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STUDIES ON THE ACTIVE CONFORMATION OF NK_1 ANTAGONIST CGP 49823. PART 1. SYNTHESIS OF CONFORMATIONALLY RESTRICTED ANALOGS.

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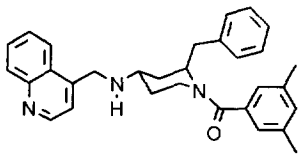
Abstract. Five conformationally restricted analogs of CGP 49823 have been synthesized. Comparison of their *in vitro* activities indicates an active conformation of CGP 49823 in which the two aromatic rings of the benzyl and the benzoyl groups are in proximity of each other.

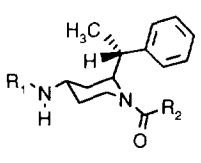
In earlier publications[1,2] we described the discovery and the structure-activity relationship (SAR) of CGP 49823 ((+)-**1**, Chart), a potent, centrally and orally active NK_1 receptor antagonist. It was shown that both the 3,5-disubstituted tertiary benzamide and the C-2 benzyl substituent moieties are particularly important for high binding affinity to the NK_1 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 NK_1 receptor, since it may be replaced by much smaller groups, such as acetamide[1].

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 NK_1 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



(+)-1, CGP 49823



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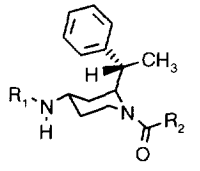

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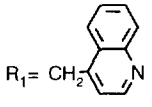
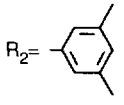
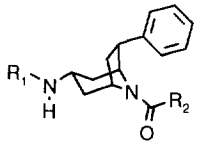


R_1= CH_2



R_2=



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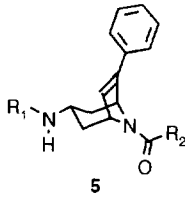

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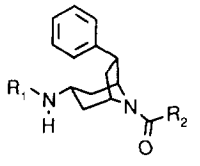

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Chemistry. Compounds **2** and **3** were synthesized according to Scheme 1. Ketoester **8**, prepared from **7**, was condensed with β-alanine ethyl ester and subsequently cyclized in a Dieckmann-type ring closure to give **9**[3]. Reduction with 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-methylamine[5] 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

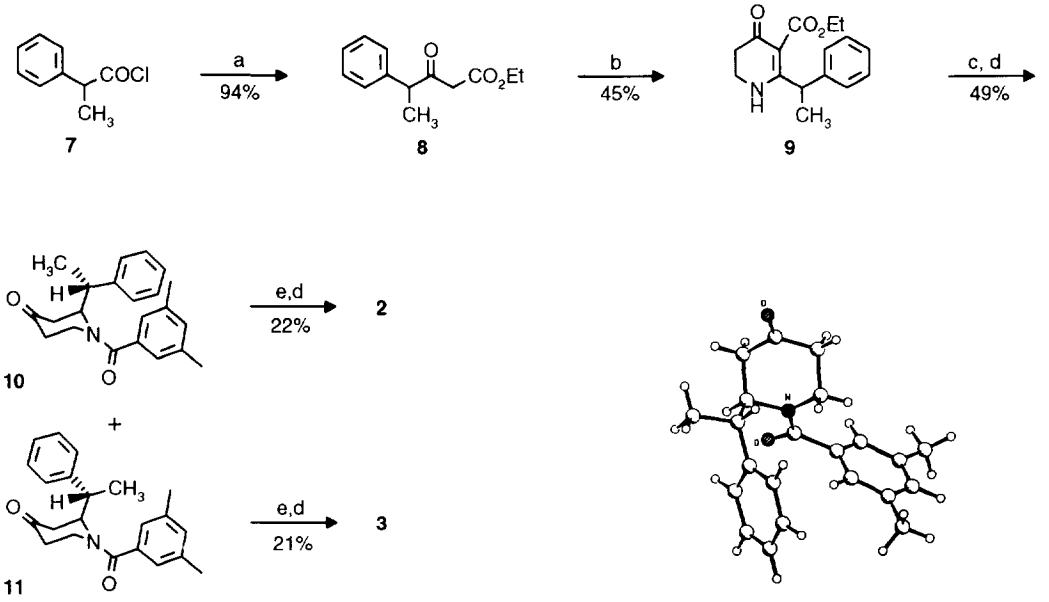
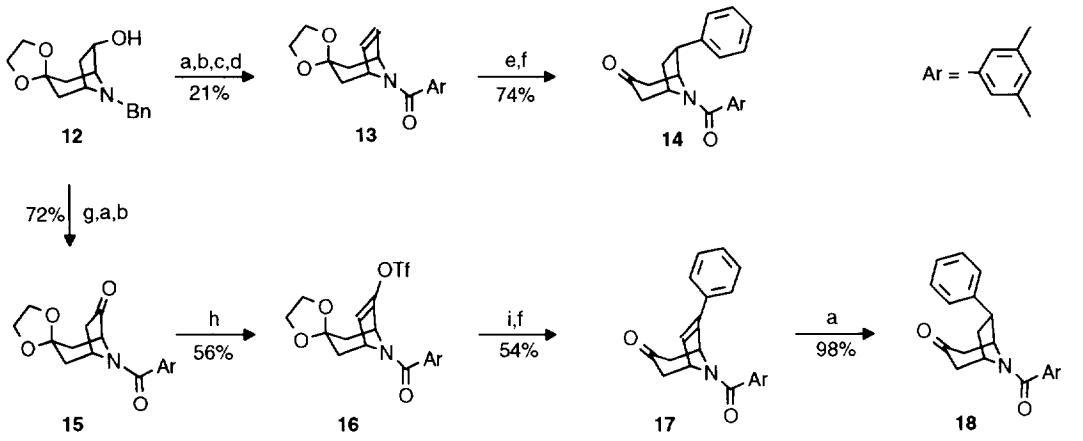


Fig. X-ray crystal structure of **10**.

Reagents and conditions: (a) malonic acid monoethyl ester, BuLi, THF[6]; (b) *i:* $H_2NCH_2CH_2CO_2Et$, toluene, azeotropical removal of water; *ii:* NaOEt, EtOH, reflux; (c) *i:* Mg, MeOH, 45°C; *ii:* 6N HCl, reflux; *iii:* 3,5-dimethylbenzoyl chloride, CH_2Cl_2 aq. $NaHCO_3$; (d) chromatographic separation on silica gel; (e) *i:* quinolin-4-yl-methylamine, toluene; *ii:* $NaCNBH_3$.

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 procedure[7] 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 iodobenzene[8] 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 PhZnCl[10] 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-methylamine[5] (in analogy to Scheme 1) failed, presumably due to steric hindrance.

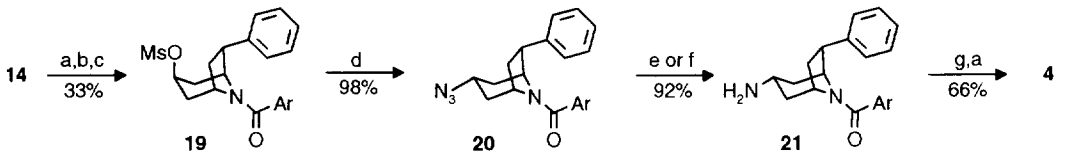
Scheme 2



Reagents and conditions: (a) Pd/C, H_2, MeOH; (b) 3,5-dimethylbenzoyl chloride, NEt_3, CH_2Cl_2, DMAP; (c) THF, BuLi, TsCl; (d) tBuOK, DMSO; (e) PhI, $Pd(OAc)_2$, PPh_3, Bu_4NI, HCOOK, DMF; (f) 6N HCl aq., THF; (g) DCC, H_3PO_4, DMSO; (h) $LiN(iPr)_2$, HMPT, THF, $PhN(SO_2CF_3)_2$; (i) PhZnCl (prepared *in situ* from PhLi and $ZnCl_2$), $Pd(PPh_3)_4$, 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. Correct stereochemical assignment was assured via NMR studies. 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 $NaBH_4$ 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) $NaBH_4$, EtOH; (b) MsCl, NEt_3, CH_2Cl_2; (c) separation via chromatography on silica gel; (d) LiN_3, DMF; (e) 10% Pd/C, H_2, MeOH; (f) PPh_3, THF, H_2O[11]; (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 NK_1 receptor[12] 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 substituent[13], 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 NK_1 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-aza-bicyclo[3,2,1]octanes, were synthesized. The comparison of their relative binding affinities to the NK_1 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.

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(11) PPh_3 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 ^{3}H-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.

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