



STUDIES ON THE ACTIVE CONFORMATION OF NK₁ ANTAGONIST CGP 49823. PART 1. SYNTHESIS OF CONFORMATIONALLY RESTRICTED ANALOGS.

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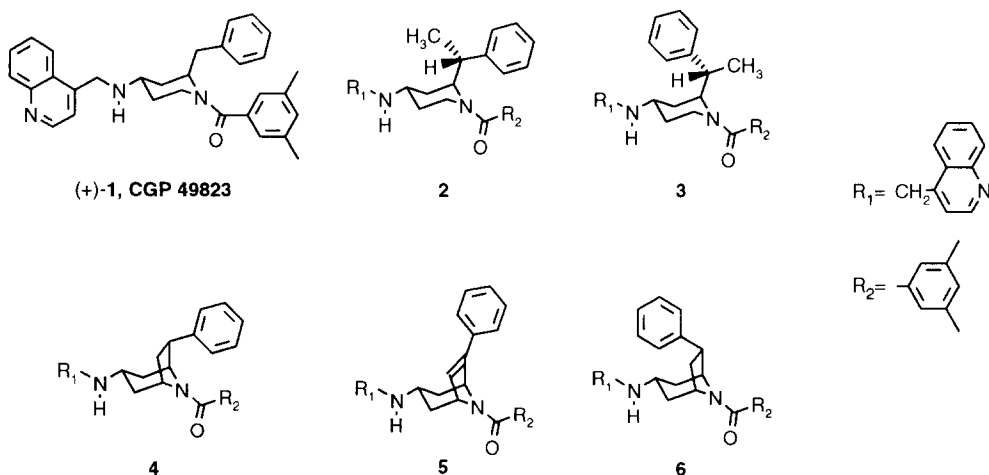
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Abstract. Five conformationally restricted analogs of CGP 49823 have been synthesized. Comparison of their *in vitro* activities indicates an active conformation of CGP 49823 in which the two aromatic rings of the benzyl and the benzoyl groups are in proximity of each other. © 1997, Elsevier Science Ltd. All rights reserved.

In earlier publications^{1,2} we described the discovery and the structure-activity relationship (SAR) of CGP 49823 ((+)-**1**, Chart), a potent, centrally and orally active NK₁ receptor antagonist. It was shown that both the 3,5-disubstituted tertiary benzamide and the C-2 benzyl substituent moieties are particularly important for high binding affinity to the NK₁ receptor. This benzyl substituent is optimal in terms of the distance between the aromatic moiety and the piperidine ring. The benzyl group may contain lipophilic substituents at 3- and/or 4-positions. The substituent at C-4 seems less critical for high binding affinity to the NK₁ receptor, since it may be replaced by much smaller groups, such as acetamide¹.

In this paper we wish to present our studies designed to determine the conformation of the C-2 benzyl side chain when bound to the NK₁ receptor. For this purpose two types of restricted analogs of (+)-**1** were synthesized. The conformational freedom of the benzyl group was reduced via the introduction of benzylic methyl substituent like in **2** and **3**. In the compounds **4**, **5** and **6** the position of the benzylic phenyl ring is fixed by an additional bridging methylene group.

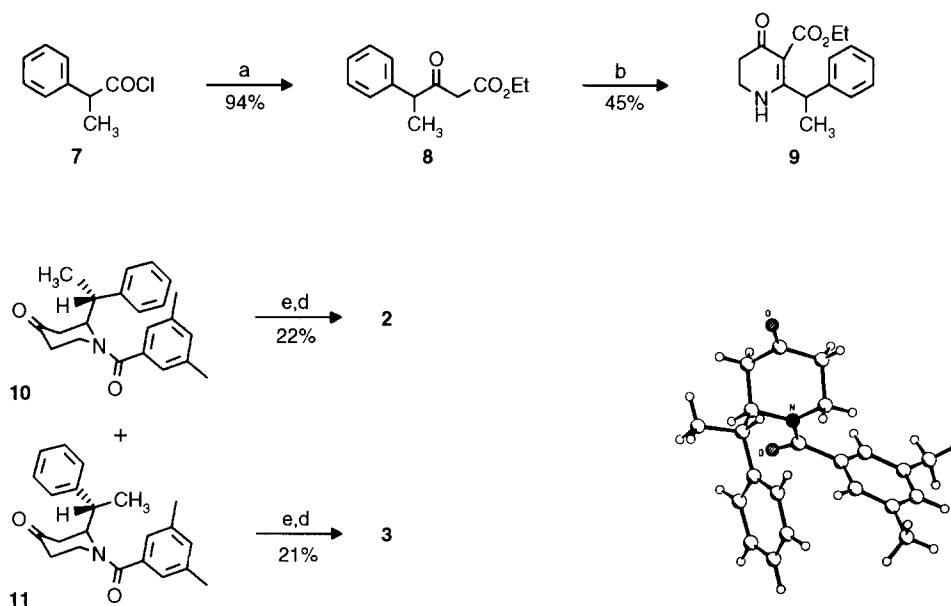
Chart



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Chemistry. Compounds **2** and **3** were synthesized according to Scheme 1. Ketoester **8**, prepared from **7**, was condensed with β -alanine ethyl ester and subsequently cyclized in a Dieckmann-type ring closure to give **9**. Reduction with magnesium in methanol, decarboxylation in refluxing aqueous HCl followed by acylation with 3,5-dimethylbenzoyl chloride, gave a 1:1 mixture of the 4-piperidones **10** and **11**. Both diastereomers were separated by chromatography on silica gel. An X-ray analysis of ketone **10** (Fig.)⁴ proved its relative stereochemistry. Reductive amination of **10** and **11** respectively with quinolin-4-yl-methylamine⁵ gave in each case a ca. 1:1 mixture of *cis*- and *trans*-substituted aminopiperidines, from which **2** and **3** were isolated by chromatography on silica gel, respectively.

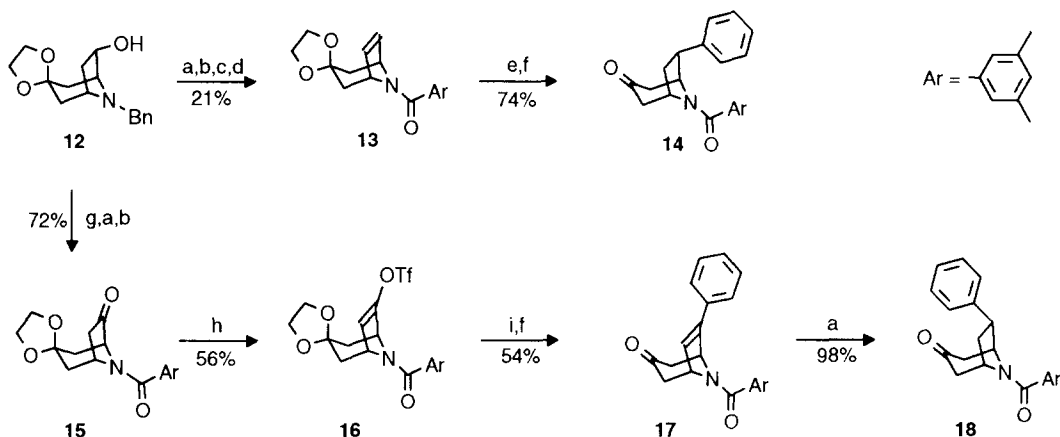
Scheme 1

Fig. X-ray crystal structure of **10**.

Reagents and conditions: (a) malonic acid monoethyl ester, BuLi, THF⁶; (b) *i*: H₂NCH₂CH₂CO₂Et, toluene, azeotropic removal of water; *ii*: NaOEt, EtOH, reflux; (c) *i*: Mg, MeOH, 45°C; *ii*: 6N HCl, reflux; *iii*: 3,5-dimethylbenzoyl chloride, CH₂Cl₂ aq. NaHCO₃; (d) chromatographic separation on silica gel; (e) *i*: quinolin-4-yl-methylamine, toluene; *ii*: NaCNBH₃.

The key bridged intermediates **14**, **17** and **18**, required for the synthesis of targets **4**, **5** and **6**, were synthesized according to Scheme 2. The starting material **12** was obtained by a literature procedure⁷ followed by protection of the carbonyl function as a 1,3-dioxolane. Replacement of the N-benzyl protective group with the 3,5-dimethylbenzoyl moiety and elimination of the hydroxyl group via its tosyl ester gave the olefin **13**. Palladium catalyzed reductive arylation of the double bond with iodobenzene⁸ followed by deprotection of the carbonyl function yielded the ketone **14**. The unsaturated ketone **17** was synthesized by the following procedure. Oxidation of the alcohol **12** and replacement of the benzyl group with the 3,5-dimethylbenzoyl moiety gave ketone **15**, which was converted to the enol triflate **16**⁹. Palladium catalyzed coupling with PhZnCl¹⁰ gave, after acid hydrolysis, the unsaturated ketone **17**. The highly stereoselective palladium catalyzed hydrogenation of **17** gave **18** in excellent yield. The two step reductive amination procedure of ketones **14**, **17** and **18** with quinolin-4-yl-methylamine⁵ (in analogy to Scheme 1) failed, presumably due to steric hindrance.

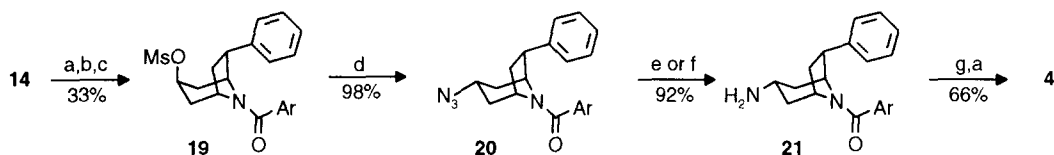
Scheme 2



Reagents and conditions: (a) Pd/C, H₂, MeOH; (b) 3,5-dimethylbenzoyl chloride, NEt₃, CH₂Cl₂, DMAP; (c) THF, BuLi, TsCl; (d) tBuOK, DMSO; (e) PhI, Pd(OAc)₂, PPh₃, Bu₄NI, HCOOK, DMF; (f) 6N HCl aq., THF; (g) DCC, H₃PO₄, DMSO; (h) LiN(iPr)₂, HMPT, THF, PhN(SO₂CF₃)₂; (i) PhZnCl (prepared *in situ* from PhLi and ZnCl₂), Pd(PPh₃)₄, THF.

An alternative five step procedure leading to **4**, **5** and **6** was therefore devised and is exemplified by the conversion of **14** to **4** (Scheme 3). Reduction of the carbonyl function gave a ca. 2:3 mixture of the axial and equatorial alcohols, respectively. After conversion to their respective mesylates, the desired axial derivative **19** was purified via chromatography on silica gel. Reaction of **19** with lithium azide in DMF gave **20**, which was reduced to the amine **21** by catalytic hydrogenation. Conversion to the Schiff's base of quinoline-4-carboxaldehyde by azeotropic removal of water and subsequent NaBH₄ reduction yielded the 6-*exo*-phenyl-8-aza-bicyclo[3.2.1]octanyl amine derivative **4**. The *endo* epimer **6** and the unsaturated 6-phenyl-8-azabicyclo[3.2.1]-oct-6-enylamine derivative **5** were prepared in a similar way from **18** and **17**, respectively.

Scheme 3



Reagents and conditions: (a) NaBH₄, EtOH; (b) MsCl, NEt₃, CH₂Cl₂; (c) separation via chromatography on silica gel; (d) LiN₃, DMF; (e) 10% Pd/C, H₂, MeOH; (f) PPh₃, THF, H₂O¹¹; (g) quinoline-4-carboxaldehyde, toluene.

Table

Compound	IC ₅₀ [nM] ¹²
(+)- 1	12
(±)- 2	30
(±)- 3	2300
(±)- 4	44
(±)- 5	1000
(±)- 6	640

Results and discussion. The methyl substituted analog **2** has a ca. 80 times higher affinity to the NK₁ receptor¹² than its diastereomer **3** (Table), and reaches the potency of (+)-**1**. A common phenomenon of N-acyl-2-alkyl piperidines is the axial position of the C-2 alkyl substituent¹³, this is confirmed by the X-ray structure of **10**. The C-2 benzyl group of (+)-**1** may rotate, but rotational conformers, which have a hydrogen atom (being the smallest substituent) positioned above the piperidine ring are strongly preferred, thus minimizing 1,3-diaxial interactions. The introduction of a methyl group at the benzylic position as shown in the diastereomers **2** and **3** will restrict the rotational freedom of the benzyl group to effectively *one* rotational conformer, where the hydrogen atom lies above the piperidine ring and the phenyl ring is either positioned towards the amide functionality (**2**) or protrudes out in space (**3**).

Comparison of the binding affinities of the bridged analogs **4**, **5** and **6** provides a similar picture (Table). The *exo* derivative **4**, with the phenyl ring positioned towards the amide functionality, shows the highest affinity to the NK₁ receptor. Compounds **5** and **6** are substantially weaker.

In conclusion, two types of conformationally restricted analogs of (+)-**1**, either with an additional methyl group at the benzylic position of the side chain, or with a bridging methylene group, as in the 8-azabicyclo[3,2,1]octanes, were synthesized. The comparison of their relative binding affinities to the NK₁ receptor produced strong evidence for an active conformation of (+)-**1**, where the benzyl side chain is oriented towards the 3,5-dimethylbenzamide group.

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References and notes.

- (1) Ofner, S.; Hauser, K.; Schilling, W.; Vassout, A.; Veenstra, S.J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1623.
- (2) Veenstra, S.J.; Hauser, K.; Schilling, W.; Betschart, C.; Ofner, S. *Bioorg. Med. Chem. Lett.* submitted.
- (3) (a) Becker, H. G. O. *J. Prakt. Chem.* **1961**, *284*, 294. (b) Schultz, A.G.; Shannon, P.J.; Tobin, P.S. *J. Org. Chem.* **1979**, *44*, 291.
- (4) Detailed X-ray crystallographic data for **10** have been deposited at the Cambridge Crystallographic Data Centre.
- (5) Work, T. S. *J. Chem. Soc.* **1942**, 426.
- (6) Katagiri, N.; Kato, T.; Nakano, J. *Chem. Pharm. Bull.* **1982**, *30*, 2440.
- (7) Markwell, R. E.; Hadley, M. S.; Blaney, F. E. **EP 95262** (1983).
- (8) (a) Brunner, H.; Kramler, K. *Synthesis* **1991**, *12*, 1121. (b) Larock, R.C.; Johnson, P.L. *J. Chem. Soc. Chem. Commun.* **1989**, *18*, 1368.
- (9) McMurry, J.E.; Scott, W.J. *Tetrahedron Lett.* **1983**, *24*, 979.
- (10) McCague, R. *Tetrahedron Lett.* **1987**, *28*, 701.
- (11) PPh₃ was used for reduction of the azide functionality in the preparation of **5**.
- (12) 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.
- (13) (a) Paulsen, H.; Todt, K.; Ripperger, H. *Chem. Ber.* **1968**, *101*, 3365. (b) Chow, Y.L.; Colon, C.J.; Tam, J.N.S. *Can. J. Chem.* **1968**, *46*, 2821.

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