1,3-Diarylindan-2-carboxylic Acids, Potent and Selective Non-Peptide Endothelin Receptor Antagonists

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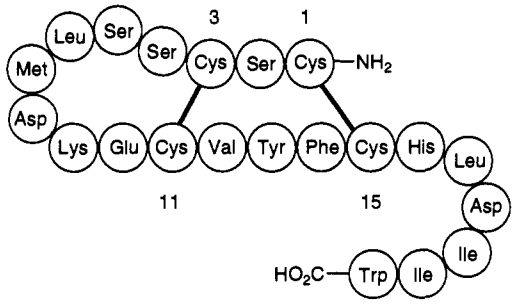
The profound vasoconstriction and mitogenic activity exerted by endothelin-1 (ET-1) and other closely related isopeptides [endothelin-2 (ET-2) and endothelin-3 (ET-3)] on the cardiovascular system[1] is suggestive of a role for the abnormal production or release of endothelins in the pathogenesis of disease. Thus an intense effort has been mounted by many research groups to prepare antagonists of the two fully characterized endothelin receptors, ET_A and ET_B.[2] The ET_A receptor, which binds ET-1 and ET-2 with greater affinity than ET-3 or the structurally similar snake venom toxin, sarafotoxin 6C (S6C), is principally located in vascular smooth muscle, where it mediates vasoconstriction[3] and smooth muscle proliferation.[4] The ET_B receptor binds all three endothelin isopeptides (as well as S6C) with equal affinity and is known to mediate vasoconstriction in certain vascular beds (e.g. rabbit pulmonary artery[3]), as well as the release of endothelium-derived nitric oxide.[5] A number of reports have appeared



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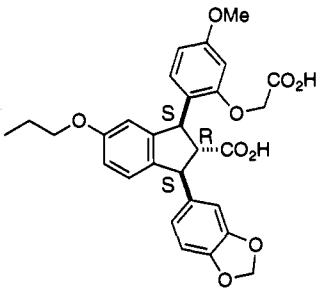
in the literature describing peptide endothelin receptor antagonists, and currently there are compounds which are selective for ET_A (BQ 123[6] and FR 139317[7]), ET_B (IRL 1038[8]), and compounds which exhibit dual ET_A/ET_B antagonism (e.g., PD 142893[9]and PD 145065[10]). BQ 123, the prototypical ET_A selective antagonist, has been shown to be efficacious in *in vivo* models of disease, most notably hypertension[11] and acute renal failure.[12] More recently, non-peptide antagonists of the endothelin receptors from Shionogi (50-235),[13] Hoffmann-La Roche (Ro 46-2005[14] and Ro 47-0203[15]), and Bristol-Myers Squibb (BMS 182874)[16] have been disclosed. In this paper, we describe the design, synthesis, and characterization of (1*S*,2*R*,3*S*)-3-[2-(carboxymethoxy)-4-methoxyphenyl]-1-[3,4-(methylenedioxy)phenyl]-5-(prop-1-yloxy)indan-2-carboxylic acid (**1**, SB 209670), a highly potent antagonist, selective for the endothelin receptors. Our approach toward the



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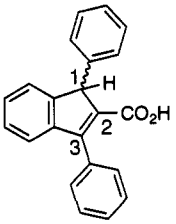

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discovery of non-peptide endothelin receptor antagonists included the screening of compounds selected for their similarity to antagonists of other G-protein coupled receptors and containing features of ET-1 known to be important to receptor binding.[17] As a result of this effort and additional similarity searching, compound **2**[18] was identified and found to bind selectively to ET_A receptors (K_i: $ET_A = 7.3 \pm 0.43\ \mu M$, $ET_B = >30\ \mu M$).[19,20] Additionally, compound **2** was shown to be a weak functional antagonist of ET_A receptors in the rat aorta ($K_B = 6.58 \pm 0.68\ \mu M$).[22]

^1H NMR-derived conformational models of ET-1 supported peptidomimetic hypotheses for **2**.[23] Comparison of a 3-dimensional structure of **2**[24] to low-energy conformations of ET-1 suggested that the 1- and 3-phenyl groups of **2** may be mimics of two of the aromatic side chains of Tyr-13, Phe-14, and Trp-21 of ET-1. The carboxylic acid moiety of **2** was found to play an important role in binding of the antagonist since the corresponding methyl ester lacked measurable affinity for either endothelin receptor (K_i's $> 30\ \mu M$). If this function were to have a counterpart in ET-1, it was considered likely that this would be either the Asp-18 or C-terminal carboxyl. While it appeared possible that **2** could mimic a number of combinations of the elements of ET-1 highlighted above, our efforts centered initially upon an overlay which matched the carboxylic acid and 1- and 3-phenyl groups of the antagonist to Tyr-13, Phe-14, and Asp-18 of the peptide. In view of the electron-rich characteristics of the aromatic side chain of Tyr-13, this overlay suggested that incorporation of electron-donating substituents onto the 1- or 3-phenyl groups of the antagonist could have a favorable effect on receptor binding affinity. Elaboration of an antagonist series based upon **2** was hampered by the instability of the indene nucleus;[25] thus our attempts to improve receptor affinity were directed toward an indane framework. Compound **3**, *trans,trans*-1,3-diphenylindan-2-carboxylic acid, has a similar binding profile (K_i: $ET_A = 11.22 \pm 0.68\ \mu M$, $ET_B = >30\ \mu M$)[20, 26] to indene **2** and incorporation of electron-donating substituents onto both the 1- and 3-phenyl moieties is beneficial for ET_A receptor binding and also leads to measurable affinity to the ET_B receptor subtype (compounds **5** and **6**, Table 1). An

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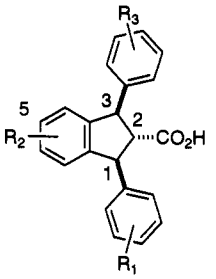
Table 1. 1,3-Diarylindan-2-carboxylic Acids



compd[a]	R_1	R_2	R_3	K_i ET_A[b] (nM)	K_i ET_B[b] (nM)	K_B[c] (nM)
1[d]	3,4-methylenedioxy	5-O-*n*-Pr	2-carboxymethoxy 4-OMe	0.43 ± 0.09	14.7 ± 3.0	0.4 ± 0.04
3	H	H	H	11222 ± 677	>30000	6161 ± 634
4	4-OMe	H	H	5666 ± 1290	>30000	6403 ± 767
5	4-OMe	H	4-OMe	422 ± 27	2443 ± 333	1096 ± 266
6	4-OMe	H	3,4-methylenedioxy	43 ± 14	757 ± 23	14.4 ± 3.2
7	3,4-methylenedioxy	5-OH	4-OMe	15 ± 3	483 ± 90	9.9 ± 3.5
8	3,4-methylenedioxy	5-O-*n*-Pr	4-OMe	11.3 ± 2.2	1044 ± 313	8.6 ± 3.2

[a] All compounds are racemic unless otherwise noted. [b] Cloned human receptor binding, see ref 20. [c] ET-1-induced isolated rat aortal strip contraction, see ref 22. [d] (+)-Enantiomer.

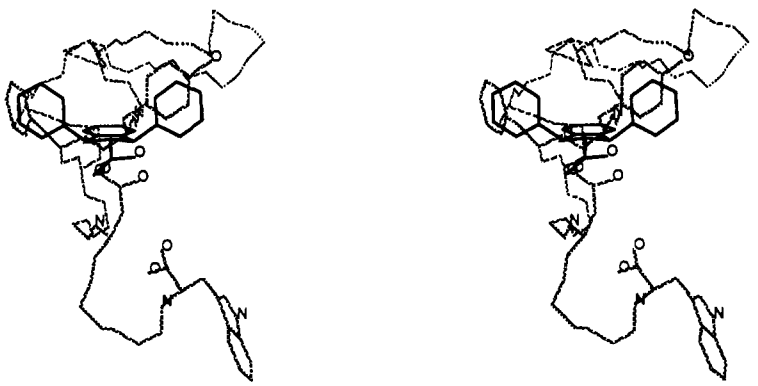


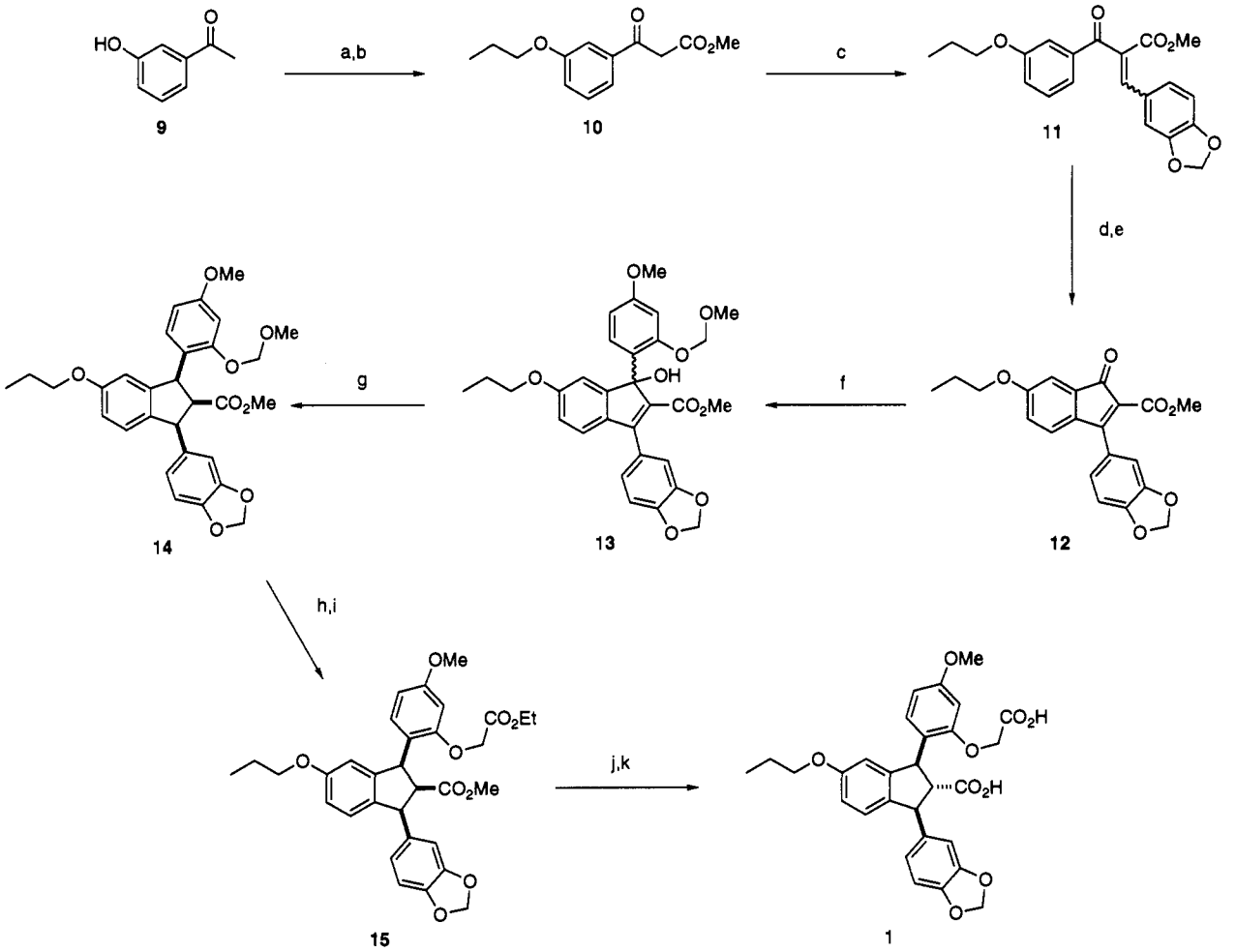
Figure 1. Stereoview of an overlay of *trans,trans*-1,3-diphenylindan-2-carboxylic acid (**3**) (solid) with a ^1H NMR derived conformational model of ET-1 (dashed).

electron-donating substituent at the 5-position, such as *n*-propyloxy, is desirable to facilitate synthesis[27] but has little effect on antagonist affinity to either receptor subtype (compounds **7** and **8**, Table 1).

The overlay shown in Figure 1 depicts our peptidomimetic hypothesis for *trans,trans*-1,3-diphenylindan-2-carboxylic acid, **3**. In view of the importance to receptor binding of the C-terminal carboxylic acid moiety of ET-1,[28] this overlay suggested that the receptor affinity of **8** might be enhanced by appendage of a group at the 2-position of one of the phenyl substituents to mimic this functionality of the peptide. It was apparent, however, that due to the flexible nature of the carboxy terminal residues, the NMR-derived conformations of ET-1 alone could not provide the necessary information to allow selection of a specific side chain. To overcome this, we hypothesized that the conformationally rigid cyclic peptide antagonist BQ 123[6,29] (cyclo-D-Trp-D-Asp-Pro-D-Val-Leu), is a mimic of residues 18–21 of ET-1, and therefore its conformation describes to some degree the conformation in this region of receptor bound ET-1. In order to introduce the conformation of BQ 123 into the tail of ET-1 in a manner which would also be consistent with the peptidomimetic hypothesis for **3**, we employed a method for the simultaneous generation of conformations for overlapping molecules called ensemble distance geometry.[30] Sets of conformers for ET-1, BQ 123, and **3** that are consistent with the peptidomimetic hypothesis of **3**, the mimetic hypothesis of BQ 123, and that also obey NMR-derived distance constraints for both ET-1 and BQ 123 were generated. The resulting conformers for ET-1 were energy minimized and the lowest energy conformer is depicted in Figure 1. Some adjustment was made to the calculated positions for **3** on low energy conformers of ET-1 to provide a better atom to atom overlap of the phenyl substituents of **3** with the aromatic rings of Tyr-13 and Phe-14. These overlays suggested the introduction of a carboxylic acid approximately 4–5 Å (to the carboxyl carbon) from the 2-position of one of the two phenyl substituents.[31] Using a chain of two or three atoms (e.g., C, N, O) to link between the carboxylic acid and the aromatic ring satisfies this distance range. For synthetic flexibility, as well as ease of synthesis, the oxyacetic acid side chain was selected, leading to compound **1**. The absolute configuration of the more potent (+) antipode of **1** (as shown) was assigned on the basis of X-ray crystallographic analysis of the (−)-amphetamine salt of the (−) antipode of **1**.[32]

Compound **1** is a potent inhibitor of [I^{125}]ET-1 binding to cloned human ET_A and ET_B receptors, with K_i values of 0.43 ± 0.09 and 14.7 ± 3.0 nM, respectively. The high potency of **1** is also apparent from *in vitro* functional activity, as evidenced by parallel rightward shifts in the concentration–response curve to ET-1 in isolated rat aorta,[22] yielding a K_B value of 0.4 ± 0.04 nM. The contractile response to ET-1 in this tissue has been demonstrated to be mediated by the ET_A receptor.[3] In

Scheme 1[a]



[a] (a) K_2CO_3, *n*-PrI, DMF (quant); (b) NaH, dimethyl carbonate (quant); (c) piperidine, acetic acid, benzene, 3,4-(methylenedioxy)benzaldehyde, reflux (48%); (d) TFA (87%); (e) DDQ, dioxane (44%); (f) [4-methoxy-2-(methoxymethoxy)phenyl]magnesium bromide, ether (91%); (g) H_2 50 psi, 10% Pd–C, EtOH/EtOAc, 50 °C, (96%); (h) cat. HCl, MeOH, H_2O (78%); (i) NaH, DMF, ethyl bromoacetate (71%); (j) resolution on Chiralpak AD column, eluant: hexane/ethanol, 1:1; (k) NaOH, H_2O, dioxane then HCl, H_2O (71%).

the isolated rabbit pulmonary artery, ET-1 produces a contractile response mediated through ET_B receptors,[3] and compound **1** antagonizes this effect with a K_B value of 199 ± 9 nM.[33] No agonist activity has been observed for compound **1**, up to a concentration of 10 μM, in the isolated rat aorta and Schild analyses of the data obtained in the isolated rat aorta and the isolated rabbit pulmonary artery are consistent with it being a competitive antagonist at both ET_A (slope = 0.96 ± 0.04, n = 6) and ET_B (slope = 1.04 ± 0.06, n = 5) receptors.

Compound **1** is selective for the ET_A and ET_B receptors since at a concentration of 10 μM it fails to affect functional activity mediated by the vasopressin-1 or α-1 adrenergic receptors in the isolated rat aorta or by angiotensin II type 1 receptors in the isolated rabbit aorta.

The synthesis of **1** is shown in Scheme 1. Propylation of the phenolic hydroxyl of *m*-hydroxyacetophenone **9** followed by carbomethoxylation α to the carbonyl afforded β-keto ester **10**. Knoevenagel condensation of **10** with piperonal gave **11** as a single unassigned geometrical isomer. Acid catalyzed cyclization of **11** followed by dehydrogenation of the resultant indanone led to the indenone **12**.[34] Addition of [4-methoxy-2-(methoxymethoxy)phenyl]magnesium bromide[35] to **12** proceeded in a 1,2 manner to give the racemic indenol **13**. Catalytic hydrogenation of **13** gave racemic **14** with the *all-cis* arrangement of substituents[37] on the 5-membered ring of the indane shown in Scheme 1. Removal of the MOM protecting group of **14** followed by alkylation of the free phenol with ethyl bromoacetate led to installation of the oxyacetic acid moiety on the 3-phenyl substituent, providing compound **15**. Resolution of **15** was achieved by preparative chiral HPLC[39] and the dextrorotatory antipode of **15** when subjected to treatment with aqueous base underwent epimerization at C-2 and saponification to afford SB 209670 (**1**).

Compound **1** is a novel, highly potent, endothelin receptor antagonist, possessing affinity for both ET_A and ET_B subtypes and should be a valuable tool with which to explore possible roles for endothelin both in physiology and pathophysiology.

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References

(1) Yanagisawa, M.; Kurihara, H.; Kimura, S.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Yazaki, Y.; Goto, K.; Masaki, T. A Novel Potent Vasoconstrictor Peptide Produced by Vascular Endothelial Cells. *Nature* **1988**, *332*, 411–415.

(2) (a) Arai, H.; Hori, S.; Aramori, I.; Ohkubo, H.; Nakanishi, S. Cloning and Expression of a cDNA Encoding an Endothelin Receptor. *Nature* **1990**, *348*, 730–732. (b) Sakurai, T.; Yanagisawa, M.; Takuwa, Y.; Miyazaki, H.; Kimura, S.; Goto, K.; Masaki, T. Cloning of a cDNA Encoding a Non-Isopeptide-Selective Subtype of the Endothelin Receptor. *Nature* **1990**, *348*, 732–735.

(3) (a) Panek, R. L.; Major, T. C.; Hingorani, G. P.; Doherty, A. M.; Taylor, D. G.; Rapundalo, S. T. Endothelin and Structurally Related Analogs Distinguish Between Endothelin Receptor Subtypes. *Biochem. Biophys. Res. Commun.* **1992**, *183*, 566-571. (b) Warner, T. D.; Allcock, G. H.; Corder, R.; Vane, J. R. Use of the Endothelin Antagonists BQ 123 and PD 142893 to Reveal Three Endothelin Receptors Mediating Smooth Muscle Contraction and the Release of EDRF. *Br. J. Pharmacol.* **1993**, *110*, 777–782.

(4) Ohlstein, E. H.; Arleth, A.; Bryan, H.; Elliott, J. D.; Sung, C. P. The Selective Endothelin-A Receptor Antagonist BQ 123 Antagonizes ET-1 Mediated Mitogenesis in Vascular Smooth Muscle. *Eur J. Pharmacol.* **1992**, *225*, 347–350.

(5) DeNucci, G.; Thomas, R.; D'Orleans-Juste, P.; Antunes, E.; Walder, C.; Warner, T. D.; Vane, J. R. Pressor Effects of Circulating Endothelin are Limited by its Removal from the Pulmonary Circulation and by the Release of Prostacyclin and Endothelium-Derived Relaxing Factor. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9797–9800.

(6) Ihara, M.; Noguchi, K.; Saeki, T.; Fukuroda, T.; Tsuchida, S.; Kimura, S.; Fukami, T.; Ishikawa, K.; Nishikibe, M.; Yano, M. Biological Profiles of Highly Potent Novel Endothelin Antagonists Selective for the ET_A Receptor. *Life Sci.* **1992**, *50*, 247–255.

(7) Sogabe, K.; Nirei, H.; Shoubo, M.; Nomoto, A.; Ao, S.; Notsu, Y.; Ono, T. Pharmacological Profile of FR 139317, a Novel, Potent Endothelin ET_A Receptor Antagonist. *J. Pharmacol. Exp. Ther.* **1993**, *264*, 1040–1046.

(8) Urade, Y.; Fujitani, Y.; Oda, K.; Watakabe, T.; Umemura, I.; Takai, M.; Okada, T.; Sakata, K.; Karaki, H. An Endothelin B Receptor Selective Antagonist: IRL 1038, [Cys^{11}-Cys^{15}]-endothelin-1(11–21). *FEBS Lett.* **1992**, *311*, 12–16.

(9) Cody, W. L.; Doherty, A. M.; He, J. X.; DePue, P. L.; Rapundalo, S. T.; Hingorani, G.A.; Major, T. C.; Panek, R. L.; Dudley, D. T.; Haleen, S. J.; LaDouceur, D.; Hill, K.E.; Flynn, M. A.; Reynolds, E. E. Design of a Functional Hexapeptide Antagonist of Endothelin. *J. Med. Chem.* **1992**, *35*, 3301–3303.

(10) Cody, W. L.; Doherty, A. M.; He, J. X.; DePue, P. L.; Waite, L. A.; Topliss, J. G.; Haleen, S. J.; LaDouceur, D.; Flynn, M. A.; Hill, K. E.; Reynolds, E. E. The Rational Design of a Highly Potent Combined ET_A and ET_B Receptor Antagonist (PD 145065) and Related Analogs. *Med. Chem. Res.* **1993**, *3*, 154–162.

(11) Ohlstein, E. H.; Vickery-Clark, L. M.; Storer, B. L.; Douglas, S. A. Antihypertensive Effects of the Endothelin Receptor Antagonist BQ 123 in Conscious Spontaneously Hypertensive Rats. *J. Cardiovasc. Pharmacol.* **1993**, *22*, S321–S324.

(12) Gellai, M.; Jugus, M.; Fletcher, T.; DeWolf, R.; Nambi, P. Reversal of Postischemic ARF with a Selective ET_A Receptor Antagonist in the Rat. *J. Clin. Invest.* In press.

(13) Mihara, S.-i.; Sakurai, K.; Nakamura, M.; Konoike, T.; Fujimoto, M. Structure-Activity Relationships of an Endothelin ET_A Receptor Antagonist, 50-235, and its Derivatives. *Eur. J. Pharmacol., Mol. Pharmacol.* **1993**, *247*, 219–221.

(14) Clozel, M.; Breu, V.; Burri, K.; Cassal, J.-M.; Fischli, W.; Gray, G. A.; Hirth, G.; Löffler, B.-M.; Müller, M.; Neidhart, W.; Ramuz, H. Pathophysiological Role of Endothelin Revealed by the First Orally Active Endothelin Receptor Antagonist. *Nature* **1993**, *365*, 759–761.

(15) Roux, S. P.; Clozel, M.; Sprecher, U.; Gray, G.; Clozel, J. P. Ro 47-0203, an New Endothelin Receptor Antagonist Reverses Chronic Vasospasm in Experimental Subarachnoid Hemorrhage. *Circulation* **1993**, *88*, I-170.

(16) Stein, P. D.; Hunt, J. T.; Floyd, D. M.; Moreland, S.; Dickinson, K. E. J.; Mitchell, C.; Liu, E. C.-K.; Webb, M. L.; Murugesan, N.; Dickey, J.; McMullen, D.; Zhang, R.; Lee, V. G.; Serafino, R.; Delaney, C.; Schaeffer, T. R.; Kozlowski, M. The Discovery of Sulfonamide Endothelin Antagonists and the Development of the Orally Active ET_A Antagonist 5-(Dimethylamino)-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide. *J. Med. Chem.* **1994**, *37*, 329–331.

(17) Hunt, J. T. SAR of Endothelin Deduced From Monocyclic Analogs. *Drug News Perspect.* **1992**, *5*, 78–82 and references therein.

(18) Koelsch, C. F. Electrophilic Properties of Ethyl 3-Phenylindone-2-Carboxylate. *J. Org. Chem.* **1960**, *25*, 2088–2091.

(19) The binding data given in the text for this compound and all others was obtained using cloned human receptors.[20] Initial screening for ET_A and ET_B binding was performed using membranes prepared, respectively, from rat mesenteric artery or rat cerebellum. Rat mesenteric artery bed was homogenized in a buffer containing 20 mM Tris HCl (pH 7.4), 5 mM EDTA, 250 mM sucrose, and protease inhibitors[21] using a polytron (4 times for a period of 15 s on ice at a setting of 70% of maximum) and the resulting homogenate left on ice for 20 min. The floating fat layer was removed by filtration through two layers of cheesecloth, and the filtrate was centrifuged for 10 min. at 1000*g*. The supernatant was centrifuged for 30 min at 40000*g* and the pellet resuspended in buffer containing 50 mM Tris HCl (pH 7.4) and 10 mM $MgCl_2$. Rat cerebellum membranes were prepared according to a literature procedure; see: Nambi, P.; Pullen, M.; Feuerstein, G. Identification of Endothelin Receptors in Various Regions of Rat Brain. *Neuropeptides* **1990**, *16*, 195–199. Binding to rat mesenteric artery and rat cerebellum membranes was performed using 10 μg of protein per tube and 1 μg of protein per tube, respectively. Using membranes from these tissues, compound **2** was shown to have K_i's of 5.4 ± 0.4 μM and >30 μM for binding to ET_A and ET_B, respectively.

(20) Human ET_A and ET_B receptors, cloned and stably expressed in CHO cells,[21] were used to evaluate endothelin receptor antagonist binding affinity. Binding of [I^{125}]ET-1 to membranes prepared from CHO cells expressing either ET_A or ET_B receptors was performed by adding [I^{125}]ET-1 (0.3 nM) to membranes (0.5 and 0.05 μg per tube for ET_A and ET_B, respectively) in the absence or presence of increasing concentrations of the unlabeled ligands. At the end of the incubation (30 °C, 1 h), free and bound ligands were separated by filtration and counted with a γ-counter . The nonspecific binding was between 8–25% and 2–5% for ET_A and ET_B receptors, respectively. Apparent K_i values were determined from the competition curves, $n \geq 3$.

(21) Elshourbagy, N. A.; Korman, D. R.; Wu, H. L.; Sylvester, D. R.; Lee, J. A.; Nuthalaganti, P.; Bergsma, D. J.; Kumar, C. S.; Nambi, P. Molecular Characterization and Regulation of the Human Endothelin Receptors. *J. Biol. Chem.* **1993**, *268*, 3873–3879.

(22) The ability of the compounds to antagonize ET-1-induced vasoconstriction mediated by the ET_A receptor was examined in the isolated rat aorta. Ring segments cut from the rat thoracic aorta were suspended in organ baths containing physiological salt solution. The ring segments were mounted over metal supports and attached to force displacement transducers which were connected to a recorder. Cumulative concentration–response curves to ET-1 were performed in the absence of or following a 30-min incubation with antagonist. Antagonist dissociation constants (K_B) were calculated by the dose ratio method using mean effective concentrations, $n \geq 3$.

(23) Details of the NMR and modeling work will be described elsewhere; however, brief descriptions of the techniques employed will be provided here and in subsequent footnotes. Conformations for ET-1 were generated via a distance geometry (DGEOM)/minimization (AMBER) procedure using NMR derived distance constraints for ET-1 in [$^2H_{38}$]dodecylphosphocholine micelles. The lowest energy conformers displayed α-helical secondary structure between residues 9 and 16, a turn at residues 5–8, and an ill-defined carboxy terminus. These features are consistent with reported NMR-derived conformations of ET-1 and related isopeptides: (a) Endo, S.; Inooka, H.; Ishibashi, Y.; Kitada, C.; Mizuta, E.; Fujino, M. Solution Conformation of Endothelin Determined by Nuclear Magnetic Resonance and Distance Geometry. *FEBS Lett.* **1989**, *257*, 149–154. (b) Mills, R. G.; Atkins, A. R.; Harvey, T.; Junius, F. K.; Smith, R.; King, G. F. Conformation of Sarafotoxin-6b in Aqueous Solution Determined by NMR Spectroscopy and Distance Geometry. *FEBS Lett.* **1991**, *282*, 247–252. (c) Mills, R. G.; O'Donoghue, S. I.; Smith, R.; King, G. F. Solution Structure of Endothelin-3 Determined Using NMR Spectroscopy. *Biochemistry* **1992**, *31*, 5640–5645. (d) Saudek, V.; Hoflack, J.; Pelton, J. T. ^{1}H-NMR Study of Endothelin, Sequence Specific Assignment of the Spectrum and a Solution Structure. *FEBS Lett.* **1989**, *257*, 145–148. DGEOM is available through QCPE, Indiana University, Bloomington, Indiana. AMBER is available through The University of California at San Francisco.

(24) Three-dimensional structures for **2** were built using Macromodel v3.5, and conformational energies were evaluated using the Macromodel implementation of MM2.

(25) Due to the oxidative lability of this type of indene and the additional complication of separating isomers of **2** in which the 1- and 3-phenyl groups are nonsymmetrically substituted, we were unable to prepare fully characterized compounds of this class.

(26) *cis,cis*-1,3-Diphenylindan-2-carboxylic acid (i.e., C-2-*epi* **3**, obtained by catalytic hydrogenation of **2**) lacked measurable affinity (K_i > 30 μM) for either the ET_A or ET_B receptor.

(27) The electron-donating substituent at C-5 (indane numbering), e.g., *n*-propyloxy in compound **11**, is needed to facilitate the acid-catalyzed cyclization (step d, Scheme 1).

(28) Nakajima, K.; Kubo, S.; Kumagaye, S.-i.; Nishio, H.; Tsunemi, M.; Inui, T.; Kuroda, H.; Chino, N.; Watanabe, T. X.; Kimura, T.; Sakakibara, S. Structure-Activity Relationship of Endothelin: Importance of Charged Groups. *Biochem. Biophys. Res. Commun.* **1989**, *163*, 424–429.

(29) NMR-derived conformations were determined for BQ 123 in both methanol and chloroform. Details can be found in the following: Bean, J. W.; Peishoff, C. E.; Kopple, K. D. Conformations of Cyclic Pentapeptide Endothelin Receptor Antagonists. *Int. J. Pept. Protein Res.* In press.

(30) Sheridan, R. P.; Nilakantan, R.; Dixon, J. S.; Venkataraghavan, R. The Ensemble Approach to Distance Geometry: Application to the Nicotinic Pharmacophore. *J. Med. Chem.* **1986**, *29*, 899–906. A 3-dimensional structure for **3** was generated in the same manner

as described for 2 in ref 24. X-ray crystallographic data for compound 1 subsequently verified the assumption that the phenyl substituents would maintain orientations approximately perpendicular to the indane aromatic ring[32] (see Figure 1).

(31) At the time of development of this hypothesis, it was not possible to predict whether the 1- or 3-phenyl substituent should be the site of elaboration of this additional carboxylic acid containing group, since the absolute configuration of the most potent antipode of 8 had not been assigned. On the basis of the subsequently established absolute configuration of 1, the overlay would have directed attachment of such a group to the 4-methoxyl bearing phenyl (assuming the most potent enantiomer of 8 has the same absolute configuration as 1). Subsequent SAR studies have failed to show any receptor binding advantage when similar substituents are appended to the 3,4-(methylenedioxy)-bearing phenyl.

(32) Eggleston, D. S. Unpublished results.

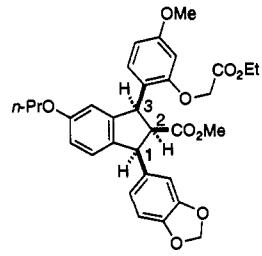
(33) Details are as given in ref 22, but using ring segments cut from rabbit pulmonary artery rather than rat thoracic aorta.

(34) A small quantity (5–10%) of the 4-propyloxy regioisomer, produced during the acid catalyzed cyclization, was removed by recrystallization at the indenone 12 stage.

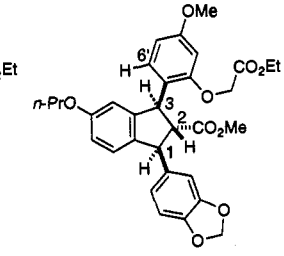
(35) 4-Bromo-3-hydroxyanisole was prepared using a literature procedure.[36] The phenolic hydroxyl was protected as a methoxymethyl ether (NaH, MOMBr, DMF) and the product converted to the desired Grignard reagent by reaction with magnesium in ether.

(36) de Paulis, T.; Kumar, Y.; Johansson, L.; Ramsby, S.; Florvall, L.; Hall, H.; Angeby-Moller, K.; Ogren, S.-O. Potential Neuroleptic Agents. 3. Chemistry and Antidopaminergic Properties of 6-Methoxysalicylamides. *J. Med. Chem.* **1985**, *28*, 1263–1269.

(37) Treatment of 14 with Schwesinger's P4 base[38] led to epimerization at C-2, giving the thermodynamically more stable C-2-*epi* 14. Further elaboration of C-2-*epi* 14 by the transformations h and i of Scheme 1 provided C-2-*epi* 15. The assignment of relative configuration of 15 and C-2-*epi* 15 and hence 14 and C-2-*epi* 14, was made on the basis of NOE experiments. Specifically, irradiation of H-2 in 15 led to an NOE with both H-1 and H-3, while similar irradiation of H-2 in C-2-*epi* 15 failed to show an NOE with either H-1 or H-3. These observations support the *all-cis* arrangement of H-1, -2, and -3 in 15 and are consistent with a *trans* stereochemical relationship between H-2 and the hydrogens 1 and 3 in C-2-*epi* 15. Furthermore, irradiation of H-1 in 15 elicited enhancement at H-3, while irradiation of H-3 in C-2-*epi* 15 produced enhancement at H-1, supporting the *cis* arrangement of the 1- and 3-aryl substituents in both molecules. Finally, irradiation of H-2 in C-2-*epi* 15, but not 15, led to an NOE with H-6′ of the 3-aryl substituent, confirming the *cis* arrangement of H-2 and the 3-aryl group in C-2-*epi* 15. Both 15 and C-2-*epi* 15 upon treatment with aqueous lithium hydroxide afford 1, the configuration of which has been established by X-ray crystallography.[32]



15



C-2-epi 15

(38) Schwesinger, R.; Schlemper, H. Peralkylated Polyaminophosphazenes-Extremely Strong, Neutral Nitrogen Bases. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1167–1169.

(39) HPLC resolution was achieved using a Chiralpak AD 4.6-mm × 250-mm column (eluant, ethanol/ hexanes, 1:1; flow rate, 1 mL/min). Retention times (+)-15, 11.5 min; (−)-15, 28.5 min.