Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 3081–3084

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Dual Neurokinin NK_1/NK_2 Antagonists: *N*-[(*R*,*R*)-(*E*)-1-arylmethyl-3-(2-oxo-azepan-3-yl)carbamoyl]allyl-*N*-methyl-3,5-bis(trifluoromethyl)benzamides and 3-[*N*′-3,5-bis(trifluoromethyl)benzoyl-*N*-arylmethyl-*N*′-methylhydrazino]-*N*-[(*R*)-2-oxo-azepan-3-yl]propionamides

Marc Gerspacher,[a,*] Luigi La Vecchia,[a] Robert Mah,[a] Andreas von Sprecher,[a] Gary P. Anderson,[b] Natarajan Subramanian,[a] Kathleen Hauser,[a] Heinrich Bammerlin,[a] Sabine Kimmel,[a] Viviane Pawelzik,[a] Karin Ryffel[a] and Howard A. Ball[a]

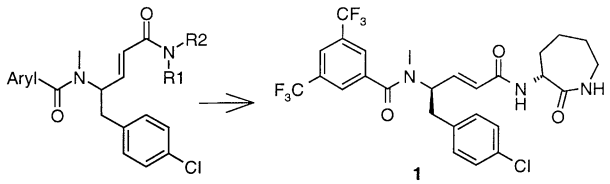
[a]*Pharma Research, Novartis Pharma AG, CH-4002 Basel, Switzerland*
[b]*Department of Pharmacology, University of Melbourne, Parkville, 3052 VIC, Australia*

Received 19 July 2001; accepted 19 September 2001

Abstract—Based on the structure of *N*-[(*R,R*)-(*E*)-1-(4-chlorobenzyl)-3-(2-oxoazepan-3-yl)carbamoyl]allyl-*N*-methyl-3,5-bis(trifluoromethyl)benzamide (**1**), attempts to improve the NK_2 affinity have resulted in the discovery of *N*-[(*R,R*)-(*E*)-1-(3,4-dichlorobenzyl)-3-(2-oxoazepan-3-yl)carbamoyl]allyl-*N*-methyl-3,5-bis(trifluoromethyl)benzamide (**9**, **DNK333**) exhibiting a 5-fold improved affinity to the NK_2 receptor in comparison to **1**. Simplification of the structure via elimination of a chiral centre led to 3-[*N*′-3,5-bis(trifluoromethyl)benzoyl-*N*-(3,4-dichlorobenzyl)-*N*′-methylhydrazino]-*N*-[(*R*)-2-oxo-azepan-3-yl]propionamide (**22**), a potent and fairly balanced NK_1/NK_2 antagonist.

Neurokinins, also known as tachykinins, are a family of small peptides and are widely distributed throughout the central and peripheral nervous system where they act as neurotransmitters and neuromodulators. Neurokinins exhibit their effects via 7-transmembrane G-protein-coupled receptors (NK_1, NK_2 and NK_3 receptors). Neurokinins are proposed to be involved in a number of pathological conditions (pain, arthritis, migraine, emesis, cancer, anxiety, depression, schizophrenia, asthma) and NK receptor antagonists have been proposed to have potential clinical benefits.[1] There is evidence that neurokinins play an important role in airway disease induction and progression via the activation of NK_1 and NK_2 receptors.[2] A number of studies suggest that neurokinin receptor antagonists, especially dual NK_1/NK_2 antagonists, may represent a new treatment option for asthma and other airway diseases, particularly since lung tissue from asthma patients has been shown to overexpress NK_1 and NK_2 receptors.[3] As a consequence, many pharmaceutical companies have shifted their efforts aiming at selective NK antagonists towards the discovery of dual NK_1/NK_2 antagonists.[4]

Recently we have reported the discovery of an orally active NK_1/NK_2 antagonist. *N*-[(*R,R*)-(*E*)-1-(4-chlorobenzyl)-3-(2-oxo-azepan-3-yl)carbamoyl]allyl-*N*-methyl-3,5-bis(trifluoromethyl)benzamide (**1**)[5] is derived from a series of *N*-[1-(4-chlorobenzyl)-3-carbamoyl]allyl-*N*-methyl-benzamides (Fig. 1).



1

Figure 1. *N*-[1-(4-chlorobenzyl)-3-carbamoyl]allyl-*N*-methyl-benzamides.

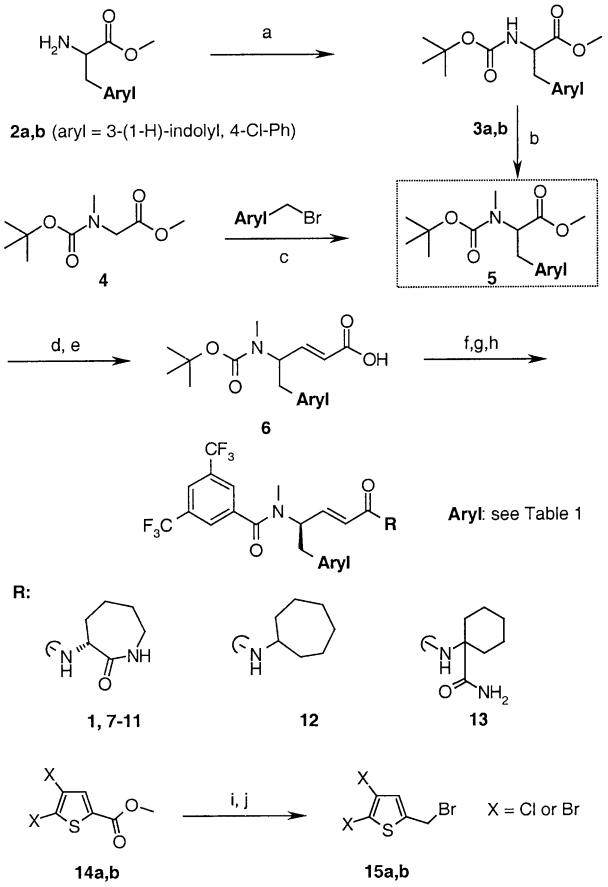
*Corresponding author. Tel.: +41-61-696-7636; fax: +41-61-696-5966; e-mail: marc.gerspacher@pharma.novartis.com

0960-894X/01/$ - see front matter
PII: S0960-894X(01)00631-X

Compound **1** exhibits a highly potent affinity to the NK_1 receptor (inhibition of ^{3}H-sar^9-substance P binding to bovine retinal membranes: $IC_{50} = 0.5$ nM) and a good affinity to the NK_2 receptor (inhibition of ^{125}I-NKA binding to human NK_2–CHO cells: $IC_{50} = 24$ nM). In addition to the potent binding affinities, **1** also shows oral activity in guinea pig bronchoconstriction.[5]

Although **1** in terms of NK_1/NK_2 antagonistic activity is very promising, we wanted to explore possible ways to improve the NK_2 affinity and to simplify the structure (elimination of chiral centres). In order to explore the effect of various benzyl substituents on the binding properties, compounds were prepared as outlined in Scheme 1. Starting from the corresponding amino acid methylesters **2a,b**, followed by BOC-protection and *N*-methylation (methylation of the indole-nitrogen also occurs in this step) the *N*-BOC-*N*-methylaryl-alanine derivatives (**5**) were prepared. For compounds where the amino acid-methylesters are not commercially available, alkylation of *N*-BOC-sarcosine methylester[6] using commercially available aryl-methyl bromides and **15a,b**[7] were used to prepare **5**.

Reduction of the esters to the aldehydes followed by chain elongation led to the α,β-unsaturated acids **6**.



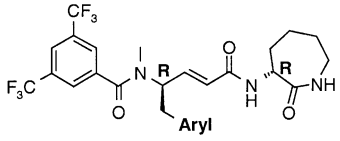
Scheme 1. Preparation of compounds **1**, **7**–**13**. (a) $(BOC)_2O$, Et_3N; (b) MeI, Ag_2CO_3, DMF; (c) LDA, THF, −78 °C to rt; (d) DIBAH, tol, −78 °C; (e) *n*-BuLi, trimethylsilyl-P,P-diethylphos-phonoacetate, then citric acid; (f) R-NH_2, EDC, DMAP, CH_2Cl_2; (g) TFA, CH_2Cl_2; (h) 3,5-bis(trifluoromethyl)benzoyl chloride; Et_3N, CH_2Cl_2, chromatography; (i) DIBAH, tol; (j) PBr_3, CH_2Cl_2.

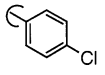
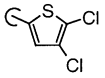
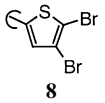
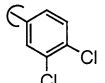
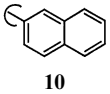
Condensation with enantiomerically pure D-α-amino-ε-caprolactam[5,8] in the presence of EDC, removal of the BOC protecting group and subsequent *N*-acylation, followed by simple chromatography on silica gel to remove the undesired diastereoisomer (diastereoisomers are easily separable in all cases) led to the final products as enantiomerically pure *R,R*-compounds.[9]

Compounds containing 4-chlorophenyl (**1**), dichlorothienyl (**7**), 3,4-dichlorophenyl (**9**), 2-naphthyl (**10**), and 3-(1-methyl)indolyl (**11**) substituents exhibit binding affinities to the NK_1 receptor in the low nanomolar region, whereas the dibromothiophene containing compound **8** has a somewhat decreased binding affinity to the NK_1 receptor. NK_2 binding affinities stay between 17–60 nM, except for compound **9** where the additional chlorine leads to a 5 times more potent affinity to the NK_2 receptor in comparison with the monochloro-derivative **1**. Both the dichlorophenyl- and the dibromothiophene derivatives **9** and **8** exhibit balanced binding affinities to both receptors (Table 1).

We also aimed at the simplification of the structure. First (in a limited effort), ways to eliminate the chiral centre in the caprolactam residue were explored. Compounds **12** and **13** were prepared by reacting **6** (aryl = 4-Cl–Ph)

Table 1. In vitro binding affinities of compounds **1**, **7**–**11** to NK_1- and NK_2-receptors



Aryl compound no.	NK_1 binding[10] IC_{50} (nM)[a]	NK_2 binding[11] IC_{50} (nM)[a]
 **1**	0.5	24
 **7**	3.6	17
 **8**	20	26
 **9 (DNK333)**[12]	4.8	5.5
 **10**	1.1	60
 **11**	0.5	24

[a]Values are means of three experiments.

with the corresponding amines instead of D-α-amino-ε-caprolactam as outlined in Scheme 1.

As can be seen from the data shown in Table 2, removal/replacement of the heteroatoms from the 7-membered ring leads to a significant decrease of binding affinities to both receptors. Replacement of the chiral amino-caprolactam with an amino-cyclohexylcarboxamide residue leads to a compound that exhibits only a minor decrease of binding affinities.

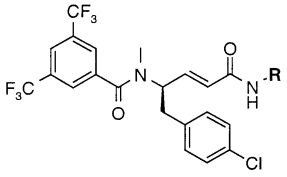
Another way to simplify the structure is the elimination of the chiral centre in the backbone of the compounds. Replacing the chiral carbon atom with a nitrogen leads to hydrazine derivatives that can be prepared as outlined in Scheme 2.

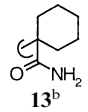
Condensation of the commercially available 3,5-bis(trifluoromethyl)benzoyl hydrazide with the corresponding commercially available aldehydes followed by *N*-methylation and reduction led to hydrazides **19a–c**. Reaction of the latter compounds with 3-oxopropionic acid ethylester[13] followed by another reduction led to the esters **20a–c**. Subsequent saponification and reaction with D-α-amino-ε-caprolactam in the presence of EDC yielded enantiopure hydrazine-derivatives **21–23**. The final compounds can be prepared in overall yields of up to 43%.[14]

Replacement of the chiral carbon atom with a nitrogen did not have a dramatic impact on the binding affinities of the resulting hydrazine derivatives to the NK_1 and NK_2 receptors. The 3,4-dichloro-benzyl-derivative **22** exhibiting an IC_{50} value of 1.4 nM (NK_1) and an IC_{50} value of 5.5 nM (NK_2) is as expected the most potent and balanced dual NK_1/NK_2 antagonist from this small series of hydrazine analogues (Table 3).

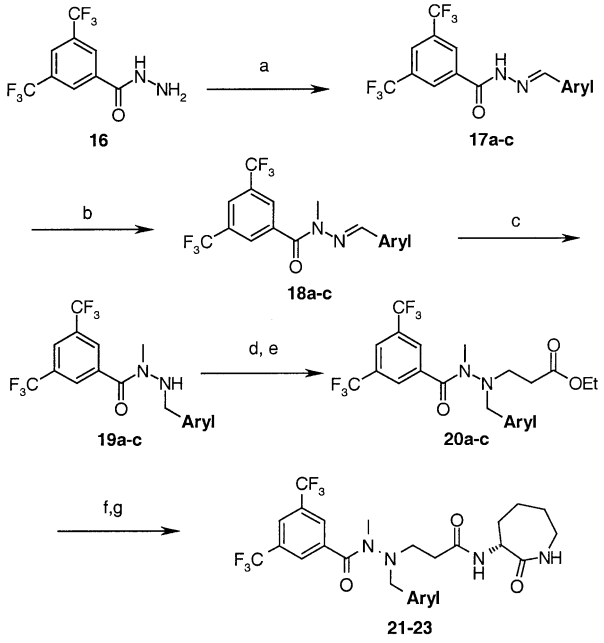
Based on the structure of *N*-[(*R,R*)-(*E*)-1-(4-chlorobenzyl)-3-(2-oxoazepan-3-yl)carbamoyl]allyl-*N*-methyl-3,5-bis(trifluoromethyl)benzamide (**1**), attempts to improve the NK_2 affinity have resulted in the discovery of the balanced NK_1/ NK_2 antagonist *N*-[(*R,R*)-(*E*)-1-(3,4-dichlorobenzyl)-3-(2-oxoazepan-3-yl)carbamoyl]allyl-*N*-methyl-3,5-bis(trifluoromethyl)benzamide (**9**) exhibiting a 5 times improved affinity to the NK_2 receptor in

Table 2. In vitro binding affinities of compounds **1**, **12**, **13** to NK_1- and NK_2-receptors



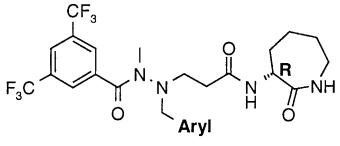
R Compound no.	NK_1 binding[10] IC_{50} (nM)[a]	NK_2 binding[11] IC_{50} (nM)[a]
 **1**	0.5	24
 **12**[b]	12	203
 **13**[b]	1	66

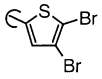
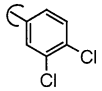
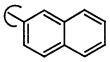
[a]Values are means of three experiments.
[b]**12** and **13** are racemic compounds.



Scheme 2. Preparation of compounds **21–23**. (a) 3,4-dichlorobenzaldehyde, EtOH, heat; (b) MeI, K_2CO_3, acetone, heat; (c) $NaCNBH_3$, H^+; (d) 3-oxopropionic acid ethylester, EtOH, HOAc; (e) $NaCNBH_3$, H^+; (f) NaOH, THF, MeOH, H_2O; (g) D-α-amino-ε-caprolactam, EDC, DMAP, CH_2Cl_2.

Table 3. In vitro binding affinities of compounds **21–23** to NK_1- and NK_2-receptors



Aryl compound no.	NK_1 binding[10] IC_{50} (nM)[a]	NK_2 binding[11] IC_{50} (nM)[a]
 **21**	18	19.5
 **22**	1.4	5.5
 **23**	6.4	55

[a]Values are means of three experiments.

comparison to **1**. In addition to this, removal of the chiral centre in the backbone of **9** resulted in the discovery of the potent dual NK_1/NK_2 antagonist 3-[*N*′-3,5-bis(trifluoromethyl)benzoyl-*N*-(3,4-dichlorobenzyl)-*N*′-methylhydrazino]-*N*-[(*R*)-2-oxoazepan-3-yl]propionamide (**22**) exhibiting balanced affinity for both receptors.

References and Notes

1. (a) Longmore, J.; Swain, C. J.; Hill, R. G. *Drug News Perspec.* **1995**, *8*, 5. (b) Kucharczyk, N. *Exp. Opin. Invest. Drugs* **1995**, *4*, 299. (c) Elliott, J.; Seward, E. M. *Exp. Opin. Ther. Pat.* **1997**, *7*, 43. (d) Longmore, J.; Hill, R. G.; Hargreaves, R. J. *Can. J. Phys. Pharmacol.* **1997**, *75*, 612. (e) von Sprecher, A.; Gerspacher, M.; Anderson, G. P. *Idrugs* **1998**, *1*, 73.

2. (a) Ford-Hutchinson, A. W.; Rodger, I. W.; Jones, T. R. *Drug News Perspec.* **1992**, *5*, 542. (b) Geppetti, P.; Bertrand, C.; Ricciardolo, F. M. L.; Nadel, J. A. *Can. J. Physiol. Pharmacol.* **1995**, *7*, 843. (c) Advenier, C.; Lagente, V.; Boichot, E. *Eur. Respir. J.* **1997**, *10*, 1892. (d) Chapman, R. W.; Hey, J. A.; McLeod, R.; Minnicozzi, M.; Rizzo, Ch. *Drug News Perspect.* **1998**, *11*, 480.

3. (a) Murai, M.; Morimoto, H.; Maeda, Y.; Kiyotoh, S.; Nishikawa, M.; Fujii, T. *J. Pharmacol. Exp. Ther.* **1992**, *262*, 403. (b) Joos, G. F.; Van Schoor, J.; Kips, J. C.; Pauwels, R. A. *Am. J. Respir. Crit. Care Med.* **1996**, *153*, 1781.

4. Gerspacher, M.; von Sprecher, A. *Drugs Future* **1999**, *24*, 883.

5. Gerspacher, M.; von Sprecher, A.; Mah, R.; Anderson, G. P.; Bertrand, C.; Subramanian, N.; Hauser, K.; Ball, H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1467.

6. Bonora, G. A.; Toniolo, C. *Gazz. Chim. Ital.* **1977**, *107*, 381.

7. **15a,b** were prepared from the corresponding methylesters (Scheme 1). 2,3-dibromothiophene-5-carboxylic acid methylester is commercially available, whereas 2,3-dichlorothiophene-5-carboxylic acid methylester can be prepared as described by Stanetty, P.; Puschantz, E. *Monatsh. Chem.* **1987**, *120*, 65.

8. Rezler, E. M.; Fenton, R. R.; Esdale, W. J.; McKeage, M. J.; Russell, P. J.; Hambley, T. W. *J. Med. Chem.* **1997**, *40*, 3508.

9. The assignment of the stereochemistry of the backbone chiral centre (*R* or *S*) was done on the basis of chromatographical behaviour on silica gel and NK receptor binding profile of the two diastereoisomers in comparison with **1**.[5] Stereoselective synthesis of the *R,R*-isomers of compounds **1**,[5] **10** and **11** starting from the corresponding D-amino acids confirmed the assignment of the absolute stereochemistry.

10. For experimental details, see: Bittiger H., Heid J. In *Substance P*; Skrabanek, P., Powell, D., Eds.; Boole: Dublin, 1983; p 198.

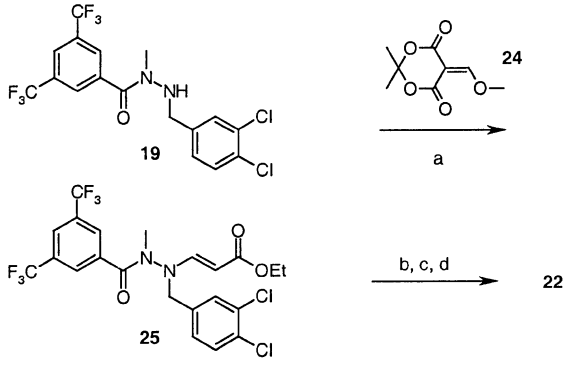
11. Inhibition of [^{125}I]-NKA binding to transfected chinese hamster ovary cells (CHO cells) expressing recombinant human neurokinin 2 receptors: The assay was performed in 96 well plates (Nunclon) containing 200 μL 20 mM HEPES buffer, pH 7.4 containing 2 mM $MnSO_4$ and 6 mM $MgCl_2$, 3×10^5 h NK_2 CHO cells, 0.05 nM [^{125}I]-NKA (2200 Ci mmol^{-1}) and various drug concentrations. Non-specific binding was estimated in the presence of 50 nM NKA. The mixture was incubated for 20 min at room temperature after which the unbound ligand was removed by rapid filtration and washed four times with ice cold Tricine buffer. Filter bound radioactivity was counted in Microscint 20 in a scintillation counter. All samples were measured in triplicate. Culture conditions and cell isolation for h NK_2 CHO cells: Subramanian, N.; Ruesch, C.; Bertrand, C. *Biochem. Biophys. Res. Comm.* **1994**, *200*, 1512.

12. Detailed pharmacology data of **DNK333** will be published in due course.

Analytical data, **9** (**DNK333**): mp 127–129 °C. $[\alpha]_D^{20} = +39.9°$ (*c* 0.94, EtOH). ee value = 99.3 (R_t = 21.64 min, Chiralcel OJ, hexane/isopropanol = 85:15 + 0.1% TFA, flow rate 1 mL/min). ^{1}H NMR (400 MHz, δ, DMSO, +150 °C) 8.02 (s, 1H); 7.65 (s, 2H); 7.55 (s,b, 1H); 7.44 (m, 2H); 7.28 (b, 1H); 7.23 (b, 1H); 6.71 (dd, 1H); 6.32 (dd, 1H); 5.03 (b, 1H); 4.51 (m, 1H); 3.18 (m, 2H); 3.05 (m, 2H); 2.82 (s, 3H); 1.96 (m, 2H); 1.75 (m, 2H); 1.45 (m, 1H); 1.3 (m, 1H). Anal. calcd for $C_{27}H_{26}ClF_6N_3O_3$: C: 51.94, H: 4.04, N: 6.78. Found: C: 51.66, H: 4.05, N: 6.73. IR (CH_2Cl_2, cm^{-1}): 1668 (–CH=CH–C=O), 1643 (Ph–C=O), 1286 (Ph–CF_3), 975 (C–H, trans disubst. C=C).

13. Sato, M.; Yoneda, N.; Katagiri, N.; Watanabe, H. *Synthesis* **1986**, 672.

14. For the preparation of larger quantities of the hydrazine derivative **22**, it proved possible to directly use the Meldrum's acid derivative **24** in the enamine-formation step thus avoiding the preparation of the unstable 3-oxopropionic acid ethylester.[13] In addition, in the enamine reductions, the triethylsilane/TFA-system[15] was used instead of sodium cyanoborohydride:



(a) EtOH, HOAc, heat (b) Et_3SiH, TFA; (c) NaOH, THF, MeOH, H_2O; (d) D-α-amino-ε-caprolactam, EDC, DMAP, CH_2Cl_2

15. Wu, P.-L.; Peng, S. Y.; Magrath, J. *Synthesis* **1995**, 435.