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DISCOVERY OF SUBSTITUTED 8,9-DICARBOXYLDIBENZO [2,3:5,6] BICYCLO [5.2.0] NONAN-4-ONES WITH MODERATE BINDING AFFINITY TO THE ENDOTHELIN ET_A AND ET_B RECEPTORS.

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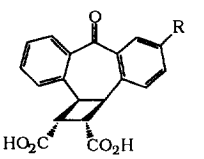
Abstract: Screening of our sample collection for novel structures with endothelin receptor (ET_A and ET_B) binding affinity, resulted in the discovery of structure **I** (R = H). This unique bicyclic diacid elicited modest affinity for both cloned human receptors (0.8 μM, ET_A and 7.9 μM, ET_B). Substitution at 'R' resulted in increased affinity for both receptors.



I

Introduction: Endothelin (ET-1), the most potent naturally occuring vasoconstrictor known, is a 21-amino acid peptide produced and secreted by endothelial cells, as well as a number of other cell types.[1] Endothelin-1 (ET-1) is one of three identified potent vasconstricting peptides which also include endothelin-2 and endothelin-3. The latter two differ from ET-1 by two and six amino acids, respectively. Interaction of these peptides with two known endothelin g-protein coupled receptors, ET_A and ET_B is responsible for their potent vasoconstricting effects. ET_A receptors are mainly found in vascular smooth muscle tissues and mediate vasoconstriction, while ET_B receptors are found in non vascular tissues as well as smooth muscle tissues.[1] It has been reported that endothelin levels are elevated compared to normal levels in a variety of disease states such as essential hypertension, acute myocardial infarction, pulmonary hypertension, subarachnoid hemorrhage, cyclosporin-induced renal failure, and atherosclerosis.[2] It is therefore hypothesized that blocking the interaction of endothelin (ET-1) to its membrane bound receptors, with a receptor antagonist, may provide a useful chemotherapeutic agent. It is also anticipated that the discovery of novel subtype selective and non-selective ET antagonists should further assist in elucidating the precise physiological roles of endothelin.[3] Screening of our sample collection for such an agent led to the identification of compound **I** (R = H) with modest affinity to both the ET_A and ET_B receptors. The structural novelty of compound **I** and its close analogs separates this class of compounds from most of the other endothelin antagonists reported recently in the literature.[3] Herein we report on the synthesis and *in vitro* SAR of **I** and several of its congeners.

Synthesis: Compound **I** (R = H) was prepared as reported in the literature by the photolysis of dibenzosubereneone with maleic anhydride followed by hydrolysis with NaOH.[4] The bromo-derivative (**Ia**), which served as a precursor for analogs **Ib** - **In** (table II), was prepared as illustrated in scheme I. O-phenethylbenzoic acid was added to a solution of bromine and TFA in sulfur dioxide cooled to -50°C and the

reaction was stirred overnight at -30°C. The desired product was isolated in 80% yield as an off-white solid. Ring closure to afford the bromo-dibenzosuberone analog is cleanly accomplished by treating the acid with thionylchloride followed by $AlCl_3$. Alternatively, heating the acid in PPA also provides the desired product in very good yield. Bromination with NBS using a catalytic amount of AIBN was followed by dehydrobromination with triethylamine to afford the necessary photolysis precursur. Photolysis, using the literature procedure used for the preparation of 8,9-dicarboxyldibenzo [2.3:5.6] bicyclo [5.2.0] nonan-4-one, of the dibenzosubereneone derivative with maleic anhydride, followed by hydrolysis, provided the desired bromo diacid **Ia** in modest yield. A modified Suzuki coupling was then used to generate compounds **Ic** through **In** in modest to high yields from the requisite boronic acids as outlined in table I.[5] The boronic acid precursors that were not commercially available were prepared from the readily available aryllithium derivatives. Treatment of **Ia** with Br_2 in acetic acid provided dibromide **Ib** in 52% yield. All the final products were purified by medium pressure reverse phase chromatography.[6,7]

Scheme I

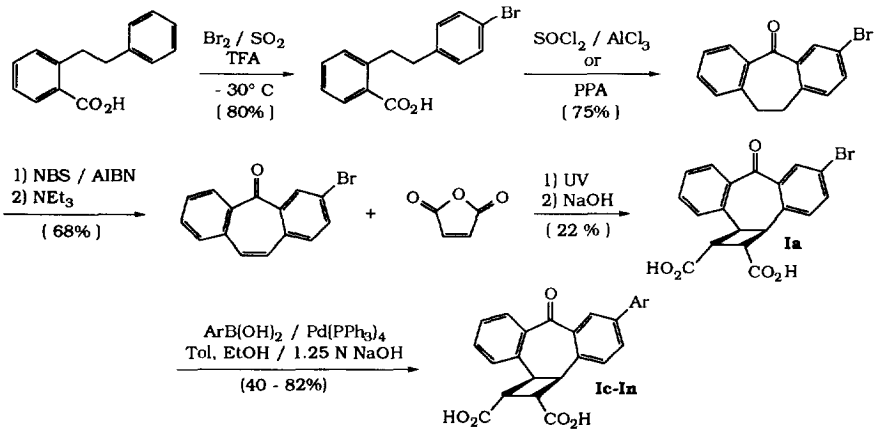


TABLE I

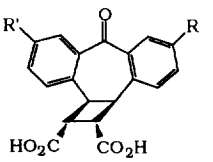
Example	$ArB(OH)_2$	Yield	Retention time (min)*
Ic	$PhB(OH)_2$	75 %	6.58
Id	1-NaphthylB$(OH)_2$	62 %	11.06
Ie	(2-MeO)PhB$(OH)_2$	69 %	6.34
If	(3-MeO)PhB$(OH)_2$	63 %	6.26
Ig	(4-MeO)PhB$(OH)_2$	76 %	6.06
Ih	(2-Me)PhB$(OH)_2$	66 %	7.86
Ii	(4-Me)PhB$(OH)_2$	79 %	8.73
Ij	(2,4-Cl_2)PhB$(OH)_2$	82 %	13.14
Ik	(3,5-Cl_2)PhB$(OH)_2$	45 %	15.97
Il	(2,4-$(CF_3)_2$)PhB$(OH)_2$	40 %	16.62
Im	(4-Et)PhB$(OH)_2$	48 %	12.14
In	(4-Cl)PhB$(OH)_2$	40 %	9.88

*C-18 Dynamax analytical column, 1 mL/min, 55% MeCN/H_2O, 0.1% TFA

Results and Discussion: Introduction of a bromine atom (**Ia**) led to improved affinity towards both cloned human receptors.[8] The more pronounced effect was seen at the ET_B receptor where the affinity improved by almost an order of magnitude. This result led us to further examine the effect of substitutions at what is formally the 4'-position of the 8,9-dicarboxyldibenzo [2,3:5,6] bicyclo [5.2.0] nonan-4-one nucleus. Bromination at the 4''-position (**Ib**), while providing an achiral symmetrical compound, afforded no advantage to binding. The phenyl analog **Ic**, nearly equipotent to the bromo derivative, provided the impetus for us to examine further substituted aryl derivatives easily prepared using the Suzuki methodology. As can be seen in the remaining examples in table II, substitutions at the phenyl had a dramatic effect on binding to both receptors. The 4-methyl and 4-ethyl analogs, **Ii** and **Im**, respectively, provided the best improvement in affinity to both receptors with nearly balanced potency. Modest ET_A selectivity combined with very good affinity was found for the 4-chloro analog (**In**), while ET_B selectivity can be achieved with a naphthyl group - example **Id**.

Representative compounds **I**, **Ia** and **Ii** demonstrtated functional antagonism by inhibiting ET-1 induced phosphatidyl inositol hydrolysis in CHO cells expressing human ET_A receptors.

TABLE II



Human Cloned Receptor IC_{50}'s

Example	R	R'	ET_A (nM)	ET_B (nM)
I	H	H	800	7,900
Ia	Br	H	400	890
Ib	Br	Br	650	1,050
Ic	Ph	H	290	1000
Id	1-Naphthyl	H	15,000	300
Ie	(2-MeO)Ph	H	48,000	2,400
If	(3-MeO)Ph	H	3,900	1,100
Ig	(4-MeO)Ph	H	530	300
Ih	(2-Me)Ph	H	5,000	2,400
Ii	(4-Me)Ph	H	150	190
Ij	(2,4-Cl_2)Ph	H	7,600	300
Ik	(3,5-Cl_2)Ph	H	26,000	2,100
Il	(2,4-$(CF_3)_2$)Ph	H	25,000	4,700
Im	(4-Et)Ph	H	350	280
In	(4-Cl)Ph	H	47	230

In summary we have described the SAR of a novel set of diacids that have a wide range of ET_a and ET_B receptor binding affinities. Our prelimanry findings indicate that this series of compounds can provide ET_A or

ET_B selective compounds, as well as, balanced antagonists. The in-vivo activity of these compounds, specifically **In**, is currently under evaluation.

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6. The structure assigned to each new compound is in accord with its mass spectrum (FAB) and high field (400 MHz) NMR spectrum.
   Compound **Ia**: H^1 NMR (400 MHz, CD_3OD) δ 3.31 (m, 2H), 4.45 (d, 2H), 7.27 (d, 1H), 7.31 (d, 1H), 7.38 (ddd, 1H), 7.52 (ddd, 1H), 7.60 (dd, 1H), 7.64 (dd, 1H), 7.71 (d, 1H).

7. Purification was carrried out using a Lobar A LiChroprep RP-8 column, eluting at 4 ml/min with 45% CH_3CN in H_2O containing 0.1% TFA.

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