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ARTICULATING A PHARMACOPHORE DRIVEN SYNTHETIC STRATEGY: DISCOVERY OF A POTENT SUBSTANCE P ANTAGONIST

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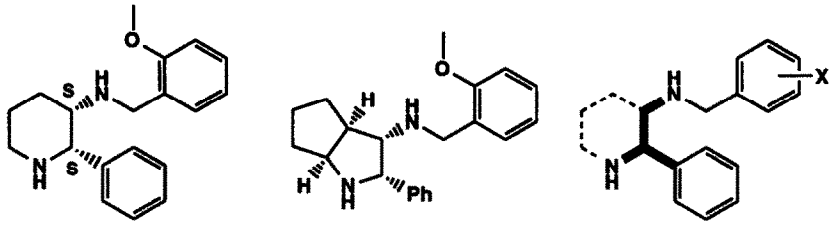
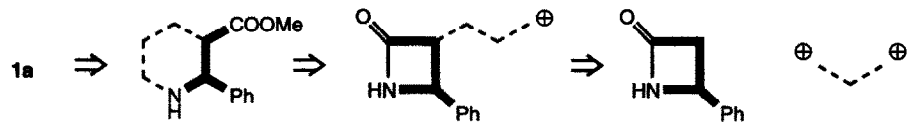
Abstract: We now reveal (2ß, 3ß, 3αß, 6αß)-(±)-octahydro-*N*-[(2-methoxyphenyl)methyl]-2-phenyl-cyclopenta[*b*]pyrrol-3-amine (**2**) as potent SP antagonist; the discovery of **2** resulted from the pharmacophore driven synthetic strategy. Furthermore we find that for **1** and **2** the spatial disposition of the C-2 phenyl group and the two nitrogen atoms as indicated by molecular modeling are similar.

Substance P (SP),[1] an eleven amino acid peptide,[2] is implicated in the pathogenesis of diseases such as arthritis, asthma, and inflammatory bowel disease.[3] Recent research in our laboratory has been focused on the application of a *structure based* arguments for the identification of non-peptidic SP antagonists; in this regard we disclosed the rationale behind the discovery of CP-99,994 (**1**) as the most potent SP antagonist.[4,5,6] We now reveal **2** as potent SP antagonist; the discovery of **2** resulted from the pharmacophore driven synthetic strategy described in detail here. Furthermore we find that for **1** and **2** the spatial disposition of the C-2 phenyl group and the two nitrogen atoms as indicated by molecular modeling are similar .



1 (CP-99,994) **2** **1a**

Scheme I



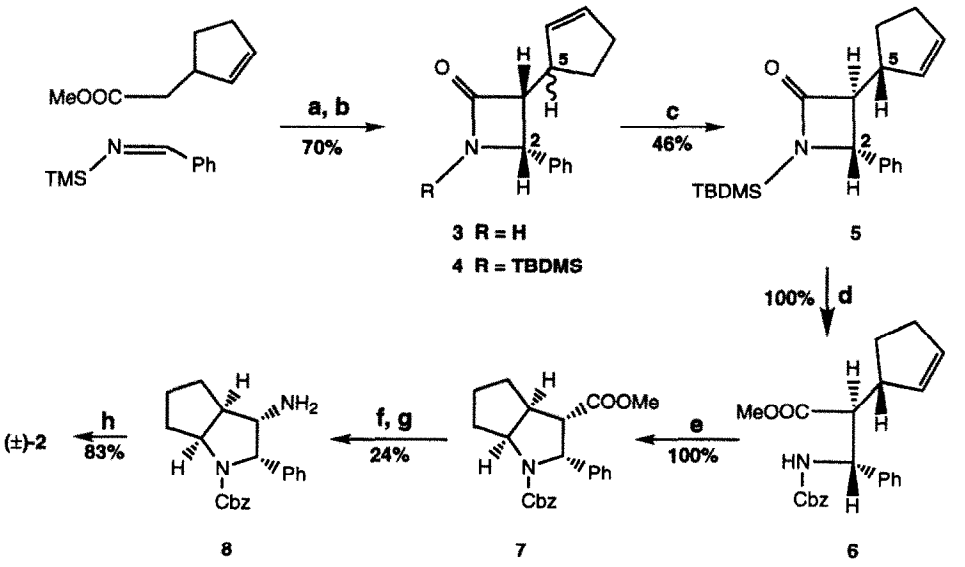
1b **1c** **1d** **1e**

Following the identification of **1** we speculated that 1-phenyl-1,2-diaminoethane (shown bold in **1a**) represents the primary pharmacophoric group, while the dotted portion (in **1a**) holds it appropriately for recognition by the SP receptor.[5a] We argued that non-piperidine prototypes **1a** with modified pharmacokinetic profiles could potentially be developed by replacing the dotted portion (the non-pharmacophoric carbon framework) so as not to disrupt the spatial arrangements of the pharmacophoric group. To fulfill this objective,

we decided to synthesize structurally constrained prototypes represented by generic structure **1a** and compare their activity. Through this exercise, we were interested in determining the optimum topographical relationship between the two nitrogens and the phenyl groups required to retain affinity for the SP receptor.

We recognized that it would be particularly attractive to synthesize these prototypes by a general protocol. This need prompted us to articulate a pharmacophore driven synthetic strategy; Scheme I outlines one means through which this strategy could serve as a basis for the synthesis of SP antagonists. As a first step, compounds with the general formula **1a** can be derived from **1b** *via* a Curtius or an equivalent reaction followed by reductive amination. The key intermediate **1b** could be elaborated by hydrolysis of the functionalized ß-lactam **1c** followed by intramolecular N-alkylation or equivalent reaction.[7] Interestingly, the latter reaction involves rotation around a C-C bond such that the *cis* stereochemistry in **1b** -generally required for good SP receptor affinity-originates from

Scheme II



Reagents : (a) 1. LDA, THF, -78°C; 2. 1N HCl; (b) TBDMS-OTf, $EtNiPr_2$, 0°C; (c) 1. LDA, THF, -78°C; 2. AcOH, -78°C; (d) 1. 5% MeOH, H_2SO_4, reflux; 2. CbzCl, aq. $KHCO_3$, EtOAc, 25°C; (e) 1. $Hg(OCOCF_3)_2$, CH_3NO_2, 25°C; 2. $NaBH_4$, C_2H_5OH; (f) Me_3Al, NH_4Cl, benzene, 50°C; (g) $C_6H_5I(O_2CCF_3)_2$, CH_3CN, 25°C; (h) 1. ArCHO, $NaBH_3CN$; 2. 10% Pd on C, $NH_4(OCOH)$; 3. Et_2O-HCl

the *trans* stereochemistry in the ß-lactam **1c**. The functionalized ß-lactam **1c** can be readily obtained by alkylation of 4-phenyl-2-azetidinone (**1d** and **1e**) or by the condensation of N-trimethylsilyl imines with ester enolates.[8] The functionalized ß-lactam **1c** contains two operational fragments: (1) the 4-phenyl-2-azetidinone ring (solid lines) from which the supposed primary pharmacophoric group is derived and (2) the dotted lines from which the scaffolding portion could originate for holding the assumed primary pharmacophore for recognition by the receptor.[9] Thus, by judicious choice of an appropriate scaffolding segment, one can project the putative pharmacophore in different three dimensional space. Analysis of the affinity of these prototypes for the SP

receptor should then permit refinement of the important geometrical properties influencing active-site recognition. The ready availability of a wide range of functionalized ß-lactams would make Scheme I the plan of choice. Described below is the application of this protocol for the synthesis of (±)-**2**.

The condensation of an ester enolate with an N-trimethylsilyl imine to afford an N-protio-ß-lactam was used as a starting point for our synthesis of the functionalized ß-lactam. Reaction of the anion of methyl 2-cyclopentene-1-acetic acid (LDA, -78°C) with N-(trimethylsilyl)benzaldimine affords **3** which was N-protected to give ß-lactam **4** (TBDMS-OTf, CH_2Cl_2, 25°C, 70%). The crude product was found to be a 3:1 mixture of diastereomers at the C-5 carbon atom while the stereochemistry between the C-2 and C-3 substituents was determined to be *cis* which is in accordance with that observed by Hart *et al.* and ^{1}H-NMR analysis ($J_{2,3}$ = 4 Hz). The next step in the synthesis involved inverting the stereochemistry at C-3; this was accomplished by treatment of **4** with LDA at -78°C followed by quenching with acid at low temperature. Rapid flash column chromatography provided **5** in 46% yield (87% based on recovered starting material). The stereochemistry at C-5 as shown in **5** was confirmed by X-ray crystallographic analysis of **2**. The intramolecular amidomercuration reaction[10] was found very convenient for the generation of the 2-azabicyclo[3.3.0]octane ring system of **7**. Compound **5** was transformed into **7** quantitatively *via* a three step protocol: (1) hydrolysis of the ß-lactam (5% H_2SO_4 in MeOH, reflux) (2) protection of the amino group to provide **6** (CbzCl, $KHCO_3$, EtOAc, 25° C), and (3) amidomercuration of **6** followed by reductive workup with sodium borohydride(1. $Hg(OCOCF_3)_2$, CH_3NO_2, 25° C; 2. $NaBH_4$, C_2H_5OH). Particularly noteworthy is the fact that the nature of the ring fusion in **7** is governed by the stereochemistry at C-5; none of the *trans* ring fused product could be detected from the ^{1}H-NMR of the crude product. Next the stereospecific elaboration of the carbomethoxy group into an amino group was achieved *via* a two step sequence: (1) conversion of the carbomethoxy group to a carboxamide (trimethylaluminum, ammonium chloride, 50°C)[11] (2) oxidation of the carboxamide to an amino group *via* Hoffmann degradation ([*I,I*-bis(trifluoroacetoxy)iodo]benzene, CH_3CN, 25°C) to yield **8** (24%).[12] Reductive amination of **8** with o-methoxybenzaldehyde followed by cleavage of the Cbz group afforded **2** in 83%. The strucutre of **2** was further confirmed by X-ray crystallography.[13]

Table I. *In vitro* binding affinity for the NK-1 receptor in human IM-9 cell using [^{3}H]-SP of substnace P antagonists

Compound	K_i (nM)
(+)-**1**	1.5
(±)-**2**	2.4

Significantly, (±)-**2** and (+)-(*2S,3S*)-**1** have similar affinity for the SP receptor (Table I).[14] In the overlay between X-ray structures of **1** and **2**, the scaffold part of **2** is contained within that of **1**. For the comparison the freely rotating benzylamino side chain of **2** is fixed in a conformation that allows the two phenyl groups to have a parallel orientation. We have suggested that such an orientation might be recognized by the receptor.[5a] Additional work to further refine the geometrical properties influencing receptor recognition of this class of compounds *via* the application of the pharmacophore driven synthetic strategy will be reported in due course.

References and Notes

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(1) (a) Iversen, L. L.; Watling K. J.; McKnight, A. T.; Williams, B. J.; Lee, C. M. in *Topics in Medicinal Chemistry;* Leeming P. R., Ed.; The Proceedings of the 4th SCI-RSC Medicinal Chemistry Symposium; Royal Society of Chemistry: London, 1988; pp 1-9. (b) Regoli, D.; Drapeau, G.; Dion, S.; Couture, R. *Trends in Pharmacology* **1988**, *9*, 290-295. (c) Dutta, A. S. *Drugs of the Future* **1987**, *12*, 781-792. (d) Pernow, B. *Pharmacol. Rev.* **1983**, *35*, 85-141.

(2) Chang, M. M.; Leeman, S. E. *J. Biol. Chem.* **1970**, *245*, 4780-4790.

(3) Maggi, C. A.; Patacchini, R.; Rovero, P.; Giachetti, A. *J. Auton. Pharmacol.* **1993**, *13*, 23-93.

(4) (a) Snider, R. M.; Constantine, J. W.; Lowe III, J. A.; Longo, K. P.; Lebel, W. S.; Woody, H. A.; Drozda, S. E.; Desai, M. C.; Vinick, F. J.; Spencer, R. W.; Hess, H. -J. *Science* **1991**, *251*, 435-437. (b) McLean, S.; Ganong, A. H.; Seeger, T. F.; Bryce, D. K.; Pratt, K. G.; Reynolds, L. S.; Siok, C. J.; Lowe III, J. A.; Heym, J. *Science* **1991**, *251*, 437-439. (c) 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*, 2591-2600.

(5) (a) Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911-4913. (b) Desai, M. C. Thadeio, P. F.; Lefkowitz, S. L. *Tetrahedron Letters* **1993**, *34*, 5831-5834. (c) Desai, M. C.; Lefkowitz, S. L. *Bioorganic & Medicinal Chemistry Letters* **1993**, *3*, 2083-2086.

(6) For a recent review see: Desai, M. C. *Exp. Opin. Ther. Patents* **1994**, *4*, 315-421.

(7) For a recent review on the use of ß-lactams in synthesis, see: Manhas, M. S.; Wagle, D. R., Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1756-1802.

(8) (a) Ha, D. -C.; Hart, D. J.; Yang, T. -K. *J. Am. Chem. Soc.* **1984**, *106*, 4819-4825. (b) Colvin E. W.; McGarry, D.; Nugent, M. J. *Tetrahedron* **1988**, *44*, 4157-4172. (c) Hart, D. J.; Ha, D.-H *Chem. Rev.* **1989**, *89*, 1447-65.

(9) An additional benefit of this strategy is that C-2 asymmetric center would not be expected to racemize. Thus this scheme could provide optically pure **1a** if one start with enantiomerically pure **1c** or **1d**. The application of this feature became the basis for the synthesis of both enantiomers of (±)-**1**. See reference 5a.

(10) (a) For a recent review see: Cardillo, G.; Orena, M.*Tetrahedron* **1990**, *46*, 3321-3408. (b) Harding, K. E.; Hollingsworth, D. R.; Reibenspies, J.*Tetrahedron Letters* **1989**, *30*, 4775-4778.

(11) Levin, J. L.; Turos, E.; Weinreb, S. M.*Synth. Commun.* **1982**, *12*, 989-939.

(12) (a) Loudon, G. M.; Radhakrishna, A. S.; Almond, M. R.; Blodgett, J. K.; Boutin, R. H. *J. Org. Chem.* **1984**, *49*, 4272-4276. (b) Almond, M. R., Stimmel, J. B.; Thompson, E. A.; Loudon, G. M. Hofmann*Org. Synth.* **1987**, *66*, 132-141.

(13) Analysis: Calcd. for $C_{21}H_{26}N_2O$•2HCl: C, 63.79; H,7.14; N, 7.06. Found. C, 63.71; H,7.23; N, 7.15.

(14) For experimental details see McLean, S.; Ganong, A.; Seymour, P. A.; Snider, R. M.; Desai, M. C.; Rosen, T.; Bryce, D. K.; Longo, K. P.; Reynolds, L. D.; Robinson, G.; Schmidt, A. W.; Heym, J. *J. Pharmacol. Exp. Ther.* **1994** *267*, 472-479.

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