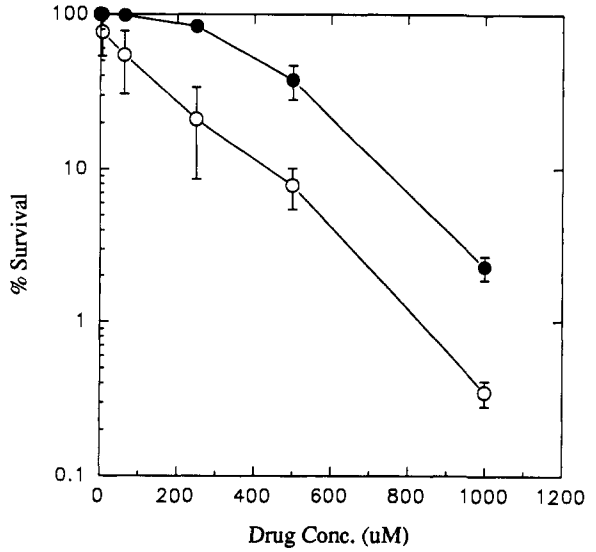

Figure 1. Survival of CHO cells following treatment with 2. Cells were subjected to aerobic or hypoxic conditions for 2 h. Survival was measured by using a clonogenic assay: (●) aerobic, (○) hypoxic. The data points represent the mean ± SE of at least triplicate determinations for each of three separate experiments.

Table III. Cytotoxicities of 1 and 2 under Normal Aerobic and Hypoxic Conditions against CHO Cells

compd	IC_{50} (μM)[a] aerobic	hypoxic
1	3.50 ± 0.46	ND
2	362 ± 63	90 ± 38

[a] Mean ± SE of three experiments carried out at least five drug concentrations. Cells were subjected to aerobic or hypoxic conditions for 2 h before drug exposure. Drug exposure time was 3 h. Survival was measured by a clonogenic assay. ND = not determined. $p < 0.01$ for 2.

chemically unstable and the other potential oxidative metabolites, e.g., monoalkylating metabolite(s) and 3, could not be quantitated and therefore not included in the calculation. The observation that more of 1 was generated in the presence of NADPH generating system suggests a possible involvement of NADPH-dependent cytochrome P-450 reductase, which has been shown to catalyze the reduction of nitromin to nitrogen mustard,[20] in the reduction of 2 to 1. These results provided the first evidence supporting the concept of enhanced bioreduction of 2 to 1 under hypoxic condition.

Subsequently, 2 was tested for its hypoxia-selective cytotoxicity against the Chinese hamster ovary (CHO) cell line under aerobic (95% air/5% CO_2) and hypoxic (95% N_2/5% CO_2) conditions (Figure 1). CHO cells have been shown to possess NADPH cytochrome P-450 reductase and DT-diaphorase which reductively metabolize mitomycin C, an alkylating agent that requires bioreductive activation.[4] The published procedure of Fracasso and Sartorelli[21] with some modifications was used to test for hypoxia selectivity. The results indicated that 1, a compound which does not require bioactivation for its toxicity, was 100-fold more cytotoxic than 2 under aerobic conditions (Table III).

When 2 was incubated with CHO cells under hypoxic conditions, there was a 4-fold enhancement of cytotoxicity as compared to aerobic conditions, on the basis of the IC_{50} values of the cell survivals. The hypoxia selectivity was however less substantial at higher drug concentrations with the enhancement of ca. 1.5–2-fold at the level of IC_{90} or greater.

In summary, these results support the exploration of properly designed sulfoxide compounds as potential anticancer agents against solid tumors, and to our knowledge, this is the first time that metabolism of sulfoxide has been applied in the design of hypoxia-selective alkylating agents. Research is in progress in the application of this methodology to provide more potent and selective cytotoxic drugs.

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Cyclic Pentapeptide Endothelin Antagonists with High ET_A Selectivity. Potency- and Solubility-Enhancing Modifications

Endothelin (ET)-1, a potent vasoconstrictor, consisting of 21 amino acids, was first isolated from porcine aortic endothelial cell culture supernatant.[1] Subsequent studies including a human genomic analysis revealed the existence of two additional related peptides, ET-2 and ET-3.[2,3] The concept is now widely accepted that many mammalian species produce these three isopeptides and that the peptides elicit diverse biological effects on vascular[1,4,5] and nonvascular tissues[6-8] through at least two distinct ET receptor subtypes termed ET_A (selective for ET-1 and ET-2) and ET_B (equally sensitive to all three peptides).[9-11]

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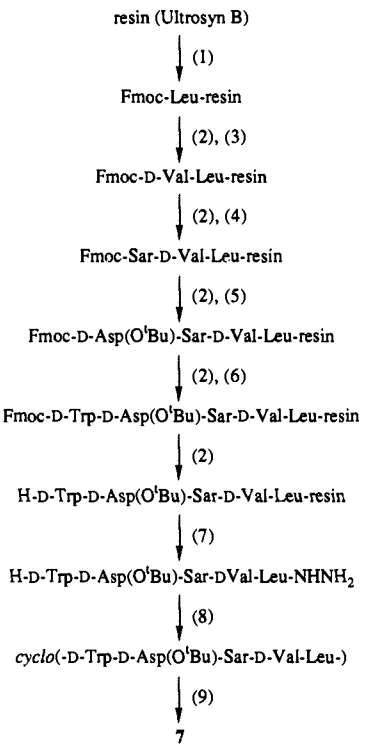
Specific ET receptor antagonists will therefore be very important for clarifying the roles of these ET family peptides in normal physiology and disease states. However, there has been only one report[12] that describes a potent and specific ET_A receptor antagonist but with a relatively high molecular weight. In this communication we report potent and highly selective ET_A receptor antagonists of a novel type of structure.[13]

ET receptor binding inhibitors 1 and 2 (BE-18257A and B) were recently isolated from *Streptomyces misakiensis* in our laboratories.[14,15] Their structures were deduced to be novel cyclic pentapeptides with the DDLDL chirality sequence, *cyclo*(-D-Trp[1]-D-Glu[2]-Ala[3]-D-Val[4]-Leu[5]-) for 1 and *cyclo*(-D-Trp[1]-D-Glu[2]-Ala[3]-D-alloIle[4]-Leu[5]-) for **2**.[16] Conformation analysis of 1 using NMR techniques revealed the presence of two intramolecular hydrogen bonds: namely, a γ'-turn in the D-Glu[2]-Ala[3]-D-Val[4] region and a type II β-turn in the D-Val[4]-Leu[5]-D-Trp[1]-D-Glu[2] region.[17] Further biological studies of **2** have made it clear that this compound antagonizes ET-1-induced vasoconstrictions with a pA_2 value of 5.9 and that the compound is highly selective for ET_A receptors: namely, although **2** inhibits [^{125}I]-ET-1 binding to porcine aortic smooth muscle membranes that are rich in ET_A receptors with an IC_{max50} value of 1.4 μM, very little inhibition of binding to porcine cerebellum membranes that contain exclusively ET_B receptors occurs even at doses of 100 μM.[14] While its selectivity is attractive, the moderate activity and poor water solubility[18] (0.21 mg/mL saline as a sodium salt[19]) of **2** limits its usefulness as a tool in pharmacological studies. We therefore attempted modification of these lead peptides to identify more potent and more soluble antagonists with high ET_A receptor selectivity.

Scheme I. Synthesis of **7**



Method: (1) (Fmoc-Leu-)$_2$O and DMAP[a]/DMF; (2) 20% piperidine/DMF; (3) Fmoc-D-Val-OH, HOBT,[b] and DIPC[c]/DMF; (4) Fmoc-Sar[d]-OH, HOBT, and DIPC/DMF; (5) Fmoc-D-Asp(O^{t}Bu)-OH, HOBT, and DIPC/DMF; (6) Fmoc-D-Trp-OH, HOBT, and DIPC/DMF; (7) (i) 10% H_2NNH_2/dioxane–MeOH (9:1), room temperature, 2 h, (ii) dry ice; (8) (i) 3.1 M HCl–dioxane (39 mL)/DMF (1 mL), −50 °C, (ii) isoamyl nitrite, −30 to −20 °C, 1.5 h, (iii) dilution with DMF (15 mL), −60 °C, (iv) triethylamine (28 mL), −60 to −20 °C, overnight, (v) evaporation followed by preparative TLC on SiO_2 (chloroform–MeOH 10:1, R_f = 0.68); (9) (i) TFA[e] (9.5 mL)–EDT[f] (0.5 mL), 0 °C to room temperature, 1 h, (ii) evaporation followed by trituration with ether.

[a] DMAP = 4-(dimethylamino)pyridine. [b] HOBT = 1-hydroxybenzotriazole. [c] DIPC = 1,3-diisopropylcarbodiimide. [d] Sar = sarcosine. [e] TFA = trifluoroacetic acid. [f] EDT = 1,2-ethanedithiol.

Cyclic pentapeptide analogues were synthesized by deprotection following cyclization of side chain-protected linear pentapeptide hydrazides having appropriate amino acid sequences. These hydrazides were prepared by Fmoc solid-phase peptide synthesis. For example, **7** was synthesized as follows: first, as outlined in Scheme I, 10.8 g of a polyamide resin (Ultrosyn B, Pharmacia LKB Biochrom Ltd., Cambridge, England) was treated with DMAP (132 mg, 1.08 mmol) and a symmetrical acid anhydride prepared from Fmoc-Leu-OH (3.27 g, 9.25 mmol) and

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(18) Solubilities of sodium salts[19] or **2**, **4**, **5**, and **6** were determined as follows: first, an excess amount of a sodium salt of each compound was shaken with saline for 6 h at room temperature. The resulting suspension was clarified by centrifugation at 3000 rpm for 10 min. An aliquot of the supernatant was diluted with EtOH and analyzed by HPLC (0.1% TFA in 55% aqueous MeOH, 280-nm detection) on a reversed-phase column (4.6 i.d. × 250 mm; Capcell Pak C_{18}, Shiseido Co. Ltd., Tokyo, Japan). The concentration of the compound was calculated from the measured peak area by reference to those of standards chromatographed under the same conditions. In the case of a sodium salt of **6**, a viscous but transparent liquid was obtained even at the nominal concentration of 1.3 g/mL.

(19) Sodium salts of **2**, **4**, **5**, and **6** were prepared by treatment of each corresponding free acid with $NaHCO_3$. For example, a sodium salt of **6** was prepared as follows: **6** of a free acid form (5.02 g, 8.21 mmol) was dissolved in MeOH (ca. 10 mL) and to the solution was dropwise added a solution of $NaHCO_3$ (690 mg, 8.21 mmol) in a minimum amount of H_2O. After evolution of CO_2 had subsided, the solution was concentrated to dryness in vacuo. The residue was then dissolved in MeOH (ca. 4 mL) with occasional sonication. Precipitation occurred on standing and the precipitate was filtered off, washed with a small amount of MeOH–ether (1:1), and dried in vacuo to give a sodium salt of **6** as a colorless powder (4.63 g, 7.33 mmol, 89%).

Table I. Receptor Binding Activity Data for Cyclic Pentapeptides

no.	compound	ET_A:[a] IC_{max50}[c] (μM)	ET_B:[b] IC_{50}[c] (μM)
1	*cyclo*-(-D-Trp^1-D-Glu^2-Ala^3-D-Val^4-Leu^5-)	3.0 ± 0.46	>100 (3)
2	*cyclo*-(-D-Trp^1-D-Glu^2-Ala^3-D-alloIle^4-Leu^5-)	1.4 ± 0.19	>100 (2)
3	*cyclo*-(-D-Trp^1-D-Asp^2-Ala^3-D-Val^4-Leu^5-)	0.11 ± 0.012	>100 (1)
4	*cyclo*-(-D-Trp^1-D-Glu^2-Pro^3-D-Val^4-Leu^5-)	0.41 ± 0.0088	>100 (4)
5	*cyclo*-(-D-Trp^1-D-Asp^2-Ala^3-D-Val^4-Pro^5-)	8.5 ± 0.87	>100 (2)
6	*cyclo*-(-D-Trp^1-D-Asp^2-Pro^3-D-Val^4-Leu^5-)	0.022 ± 0.0017	18 ± 2.2
7	*cyclo*-(-D-Trp^1-D-Asp^2-Sar^3-D-Val^4-Leu^5-)	0.032 ± 0.0021	30 ± 0.6
8	*cyclo*-(-D-Trp^1-D-Asp^2-MeAla^3-D-Val^4-Leu^5-)	0.034 ± 0.0046	47 ± 8.2
9	*cyclo*-(-D-Trp^1-D-Asp^2-Pro^3-D-Val^4-MeLeu^5-)	0.035 ± 0.0010	>100 (2)

[a] Porcine aortic smooth muscle membranes. [b] Porcine cerebellum membranes. [c] IC_{max50} or IC_{50} values are group means ± SE for three or more replicate determinations unless otherwise noted in parentheses.

1,3-dicyclohexylcarbodiimide (1.01 g, 4.9 mmol) to yield Fmoc-Leu-resin (0.093 mmol/g, 10.89 g). Using an aliquot (1.0 g) of the Fmoc-Leu-resin, a resin-bound side chain-protected linear pentapeptide, H-D-Trp-D-Asp(O^{t}Bu)-Sar-D-Val-Leu-resin, was prepared with a manual peptide synthesizer (Biolynx 4175, Pharmacia LKB Biochrom Ltd., Cambridge, England). According to the instructions for the standard operation of the synthesizer, 2.5 equiv of N-fluorenylmethoxycarbonylated (side chain-protected, if necessary) amino acid, HOBT, and DIPC were used in each condensation step. The resulting resin-bound peptide was washed in succession with DMF (6 mL × 3), *tert*-amyl alcohol (6 mL × 2), acetic acid (6 mL × 2), *tert*-amyl alcohol (6 mL × 2), DMF (6 mL × 3), and ether (6 mL × 3), and was then dried under reduced pressure. The resin-bound peptide was next treated with 4 mL of 10% hydrazine hydrate in dioxane/MeOH (9:1). Neutralization (pH 6) of the solution with dry ice followed by evaporation yielded a peptide hydrazide as a viscous solid (crude, 28 mg, 42%). The cleaved peptide hydrazide (27 mg) was then treated with isoamyl nitrite (12.4 μL, 92.4 μmol) at pH 2 at −30 to −20 °C. Cyclization of the resulting azide at the Leu^5-D-Trp^1 bond was effected by making the solution basic (pH 8–9) with triethylamine to give a side chain-protected cyclic pentapeptide (16 mg, 62%). Deprotection of the protected cyclic pentapeptide (15 mg) with TFA/EDT (95:5) followed by trituration with ether afforded the target compound **7** as a colorless powder (10.3 mg, 76%). The synthesis of **4** was started from Fmoc-Ala-resin to avoid formation of the diketopiperazine, (-D-Val-Pro-). In the case of the synthesis of **9**, an attempt to introduce D-Val by the above-mentioned method resulted in incomplete acylation. The introduction of D-Val was eventually achieved by treatment with the symmetrical acid anhydride (Fmoc-D-Val-)$_2$O and DMAP. The purity of the final products was found to be more than 98% by HPLC analysis. All of the compounds exhibited ^{1}H-NMR spectra and high-resolution fast atom bombardment mass spectra, both of which were consistent with the assigned structures.

Analogues thus obtained were assayed for their ability to inhibit [^{125}I]-ET-1 binding to ET_A and ET_B receptors according to previously described procedures.[14] Table I lists assay results for analogues **3–9** along with those for leads **1** and **2**.

First, D-Glu^2 in **1** was modified because we have supposed that the side-chain carboxyl group of this residue mimics the C-terminal carboxyl group of ET-1 and because it has been reported that the C-terminal carboxyl group of ET-1 is important for expressing biological activity:[20] the replacement with D-Asp^2 (**3**) resulted in a marked increase in ET_A receptor binding inhibition. On the other hand, our effort to improve solubility focussed on replacement of an amino acid residue with an imino acid residue such as Pro, because it has been reported that the incorporation of a tertiary peptide bond can enhance solubility.[21,22] Mainly for the purpose of enhancing solubility, Ala^3 or Leu^5 was replaced with Pro, because in this case the NH hydrogens of these two residues as well as that of D-Trp^1 do not participate in the formation of the above-mentioned intramolecular hydrogen bonds. As expected, both replacements increased solubility: namely, solubilities of **4** and **5** as a sodium salt were found to be 120 and 110 mg/mL saline, respectively. However, the replacement of Ala^3 with Pro^3 (**4**) rather unexpectedly resulted in a considerable enhancement of ET_A receptor binding inhibition, whereas the replacement of Leu^5 in **3** with Pro^5 (**5**) caused a marked decrease in activity. This implies that Pro^3 may be important for conformational reasons and that the isobutyl side chain of Leu^5 may have a direct and major influence on the interaction with ET receptors. Next, we combined these D-Asp^2 substitution and Pro^3 substitution findings. The double substitution of D-Asp^2-Pro^3 for D-Glu^2-Ala^3 (**6**) resulted in an additive effect: i.e., the inhibition activity of **6** for ET_A receptors was enhanced by about 2 orders of magnitude over that of **1** with retention of high selectivity for ET_A receptors. The Sar^3 and MeAla^3 substitution analogues of **6** (**7** and **8**) also proved to be almost equipotent to **6**. In contrast to the marked decrease in activity caused by the replacement of Leu^5 in **3** with Pro^5 (**5**), that of Leu^5 in **6** with MeLeu^5 (**9**) resulted in only a slight decrease in activity. This clearly confirms the importance of the isobutyl side chain. It is noteworthy that none of the chemical modifications performed thus far have changed the high ET_A selectivity of the lead compounds: for example, the analogues **6–9** all inhibited [^{125}I]-ET-1 binding to ET_A receptors ca. 1000-fold more potently than binding to ET_B receptors.

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According to the previously described method,[14] the representative compound 6 has been further characterized and it has been found that this compound potently antagonizes Et-1-induced contraction of porcine coronary arteries with a pA_2 of 7.4, a value that is in accord with its IC_{max50} value for ET_A receptors (22 nM), but does not antagonize vasoconstrictions induced by ET-3, norepinephirine, or potassium chloride. Compound 6 has been also found to be highly water-soluble (>1 g/mL saline as a sodium salt).

Compound 6 (BQ-123) may therefore be an interesting tool for studying the physiological and pathophysiological roles of endothelins and their receptor subtypes, especially ET_A receptors. Extensive studies of this compound are now in progress.

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Supplementary Material Available: Physicochemical data including melting point, IR, high-resolution MS, NMR, and HPLC data for compounds 3–9 and NMR data on conformation analysis of compound 1 (4 pages). Ordering information is given on any current masthead page.

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Book Reviews

Introduction to Stereochemistry and Conformational Analysis. By Eusebio Juaristi. John Wiley & Sons, Inc., New York. 1991. xv + 331 pp. 16 × 24 cm. ISBN 0-471-54411-6. $49.95.

Although stereochemistry is a fundamental and integral part of organic and biological chemistry, its relevance continues to increase with the advent of stereoselective syntheses of more sophisticated molecules and the more clearly appreciated significance of stereoisomers in biology. This textbook provides highly readable descriptions of the most important principles of stereochemistry and conformational analysis. It describes a number of important topics such as chirality and prochirality, chirotropic properties, stereochemistry of organic reactions, stereochemical descriptors, determination of absolute configuration, and means for evaluating optical purity. Also presented in this book are detailed accounts of stereogenicity, asymmetric synthesis, resolution of racemates, conformational analysis of alkenes and heterocycles, comparison of theoretically calculated and experimentally determined conformational energies, and anomeric and gauche conformational effects. Each of the 18 chapters is followed with a list of pertinent references. Adequate author and subject indexes are also included.

Introduction to Stereochemistry and Conformational Analysis clearly describes the major concepts and principles of stereochemistry. This textbook is an excellent introduction for chemistry students. It provides a lucid description of timely principles of stereochemistry that may also benefit many practicing chemists.

Staff

Organic Photochemistry: A Visual Approach. By Jan Kopecký (Long Island University). VCH, New York. 1991. ix + 285 pp. 16 × 24 cm. ISBN 0-89573-296-3. $65.00.

Many synthetic chemists are reluctant to use photochemistry. Most texts on the subject tend to emphasize photophysics and detailed mechanistic analysis. Consequently, there is a belief that one needs to surmount a considerable learning curve before attempting photochemical reactions. This introductory text on organic photochemistry should do much to dispel that misperception. The book will be specially useful for synthetic and medicinal chemists who have no background in photochemistry, but wish to make use of it in their endeavors.

The "Visual Approach" in the title refers to the unusual format that is used. The book has no running or continuous text. Rather, it consists of a series of figures on the left half of the page with brief captions on the right. Most of the figures/captions are self-contained. That is, they can be understood without having read the earlier material. Thus, the reader can scan the chapters, find an interesting transformation, and incorporate it into his/her work. Each caption contains extensive references to the primary and review literature. These allow the interested reader to pursue each topic in more detail. In an age where information is becoming increasingly available, the limiting factor for most scientists is time, rather than available information. Thus, useful shortcuts such as this visual presentation format should be taken seriously.

The first four chapters cover photophysics and theoretical concepts. The next nine chapters are on reaction chemistry grouped by functional groups of the reactant (e.g. alkenes, nitrogen-containing compounds, singlet oxygen). The last three chapters cover preparative photochemical techniques, factors influencing photochemical reactions, and applications of photochemistry. There is a subject index, but no author index.

This self-contained approach is very useful for presenting reaction chemistry where relationships between the individual topics are not critical. For example, one could understand and make use of the di-π-methane rearrangement without necessarily knowing about the Norrish I reaction. In my opinion, the format is less successful at presenting the fundamentals of photochemistry. For example, exciplexes, electron transfer, and energy transfer are all interrelated phenomena. A conventional, unified treatment of these would be more effective. Photochemists, or those who intend to make extensive use of photochemistry, would probably want to own a traditional text in addition to this one.

In sum, this is a worthwhile book which fills an important need: presenting photochemistry to the nonspecialist. The unique format makes it possible to rapidly find relevant information.

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Textbook of Pharmacology. Edited by C. M. Smith and A. M. Reynard. W. B. Saunders Company, Philadelphia. 1992. xviii + 1213 pp. 22 × 28.5 cm. ISBN 0-7216-2442-1. $45.00.

The preface to this multiauthored textbook states that "The book is designed to serve, not as a reference source, but as a readable text for the initial course in medical pharmacology [to be] used by the medical student and eventual medical practitioner." The book covers all the traditional topics of a standard pharmacology textbook, in addition to chapters on diagnostic