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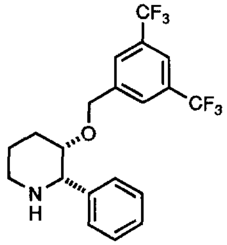
Piperidine-Ether Based hNK$_1$ Antagonists 2: Investigation of the Effect of N-Substitution

T. Harrison*, A.P. Owens, B. J. Williams, C. J. Swain, R. Baker, P. H. Hutson§, S. Sadowski$ and M. A. Cascieri$,

Department of Medicinal Chemistry , §Department of Biochemistry , Neuroscience Research Centre, Merck Sharp and Dohme Research Laboratories, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, U.K.
$Department of Molecular Pharmacology and Biochemistry, Merck Research Laboratories, Rahway, New Jersey 07065

Abstract: The effect of nitrogen substitution on the binding affinity of the piperidine-ether substance P antagonist L-733,060 for the hNK$_1$ receptor and L-type Ca^{2+} channel is discussed.

A recent report from these laboratories has described the synthesis of a series of piperidine-ether based human NK$_1$ (hNK$_1$) antagonists (eg L-733,060)[1]. Although L-733,060 (hNK$_1$ IC_{50} 0.87nM) shows high affinity for the hNK$_1$ receptor and excellent selectivity with respect to the other neurokinin receptors (hNK$_2$, hNK$_3$, $IC_{50} > 1000$nM) it also shows modest affinity for the L-type Ca^{2+} channel (inhibition of [^{3}H] diltiazem binding in rabbit skeletal muscle, $IC_{50} = 0.76\mu M$)[2]. Binding at the L-type Ca^{2+} channel has been observed in several other series of hNK$_1$ antagonists which contain a basic amino group[3,4], and it has been suggested that calcium channel blockade is responsible for the adverse cardiovascular effects of the quinuclidine-based hNK$_1$ antagonists such as CP 96,345[3].



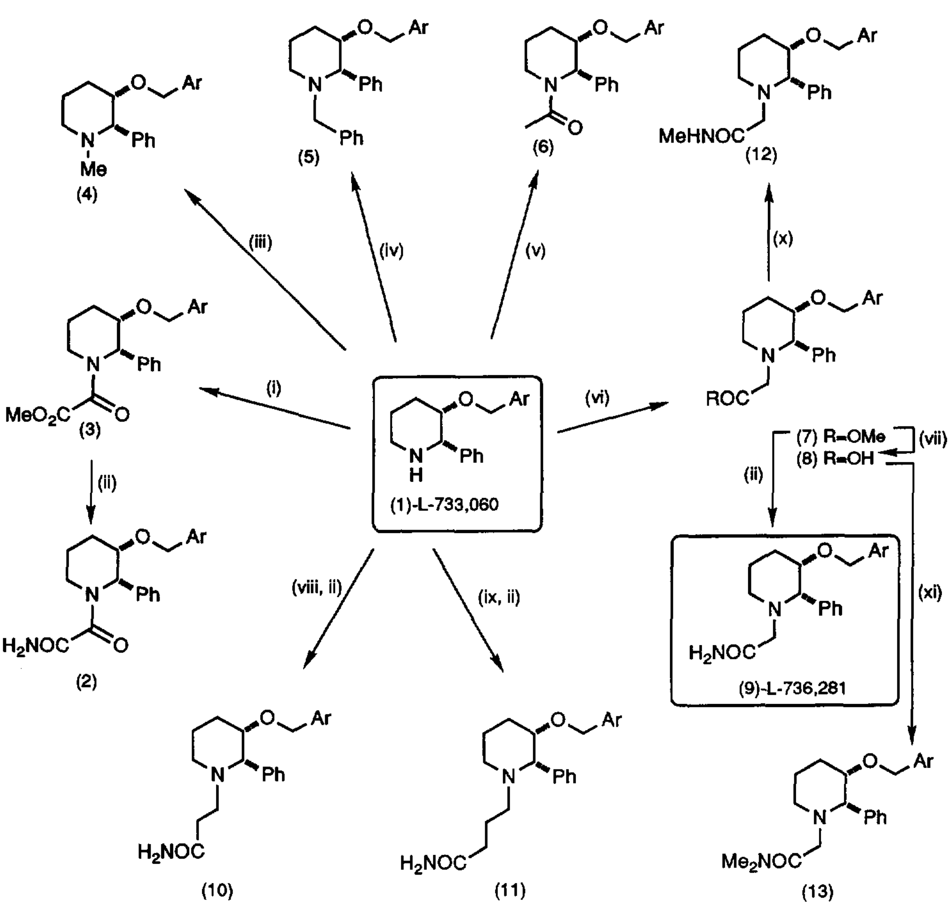
L-733,060

We have recently shown in the acyclic benzhydryl amino-ether series of hNK$_1$ antagonists that substitution on nitrogen with electron-withdrawing polar substituents leads to an *increase* in hNK$_1$ affinity and a dramatic *decrease* in binding at the L-type Ca^{2+} channel[4]. In this communication we describe the effects of N-substitution in the piperidine ether series and show that a similar strategy can be used to reduce Ca^{2+} activity without compromising affinity at the hNK$_1$ receptor.

The synthesis of a range of N-alkyl, acyl and substituted alkyl derivatives of L-733,060 is shown in Scheme 1. The alkyl substituted piperidines were prepared from L-733,060[1] by reductive alkylation (**4**) or by reaction with the appropriate alkyl halide (**5**, **7**, **11**) or with methyl acrylate (**10**) followed by functional group modification (**8**, **9**, **12**, **13**). The acyl analogues (**2**, **3**, **6**) were prepared by reaction of L-733,060 with the appropriate acid chloride. The affinities of the various derivatives for the hNK$_1$ receptor are summarised in Table 1.

It can be seen that although simple alkyl (eg **4, 5**) and acyl (**6**) substitution leads to a decrease in binding affinity, the introduction of polar alkyl substituents (eg L-736,281) is well tolerated. Furthermore, binding affinity at the Ca^{2+} channel is all but abolished, in line with the decreased pK_a of the piperidine nitrogen (L-733,060, pK_a=8.3, L-736,281, pK_a=5.4,)[6]. Saponification of (**7**) provides the amino-acid (**8**) which shows much reduced affinity at the hNK_1 receptor compared to either the ester or the amide. The substitution of the methylene spacer (in **7** and L-736,281) for a carbonyl group leads to the keto ester (**3**) and the keto-amide (**2**) respectively which again show much reduced affinity at the hNK_1 receptor. The possibility that this reduction in affinity is as a result of a conformational change in the piperidine ring induced by $A^{1,3}$ strain[7] is currently being investigated.

Scheme 1



Reagents: (i) MeO_2CCOCl, Et_3N, CH_2Cl_2; (ii) NH_3, EtOH; (iii) HCHO, $NaCNBH_3$, MeOH, AcOH; (iv) $PhCH_2Br$, K_2CO_3, DMF; (v) AcCl, pyridine, CH_2Cl_2; (vi) $BrCH_2CO_2Me$, K_2CO_3, DMF; (vii) KOH, MeOH; (viii) $CH_2{=}CHCO_2Me$ (neat); (ix) $Br(CH_2)_3CO_2Me$, K_2CO_3, DMF; (x) $MeNH_2$, MeOH; (xi) 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide HCl, hydroxybenzotriazole, Me_2NH, DMF.

Compound	hNK$_1$ (IC$_{50}$/nM)[5,11]	Ca^{2+} binding[2,10]
1 (L-733.060)	0.87 ± 0.51	IC$_{50}$ 760nM
2	25 ± 7	0% @ 5μM
3	68 ± 27	0% @ 5μM
4	14 ± 4	IC$_{50}$ 720nM
5	110 ± 66	IC$_{50}$ 4.1μM
6	35 ± 18	0% @ 5μM
7	2.8 ± 1.8	IC$_{50}$ 26μM
8	85 ± 13	7% @ 5μM
9 (L-736,281)	1.3 ± 0.5	16% @ 30μM
10	1.8 ± 0.4	98% @ 5μM
11	2.7 ± 0.2	98% @ 5μM
12	0.63 ± 0.05	0% @ 5μM
13	0.3 ± 0.07	0% @ 5μM

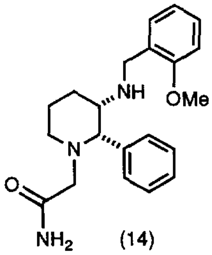
Table 1

Having confirmed that in the piperidine series we could reduce binding affinity at the L-type Ca^{2+} channel whilst retaining high affinity at the hNK$_1$ receptor we next sought to investigate the effect of increasing the length of the methylene spacer between the piperidine nitrogen and the carboxamido group in L-736,281. Accordingly, the homologated amides (**10**) and (**11**) were prepared as shown in Scheme 1. The binding data is summarised in Table 1.

It can be seen that homologation of the amide in L-736,281 by one or two methylene units has minimal effect on the binding affinity. Importantly however, as the length of the tether is increased there is a marked increase in Ca^{2+} channel binding, in line with the increased pK$_a$ of the piperidine nitrogen. (L-736,281, pK$_a$=5.4, **10**, pK$_a$=6.5)[6]. Thus in this series of piperidine derivatives the one carbon spacer would appear to be optimal for high-affinity binding at the hNK$_1$ receptor and low affinity binding at the L-type Ca^{2+} channel.

We were also interested in establishing whether the carboxamido function in (9) was functioning as a H-bond donor by the preparation of the corresponding N-methyl and N,N-dimethyl analogues (12) and (13). (Scheme 1). It can be seen from Table 1 that there is no decrease in hNK$_1$ binding affinity as the H-bonding capability of the amide is removed. Clearly however, in each of these derivatives the amide remains as a powerful H-bond acceptor.

It is interesting to compare the binding affinity of L-736,281 with that of (**14**), an analogous compound from the piperidine amine series[8]. Whereas in the piperidine ether series the incorporation of electron-withdrawing substituents on the piperidine nitrogen can be used to modulate the basicity of the nitrogen without affecting hNK$_1$ binding affinity, in the piperidine amine series binding affinity at the hNK$_1$ receptor is severely compromised ((±)-**14**: hNK$_1$ IC$_{50}$ 227nM; cf. CP-99,994, IC$_{50}$ 0.6nM)[9].



(14)

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References and Notes

1. Harrison, T.; Williams, B.J.;Swain, C.J.; Ball, R.G. *Bioorganic and Medicinal Chem. Lett.* **1994**, *4,* 2545.
2. Ca^{2+} channel binding was determined using a method similar to that described by: Reynolds, I.; Snowman, A.M.; Snyder, S.H. *J. Pharmac. Exp. Therap.* **1986,** *237,* 731.
3. Schmidt, A.W.; McLean, S.; Heym, J. *European J. Pharmacol..* **1992,** *219,* 491.
4. Williams, B.J.; Teall, M.; McKenna, J.; Harrison, T.; Swain, C.J.; Cascieri, M.A.; Sadowski, S.; Strader, C.; Baker, R. *Bioorganic and Medicinal Chem. Lett.,* **1994,***4,* 1903.
5. 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: 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.
6. pK_a measurements were made using the log P-pH method, see: Schaper. K.J. *J. Chem. Res. (S)* **1979,** 357.
7. Hoffmann, R. W. *Chem Rev.* **1989,** *89,* 1841.
8. Desai, M.C.; Rosen, T.J. EP 436 334 A2.
9. It should be noted that L-736,281 and CP-99,994 are single enantiomers whilst **14** is a racemate.
10. All experiments were carried out using diltiazem as a positive control, n=1 for all experiments.
11. n=3 for all compounds except L-733,060 for which n=7. Values quoted are mean IC_{50} values ± SEM.

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