inhibitors of MAO-B provides a new direction for efforts aimed at elucidating the mechanism(s) of dose-limiting peripheral neurotoxicity of the vinca alkaloids and the relationships between these toxicities and antitumor activity.

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Potent and Highly Selective Neurokinin Antagonists

Sir:

Receptors for the mammalian tachykinins [substance P (SP), neurokinin A (NKA), and neurokinin B (NKB)] have been classified into three subgroups (NK-1, NK-2, and NK-3) largely on the basis of the activities of selective agonists.[1] The characterization of receptors, an understanding of the pathophysiological roles of the tachykinins, and the possible relevance of selective compounds to therapeutics would be greatly aided by the availability of potent and selective antagonists. Most of the neurokinin antagonists described in the literature are empirically derived from naturally occurring tachykinins by multiple D-amino acid substitution.[2] However, it has not proved possible to obtain highly potent and selective antagonists in this way (see ref 3). We describe here a new approach involving the incorporation of a bicyclic conformational constraint into a SP-related sequence culminating in a competitive antagonist, GR71251, with high affinity (pK_B = 7.7) and selectivity for NK-1 receptors. This strategy may have more general application in the logical and efficient design of antagonists at other peptide receptors.

The molecular mechanisms underlying the activation of cell membrane receptors are essentially unknown. Nevertheless, it is widely believed that binding of an agonist may induce a conformational change in the extracellular domain which is transmitted through the transmembrane region of the receptor. Such a mechanism implies that a peptide agonist might adopt a specific "bioactive conformation" during the receptor activation process. Conceivably, alternative conformers, perhaps energetically disfavored in the naturally occurring agonist, could bind to the receptor without initiating a response. If so, the intrinsic potential for competitive antagonist activity in a peptide sequence might be realized in analogues containing conformational constraints designed to render inaccessible the agonist bioactive conformation. Thus, the antagonist activity of the oxytocin analogue (1-L-penicillaminyl)oxytocin was suggested to result from reduced conformational flexibility compared to the parent hormone.[4] Moreover, Hruby has tentatively associated antagonism in this series with a tendency to populate only one of the two distinct disulfide bridge conformations observed in the X-ray crystal structure of the agonist deaminooxytocin.[5] In applying such considerations to the design of neurokinin antagonists, the first step was to identify key conformational requirements for the receptor-selective agonist activity of analogues of SP.

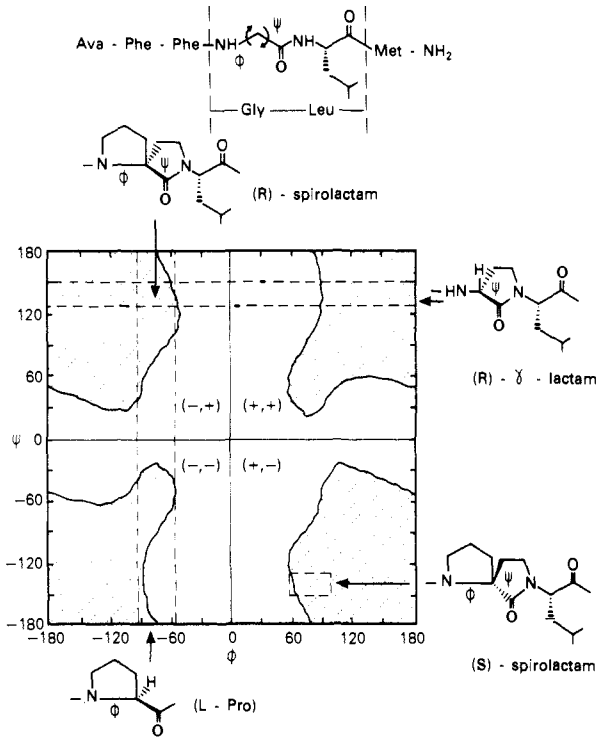

Figure 1. Conformational ϕ,ψ energy map for *N*-acetyl-*N'*-methylglycinamide (2 kcal mol^{-1} contour; low-energy areas are shaded). Parallel dotted lines represent the approximate observed ranges of torsion angles in proline (ϕ) and appropriate γ-lactam (ψ) containing structures from the Cambridge Structural Database.[30] These intersect in the (−,+) region to enclose an area of ϕ,ψ space that approximates to the maximum torsional limits allowed by the (*R*)-spirolactam constraint. A symmetry-related area in the (+,−) region represents ϕ,ψ limits for the (*S*)-spirolactam; ϕ = +75 ± 20°, ψ = −140 ± 10°.

Agonist activity was determined at NK-1 receptors in the guinea pig ileum longitudinal smooth muscle–myenteric plexus strip preparation (GPI), in the presence of atropine (1 μM) to eliminate the indirect effects of activation of neuronal NK-3 receptors.[6] For determination of activity at NK-2 receptors, the rat colon muscularis mucosae preparation (RC) was used. This preparation is believed to contain only NK-2 receptors, as shown by functional[7] and autoradiographic binding studies.[8]

The C-terminal "active core"[9] hexapeptide analogue [Ava[6]]-SP(6–11)[10,11] (1) was chosen as the parent com-

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Table I. EC_{50} Values in NK-1 and NK-2 Preparations for Analogues of [Ava^6]-SP(6–11)

6 7 8 9 10 11
Ava-Phe-Phe-Gly-Leu-Met-NH_2

no.	substitn[a]	EPMR[b] (95% CL) NK-1	EPMR[b] (95% CL) NK-2	calculated EC_{50}, nM NK-1	calculated EC_{50}, nM NK-2
1	Gly^{9c}	6.9 (3.9–10.6)	7.1 (6.7–7.6)	34	1190
2	Ala^9	1.2 (1.0–1.8)	11.1 (9.2–13.8)	5.9	1860
3	D-Ala^9	129.9 (106.4–169.5)	2.7 (2.1–3.5)	638	452
4	Pro^9	3.6 (3.2–4.2)	188.0 (176.0–200.0)	17.7	31500
5	D-Pro^9	400.0 (322.6–500.0)	0.4 (0.3–0.5)	1960	67
6	(*R*)-γ-lactam^{9,10d}	15.3 (13.2–17.8)	0.4 (0.2–0.7)	75	67
7	(*S*)-γ-lactam^{9,10}	>10000	59.7 (45.1–78.7)	>49000	9990
8	(*R*)-spirolactam^{9,10}	62.5 (42.5–85.9)	8.3 (6.4–10.5)	307	1390
9	(*S*)-spirolactam^{9,10}	>20000	>500	>98000	>80000
10	Trp^{11}	892.3 (384.1–3761.7)	>100	4380	>16000
11	D-Met^{11}	>3570	>300	>17000	>50000
substance P		1.0	1.0	4.91 (4.02–5.80) n = 15	167.4 (118.7–216.1) n = 8

[a] Numbering follows SP(1–11) sequence Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2. [b] Agonist activity at NK-1 receptors in quinea pig ileum longitudinal smooth muscle (GPI) and at NK-2 receptors in the rat colon muscularis mucosae (RC) was determined from contractile responses recorded under isotonic conditions, at 35 °C, in the presence of atropine (1 μM), mepyramine (1 μM), methysergide (1 μM), and indomethacin (1 μM).[26] Experiments were conducted as 3 + 3 (GPI) or 2 + 2 (RC) assays against substance P as standard using a randomized block design. Equipotent molar ratios (EPMR) were calculated from the assays and these values have been converted to EC_{50} values by relating them to mean EC_{50} values for the standard agonists in order to give a clearer impression of the selectivity of each compound. [c] All peptide analogues were characterized by reverse-phase HPLC (95% purity), amino acid analysis, and FAB mass spectrometry.[27] [d] See Figure 1 for γ-lactam and spirolactam structures. The protected γ-lactam constraints were synthesized by published procedures.[16] The synthesis of a related (*R*)-spirolactam constraint by a different route from that used here has been described recently.[28]

pound for conformation–activity studies. This analogue is a water-soluble and chemically stable compound with full agonist activity in the NK-1 and NK-2 receptor-containing preparations (GPI and RC, respectively). Modifications of Gly^9 were explored since this residue serves a unique conformational role in peptides and proteins (for example, as a frequent constituent of β-turns[12]). The high torsional flexibility of glycine is represented by the extensive low-energy areas in all quarters of the conformational energy map for *N*-acetyl-*N'*-methylglycinamide (Figure 1). For comparison, low-energy conformations of *N*-acetyl-*N'*-methylalaninamide are restricted mainly to the (−,+) and (−,−) regions of ϕ,ψ space.[13]

Replacement of Gly^9 in the parent hexapeptide by L residues (Ala, Pro), maintained or increased NK-1 agonist activity (**2** and **4**, respectively) and selectivity with respect to the NK-2 receptor, whereas the corresponding D residue substitutions (**3** and **5**) promoted NK-2 activity and selectivity. Both L-Pro and D-Pro modifications have been identified by other groups as important structural determinants of functional activity and binding affinity at neurokinin receptors.[14,15] We interpret these results to indicate a Gly^9 bioactive conformation for the NK-1 receptor in the (−,+) or (−,−) regions of the ϕ,ψ map (Figure 1) and in the (+,+) or (+,−) regions for the NK-2 receptor. The covalent constraint provided by the proline ring allowed further definition of the torsion angles ϕ_9 (NK-1) = −75 ± 20° (L-Pro) and ϕ_9 (NK-2) = +75 ± 20° (D-Pro) in the respective bioactive conformations.

The torsion angle ψ_9 was similarly mapped by introducing γ-lactam constraints[16] having *R* and *S* configurations (Table I). Only (*R*)-γ-lactam **6** was compatible with high NK-1 activity (EC_{50} 75 nM), a result essentially in agreement with the functional activities of the corresponding [pGlu^6]-SP(6–11) analogues reported by Cascieri et al.[17] We interpret the small (approximately 2-fold) reduction in NK-1 activity compared with the parent structure as being consistent with a Gly^9 conformation in the (+,+) or (−,+) regions, but perhaps not lying within the more limited ψ range (+140 ± 10°) constrained by the (*R*)-γ-lactam. In constrast, the 18-fold increase in activity at NK-2 receptors presumably results from closer mimicry of the NK-2 bioactive conformation.

From the above interpretation of structure–activity data, we designed and synthesized a spirobicyclic lactam ring system [(*R*)-spirolactam, Figure 1] which combines the structural features of L-Pro and (*R*)-γ-lactam and thus constrains both torsion angles within the putative NK-1 bioactive range (ϕ_9 = −75 ± 20°, ψ_9 = +140 ± 10°). Conversely, the enantiomeric (*S*)-spirolactam, which locks the residue 9 backbone in the (+,−) region, should exclude both NK-1 and NK-2 bioactive conformations and thereby abolish agonist activity. Analogues containing the latter constraint were of interest as potential receptor antagonists.

As anticipated, the hexapeptide analogue **8** containing the (*R*)-spirolactam constraint was a full agonist at NK-1 receptors in the GPI, albeit about 9-fold less potent than the parent structure **1**. The reduced potency may reflect some departure from the ideal bioactive conformation as proposed for monocyclic (*R*)-γ-lactam derivative **6**. In contrast, (*S*)-spirolactam-constrained analogue **9** showed no agonist activity in the GPI at concentrations up to 30 μM. However, it retained sufficient affinity for the NK-1 receptor to act as an antagonist, causing a parallel rightward shift of the substance P methyl ester concentration–response curve in the GPI (pK_B 5.6; Table II) whereas, in the rat colon, it was a weak partial agonist. Further investigation of this structure demonstrated that even

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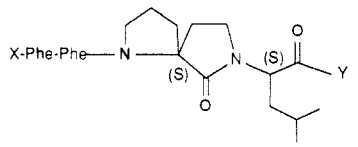
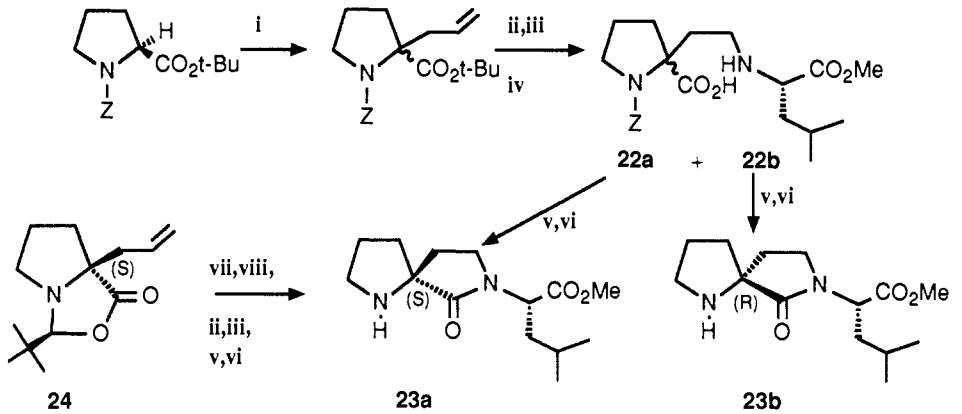
Table II. Antagonist Activities of (*S*)-Spirolactam-Substituted Compounds[a]



no.	X	Y	pK_B[b] NK-1	pK_B[b] NK-2
9	Ava	Met-NH_2	5.60	*c*
12	Ava	D-Met-NH_2	5.66	<4.5
13	Ava	Phe-NH_2	6.28 ± 0.09	5.36
14	Ava	Cha-NH_2	6.43 ± 0.09	5.86
15	Ava	HPhe-NH_2	6.64 ± 0.09	5.84
16	Ava	Trp-NH_2	6.62 ± 0.06	5.27
17	Ava	NH-CH_3	<4.5	<4.5
18	Pro-Gln-Gln	Met-NH_2	5.80	<4.5
19	Pro-Lys-Pro-Gln-Gln	Met-NH_2	6.44 ± 0.04	<4.5
20	Arg-Pro-Lys-Pro-Gln-Gln	Met-NH_2	6.93 ± 0.03	4.8
21 (GR71251)	Arg-Pro-Lys-Pro-Gln-Gln	Trp-NH_2	7.70 ± 0.06	4.8

[a] Abbreviations: Cha, L-cyclohexylalanyl; HPhe, L-homophenylalanyl [(*S*)-2-amino-4-phenylbutanoyl]. [b] pK_B values were determined for potential antagonists against the highly selective NK-1 agonist substance P methyl ester in GPI[29] and against neurokinin A in RC under the conditions described for measuring agonist activity (Table I). Dose ratios (DR) were estimated from the rightward shift of the agonist concentration–response curve obtained in the presence of the antagonist and pK_B values were calculated from the equation pK_B = log [DR − 1] − log [B], where [B] = molar concentration of antagonist. [c] Partial agonist, α = 0.40.

Scheme I[a]



[a] (i) $LiNPr^i_2$, CH_2=$CHCH_2I$, THF; (ii) O_3, CH_2Cl_2 then Ph_3P; (iii) H-Leu-OMe, THF, molecular sieve 3A, $NaCNBH_3$, MeOH; (iv) CF_3CO_2H; (v) *N*-[(dimethylamino)propyl]-*N'*-ethylcarbodiimide, CH_2Cl_2; (vi) H_2, 10% Pd-C, MeOH, HCl; (vii) silica gel, MeOH–H_2O; (viii) Z-O-Su, DMF, Na_2CO_3 (Z = benzyloxycarbonyl; Su = *N*-succinimidyl).

conservative modifications of Phe[7] and Phe[8] substantially reduced antagonist activity. However, considerable structural variation of the C-terminal residue was tolerated with a trend toward increasing activity with increasing size and lipophilicity (compounds **13–16**). This is in contrast to the marked reductions in agonist activity caused by the same substitutions (Trp[11], D-Met[11]) in [Ava[6]]-SP(6–11) (**10** and **11**, respectively; Table I) and suggests that the antagonists adopt a different receptor binding mode.

Progressive increases in antagonist potency were achieved by extension of the N-terminal sequence corresponding to the native SP sequence (compounds **18–20**). The effective N-terminal extension and C-terminal modification were then combined in compound **21** (GR71251) to provide the most potent NK-1 antagonist reported to date (pK_B 7.7). In common with prototype **9**, GR71251 was devoid of agonist activity at NK-1 receptors in the GPI at concentrations up to 30 μM. That the antagonism is of a competitive nature is demonstrated by Schild analysis[18] (pA_2 7.76 ± 0.18, slope 0.98 ± 0.11). GR71251 is highly selective with respect to other neurokinin receptors. Thus, at 30 μM it is without agonist activity at NK-2 receptors in RC or NK-3 receptors in rat portal vein (RPV).[19] In terms of antagonist activity, it is approximately 1,000-fold selective over NK-2 receptors (pK_B 4.8) and NK-3 receptors (antagonism of NKB-induced contractions of RPV; pK_B < 4.6). Furthermore, it is essentially inactive against non-peptide agonists (acetylcholine and histamine in the GPI—pK_B < 5.0). Also, in the guinea pig gallbladder in vitro, up to 10 μM, it caused no shift in the concentration–response curves to the two neuropeptides, cholecystokinin octapeptide and bombesin.

(*S*)- and (*R*)-spirolactam pseudodipeptide esters (**23a** and **23b**) were prepared initially by using a nonchiral route via the separable diastereoisomeric intermediates **22a,b** (Scheme I). The unequivocal configurational assignment followed from a subsequent stereospecific synthesis of (*S*)-spirolactam **23a** from the known chiral (*S*)-α-allylproline derivative **24** [$[\alpha]_D$ −12.2°, (*c* = 1.8, $CHCl_3$) [lit.[20]

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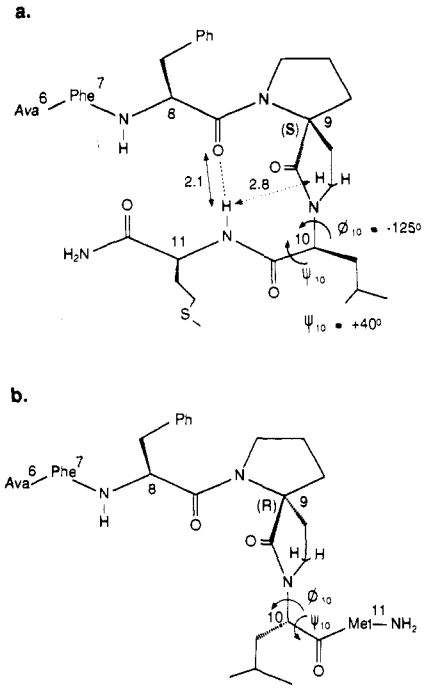

Figure 2. Proposed solution conformations of spirolactam-containing peptides, as determined from ^{1}H NMR data and energy calculations. (a) (*S*)-spirolactam (compound **9**). The conformation shown lies within the major low energy area of ϕ_{10},ψ_{10} conformational space for the model dipeptide analogue, CH_3CO-(*S*)-spirolactam-$NHCH_3$, and closely resembles a classical type II′ β-turn.[12,22] An intramolecular hydrogen bond (linking the NH of Met^{11} and CO of Phe^8) of acceptable geometry[31] is evidenced by the low value of the temperature coefficient of the Met^{11}-NH resonance (-1.0×10^{-3} ppm/K in DMSO-d_6 at 298–338 K).[32] The conformation is also consistent with the NOE observed between the Met^{11}-NH and a γ-lactam ring proton (modeled distance 2.8 Å). (b) (*R*)-spirolactam (compound **8**). The extended conformation shown is favored by energy calculations. ^{1}H NMR studies failed to identify intramolecular hydrogen bonding or to provide other evidence for a predominant turn conformation in DMSO-d_6 solution. Models were constructed with standard geometries for peptide fragments[33] and from structures in the Cambridge Structural Database.[30] Conformational energy was calculated as a function of rotation about the ϕ_{10},ψ_{10} torsion angles using a published force field.[34]

$[\alpha]_D$ −13.1° (c = 1.8, $CHCl_3$)]]. After ester hydrolysis and appropriate amino protection [*tert*-butoxycarbonyl (Boc) or (9-fluorenylmethoxy)carbonyl (Fmoc)] the spirolactam constraints were incorporated into peptide analogues by using the Fmoc-polyamide solid-phase strategy[21] or standard solution-phase methods.

Molecular modeling studies indicate that the (*S*)-spirolactam is an effective replacement for the (i + 1)th residue of a classical Type II′ β-turn[12,22] (Figure 2a) whereas the (*R*)-spirolactam favors an extended conformation (Figure 2b). ^{1}H NMR measurements (including temperature coefficients of NH resonances and nuclear Overhauser enhancement [NOE] observed in ROESY experiments[23]) on [Ava^6]-SP(6–11) analogues **8** and **9** in dimethyl sulfoxide-d_6 (DMSO-d_6) solution support this conclusion. Structure–activity relationships are consistent with a receptor binding model for compounds **20** and **21** in which the N-terminal (1–8) residues bind in an analogous fashion to SP itself, whereas the C-terminal (10 and 11) residues are diverted to a nonactivating binding mode by the (*S*)-spirolactam-constrained β-turn. The presence of a C-terminal residue is essential for antagonist activity in this series (see, e.g., compound **17** in Table II).

The present study represents a new, systematic approach to the development of peptide receptor antagonists based on the rational design of a bicyclic backbone constraint derived from agonist conformation–activity relationships. This constraint eliminates receptor activating conformations but allows the expression of residual binding affinity in the peptide as antagonist activity. The availability of selective and potent NK-1 antagonists such as those described here, together with cyclic peptides reported recently as NK-2 antagonists,[24,25] will allow more rigorous characterization of neurokinin receptor subtypes in different tissues than was formerly possible. The opportunity now exists to investigate further the pathophysiological roles of the tachykinins and hence to predict the possible therapeutic potential of neurokinin receptor antagonists.

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