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Communications to the Editor

Importance of Parallel Vectors and "Hydrophobic Collapse" of the Aligned Aromatic Rings: Discovery of a Potent Substance P Antagonist

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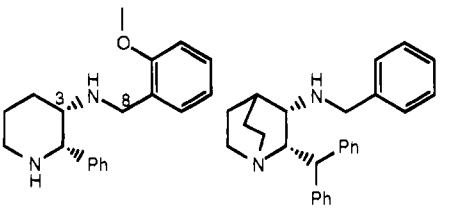
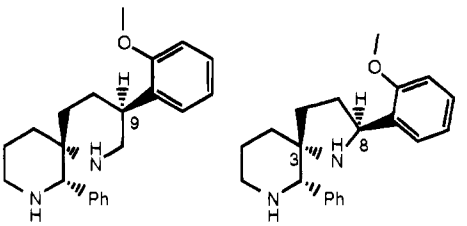
Electron-rich π clouds are commonly thought to contribute significantly to the interaction of aromatic rings of ligands with protein structures *via* lipophilic–lipophilic interactions,[1] cation–π interaction[2] or face-on hydrogen bonding to π-clouds.[3] Additionally, intraligand self-association of aromatic rings (termed "hydrophobic collapse") has been proposed to account for the presentation of the bioactive conformation of a ligand to its receptor.[1] Our laboratory recently reported the discovery of **1** (CP-99,994) as one of the most potent substance P (SP) antagonists.[4–6] This followed from prior elucidation of the quinuclidine **2**, identified by directed screening, as a SP antagonist. The C-2 phenyl group of 1 was shown by molecular modeling to occupy the same space as the inner phenyl ring of the benzhydryl group in **2**. Subsequent studies found that the precise orientation of the two nitrogens and the C-2 phenyl group is critical to retain affinity for the SP receptor.[7] A far more important issue, however, remained to be probed: in what conformation are the two aromatic rings of **1** recognized by the receptor? The possibility that in the bound conformation of **1** the two aromatic rings could be stacked has been proposed by us.[4] In this communication, we report the discovery of (±)-**3** as a potent SP antagonist, *the spirocyclic frame work of* ***3*** *was designed to project the two aromatic rings in parallel, inducing by such conformational restriction the self-association of the pendant aromatic rings.*

Following the identification of **1** as a SP antagonist, we conceived **4** in which the orientation of the benzylamino side chain was fixed by a two-carbon scaffold between C-3 and C-8. The β orientation at the C-8 in **4** is desirable to position the aromatic ring in the vicinity of C–2 phenyl ring; we assumed the closer proximity of the two aromatic rings was essential for activity. Furthermore, the *cis* stereochemistry between the C-2 phenyl and C-3/nitrogen bond is in accordance with that present in structure **1**. Unfortunately, **4** was devoid of meaningful affinity for the SP receptor; the lack of activity prompted us to investigate alternate ways of affixing the 2-methoxyphenyl ring.[8]



1 **2**



3 **4**

Taking a cue from the X-ray crystal structure of **1** and related compounds, we desired to examine our initial inclination that the aromatic rings of **1** be recognized in the parallel orientation by the SP receptor. We ascribed the lack of activity of **4** to the inability of the aromatic rings to acquire presumed bioactive conformation with parallel orientation produced by the self-association (see stereoscopic view in ref 8). The objective therefore became to modify the spirocyclic structure **4** so that the vectors of the two aromatic rings have a chance to become parallel without compromising the distance between the two nitrogens and the C-2 phenyl group.

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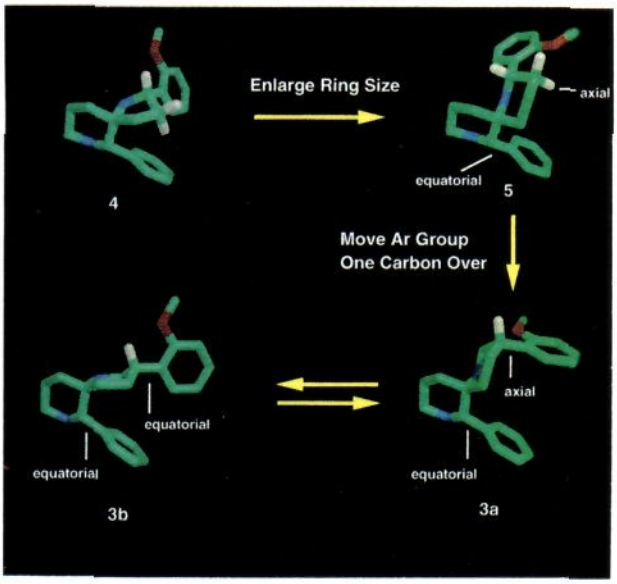


While working with molecular models we realized that when one enlarges the five-membered ring of **4** to a six-membered ring as in **5**, the overall effect is to position the 2-methoxyphenyl group farther away from the C-2 phenyl group. We noted, however, that in the conformation **5** the C-9 axial and the C-2 equatorial valencies are parallel. To fix the two aromatic rings in a parallel orientation, we decided to move the 2-methoxyphenyl group to the adjacent carbon, thereby generating the conformation **3a**. In conformation **3a** not only will the two critical rings be projected from the two parallel vectors, but the distances between the two nitrogens and the C-2 phenyl group will be similar to that in **1**. In **3a**, the C-2 phenyl group is equatorial and the 2-methoxyphenyl group is axial; the conformation **3a**, however, can flip to an all equatorial conformation **3b**. Interestingly, the energy profile obtained by semiempirical molecular modeling programs for **3a** and **3b** ($\Delta E \cong 0.1$ kcal/mol; favors **3a**) is very similar.[9] It would appear therefore that both **3a** and **3b** are equally

Table 1. *In Vitro* Binding Affinity for the Substance P (NK-1) Receptor in Human IM-9 Cell Using [^{125}I]BH-SP of Substance P Antagonist[15]

compd	K_i (nM)
(+)-**1**	0.17 ± 0.14
(±)-**3**	2 ($n = 3$)
(±)-**4**	>10000 ($n > 3$)

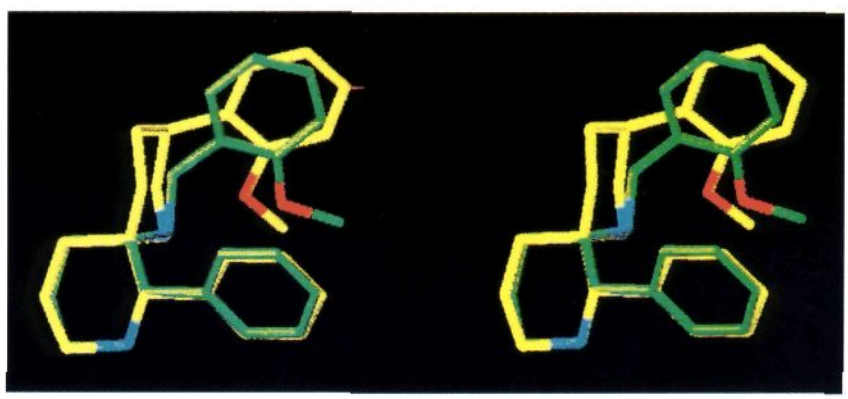
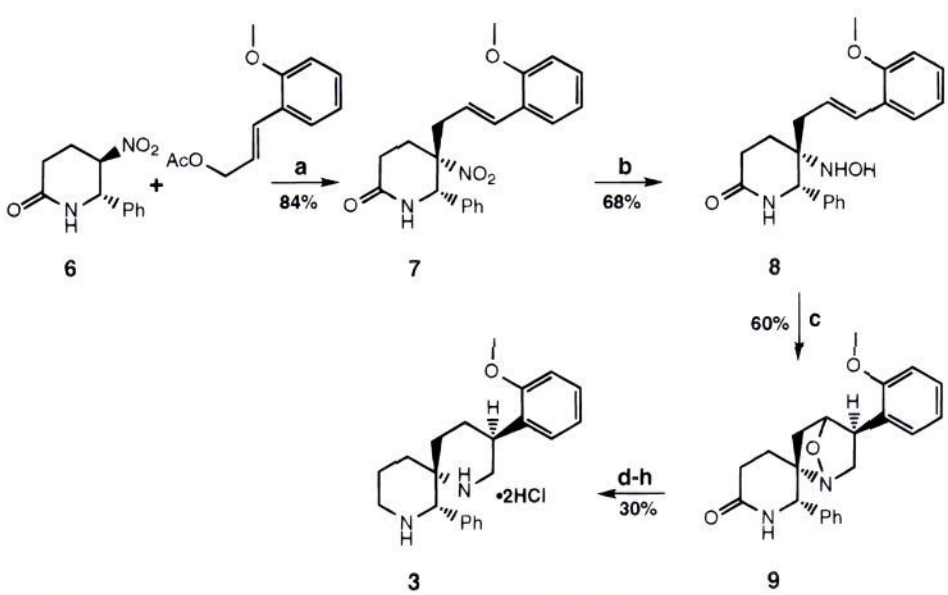


Figure 1. Stereoscopic view of overlap between **3a** (yellow) and conformation of **1** (green) with two aromatic rings in the parallel orientation.

Scheme 1[a]



[a] Reagents: (a) LiOMe, $Pd(PPh_3)_4$, THF, 25 °C; (b) Zn, NH_4OAc, MeOH, 60–65 °C; (c) 37% HCHO solution, toluene, 120 °C; (d) Zn, AcOH, H_2O, 70 °C; (e) Im_2CS, TEA, 1,2-dichloroethane, 75 °C; (f) Bu_3SnH, AIBN, toluene 120 °C; (g) BH_3–THF, reflux; (h) Et_2O·HCl.

accessible conformations for **3**. Interestingly in **3**, the 2-methoxyphenyl group is on the β carbon and not on the α carbon as in **1**, **2**, and **4**. Furthermore, Figure 1 shows the overlap between the conformation of **3a** and the conformation of **1** in which the two aromatic rings are parallel; the aromatic rings occupy the same region. Compound **3** thus became a legitimate target for synthesis.

The attractive feature of the stereoselective synthesis depicted in Scheme 1 is that it could produce (±)-**3** without chromatography; the yields for the intermediates are shown for pure products obtained by trituration. The synthesis began with **6**, which could be readily obtained in quantitative yield by the Knoevenagel reaction of benzaldehyde with methyl 4-nitrobutanoate in the presence of ammonium acetate.[10] We anticipated the possibility of creating the incipient spiro center of **3** by palladium(0)-catalyzed C-allylation of the nitronate of **6**;[11] in accordance with our earlier report, the C-2 phenyl group was expected to direct the incoming electrophile to generate the desired stereochemistry at the spiro center.[8] Thus, the treatment of **6** with 2-methoxycinnamyl acetate and lithium methoxide in the presence of tetrakis(triphenylphosphine)palladium-(0)[11] afforded the C-alkylated product **7** in 86% yield. We planned to form the second ring *via* intramolecular *N*-alkenylnitrone cycloaddition reaction.[12] The hydroxylamine **8** available from **7** by reduction (zinc–ammonium acetate; MeOH) in 68% yield on heating with aqueous formaldehyde in refluxing toluene afforded the cyclized product **9** in 60% yield.[13] The next three sequential reductions provided the desired spirocycle **3** from **9** (30%): (1) the cleavage of the N–O bond with zinc/acetic acid (99%), (2) the deoxygenation with tributyltin hydride of the corresponding thioimidazolide,[14] and (3) the reduction of the lactam ring with borane dimethyl sulfide (33%; combined yield for the last two steps). The structure of **3** was confirmed by single crystal X-ray analysis.

The substance P binding affinity for (+)-**1** and (±)-**3** is presented in Table 1.[15] It was gratifying indeed to find that **3** has high affinity for the SP receptor (K_i = 2–3 nM). An intriguing question to ask is what is the bound conformation for **3**:**3a** or **3b**? In single-crystal X-ray crystallography, **3** crystallizes in the **3b** conformation with both the phenyl groups in the equatorial positions. However, ^{1}H-NMR analysis of **3** in $CDCl_3$ suggested that the solution conformation is **3a** (symmetrical quintet J = 5 Hz; this is reminiscent of the equatorial C-9 proton in **3a**). At present, we can confidently say that the compound conceived to project aromatic rings through parallel vectors does have high affinity for the SP receptor and that its solution conformation in chloroform is **3a**. It is possible that the two aromatic rings in **3a** are not parallel but remain end on.

The lack of activity of **4** and the remergence of activity by the introduction of a strategic methylene group (**4** → **3**) serves to emphasize the importance of specific conformational bias of the aromatic rings required for binding to the SP receptor. Interestingly, in addition to the appropriately situated basic nitrogen atom, all the SP antagonists reported to date[16] have two aromatic rings that possess the capacity to collapse on each other to acquire an ordered conformation; the term "hydrophobic collapse" has been proposed to described such phenomenon by Rich.[1] The driving force for such phenomenon is thought to be the exclusion of water molecule(s) by such hydrophobic collapse in an aqueous environment. The focus is now to identify the amino acid pocket that recognizes precise orientation of the aromatic rings for binding and utilize this type of information in the design of scaffolds. Such templates, with built-in pharmacophoric features, may provide leads for other receptors.

Supplementary Material Available: Crystallographic data, ^{1}H-NMR data (500 MHz; 2D-NMR; NOE studies), and experimental details for the synthesis of (±)-**3** (21 pages). Ordering information is given on any current masthead page.

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