Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 24, pp. 3029-3034, 1996
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0960-894X/96 $15.00 + 0.00

PII: S0960-894X(96)00563-X

SAR OF 2-BENZYL-4-AMINOPIPERIDINES NK_1 ANTAGONISTS. PART 2[1].
SYNTHESIS OF CGP 49823.

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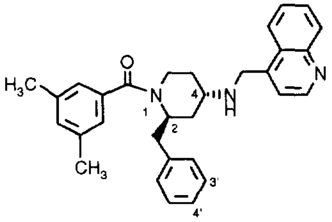
Abstract: CGP 49823 is a potent NK_1 antagonist which is centrally active after oral administration. The SAR of the C-2 substituent was investigated with respect to the affinity to the NK_1 receptor. A practical synthesis of CGP 49823, suitable for scale-up, was developed. The key-step, a tandem acyliminium ion cyclization / Ritter reaction, gave *trans* 2-benzyl-4-acetamido-piperidines with high diastereoselectivity.

NK_1 receptor antagonists[2] antagonize the effect of Substance P (SP)[3], an eleven amino acid peptide, which is implicated in numerous disease states including asthma[4a], arthritis[4b], inflammatory bowel disease[4c], pain[4d], emesis[4e,f] and psychiatric disorders[3]. CGP 49823[1] (**1**) is a potent NK_1 antagonist, which is centrally active after oral administration. The structure-activity relationship (SAR) of **1** has thus far revealed certain prerequisites for high affinity to the NK_1 receptor: the (*2R,4S*)-stereochemistry, the carbonyl group of the benzamide and its 3,5-substitution with small lipophilic groups.



1, CGP 49823

The SAR of the 2-benzyl substituent has, until now, remained unexplored. Two synthetic routes, which we developed for this class of compounds[1,5], were lengthy and not sufficiently versatile for a broad exploration of the SAR at C-2. An alternative synthesis for 2-substituted-4-aminopiperidines should preferably be compatible with a variety of functionalities, be *trans*- and enantioselective, and be suitable for scale-up. Herein we wish to report on a selective synthesis for **1** (Scheme 1) and the SAR of the C-2 substituent of 4-amino-piperidines as a novel class of highly potent and selective NK_1 receptor antagonists.

The readily accessible acid **2**[6] was converted to its primary carboxamide. Hofmann reaction[6] and coupling with benzyloxycarbonyl chloride gave the urethane **3**. Alkylation with chloromethyl ethyl ether under phase-transfer conditions gave the acyl-iminium precursor **4**. In the presence of two equivalents of chlorosulfonic acid[7] in acetonitrile as a solvent at -20°C, **4** cyclized smoothly and after aqueous work-up and crystallization of the crude product the pure *trans*-4-acetamido-piperidine **6**[8] was isolated in 73% yield (*trans/cis* ratio 20 : 1). Deprotection and classical resolution[9] of (±)-**7** with (-)-O,O'-dibenzoyl tartaric acid gave (*2R,4S*)-**7** (> 98%ee[10]; $[\alpha]_D$ -30.2°, c=1, CH_2Cl_2).

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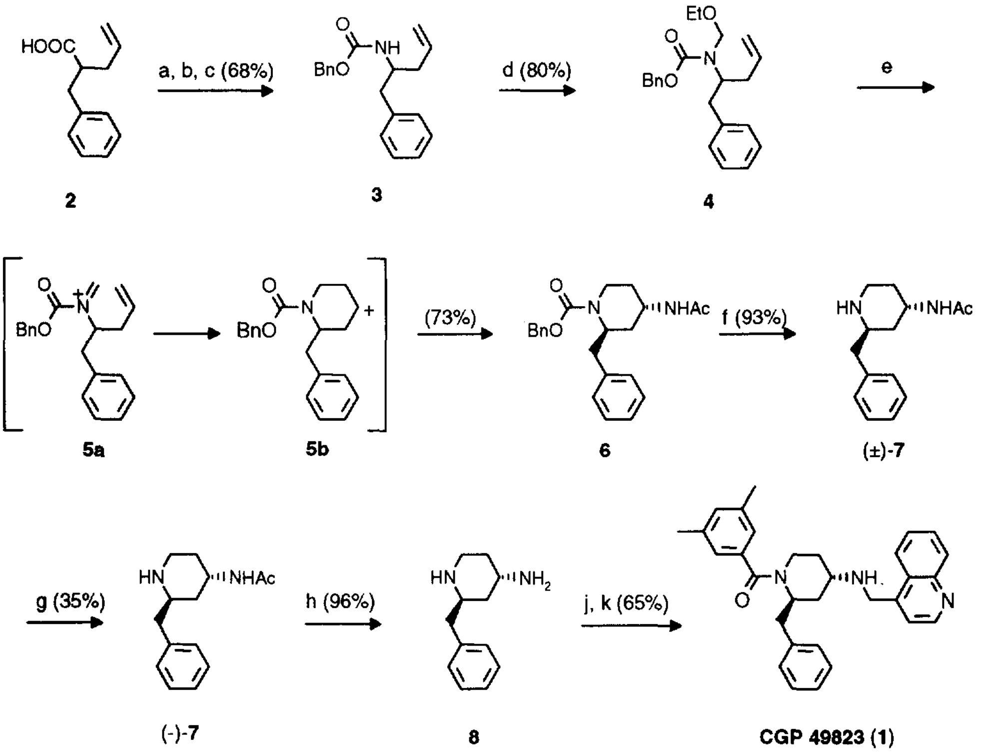
Scheme 1



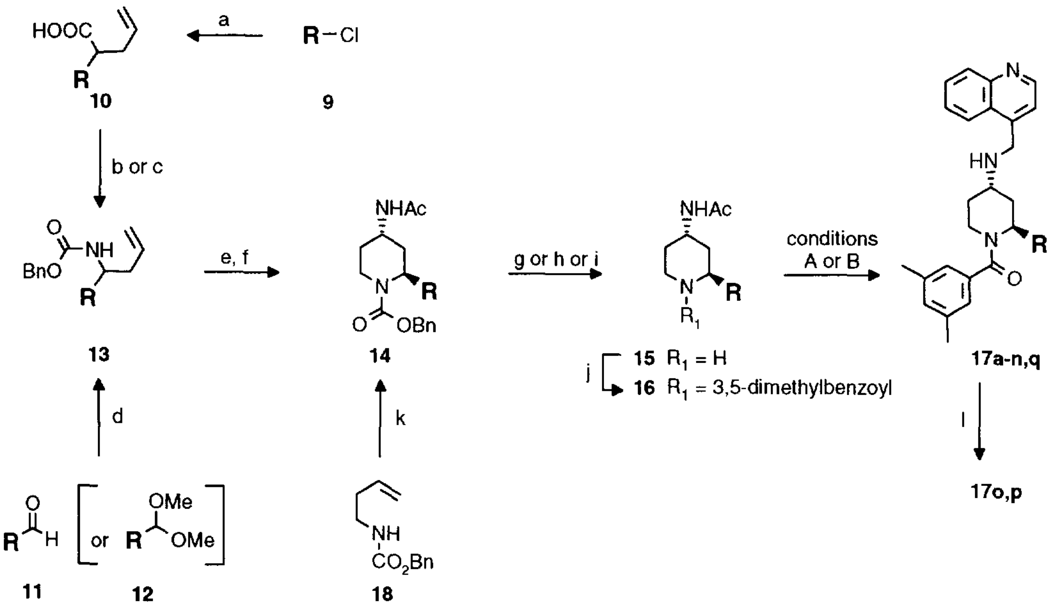
Reagents and conditions: (a) *i:* $SOCl_2$; *ii:* aq. NH_3; (b) Br_2, NaOH; (c) $ClCO_2Bn$, aq. $NaHCO_3$; (d) $ClCH_2OEt$, 50% aq. NaOH, CH_2Cl_2, cat. benzyltributylammonium chloride, 5-10°C; (e) $ClSO_3H$, CH_3CN, -20°C, 30 min.; (f) 6N HCl, 50°C; (g) fractional crystallization with (-)-O,O'-dibenzoyl tartaric acid; (h) 6N HCl, 115°C; (j) *i:* PhCHO, toluene; *ii:* 3,5-dimethylbenzoyl chloride, Et_3N, toluene; *iii:* 1N HCl; (k) *i:* quinoline-4-carboxaldehyde, toluene; *ii:* $NaBH_4$, MeOH.

After hydrolysis the diamine **8** was selectively acylated with 3,5-dimethyl-benzoyl chloride at the secondary nitrogen atom using the Schiff's base of benzaldehyde for transient protection of the primary amine[11]. A two-step reductive amination with quinoline-4-carboxaldehyde completed the synthesis of **1** in 8% overall yield from **2** without chromatographic separation.

The intramolecular cyclization of an acyliminium ion onto an unactivated olefin has been established as a mild and versatile method for the construction of nitrogen containing 5- or 6-membered heterocycles[12]. The use of acetonitrile as a solvent for this reaction, although little known[13], represents a useful variation. Concurrently, in a Ritter type process, a second nitrogen atom in the form of an acetamide is introduced in the 4-position of the piperidine ring. The key-step for the construction of the *trans*-2-substituted-4-aminopiperidine skeleton was the transformation **4** → **6** (Scheme 1). The acyl-iminium ion **5a**[12], which is presumably generated upon acid treatment of **4**, cyclizes to **5b** and the resulting carbenium ion is trapped by the solvent acetonitrile. Aqueous work-up gives the 4-acetamido-piperidine as the product. *Trans* selectivity for this process was to be expected, as N-acylated-2-alkylpiperidines have a strong preference for an axial conformation[14]. Presumably some of this preference is maintained in the cation **5b**. For steric reasons, the cation is trapped from the opposite site of the ring leading to the *trans* product **6**.

For the purpose of studying the SAR of the C-2 substituent we prepared the derivatives **17** (of **1**) in racemic form (Scheme 2). The benzyloxycarbonyl protected homoallyl amines **13** served as key intermediates. Compounds **13** were usually prepared via known routes[6,15] from the appropriately substituted benzylchlorides **9** via the substituted 4-pentenoic acids **10**. Alternatively, **13** was obtained in a single step from aldehydes **11** (entries 2 and 3) or from acetals **12** (entries 9, 10 and 15) via a novel, highly versatile, one-pot condensation reaction. When an equimolar mixture of an aldehyde **11** (or an acetal **12**), benzylcarbamate and allyltrimethylsilane in acetonitrile was treated at 0-25°C with one equivalent of borontrifluoride diethyletherate, the respective benzyloxycarbonyl protected homoallylamines **13** were produced in good to excellent yields[16]. Alkylation of the urethanes **13** with chloromethyl ethyl ether under phase-transfer conditions followed by cyclization with trifluoromethane sulphonic acid in acetonitrile at -20°C gave the *trans* substituted piperidines **14**. Cleavage of the carbamate and acylation with 3,5-dimethylbenzoyl chloride led to benzamide **16**. Selective cleavage of the acetamide versus the benzamide was usually accomplished in acceptable yields by careful hydrolysis with 6N HCl at 90°C (Conditions A: i)[17].

Scheme 2

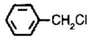
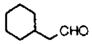
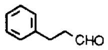
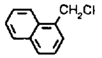
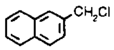
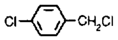
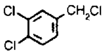
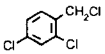
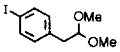
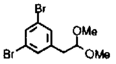
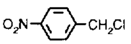
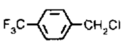
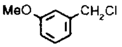
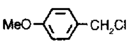
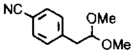
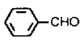


Reagents and conditions: (a) *i:* allylmalonic acid diethyl ester, NaOMe, MeOH; *ii:* NaOH, H_2O; *iii:* H_2SO_4, H_2O; *iv:* 160°C; (b) *i:* $SOCl_2$; *ii:* aq. NH_3; *iii:* Br_2, NaOH; *iv:* $ClCO_2Bn$, aq. $NaHCO_3$; (c) $(PhO)_2P(O)N_3$, Et_3N, benzyl alcohol, toluene, 50-110°C; (d) $BnOCONH_2$, allyltrimethylsilane, $BF_3{\cdot}OEt_2$, acetonitrile, 0-25°C; (e) $ClCH_2OEt$, 50% aq. NaOH, CH_2Cl_2, cat. benzyltributylammonium chloride; (f) CF_3SO_3H, acetonitrile, -20°C, 30 min; (g) 10N HCl, 50°C; (h) 10% Pd-C, H_2, MeOH, 1N HCl; (i) TMSCl, NaI, acetonitrile; (j) 3,5-dimethylbenzoyl chloride, CH_2Cl_2, aq. $NaHCO_3$; (k) PhCHO, $SnCl_4$, Ac_2O, acetonitrile, -20°C; (l) LiOH.

Conditions A: *i:* 6N HCl, 90°C; *ii:* quinoline-4-carbaldehyde, toluene, azeotropic removal of water; *iii:* $NaBH_4$, MeOH.

Conditions B: *i:* $(Boc)_2O$, DMAP, Et_3N, toluene, 60°C; *ii:* MeOLi, MeOH; *iii:* TFA; *iv:* quinoline-4-carbaldehyde, toluene, azeotropic removal of water; *v:* $NaBH_4$, MeOH.

Table

Entry	Starting material	Conditions	R	Compound	IC_{50} [nM][18]
1		Scheme 1	benzyl	**(+)-1**[a]	12
2		d,e,f,i / A	cyclohexyl-methyl	**17a**	310
3		d,e,f,h / A	phenethyl	**17b**	190
4		a,c,e,f,h / A	1-naphtyl-methyl	**17c**	29
5		a,c,e,f,i / A	2-naphtyl-methyl	**17d**	14
6		a,c,e,f,h / A	4-chloro-benzyl	**17e**	13
7		a,c,e,f,h / A	3,4-dichloro-benzyl	**17f**	9
8		a,c,e,f,h / A	2,4-dichloro-benzyl	**17g**	600
9	 b)	d,e,f,h / B	4-iodo-benzyl	**17h**	7
10	 b)	d,e,f,h / A	3,5-dibromo-benzyl	**17i**	52
11		a,c,e,f,h / B	4-nitro-benzyl	**17j**	3
12		a,c,e,f,i / A	4-trifluoromethyl-benzyl	**17k**	11
13		a,c,e,f,i / A	3-methoxy-benzyl	**17l**	27
14		a,c,e,f,h / A	4-methoxy-benzyl	**17m**	14
15	 b)	d,e,f,j / B	4-cyano-benzyl	**17n**	21
16	**17n**	l	4-carbamoyl-benzyl	**17o**	100
17	**17n**	l	4-carboxy-benzyl	**17p**	>10000
18	 + **18**	g,h / A	phenyl	**17q**	2670

a) CGP 49823 b) prepared in analogy to a published procedure[19]

A better selectivity in the cleavage of the acetamide **16** was obtained via an alternative three step procedure (Conditions B: i-iii; entries 9, 11 and 15): Boc-protection of the secondary acetamide **16**, followed by successive treatment with a catalytic amount of LiOMe in MeOH to cleave the acetyl group under mild conditions and, finally, cleavage of the Boc-amide with trifluoroacetic acid. The precursor **14q** for compound **17q** (entry 18) was obtained in a single step by treatment of **18**[20] and benzaldehyde in the presence of equimolar amounts of $SnCl_4$ and acetic anhydride in acetonitrile at -20°C[21]. A two-step reductive amination with quinoline-4-carboxaldehyde completed the synthesis for compounds **17a-n,q** (Conditions A: ii and iii). Partial saponification with LiOH in aqueous MeOH of the derivative **17n** gave the carbamoyl and carboxy derivatives **17o** and **17p** respectively.

The NK_1 binding results of compounds **17a-q** are summarized in the Table. IC_{50} values were determined by displacement of ^3H-SP from bovine retina membranes[18]. The linker between the phenyl ring and the piperidine ring is important and should be one methylene group. Direct attachment of the phenyl group onto the piperidine ring gives an almost inactive compound (entry 18). Chain elongation weakens the binding potency considerably (entry 3). The aromaticity of the benzyl group is also important for good NK_1 affinity (entry 2). Various hydrophobic substitutions (benzo-annelation, Cl, I, NO_2, CF_3, OMe, and CN; entries 4-7, 9 and 11-15) can be made at the 3'- and/or 4'-position(s), while the compounds maintain excellent potency. Ortho-substitution with a chlorine atom presumably does not allow the side chain to adapt the optimal conformation for potent binding (entry 8). The presence of a hydrophilic carbamoyl group (entry 16) weakens the activity considerably and the presence of a carboxylic acid (entry 17) is deleterious for NK_1 binding.

In conclusion, the SAR of the benzyl side chain of CGP 49823, a highly potent, selective and orally active NK_1 antagonist, for affinities at the NK_1 receptor showed a high tolerability for hydrophobic substituents at the 3'- and/or 4'-position(s). A short and selective synthesis for CGP 49823, suitable for scale-up, has been developed.

Acknowledgments. The authors wish to express their thanks to U. Bützberger, A. Koblet, C. Riegert, M. Roggwiller, B. Schaub and P. Schmid for their skillful technical assistance, and our colleagues from the Analytical Department for providing spectral and analytical data.
We further wish to thank Dr. H. Hiemstra, University of Amsterdam, for his suggestion to use acetonitrile as a solvent for the acyl-iminium ion cyclisation.

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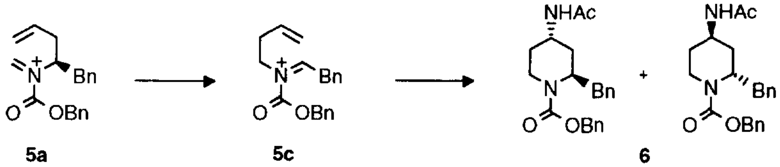
(7) CF_3SO_3H/CH_3CN gave identical results; $SnCl_4/Ac_2O/CH_3CN$ gave good yields, but a lower *trans/cis* ratio; other acids gave unsatisfactory results.

(8) The *trans*-stereochemistry of **6** was confirmed after cleavage of the benzyloxycarbonyl group: (±)-**7**: resin, ^{1}H-NMR (400 MHz, CD_3CN) 7.33 - 7.27 (m, 2H), 7.24 - 7.18 (m, 3H), 6.45 - 6.31 (br, NH), 4.08 - 4.02 (m, 1H), 3.00 - 2.92 (m, 1H), 2.79 (dt, J=4.1 and 12.5 Hz, 1H), 2.71 (ddd, J=3.0, 11.5 and 12.2 Hz, 1H), 2.64 (dd, J=5.6 and 13.6 Hz, 1H), 2.57 (dd, J=7.8 and 13.6 Hz, 1H), 1.84 (s, 3H), 1.63 - 1.56 (m, 2H), 1.53 - 1.46 (m, 1H), 1.38 (ddd, J=4.0, 10.0 and 14.4 Hz, 1H).

Cis-isomer of **7**: m.p. 133° C, ^{1}H-NMR (400 MHz, CD_3CN) 7.32 - 7.26 (m, 2H), 7.23 - 7.18 (m, 3H), 6.26 - 6.15 (br, 1H), 3.60 (ttd, J=3.8, 11.6 and 7.7 Hz, 1H), 2.96 (ddd, J= 2.5, 4.2 and 12.0 Hz, 1H), 2.76 - 2.68 (m, 1H), 2.66 - 2.58 (m, 2H), 2.52 (dt, J=2.5 and 12.0 Hz, 1H), 1.80 -1.69 (m, 2H), 1.43 - 1.28 (br, 1H), 1.17 (dt, J=4.2 and 12.0 Hz, 1H), 0.90 (q, J=11.6 Hz, 1H).

(9) In order to avoid this resolution step late in the synthesis, we studied the key-step **4** → **6** starting with optically pure (S)-**4** ($[\alpha]_D$ +23.5°, c=1, CH_2Cl_2) obtained from racemic **4** via a classical resolution with (-)-O,O'-dibenzoyl tartaric acid. Unfortunately, the product **6** from this reaction (CF_3SO_3H, acetonitrile, -20°C) had racemised considerably and showed only 42% ee[10]. A concomitantly occurring 2-aza-Cope rearrangement **5a**→**5c** ,which then cyclizes to racemic **6**, would explain this result:



See for instance: (a) Ref. 11; (b) Guiles, J.W.; Meyers, A.I. *J. Org. Chem.* **1991**, *56*, 6873; (c) Hart, D.J.; Tsai, Y-M. *Tetrahedron Lett.* **1981**, *22*, 1567.

(10) Ee of **7** was determined via HPLC analysis (chiralcel-OD®) of its benzyloxycarbonyl derivative **6**.

(11) To our best knowledge this procedure is the first example of a selective acylation of a secondary amine in presence of a primary amine using an *acid chloride* as acylating agent. Selective Boc-protection of a secondary amine in presence of a primary amine has been reported: Prugh, J.D.; Birchenough, L.A.; Egbertson, M.S. *Synth. Commun.* **1992**, *22*, 2357.

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(17) A side reaction was the simultaneous cleavage of the benzamide.

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(*Received in Belgium* 16 *September* 1996; *accepted* 18 *November* 1996)