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STUDIES ON THE ACTIVE CONFORMATION OF THE NK_1 ANTAGONIST CGP 49823. PART 2[1]. FLUORO-OLEFIN ANALOGS OF TERTIARY AMIDE ROTAMERS.

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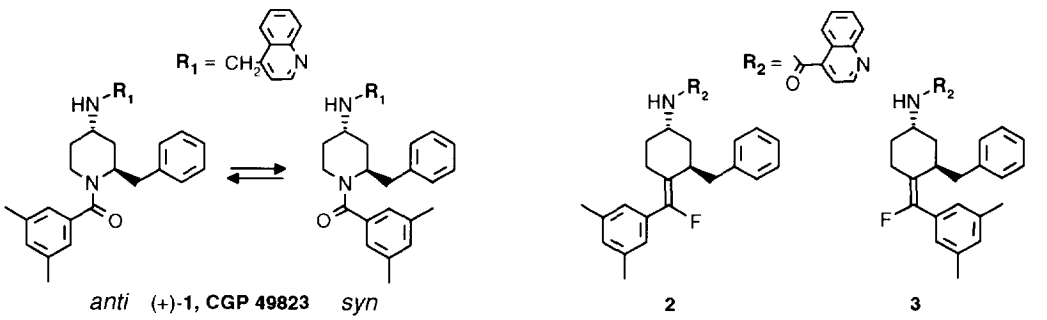
Abstract. Four fluoro-olefin analogs of CGP 49823 have been synthesized. Comparison of their binding affinities for the NK_1 receptor suggests an active conformation of CGP 49823, where the aromatic ring of the benzamide has a *syn* orientation towards the 2-benzyl substituent. © 1997, Elsevier Science Ltd. All rights reserved.

In previous papers[2] we described the discovery and structure-activity relationship (SAR) of CGP 49823 ((+)-**1**, Chart 1), a potent NK_1 antagonist, which is centrally active after oral administration. These SAR studies indicated that the 3,5-dimethylbenzoyl and benzyl substituents are a prerequisite for high affinity to the NK_1 receptor. The substituent at C-4 seems to be less critical for its NK_1 receptor affinity, since it may be replaced by much smaller groups like acetamide[2a]. In the preceding paper[1] we described studies designed to determine the bioactive conformation of the 2-benzyl substituent of **1**. In this paper we wish to present results of investigations aimed to determine, which amide rotamer of **1** has the higher affinity to the NK_1 receptor.

The fluoro-olefin isostere was proposed as early as 1984[3] as a superior isoelectronic and isosteric replacement for the amide moiety. Ever since various synthetic approaches have been employed for the preparation of fluoro-olefin dipeptide mimics[4]. At room temperature, in a variety of solvents, **1** exists as a mixture of two tertiary amide rotamers[5]. Fluoro-olefin analogues have a stable configuration and would allow the independent determination of NK_1 receptor affinity for both rotamer mimics. In this paper we describe the synthesis of *anti* and *syn* fluoro-olefins **2** and **3**, respectively (Chart 1).

Chart 1



anti (+)-**1, CGP 49823** *syn* **2** **3**

Chemistry. The 2-benzyl substituted cyclohexanone **4** (*cis/trans* mixture) was synthesized from diethyl malonate according to a literature procedure[6]. The fluorophosphonate ester **5** was prepared from 3,5-dimethylbenzaldehyde in analogy to a published method[7]. Wittig-Horner coupling of **4** and **5**, using potassiumhexamethyldisilazide ($KN(TMS)_2$) as a base gave a 4.5 : 1 mixture of *trans* products **6** and **7**. The major isomer **6** crystallized selectively leaving almost pure **7** in the mother liquor.

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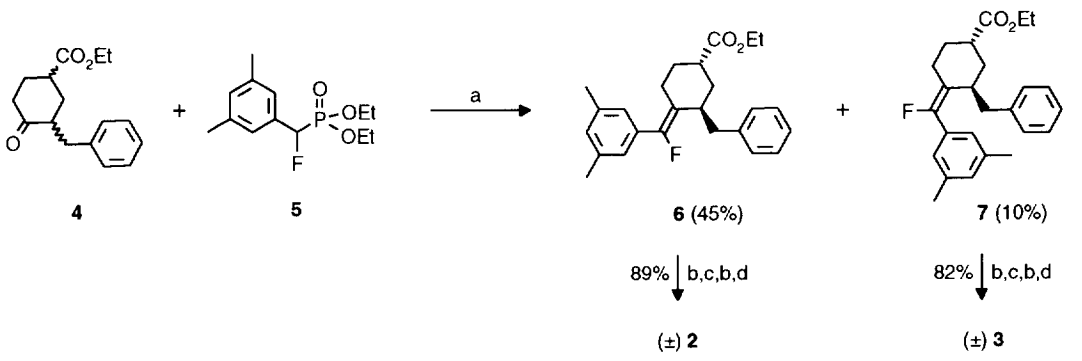
Scheme 1

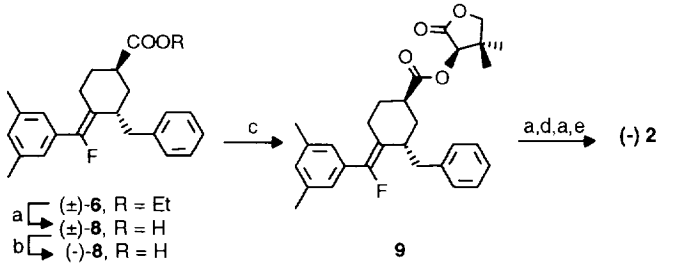


Reagents and conditions: (a) $KN(TMS)_2$, THF; (b) LiOH, THF, H_2O; (c) $ClCO_2iBu$, Et_3N, NaN_3, 20-65°C; (d) quinoline-4-carboxylic acid, propane phosphonic acid anhydride, Et_3N.

^1H NMR studies indicated the *trans*-relationship between the benzyl and ester substituents, the axial orientation of the benzyl group as well as the respective *anti* and *syn* geometry for **6** and **7**. An X-ray analysis of a derivative of **6** unambiguously confirmed these findings (*vide infra*). Moreover, due to the strongly basic reaction conditions any *cis* isomers had epimerized to the thermodynamically more stable *trans* products. The conversion of **6** and **7** to (±)-**2** and (±)-**3**, respectively, was carried out by an efficient three step procedure: ester hydrolysis, Curtius degradation and acylation of the primary amine with quinoline-4-carboxylic acid[8] (Scheme 1). The respective enantiomers (+)-**2**, (-)-**2**, (+)-**3** and (-)-**3** were obtained by chromatography of the racemic products **2** and **3** on a chiralcel-OD® column.

The next step was to determine the absolute stereochemistry for the pure enantiomers. For compound (-)-**2** this was achieved as shown in Scheme 2.

Scheme 2



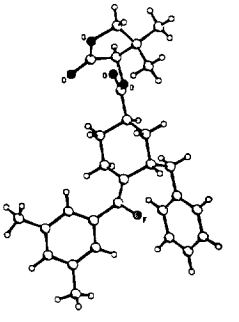


Fig. 1. X-ray crystal structure of **9**.

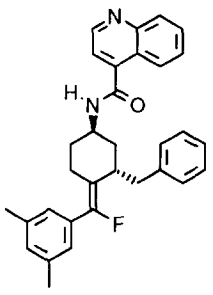
Reagents and conditions: (a) LiOH, THF, H_2O; (b) chromatography on chiralcel-OJ®; (c) *i:* 1-chloro-N,N,2-trimethylpropenylamine[9]; *ii:* R-(-)-pantolactone, Et_3N; (d) $ClCO_2iBu$, Et_3N, NaN_3, 20-65°C; (e) quinoline-4-carboxylic acid, propane phosphonic acid anhydride, Et_3N.

The racemic ester **6** was hydrolysed to **8** and its enantiomers separated via chromatography on a chiralcel-OJ® column. The (-)-enantiomer of **8** was coupled with R-(-)-pantolactone to yield the crystalline ester **9** (Scheme 2). An X-ray analysis[10] of **9** revealed the indicated structure (Fig. 1). The benzyl group was found to be axial and

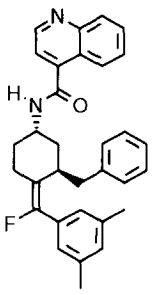
the stereochemistry of the substituents of the cyclohexane ring was *2S,4R*. Using identical conditions to those in Scheme 1, **9** was converted to (-)-**2** (Scheme 2), implicitly proving the absolute configuration of (+)-**2** as well.

Despite exhaustive efforts directed towards the identification of a suitable crystalline chiral derivative, direct proof of the absolute stereochemistry for one of the *syn* compounds (+)-**3** or (-)-**3**, or any of the intermediates in its synthesis, was not obtained. The stereochemical assignment for (+)-**3** and (-)-**3** is therefore tentative, and based upon their respective binding affinities for the NK_1 receptor (*vide infra*).

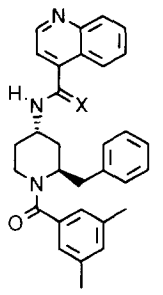
Chart 2



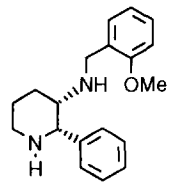
(-)-**2**



(-)-**3**



X = H_2 (+)-**1** (*syn*-rotamer)
X = O **10**



CP-99,994

Table

Stereochemistry	$[\alpha]_D^{20}$	Compound	IC_{50} [nM][11]
2R,4S	+27.8° (c = 2.1, MeOH)	(+)-**1**	12
2S,4R	-25.1° (c = 1.0, EtOH)	(-)-**1**	130
2R,4S	+27.2° (c = 1.0, EtOH)	**10**	15
trans		(±)-**2**	620
trans		(±)-**3**	710
2R,4S - anti	+48° (c = 0.2, CH_2Cl_2)	(+)-**2**	> 10.000
2S,4R - anti	-50° (c = 0.2, CH_2Cl_2)	(-)-**2**	270
syn	-3° (c = 0.2, CH_2Cl_2)	(-)-**3**	380
syn	+1° (c = 0.2, CH_2Cl_2)	(+)-**3**	> 10.000

Discussion. Both racemic *anti* and *syn* fluoro-olefins (±)-**2** and (±)-**3** show a moderate affinity to the NK_1 receptor. Both enantiomers of **1**, *(2R,4S)*-(+)-**1** (CGP 49823) and *(2S,4R)*-(-)-**1**, are active: the (-)-**1** enantiomer being about 10 times weaker than (+)-**1**(Table). Both enantiomers of **1** exist as a pair of *syn* and *anti* rotamers. We assume that *(2R,4S)*-(+)-**2** and *(2S,4R)*-(-)-**2** are valid mimics for the *anti*-rotamers of (+)-**1** and (-)-**1** respectively, the absolute stereochemistry of (+)-**1** being proven[2a]. The (-)-enantiomers of **2** and **3** were active, whereas their (+)-enantiomers were inactive. This suggests that for (+)-**1** as well as for (-)-**1** only *one* of their respective rotamers should have affinity to the NK_1 receptor. The enantiomer (-)-**2**, with confirmed *(2S,4R)*-stereochemistry, binds to the NK_1 receptor, whereas (+)-**2** is inactive, suggesting that the *anti* rotamer is the active component of (-)-**1**. This means that for (+)-**1** (CGP 49823) the *anti* rotamer, mimicked by inactive (+)-**2**, should have a low affinity to the NK_1 receptor. Since (+)-**1** is a potent NK_1 receptor antagonist, its binding affinity should reside in its *syn* rotamer.

In conclusion, the fluoro-olefin mimics of tertiary amide rotamers of (+)-**1** described in this paper provided a tool to demonstrate that the *syn* rotamer preferentially interacts with the NK_1 receptor. In addition, it was found that the NK_1 activity of (-)-**1** resides in its *anti* rotamer.

In summary, the studies presented in this paper and in the previous paper[1] yield strong evidence for a pharmacophore of (+)-**1**, where the aromatic rings of the 3,5-dimethylphenyl and benzyl groups are in close

proximity to each other with an aryl-aryl face to face[12] orientation. Similar structural elements have been found for other NK_1 receptor antagonists[13]. This is illustrated by the overlays[14] of *syn*-(+)-**1** and CP 99,994[13e], and *syn*-(+)-**1** and *anti*-(-)-**1** as shown in Figures 2 and 3, respectively. The 3,5-dimethylphenyl and benzyl groups of *syn*-(+)-**1** show a good overlap with the 2-methoxybenzyl and phenyl groups of CP 99,994, respectively. In addition, the surprisingly high potency of (-)-**1** (IC_{50}: 130 nM) is explained by the reasonably good overlap between the minimal energy conformation of the *syn* rotamer of (+)-**1** and a conformation of the *anti* rotamer of (-)-**1** 1.5 kcal above the computed minimum.

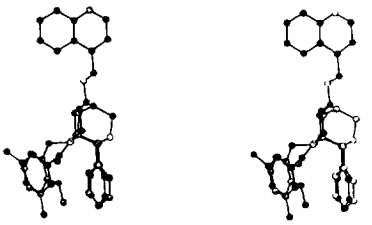


Figure 2. Stereoview of an overlay of *syn*-(+)-**1** (dark) and CP 99,994 (light).

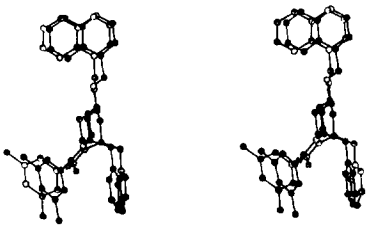


Figure 3. Stereoview of an overlay of *syn*-(+)-**1** (dark) and *anti*-(-)-**1** (light).

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References and Notes.

(1) Part 1: Veenstra, S.J.; Hauser, K.; Betschart, C. *Bioorg. Med. Chem. Lett.* **1997,** submitted, preceding paper.
(2) (a) Ofner, S.; Hauser, K.; Schilling, W.; Vassout, A.; Veenstra, S.J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1623. (b) Veenstra, S.J.; Hauser, K.; Schilling, W.; Betschart, C.; Ofner, S. *Bioorg. Med. Chem. Lett.* **1996**, submitted.
(3) Ellison, S.L.R. Ph.D. Dissertation, University of Liverpool, Liverpool, England, **1984**.
(4) (a) Allmendinger, T.; Hungerbühler, E.; Lattmann, R.; Ofner, S.; Schilling, W.; von Sprecher, G.; Felder, E., Eur. Pat. appl. 0353732, prior. 05.08.1988, CH. (b) Allmendinger, T.; Furet, P.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7297. (c) Allmendinger, T.; Felder, E.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7301. (d) Boros, L.G.; De Corte, B.; Gimi, R.; Welch J.T., Wu, Y.; Handschumacher, R.E. *Tetrahedron Lett.* **1994**, *33*, 6033. (e) Bartlett, P.A.; Otake, A. *J. Org. Chem.* **1995**, *60*, 3107. (f) Tsai, H-J. *Tetrahedron Lett.* **1996**, *37*, 629. (g) Takeuchi, Y.; Yamada, A.; Suzuki, T.; Koizumi, T. *Tetrahedron* **1996**, *52*, 225. (h) Welch, J.T.; Lin, J. *Tetrahedron* **1996**, *52*, 291.
(5) The ^1H NMR spectrum of CGP 49823 in $CDCl_3$ at room temperature shows a 3:2 mixture of two tertiary amide rotamers in equilibrium with each other.
(6) Chakrabortty, P.N.; Dasgupta, R.; Dasgupta, S.K.; Ghosh, S.R.; Ghatak, U.R. *Tetrahedron* **1972**, *28*, 4653.
(7) Blackburn, G.M.; Kent, D.E. *J. Chem. Soc. Perkin Trans. I* **1986**, 913.
(8) The quinoline-4-carboxamide analog of (+)-**1** (**10**) is a potent NK_1 receptor antagonist (see Table).
(9) Devos, A.; Remion, J.; Frisque-Hesbain, A.M.; Colens, A.; Ghosez, L. *J. Chem. Soc. Chem. Commun.* **1979**, *24*, 1180.
(10) Detailed X-ray crystallographic data for **9** have been deposited at the Cambridge Crystallographic Data Centre.
(11) For experimental details see: Bittiger, H. and Heid, J. "The retina, a part of the central nervous system with a very high density of ^3H-Substance P binding sites", in *Substance P - Dublin 1983, Proc. Int. Symp. (1983)*, pp. 198-199, Skrabanek, P.; Powell, D., Eds.; Boole Press Ltd.; Dublin, 1983.
(12) Hunter, C.A. *Chem. Soc. Rev.* **1994**, *23*, 101.
(13) (a) Lewis, R. T. *J. Med. Chem.* **1995**, *38*, 923. (b) Desai, M. C.; Lawrence, A. V.; Rizzi, J. P. *J. Med. Chem.* **1994**, *37*, 4263. (c) Regoli, D.; Boudon, A. Fauchère, J.-L. *Pharmacol. Rev.* **1994**, *46*, 551. (d) MacLeod, A. M. et al, *J. Med. Chem.* **1994**, *37*, 1269. (e) Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911.
(14) Conformational analyses were carried out for three structures: *syn*-rotamer of (+)-**1**, *anti*-rotamer of (-)-**1** and CP 99,994, using the Monte Carlo module of MacroModel 5.0. The AMBER[15] force field was used for all calculations. 2'000 Monte Carlo steps were used (5'000 for the *anti*-rotamer of (-)-**1**).
(15) Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *7*, 230.

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