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SAR OF 2-BENZYL-4-AMINOPIPERIDINES: CGP 49823, AN ORALLY AND CENTRALLY ACTIVE NON-PEPTIDE NK_1 ANTAGONIST

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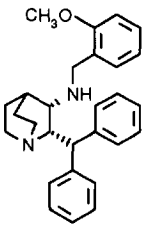
Abstract: Novel 2-benzyl-4-aminopiperidines have been shown to be potent and selective antagonists at the NK_1 receptor. Some compounds of this series, e.g. CGP 49823 (**2**), show CNS activity after oral administration.

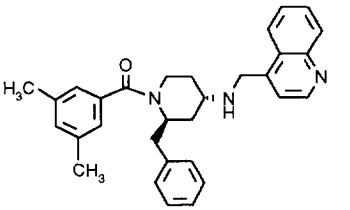
Substance P (SP), an eleven amino acid peptide (Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2) belongs to a family of neuropeptides referred to as the tachykinins[1] and acts via the NK_1 receptor. Studies with peptidic NK_1 receptor agonists and antagonists revealed that Substance P is likely to be associated with a wide range of diseases such as inflammatory processes, e.g. asthma,[2a] arthritis,[2b] inflammatory bowel disease,[2c] with pain,[2d] emesis[2e,f] and psychiatric disorders.[1]

However, due to the known disadvantages of peptidic receptor ligands, i.e. poor bioavailability and metabolic instability, there was little progress until the first non-peptidic antagonist of SP, CP-96,345 (**1**) was discovered[3] (Chart I). Several reports on non-peptidic low molecular weight antagonists like CP-99,994[4], RPR-100,893[5] and SR-140,333[6] followed.

Chart I



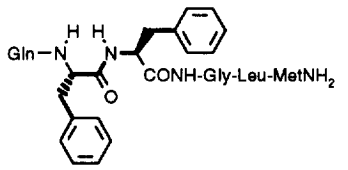
1, CP-96,345



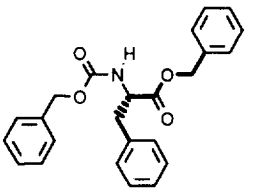
2, CGP 49823

When we became interested in this field it was known that the minimal structural element of SP which retains biological activity is its C-terminal hexapeptide (**3**, IC_{50} = 3 μM, Chart II). Surprisingly, the simple phenylalanine derivative Z-Phe-OBn (**4**, IC_{50} = 3 μM), showed a similar affinity for the NK_1 receptor but had antagonist activity.[7] The assumption that the two aromatic groups in **3** are essential for the affinity towards the NK_1 receptor prompted us to selectively screen compounds from the Ciba compound collection which had at least two aromatic groups five to nine atoms apart. Compound **5** (IC_{50} = 1.1 μM) is one example of the compounds with moderate affinity thus identified. By comparing **4** and **5** with **3** we argued that two of the aromatic rings in **4** mimic the phenyl groups in the Phe^7-Phe^8 subunit of **3**. Furthermore, **5** represents a partly rigidified scaffold for the backbone of the Phe^7-Phe^8-moiety lacking a benzyl group. Combining these two features we prepared a series of piperazinones such as **6** (IC_{50} = 1.5 μM) which is equipotent to **5**, but showed higher selectivity for the NK_1 receptor over the NK_2 or NK_3 receptors.

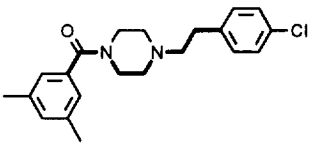
Chart II



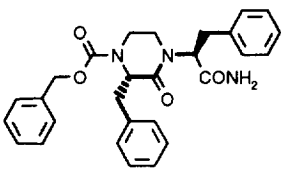
3, SP(6-11)
Gln^6-Phe^7-Phe^8-Gly^9-Leu^{10}-Met^{11}-NH_2



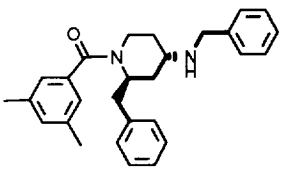
4, Z-Phe-OBn



5



6



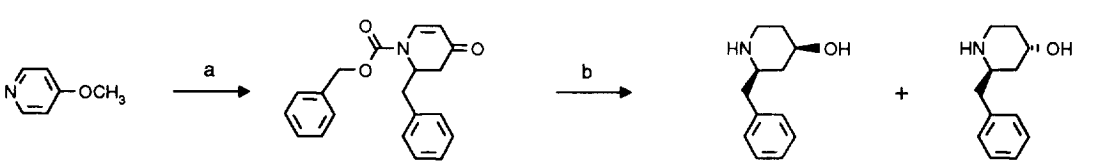
7

One way to avoid the inherent high lipophilicity and low solubility of the piperazinones as **6** was to transpose the lactam nitrogen to the exocyclic position thus gaining a basic center. This led to the 4-amino-piperidine **7** (IC_{50} = 0.22 μM), a lead compound for extensive structure activity studies.[7]

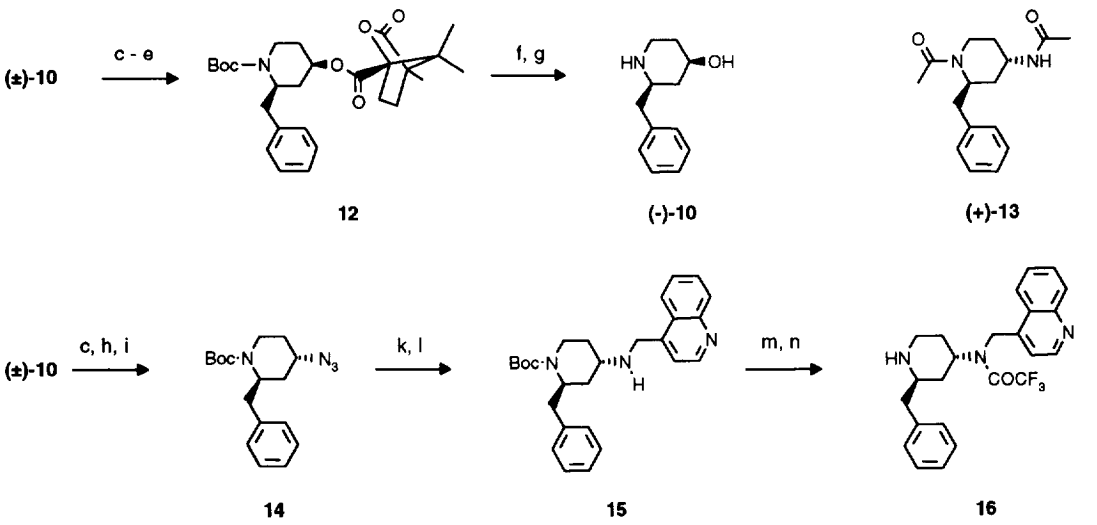
Herein we wish to report on CGP 49823 (**2**, Chart I) and the SAR of substituted 4-amino-piperidines as a novel class of highly potent and selective NK_1 receptor antagonists with good CNS activity after oral administration.

The synthesis of the target compounds started with a *Comins*-reaction[8] in which compound **9** was obtained in 65% yield by treating 4-methoxy-pyridine **8** with benzyl chloroformate and benzylmagnesium chloride in THF at -70 °C (Scheme 1). Sequential hydrogenation afforded a 3.5:1 mixture of the *cis* and *trans* di-substituted piperidines **10** and **11**. Selected target compounds were prepared in enantiomerically pure form *via* chiral intermediate (-)-**10** which was obtained by Boc-protection and subsequent esterification of racemic **10** with (-)-camphanoyl chloride, chromatographic separation of the diastereomers to afford pure enantiomer **12**, subsequent ester hydrolysis and deprotection. The absolute stereochemistry of (-)-**10** was confirmed by comparison of the diacetyl derivative (+)-**13**, derived from (-)-**10**, with that independently prepared from (R)-phenylalanine as starting material.[9] For SAR comparison, all other compounds have been synthesized in racemic form. Racemic **10** was converted to the azide **14** using a standard reaction sequence.[10] Hydrogenation and a two-step reductive amination with quinoline-4-carbaldehyde to **15** followed by protection / deprotection afforded **16** in 28% overall yield starting from **8**.

Scheme 1



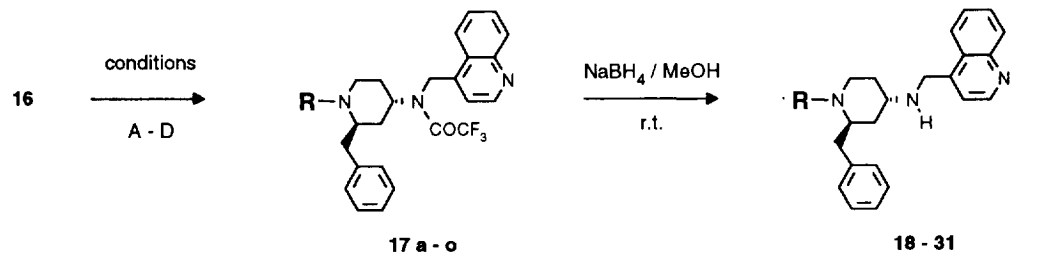
8 **9** **10** (3.5 : 1) **11**



Reagents and conditions: (a) $PhCH_2OCOCl$, $PhCH_2MgCl$, THF, Et_2O, -70 °C; (b) *i:* H_2, Pd/C (10%), MeOH; *ii:* H_2, RaNi, MeOH; *iii:* separation by flash chromatography; (c) $(Boc)_2O$, $CHCl_3$; (d) (-)-camphanoyl chloride, pyridine; (e) separation by flash chromatography; (f) NaOH, MeOH; (g) TFA; (h) MsCl, pyridine; (i) LiN_3, DMF, 80 °C; (k) H_2, Pd/C (10%); (l) *i:* quinoline-4-carbaldehyde, $MgSO_4$, toluene; *ii:* $NaBH_4$, MeOH; (m) $(CF_3CO)_2O$, CH_2Cl_2, NEt_3; (n) HCl, dioxane.

In order to obtain SAR information substituents R were attached at the piperidine nitrogen using derivatization procedures A-D as outlined in Scheme 2. The binding results are summarized in Table 1. IC_{50} values were determined by displacement of ^{3}H-SP from bovine retina membranes.[11]

Scheme 2



Conditions: **A**: RCOCl, NEt_3, CH_2Cl_2; **B**: RCOOH, BOPC, NEt_3; **C**: R-Br, K_2CO_3, DMF, 60 °C; **D**: R-Cl, NEt_3, CH_2Cl_2.

Alkyl as well as sulfonyl and alkanoyl substituents at the piperidine nitrogen gave compounds with only weak affinity towards the NK_1 receptor (entries a - c). Comparing entries d - g reveals that substitution at the benzoyl group is necessary and is best at position 3. Disubstitution further enhances the binding affinity if the aromatic substituents are in 3,5 position and are either methyl, halogen or bistrifluoromethyl (entries i - k), but not phenolic derivatives (entries l - m). Condensed aromatic groups like naphthoyl (entries n - o) do not fit as well to the binding site at the receptor.

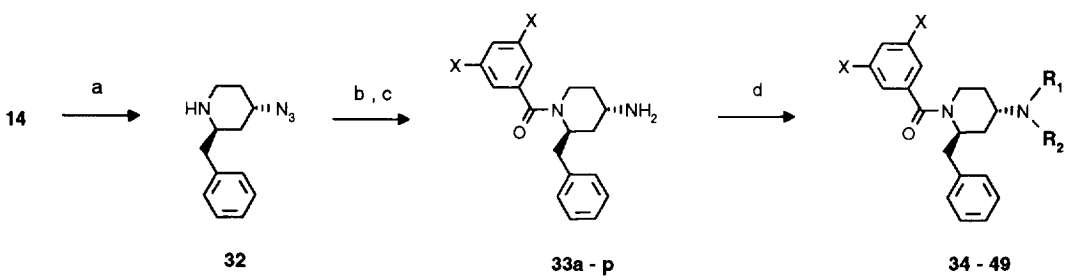
Table 1

Entry	R	conditions*)	compound	IC_{50} [nM][11]
a	3,5-bis(trifluoromethyl)benzyl	D	**18**	880
b	3,5-bistrifluoromethylphenyl-sulfonyl	C	**19**	> 10'000
c	phenyl acetyl	A	**20**	3300
d	benzoyl	A	**21**	1380
e	2-chlorobenzoyl	B	**22**	1040
f	3-chlorobenzoyl	A	**23**	54
g	4-chlorobenzoyl	B	**24**	1370
h	3,5-dichlorobenzoyl	A	**25**	26
i	3,5-dimethylbenzoyl		(+)-**2**[13] **)	12
j	3,5-dibromobenzoyl	A	**26**	24
k	3,5-bis(trifluoromethyl)benzoyl	B	**27**	17
l	3,5-dimethoxybenzoyl	B	**28**	92
m	3,5-dihydroxybenzoyl	B	**29**	520
n	1-naphthoyl	A	**30**	110
o	2-naphthoyl	A	**31**	700

*) see Scheme 2 **) CGP 49823

The substituents at the exocyclic amino function were explored following a reaction sequence outlined in Scheme 3.[12] The results are summarized in Table 2. At least one small substituent at the exocyclic nitrogen is necessary for good *in vitro* activity, although no clear requirements as to the size of the substituent and/or the positioning of functional groups can be read from entries a - f. The distance and/or the bulk of an aromatic group from the amino piperidine moiety seems to be crucial, as is exemplified with entries g - j. Good to excellent binding affinities can also be obtained with an amide or urea functionality, but as these compounds lack a basic nitrogen they are less water soluble (entries k - m). Enhancing the water solubility by introducing oxygen functionalities retains *in vitro* activity (entries n - o), but these compounds suffer from poor bioavailability (*vide infra*). Double substitution at the exocyclic amino group is not favourable (entries p - q).

Scheme 3



32 **33a - p** **34 - 49**

Reagents and conditions: (a) TFA; (b) 3,5-$X_2C_6H_3COCl$, NEt_3, CH_2Cl_2 or 3,5-$X_2C_6H_3COCl$, $NaHCO_3$, toluene, water, 0 °C; (c) H_2, Pd/C (10%), MeOH; (d) ***A***: Ac_2O, NEt_3, CH_2Cl_2; ***B***: *i:* $BrCH_2COOMe$, NEt_3, THF; *ii:* MeOH, NH_3; ***C***: *i:* $BocNHCH_2COOH$, BOPC, NEt_3, CH_2Cl_2; *ii:* TFA; ***D***: $Cl(CH_2)_3NMe_2$, K_2CO_3, CH_3CN, 80 °C; ***E***: *i*PrNCO, toluene, DMAP; ***F***: BnBr, NEt_3, THF; ***G***: *i:* RCHO, $MgSO_4$, toluene; *ii:* $NaBH_4$, MeOH or $NaCNBH_3$, AcOH, MeOH; ***H***: RCOOH, BOPC, NEt_3, CH_2Cl_2; ***I***: $PhCH_2COCl$, $NaHCO_3$, toluene, water, 0 °C.

Table 2

Entry	conditions (see scheme 3)	compound	X	R_1	R_2	IC_{50} [nM][11]
a		**(-)-34**	CF_3	H	H	180
b	*A*	**(+)-35**	CF_3	acetyl	H	19
c	*B*	**(+)-36**[14]	CF_3	carbamoylmethyl	H	10
d	*C*	**(+)-37**	CF_3	2-amino-acetyl	H	62
e	*D*	**38**[15]	CF_3	3-dimethylamino-propyloxycarbonyl	H	11
f	*E*	**(+)-39**	CF_3	isopropylcarbamoyl	H	20
g	*F*	**(+)-40**[13]	CH_3	benzyl	H	220
h	*G*	**41**[13]	CH_3	pyridin-4-ylmethyl	H	210
i	*G*	**42**[13]	CH_3	quinoline-3-ylmethyl	H	30
j	*G*	**43**[13]	CH_3	quinoline-2-ylmethyl	H	19
k	*H*	**44**	Cl	quinoline-4-carbonyl	H	10
l	*I*	**45**	Cl	2-phenyl-acetyl	H	60
m	PhNCO, 100°	**46**	Cl	phenylcarbamoyl	H	72
n	*H*	**(+)-47**	CF_3	2-hydroxy-quinoline-4-carbonyl	H	9
o	2-(3,5-dimethoxy-phenyl)-acetic acid, DCC, THF	**48**	CH_3	2-(3,5-dimethoxy-phenyl)-acetyl	H	12
p	**25**, NaH, DME, MeI	**49**	Cl	quinoline-4-ylmethyl	CH_3	390
q		**17h**	Cl	quinoline-4-ylmethyl	$COCF_3$	600

We then investigated the absolute stereochemistry required for high affinity NK_1 binding. We found that the (2R,4S)-stereoisomer **(+)-2** (CGP 49823, Chart I) is the most potent of the diastereoisomers (Table 3). Hence the stereochemistry at the 2-position does not correspond to the stereochemistry of the Phe^7 benzyl side chain in **3** as was initially anticipated. The remarkably good overlap of a minimal energy conformation with one of CP-96,345 **1**, suggests that this compound binds to the same antagonist binding site of the NK_1 receptor as does **1**. Confirmation was obtained by competitive binding studies of CP-96,345 (IC_{50} = 0.79 nM; N_H = 0.99) with $^3H_2$-CGP 49823.[16] This site in turn is not directly involved in the binding of Substance P[17]. Next, the *in vitro* functional activities, receptor selectivities and oral activities of CGP 49823 along with some of the more interesting compounds and, for comparison purposes, of CP-96,345 were evaluated (Table 3).

Table 3

		IC_{50}	IC_{50}				% Inhib. (2 h)
compound	configuration	PI turnover[a]	NK_1[b]	NK_2[c]	NK_3[d]	NK_1(g)[e]	thumping[f]
(+)-2	2R , 4S	12	13	2790	2650	55	34
(-)-2	2S , 4R	150	130	(5%)	na	690	54[g]
(-)-50[h]	2R , 4R	nt	540	nt	nt	nt	20[i]
(+)-50[h]	2S , 4S	nt	220	nt	nt	nt	nt
42	2R* , 4S *	210	30	(22%)	10'000	70	21
44	2R* , 4S *	24	10	4500	3300	48	66
(+)-47	2R , 4S	nt	9	(28%)	450	10	24
(±)-CP-96,345 (**1**)		9	10	(24%)	na	16	61[j]

[a] Inhibition of substance P induced phosphatidyl inositol turnover in **human** U-373 cells in nM units (see Ref. [18]). [b] ^{3}H-SP radioligand binding, bovine retina in nM units (see Ref. [11]). [c] ^{125}I-NKA radioligand binding, bovine bladder in nM units or % inhibition at 1 μM (see Ref. [19]). [d] ^{125}I-Eledoisin radioligand binding, gerbil cortex in nM units (see Ref. [20]). [e] see Ref. [21]. [f] Inhibition of thumping behaviour in gerbils induced by i.c.v. administration of SP-methyl ester 2 hours after p.o. administration of 30 mg /kg of the compound; values given in % (100% = full inhibition; see Ref [22]). [g] 300 mg /kg p.o.. [h] cis isomer of **2**. [i] 60 mg/kg i.p.. [j] 300 mg/kg p.o.. na = no activity; nt = not tested.

The relevance of the inhibition of the thumping behaviour in gerbils for humans is illustrated by the good correlation of the binding to the NK_1 receptor in gerbils with the inhibition of the PI turnover in **human** cells (see table 3).

In conclusion, the novel 2-benzyl-4-aminopiperidines are highly potent and selective antagonists at the NK1 receptor. The piperidine ring system described herein provides a scaffold for extensive SAR studies. Some of the compounds show central activity after oral administration in antagonizing the effects of Substance P methyl ester.

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(-)-10: oil, ^{1}H-NMR (500 MHz, $CDCl_3$) 7.35 - 7.20 (m, 5H), 3.63 (tt, J=11.5 and 4.4 Hz, 1H), 3.06 (ddd, J=12.5, 4.4 and 2.4 Hz, 1H), 2.78 - 2.71 (m, 2H), 2.69 - 2.62 (m, 1H), 2.54 (td, J=12.5 and 2.4 Hz, 1H), 2.02 (dtd, J=11.5, 4.5 and 2.4 Hz, 1H), 1.93 (ddq, J=12, 4.5 and 2.4 Hz, 1H), 1.45 (b, 2H), 1.38 (qd, J=11.5 and 4.4 Hz, 1H), 1.16 (q, J=11.5 Hz, 1H); $[\alpha]_D^{20}$ = -11.8° (c = 0.5, MeOH). **(+)-13**: m.p. 139° C.; $[\alpha]_D^{25}$ = +20.2° (c = 0.8, MeOH).

(10) Azidolysis to **14** was accompanied by elimination to an unsaturated piperidin derivative (3:1 w/w) according to ^{1}H-NMR. The mixture could only be separated chromatographically after hydrogenolysis.

(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 ^{3}H-Substance P binding sites", in *Substance P - Dublin*, pp 198-199, Skrabanek, P.; Powell, D., Ed.; Boole Press Ltd., Dublin, 1983.

(12) Intermediates **33** can also be prepared according to Ref. [9].

(13) Prepared according to Ref. [9];
(+)-2: m.p.: 143° C.; ^{1}H-NMR (300 MHz, $CDCl_3$) 8.89 (d, J=5 Hz, 1H), 8.16 (d, J=8 Hz, 1H), 8.09 (d, J=8 Hz, 1H), 7.73 (t, J=8 Hz, 1H), 7.60 (t, J=8 Hz, 1H), 7.46 (d, J=5 Hz, 1H), 7.35 - 7.20 (m, 4H), 7.04 - 6.74 (m, 3H), 6.42 (b, 1H), 5.35 - 5.20 (m, 0.4H), 4.89 - 4.75 (m, 0.6H), 4.40 - 4.20 (m, 2H), 4.15 - 4.00 (m, 0.6H), 3.75 - 3.60 (m, 0.4H), 3.30 - 2.90 (m, 3.4H), 2.76 - 2.60 (m, 0.6H), 2.28 (b, 2.4H, minor rotamer), 2.22 (b, 3.6H, major rotamer), 2.1 - 1.2 (m, 5H) ;$[\alpha]_D^{20}$ = +27.8 ± 0.5° (c = 2.08, MeOH).

(14) Dialkylation was also observed (mono : di = 2:1).

(15) The major product resulted from CO_2 insertion.

(16) $^3H_2$-CGP 49823 ((2R,4S)-2-(3,5-Bis-^{3}H-benzyl)-1-(3,5-dimethylbenzoyl)-N-(4-chinolylmethyl)-4-piperidinamin) radioligand binding, bovine retina; CGP 49823: IC_{50} = 1.56 nM; N_H = 1.13)

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