Expedited Articles

Discovery and Optimization of a Novel Class of Orally Active Nonpeptidic Endothelin-A Receptor Antagonists

Hartmut Riechers,*,† Hans-Peter Albrecht,† Willi Amberg,† Ernst Baumann,† Harald Bernard,† Hans-Joachim Böhm,† Dagmar Klinge,† Andreas Kling,† Stefan Müller,† Manfred Raschack,‡ Liliane Unger,‡ Nigel Walker,† and Wolfgang Wernet‡

Hauptlaboratorium, BASF AG, 67056 Ludwigshafen, Germany, and Knoll AG, 67008 Ludwigshafen, Germany

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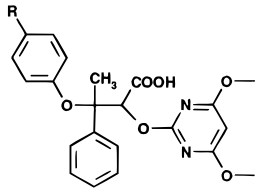
A novel class of endothelin-A receptor ligands was discovered by high-throughput screening. Lead structure optimization led to highly potent antagonists which can be synthesized in a short sequence. The compounds are endothelin-A-selective, are orally available, and show a long duration of action.

Introduction

Endothelin is a recently discovered peptide consisting of 21 amino acids.[1] First characterized as a potent vasoconstrictor, endothelin-1 (ET-1) and the close homologs ET-2 and ET-3 have been shown to be implicated in a number of diseases such as hypertension, congestive heart failure, renal failure, cerebral vasospasm, and atherosclerosis.[2−8] At present, two receptor subtypes known as ET_A and ET_B have been identified.[9−12] The ET_A receptor exhibits a higher affinity for ET-1 and ET-2 and is predominantly found in smooth muscle cells. This receptor therefore appears to be the primary target for cardiovascular diseases.

A number of ET antagonists have been reported including the ET_A-selective compounds BQ123,[13,14] FR139317,[15] SB 209670,[16] L-749,329,[17] BMS 182874,[18] and PD155080,[19] the balanced ET_A/ET_B antagonists Ro 46-2005[8] and Ro 47-0203,[20] and the ET_B-selective compounds BQ-788[21] and IPI-950.[22]

In the present article we wish to report the discovery of a novel class of nonpeptidic ET_A-selective receptor antagonists. Two initial lead structures, LU 110896 and LU 110897, compounds **1a**,**b** (originally designed as herbicides), were discovered by screening the chemical library of BASF for compounds that bind to the recombinant human ET_A receptor (Figure 1). **1a**,**b** bind to the ET_A receptor with K_i values of 250 and 160 nM, respectively. The binding to the ET_B receptor is much weaker (K_i = 3000 and 4700 nM). **1a**,**b** have two stereocenters. The primary goal was to enhance the binding affinity while simplifying the structure. As our first attempt to improve our lead, we decided to synthesize compounds with the general structure **6** (Scheme 1). The idea was to introduce two identical substituents at one chiral center. This effort immediately resulted in the discovery of a novel series of potent ET_A-selective antagonists.



1a (LU 110896, R=iPr)

1b (LU 110897, R=SMe)

Figure 1.

Chemistry

The synthesis of compound **6** is shown in Scheme 1. Reaction of a symmetrically substituted benzophenone derivative (**2**) with methyl chloroacetate gave the glycidic ester **3** in 70−95% yield. The epoxide **3** was then opened via Lewis acid-catalyzed addition of an alcohol providing α-hydroxy ester **4** in about 90% yield. Nucleophilic substitution of a pyrimidine derivative with **4** resulted in compound **5** in 70−80% yield. Finally, the methyl ester was hydrolyzed using KOH to produce the carboxylic acid **6** in 70−90% yield.

Results and Discussion

The structure−activity relationships of our novel series of endothelin receptor antagonists are summarized in Tables 1−3. The effect of the substitution pattern of R_1 is shown in Table 1. None of the investigated substituents resulted in improved binding as compared to the unsubstituted compound **6a**. Those substituents in meta-position, which have been prepared, seem to be tolerated. Table 2 highlights our results for the variation of R_2. Compounds **6** with R_2 = Me and Et show the highest receptor affinities. Longer or more bulky groups lead to a reduced affinity. Replacement of R_2 = Me by R_2 = H strongly decreased the binding affinity to K_i = 130 nM (ET_A).

Table 3 describes the structure−activity relationships for a variation of R_3. The selection of possible substituents R_3 was guided in part by a structural comparison of **6a** with **7**.[16] Both compounds contain a carboxy group roughly in the center of the structure flanked by two lipophilic side chains. A comparison of the putative 3D-structures of **6a** with **7** is shown in Figure 2.

This structural overlay suggested that an annellated ring as a lipophilic substituent R_3 at the pyrimidine

* To whom correspondence should be addressed. Tel: +49 621 60 49628. Fax: +49 621 60 20440.
† BASF AG.
‡ Knoll AG.
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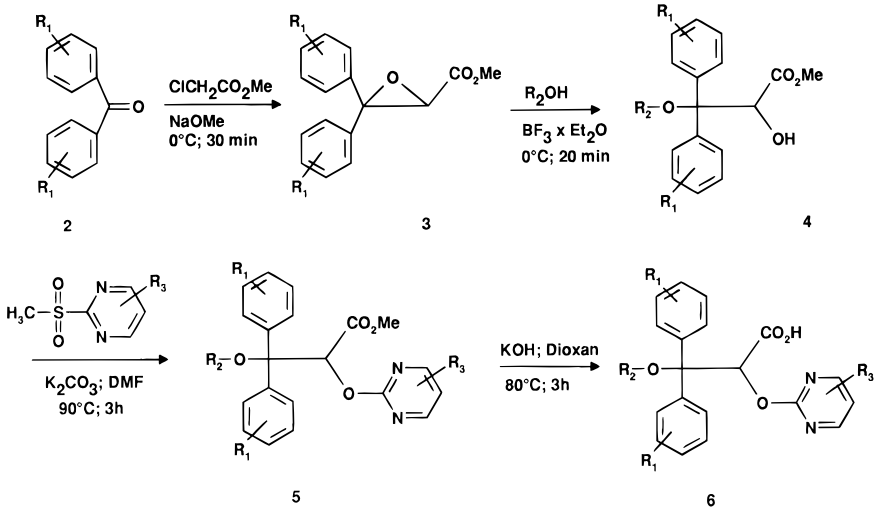
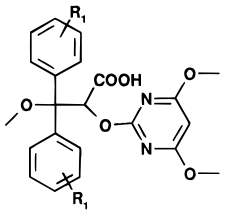
Scheme 1



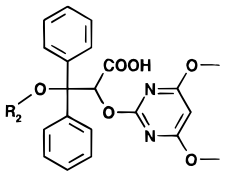
[a] For specification of residues R_1, R_2, and R_3, see Tables 1−3.

Table 1. Effect of a Variation of R_1 on the Binding Affinity



		K_i, nM (*n*)	
compd	R_1	ET_A	ET_B
6a	H	6 ± 0.87 (3)	1000 (1), h-ET_B: 371 ± 106 (3)
6b	*p*-F	33 ± 14.5 (3)	970 (1)
6c	*p*-Cl	245 (1)	1300 (1)
6d	*p*-Me	200 ± 94 (3)	1000 (1)
6e	*m*-F	11 ± 1.8 (3)	1800 (1)
6f	*m*-OMe	22 ± 9.7 (3)	1300 (1)
6g	*m*-Me	24 ± 10.8 (3)	1300 (1)
6h	*o*-F	150 (1)	6000 (1)

Table 2. Effect of a Variation of R_2 on the Binding Affinity



		K_i, nM (*n*)	
compd	R_2	ET_A	ET_B
6i	Et	7 ± 4.2 (3)	2500 (1)
6j	Pr	19 ± 9 (3)	1700 (1)
6k	Ph	86 ± 12 (3)	1500 (1)
6l	$(CH_2)_2$-tBu	340 ± 80 (3)	1400 (1)
6m	H	130 ± 19 (3)	3500 (1)

should improve the binding affinity because the structure−activity relationships of analogs of **7** (SB 209670) showed a strong dependence of the binding affinity on the substituent at the corresponding position. This consideration led to the design and synthesis of **6p**,**q**, which were found to be very potent antagonists with binding constants of 0.9 and 0.4 nM (ET_A), respectively, and weaker binding to the ET_B receptor (K_i = 24.5 and 20.4 nM, data for the h-ET_B). However, the most potent compound *in vitro* in the present series of compounds was **6s**. In view of the rather small structural difference between **6a** and **6s**, the 50-fold improvement in binding affinity seems remarkable. It should be noted that the ET_A/ET_B receptor binding ratio does not change significantly between compounds **6a**, **6p**, **6q**, and **6s**.

Compound **6a** was separated into the pure enantiomers, and these exhibited K_i values of 3 and 150 nM (ET_A). In order to establish the absolute configuration of the biologically active enantiomer, the derivative **4a** (the corresponding free carboxylic acid of compound **4**) was crystallized with (*R*)-phenylethylamine. The X-ray structure of the salt revealed the *S*-configuration for the enantiomer **4a**. Synthesis of **6a** starting from this enantiomerically pure compound led to the more potent enantiomer. We therefore conclude (*S*)-**6a** as the biologically active enantiomer.

Functional vascular ET-1 antagonism was determined in rabbit aorta rings with intact endothelium.[23] pA_2 values are summarized in Table 4. The pA_2 values correlate with the binding affinities for the ET_A receptor.[24]

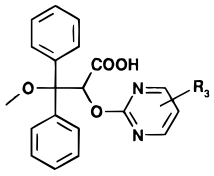
Finally, the model of ET-induced sudden death was used to demonstrate the oral bioavailability of selected compounds.[23] The results are summarized in Table 5. Four hours after treatment with 30 mg/kg po compound **6a**, a complete protection was observed. Even 8 h after treatment with **6a** (100 mg/kg po), complete protection still exists. In comparison, 10 mg/kg iv **6a** was necessary to obtain the same effect. Compound **6p** showed higher *in vivo* potency than **6a** after intravenous administration (ED 100% = 3 mg/kg iv). However, after po administration the *in vivo* activity of **6p** was less than that of **6a**.

In summary, we have discovered a novel class of nonpeptidic endothelin receptor antagonists. Compound **6a** is an orally active, highly ET_A-selective receptor antagonist with a long duration of action.

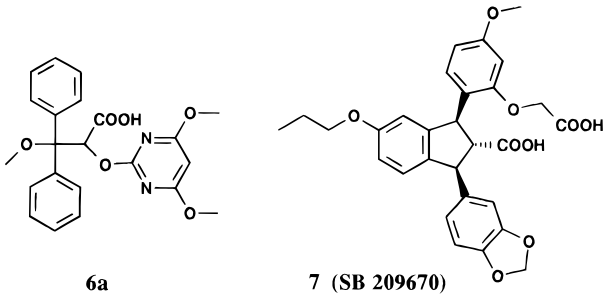
Experimental Section

Radioligand Binding Assays.[24] All receptor binding studies were carried out as follows. Membranes (50 mg of protein) from stably transfected CHO cells expressing human ET_A receptors or human ET_B receptors or guinea pig cerebellum containing ET_B receptors were incubated with either 25 pmol/L [^{125}I]ET-1 or [^{125}I]ET-3 with or without drugs. Nonspecific binding was defined at 0.1 mmol/L ET-1. K_i values were determined by nonlinear regression analysis.

Table 3. Effect of a Variation of R_3 on the Binding Affinity



		K_i, nM (*n*)	
compd	R_3	ET_A	ET_B
6n	4,6-OEt	174 ± 33 (3)	2500 (1)
6o	4,6-Me	1 ± 0.39 (3)	195 (1)
6p	4-OMe, 5,6-CH_2CH_2O−	0.9 ± 0.09 (3)	57 ± 10 (3), h-ET_B: 24.5 ± 10.5 (3)
6q	4-OMe, 5,6-$CH_2CH_2CH_2$−	0.4 ± 0.06 (3)	56 ± 18 (3), h-ET_B: 20.4 ± 6.9 (3)
6r	4-Me	19 (1)	1900 (1)
6s	4-OMe, 6-Me	0.12 ± 0.06 (3)	29 (1), h-ET_B: 19.7 ± 7.6 (3)
6t	4,6-Et	1 ± 0.8 (3)	1100 (1)
6u	4-Et, 6-Me	0.7 ± 0.12 (3)	160 (1)



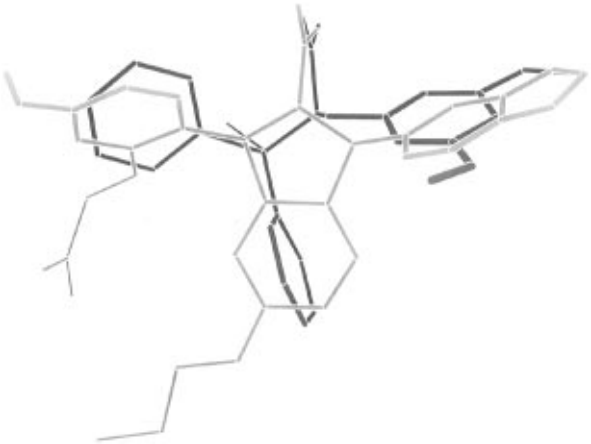


Figure 2. Superposition of the calculated 3D-structures of **6a** (dark bonds) and SB 209670 (gray bonds). The carboxylate groups are in the center, and the dimethoxypyrimidine group of **6a** is on the right.

***In Vitro* Functional Assay.[23] Vascular ET-1 antagonism:** In rabbit aorta segments (2 mm length, 2 g) preloaded in Krebs-Henseleit solution, after 1 h relaxation, a reference contraction to KCl (40 mmol/L) was registered isometrically; 30 min after washout, a cumulative ET-1 concentration−response curve was established without (control) or with 15 min antagonist preincubation. pA_2 values were determined by comparing collectives of 4−5 rings/concentration to control rings from the same aorta.

***In Vivo* Studies.[23] Prevention of ET-1-induced sudden death in rats by pretreatment with endothelin receptor antagonists:** ET-1 (6 nmol/kg) causing severe ECG disturbances and lethality within a few minutes was injected into a tail vein of male Sprague−Dawley rats of 280−320 g (control). After po (4 h) pretreatment with ET antagonists, the doses providing complete protection were determined (ED 100%).

General Chemical Procedures. Unless otherwise specified all solvents and reagents were obtained from commercial suppliers and used without further purification. Benzophenone and the 4,4′-substituted analogs used as starting materials were purchased from Aldrich; 3,3-difluorobenzophenone was available from Acros Organics; the other derivatives were prepared according to the procedure described in ref 25.

Table 4. Functional Vascular ET-1 Antagonism[24]

compd[a]	pA_2
6a (LU 127043)	7.34
6p (LU 134981)	9.03
6q (LU 136181)	9.24
Ro 46-2005	<6
BMS 182874	7.09
7 (SB 209670)	9.80

[a] Ro 46-2005, 4-*tert*-butyl-*N*-[6-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-4-pyrimidinyl]benzenesulfonamide; BMS 182874, 5-(dimethylamino)-*N*-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide; **7** (SB 209670), (1*S*,2*R*,3*S*)-3-[2-(carboxymethoxy)-4-methoxyphenyl]-1-[3,4-(methylenedioxy)phenyl]-5-(prop-1-yloxy)indan-2-carboxylic acid.

Table 5. Prevention of ET-1-Induced Sudden Death in Rats[23]

compd	10 mg/kg po	30 mg/kg po	100 mg/kg po	ED 100% (mg/kg)
6a (LU 127043)	5/5[a]	0/6	nd	30[b]
6p (LU 134981)	6/6	2/6	0/5	100
6q (LU 136181)	nd	9/9	0/5	100
Ro 46-2005	nd	nd	6/6	>100
BMS 182874	nd	nd	6/6	>100
7 (SB 209670)	nd	6/6	0/6	100

[a] Lethatliy: *x*/*n*. [b] With 8 h pretreatment: ED 100% = 100 mg/kg.

All reactions were performed under nitrogen atmosphere unless specifically noted. Melting points were determined on a Büchi 530 apparatus and are uncorrected. Analytical TLC was performed on silica gel plates (Merck silica gel 60 F_{254}). All final compounds were shown to be a single homogeneous peak by gradient HPLC on a HP 1090 liquid chromatograph with UV detection. ^{1}H-NMR spectra were recorded using a Bruker AC250 spectrometer (250 MHz), and all values are reported as chemical shifts in δ units (ppm) relative to tetramethylsilane as internal standard. Mass spectral analysis was accomplished on a Finnigan MAT 90 instrument using direct chemical ionization techniques. Elemental analyses were determined on a Leco CHN 800 apparatus; oxygen was determined separately on a Leco RO-478. All values are consistent with the theoretical data to within ±0.4% unless indicated otherwise.

Abbreviations: DMF, dimethylformamide; NaOMe, sodium methoxide; THF, tetrahydrofuran.

3,3′-Dimethylbenzophenone. (a) A solution of 8.55 g (50 mmol) of 3-bromotoluene in 10 mL of THF was added slowly to 1.3 g (53 mmol) of magnesium in 10 mL of THF and refluxed

for 2 h. After cooling to room temperature the mixture was treated with 16.25 g (50 mmol) of tributyltin chloride in 15 mL of THF and refluxed for 2 h. The reaction was then quenched with an aqueous solution of ammonium chloride; the organic layer was separated and the aqueous layer extracted again with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated yielding 18 g of the organotin compound as an oil. The crude product was used in the next step without further purification.

(b) To a mixture of 6.95 g (45 mmol) of 3-methylbenzoic acid chloride and 150 mg of bis(triphenylphosphine)palladium(II) chloride in 9 mL of $CHCl_3$ was added the crude organotin compound in 36 mL of $CHCl_3$, and the whole mixture was heated for 10 h to reflux temperature. Afterwards the solution was diluted with 200 mL of diethyl ether and extracted twice with H_2O. The organic layer was washed with an aqueous KF solution and the resulting precipitate (tributyltin fluoride) removed by filtration. The organic layer was dried ($MgSO_4$), evaporated, and purified by chromatography on silica gel (heptane/ethyl acetate, 4:1) to give 7 g (58%) of the product as an oil: ^{1}H-NMR ($CDCl_3$) δ 2.40 (s, 6H), 7.25−7.65 (m, 8H).

3,3′-Dimethoxybenzophenone. The compound was prepared as described for 3,3′-dimethylbenzophenone using 3-methoxybromobenzene and 3-methoxybenzoic acid chloride as starting material giving 6.2 g (50%) of the product as an oil: ^{1}H-NMR ($CDCl_3$) δ 3.85 (s, 6H), 7.10 (m, 2H), 7.35 (m, 6H).

2,2′-Difluorobenzophenone. The compound was prepared as described for 3,3′-dimethylbenzophenone using 2-fluorobromobenzene and 2-fluorobenzoic acid chloride as starting material giving 5.8 g (46%) of the product as an oil: ^{1}H-NMR ($CDCl_3$) δ 6.80−7.80 (m, 8H).

3,3-Diphenyloxirane-2-carboxylic Acid Methyl Ester (3, R_1 = H). In a 2 L flask 259 g (4.8 mol) of NaOMe was stirred in 800 mL of THF and cooled to 0 °C. A solution of 500 g (2.74 mol) of benzophenone and 420 mL (4.8 mol) of chloroacetic acid methyl ester in 100 mL of THF was added. The mixture was stirred for 0.5 h and then partitioned between diethyl ether (2 × 500 mL) and water (2 L). The organic phase was separated, washed with brine, and dried over magnesium sulfate. The solvents were evaporated in vacuo to give an oil which was crystallized from diethyl ether/hexane to give 620 g (89%) of compound **3** as a white solid: ^{1}H-NMR ($CDCl_3$) δ 3.50 (s, 3H), 3.98 (s, 1H), 7.30−7.45 (m, 10H); mass spectra (CI^+) 255; mp 50−51 °C. Anal. ($C_{16}H_{14}O_3$) C, H, O.

2-Hydroxy-3-methoxy-3,3-diphenylpropionic Acid Methyl Ester (4, R_1 = H, R_2 = Me). A solution of 156.4 g (0.61 mol) of **3** in 50 mL of MeOH was cooled to 0 °C, and 1 mL of BF_3−Et_2O was added. After 20 min 500 mL of H_2O was added, and the solution was extracted three times with 300 mL of Et_2O. The organic layer was cooled to 0 °C and the precipitate collected by filtration to give 171 g (98%) of a white solid (**4**, R_1 = H, R_2 = Me): ^{1}H-NMR ($CDCl_3$) δ 3.18 (s, 3H), 3.63 (s, 3H), 5.18 (d, 1H), 7.25−7.42 (m, 10H); mass spectra (CI^+) 255 (M^+ − MeOH); mp 90−92 °C. Anal. ($C_{17}H_{18}O_4$) C, H, O.

2-[(4,6-Dimethoxypyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropionic Acid Methyl Ester (5, R_1 = H, R_2 = Me, R_3 = 4,6-OMe). **4** (10 g, 35 mmol) was dissolved in 100 mL of DMF; 2.4 g (17.5 mmol) of K_2CO_3 was added and the suspension stirred for 0.5 h; 7.63 g (35 mmol) of 2-(methylsulfonyl)-4,6-dimethoxypyrimidine was added, and the mixture was stirred at 90 °C for 3 h; 200 mL of ethyl acetate was added, and the solution was washed with water (50 mL), citric acid (50 mL, 2 N), and brine (50 mL). The organic layer was separated and dried over magnesium sulfate. The solvent was evaporated, and the resulting oil was crystallized from diethyl ether/hexane to give 13 g (87%) of **5** as a white solid: ^{1}H-NMR ($CDCl_3$) δ 3.43 (s, 3H), 3.50 (s, 3H), 3.85 (s, 6H), 5.70 (s, 1H), 6.05 (s, 1H), 7.22−7.50 (m, 10H); mass spectra (CI^+) 392 (M^+ − MeOH); mp 80−82 °C. Anal. ($C_{23}H_{24}N_2O_6$) C, H, N, O.

2-[(4,6-Dimethoxypyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropionic Acid (6a). **5** (10 g, 23.6 mmol) was dissolved in 100 mL of dioxane and 50 mL of NaOH (1 N) and stirred for 3 h at 80 °C. The solution was diluted with water (100 mL), neutralized with HCl (1 N), and extracted with diethyl ether (3 × 200 mL). The organic layer was dried over magnesium sulfate, the solvent was removed, and the product was crystallized from diethyl ether to give 6 g (62%) of **6a** as a white solid: ^{1}H-NMR ($CDCl_3$) δ 3.32 (s, 3H), 3.83 (s, 6H), 5.75 (s, 1H), 6.11 (s, 1H), 7.22−7.55 (m, 10H); mass spectra (CI^+) 379 (M^+ − MeOH); mp 165−168 °C. Anal. ($C_{22}H_{22}N_2O_6$) C, H, N, O.

2-[(4,6-Dimethoxypyrimidin-2-yl)oxy]-3,3-bis(4-fluorophenyl)-3-methoxypropionic Acid (6b). Compound **6b** was synthesized as in example **6a** starting with 4,4′-difluorobenzophenone giving 2.3 g (55%, final step): ^{1}H-NMR ($CDCl_3$) δ 3.28 (s, 3H), 3.90 (s, 6H), 5.75 (s, 1H), 6.08 (s, 1H), 6.95−7.50 (m, 8H); mass spectra (CI^+) 415 (M^+ − MeOH); mp 163−165 °C. Anal. ($C_{22}H_{20}F_2N_2O_6$) C, H, N, O, F.

2-[(4,6-Dimethoxypyrimidin-2-yl)oxy]-3,3-bis(4-chlorophenyl)-3-methoxypropionic Acid (6c). Compound **6c** was synthesized as in example **6a** starting with 4,4′-dichlorobenzophenone giving 1.8 g (65%, final step): ^{1}H-NMR ($CDCl_3$) δ 3.33 (s, 3H), 3.83 (s, 6H), 5.77 (s, 1H), 6.02 (s, 1H), 7.22−7.42 (m, 8H); mass spectra (CI^+) 447 (M^+ − MeOH); mp 186−190 °C. Anal. ($C_{22}H_{20}Cl_2N_2O_6$) Calcd: C, 55.13; H, 4.21; O, 20.03; N, 5.84; Cl, 14.79. Found: C, 56.1; H, 4.9; O, 18.6; N, 5.3; Cl, 13.

2-[(4,6-Dimethoxypyrimidin-2-yl)oxy]-3,3-bis(4-methylphenyl)-3-methoxypropionic Acid (6d). Compound **6d** was synthesized as in example **6a** starting with 4,4′-dimethylbenzophenone giving 1.9 g (50%, final step): ^{1}H-NMR ($CDCl_3$) δ 2.30 (s, 3H), 2.32 (s, 3H), 3.26 (s, 3H), 3.84 (s, 6H), 5.73 (s, 1H), 6.18 (s, 1H), 7.10−7.40 (m, 8H); mass spectra (CI^+) 407 (M^+ − MeOH); mp 168−170 °C. Anal. ($C_{24}H_{26}N_2O_6$) C, H, N, O.

2-[(4,6-Dimethoxypyrimidin-2-yl)oxy]-3,3-bis(3-fluorophenyl)-3-methoxypropionic Acid (6e). Compound **6e** was synthesized as in example **6a** starting with 3,3′-difluorobenzophenone giving 0.8 g (63%, final step): ^{1}H-NMR ($CDCl_3$) δ 3.44 (s, 3H), 3.82 (s, 6H), 5.97 (s, 1H), 6.14 (s, 1H), 7.05−7.45 (m, 8H); mass spectra (CI^+) 447; mp 175−177 °C. Anal. ($C_{22}H_{20}F_2N_2O_6$) C, H, N, O, F.

2-[(4,6-Dimethoxypyrimidin-2-yl)oxy]-3,3-bis(3-methoxyphenyl)-3-methoxypropionic Acid (6f). Compound **6f** was synthesized as in example **6a** starting with 3,3′-dimethoxybenzophenone giving 1.2 g (55%, final step): ^{1}H-NMR ($CDCl_3$) δ 3.33 (s, 3H), 3.70 (s, 3H), 3.74 (s, 3H), 3.85 (s, 6H), 5.75 (s, 1H), 6.15 (s, 1H), 6.70−7.34 (m, 8H); mass spectra (CI^+) 439 (M^+ − MeOH); mp 137−140 °C. Anal. ($C_{24}H_{26}N_2O_8$) C, H, N, O.

2-[(4,6-Dimethoxypyrimidin-2-yl)oxy]-3,3-bis(3-methylphenyl)-3-methoxypropionic Acid (6g). Compound **6g** was synthesized as in example **6a** starting with 3,3′-dimethylbenzophenone giving 2.4 g (68%, final step): ^{1}H-NMR ($CDCl_3$) δ 2.30 (s, 3H), 2.35 (s, 3H), 3.30 (s, 3H), 2.85 (s, 6H), 5.75 (s, 1H), 6.12 (s, 1H), 7.10−7.32 (m, 8H); mass spectra (CI^+) 407 (M^+ − MeOH); mp 152−156 °C. Anal. ($C_{24}H_{26}N_2O_6$) Calcd: O, 21.89. Found: O, 22.1.

2-[(4,6-Dimethoxypyrimidin-2-yl)oxy]-3,3-bis(2-fluorophenyl)-3-methoxypropionic Acid (6h). Compound **6h** was synthesized as in example **6a** starting with 2,2′-difluorobenzophenone giving 0.6 g (45%, final step): ^{1}H-NMR ($CDCl_3$) δ 3.50 (s, 3H), 3.82 (s, 6H), 5.92 (s, 1H), 6.30 (s, 1H), 7.00−7.83 (m, 8H); mass specttra (CI^+) 447; mp 193−194 °C. Anal. ($C_{22}H_{20}F_2N_2O_6$) C, H, N, O, F.

2-[(4,6-Dimethoxypyrimidin-2-yl)oxy]-3-ethoxy-3,3-diphenylpropionic Acid (6i). Compound **6i** was synthesized as in example **6a** starting with compound **3** and ethanol giving 6.8 g (58%, final step): ^{1}H-NMR ($CDCl_3$) δ 1.27 (t, 3H), 3.50 (m, 2H), 3.88 (s, 6H), 5.76 (s, 1H), 6.22 (s, 1H), 7.25−7.55 (m, 10H); mass spectra (CI^+) 379 (M^+ − EtOH); mp 93−94 °C. Anal. ($C_{23}H_{24}N_2O_6$) C, H, N, O.

2-[(4,6-Dimethoxypyrimidin-2-yl)oxy]-3-propoxy-3,3-diphenylpropionic Acid (6j). Compound **6j** was synthesized as in example **6a** starting with compound **3** and propanol giving 4.3 g (52%, final step): ^{1}H-NMR ($CDCl_3$) δ 0.95 (t, 3H), 1.63 (m, 2H), 3.40 (m, 2H), 3.90 (s, 6H), 5.75 (s, 1H), 6.23 (s, 1H), 7.24−7.60 (m, 10H); mass spectra (CI^+) 379 (M^+ − PrOH); mp 172−174 °C. Anal. ($C_{24}H_{26}N_2O_6$) C, H, N, O.

2-[(4,6-Dimethoxypyrimidin-2-yl)oxy]-3-phenoxy-3,3-diphenylpropionic Acid (6k). Compound **6k** was synthesized as in example **6a** starting with compound **3** and phenol giving 5.1 g (46%, final step): ^{1}H-NMR ($CDCl_3$) δ 3.85 (s, 6H), 5.72 (s, 1H), 6.33 (s, 1H), 6.79−7.78 (m, 15H); mass spectra (CI^+) 379 (M^+ − PhOH); mp 136−140 °C. Anal. ($C_{27}H_{24}N_2O_6$) C, H, N, O.

2-[(4,6-Dimethoxypyrimidin-2-yl)oxy]-3-(3,3-dimethylbutoxy)-3,3-diphenylpropionic Acid (6l). Compound **6l** was synthesized as in example **6a** starting with compound **3** and 3,3-dimethylbutanol giving 1.7 g (50%, final step): ^{1}H-NMR ($CDCl_3$) δ 0.85 (s, 9H), 1.58 (m, 2H), 3.40 (m, 1H), 3.50 (m, 1H), 3.87 (s, 6H), 5.72 (s, 1H), 6.22 (s, 1H), 7.25−7.55 (m, 10H); mass spectra (CI^+) 481; mp 154−157 °C. Anal. ($C_{27}H_{32}N_2O_6$) C, H, N, O.

2-[(4,6-Dimethoxypyrimidin-2-yl)oxy]-3-hydroxy-3,3-diphenylpropionic Acid (6m). Compound **6m** was synthesized by debenzylation of 3-(benzyloxy)-2-[(4,6-dimethoxypyrimidin-2-yl)oxy]-3,3-diphenylpropionic acid using H_2 and Pd/C as a catalyst giving 4 g (96%, final step): ^{1}H-NMR (DMSO) δ 3.82 (s, 6H), 5.90 (s, 1H), 6.10 (s, 1H), 6.20−6.40 (1H), 7.15−7.50 (m, 10H); mass spectra (CI^+) 397; mp 178−180 °C. Anal. ($C_{21}H_{20}N_2O_6$) C, H, N, O.

2-[(4,6-Diethoxypyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropionic Acid (6n). Compound **6n** was synthesized as in example **6a** starting with compound **4** and 2-(methylsulfonyl)-4,6-diethoxypyrimidine giving 0.7 g (45%, final step): ^{1}H-NMR ($CDCl_3$) δ 1.33 (t, 3H), 3.31 (s, 3H), 4.30 (q, 2H), 5.70 (s, 1H), 6.15 (s, 1H), 7.25−7.55 (m, 10H); mass spectra (CI^+) 407 (M^+ − MeOH); mp 138−140 °C. Anal. ($C_{24}H_{26}N_2O_6$) Calcd: C, 65.74; H, 5.98; O, 21.89; N, 6.39. Found: C, 64.7; H, 6.2; O, 22.2; N, 5.8.

2-[(4,6-Dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropionic Acid (6o). Compound **6o** was synthesized as in example **6a** starting with compound **4** and 2-(methylsulfonyl)-4,6-dimethylpyrimidine giving 0.3 g (51%, final step): ^{1}H-NMR (DMSO) δ 2.35 (s, 6H), 3.38 (s, 3H), 6.15 (s, 1H), 6.95 (s, 1H), 7.20−7.38 (m, 10H); mass spectra (CI^+) 347 (M^+ − MeOH); mp 190−191 °C. Anal. ($C_{22}H_{22}N_2O_4$) Calcd: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.2; H, 6.0; N, 7.0.

3-Methoxy-2-[(4-methoxy-5,6-dihydrofuro[2,3-*d*]pyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (6p). Compound **6p** was synthesized as in example **6a** starting with compound **4** and 2-(methylsulfonyl)-4-methoxy-5,6-dihydrofuro[2,3-*d*]pyrimidine giving 2.8 g (58%, final step): ^{1}H-NMR ($CDCl_3$) δ 3.02 (t, 2H), 3.3 (s, 3H), 3.92 (s, 3H), 4.64 (t, 2H), 6.20 (s, 1H), 7.20−7.50 (m, 10H); mass spectra (CI^+) 391 (M^+ − MeOH) mp 126−128 °C. Anal. ($C_{23}H_{22}N_2O_6$) C, H, N, O.

3-Methoxy-2-[(4-methoxy-6,7-dihydro-5*H*-cyclopentapyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (6q). Compound **6q** was synthesized as in example **6a** starting with compound **4** and 2-(methylsulfonyl)-4-methoxy-6,7-dihydro-5*H*-cyclopentapyrimidine giving 4.2 g (60%, final step): ^{1}H-NMR (DMSO) δ 2.10 (t, 2H), 2.70 (t, 2H), 2.83 (m, 2H), 3.38 (s, 3H), 3.88 (s, 3H), 6.12 (s, 1H), 7.20−7.40 (m, 10H); 389 (M^+ − MeOH); mp 149−151 °C. Anal. ($C_{24}H_{24}N_2O_5$) C, H, N, O.

3-Methoxy-2-[(4-methylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (6r). Compound **6r** was synthesized as in example **6a** starting with compound **4** and 2-(methylsulfonyl)-4-methylpyrimidine giving 0.2 g (38%, final step): ^{1}H-NMR (DMSO) δ 2.40 (s, 3H), 3.38 (s, 3H), 6.15 (s, 1H), 6.85 (d, 1H), 7.12−7.40 (m, 10H), 8.34 (d, 1H); mass spectra (CI^+) 333 (M^+ − MeOH); mp 174−175 °C. Anal. ($C_{21}H_{20}N_2O_4$) C, H, N, O.

3-Methoxy-2-[(4-methoxy-6-methylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (6s). Compound **6s** was synthesized as in example **6a** starting with compound **4** and 2-(methylsulfonyl)-4-methoxy-6-methylpyrimidine giving 5.2 g (66%, final step): ^{1}H-NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.31 (s, 3H), 3.85 (s, 3H), 6.20 (s, 1H), 6.23 (s, 1H), 7.22−7.50 (m, 10H); mass spectra (CI^+) 363 (M^+ − MeOH); mp 148−150 °C. Anal. ($C_{22}H_{22}N_2O_5$) C, H, N, O.

2-[(4,6-Diethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropionic Acid (6t). Compound **6t** was synthesized as in example **6a** starting with compound **4** and 4,6-diethyl-2-(methylsulfonyl)pyrimidine giving 1.1 g (50%, final step): ^{1}H-NMR ($CDCl_3$) δ 1.24 (t, 6H), 2.65 (q, 4H), 3.36 (s, 3H), 6.38 (s, 1H), 6.70 (s, 1H), 7.22−7.58 (m, 10H); mass spectra (CI^+) 407; mp 142−143 °C. Anal. ($C_2H_{26}N_2O_4$) C, H, N, O.

2-[(4-Ethyl-6-methylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropionic Acid (6u). Compound **6u** was synthesized as in example **6a** starting with compound **4** and 4-ethyl-2-(methylsulfonyl)-6-methylpyrimidine giving 0.8 g (46%, final step): ^{1}H-NMR ($CDCl_3$) δ 1.23 (t, 3H), 2.40 (s, 3H), 2.65 (q, 2H), 3.35 (s, 3H), 6.38 (s, 1H), 6.70 (s, 1H), 7.22−7.57 (m, 10H); mass spectra (CI^+) 361 (M^+ − MeOH); mp 163−165 °C. Anal. ($C_{23}H_{24}N_2O_4$) C, H, N, O.

Supporting Information Available: Experimental data for intermediates of the type **3**−**5** (Scheme 1) (13 pages). Ordering information can be found on any current masthead page.

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) Inoue, A.; Yanagisawa, M.; Kimura, S.; Kasuya, Y.; Miyauchi, T.; Goto, K.; Masaki, T. The human endothelin family; three structurally and pharmacologically distinct isopeptides predicted by three separate genes. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 2863−2867.

(3) Watanabe, T.; Suzuki, N.; Shimamoto, N.; Fujino, M.; Imada, A. Endothelin in myocardial infarction. *Nature* **1990**, *344*, 114.

(4) Saito, Y.; Nakao, K.; Mukoyama, M.; Imura, H. Increased plasma endothelin level in patients with essential hypertension. *N. Engl. J. Med.* **1989**, *322*, 205.

(5) Giaid, A.; Yanagisawa, M.; Langleben, D.; Michel, R.; Levy, R.; Shennib, H.; Kimra, S.; Masaki, T.; Duguid, W.; Path, F. R. C.; Stewart, D. J. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N. Engl. J. Med.* **1993**, *328*, 1732−1739.

(6) Takahashi, K.; Totsune, K.; Mouri, T. Endothelin in chronic renal failure. *Nephron* **1994**, *66*, 373−379.

(7) Cosentino, F.; Katusic, Z. S. Does Endothelin-1 play a role in the pathogenesis of cerebral vasospasm? *Stroke* **1994**, *25*, 904−908.

(8) Clozel, M.; Breu, V.; Burri, K.; Cassao, J.-M.; Fischli, W.; Gray, G. A.; Hirth, G.; Loffler, B.-M.; Muller, M.; Neidhart, W.; Ramuz, H. Pathophysiological role of endothelin revealed by the first orally active endothelin receptor antagonist. *Nature* **1993**, *365*, 759−761.

(9) 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.

(10) 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.

(11) Sakamoto, A.; Yanagisawa, M.; Sakurai, T.; Takuwa, Y.; Yanagisawa, H.; Masaki, T. Cloning and functional expression of human cDNA for the ET_B endothelin receptor. *Biochem. Biophys. Res. Commun.* **1991**, *178*, 656−663.

(12) Hosoda, K.; Nakao, K.; Arai, H.; Suga, S.; Ogawa, Y.; Mukoyama, M.; Shirakami, G.; Saito, Y.; Nakanishi, S.; Imura, H. Cloning and expression of human endothelin-1 receptor cDNA. *FEBS Lett.* **1991**, *187*, 23−26.

(13) Ishikawa, K.; Fukami, T.; Nagase, T.; Fujita, K.; Hayama, T.; Niyama, K.; Mase, T.; Ihara, M.; Yano, M. Cyclic pentapeptide endothelin antagonists with ET_A selectivity. Potency and solubility enhanding modifications. *J. Med. Chem.* **1992**, *35*, 2139−2142.

(14) Ihara, M.; Noguchi, K.; Saeki, T.; Fukoroda, T.; Tsuchida, S.; Kimura, S.; Fukami, F.; Ishikawa, K.; Nishikibe, M.; Yano, M. Biological profiles of highly potent novel endothelin antagonists selective for ET_A receptor. *Life Sci.* **1991**, *50*, 247−255.

(15) 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.

(16) Elliott, J. D.; Lago, M. A.; Cousins, R. D.; Gao, A.; Leber, J. D.; Erhard, K. F.; Nambi, P.; Elshourbagy, N. A.; Kumar, C.; Lee, J. A.; Bean, J. W.; DeBrosse, C. W.; Eggleston, D. S.; Brooks, D. P.; Feuerstein, G.; Ruffolo, R. R.; Weinstock, J.; Gleason, J. G.; Peishoff, C. E.; Ohlstein, E. H. 1,3-Diarylindan-2-carboxylic acids, potent and selective non-peptide endothelin receptor antagonists. *J. Med. Chem.* **1994**, *37*, 1553−1557.

(17) Walsh, T. F.; Fitch, K. J.; Chakravarty, K.; Williangs, D. L.; Murphy, K. A.; Nolan, N. A.; O'Brien, J. A.; Lis, E. V.; Pettibone, D. J.; Kivlighn, S. D.; Gabel, R. A.; Zingaro, G. J.; Krause, S. M.; Siegl, P. K. S.; Clineschmidt, B. V.; Greenlee, W. J. Discovery of L-749,329, a highly potent, orally active antagonist of endothelin receptors. ACS National Meeting, Washington, August 1994; MEDI 145.

(18) 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.

(19) Doherty, A. M.; Patt, W. C.; Edmunds, J. J.; Berryman, K. A.; Reisdorph, B. R.; Plummer, M. S.; Shahripour, A.; Lee, C.; Cheng, X. M.; Walker, D. M.; Haleen, S. J.; Keiser, J. A.; Flynn, M. A.; Welch, K. M.; Hallak, H.; Taylor, D. G.; Reynolds, E. E. Discovery of a Novel Series of Orally Active Non-Peptide Endothelin-A (ET_A) Receptor-Selective Antagonists. *J. Med. Chem.* **1995**, *38*, 1259−1263.

(20) Roux, S. P.; Clozel, M.; Sprecher, U.; Gray, G.; Clozel, J. P. Ro 47-0203, a new endothelin receptor antagonist reverses chronic vasospasm in experimental subarachnoid hemorrhage. *Circulation* **1993**, *88*, I-170.

(21) Ishikawa, K.; Ihara, M.; Noguchi, K.; Mase, T.; Mino, N.; Saeki, T.; Fukuroda, T.; Fukami, T.; Ozaki, S.; Nagase, T.; Nishikibe, J.; Yano, M. Biochemical and pharmacological profile of a potent and selective endothelin B-receptor antagonist BQ-788. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4892−4896.

(22) Chan, M. F.; Kois, A.; Raju, B.; Castillo, R. S.; Verner, E. J.; Wu, C.; Venkatachalapathi, Y. V.; Okun, I.; Stavros, F. D.; Balaji, V. N. The Discovery of Non-Peptide, Low Molecular Weight, ET_B Selective Endothelin Antagonists. ACS National Meeting, Anaheim, April 1995; MEDI 168.

(23) Raschack, M.; Unger, L.; Riechers, H.; Klinge, D. Receptor Selectivity of Endothelin Antagonists and Prevention of Vasoconstriction and Endothelin-Induced Sudden Death. *J. Cardiovasc. Pharmacol.* **1995**, *26* (Suppl. 3), S397−S399.

(24) (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) Sokolovsky, M.; Ambar, I.; Galron, R. A novel subtype of endothelin receptors. *J. Biol. Chem.* **1992**, *29*, 20551−20554.

(25) Labadie, J. W.; Stille, J. K. Mechanisms of the Palladium-Catalyzed Couplings of Acid Chlorides with Organotin Reagents. *J. Am. Chem. Soc.* **1983**, *105* (No. 19), 6129−6137.

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