*Bioorganic & Medicinal Chemistry Letters*, Vol.3, No.8, pp. 1703-1706, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00
Pergamon Press Ltd

# Quinuclidine Based NK-1 Antagonists 2: Determination of the Absolute Stereochemical Requirements

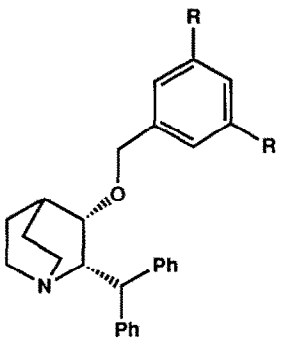
C. J. Swain*, E. M. Seward, V. Sabin, S. Owen, R. Baker, M. A. Cascieri[1], S. Sadowski[1], C. Strader[1], R. G. Ball[2]

*Department of Medicinal Chemistry, Neuroscience Reseach Centre, Merck, Sharp and Dohme Research Laboratories, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, U.K., [1]Department of Molecular Pharmacology and Biochemistry, Merck Research Laboratories, Rahway, New Jersey, [2]Department of Biophysical Chemistry, Merck Research Laboratories, Rahway, New Jersey*

(*Received in USA* 13 *May* 1993)

**Abstract**: The relative and absolute stereochemical requirements for high affinity binding to the human NK-1 receptor are defined for a series of quinuclidine ethers. Whilst the *S* stereochemistry at C-3 is essential for high affinity, surprisingly both epimers at C-2 are active.

The series of neuropeptides known as the tachykinins are thought to have an important role in pain, neuroimmune interactions and neuromodulation.[1] The biological actions of the tachykinins are mediated through specific cell-surface receptors, designated NK-1, NK-2 and NK-3. Three receptor subtypes have been identified on the basis of marked differences in the rank order of potencies of agonist peptides in different tissues, with Substance P (SP) being the preferred agonist for NK-1 receptors, Neurokinin A (NKA) for NK-2 receptors and Neurokinin B (NKB) for NK-3 receptors. The existence of these three receptor subtypes has been confirmed by the cloning and sequencing of three distinct genes from mammalian sources.[2,3,4] Recently several potent non-peptide NK-1 antagonists have been described[5,6], which have demonstrated activity in a number of animal models of inflammation.

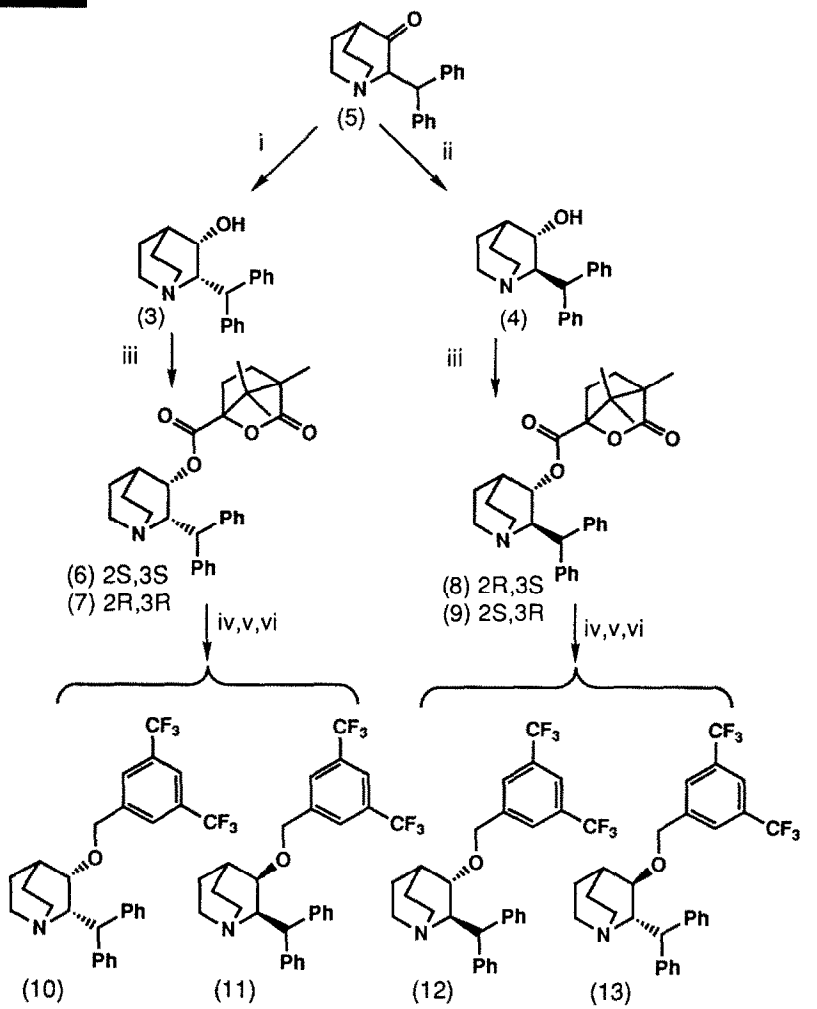



(1) R= $CH_3$
(2) R= $CF_3$

In part 1 of this series we described the identification of a series of quinuclidine based NK-1 antagonists, and the work undertaken to optimise the benzyl ether substitution[7] in

these structures. In particular the importance of the 3,5-disubstitution (**1**) was highlighted. In this communication we describe the relative and and absolute stereochemical requirements for high affinity binding, using the 3,5-bis(trifluromethyl)benzyl analogues (**2**) .

**Scheme 1**




**Reagents**: i. $LiEt_3BH$, THF; ii. Na, iPrOH, Toluene; iii. Camphanic acid chloride, $Et_3N$, $CH_2Cl_2$; iv. Recrystallise from EtAc/Hexane; v. KOH, EtOH, reflux; vi. KHMDS, DME, 3,5-(Bistrifluromethyl)benzyl bromide.

The two diastereomeric alcohols (**3**) and (**4**) were prepared by stereoselective reduction of the benzhydryl ketone (**5**)[8] (Scheme 1). Reduction with the hindered reagent $LiEt_3BH$ afforded the *cis* alcohol (**3**) in 80 % yield. In contrast, reduction with sodium and isopropanol afforded the corresponding *trans* alcohol (**4**).in 50 % yield. The isomeric alcohols were then independently treated with camphanic acid chloride to afford the corresponding diastereomeric esters (80%). Each pair of diastereomeric esters was then separated by recrystallisation to afford the four individual diastereoisomers (**6-9**). Hydrolysis with ethanolic hydroxide (80%) and subsequent alkylation with bis(trifluoromethyl)benzyl bromide afforded the required benzylethers (**10-13**) in yields of 50-60 %. Single crystal X-ray determination of two (**6 & 9**) of the four intermediate camphanate esters[9] allowed elucidation of the absolute configuration of all the resulting benzyl ethers. The affinities of the four stereoisomers for the human NK-1 (hNK-1) receptor stably expressed in CHO cells were determined by competition with $^{125}$I-SP [10,11], and the results are collated in Table 1.

**Table 1**: Displacement of [$^{125}$I] Substance P from hNK-1 receptor in CHO Cells

| Number | Stereo | $IC_{50}$ (nM) Mean±S.D.(n) |
|---|---|---|
| 10 | 2S,3S | 1.3 ± 0.9 (6) |
| 11 | 2R,3R | 570 ± 300 (6) |
| 12 | 2R,3S | 0.7 ± 0.3 (4) |
| 13 | 2S,3R | 270 ± 160 (4) |

As anticipated, the 2S,3S stereoisomer (10) of the *cis* compounds showed high affinity for the hNK-1 receptor[12], with the 2R,3R enantiomer (11) displaying a 1000-fold reduction in affinity, this observation paralleling that found for the analogous benzylamines[13]. However in contrast to the analogous benzylamines in which the *trans* isomer had greatly reduced affinity[13], it was of interest that the 2R,3S stereoisomer (12) also showed high affinity. Comparison of the two active stereoisomers indicates that the stereocenter at C-3 is crucial for high affinity binding, suggesting that the ether oxygen may accept a hydrogen bond from the receptor. In addition, both epimers at C-2 display high affinity binding, however superimposition of the structures would not allow for overlay of both rings of the benzhydryl and the benzyl ether. This observation suggests only one of the rings of the benzhydryl group is required for high affinity . These results help to refine the binding model proposed previously[13]; in addition to the two aromatic interactions, one of which has been shown to interact with His-197 of the NK-1 receptor[14], and the binding of the protonated bridgehead nitrogen, the present study would also suggest a possible hydrogen bonding interaction with the benzylic heteroatom.

## References

1) B. Peernow, Pharmacol. Rev. **35**, 65 1983: J.E. Maggio, Ann. Rev. Neurosci. **11**, 13, 1988.

2) Y. Yoshifumi, Y. Sasai, K. Tanaka, T. Fujiwara, K. Tsuchida, R. Shigemoto, A. Kakizuka, H. Ohkubo and S Nakanishi, J. Biol. Chem. 264, (30), 17649, 1989

3) Y. Masu, K. Nakayama, H. Tamaki, Y. Harada, M. Kuno and S. Nakanishi, Nature, 329, 836, (1987)

4) R. Shigemoto, Y. Yokota, K. Tsuchida, and S. Nakanishi, J. Biol. Chem. 265, (2), 623, 1990.

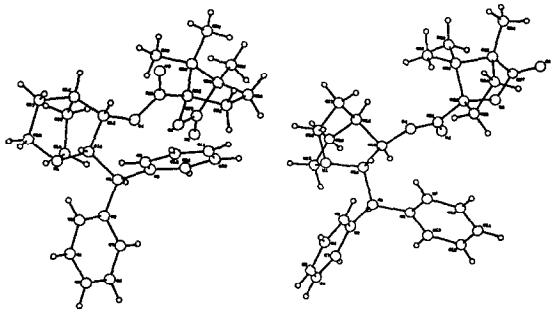
5) R.M. Snider, J. W. Constantine, J. A. Lowe, III, K. P. Longo, W.S. Lebel, H. a. Woody, S.E. Drozda, M.C. Desai, F.J. Vinick, R. W. Spencer and H-J. Hess, .Science, **251**, 435, 1991

6) C. Garret , A. Carrutte, V. Fardin, S. Moussaoui, J.-F. Peyronel, J.-C. Blanchard, and P. M. Laduron, Proc. Nat. Acad. Sci. **88**, 10208, 1991.

7) E.M. Seward, S. Owen, V. Sabin, C. J. Swain, M.A. Cascieri, S. Shadowski, C. Strader . Bioorganic and Medicinal Chemistry Letters. Accepted for publication

8) E.J.Warawa, N.J. Mueller and R. Jules J. Med. Chem. **17,** 497, 1974.

9) Figure (PLUTO) of the X-ray structures 6 and 9, tables of coordinates and geometrical parameters have been deposited with the Cambridge Data Centre.



10) M.A. Cascieri , E. Ber, T. M. Fong, S. Sadowski, A. Bansal, C. Swain, E. Seward, B. Frances, D. Burns, C.D. Strader, Mol. Pharm. **42**, 458, 1992.

11) T. M. Fong, S. A. Anderson, H. Yuh, R. R. C. Huang, and C. D. Strader, Mol. Pharm. **41**, 24, 1992.

12) All compounds are are >1000nM at hNK-2 and hNK-3 receptors .

13) J. A. Lowe III, S.E. Drozda, R.M. Snider, K,P, Longo, S.H, Zorn, J. Morrone, E.R. Jackson, S. McLean, D.K. Bryce, J. Bordner, A. Nagahisa, Y. Kanai, O. Suga, and M. Tsuchiya . J. Med. Chem., **35**, 2591, 1992.

14) T.M. Fong, M.A. Cascieri, H. Yu, A. Bansal, C. J. Swain and C.D. Strader, Nature, **362**, 350, 1993