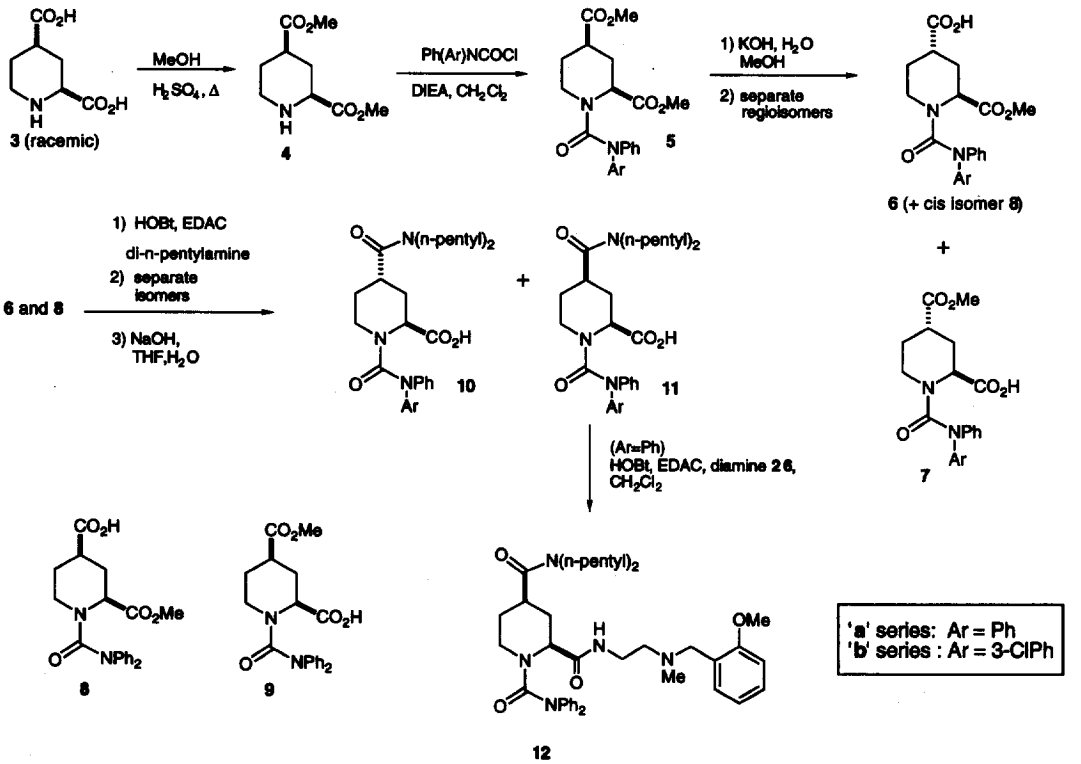




Preparation of the requisite scaffold for derivatives of **2** began with commerically available racemic cis-2,4-piperidinedicarboxylic acid (Scheme 1). Esterification under acidic conditions provided diester **4**, which on treatment with diphenylcarbamyl chloride gave urea **5**. Hydrolysis of **5** with potassium hydroxide in methanol containing a small amount of water led to a mixture of mono-acids **6** and **7** in 56% and 33% yields, respectively,

separable by flash chromatography on silica. The regiochemistry was assigned mainly on the basis of mass spectral fragment patterns for **6**, **7** and several of their derivatives. The peaks corresponding to loss of the group adjacent to the ring nitrogen was uniformly more intense than the peak for loss of the 4-substituent.[12]

Scheme 1

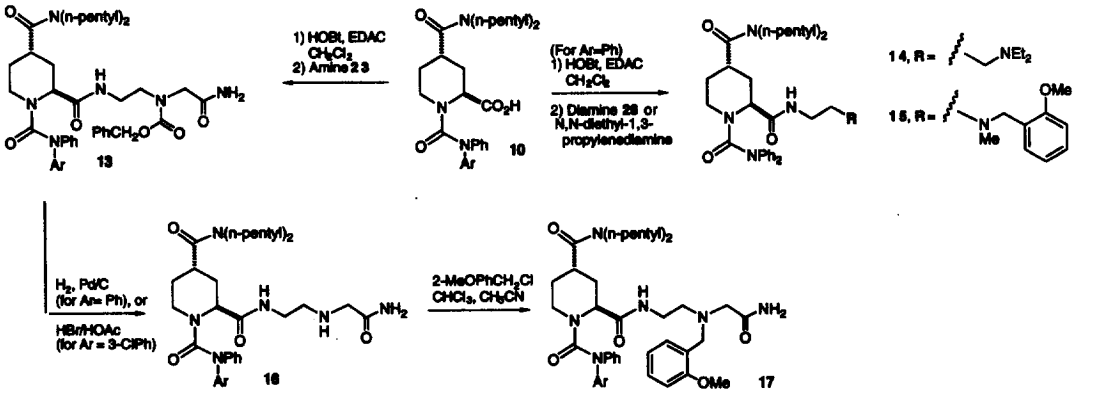


The 2,4-*trans* stereochemistry was assigned to **6** and **7** on the basis of several considerations. In particular, significant shifts in the proton NMR characteristics of the two products relative to the starting diester **5** were observed. When the hydrolysis reaction was carried out with larger amounts of water present, substantial quantities of two isomeric mono-acids were formed. Each displayed a proton NMR spectrum quite similar to the starting material, and they were assigned as the *cis*-esters **8** and **9**. This observation suggests that in a sufficiently aqueous environment, hydrolysis could precede epimerization. Further, it is known that with bulky groups present on the nitrogen of a piperidine, $A_{1,3}$ strain leads to a preference for axial substituents at the 2- or 6-position.[13] When derivatives assigned as possessing cis-stereochemistry were heated with DBU, nearly complete conversion to the *trans*-isomers **6** and **7** was observed.

With the separated acids **6** and **7** in hand, the remaining derivatizations were carried out as follows. Coupling of **6** (containing some **8**) with dipentylamine led to the readily separable methyl esters of **10** and **11**.

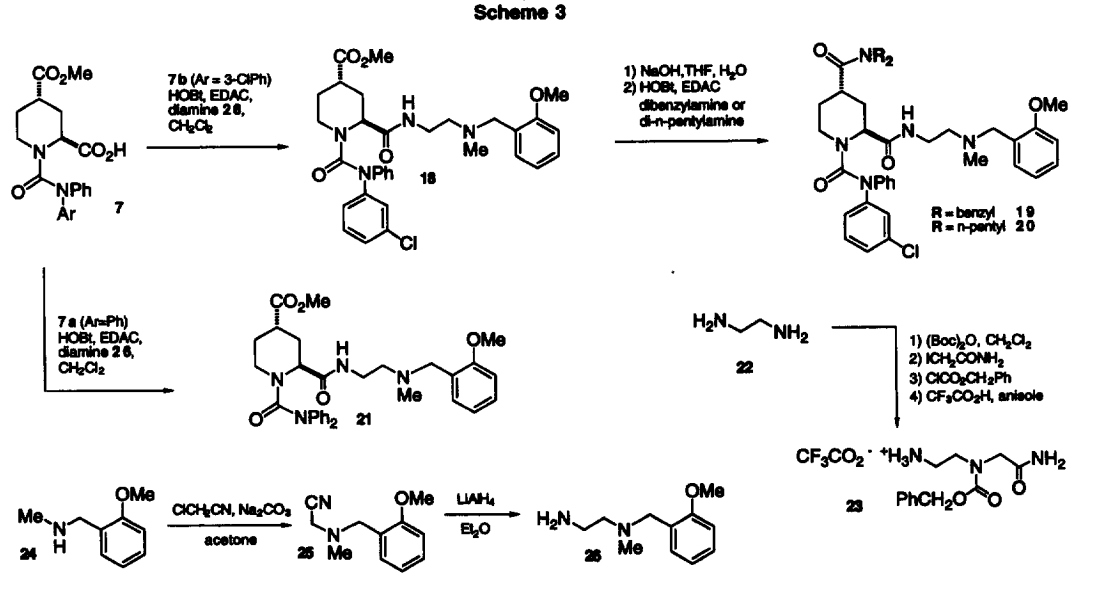
These compounds were individually hydrolysed to the respective C2 acids, which were then converted to the amides under standard conditions (HOBt, EDAC, amine; see Schemes 1 and 2). Elaboration of the glycine

Scheme 2



amide analog **13** (prepared from **10**) was carried out by hydrogenolysis followed by alkylation with 2-methoxybenzyl chloride in refluxing acetonitrile. Synthesis of the ethylenediamine derivatives **23** and **26** is illustrated in Scheme 3, as is the conversion of acid **7a** (Ar = Ph) to ester **21**. The 3-chlorophenyl analogs discussed below were synthesized starting from 3-chlorodiphenylcarbamyl chloride (prepared from 3-chlorodiphenylamine and phosgene). Conversion to final products was carried out by general analogy to the parent series, with two exceptions: (1) The side chain CBZ cleavage for compound **13b** (R=3-ClPh) was carried

Scheme 3



out with HBr/HOAc (Scheme 2); (2) Dibenzyl amide **19** and the dipentyl amide **20** were prepared from acid **7b** (R= 3-ClPh), by standard coupling with **26** followed by hydrolysis and coupling with dipentylamine or dibenzylamine to give the product triacyl derivatives (Scheme 3).

The structure-activity relationships for simple derivatives of these piperidines mirrored that observed for the piperazine case, although in general the former binds more tightly to the NK-1 receptor (Table 1).[10, 14] For example, the racemic acid **10a** (Ar = Ph) is about 4-fold more potent than the corresponding (S)-piperazine (NK-1 IC_{50} = 130 nM), while the diethylamino antagonist **14** has a 7-fold greater affinity for the receptor than the related piperazine **1** (R = H; hNK-1 IC_{50} = 41 nM).[10] The relative stereochemistry on the piperidine ring was quite important, since the 2,4-*trans* compound was substantially more active than the 2,4-*cis* (cf. **12** and **15**). As had been observed in the piperazine study, N-(2-methoxybenzyl)-N-methylethylenediamine derivatives at the 2 position (such as compound **15**) provided very potent antagonists of the NK-1 receptor. Replacement of the 4-di(n-pentyl)amide with the 4-dibenzylamide identified in other studies as a potency-enhancing group[15] led to compound **19**, which featured a sub-nanomolar IC_{50} at the hNK-1 receptor. Interestingly, although 3-chlorophenyl derivatives showed some improvement in binding in the piperazine series (compare **1a** (R = H) [NK-1 IC_{50} = 41 nM] to **1b** (R = Cl) [NK-1 IC_{50} = 8 nM]), less significant and consistent shifts were seen in the present study (see Table 1).[16]

Table 1 Inhibition of ^{125}I-Substance P Binding to hNK-1 Receptors in CHO Cells and Inhibition of ^{3}H-Diltiazem Binding to L-Type Calcium Channels by Racemic 1,2,4-Triacylpiperidines

	IC_{50}, nM	
Compound	[a]**hNK-1**	**Ca^{2+} Channel**
10a	33 +/- 9.4 (3)	>>5000
10b	20 +/- 7 (3)	>>5000
12	73 +/- 31 (3)	-
13b	1.8 +/- 0.2 (3)	>5000
14	5.5 +/-2.5 (3)	820
15	1.8 +/- 0.5 (3)	200
16a	13 +/- 7.2 (3)	2700
16b	3.5 +/- 1.5 (3)	3700
17a	1.8 +/- 1 (3)	5600
17b	3.8 +/- 3 (3)	16200
19	0.7 +/- 0.3 (3)	110
20	1.4 +/-0.6 (3)	210
21	250 +/- 108 (3)	470
CP 96,345	0.5 +/- 0.2 (2)	240

[a] mean +/- SD (number of determinations)

Recently, several series of hNK-1 antagonists containing basic groups have been found to possess significant affinity for the L-type calcium channel,[5,6b,11] and this property has been implicated as the possible cause of the cardiovascular effects observed with the quinuclidine CP 96,345 and its NK-1 inactive enantiomer CP 96,344.[11] Several analogs in the present study were therefore screened for Ca^{2+} channel binding,[17] and it was observed that basic amines **14**,**15**,**19** and **20** all showed sub-micromolar IC_{50}s in inhibiting diltiazem

binding to this protein (Table 1). In contrast, the carboxylic acids **10a** and **10b** displayed virtually no affinity for the calcium channel (less than 10% inhibition of diltiazem binding at 5 μM), consistent with the suggestion that basic groups mediate binding to the L-type calcium channel. This property was not correlated with NK-1 binding, since the methyl ester **21**, which had minimal affinity for hNK-1, nevertheless showed an IC_{50} on the L-type Ca^{2+} channel similar to that observed for other basic compounds in this series.

One approach to lessen the Ca^{2+} channel affinity of neurokinin receptor antagonists is to decrease the pKa by appending an electron-withdrawing substituent to the amine nitrogen. This strategy has been described by Williams *et al*[5] and by Harrison et al,[6b] who showed that the N-(aminocarbonylmethyl) group simultaneously lowered the calcium channel affinity and raised the hNK-1 affinity of analogs in two series of potent substance P antagonists. When this approach was applied to the present series of triacylpiperidines, significant decreases in calcium channel binding were observed (compare **15** to **17a** and **20** to **17b**) with maintenance of good NK-1 affinity. The intermediate secondary N-(aminocarbonylmethyl) analogs **16a** and **16b** were also good NK-1 antagonists. In the case of the latter compound, the 2-methoxybenzyl group was seen to be superfluous with respect to NK-1 binding, although it did provide an additional decrease in calcium channel affinity. Finally, the benzyloxycarbonyl-protected intermediate **13b**, which was also a good ligand for the NK-1 receptor, showed little binding to the L-type calcium channel, as would be expected from a non-basic entity.

In summary, we have shown that altering the geometry at the 4-position of the original piperazine lead from sp^2 to sp^3 enhances affinity for the hNK-1 receptor, and that the most active configuration features the 2- and 4-substituents in a *trans* relationship. This arrangement is most consistent with an axial orientation for the amide at C2 to minimize $A_{1,3}$ strain and an equatorial disposition for the C4 substituent. This topography is in qualitative agreement with that expected for the related piperazine derivatives. In addition, this study shows that Ca^{2+} channel affinity of these compounds can be effectively modulated without loss of hNK-1 receptor binding through alterations in the pK_a of the C2 side chain amine functionality.

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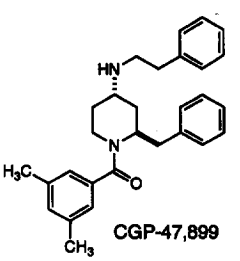
15. Studies of substituent effects at N1 and N4 of the related piperazines have been carried out and will be reported separately (C. J. Dorn, Jr., Merck Research Laboratories, unpublished observations).
16. A series of 1-acyl-2,4-disubstituted piperidine NK-1 antagonists such as CGP-47,899 have been disclosed by workers at Ciba-Geigy (Schilling, W. *et al Perspect. Med. Chem.;* Testa, B., *et al*, Ed.; Verlag Helvetica Chim Acta: Basel, 1993; pp. 207-220.). Although the scaffold is similar to that described here, the pharmacophores do not appear to overlap well. For example, note the basic amine of CGP-47,899 relative to the neutral amide in generic structure **2**. Additional studies would be needed to determine the degree of similarity of the binding modes of 1,2,4-triacylpiperidine and 1-acyl-2,4-disubstituted piperidine NK-1 antagonists.



CGP-47,899

17. The affinities of the compounds for the L-type Ca channel were determined by displacement of [^{3}H]-Diltiazem binding to rabbit skeletal muscle using a method adapted from : Reynolds, I.; Snowman, A.M.; Snyder, S.H.; *J. Pharmacol. Exp. Therap.* **1986**, *237*, 1731.

(*Received in USA* 20 *December* 1994; *accepted* 1 *February* 1995)