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# Nuclear Variations of Quinuclidine Substance P Antagonists: 2-Diphenylmethyl-1-azabicyclo[3.2.2]nonan-3-amines

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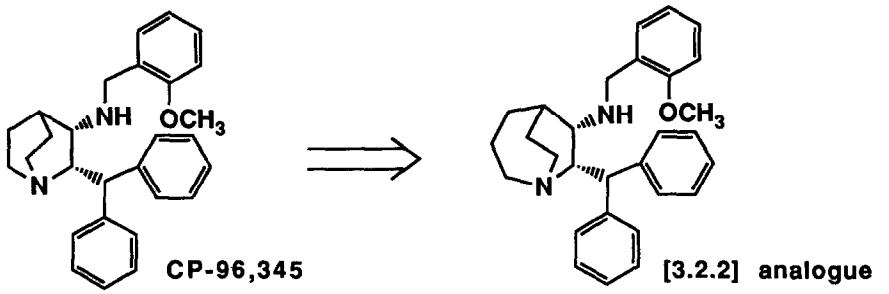
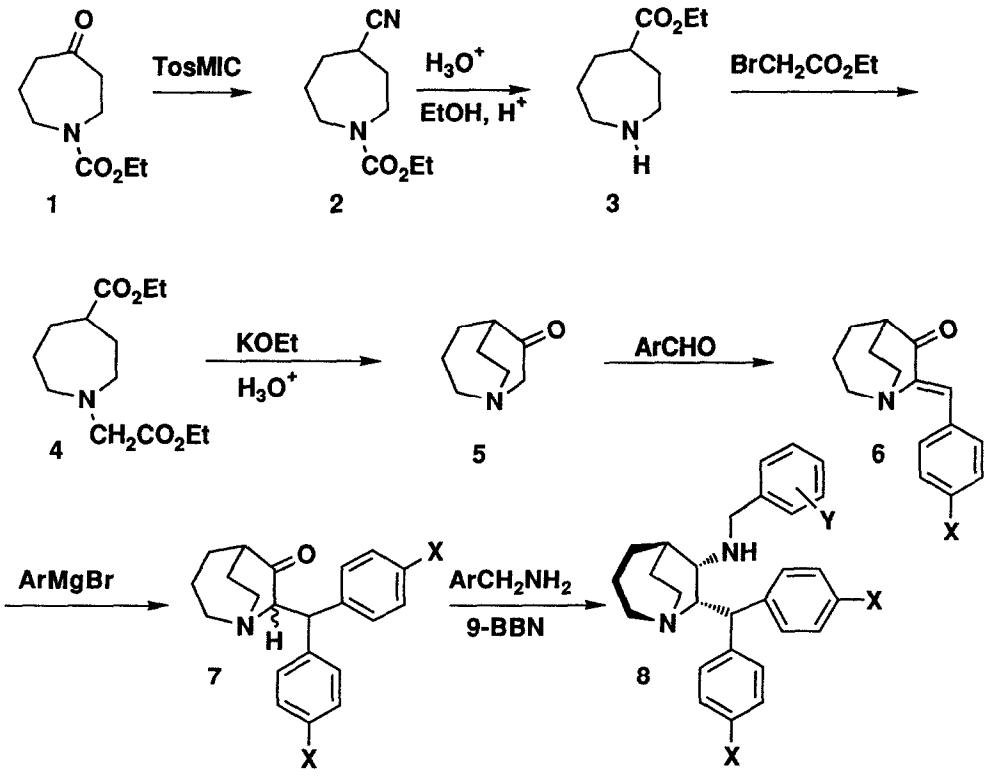
**Abstract:** The synthesis and SAR of a series of 1-azabicyclo[3.2.2] analogues of the nonpeptide substance P antagonist CP-96,345 are described. The results demonstrate the sensitivity of the substance P receptor toward alterations in the nuclear structure of CP-96,345.

We recently described the synthesis[1] and SAR[2] of CP-96,345, the first nonpeptide substance P (SP) antagonist. The SAR investigation delineated three structural features in CP-96,345 important for SP antagonist activity: the bridgehead nitrogen at N-1, the diphenylmethyl group at C-2, and the 2-methoxybenzyl side chain at C-3. In order to investigate receptor interactions not explored by these three structural elements, we have prepared a version of CP-96,345 with an expanded, bicyclo[3.2.2]nonane, nucleus. Although it represents a modest structural alteration, this analogue shows significantly decreased $NK_1$ receptor affinity compared to CP-96,345.




The synthesis of the 1-azabicyclo[3.2.2]nonane analogue of CP-96,345 is depicted in Scheme 1. A key step allowing rapid construction of the required homopiperidine nucleus for cyclization to the [3.2.2] bicyclic system was conversion of ketone **1**[3] to nitrile **2** *via* reaction with tosylmethylisocyanide[4]. After hydrolysis and attachment of the N-carboethoxymethyl group giving **4**, cyclization to the bicyclo[3.2.2] system was achieved with potassium ethoxide in refluxing toluene[5]. The parent heterocycle **5** was formed by acidic hydrolysis, and derivatized to benzylidene adduct **6**. Addition of phenyl magnesium bromide afforded a modest, 22%, yield of the desired 1,4-addition product **7**[6], which differs from the parent [2.2.2] system, where 1,4-addition proceeds in 50% yield. The greater flexibility of the [3.2.2] system apparently allows more access to the C-3 carbonyl group and thus a higher proportion of 1,2-addition. Finally, imine formation followed by 9-BBN reduction afforded almost exclusively the desired *cis* stereoisomer **8**, illustrating the versatility of this reduction step which is adapted from the bicyclo[2.2.2] system. Although two diasteromeric forms of **8** are possible, with the substituents at C-2 and C-3 oriented toward the 3-membered bridge or the 2-membered bridge, a single isomer was observed by $^1H$-




| CPD | X | Y | $IC_{50}$, nM* |
|---|---|---|---|
| 8a | H | 2-$OCH_3$ | 34.3 ± 3.3 |
| 8b | H | 2-Cl | 560 ± 58.6 |
| 8c | H | 2,4-di$OCH_3$ | 86.3 ± 3.8 |
| 8d | F | 2-$OCH_3$ | 310 ± 106 |
| CP-96,345 | | | 4.2 ± 1.9 |

*$IC_{50}$ value (± SEM) in nM units for displacement of [$^3$H]SP in human IM-9 cells.

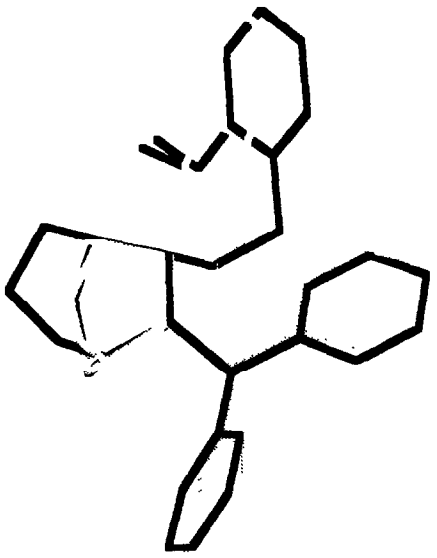
**Scheme 1. Synthesis and SAR of 1-azabicyclo[3.2.2] SP antagonists**

and $^{13}$C-NMR[7]. This isomer is presumed to be the latter since MMP2 calculations indicate the 2-diphenylmethyl substituent feels less steric congestion when placed next to the 2-membered bridge.

The SAR developed by synthesis of analogues in the bicyclo[3.2.2] system is outlined at the bottom of Scheme 1[8]. In comparison with CP-96,345, compound **8a** is less active by approximately 8-fold, with the remaining compounds showing greater decreases in receptor affinity. The SAR pattern is similar to that reported previously for analogues of CP-96,345[2], with *para*-substitution on the benzylamine ring and on the benzhydryl group both leading to loss of receptor affinity. This similarity in the SAR suggests these compounds bind to the same site in the $NK_1$ receptor as that occupied by CP-96,345 albeit with lower affinity.

To account for this loss in $NK_1$ receptor affinity in the bicyclo[3.2.2.] system, a molecular overlap comparison with CP-96,345 was generated with the Nemesis program (copyright Oxford Molecular). As can be seen below, the N-1, C-2 diphenylmethyl, and C-3 2-methoxybenzylamino features all occupy the same space, with slight variations in the 2-methoxybenzyl group of little consequence because of its conformational mobility in finding its binding site. The most significant structural difference is the protrusion of the 3-membered bridge in the [3.2.2] compound into a space not occupied by the parent [2.2.2] system:

**Overlap of CP-96,345 and compound 8a.**
The conformation of CP-96,345 (light gray) is derived from X-ray coordinates, while that of **8a** (dark gray) was calculated using the **Nemesis** program (copyright Oxford Molecular).



This result suggests that the $NK_1$ receptor is very sensitive in this region to steric bulk; since these molecules are quite rigid, this inflexible component of steric congestion apparently interferes with proper alignment of the critical N-1, C-2, and C-3 binding elements.

In summary, the synthesis and SAR of a series of bicyclo[3.2.2] variants of the quinuclidine SP antagonist CP-96,345 has allowed exploration of additional features of the interaction of this class of compounds with the $NK_1$ receptor. Continued probing of the SAR of nonpeptide antagonists at the SP receptor in an effort to unravel the details of the structure and function of this receptor will be the subject of future accounts of our work in this area.

## References

1. Lowe, J.A., III; Drozda, S.E.; Snider, R.M.; Longo, K.P.; Bordner, J. *Bioorg. Med. Chem. Let.*, **1991**, *1*, 129.

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

3. Finney, Z.G.; Riley, T.N. *J. Med Chem.*, **1980**, *23*, 895.

4. Oldenziel, O.H.; Wildeman, J.; van Leusen, A.M. *Org. Syntheses, Coll. Vol.*, **1988**, *6*, 41.

5. In analogy with Daenicker, H.U.; Grob, C.A. *Org. Syntheses, Coll. Vol.*, **1973**, *5*, 989.

6. The conversion of **5** to **7** follows the procedure of Warawa, E.J.; Mueller, N.J.; Jules, R. *J. Med. Chem.* **1974**, *17*, 497.

7. Spectral data for **8a**: 2-(Diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[3.2.2]nonan-3-amine: mp 170-190°C as the dihydrochloride salt hydrate. **$^1$H-NMR** (δ, $CDCl_3$): 1.5-1.7 (m, 3H), 1.7-1.9 (m, 3H), 2.21 (m,1H), 2.6 (m, 1H), 2,7 (m, 1H), 2.84 (m, 1H), 2.95 (m, 1H), 3.2 and 3.6 (m, 2H), 3.25 (m, 1H), 3.63 (s, 3H), 3.94 (dd, J=7.7,11.3, 1H), 4.34 (d, J=11.3, 1H), 6.6-7.4 (m, 14H). **$^{13}$C-NMR** (δ, $CDCl_3$): 21.7, 25.2, 28.9, 30.0, 41.8, 46.3, 51.3, 55.3, 57.4, 59.5, 63.9, 110.1, 120.3, 125.4, 126.1, 127.7, 127.96, 127.04, 128.2, 128.34, 128.37, 128.4, 128.6, 128.8, 129.0, 129.5, 143.0, 145.8, 157.3. **IR** (cm.$^{-1}$, KBr): 1620 (C=C). **MS** (%): 427 (2, parent+1), 260 (39), 259 (100), 121 (74), 110 (41), 91 (55). **Analysis** Calc'd. for $C_{29}H_{34}N_2O \cdot 2HCl \cdot H_2O$: C 67.30, H 7.40, N 5.41. Found: C 67.11, H 7.21, N 5.18.

8. The procedure for [$^3$H]SP binding to human IM-9 cells which was used for SAR evaluation was based on the literature protocol of Payan, D.G.; Brewster, D.R.; Goetzl, E.J. *J. Immunol.*, **1984**, *133*, 3260. Cells were counted, isolated by centrifugation and washed twice in Hank's balanced salt solution (HBSS) pH 7.4. The assay was conducted in HBSS in 5 mL polystyrene tubes with 100 µL of test compound solution, 100 µL of ligand solution (0.5 nM final concentration, 36-55 Ci/mmol), and 800 µL cell preparation. After incubation in the dark at room temperature for 20 min, the assay was terminated by filtration onto GF/B filters which had been presoaked in 0.2% polyethyleneimine for 1-2 hr. The filters were washed (5 x 1 sec) with ice-cold 50 mM TRIS-HCl buffer (pH 7.7) using a Brandell Harvesting System, and the filters quantified for radioactivity by liquid scintillation counting. Standard errors are indicated following the $IC_{50}$ values for triplicate determinations using 8 concentrations.