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Linear Amides as Substance P Antagonists

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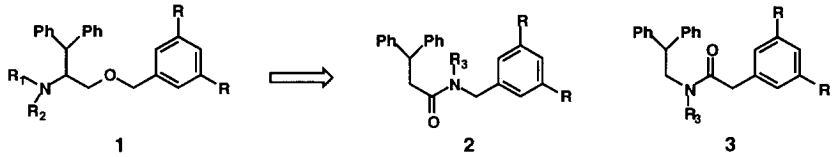
Abstract: In the present study we demonstrate that an amide linking group provides an excellent template for the positioning of a benzhydryl group and a suitably functionalized aromatic ring in an orientation which allows for high affinity binding to the hNK_1 receptor. Copyright © 1996 Elsevier Science Ltd

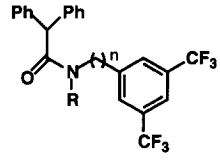
In a recent publication we described a novel series of human NK_1 (hNK_1) receptor antagonists **1**, derived from diphenylalanine.[1] The elements essential for high affinity binding were two suitably substituted aromatic domains separated by an ether oxygen, which functions as an H-bond acceptor. The amine substituent allows for further substitution but can be replaced with oxygen and the affinity is maintained.[1]



On this basis, we reasoned that an amide group may act as the H-bond acceptor between suitably substituted aromatic rings leading us to consider targets such as **2** and **3**. These compounds would not only have the advantage of rapid and easy synthesis from readily available starting materials but would also be achiral.

A series of four amides was synthesised from 2,2-diphenylethanoic acid and the appropriate amine under standard water-soluble carbodiimide coupling conditions.[2] Each amide was then methylated[3] to give the corresponding *N*-methyl derivative. Examination of the NH amides by ^1H NMR showed exclusive adoption of the *trans* geometrical isomer as expected. ^1H NMR studies on the *N*-methyl derivatives showed the presence of both the *trans* and *cis* rotamers in the ratio of approximately 7:3 respectively. The energy of rotation was however relatively low.[4]

It can be seen in the N-H series (**4a**-**7a**, Table 1) that a progressive increase in hNK_1 affinity was observed as the length of the connecting chain was increased from three to four atoms and again from four to five, which was optimal (**6a**, IC_{50}=46 nM). Even though the compounds exist as the *trans* rotamers, presumably as the length of the connecting chain increases the aromatic rings can adopt an orientation which will allow π–π interaction.[5] A decrease in affinity was observed as the connectivity was extended to six atoms, when increased flexibility begins to negate the π–π interaction. *N*-Methylation of these derivatives consistently gave an improvement in hNK_1 affinity, presumably due to the increase in population of the *cis* amide conformer. It is interesting to note that in this series the five atom spacer is again optimal for hNK_1 affinity (**6b**, IC_{50}=14 nM).

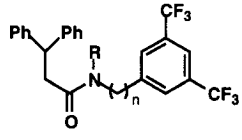


Compound*	n	Connectivity	$hNK_1(IC_{50}/nM)^6$ R = H	R =Me
4a/b	0	3	6561 ± 307	301 ± 171
5a/b	1	4	526 ± 235	47 ± 41
6a/b	2	5	46 ± 16	14 ± 5
7a/b	3	6	593 ± 252	323 ± 154

Table 1

*a, R=H; b, R=Me.

The homologated analogues (**8-11**) were prepared in a similar fashion from 3,3-diphenylpropionic acid and the same series of amines (Table 2). These analogues showed a similar pattern of affinity for the hNK_1 receptor but with compound **10a** (possessing the connectivity of six atoms) having the highest affinity (IC_{50}=112 nM). Presumably in this series, with the extra methylene spacer between the benzhydryl group and the amide, the connectivity has to increase in order to maintain the favorable interaction between the aromatic binding domains. *N*-Methylation increased the affinity of all the compounds providing the high affinity hNK_1 antagonist **10b**. (IC_{50}=10 nM).

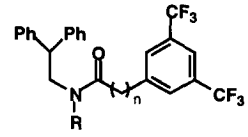


Compound*	n	Connectivity	$hNK_1(IC_{50}/nM)^6$ R = H	R = Me
8a/b	0	4	3005 ± 1787	121 ± 59
9a/b	1	5	235 ± 85	56 ± 5
10a/b	2	6	112 ± 56	10 ± 3
11a/b	3	7	620 ± 242	304 ± 109

Table 2

*a, R=H; b, R=Me

Reversal of the amide linking group was achieved by coupling 2,2-diphenylethylamine with a series of acids to give compounds **12-14** (Table 3). These reverse amides had reduced affinity at the hNK_1 receptor when compared with the corresponding derivatives in the original series, which may be due to the H-bond acceptor now not being in the optimal position. Methylation led to only a modest increase in affinity.

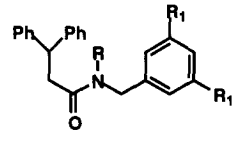


			$hNK_1(IC_{50}$ /nM)[6]	
Compound*	n	Connectivity	R = H	R = Me
12a/b	0	4	3917 ± 1990	297 ± 32
13a/b	1	5	378 ± 170	114 ± 35
14a/b	2	6	42% at 1μM	50% at 1μM

Table 3

***a**, R=H; **b**, R=Me.

Investigation of aromatic substitution in the homologated amide series showed that affinity was retained when replacing the 3,5-bistrifluoromethyl substituents with 3,5-dichloro but slightly reduced by the introduction of 3,5-dimethoxy substituents on the aromatic ring (Table 4).



			$hNK_1(IC_{50}$ /nM)[6]
Compound	Aromatic substitution R_1	R = H	R = Me
15a/b	MeO	2235 ± 1148	226 ± 108
16a/b	Cl	226 ± 108	45 ± 41
9a/b	CF_3	235 ± 85	56 ± 5

Table 4

***a**, R=H; **b**, R=Me.

Conclusion:

Two series of linear amides have been synthesised and it was demonstrated that an amide moiety provides an excellent linking group between two appropriately substituted aromatic rings to achieve high affinity binding to the hNK_1 receptor. The amides further reinforce the proposal that a basic amino group is not required for high affinity binding.[1] The compounds described are achiral and can be prepared in two simple steps from readily available starting materials.

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References and Notes.

1.Williams, B.J.; Teall, M.; McKenna, J.; Harrison, T.; Swain, C.J.; Cascieri, M.A.; Sadowski, S.; Strader, C.; Baker, R. *BioMed. Chem. Lett.* **1994**, *4*, 1903.

2.The amine (5 mmol) was stirred overnight with the acid (10 mmol), carbodiimide (10 mmol), hydroxybenzotriazole (10 mmol) and triethylamine (20 mmol) in dichloromethane (50 mL). After aqueous work up and sequential washing with HCl, brine and water, the crude concentrate was recrystallized from hexane/ethyl acetate.

3.The amine (2.2 mmol) in dimethylformamide (15 mL) was treated with NaH (4.4 mmol) for 30 minutes before the addition of methyl iodide (11 mmol). After 18 hours the reaction mixture was partitioned between water and ethyl acetate, the separated organic phase washed with water, dried ($MgSO_4$) and evaporated to dryness. The product was purified by flash silica chromatography using hexane/ethyl acetate mixtures.

4.The energy barrier to rotation calculated from ^1H NMR was approximately 17.6 kcal/mol, for method see: Smith, R.J.; Williams, D.H.; James, K. *J. Chem. Soc. Chem. Commun.* **1989**, 682.

5.Swain, C.J.; Seward, E.M.; Cascieri, M.A.; Fong, T.M.; Herbert, R.; MacIntyre, D.E.; Merchant, K.J.; Owen, S.N.; Owens, A.P.; Sabin, V.; Teall, M.; VanNiel, M.B.; Williams, B.J.; Sadowski, S.; Strader, C.; Ball, R.G. and Baker, R. *J. Med. Chem.* **1995**, 38.

6.The affinities of the compounds for the hNK_1 receptor were determined by displacement of [^{125}I] Substance P from hNK_1 receptor in CHO cells (n=3 for all compounds unless stated; values quoted are mean IC_{50} values ± SEM): see (i) Cascieri, M.A.; Ber, E.; Fong, T.M.; Sadowski, S.; Bansal, A.; Swain, C.J.; Seward, E.; Frances, B.; Burns, D.; Strader, C.D. *Mol. Pharm.* **1992**, *42*, 458. (ii) Fong, T.M.; Anderson, S.A.; Yuh, H.; Huang, R.R.C.; Strader, C.D. *Mol. Pharm.* **1992**, *41*, 24.

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