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2-Aryl-1-azabicyclo[2.2.2]octanes as Novel Nonpeptide Substance P Antagonists

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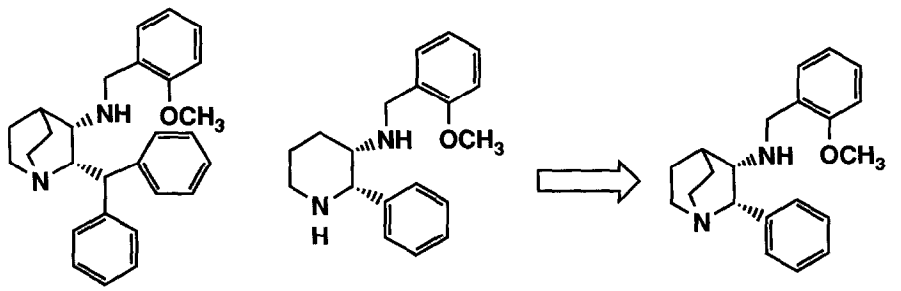
Abstract: The synthesis and SAR of a series of 2-aryl-1-azabicyclo[2.2.2]octanes structurally related to the nonpeptide substance P antagonists CP-96,345 and CP-99,994 are described. The novel SAR observed at the 2-position in these derivatives represents a hybrid between that seen in the two previous series.

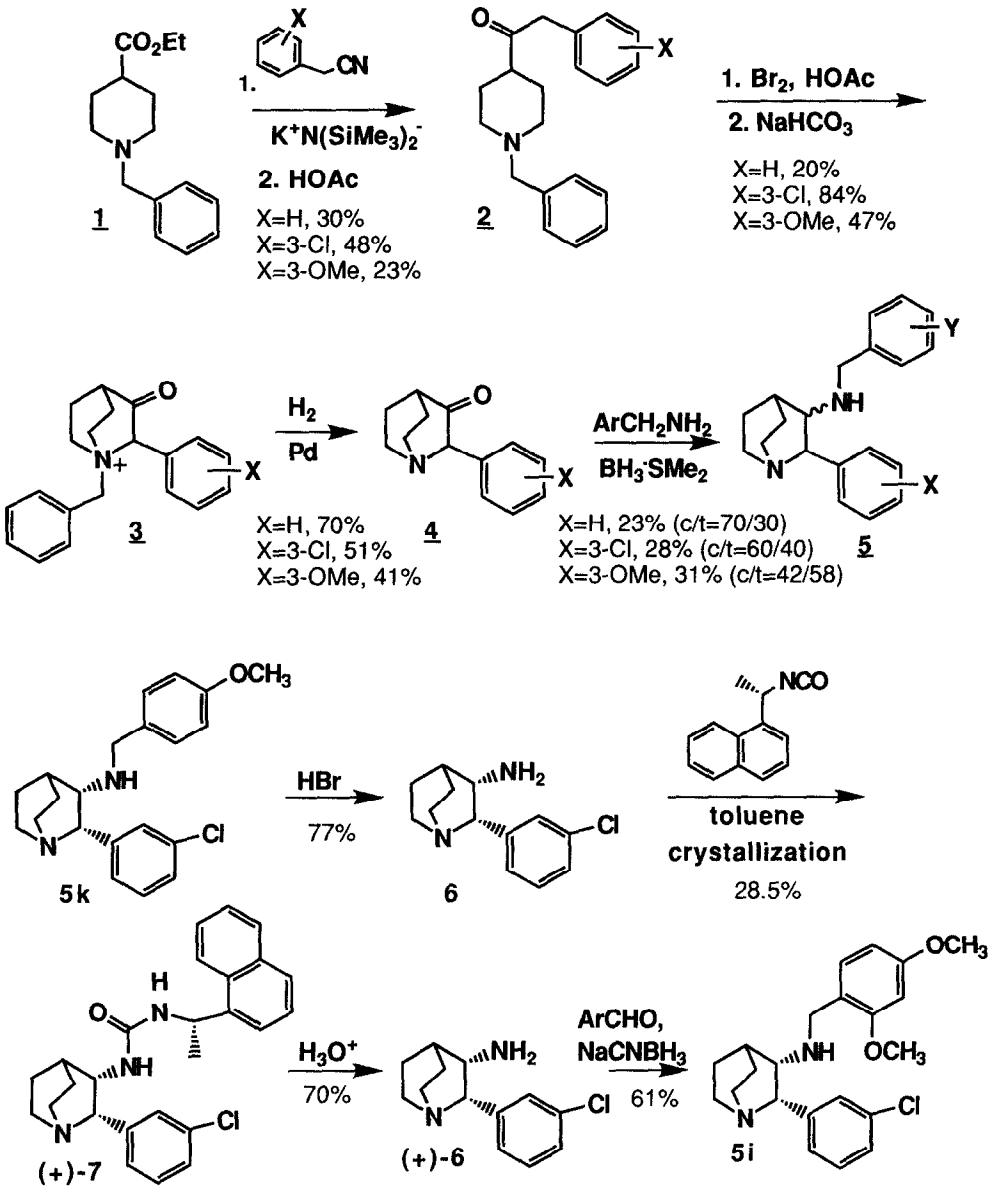
The discovery of the quinuclidine substance P (SP) antagonist CP-96,345[1] was followed by the report of a structurally novel series of piperidine SP antagonists exemplified by CP-99,994[2]. To examine further the structural possibilities for novel SP antagonists, we selected a hybrid of the quinuclidine and piperidine systems as a target:



CP 96,345 **CP 99,994**

Figure 1. Hybridization of Nonpeptide Substance P Antagonists.

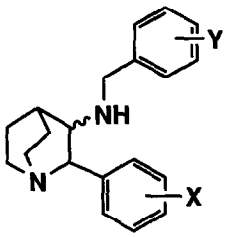
The synthesis of this new 2-aryl-1-azabicyclo[2.2.2]octane ring system is outlined in Scheme 1. The key step is ring closure of an appropriately functionalized N-benzylpiperidine, **2**, to the quinuclidine **3**, which is based on a previously developed quinuclidone synthesis[3]. In analogy with this previous work, the N-benzyl substituent in **2** is required for cyclization, presumably because it helps the piperidine achieve the boat conformation necessary for ring closure. Attachment of the benzylamino side chain to afford **5** was effected by borane/methyl sulfide reduction of the corresponding imine, giving roughly equal mixtures of *cis* and *trans* isomers which were separated by column chromatography. Resolution of **5h** was achieved in analogy with that reported previously for CP-96,345[4] as shown at the bottom of Scheme 1. Thus preparation of 2-(3-chlorophenyl)-1-azabicyclo[2.2.2]octan-3-amine **6** by deprotection of the 4-methoxybenzyl derivative **5k** was followed by derivatization with 1-naphthylethylisocyanate. As before, one diastereomer could be preferentially crystallized, then hydrolyzed to optically pure **6**, which was analyzed by single crystal X-ray diffraction to establish the absolute configuration of (+)-**6** as (2S,3S)[5]. The amine was then converted to **5i** or **5j** by reductive amination.



Scheme 1. Synthesis and resolution of 3-amino-2-arylquinuclidines

The SAR of this series of compounds, evaluated using [^{3}H]-SP binding in human IM-9 cells[9], demonstrates the importance of the *cis* stereochemistry for optimal activity (**5a** *vs.* **5b**, **5c** *vs.* **5d**, **5e** *vs.* **5f**), the superiority of a 2-methoxy as compared with a 2-chloro substituent on the benzylamine side chain (**5c** *vs.* **5g**, other substituents such as CH_3 and CF_3 were less active as well), and the increased affinity afforded by a 3-chloro subtituent on the 2-phenyl ring (**5c** *vs.* **5a**).

CPD	X	Y	c/t	IC_{50}, nM*
5a	H	2-OCH_3	cis	140 ± 8.8
5b	H	2-OCH_3	trans	700 ± 88
5c	3-Cl	2-OCH_3	cis	20 ± 1.7
5d	3-Cl	2-OCH_3	trans	240 ± 67
5e	3-OCH_3	2-OCH_3	cis	160 ± 22
5f	3-OCH_3	2-OCH_3	trans	1,400 ± 370
5g	3-Cl	2-Cl	cis	230 ± 65
5h	3-Cl	2,4-diOCH_3	cis	39 ± 9.9
5i	3-Cl	2,4-diOCH_3	cis 2S,3S	9.2 ± 2.3
5j	3-Cl	2,4-diOCH_3	cis 2R,3R	350 ± 180
CP-96,345				2.0 ± 0.93



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*IC_{50} ± sem values for displacement of [^{3}H]-SP in human IM-9 cells.

While the first two SAR features parallel results from the CP-96,345 series, the last SAR element distinguishes this series of SP antagonists from the previous compounds, which are intolerant of substitution on their respective groups at the 2-position[4]. It is worth noting that as the 2-aryl-1-azabicyclo[2.2.2]octane series is a hybrid between CP-96,345 and CP-99,994, so is its SAR at the 2-position, suggesting further opportunities for SAR exploration. Finally, as was found for CP-96,345 and CP-99,994, the activity in this series resides predominantly in the (2S,3S) isomer, compound **5i**.

Compound **5i** was tested in the dog isolated carotid artery system (DCA), where we have previously shown that CP-96,345 competitively antagonizes the relaxation by SP of tissue precontracted with norepinephrine[1]. Compound **5i** was found to be an NK_1 antagonist, producing a parallel, rightward shift of the dose response curve to SP compared to the control curve at a concentration of $5X10^{-6}$M (n=4), giving a calculated pK_B value of 7.0[10]. When higher concentrations of **5i** were tested in the DCA in order to determine a pA_2 value, however, contraction of the tissue by the compound alone occurred before norepinephrine was added, indicating another activity of the compound unrelated to NK_1 receptors (NK_1 agonist activity would have produced a relaxation response). This unknown activity, the source of which is still under investigation, precluded further pursuit of this series of compounds since it occurs at concentrations close to those required for NK_1 blockade.

The 2-aryl-1-azabicyclo[2.2.2]octanes reported here illustrate the application of a strategy of hybridizing two previous series of SP antagonists. While this series of compounds, **5**, does not achieve the potency of these earlier series, it does suggest that flexibility exists for new substituents at the 2-position in

these structures, opening the way to new series of SP antagonists. These possibilities will be reported in future communications from this laboratory.

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5. **Single Crystal X-ray Analysis of (+)-6.** A representative crystal of **(+)-6**, grown from methylene chloride, was surveyed and a 1 Å data set (maximum sin θ/λ=0.5) was collected on a Nicolet R3m/m diffractometer. A full set of Friedel pairs was collected to aid the determination of absolute configuration. Atomic scattering factors were taken from the International Tables for X-ray Crystallography[6]. All crystallographic calculations were facilitated by the SHELXTL[7] system. All diffractometer data were collected at room temperature. A trial structure was obtained by direct methods. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The hydrogens on nitrogen were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R-index was 0.040. A final difference Fourier revealed no missing or misplaced electron density. The refined structure was plotted using the SHELXTL plotting package. The absolute configuration was determined by the method of Ibers and Hamilton[8] . Coordinates, anisotropic temperature factors, distances and angles are available. From this analysis, the absolute configuration of the (+) isomer was shown to be 2S,3S.
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9. 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.
10. Rings of dog carotid artery were cut into pieces 3-5 mm long, slid onto 2 stainless steel hooks and suspended in tissue baths. The 4 mL tissue baths were aerated with 95% O_2/5% CO_2 and maintained at 37°C. During an equilibration period of 1-2 hr, resting tension was adjusted to 2 g. Contractions were measured with a Grass model FT03 force transducer connected to an amplifier which continously supplied an analog signal to a Heath model EU 20B servorecorder for analysis. All tissues were contracted with norepinephrine (NE) and, after a plateau had been reached, washed until they returned to baseline. This was repeated using various concentrations of NE (between $5X10^{-8}$M and $5X10^{-7}$M) until a tension between 1 and 1.5 g was attained. A test compound or solvent was then added to the tissue baths for 30 min; NE (the same concentration that caused a 1 to 1.5 g response) was then added; after a plateau was reached, cumulative concentrations of substance P were added to the bath, allowing for a relaxation plateau to be reached between each concentration. This continued until a maximal relaxation had occurred. Results were expressed as percent relaxation of the NE-induced response.

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