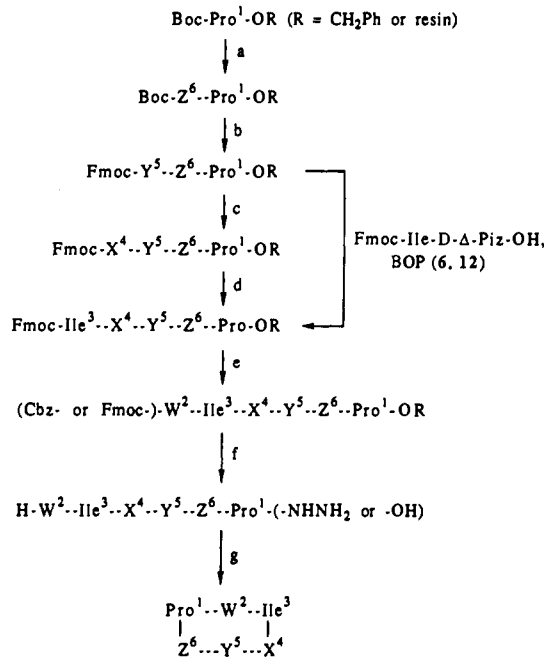
Scheme I.[a] Synthesis of Cyclic Hexapeptides



[a] (a) HCl or TFA; Boz-Z^6-OH, BOP;[b] (b) HCl; Fmoc-Y^5-Cl or Fmoc-(N^δ-Boc)Orn-OH, BOP (6, 8); (c) piperidine or Et_2NH; Fmoc-X^4-Cl; (d) piperidine or Et_2NH; Fmoc-Ile-Cl or Fmoc-Ile-Cl/AgCN/toluene/80 °C (3, 5, 13) or Fmoc-Ala-Cl (15); (e) piperidine or Et_2NH; Fmoc-W^2-OH, BOP or Fmoc-D-Phe^2-Cl (2) or Cbz-D-Phe^2-Cl (3) or Boc-D-(O-Et)TyrOH, BOP (13); (f) piperidine or Et_2NH; NH_2NH_2 or H_2, $Pd(OH)_2$ (3) or HCO_2H (13); (g) *i*-$C_5H_{11}ONO$ or DPPA[c] (3, 4, 13); compounds 6 and 8 were obtained by treatment with HCO_2H and TFA, respectively, to remove the N^δ-Boc group on Orn^5; compound 9 was obtained by hydrogenolysis (H_2, $Pd(OH)_2$) to remove the N^δ-Cbz group on Ppz^5; compound 5 was obtained by hydrogenolysis (H_2, $Pd(OH)_2$) to remove the N^δ-Cbz group on D-Piz^4, followed by oxidation to D-Δ-Piz^4 with *t*-BuOCl. Compound 4 was prepared on solid phase using Boc protection, TFA deblocking, and symmetrical-anhydride couplings. The linear hexapeptide was cleaved from the resin with HF and cyclized with DPPA. [b] BOP = [(benzotriazol-1-yl)oxy]tris(dimethylamino)phosphonium hexafluorophosphate. [c] DPPA = diphenyl phosphoroazidate.

good potency and aqueous solubility but shows that the potency-enhancing modifications at the 2- and 4-positions are not strictly additive.

The importance of the D-Phe^2-Ile^3 dipeptide in the cyclic hexapeptide series suggests a possible structural homology with the identical dipeptide[14] or the D-(OEt)Tyr^2-Ile^3 dipeptide moiety[4] found in many oxytocin antagonists more closely related to the structure of the hormone. Consistent with this idea is the observation that D-(OEt)Tyr^2 analogue 13 possesses good binding affinity. This homology, however, has not offered fully predictive value for antagonist design. We continue to try to understand the true structural relationship between the two antagonist classes.

In summary, the structure–activity profile for cyclic hexapeptide analogues related to the natural product-derived lead 1 shows that high levels of oxytocin receptor affinity can be realized with certain amino acids at the 2- and 4-positions and that aqueous solubility can be increased substantially by introducing basic groups at the 5- and 6-positions. Several potent and selective oxytocin receptor ligands which have sufficient aqueous solubility for iv administration have been identified. All of the new high-potency analogues cited here have been characterized as functional oxytocin antagonists similar to L-365,209 (1) in the blockade of oxytocin-stimulated rat uterine contractions in vitro and in vivo.[5] Furthermore, these compounds behave as pure antagonists and have shown no oxytocin agonist activity in stimulating phosphatidylinositol turnover in vitro or rat uterine contractions in vitro or in vivo. These detailed studies will be reported separately. Such compounds may have utility as research tools and in certain therapeutic applications.

Acknowledgment. We are pleased to acknowledge the contributions of Dr. S. M. Pitzenberger (^1H NMR studies), C. F. Homnick (HPLC analysis), J. P. Moreau (elemental analysis), and V. W. Finley (manuscript preparation). We also thank Dr. P. S. Anderson for encouragement and support.

† New Lead Pharmacology.
‡ Pharmaceutical Research and Development.

R. M. Freidinger,* P. D. Williams, R. D. Tung
M. G. Bock, D. J. Pettibone,† B. V. Clineschmidt†
R. M. DiPardo, J. M. Erb, V. M. Garsky
N. P. Gould, M. J. Kaufman,‡ G. F. Lundell
D. S. Perlow, W. L. Whitter, D. F. Veber
Departments of Medicinal Chemistry, New Lead Pharmacology, and Pharmaceutical Research and Development, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486
Received February 26, 1990

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Vinblastine and Vincristine Are Inhibitors of Monoamine Oxidase B

Sir:

Vinblastine (VBL) and vincristine (VCR) are widely used antitumor agents, and either VBL or VCR is an indispensable part of most curative and adjuvant chemotherapy regimens for metastatic malignancy.[1,2] The major mechanism of antitumor action attributed to these vinca alkaloids is cellular metaphase arrest, caused when the compounds disrupt cell microtubule assembly. VBL and VCR are structurally very similar, differing only in the state of oxidation of a single carbon atom attached to a nitrogen atom on the aspidosperma ring (Chart I). Despite this subtle structural difference, VBL and VCR exhibit different potencies, clinical applications, metabolic fates, and dose-limiting toxicities. Ample evidence indicates that the vinca alkaloids are extensively metabolized in mammals.[3-5] However, the possible role of drug metabolism in the mechanism(s) of action and/or dose limiting side-effects of the vinca alkaloids is unknown. Furthermore, the precise molecular basis for neurotoxicity[6] for this im-

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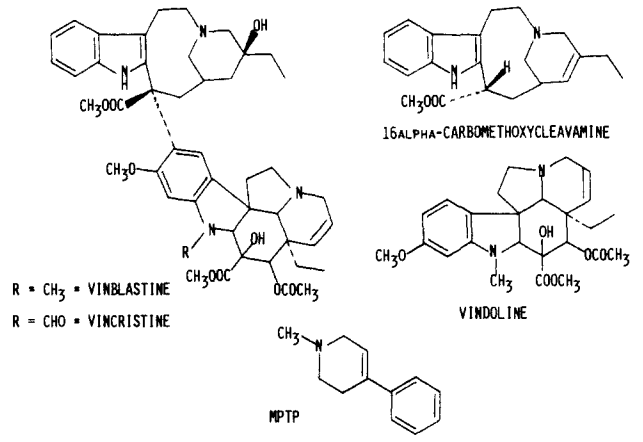
Chart I



portant group of anticancer drugs is unclear.

Previous investigations in our laboratories have focused on elaborating biochemical and chemical mechanisms by which vinca alkaloids are oxidized. We have examined peroxidases,[7,8] copper oxidases,[9-12] and an enzyme system of a bacterium[13] and have identified the structures of metabolites formed from both monomeric and dimeric vinca alkaloids. Detailed investigations have clearly established that oxidative vinca alkaloid biotransformations usually involve one-electron oxidation,[7,9,11,14-16] leading to the formation of reactive radical, enamine, and iminium intermediates. In our continuing examination of enzymes known to catalyze one-electron oxidation/reduction reactions, we examined brain and hepatic mitochondria, and purified monoamine oxidase (MAO) as an enzyme that may be implicated in the metabolism of the vinca alkaloids.

MAO catalyzes oxidations of endogenous neurotransmitter monoamines and various exogenous primary, secondary, and tertiary amines. MAO exists in distinct forms designated A and B. The tissue distribution, assay, isolation, and properties of MAO-A and MAO-B have been recently reviewed.[17-19] Within neural tissue, MAO-A activity has been correlated with noradrenergic activity and norepinephrine content of the cell type. MAO-B is predominantly localized in serotonin-rich regions of neural

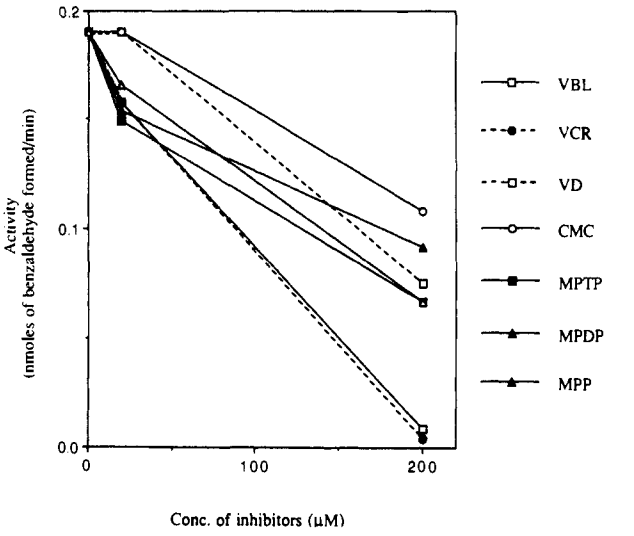


Figure 1. Inhibition of benzylamine oxidation catalyzed by a rat brain mitochondrial fraction. Brain tissue from three male Sprague-Dawley rats was pooled to prepare mitochondrial fractions by the method of Roth.[28] Protein concentrations were determined[29] with bovine serum albumin as the standard. Reaction mixtures contained 0.05 M sodium phosphate at pH 7.2, benzylamine (0.2 mM), various indicated concentrations of possible inhibitors, and 1.8 mg of mitochondrial protein in a final assay volume of 1.0 mL. Reactions were conducted at 30 °C and were initiated by addition of mitochondria. Initial velocities of product formation were determined spectrophotometrically at 250 nm.[17] The abbreviations used are VBL = vinblastine, VCR = vincristine, VD = vindoline, CMC = 16α-carbomethoxycleavamine, MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPDP = 1-methyl-4-phenyl-2,3-dihydropyridinium, and MPP = 1-methyl-4-phenylpyridinium.

tissue, as well as in extraneuronal cells, e.g., glia cells.[18,20-22] Both A and B forms of the enzyme are in the peripheral nervous system, a major site of VCR neurotoxicity.

Relationships between MAO and neurotoxicity have not been established with the vinca alkaloids. There is, however, a common structural feature (Chart I) between the vindoline portion of the vinca alkaloid dimers and the tertiary allylamine moiety within the piperidine ring of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin that causes Parkinsonian symptoms in primates.[23,24] MAO-B catalyzes the oxidation of MPTP to the dihydropyridine derivative $MPDP^+$ and to the fully oxidized pyridinium derivative MPP^+.[25] MPP^+ accumulates in the *substantia nigra* within the brain,[26] and this is most likely involved in the neurotoxic effects of MPTP. The presence of the tertiary allylamine moiety in vinca alkaloids prompted previous studies on the metabolism of

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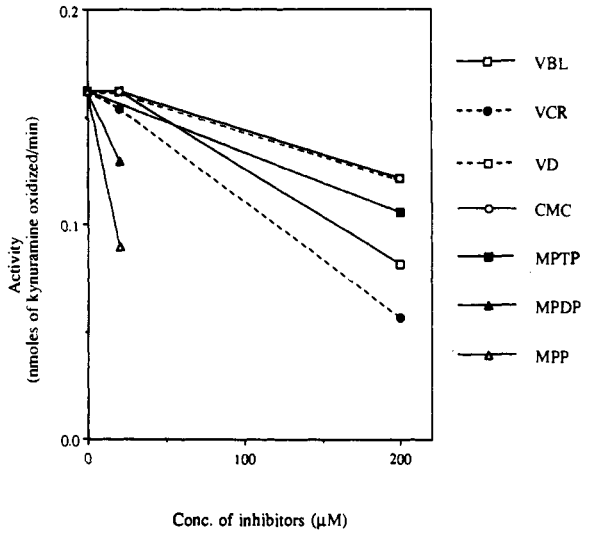

Figure 2. Inhibition of kynuramine oxidation catalyzed by rat brain mitochondrial fraction. Mitochondrial fractions were prepared as described in Figure 1. Reaction mixtures contained 0.05 M sodium phosphate at pH 7.2, kynuramine (0.1 mM), various indicated concentrations of possible inhibitors, and 1.8 mg of brain mitochondrial protein in a final assay volume of 1.0 mL. Reactions were conducted at 30 °C and were initiated by addition of mitochondria. Initial velocities of product formation were determined spectrophotometrically at 314 nm.[17] Abbreviations are as listed in Figure 1.

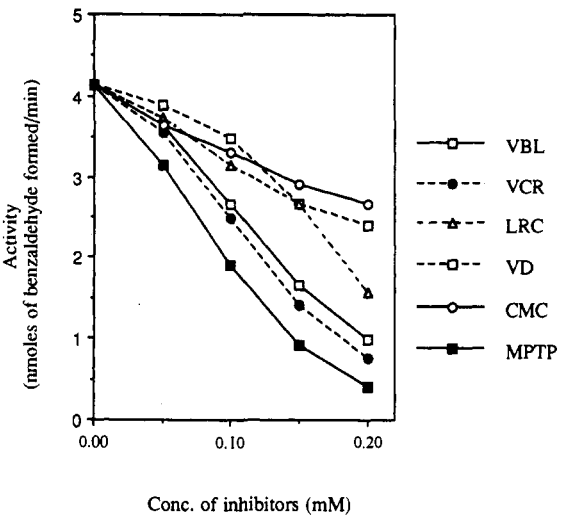

Figure 3. Inhibition of purified bovine liver MAO-B. MAO-B was purified by the method described by Salach and Weyler[19] until the enzyme was >80% pure by SDS polyacrylamide gel electrophoresis (Coomassie Blue staining), with a specific activity of 2.3 units/mg. Units of enzyme activity were defined as the amount of enzyme required to catalyze oxidation of 1 μmol of substrate per min at 30 °C and pH 7.2. Assays were carried out as described in Figure 1 with the exception that 2 μg of purified MAO-B was used for each assay instead of a crude mitochondrial fraction. All reactions contained 0.1 mM benzylamine and the indicated concentration of inhibitors. The abbreviations used are VBL vinblastine, VCR vincristine, LRC leurosine, VD vindoline, CMC = 16-carbomethoxycleavamine, and MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

MPTP by enzymes that catalyze vinca alkaloid oxidation.[27] Since MPTP is both a substrate and an inhibitor for MAO-B, it was logical to examine whether vinca alkaloids were either substrates or inhibitors for that enzyme.

Preliminary experiments were conducted with mitochondria from rat brain. These mitochondrial preparations were used to catalyze oxidation of either kynuramine or benzylamine alone or in the presence of VBL, VCR, MPTP, $MPDP^+$, MPP^+, or the antitumor-inactive monomeric vinca alkaloids vindoline and 16α-carbomethoxycleavamine. The oxidation of kynuramine is catalyzed by both MAO-A and -B, while the oxidation of benzylamine is predominantly catalyzed by MAO-B.[17,18] Inhibition of kynuramine or benzylamine oxidation would suggest vinca alkaloid interaction with MAO as either a substrate or an inhibitor. For the oxidation of 0.1 mM benzylamine catalyzed by intact rat brain mitochondria (see Figure 1), the relative inhibitory effects at 0.2 mM inhibitor concentrations were VBL = VCR > MPTP = MPP^+ > vindoline > $MPDP^+$ > 16α-carbomethoxycleavamine. For the oxidation of 0.1 mM kynuramine catalyzed by intact rat brain mitochondria (Figure 2), the relative inhibitory effects were MPP^+ > $MPDP^+$ > VCR > VBL > MPTP > vindoline = 16α-carbomethoxycleavamine.

Subsequent experiments with highly purified MAO-B isolated from beef liver mitochondria indicated that VCR and VBL were, however, slightly less effective inhibitors than MPTP. In studies with the purified enzyme, MAO-B inhibition was evaluated at 0.1 mM benzylamine and from 0 to 0.2 mM concentrations of inhibitors. As shown in Figure 3, the relative inhibitory effects were as follows: MPTP > VCR > VBL > leurosine > vindoline > 16α-carbomethoxycleavamine. A preliminary evaluation of VBL as an inhibitor was accomplished by initial velocity experiments performed with varied concentrations of benzylamine (0.05, 0.1, 0.2, and 0.3 mM) at fixed concentrations of VBL (0, 0.05, 0.1, and 0.15 mM). VBL was a competitive inhibitor, with an estimated K_i of 77 μM. The inhibition of MAO-B activity was reversible and not time-dependent, as seen by preincubating the enzyme with VBL for a series of time intervals and then diluting both enzyme and VBL in a standard assay for benzylamine oxidation. In addition, no detectable metabolites were identified when purified MAO-B was incubated with VBL, and the reaction mixture was analyzed by HPLC and TLC at time intervals of 0, 30, 60, and 120 min and 24 h. These results were confirmed by the fact that there was no oxygen consumption from the same reaction mixture when monitored by using previously described methods[30] for an oxygraph equipped with a Clark oxygen probe (YSI Model 4004). Thus, while MPTP, VBL, and VCR are comparable in their ability to inhibit the initial velocity of benzylamine oxidation catalyzed by MAO-B, VBL and VCR differ from MPTP in that the two vinca alkaloids are not substrates for the enzyme.

MAO is an essential component of neurotransmitter metabolism, and it is clear that this enzyme is involved in the metabolically based neurotoxic effects of MPTP. The significance of our observation that vinca alkaloids inhibit MAO-B and its potential importance to the neurotoxicity of these compounds remain to be established. Indeed, little is known of the possible relationship of vinca alkaloids to MAO activity. In the only report published to date, elevated serum levels of MAO enzyme activity in some forms of lung cancer were decreased after treatment with VCR.[31] The basis for this clinical observation, however, was unknown. The current discovery that VBL and VCR are

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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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Jong-Keun Son, John P. N. Rosazza
Michael W. Duffel*
Division of Medicinal and Natural Products Chemistry
College of Pharmacy
University of Iowa
Iowa City, Iowa 52242
Received February 21, 1990

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.

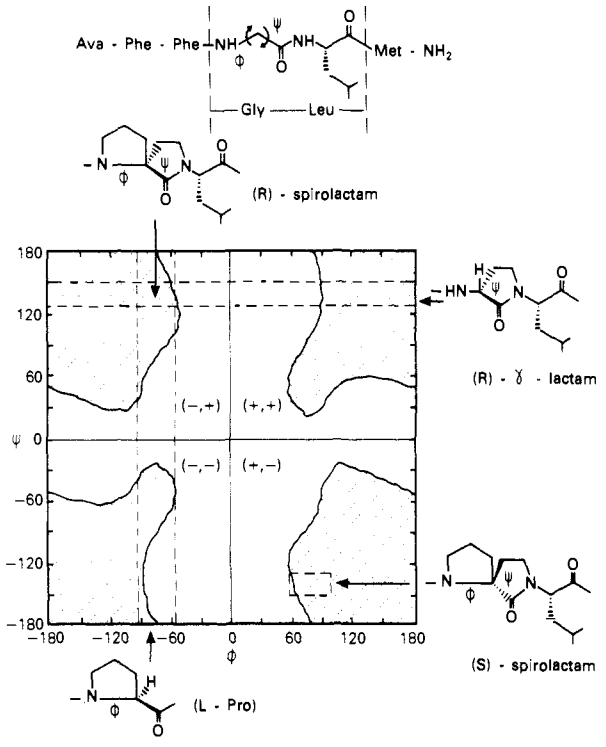

Figure 1. Conformational ϕ,ψ energy map for *N*-acetyl-*N'*-methylglycinamide (2 kcal mol^{-1} contour; low-energy areas are shaded). Parallel dotted lines represent the approximate observed ranges of torsion angles in proline (ϕ) and appropriate γ-lactam (ψ) containing structures from the Cambridge 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; $\phi = +75 \pm 20°$, $\psi = -140 \pm 10°$.

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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