Pergamon

Bioorganic & Medicinal Chemistry 9 (2001) 255–268

BIOORGANIC & MEDICINAL CHEMISTRY

Design, Syntheses, and Structure–Activity Relationships of Indan Derivatives as Endothelin Antagonists; New Lead Generation of Non-peptidic Antagonist from Peptidic Leads

Hiroshi Morimoto, Chiaki Fukushima, Rikako Yamauchi, Tomoko Hosino, Kohei Kikkawa, Kosuke Yasuda and Koichiro Yamada*

Discovery Research Laboratory, Tanabe Seiyaku Co., Ltd, 2-2-50 Kawagishi, Toda-shi, Saitama 335-8505, Japan

Received 30 May 2000; accepted 26 August 2000

Abstract—A new lead generation of non-peptidic ET_A antagonists from two peptidic ET_A-selective ones, BQ-123 and FR139317, was performed. Using computer assisted molecular modeling, a putative pharmacophore was constructed from the superposition of the reported three-dimensional structure of the cyclic peptide BQ-123 and a presumable β-turn active conformation of the linear peptide FR139317 formed by an intramolecular hydrogen bond. According to this model, a new series of indan derivatives were designed and synthesized. Among these, 5-isobutyrylamino-6-(1-naphthylmethyloxy)-3-(2-thienyl)-1-indancarboxylic acid (**1b**) showed a moderate ET_A antagonistic activity ($IC_{50} = 28\ \mu M$).

Introduction

Endothelin-1 (ET-1) was first isolated from cultured porcine vascular endothelial cells in 1988 and has been found to be the most potent and long-lasting vasoconstrictor peptide.[1] ET has been implicated in the pathogenesis of a number of disease states including renal failure, pulmonary hypertension, cerebral ischemia, vasospasm, endotoxic shock, and congestive heart failure.[2] Inhibition of the biological actions of ET has been suggested to offer potential utility in the treatment of these diseases. In the early 1990s, ET_A-selective peptidic antagonists such as cyclic peptide BQ-123[3] and linear peptide FR139317[4] were disclosed. They have made numerous contributions to clarifying the roles of ETs in the physiological and pathophysiological processes.[5] However, these peptidic antagonists have poor oral activity and very short duration of action, probably due to their low metabolic stability in vivo. For these, they are unsuitable for therapeutic uses in chronic diseases in which ETs are involved. To overcome these problems, orally active and much durable non-peptidic antagonists have been desired. A number of non-peptidic antagonists have been disclosed and the effects for the disease states have been investigated.[6]

Intending to find non-peptidic compounds from peptides, there have been numerous reports of the peptidomimetic approaches using nucleic templates, which amino acid side chains were arranged around, based on the hypothesis that the geometry of the side chain substituents in the parent peptides is critically important for biological activities.[7] Regarding the peptidic antagonists BQ-123 and FR139317, we focused on the structure and the difference of the activity. The similarity of the substituents between BQ-123 and FR139317 gave us a hypothesis that the active conformation of FR139317 was in the β-turn structure with a possible intramolecular hydrogen bond between urea CO and D-pyridylalanine (Pya) NH. The three-dimensional (3-D) structure of the cyclic peptide BQ-123 has been studied in detail,[8] and the NMR conformational analysis in solution was reported. It was proved that BQ-123 is stabilized by two intramolecular hydrogen bonds.[9] As for the activity for ET_A receptor (porcine aortic membrane), FR139317 shows higher affinity than BQ-123 (FR139317, $IC_{50} = 0.53$ nM and BQ-123, $IC_{50} = 22$ nM). Investigating the reason for the difference, we superimposed the main chain of the putative β-turn structure of FR139317 and one of the most stable conformations of BQ-123 reported using computer assisted molecular modeling. The superposition is shown in Figure 2 (left side). Indeed almost all the side chain substituents overlapped, but the location and direction of the carboxylic acids were different. Then, we constructed a

*Corresponding author. Discovery Research Laboratory, Tanabe Seiyaku Co., Ltd, 2-2-50 Kawagishi, Toda-shi, Saitama 335-8505, Japan.

0968-0896/01/$ - see front matter
PII: S0968-0896(00)00241-8

putative pharmacophore that might be important for ET antagonistic activities taking into consideration that the difference of the affinity of these antagonists would depend on the location of the carboxylic acid.

According to the pharmacophore, seeking a new class of non-peptidic ET antagonists, we investigated some skeletons by computer assisted molecular design. Among these, an indan template was selected and some most promising side chain substituents were attached on it.

We report herein the design and the syntheses of the indan derivatives and their affinities for ET_A receptor.

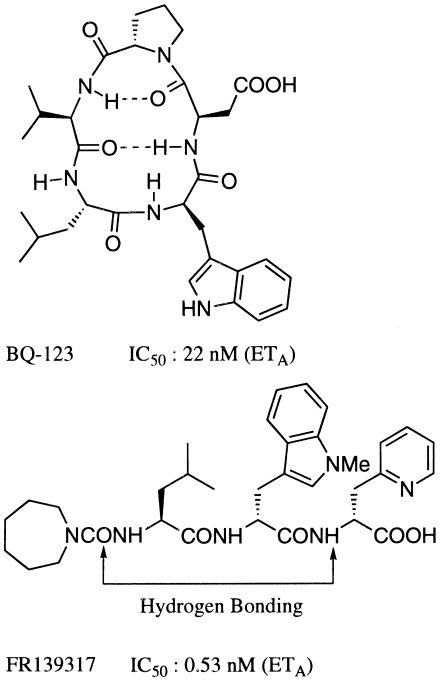


Figure 1. Structures of peptidic ET_A antagonists BQ-123 and FR139317. The two reported hydrogen bonds in BQ-123 are indicated with dashed lines, and the possible hydrogen bond in FR139317 is indicated with an arrow.

Methods

Molecular modeling of BQ-123 and FR139317

The initial structure of BQ-123 was constructed based on the reported solution structure determined by NMR.[8b] The structure was then energy minimized with distance constraints between two pairs of hydrogen-bonded atoms, so that it could match the γ-turned NMR structure. The initial structure of FR139317 was constructed to overlap the main chain of BQ-123, and the structure was energy minimized with a distance constraint between the oxygen of the urea CO and the hydrogen of the D-Pya NH which were likely to make a hydrogen bond.

The whole shape of FR139317 after the energy minimization was very similar to that of BQ-123. Their superposition is shown in Figure 2 (left side). In this model, homopiperidine ring, L-Leu residue, D-Trp(Me) residue, and pyridine ring of FR139317 match with D-Val residue, L-Leu residue, D-Trp residue, and L-Pro residue of BQ-123, respectively. However, the carboxylic acids of FR139317 and BQ-123 did not overlap completely.

Construction of pharmacophore model

On the supposition that the relative geometry of the side chain residues of these peptidic antagonists was the most important for the interaction with ET receptor in these peptidic antagonists, a pharmacophore model was constructed from the obtained superposition. As shown in Figure 2 (right side), the carboxylic acid, aromatic ring, and two hydrophobic groups were regarded as the most important components for the pharmacophore, and the approximate distances among these groups were calculated. At this point, the area of the carboxylic acid was estimated as large for the reason described above. The area occupied by pyridine ring of FR139317 and L-Pro of BQ-123 was omitted because the Pro residue of BQ-123 just played a role to fix conformation as the backbone ring of the peptide.[9]

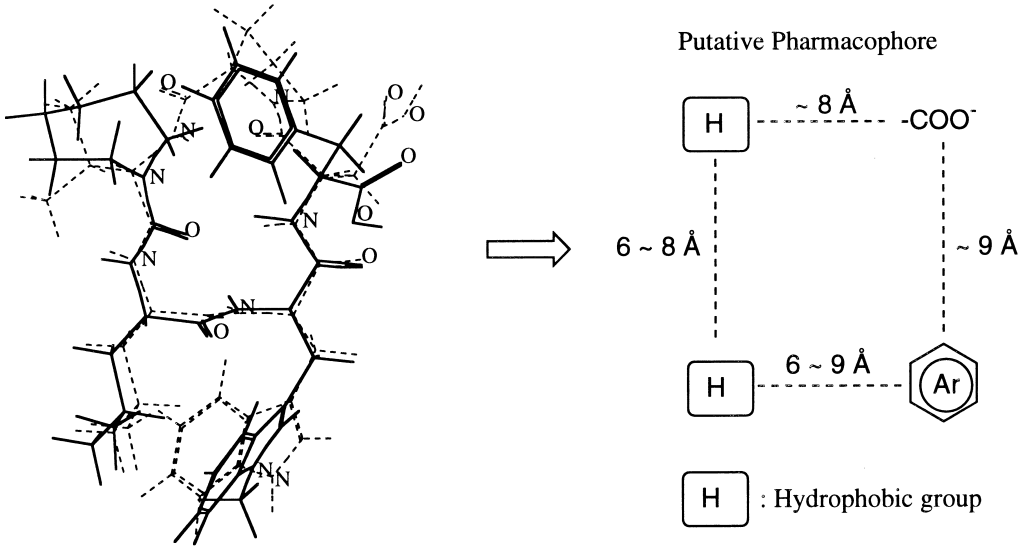


Figure 2. A putative pharmacophore model derived from a superposition between BQ-123 (dashed line) and FR139317 (solid line).

Design of indan derivatives

By the molecular modeling study of the peptides, relatively rigid bicyclic rings such as indan, 2-indolinone, and tetralin were thought to be suitable as a nucleus for the pharmacophore because those templates could fit the size and shape of the peptidic backbone. From preliminary conformational analysis and for facility in synthesis, we selected indan as a nucleus, in which the proper substituents were introduced onto 1-, 3-, 5-, and 6-positions. For BQ-518, having 2-thienyl group instead of the Val residue of BQ-123, reported to be a more potent ET_A-selective antagonist than BQ-123,[9] we adopted 2-thienyl group as a substituent at 3-position. Adjusting the distances among each residue and making it easy to modify the residues synthetically, spacers such as amide bond, ether bond, and methylene were introduced between indan and the residues at 6-position. In addition, it was found that *cis*-indan derivatives fit the pharmacophore more suitably than *trans* ones. As the area occupied by the carboxylic acid could not be fixed in a small range in the pharmacophore, the number of the methylene which linked the carboxylic acid moiety to the indan skeleton varied from 0 to 2 (Figure 3).

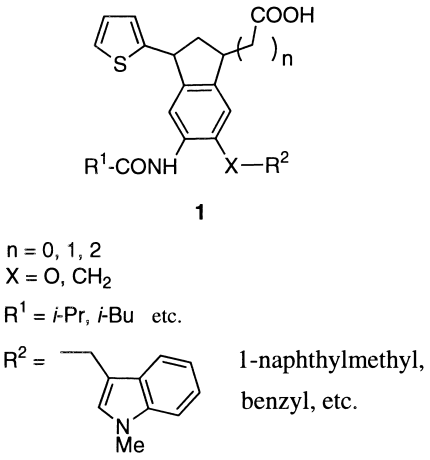


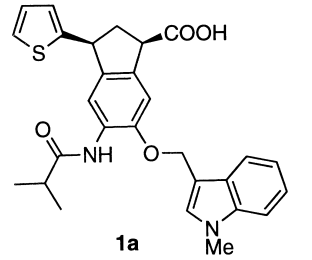
Figure 3. Indan derivatives designed on the basis of the putative pharmacophore.

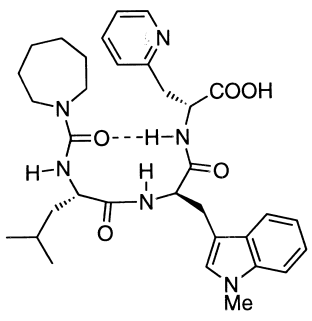
Conformational analysis of indan derivatives

When the designed *cis*-indan derivative **1a** ($n=0$, X = O, R^1 = isopropyl, and R^2 = 1-methylindol-2-ylmethyl; *cis*-form) was superimposed on the putative conformation of FR139317, we found that the four residues described above occupied nearly the same area as its residues did (Fig. 4). The location of the carboxylic acid in the modeled indan derivative, with $n=0$, was the nearest to that in the putative conformation of FR139317. The method of the superposition in Figure 4 was as follows: (1) an initial structure of *cis*-form of **1a** was constructed, (2) conformational analysis was performed (computational details are described in the Experimental section), and (3) one of the local minimum conformations which could fit to the pharmacophore was superimposed on the conformation of FR139317 constructed above.

Chemistry

Synthesis of indancarboxylic acid derivatives ($n=0$). The synthetic route to **1b** is shown as a representative in Scheme 1. Diethyl (3-methoxyphenyl)malonate (**2**) was treated with benzyl 2-bromoacetate in the presence of NaH, followed by catalytic hydrogenation to afford **3** in 82% yield. The palladium-catalyzed cross-coupling of tributyl-2-thienyltin with the acid chloride derived from **3** afforded the desired ketone (**4**) in 95% yield. The cyclization with polyphosphoric acid of **4** followed by $NaBH_4$–TFA reduction[10] of the resulting indenes





FR139317 (putative β-turned conformation)

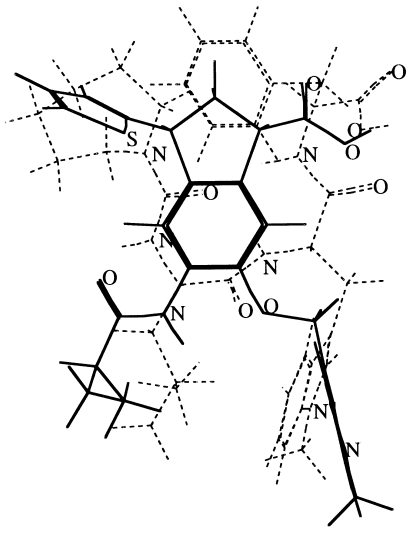
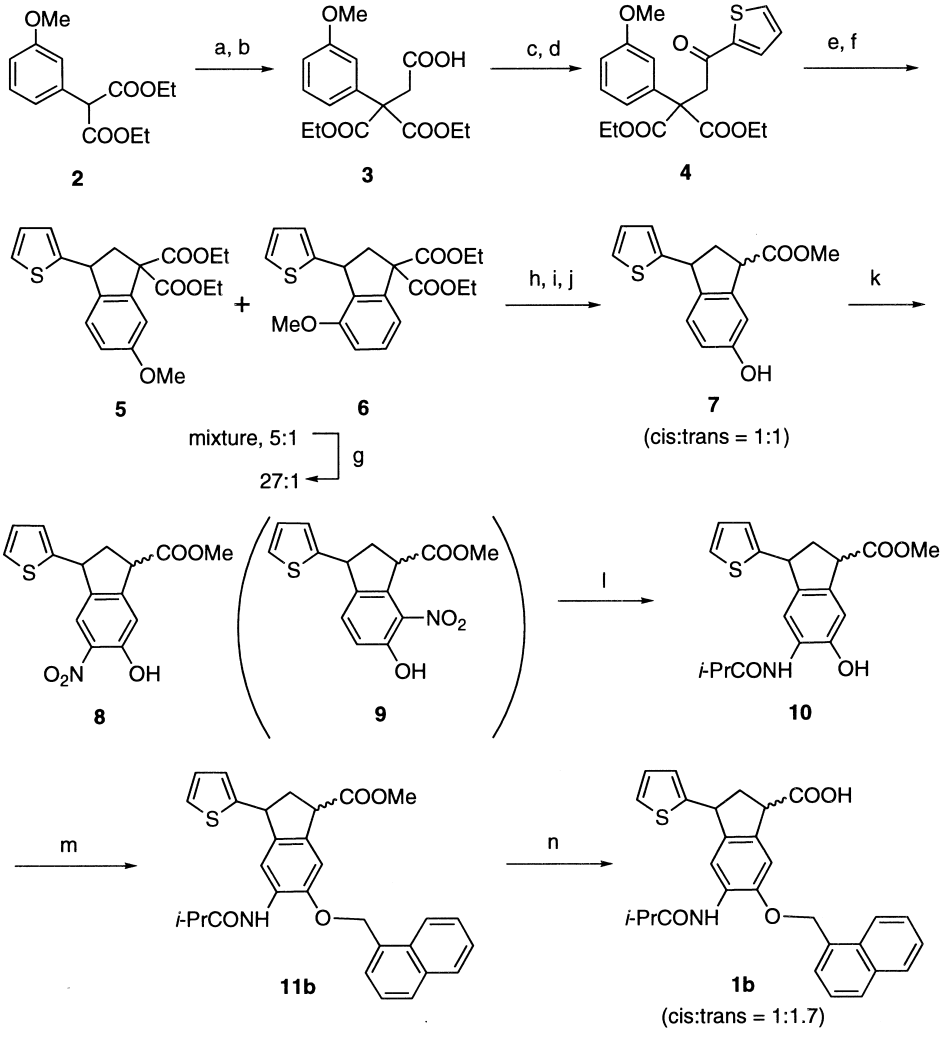
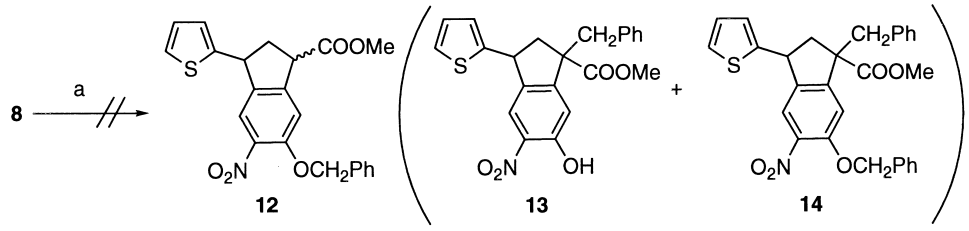


Figure 4. A superposition between the indan derivative **1a** (dashed line) and FR139317 (solid line).

afforded a 5:1 mixture of the indan derivatives **5** and **6**. The ratio of the desired isomer (**5**) was improved up to 27:1 by single recrystallization from EtOH–H_2O of the crude mixture (71% yield from **4**). BBr_3 treatment of **5** followed by decarboxylation and esterification furnished the compound **7** (the ratio of *cis*:*trans* isomer = 1:1 assigned by NMR spectrum)[11] in 84% yield. Nitration of **7** with aq HNO_3 in AcOH gave a mixture of the 5- and 7-nitro derivatives, which was separated by silica gel column chromatography to afford **8** and **9** in 48% and 47% yields, respectively. Due to high acidity of the benzylic proton by both electron-withdrawing groups (i.e., NO_2 and carboxylic acid), **8** and **9** might be in equilibrium between *cis* and *trans* isomers. Catalytic hydrogenation of NO_2 group of **8** over Pd/C in the presence of isobutyric anhydride gave the *N*-amides **10** in good yield. Finally, alkylation of phenolic hydroxyl group of **10** with 1-(chloromethyl)naphthalene, then followed by alkaline hydrolysis of the ester group, furnished the target compound **1b** as a mixture of *cis* and



Scheme 1. Synthesis of indancarboxylic acid derivatives ($n = 0$). (a) $BrCH_2CO_2CH_2Ph$, NaH; (b) H_2, Pd/C (82% in 2 steps); (c) $(COCl)_2$; (d) tributyl-2-thienyltin, $PdCl_2(PPh_3)_2$ (95% in 2 steps); (e) PPA; (f) $NaBH_4$, TFA (71% in 2 steps); (g) recrystallization from EtOH–H_2O; (h) BBr_3; (i) reflux in xylene–dioxane; (j) HCl–MeOH (84% in 3 steps); (k) aq HNO_3, AcOH (**8**: 48%, **9**: 47%); (l) H_2, Pd/C, $(i\text{-PrCO})_2O$ (93%); (m) 1-(chloromethyl)naphthalene, K_2CO_3 (43%); (n) aq NaOH–EtOH (78%).



Scheme 2. Introduction of benzyl group to compound **8.** (a) $PhCH_2Br$, K_2CO_3 (**13**: 11%, **14**: 25%).

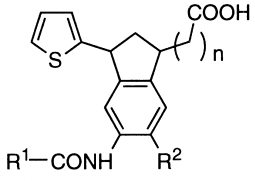
trans isomers. As shown in Scheme 2, alkylation of nitrophenol **8** with benzyl chloride in the presence of K_2CO_3 afforded a mixture of **13** and **14** instead of **12**, due to high acidity of the benzylic proton. The synthesis of the 6-(1-methylindol-2-ylmethoxy)indan derivative (**1a**), designed at first, from **10** was suspended, because the alkylating agents such as 1-methylindol-2-ylmethyl chloride or (1-methylindol-2-ylmethyl)methanesulfonate[12] could not be obtained due to their instability. The other indancarboxylic acid derivatives (**1c**–**p**) (see Table 1) were synthesized by the same manner described above.

Synthesis of indanacetic acid derivative ($n=1$). In order to synthesize the indan acetic acid derivative (**1l**), Arndt–Eistert reaction was first applied to the carboxylic acid **1b**, but the corresponding diazoketone was not obtained. Therefore, we next attempted to synthesize **1l** via Wittig reaction of the aldehyde **18** with (1,3-dithian-2-yl)triphenylphosphonium chloride[13] as shown in Scheme 3. Acidic hydrolysis of **8** followed by B_2H_6 reduction of NO_2 and CO_2H groups gave the amino-alcohol **15**, which was acylated by isobutyric anhydride to afford **16** in 43% yield from **8**. *O*-alkylation of **16** with 1-(chloromethyl)naphthalene chloride followed by Swern-oxidation gave the desired aldehyde **18**, which was converted directly to the dithian derivative **19** due to its instability. $HgCl_2$[14] treatment of **19** in methanol followed by hydrolysis of the ester group led to the target compound **1l**.

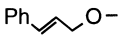
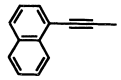
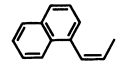
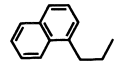
Indanpropanoic acid derivative ($n=2$). The indanpropanoic acid derivative (**1m**, *cis*:*trans* isomers = 1:1) was prepared from the aldehyde **18** as a starting material by using Horner–Emmons olefination, followed by reduction of the olefin **21** with $NiCl_2$–$NaBH_4$[15] system (Scheme 4).

Indancarboxylic acid carba-analogues ($n=0$, X = C). In order to investigate the substituent effects at 6-position of **1b**, we next attempted to synthesize the carba-analogues (**1n**, **1o** and **1p**). The hydroxyl group of **10** was converted to the corresponding *O*-trifluoromethanesulfonate, followed by the palladium-catalyzed cross-coupling reaction with tributyl-1-naphthylethynyltin[16] in the presence of LiCl afforded the compound **23**, which was converted into the targeted **1n** by alkaline hydrolysis in good yield. Partial reduction of **23** with palladium/carbon catalyst under H_2 atmosphere gave a mixture of the *cis*-olefin derivative **24** and the saturated compound **25**, which were separated by chromatography on silica gel to afford **24** and **25** in 40% and 51% yields, respectively. The obtained methyl ester derivatives were hydrolyzed to the corresponding carboxylic acids **1o** and **1p** (Scheme 5).

Table 1. Structure–activity relationship of indan derivatives **1**



1

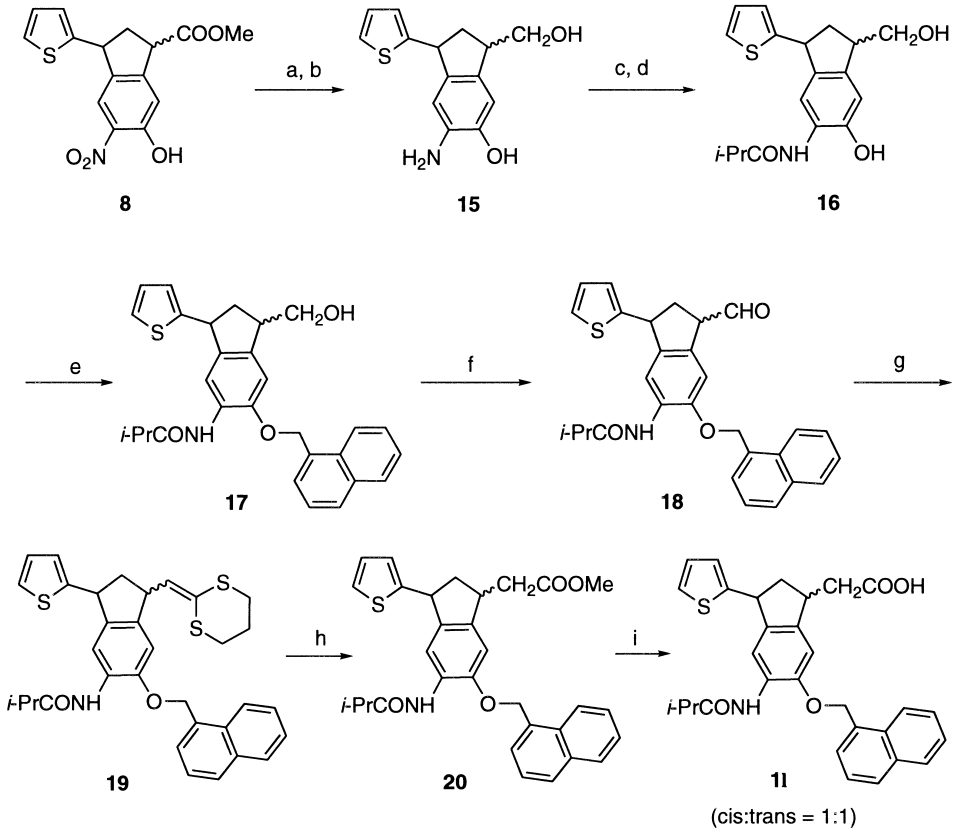
Compound	R^1	R^2	*n*	*cis*:*trans*	mp (°C)	mol. formula	IC_{50} (μM)[a]
b	*i*-Pr	1-naphthyl-CH_2O—	0	1:1.7	190–192	$C_{29}H_{27}NO_4S{\cdot}0.2H_2O$	28
c	*i*-Pr	2-naphthyl-CH_2O—	0	1:1.7	195–199	$C_{29}H_{27}NO_4S{\cdot}0.2H_2O$	> 100
d	*i*-Pr	$PhCH_2O$—	0	1:2	182–185	$C_{25}H_{25}NO_4S$	> 100
e	*i*-Pr	$PhCH_2CH_2O$—	0	1:1.8	203–210	$C_{26}H_{27}NO_4S$	> 100
f	*i*-Pr	Ph_2CHO—	0	1:1.7	157–164	$C_{31}H_{29}NO_4S{\cdot}0.5H_2O$	> 100
g	*i*-Pr		0	1:2	178–181	$C_{27}H_{27}NO_4S$	60
h	*i*-Pr	$PhCOCH_2O$—	0	1:1.6	188–190	$C_{26}H_{25}NO_5S$	80
i	*i*-Pr	OH	0	1:1.1	(amorphous)	$C_{18}H_{19}NO_4S$	> 100
j	*i*-Bu	1-naphthyl-CH_2O—	0	1:1.7	184–188	$C_{30}H_{29}NO_4S{\cdot}0.1H_2O$	80
k	*t*-Bu O	1-naphthyl-CH_2O—	0	1:1.7	176–178 (dec)	$C_{30}H_{29}NO_5S$	> 100
l	*i*-Pr	1-naphthyl-CH_2O—	1	1:2.4	177–180	$C_{30}H_{29}NO_4S{\cdot}0.2H_2O$	> 100
m	*i*-Pr	1-naphthyl-CH_2O—	2	1:1	162.5–166	$C_{31}H_{31}NO_4S{\cdot}0.1H_2O$	> 100
n	*i*-Pr		0	1:1.7	201.5—	$C_{30}H_{25}NO_3S$	70
o	*i*-Pr		0	[b]	(amorphous)	$C_{30}H_{27}NO_3S{\cdot}0.3H_2O$	52
p	*i*-Pr		0	1:2	229–230	$C_{30}H_{29}NO_3S{\cdot}0.3H_2O$	75

[a]Inhibition of [^{125}I]ET-1 binding in vitro to porcine aortic membrane ET_A receptors.
[b]Not determined.

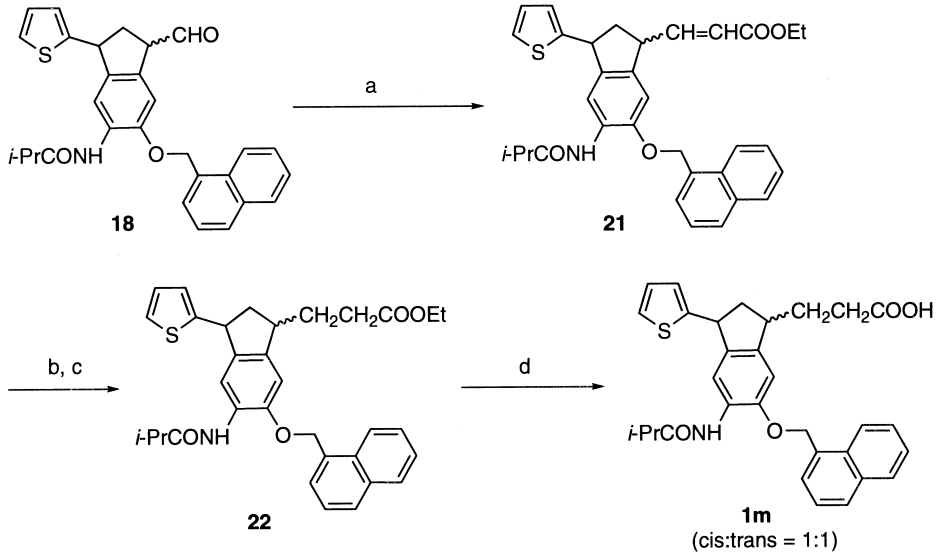
All the compounds synthesized were obtained as inseparable mixtures of *cis* and *trans* forms neither by recrystallization nor chromatography on silica gel, which were therefore subjected to ET_A receptor binding assay as such. The configurations of *cis-trans* isomers were presumed by the analogy of ^1H NMR spectrum with that of the compound **7**.[11]

Results

Receptor binding was evaluated by concentration-dependent inhibition of the binding of ^{125}I-labeled ET-1 to porcine aortic membrane known to contain ET_A receptors. The structure–activity relationships of the indan derivatives synthesized are shown in Table 1.



Scheme 3. Synthesis of indanacetic acid derivative ($n=1$). (a) aq HCl–dioxane; (b) $NaBH_4$, $BF_3{\cdot}OEt_2$; (c) $(i\text{-PrCO})_2O$, pyridine; (d) K_2CO_3 (43% from **8**); (e) 2-(chloromethyl)naphthalene, K_2CO_3, NaI (87%); (f) TFAA, Et_3N; (g) (1,3-dithian-2-yl)triphenylphosphonium chloride, NaH (45% from **17**); (h) $HgCl_2$, H_2O, THF–MeOH (69%); (i) aq NaOH–EtOH (95%).



Scheme 4. Synthesis of indanpropanoic acid derivative ($n=2$). (a) $Ph_3P{=}CHCOOEt$ (73%); (b) $NiCl_2{\cdot}6H_2O$, $NaBH_4$; (c) 2-(chloromethyl)naphthalene, K_2CO_3, NaI (46% in 2 steps); (d) aq NaOH–EtOH (94%).

Among these, the compound **1b** bearing 1-naphthylmethyl group at 6-position showed moderate affinity for ET_A receptor with an IC_{50} value of 28 μM. Nevertheless, this activity was much lower than those of BQ-123 and FR139317. Substitutions of R^2 group to 2-naphthylmethyl (compound **1c**) or other groups (compounds **1d**–**h**) reduced the activity. Substitutions from isopropyl to *tert*-butyl or *tert*-butyloxy groups in R^1 group (compounds **1j**, **k**), elongation of methylene at 1-position [**1l** ($n=1$), **m** ($n=2$)], and conversion to the carba-analogues at 6-position (**1n**–**p**) also lowered the activity compared to **1b**.

In functional assay, **1b** suppressed ET-1-induced contraction in the isolated rat aorta (endothelium denuded; data were not shown); however, it reduced K^+-induced contraction of the same preparation as well.

Discussion

Aiming to find orally active and much durable non-peptidic antagonists, design and syntheses of a new series of indan derivatives were performed.

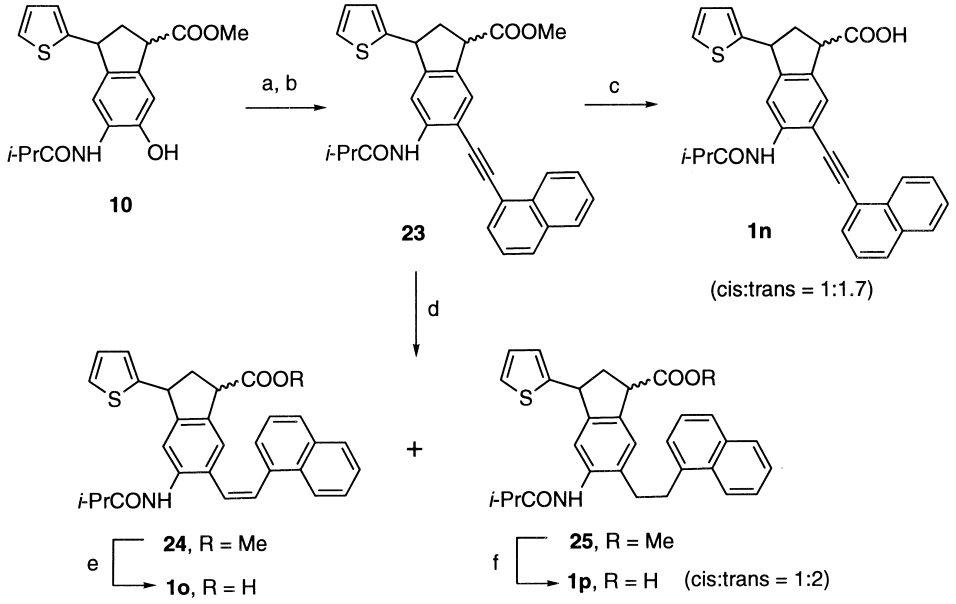
We were interested in the similarity of the side chains between BQ-123 and FR139317 (CO_2H, indole, and isopropyl groups) and hypothesized that the active conformation of the linear peptide FR139317 was also the turned one by the possible intramolecular hydrogen bond between urea CO and D-Pya NH. According to this hypothesis, we performed a computer assisted molecular modeling as shown in Figure 1, constructed a putative pharmacophore model, and designed indan derivatives to be matched to this model. We selected the rigid indan as a suitable template to fix the residues at the proper areas. The indan derivatives synthesized showed moderate ET_A receptor binding activities. Among them, the derivative **1b** bearing carboxylic acid, 2-thienyl, isobutyrylamino, and 1-naphthylmethyloxy groups at 1-, 3-, 5-, and 6-positions, respectively, appeared the highest affinity for the receptor.

Murugesan, N. et al.[7d] and Diguarher, T. L. et al.[7e] reported designs and syntheses of ET_A antagonists using dibenzodiazepine and sugar as scaffolds respectively to support appropriate side-chains which mimic BQ-123. The dibenzodiazepine-10-acetic acid derivatives showed moderate activity ($K_i=7$ μM for ET_A receptor) but the glucose and allose derivatives showed no significant binding. The hydrophilic main chain with hydrogen bondings of the peptidic antagonists might play an important role for the affinity for the receptor. While we were studying the indan compounds, Ohlstein, E. H. et al. reported the results of their indan-2-carboxylic acid derivatives SB 209670[17a] and SB 217242[17b] independently. But the relationships of our indan derivatives to those remain unclear.

Although the most active compound **1b** was proved not to be specific in the functional assay, we successfully developed non-peptidic ET_A receptor antagonists from peptides. Since the activities of these indan derivatives in the micromolar range were not enough for therapeutic use, further modifications of the template, the residue, and the spacer will be necessary for increasing the activity.

Experimental

All melting points were determined on a Büchi 535 digital melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on an Analect RFX-65 or an Analect FX-6200 FT-IR spectrophotometer. ^1H NMR spectra were recorded on a JEOL JNM-FX200, a



Scheme 5. Synthesis of indancarboxylic acid carba-analogues ($n=0$, X = C). (a) Tf_2O, Et_3N; (b) LiCl, $PdCl_2(PPH_3)_2$, tributyl-1-naphthylethynyltin (77% in 2 steps); (c) aq NaOH–EtOH (92%); (d) H_2, Pd/C (**24**: 40%, **25**: 51%); (e) aq NaOH–EtOH (76%); (f) aq NaOH–EtOH (72%).

Varian Gemini 300, or a JEOL JNM-GSX400 spectrometer. Mass spectra were recorded on a JEOL JMS-HX100 mass spectrometer. Elemental analyses were performed on a Perkin–Elmer 2400 C, H, N analyzer and a YOKOGAWA IC 7000S ion chromatographic analyzer with oxygen flask combustion for sulfur atom, and were within ±0.3% of the calculated values.

Molecular modelings

All molecular modeling works were performed with SYBYL 5.5[18] running on a Silicon Graphics IRIS 4D/80 workstation.

Geometries of the molecules were optimized by using MAXIMIN2 implemented in SYBYL with the TRIPOS force field. For the coulombic electrostatic energy term, atomic charges were derived from MNDO calculations with the semiempirical molecular orbital calculation package MOPAC 5.01,[19] and the dielectric constant was set to 1r (i.e., interatomic distance dependent) so that the effect of the solvent was included implicitly. The minimization calculations were terminated when the RMS change from one iteration to the next was below 0.05 kcal/mol Å.

Conformations of the indan derivative **1a** were generated with the SYBYL/Systematic Search routine. Seven rotatable bonds (one for the carboxyl group, one for the thienyl group, two for the group on the 5-position, three for the group on the 6-position) were scanned with 30° increments within a 0–359° interval. A family of conformations which could fit to the pharmacophore was selected by using distances between pharmacophoric groups, then the geometry of the lowest energy conformation among the family was optimized.

2,2-Bis(ethoxycarbonyl)-2-(3-methoxyphenyl)propionic acid (3). To a stirred solution of diethyl 3-methoxyphenylmalonate (20.0 g, 75.1 mmol) in dry DMF (200 mL) was added 60% NaH in mineral oil (3.45 g, 90.1 mmol) on an ice bath. After 10 min, benzyl bromoacetate (20.6 g, 90.1 mmol) was added. The mixture was stirred at room temperature for 16 h, diluted with H_2O, acidified with 10% aq HCl, and then extracted with EtOAc. The extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:EtOAc, 10:1, v/v) to afford a colorless oil. A solution of the obtained oil (benzyl ester) in EtOH (250 mL) was hydrogenated over 10% Pd/C (water content 50%) (5.0 g) under atmospheric pressure at room temperature for 4 h. The catalyst was filtered off and the filtrate was concentrated in vacuo to afford **3** as a colorless crystalline powder (20.0 g, 82%): mp 113.5–114.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 (1H, t, J = 8.0 Hz), 6.93 (1H, t, J = 2.0 Hz), 6.91 (1H, ddd, J = 0.9, 2.0, 8.0 Hz), 6.84 (1H, ddd, J = 0.9, 2.0, 8.0 Hz), 4.28 (2H, dq, J = 7.0, 11.0 Hz), 4.26 (2H, dq, J = 7.0, 11.0 Hz), 3.78 (3H, s), 3.37 (2H, s), 1.25 (6H, t, J = 7.1 Hz); IR (Nujol) cm^{-1} 2780, 2660, 2580, 1745, 1720, 1715, 1610, 1585, 1495; EI–MS m/z 324 (M^+), 278, 206, 178, 161, 133.

Diethyl 3-methoxyphenyl-2-thenoylmethylmalonate (4). A solution of **3** (100.0 g, 0.308 mol) in dry toluene (1 L) with $(COCl)_2$ (80 mL, 0.92 mol) was stirred at 80 °C for 2.5 h. The volatile was removed under reduced pressure, and the resulting oil was chased with toluene twice. A mixture of the obtained oil (acid chloride), tributyl-2-thienyltin (172 g, 0.462 mol), and $PdCl_2(PPh_3)_2$ (10.8 g, 15.4 mmol) in dry dioxane (2 L) was degassed three times under argon and refluxed for 20 h. 10% aq KF (1 L) was added on an ice bath, and the whole was stirred at room temperature for 1 h. Insoluble material was removed off through Celite and washed with H_2O and EtOAc. The aqueous layer of the filtrate and the washings were extracted with EtOAc. The extracts were washed with H_2O, aq $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, treated with an active charcoal, and concentrated in vacuo. The residue was recrystallized from i-Pr_2O to give colorless crystalline powder **4**, and the mother liquor was concentrated and purified by silica gel column chromatography (hexane:EtOAc, 4:1–3:1, v/v) to afford a colorless crystalline powder **4** (total 114.4 g, 95%): mp 79.5–80.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.8–7.8 (7H, m), 4.21–4.33 (4H, m), 3.95 (2H, s), 3.78 (3H, s), 1.25 (6H, t, J = 7.1 Hz); IR (Nujol) cm^{-1} 3470, 3090, 1735, 1685, 1600, 1585, 1520, 1490; EI–MS m/z 390 (M^+), 345, 111.

Diethyl 6-methoxy-3-(2-thienyl)-1,1-indandicarboxylate (5) and diethyl 4-methoxy-3-(2-thienyl)-1,1-indandicarboxylate (6). To pre-heated polyphosphoric acid (>75% purity, 2.0 kg) was added **4** (123.1 g, 0.315 mol) in small portions at 75–80 °C over 10 min. The solution was stirred at 75–83 °C for 1 h, poured into ice water (2 L), and extracted with EtOAc. The extracts were washed with H_2O, aq $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford a brown oil (117.4 g). To a stirred suspension of $NaBH_4$ (22.2 g, 0.587 mol) in dry CH_2Cl_2 (1 L) was added CF_3COOH (158 mL, 2.06 mol) dropwise over 30 min with vigorous stirring at 3–15 °C on an ice bath, and the mixture was stirred at 22 °C for 1 h. A solution of the oil obtained above (109.4 g, 0.294 mol) in CH_2Cl_2 (0.4 L) was added at 7–10 °C over 5 min, and the mixture was stirred at 7–25 °C for 2 h. H_2O (1 L) was added slowly on an ice bath, and the mixture was stirred at room temperature for 1 h. The aqueous layer was extracted with $CHCl_3$, and the extracts were washed with H_2O, aq $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting oil (a mixture of **5** and **6** (5:1)) was crystallized from EtOH (190 mL)–H_2O (40 mL) to afford a mixture of **5** and **6** (27:1) as a brown solid (81.1 g, 71%): mp 65.5–67.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 5 δ 7.19 (1H, dd, J = 1.2, 5.0 Hz), 7.16 (1H, d, J = 2.5 Hz), 7.01 (1H, dd, J = 1.0, 8.4 Hz), 6.95 (1H, dd, J = 3.5, 5.0 Hz), 6.90–6.93 (1H, m), 6.85 (1H, dd, J = 2.5, 8.5 Hz), 4.78 (1H, br t, J = 8.3 Hz), 4.10–4.35 (4H, m), 3.82 (3H, s), 3.33 (1H, dd, J = 7.6, 13.3 Hz), 2.63 (1H, dd, J = 9.1, 13.3 Hz), 1.28 (3H, t, J = 7.0 Hz), 1.26 (3H, t, J = 7.0 Hz); **6** δ 7.32 (1H, t, J = 8.1 Hz), 7.20 (1H, dd-like, J = 1.0, 8.0 Hz), 7.09 (1H, dd, J = 1.5, 5.3 Hz), 6.81–6.88 (2H, m), 6.66 (1H, dt, J = 3.5, 1.0 Hz), 4.85 (1H, dd, J = 4.5, 9.0 Hz), 4.05–4.34 (4H, m), 3.69 (3H, s), 3.34 (1H, dd, J = 8.7, 13.8 Hz),

2.79 (1H, dd, $J=4.3$, 13.8 Hz), 1.27 (3H, t, $J=7.1$ Hz), 1.16 (3H, t, $J=7.1$ Hz); IR (Nujol) cm^{-1} 1750, 1725, 1610, 1580; EI–MS m/z 374 (M^+), 300, 227.

Methyl 6-hydroxy-3-(2-thienyl)-1-indancarboxylate (7). To a stirred solution of **5** (containing 1/28 of **6**, 79.8 g, 0.123 mol) in dry CH_2Cl_2 (1.6 L) was added BBr_3 (213.4 g, 0.852 mol) on an ice bath over 20 min. The mixture was stirred at room temperature overnight, and then poured into ice water (2 L). After removal of CH_2Cl_2, the aqueous layer was extracted with EtOAc. The extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford a brown oil. The oil was dissolved in a mixture of xylene (1 L)–dioxane (0.5 L) and refluxed for 14 h. After removal of the solvent, the residue was extracted three times with aq $NaHCO_3$. The aqueous layers were acidified with 10% aq HCl and extracted with EtOAc. The extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford a dark brown oil. The obtained oil was treated with 28% HCl–MeOH (0.6 L) at reflux temperature for 2 h. After removal of the solvent, the residual oil was diluted with H_2O and extracted with EtOAc. The extracts were washed with H_2O, aq $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:EtOAc, 20:1, v/v) to afford a dark green oil **7** (48.8 g, 84%) as a diastereomixture (1:1): ^1H NMR ($CDCl_3$, 300 MHz) *cis*-form δ 6.70–7.25 (3H, m), 5.25 (1H, s), 4.55 (1H, dd, $J=8.2$, 19.1 Hz), 4.05 (1H, ddd, $J=1.1$, 7.7, 8.8 Hz), 3.80 (3H, s), 2.88 (1H, dt, $J=7.6$, 12.8 Hz), 2.52 (1H, dt, $J=9.9$, 12.9 Hz); *trans*-form δ 6.70–7.25 (3H, m), 5.23 (1H, s), 4.84 (1H, t, $J=7.6$ Hz), 4.15 (1H, dd, $J=4.3$, 8.3 Hz), 3.75 (3H, s), 2.98 (1H, ddd, $J=4.3$, 7.9, 13.1 Hz), 2.40 (1H, ddd, $J=7.3$, 8.3, 13.1 Hz); IR (Neat) cm^{-1} 3600–3100, 1735, 1710, 1610, 1590, 1490; EI–MS m/z 274 (M^+), 214, 181, 131.

Methyl 6-hydroxy-5-nitro-3-(2-thienyl)-1-indancarboxylate (8) and methyl 6-hydroxy-7-nitro-3-(2-thienyl)-1-indancarboxylate (9). To a suspension of **7** (50 mg, 0.182 mmol), acetic acid (0.5 mL), and CH_2Cl_2 (1.5 mL) was added 60% aq HNO_3 (19.1 mg, 0.182 mmol) in acetic acid (0.5 mL) dropwise over 10 min at −33 to −28 °C. The mixture was stirred at −15 to −5 °C for 1 h then at 5 °C for 1 h, diluted with EtOAc, and washed with H_2O and aq $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Separation on preparative TLC ($CHCl_3$:hexane, 1:1 v/v, three times) afforded **8** (28 mg, 48%) and **9** (27 mg, 47%) both as yellow oils. In a case of 0.169 mol scale, **8** was separated by silica gel column chromatography in 28% yield. **8**: ^1H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:1) δ 10.70 (0.5H, s) and 10.70 (0.5H, s), 7.86 (0.5H, d, $J=1.3$ Hz) and 7.80 (0.5H, d, $J=1.5$ Hz), 7.27 (0.5H, d, $J=1.7$ Hz) and 7.23 (0.5H, d, $J=1.0$ Hz), 7.26 (0.5H, dd, $J=1.3$, 5.0 Hz) and 7.22 (0.5H, dd, $J=1.2$, 5.1 Hz), 7.02 (0.5H, dd, $J=3.5$, 5.0 Hz) and 6.98 (0.5H, dd, $J=3.5$, 5.1 Hz), 6.97–6.99 (0.5H, m) and 6.89–6.91 (0.5H, m), 4.57 (*cis*) (0.5H, dd, $J=8.5$, 9.4 Hz) and 4.86 (*trans*) (0.5H, t, $J=7.8$ Hz), 4.09 (*cis*) (0.5H, dd, $J=7.8$, 10.4 Hz) and 4.21 (*trans*) (0.5H, ddd, $J=1.0$, 4.1, 8.4 Hz), 3.84 (1.5H, s) and 3.77 (1.5H, s), 2.89–3.07 (1H, m) and 2.40–2.63 (1H, m); IR (Neat) cm^{-1} 3400–3000, 1740, 1735, 1630, 1585, 1540; EI–MS m/z 319 (M^+), 259, 213, 184. **9**: ^1H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:1) δ 10.72 (0.5H, s) and 10.68 (0.5H, s), 7.34 (0.5H, d, $J=8.5$ Hz) and 7.31 (0.5H, d, $J=8.5$ Hz), 7.22 (0.5H, dd, $J=1.2$, 5.5 Hz) and 7.20 (0.5H, dd, $J=1.2$, 5.3 Hz), 7.11 (0.5H, dd, $J=0.8$, 8.5 Hz) and 7.10 (0.5H, d, $J=8.7$ Hz), 6.98 (0.5H, dd, $J=3.5$, 5.1 Hz) and 6.95 (0.5H, dd, $J=3.5$, 5.1 Hz), 6.89–6.91 (0.5H, m) and 6.83–6.86 (0.5H, m), 4.75–4.82 (1H, m) and 4.58–4.69 (1H, m), 3.74 (1.5H, s) and 3.69 (1.5H, s), 2.29–3.19 (4H, m); IR (Neat) cm^{-1} 3500–3000, 1735, 1615, 1590, 1535; EI–MS m/z 319 (M^+), 301, 269.

Methyl 6-hydroxy-5-isopropylamino-3-(2-thienyl)-1-indancarboxylate (10). A mixture of **8** (800 mg, 2.51 mmol), isobutyric anhydride (627 mg, 3.77 mmol) in THF (15 mL) was hydrogenated over 10% Pd/C (water wet) (160 mg) under atmospheric pressure at room temperature for 2 days. The catalyst was filtered off and the filtrate was concentrated in vacuo. Purification by silica gel column chromatography (hexane:EtOAc, 4:1, v/v) afforded a yellow caramel **10** (836 mg, 93%): ^1H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:1) δ 8.80 (0.5H, s) and 8.74 (0.5H, s), 7.49 (0.5H, br s) and 7.45 (0.5H, br s), 7.20 (0.5H, dd, $J=1.2$, 5.1 Hz) and 7.17 (0.5H, dd, $J=1.2$, 5.1 Hz), 7.04–7.07 (1H, m), 6.98 (0.5H, dd, $J=3.5$, 5.0 Hz) and 6.95 (0.5H, dd, $J=3.5$, 5.0 Hz), 6.92–6.95 (0.5H, m) and 6.84–6.87 (0.5H, m), 6.75 (0.5H, br s) and 6.74 (0.5H, d, $J=1.0$ Hz), 4.52 (*cis*) (0.5H, dd, $J=8.5$, 9.3 Hz) and 4.80 (*trans*) (0.5H, t, $J=7.7$ Hz), 4.03 (*cis*) (0.5H, t, $J=8.9$ Hz) and 4.12 (*trans*) (0.5H, dd, $J=3.4$, 8.5 Hz), 3.79 (1.5H, s) and 3.71 (1.5H, s), 2.47–2.63 (2H, m), 2.96 (0.5H, ddd, $J=3.6$, 7.8, 13.1 Hz), 2.85 (0.5H, dt, $J=7.6$, 12.9 Hz), 2.53 (0.5H, dt, $J=10.0$, 13.0 Hz) and 2.36 (0.5H, dt, $J=8.2$, 13.0 Hz), 1.25 (3H, d, $J=7.1$ Hz) and 1.24 (3H, d, $J=6.9$ Hz); IR (Neat) cm^{-1} 3500–2400, 1735, 1660, 1650, 1610; EI–MS m/z 359 (M^+), 289, 230.

Methyl 5-isopropylamino-6-(1-naphthylmethyloxy)-3-(2-thienyl)-1-indancarboxylate (11b). To a stirred solution of **10** (120 mg, 0.334 mmol) in dry DMF (3 mL) was added 60% NaH in mineral oil dispersion (13.4 mg, 0.351 mmol) on an ice bath, and the mixture was stirred at room temperature for 30 min. A solution of 1-(chloromethyl)naphthalene (62 mg, 0.351 mmol) in dry DMF (0.2 mL) was added, and the mixture was stirred at room temperature for 20 h, diluted with 10% aq HCl, and extracted with EtOAc. The extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by silica gel column chromatography (hexane:EtOAc, 7:1, v/v) and following trituration with hexane afforded a light blue crystalline powder **11b** (72 mg, 43%): mp 144.0–150.0 °C; ^1H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:1.3) δ 8.16 (*cis*) (0.43H, s) and 8.22 (*trans*) (0.57H, s), 7.88–8.08 (3H, m), 7.64–7.72 (1H, broad), 7.45–7.59 (4H, m), 7.12–7.23 (2H, m), 6.87–6.97 (2H, m), 5.55 (2H, s), 4.61 (*cis*) (0.43 H, dd, $J=8.0$, 9.4 Hz) and 4.87 (*trans*) (0.57H, t, $J=7.5$ Hz), 4.08 (*cis*) (0.43H, dd, $J=8.2$, 9.3 Hz) and

4.20 (*trans*) (0.57H, dd, $J=4.4$, 8.3 Hz), 3.78 (*cis*) (1.3H, s) and 3.73 (*trans*) (1.7H, s), 2.86–3.02 (1H, m), 2.39–2.58 (1H, m), 2.09–2.22 (1H, m), 0.94–1.01 (6H, m); IR (Nujol) cm^{-1} 3300, 3180, 2720, 2670, 1730, 1660, 1610, 1600; EI–MS *m/z* 499 (M^+), 288, 141.

5-Isopropylamino-6-(1-naphthylmethyloxy)-3-(2-thienyl)-1-indancarboxylic acid (1b). A mixture of **11b** (61 mg, 0.122 mmol) and 10% aq NaOH (2 mL) in EtOH (2 mL)–THF (2 mL) was stirred at 0 °C for 2 h and then diluted with H_2O. The aqueous layer was washed with ether, acidified with 10% aq HCl, and extracted with EtOAc. The extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Recrystallization from EtOAc–hexane afforded colorless needles **1b** (46 mg, 78%): mp 189.5–191.5 °C; ^1H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:1.7) δ 8.17 (*cis*) (0.37H, s) and 8.24 (*trans*) (0.63H, s), 6.87–8.08 (10H, m), 7.67 (*cis*) (0.37H, br s) and 7.69 (*trans*) (0.63H, br s), 5.56 (1H, d, $J=12$ Hz), 5.52 (1H, d, $J=12$ Hz), 4.63 (*cis*) (0.37H, t, $J=8.7$ Hz) and 4.89 (*trans*) (0.63H, t, $J=7.6$ Hz), 4.14 (*cis*) (0.37H, t, $J=8.2$ Hz) and 4.24 (*trans*) (0.63H, dd, $J=4.3$, 8.1 Hz), 2.90–3.06 (1H, m), 2.40–2.63 (1H, m), 2.08–2.23 (1H, m), 0.92–0.99 (6H, m); IR (Nujol) cm^{-1} 3310, 3200–2400, 1715, 1690, 1660, 1610, 1600; EI–MS *m/z* 485 (M^+), 274, 141. Anal. calcd for $C_{29}H_{27}NO_4S$ (+0.2 H_2O): C, 71.73 (71.20); H, 5.60 (5.65); N, 2.88 (2.86); S, 6.60 (6.55). Found: C, 71.20; H, 5.64; N, 2.82; S, 6.55.

5-Isopropylamino-6-(2-naphthylmethyloxy)-3-(2-thienyl)-1-indancarboxylic acid (1c). 2-Naphthylmethylation of **10** and subsequent alkaline hydrolysis of **11c** afforded **1c** as colorless needles: mp 195–199 °C; ^1H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:1.7) δ 8.18 (*cis*) (0.37H, s) and 8.25 (*trans*) (0.63H, s), 7.12–7.91 (10H, m), 6.86–6.97 (2H, m), 5.22–5.33 (2H, m), 4.61 (*cis*) (0.37H, dd, $J=8.3$, 9.3 Hz) and 4.88 (*trans*) (0.63H, t, $J=7.4$ Hz), 4.09 (*cis*) (0.37H, dd, $J=8.1$, 9.0 Hz) and 4.19 (*trans*) (0.63H, dd, $J=4.4$, 8.2 Hz), 2.87–3.03 (1H, m), 2.38–2.59 (2H, m), 1.16 (*cis*) (2.22H, d, $J=6.9$ Hz) and 1.16 (*trans*) (3.78H, d, $J=6.9$ Hz); IR (Nujol) cm^{-1} 3320, 3200–2400, 1715, 1695, 1665, 1655, 1610, 1595; EI–MS *m/z* 485 (M^+), 274, 141. Anal. calcd for $C_{29}H_{27}NO_4S$ (+0.2 H_2O): C, 71.73 (71.20); H, 5.60 (5.65); N, 2.88 (2.86); S, 6.60 (6.55). Found: C, 71.03; H, 5.54; N, 2.84; S, 6.66.

6-Benzyloxy-5-isopropylamino-3-(2-thienyl)-1-indancarboxylic acid (1d). Benzylation of **10** and subsequent alkaline hydrolysis of **11d** afforded **1d** as colorless needles: mp 184–187 °C; ^1H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:2) δ 8.16 (*cis*) (0.33H, s) and 8.23 (*trans*) (0.67H, s), 6.86–7.84 (10H, m), 5.07–5.17 (2H, m), 4.61 (*cis*) (0.33H, t, $J=8.7$ Hz) and 4.87 (*trans*) (0.67H, t, $J=7.5$ Hz), 4.08 (*cis*) (0.33H, t, $J=8.7$ Hz) and 4.19 (*trans*) (0.67H, dd, $J=4.3$, 8.2 Hz), 2.86–3.30 (1H, m), 2.37–2.58 (2H, m), 1.17 (*cis*) (2H, d, $J=6.9$ Hz) and 1.17 (*trans*) (4H, d, $J=6.9$ Hz); IR (Nujol) cm^{-1} 3320, 3280, 3180, 1715, 1700, 1670, 1655, 1605, 1595, 1525; EI–MS *m/z* 435 (M^+), 365, 344, 274, 228. Anal. calcd for $C_{25}H_{25}NO_4S$: C, 68.94; H, 5.79; N, 3.22; S, 7.36. Found: C, 68.76; H, 5.81; N, 3.19; S, 7.37.

5-Isopropylamino-6-(2-phenethyloxy)-3-(2-thienyl)-1-indancarboxylic acid (1e). 2-Phenethylation of **10** and subsequent alkaline hydrolysis of **11e** afforded **1e** as colorless needles: mp 203–210 °C; ^1H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:1.3) δ 6.84–7.99 (11H, m), 4.57 (*cis*) (0.43H, dd, $J=8.0$, 9.2 Hz) and 4.84 (*trans*) (0.57H, t, $J=7.3$ Hz), 4.23–4.36 (2H, m), 4.05 (*cis*) (0.43H, dd, $J=8.1$, 9.4 Hz) and 4.16 (*trans*) (0.57H, dd, $J=4.4$, 8.3 Hz), 3.13 (2H, t, $J=6.4$ Hz), 2.84–2.99 (1H, m), 2.26–2.56 (2H, m), 1.14 (*cis*) (2.61H, d, $J=6.9$ Hz) and 1.13 (*trans*) (3.39H, d, $J=6.9$ Hz); IR (Nujol) cm^{-1} 3300, 3200–2400, 1720, 1690, 1665; EI–MS *m/z* 449 (M^+), 379, 275, 105. Anal. calcd for $C_{26}H_{27}NO_4S$: C, 69.46; H, 6.05; N, 3.12; S, 7.13. Found: C, 69.48; H, 6.02; N, 2.90; S, 6.95.

6-Diphenylmethyloxy-5-isopropylamino-3-(2-thienyl)-1-indancarboxylic acid (1f). Diphenylmethylation of **10** and subsequent alkaline hydrolysis of **11f** afforded **1f** as light brown needles: mp 157–164 °C; ^1H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:1.7) δ 6.84–8.22 (16H, m), 6.20 (*cis*) (0.37H, s) and 6.19 (*trans*) (0.63H, s), 4.56 (*cis*) (0.37H, t, $J=8.6$ Hz) and 4.83 (*trans*) (0.63H, t, $J=7.3$ Hz), 3.96 (*cis*) (0.37H, t, $J=8.5$ Hz) and 4.05 (*trans*) (0.63H, dd, $J=4.1$, 7.8 Hz), 2.80–2.97 (1H, m), 2.30–2.53 (2H, m), 1.11–1.16 (6H, m); IR (Nujol) cm^{-1} 3350, 3300–2400, 1715, 1695, 1675, 1655, 1590; EI–MS *m/z* 511 (M^+), 275, 230, 167. Anal. calcd for $C_{31}H_{29}NO_4S$ (+0.5 H_2O): C, 72.77 (71.52); H, 5.71 (5.81); N, 2.74 (2.69); S, 6.27 (6.15). Found: C, 71.69; H, 5.72; N, 2.56; S, 5.82.

6-Cinnamyloxy-5-isopropylamino-3-(2-thienyl)-1-indancarboxylic acid (1g). Cinnamylation of **10** and subsequent alkaline hydrolysis of **11g** afforded **1g** as colorless needles: mp 178–181 °C; ^1H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:2) δ 6.85–7.90 (11H, m), 6.74 (1H, d, $J=15.9$ Hz), 6.41 (1H, dt, $J=6.0$, 15.9 Hz), 4.60 (*cis*) (0.33H, dd, $J=8.1$, 9.2 Hz) and 4.86 (*trans*) (0.67H, t, $J=7.3$ Hz), 4.70–4.83 (2H, m), 4.08 (*cis*) (0.33H, dd, $J=8.2$, 9.3 Hz) and 4.18 (*trans*) (0.67H, dd, $J=4.4$, 8.3 Hz), 2.85–3.02 (1H, m), 2.37–2.58 (2H, m), 1.22 (*cis*) (2H, d, $J=6.9$ Hz) and 1.21 (*trans*) (4H, d, $J=6.9$ Hz); IR (Nujol) cm^{-1} 3300, 3200–2400, 1690, 1665, 1610, 1595; EI–MS *m/z* 461 (M^+), 443, 371, 117. Anal. calcd for $C_{27}H_{27}NO_4S$: C, 70.26; H, 5.90; N, 3.03; S, 6.95. Found: C, 70.27; H, 5.83; N, 2.79; S, 6.82.

5-Isopropylamino-6-phenacyloxy)-3-(2-thienyl)-1-indancarboxylic acid (1h). Phenacylation of **10** and subsequent alkaline hydrolysis of **11h** afforded **1h** as faintly gray needles: mp 188–190 °C; ^1H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:1.6) δ 6.84–8.82 (11H, m), 5.93 (2H, s), 4.59 (*cis*) (0.38H, dd, $J=8.1$, 8.8 Hz) and 4.85 (*trans*) (0.62H, t, $J=7.4$ Hz), 4.06 (*cis*) (0.38H, dd, $J=8.7$, 9.1 Hz) and 4.16 (*trans*) (0.62H, dd, $J=4.4$, 8.1 Hz), 2.84–3.01 (1H, m), 2.65 (1H, septet, $J=6.9$ Hz), 2.36–2.56 (1H, m), 1.26 (6H, d, $J=6.8$ Hz); IR (Nujol) cm^{-1} 3400, 3350, 3200–2400, 1715, 1710, 1675, 1640, 1605; EI–MS *m/z* 463 (M^+), 393, 343, 300, 274, 105. Anal. calcd for $C_{26}H_{25}NO_5S$: C, 67.38; H, 5.44; N, 3.02; S, 6.92. Found: C, 67.39; H, 5.41; N, 2.82; S, 6.80.

6-Hydroxy-5-isopropylamino-3-(2-thienyl)-1-indancarboxylic acid (1i). Alkaline hydrolysis of **10** afforded **1i** as light brown amorphous powder: ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) (*cis*:*trans*, 1:1.1) δ 9.37 (1H, br s), 6.85–8.70 (6H, m), 4.57 (*cis*) (0.48H, t, J = 8.8 Hz) and 4.82 (*trans*) (0.52H, t, J = 7.7 Hz), 3.97 (*cis*) (0.48H, t, J = 8.7 Hz) and 4.07 (*trans*) (0.52H, dd, J = 4.1, 8.1 Hz), 2.78–3.00 (1H, m), 2.29–2.68 (2H, m), 1.20 (3H, d, J = 6.8 Hz), 1.20 (3H, d, J = 6.8 Hz); IR (Nujol) cm^{-1} 3420, 3400–2400, 1705, 1665, 1645, 1610; EI–MS m/z 345 (M^+), 327, 275, 230. Anal. calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.05; S, 9.58. Found: C, 62.36; H, 5.62; N, 3.96; S, 8.94.

5-Isobutyrylamino-6-(1-naphthylmethyloxy)-3-(2-thienyl)-1-indancarboxylic acid (1j). 1j was prepared in a similar manner as for **1b** starting from **8** using isovaleric anhydride instead of isobutyric anhydride: colorless needles; mp 184–187.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:1.7) δ 6.84–8.24 (13H, m), 5.54 (1H, d, J = 11.0 Hz), 5.53 (1H, d, J = 11.0 Hz), 4.63 (*cis*) (0.37H, dd, J = 8.3, 8.8 Hz) and 4.89 (*trans*) (0.63H, t, J = 7.5 Hz), 4.13 (*cis*) (0.37H, dd, J = 8.1, 9.2 Hz) and 4.24 (*trans*) (0.63H, dd, J = 4.3, 8.1 Hz), 2.89–3.05 (1H, m), 2.40–2.62 (1H, m), 1.78–1.97 (3H, m), 0.74–0.80 (6H, m); IR (Nujol) cm^{-1} 3340, 3200-2400, 1720, 1690, 1660, 1610, 1600, 1525; EI–MS m/z 499 (M^+), 415, 274, 141. Anal. calcd for $C_{30}H_{29}NO_4S$ (+0.1 H_2O): C, 72.12 (71.86); H, 5.85 (5.87); N, 2.80 (2.79); S, 6.42 (6.39). Found: C, 71.75; H, 5.84; N, 2.73; S, 6.20.

5-*tert*-Butoxycarboxamido-6-(1-naphthylmethyloxy)-3-(2-thienyl)-1-indancarboxylic acid (1k). 1k was prepared in a similar manner as for **1b** starting from **8** using di-*tert*-butyl dicarbonate instead of isobutyric anhydride: colorless needles; mp 176–178 °C (dec); ^{1}H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:1.7) δ 6.86–8.08 (13H, m), 4.47–5.57 (2H, m), 4.67 (*cis*) (0.37H, t, J = 8.5 Hz) and 4.85 (*trans*) (0.63H, t, J = 7.4 Hz), 4.10 (*cis*) (0.37H, t, J = 8.6 Hz) and 4.21 (*trans*) (0.63H, dd, J = 4.7, 8.2 Hz), 2.88–3.03 (1H, m), 2.33–2.60 (1H, m), 1.37 (*cis*) (3.33H, s) and 1.38 (*trans*) (5.67H, s); IR (Nujol) cm^{-1} 3370, 3300–2400, 1710, 1685, 1610, 1600, 1525, 1490; EI–MS m/z 515 (M^+), 459, 415, 141. Anal. calcd for $C_{30}H_{29}NO_5S$: C, 69.88; H, 5.67; N, 2.72; S, 6.22. Found: C, 69.85; H, 5.69; N, 2.62; S, 5.97.

6-Hydroxy-5-isobutyrylamino-3-(2-thienyl)-1-indanmethanol (16). A mixture of **8** (5.0 g, 15.7 mmol), 10% aq HCl (50 mL), and dioxane (100 mL) was refluxed for 6 h. After removal of the solvent, the residue was extracted with EtOAc. The extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, treated with an active charcoal, and concentrated in vacuo to afford a yellow oil (4.96 g). To a stirred suspension of $NaBH_4$ (3.32 g, 98.3 mmol) in dry THF (100 mL) was added $BF_3{\cdot}(C_2H_5)_2O$ (16 mL, 128 mmol) dropwise on an ice bath, and the reaction mixture was stirred at 0 °C for 1 h. A solution of the carboxylic acid obtained (3.0 g, 9.83 mmol) in dry THF (15 mL) was added dropwise over 15 min on an ice bath, and the whole was stirred at room temperature for 4 h. The reaction mixture was poured into ice water (0.3 L), neutralized with aq $NaHCO_3$, saturated with NaCl, and extracted three times with EtOAc. The extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford **15** as a light yellow solid. To a stirred solution of the crude **15** in dry pyridine (30 mL) was added isobutyric anhydride (1.64 g, 9.83 mmol) on an ice bath. The mixture was stirred at room temperature for 14 h and concentrated in vacuo. The residual oil was treated with K_2CO_3 (5.00 g, 36.4 mmol) in MeOH (50 mL) at room temperature for 6 h, diluted with H_2O, acidified with 10% aq HCl, and then extracted with EtOAc. The extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 50:1–20:1, v/v) to afford a light brown caramel **16** (1.39 g, 43% from **8**): ^{1}H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:1) δ 8.83 (0.5H, br s) and 8.81 (0.5H, br s), 7.58 (1H, br s) and 7.48 (1H, br s), 6.76–7.19 (5H, m), 4.51 (*cis*) (0.5H, t, J = 8.6 Hz) and 4.63 (*trans*) (0.5H, t, J = 7.7 Hz), 3.87 (1H, d, J = 5.7 Hz) and 3.67–3.80 (1H, m), 3.25–3.45 (1H, m), 1.95–2.81 (3H, m), 1.7–1.9 (1H, broad), 1.24 (6H, d, J = 6.8 Hz); IR (Nujol) cm^{-1} 3600–2400, 1660, 1610, 1520; EI–MS m/z 331 (M^+), 300, 261, 230.

5-Isobutyrylamino-6-(1-naphthylmethyloxy)-3-(2-thienyl)-1-indanmethanol (17). A mixture of **16** (1.34 g, 4.04 mmol), 1-(chloromethyl)naphthalene (786 mg, 4.44 mmol), NaI (606 mg, 4.04 mmol), and K_2CO_3 (1.68 g, 12.1 mmol) in dry DMF (15 mL) was stirred at room temperature for 8 h, acidified with 10% aq HCl, and extracted with EtOAc. The extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 50:1, v/v) and recrystallized from THF–EtOAc to afford colorless needles **17** (1.65 g, 87%): mp 176.5–180.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:1) δ 7.88–8.22 (4H, m), 7.64–7.69 (1H, broad), 7.45–7.58 (4H, m), 7.10–7.19 (2H, m), 6.85–6.95 (2H, m), 5.56 (1H, d, J = 11.0 Hz) and 5.52 (1H, d, J = 11.0 Hz), 4.72 (0.5H, t, J = 7.3 Hz) and 4.61 (0.5H, t, J = 8.4 Hz), 3.93 (1H, t, J = 6.0 Hz) and 3.73–3.89 (1H, m), 3.45–3.57 (0.5H, m) and 3.33–3.45 (0.5H, m), 1.51 (0.5H, t, J = 6.0 Hz) and 1.46 (0.5H, t, J = 6.0 Hz), 0.94–1.00 (6H, m); IR (Nujol) cm^{-1} 3310, 3110, 3060, 1665, 1610, 1600, 1530; EI–MS m/z 471 (M^+), 440, 401, 330, 260, 141.

5-Isobutyrylamino-6-(1-naphthylmethyloxy)-3-(2-thienyl)-1-indancarbaldehyde (18). To a stirred solution of DMSO (0.79 mL, 11.1 mmol) in dry CH_2Cl_2 (20 mL) was added $(CF_3CO)_2O$ (1.26 mL, 8.92 mmol) dropwise at −65 to −62 °C, and the mixture was stirred at the same temperature for 20 min. A solution of **17** (1.05 g, 2.23 mmol) in dry CH_2Cl_2 (20 mL)–DMSO (3 mL) was added over 5 min at −62 to −57 °C, and the mixture was stirred at −65 °C for 1 h. Triethylamine (1.86 mL, 13.4 mmol) was added dropwise over 1 min at −65 to −60 °C, and the mixture was stirred at −65 to −10 °C for 2.5 h. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford a yellow semisolid **18**

(1.64 g), which was used without purification due to its instability.

2-(5-Isobutyrylamino-6-(1-naphthylmethyloxy)-3-(2-thienyl)indan-1-ylmethylene)-1,3-dithiane (19). To a stirred suspension of (1,3-dithian-2-yl)triphenylphosphonium chloride (2.95 g, 7.1 mmol) in dry THF (20 mL) was added 60% NaH in mineral oil (243 mg, 6.36 mmol) at room temperature, and the whole was stirred for 30 min. H_2O (0.3 mL) was added slowly to this mixture. After 5 min, a solution of crude **18** (520 mg, 0.707 mmol) in dry THF (5 mL) was added, and then stirred at room temperature for 14 h. The reaction mixture was diluted with H_2O and extracted with EtOAc. The extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (toluene:EtOAc, 40:1, v/v (twice), then hexane:EtOAc, 4:1, v/v) to afford a light orange crystalline solid **19** (181 mg, 45% from **17**): ^{1}H NMR ($CDCl_3$, 300 MHz) (diastereomer ratio 1:2.4) δ 7.87–8.28 (4H, m), 7.62–7.70 (1H, broad), 7.46–7.59 (4H, m), 6.79–7.18 (4H, m), 6.05 (0.29H, d, J = 8.4 Hz) and 5.99 (0.71H, d, J = 9.1 Hz), 5.33 (2H, s), 4.29–4.72 (2H, m), 2.80–3.00 (4H, m), 1.87–2.55 (5H, m), 0.93–1.00 (6H, m); IR (Nujol) cm^{-1} 3420, 3310, 2720, 2670, 1685, 1665, 1600; FAB–MS m/z 572 ($M+H^+$), 441, 430, 300, 141.

Methyl 5-isobutyrylamino-6-(1-naphthylmethyloxy)-3-(2-thienyl)-1-indanacetate (20). A mixture of **19** (189 mg, 0.331 mmol), $HgCl_2$ (224 mg, 0.828 mmol), MeOH (27 mL), H_2O (3 mL), and THF (10 mL) was refluxed for 3 h. After cooling, the resulting precipitate was filtered off and washed with EtOAc. The filtrate and the washings were combined and concentrated in vacuo. The residue was dissolved in EtOAc and washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (toluene:EtOAc, 50:1–30:1, v/v) and recrystallized from toluene–hexane to afford colorless needles **20** (117 mg, 69%): mp 116.5–119.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:2.5) δ 8.15 (*cis*) (0.29H, s) and 8.20 (*trans*) (0.71H, s), 8.01–8.08 (1H, m), 7.88–7.95 (2H, m), 7.62–7.68 (1H, broad), 7.45–7.58 (4H, m), 7.10–7.17 (1H, m), 7.00 (*cis*) (0.29H, s) and 7.03 (*trans*) (0.71H, s), 6.83–6.96 (2H, m), 5.52 (2H, s), 4.57 (*cis*) (0.29H, t, J = 8.5 Hz) and 4.69 (*trans*) (0.71H, t, J = 7.1 Hz), 3.71 (*cis*) (2.1H, s) and 3.70 (*trans*) (0.86H, s), 3.50–3.85 (1H, m), 2.31–2.98 (4H, m), 2.09–2.21 (1H, m), 0.94–1.01 (6H, m); IR (Nujol) cm^{-1} 3300, 1735, 1660, 1610, 1600, 1525, 1495; EI–MS m/z 513 (M^+), 443, 401, 372, 302, 228, 141.

Methyl 5-isobutyrylamino-6-(1-naphthylmethyloxy)-3-(2-thienyl)-1-indanacetic acid (1l). 20 (113 mg, 0.220 mmol) was treated in a similar manner described for the preparation of **1b** and recrystallized from EtOAc–hexane to afford colorless needles **1l** (104 mg, 95%): mp 177.0–180.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:2.4) δ 6.80–8.22 (12H, m), 7.63–7.68 (1H, broad), 5.51 (2H, s), 4.55 (*cis*) (0.29H, t, J = 8.6 Hz) and 4.68 (*trans*) (0.71H, t, J = 7.1 Hz), 3.50–3.65 (*cis*) (0.29H, m) and 3.72–3.84 (*trans*) (0.71H, m), 1.8–3.0 (5H, m), 0.94–1.00 (6H, m); IR (Nujol) cm^{-1} 3300, 1715, 1695, 1660, 1610, 1600, 1530, 1495; EI–MS m/z 499 (M^+), 429, 358, 141. Anal. calcd for $C_{30}H_{29}NO_4S$ (+0.2 H_2O): C, 72.12 (71.60); H, 5.85 (5.89); N, 2.80 (2.78); S, 6.42 (6.37). Found: C, 71.54; H, 5.82; N, 2.69; S, 6.14.

Ethyl 5-isobutyrylamino-6-(1-naphthylmethyloxy)-3-(2-thienyl)-1-indanacrylate (21). A mixture of the crude **18** (820 mg, 1.12 mmol) and $(C_6H_5)_3P{=}CHCOOC_2H_5$ (0.78 g, 2.24 mmol) in $CHCl_3$ (10 mL) was stirred at room temperature for 3 days. After removal of solvent, the residue was purified by silica gel column chromatography (toluene:EtOAc, 30:1, v/v) to afford a light brown solid **21** (439 mg, 73%) as a mixture of *Z*- and *E*-forms. A small portion of **21** was separated on preparative TLC (EtOAc:hexane, 4:1, v/v, then toluene:EtOAc, 2:1, v/v) to afford *Z* main-portion as a colorless semi-solid and *E* main-portion as a colorless crystalline powder. *Z* main-portion: ^{1}H NMR ($CDCl_3$, 200 MHz) (diastereomer ratio, 1:2) δ 6.8–8.3 (13H, m), 6.26 (0.33H, t, J = 10.3 Hz) and 6.21 (0.67H, t, J = 11.2 Hz), 5.96 (0.67H, dd, J = 1.0, 10.3 Hz) and 5.90 (0.33H, dd, J = 1.0, 11.2 Hz), 5.50 (2H, s), 4.1–5.4 (4H, m), 1.85–3.05 (3H, m), 1.2–1.4 (3H, m), 0.90–1.05 (6H, m); IR (Nujol) cm^{-1} 3300, 1720, 1660, 1610, 1600, 1525; EI–MS m/z 539 (M^+), 469, 398, 328, 141. *E* main-portion: mp 140.0–147.0 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) (diastereomer ratio, 2:3) δ 6.8–8.3 (14H, m), 6.06 (0.4H, d, J = 16.1 Hz) and 5.91 (0.6H, dd, J = 1.0, 15.6 Hz), 5.52 (2H, s), 4.55–4.75 (1H, m), 3.85–4.30 (3H, m), 1.95–3.00 (3H, m), 1.2–1.4 (3H, m), 0.90–1.05 (6H, m); IR (Nujol) cm^{-1} 3300, 1720, 1705, 1685, 1660, 1665, 1650, 1610, 1600; EI–MS m/z 539 (M^+), 398, 328, 141.

Ethyl 5-isobutyrylamino-6-(1-naphthylmethyloxy)-3-(2-thienyl)-1-indanpropionate (22). To a stirred mixture of **21** (501 mg, 0.928 mmol) and $NiCl_2{\cdot}6H_2O$ (44 mg, 0.186 mmol) in THF (15 mL)–EtOH (15 mL) was added $NaBH_4$ (229 mg, 6.03 mmol) portionwise at 0.5–1 h intervals at 0 °C. The whole was stirred at room temperature for 14 h, diluted with H_2O, and extracted with EtOAc. The extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was dissolved in DMF (5 mL). 1-(Chloromethyl)naphthalene (66 mg, 0.371 mmol), NaI (56 mg, 0.928 mmol), and K_2CO_3 (128 mg, 0.928 mmol) were added to this solution, and the whole was stirred at room temperature for 2.5 h, diluted with H_2O, and extracted with EtOAc. The extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (toluene:EtOAc, 30:1, v/v) and recrystallized from EtOAc–hexane to afford light brown needles **22** (230 mg, 46%): mp 121.0–123.0 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) (diastereomer ratio, 1:1.5) δ 6.75–8.25 (13H, m), 5.54 (2H, s), 4.68 (0.6H, t, J = 6.8 Hz) and 4.55 (0.4H, dd, J = 8.0, 11.0 Hz), 4.05–4.35 (2H, m), 3.05–3.45 (1H, m), 1.3–2.9 (7H, m), 1.1–1.4 (3H, m), 0.7–1.1 (6H, m); IR (Nujol) cm^{-1} 3360, 1735, 1660, 1610, 1530; FAB–MS m/z 542 ($M+H^+$), 400, 318, 141.

5-Isobutyrylamino-6-(1-naphthylmethyloxy)-3-(2-thienyl)-1-indanpropionic acid (1m). 22 (214 mg, 0.395 mmol) was treated in a similar manner described for the preparation of **1b** to afford **1m** as colorless needles (191 mg, 94%): mp 162.5–166.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) (diastereomer ratio, 1:1) δ 6.81–8.20 (12H, m), 7.64 (0.5H, broad) and 7.66 (0.5H, broad), 5.53 (2H, s), 4.68 (0.5H, t, J = 7.0 Hz) and 4.54 (0.5H, t, J = 8.7 Hz), 3.26–3.42 (0.5H, m) and 3.11–3.25 (0.5H, m), 1.80–2.80 (7H, m), 1.2–1.4 (3H, m), 0.93–0.99 (6H, m); IR (Nujol) cm^{-1} 3300, 2730, 2670, 1705, 1665, 1610, 1600, 1530, 1495; FAB–MS m/z 514 ($M+H^+$), 372, 303, 290, 141. Anal. calcd for $C_{31}H_{31}NO_4S$ (+0.1 H_2O): C, 72.49 (72.23); H, 6.08 (6.10); N, 2.73 (2.66); S, 6.24 (6.03). Found: C, 72.14; H, 6.09; N, 2.66; S, 6.03.

Methyl 5-isobutyrylamino-6-(1-naphthylethynyl)-3-(2-thienyl)-1-indancarboxylate (23). To a stirred suspension of **10** (477 mg, 1.33 mmol) and triethylamine (213 μL, 1.53 mmol) in dry CH_2Cl_2 (5 mL) was added $(CF_3SO_2)_2O$ (246 μL, 1.46 mmol) at 0 °C, and the mixture was stirred at the same temperature for 30 min. 10% aq HCl was added to the reaction mixture and the aqueous layer was extracted with $CHCl_3$. The extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane: EtOAc, 4:1, v/v) to afford a light reddish caramel (548 mg). A mixture of the obtained caramel (260 mg, 0.529 mmol) and LiCl (56 mg, 1.32 mmol) was chased with toluene. A mixture of the caramel obtained, tributyl-1-naphthylethynyltin (350 mg, 0.794 mmol), and $PdCl_2(PPh_3)_2$ (19 mg, 0.0265 mmol) in dry dioxane (10 mL) was refluxed under argon atmosphere for 4 h and concentrated in vacuo. The residue was purified by silica gel column chromatography (toluene:EtOAc, 50:1, v/v) and recrystallized from EtOAc–hexane to afford faintly yellow needles **23** (200 mg, 77%): mp 133.0–146.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:1.2) δ 8.15–8.25 (1H, broad), 6.90–8.40 (12H, m), 4.66 (*cis*) (0.45H, dd, J = 8.4, 9.4 Hz), and 4.94 (*trans*) (0.55H, t, J = 7.7 Hz), 4.08 (*cis*) (0.45H, t, J = 8.8 Hz) and 4.21 (*trans*) (0.55H, dd, J = 4.1, 8.0 Hz), 3.83 (*cis*) (1.4H, s) and 3.76 (*trans*) (1.6H, s), 2.88–3.50 (1H, m), 2.41–2.63 (2H, m), 1.22–1.27 (6H, m); IR (Nujol) cm^{-1} 3280, 3180, 2720, 2670, 1740, 1735, 1665, 1570, 1520, 1465; EI–MS m/z 493 (M^+), 422, 364.

Methyl 5-isobutyrylamino-6-(2-(1-(*Z*)-naphthyl)ethenyl)-3-(2-thienyl)-1-indancarboxylate (24) and methyl 5-isobutyrylamino-6-(2-(1-naphthyl)ethyl)-3-(2-thienyl)-1-indancarboxylate (25). A solution of **23** (102 mg, 0.207 mmol) in THF (10 mL)–MeOH (20 mL) was hydrogenated over 10% Pd/C (water wet) (100 mg) at 3.5 atm for 34 h. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (toluene: EtOAc, 20:1, v/v) to afford **24** (41 mg, 40%) as a light yellow crystalline powder which was recrystallized from ether–hexane and **25** (52 mg, 51%) as colorless needles which was recrystallized from EtOAc–hexane, respectively. **24**: mp 142.5–154.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) (diastereomer ratio was not determined) δ 6.78–8.21 (15H, m), 4.51–4.99 (1H, m), 3.97–4.27 (1H, m), 3.52–3.83 (3H, m), 1.65–3.07 (3H, m), 0.75–1.28 (6H, m); IR (Nujol) cm^{-1} 3290, 1735, 1665, 1570, 1510; EI–MS m/z 495 (M^+), 452, 424. 25: mp 161.0–165.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:1.5) δ 6.83–8.08 (12H, m), 5.91 (1H, broad), 4.59 (*cis*) (0.4H, t, J = 8.8 Hz) and 4.87 (*trans*) (0.6H, t, J = 7.6 Hz), 4.18 (*trans*) (0.6H, dd, J = 4.4, 8.2 Hz) and 4.06 (*cis*) (0.4H, t, J = 8.7 Hz), 3.81 (*cis*) (1.2H, s) and 3.73 (*trans*) (1.8H, s), 3.25–3.54 (2H, m), 2.83–3.09 (3H, m), 2.34–2.57 (1H, m), 1.5–1.7 (1H, m), 0.89 (*cis*) (2.4H, d, J = 6.9 Hz) and 0.90 (*trans*) (3.6H, d, J = 6.9 Hz); IR (Nujol) cm^{-1} 3290, 1740, 1665, 1585, 1520; EI–MS m/z 495 (M^+), 356.

5-Isobutyrylamino-6-(1-naphthylethynyl)-3-(2-thienyl)-1-indancarboxylic acid (1n). A solution of **23** (60 mg, 0.122 mmol) in THF (2 mL)–MeOH (2 mL) was treated in a similar manner described for the preparation of **1b** to afford **1n** as colorless needles (54 mg, 92%): mp 201.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:1.7) δ 8.19–8.25 (1H, broad), 6.90–8.39 (12H, m), 4.68 (*cis*) (0.37H, t, J = 9.0 Hz) and 4.95 (*trans*) (0.63H, t, J = 7.5 Hz), 4.13 (*cis*) (0.37H, t, J = 8.8 Hz) and 4.24 (*trans*) (0.63H, dd, J = 4.4, 8.1 Hz), 2.43–2.64 (2H, m), 1.25 (6H, d, J = 7.0 Hz); IR (Nujol) cm^{-1} 3300, 3200–2400, 1710, 1690, 1665, 1570, 1515; EI–MS m/z 479 (M^+), 408, 364. Anal. calcd for $C_{30}H_{25}NO_3S$: C, 75.13; H, 5.25; N, 2.92; S, 6.69. Found: C, 74.87; H, 5.27; N, 2.73; S, 6.39.

5-Isobutyrylamino-6-(2-(1-(*Z*)-naphthyl)ethenyl)-3-(2-thienyl)-1-indancarboxylic acid (1o). A solution of **24** (45 mg, 0.0908 mmol) in THF (2 mL)–MeOH (2 mL) was treated in a similar manner described for the preparation of **1b** to afford **1o** as faintly brown amorphous powder (33 mg, 76%): ^{1}H NMR ($CDCl_3$, 300 MHz) (diastereomer ratio was not determined) δ 6.75–8.20 (15H, m), 4.53–5.02 (1H, m), 3.95–4.30 (1H, m), 2.8–3.6 (1H, m), 2.3–2.7 (1H, m), 1.55–1.78 (1H, m), 0.65–1.30 (6H, m); IR (Nujol) cm^{-1} 3400, 3200–2400, 1710, 1695, 1660; EI–MS m/z 481 (M^+), 410, 366, 326. Anal. calcd for $C_{30}H_{27}NO_3S$ (+0.3 H_2O): C, 74.82 (74.00); H, 5.65 (5.71); N, 2.91 (2.88); S, 6.66 (6.58). Found: C, 74.08; H, 5.72; N, 2.74; S, 6.51.

5-Isobutyrylamino-6-(2-(1-naphthyl)ethyl)-3-(2-thienyl)-1-indancarboxylic acid (1p). A solution of **25** (54 mg, 0.112 mmol) in THF (2 mL)–MeOH (2 mL) was treated in a similar manner described for the preparation of **1b** to afford **1p** as colorless needles (39 mg, 72%): mp 229.0–230.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) (*cis*:*trans*, 1:2) δ 7.72–8.10 (3H, m), 7.46–7.56 (3H, m), 7.27–7.37 (2H, m), 7.09–7.22 (2H, m), 6.83–6.97 (2H, m), 6.14 (1H, broad), 4.55–4.64 (*cis*) (0.33H, m) and 4.88 (*trans*) (0.67H, t, J = 7.7 Hz), 4.05 (*cis*) (0.33H, t, J = 9.1 Hz) and 4.16 (*trans*) (0.67H, dd, J = 4.2, 8.2 Hz), 3.25–3.51 (2H, m), 2.84–3.06 (3H, m), 2.33–2.60 (1H, m), 1.67 (1H, quintet, J = 6.9 Hz), 0.90 (*cis*) (1H, d, J = 6.8 Hz) and 0.90 (*trans*) (2H, d, J = 6.8 Hz); IR (Nujol) cm^{-1} 3280, 3200–2500, 1720, 1690, 1655; EI–MS m/z 483 (M^+), 440, 342, 272, 141. Anal. calcd for $C_{30}H_{29}NO_3S$ (+0.3 H_2O): C, 74.51 (73.95); H, 6.04 (6.08); N, 2.90 (2.87); S, 6.63 (6.58). Found: C, 73.91; H, 6.00; N, 2.74; S, 6.60.

Receptor binding assay: porcine aortic membrane

Porcine aorta (known to contain ET_A receptors) from which endothelium was removed was homogenized in 10 mM MOPS buffer (pH 7.4) containing 20% sucrose. The homogenate was centrifuged under cooling for 15 min at 1000×g. The supernatant was centrifuged under cooling for 45 min at 90,000×g. The precipitate was re-suspended in 5 mM HEPES–Tris buffer to obtain a membrane preparation. 50 μL of the diluted membrane preparation (2 mg/mL), 50 μL of ^{125}I-labeled endothelin-1 (final concentration of ^{125}I-labeled endothelin-1: 20 pM, specific activity: 74 TBq/mmol, Amersham Japan), and 50 μL of a test compound solution in various concentrations were admixed. The mixture was added to 150 μL of assay buffer (50 mM Tris–HCl buffer (pH 7.4) containing 0.1% BSA, 0.1 mM phenylmethylsulfonyl fluoride, 1 μM pepstatin A, 2 μM leupeptin, 1 mM 1,10-phenanethrorine and 1 mM EDTA), and incubated for 2 h at 25 °C. The incubation was terminated by rapid filtration through Whatman GF/B glass fiber filters. The filters were washed with ice-cooled 5 mM HEPES–Tris buffer (pH 7.4) containing 0.1% BSA and the radioactivity was counted by a gamma counter (ARC-360, Aloka Ltd). The antagonistic activity of the test compound (inhibitory effect on ^{125}I-labeled endothelin-1 binding to porcine aortic membranes) was estimated as IC_{50} which is the concentration (M) required to inhibit the specific binding of ^{125}I-labeled endothelin-1 by 50%. Meanwhile, the non-specific binding of endothelin was estimated in the presence of 2×10^{-7} M endothelin-1.

Acknowledgements

The authors are grateful to Dr. M. Ozeki for his encouragement. Thanks are also due to the staff of the analytical section of our research laboratory for spectral measurements and elemental analyses.

References and Notes

1. Yanagisawa, M.; Kurihara, H.; Kimura, H.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Yazaki, Y.; Goto, K.; Masaki, T. *Nature* **1988**, *332*, 411.
2. (a) Ihara, M.; Fukuroda, T.; Saeki, T.; Nishikibe, M.; Kojiri, K.; Suda, H.; Yano, M. *Biochem. Biophys. Res. Commun.* **1991**, *178*, 132. (b) Ishihara, K.; Fukami, T.; Nagase, T.; Fujita, K.; Hayama, T.; Niiyama, K.; Mase, T.; Ihara, M.; Yano, M. *J. Med. Chem.* **1992**, *35*, 2139.
3. (a) Ihara, M.; Fukuroda, T.; Saeki, T.; Nishikibe, M.; Kojiri, K.; Suda, H.; Yano, M. *Biochem. Biophys. Res. Commun.* **1991**, *178*, 132. (b) Ishikawa, K.; Fukami, T.; Nagase, T.; Fujita, K.; Hayama, T.; Niiyama, K.; Mase, T.; Ihara, M.; Yano, M. *J. Med. Chem.* **1992**, *35*, 2139.
4. Sogabe, K.; Nirei, H.; Shoubo, M.; Nomoto, A.; Ao, S.; Notsu, Y.; Ono, T. *J. Pharmacol. Exp. Ther.* **1993**, *264*, 1040.
5. (a) Ihara, M.; Noguchi, K.; Saeki, T.; Fukuroda, T.; Tsuchida, S.; Kimura, S.; Fukami, T.; Ishikawa, K.; Nishikibe, M.; Yano, M. *Life Sci.* **1992**, *50*, 247. (b) Huggins, J. P.; Pelton, J. T.; Miller, R. C. *Pharmacol. Ther.* **1993**, *59*, 55. (c) Gray, G. A.; Webb, D. J. *Pharmacol. Ther.* **1996**, *72*, 109.
6. (a) Warner, T. D. *Cardiovascular Drug Reviews* **1994**, *12*, 105. (b) Peishoff, C. E.; Lago, M. A.; Ohlstein, E. H.; Elliott, J. D. *Current Pharmaceutical Design* **1995**, *1*, 425. (c) Doherty, A. M. *Drug Discovery Today* **1996**, *1*, 60.
7. (a) Hirschmann, R.; Nicolau, K. C.; Pietranico, S.; Salvino, J.; Leahy, E. M.; Sprengeler, P. A.; Furst, G.; Smith III, A. B.; Strader, C.; Cascieri, M. A.; Candelore, M. R.; Donaldson, C.; Vale, W.; Maechler, L. *J. Am. Chem. Soc.* **1992**, *114*, 9217. (b) Hirschmann, R.; Sprengeler, P. A.; Kawasaki, T.; Leahy, J. W.; Shakspeare, W. C.; Smith III, A. B. *J. Am. Chem. Soc.* **1992**, *114*, 9699. (c) Giannis, A.; Kolter, T.; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244. (d) Murugesan, N.; Gu, Z.; Lee, V.; Webb, M. L.; Liu, E. C.-K.; Hermsmeier, M.; Hunt, J. T. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 253. (e) Diguarher, T. L.; Boudon, A.; Elwell, C.; Paterson, D. E.; Billington, D. C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1983.
8. (a) Atkinson, R. A.; Pelton, J. T. *FEBS Lett.* **1992**, *296*, 1. (b) Krystek Jr., S. R.; Bassolino, D. A.; Bruccoleri, R. E.; Hunt, J. T.; Porubcan, M. A.; Wandler, C. F.; Andersen, N. H. *FEBS Lett.* **1992**, *299*, 255. (c) Reily, M. D.; Thanabal, V.; Omecinsky, D. O.; Dunbar Jr., J. B.; Doherty, A. M.; DePue, P. L. *FEBS Lett.* **1992**, *300*, 136. (d) Coles, M.; Sowemimo, V.; Scanlon, D.; Munro, S. L. A.; Craik, D. J. *J. Med. Chem.* **1993**, *36*, 2658.
9. Fukami, T.; Nagase, T.; Fujita, K.; Hayama, T.; Niiyama, K.; Mase, T.; Nakajima, S.; Fukuroda, T.; Saeki, T.; Nishikibe, M.; Ihara, M.; Yano, M.; Ishikawa, K. *J. Med. Chem.* **1995**, *38*, 4309.
10. Reduction of the indene **4** under H_2 atmosphere in the presence of acetic acid with palladium catalysts such as palladium on activated carbon or colloidal palladium resulted in low yield of the indan derivatives **5** and **6**.
11. The configurations of *cis-trans* isomer were assigned by analysis of nuclear Overhauser effect (NOE) in ^{1}H NMR. In *cis* isomer, NOEs between one of the protons at 2-position and both of the protons at 1- and 3-positions were observed, but not in *trans* isomer.
12. 1-Methyl-3-hydroxymethylindole was synthesized by the method of Mattocks, A. R. *J. C. S. Perkin I* **1978**, 896. However, neither a chlorination nor a mesylation of the hydroxyl group was not successful, probably due to instability of the generated alkylating agents.
13. Kruse, C. G.; Broekhof, N. L. J. M.; Wijsman, A.; van der Gen, A. *Tetrahedron Lett.* **1977**, *10*, 885.
14. Chamberlin, A. R.; Nguyen, H. D.; Chung, J. Y. L. *J. Org. Chem.* **1984**, *49*, 1682.
15. Ganem, B.; Osby, J. O. *Chem. Rev.* **1986**, *86*, 763.
16. 1-Ethynylnaphthalene, synthesized by the method of Corey, E. J. and Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769, led to tributyl-1-naphthylethynyltin by a reaction with *n*-BuLi and *n*-Bu_3SnCl.
17. (a) Ohlstein, E. H.; Nambi, P.; Douglas, S. A.; Edwards, R. M.; Gellai, M.; Lago, M. A.; Leber, J. D.; Cousins, R. D.; Gao, A.; Frazee, J. S.; Peishoff, C. E.; Bean, J. W.; Eggleston, D. S.; Elshourbagy, N. A.; Kumar, C.; Lee, J. A.; Yu, T.-L.; Louden, C.; Brooks, D. P.; Weinstock, J.; Feuerstein, G.; Poste, G.; Ruffolo Jr., R. R.; Gleason, J. G.; Elliott, J. D. *Proc. Natl. Acad. Sci., U.S.A.* **1994**, *91*, 8052. (b) Ohlstein, E. H.; Nambi, P.; Lago, A.; Hay, D. W. P.; Beck, G.; Fong, K.-L.; Eddy, E. P.; Smith, P.; Ellens, H.; Elliot, J. D. *J. Pharmacol. Exp. Ther.* **1996**, *276*, 609.
18. SYBYL ver. 5.5, Tripos Inc., 1699 South Hanley Road, St. Louis, MO 63144-2913.
19. MOPAC ver. 5.01, J. J. P. Stewart, QCPE #455; Revised as ver. 5.01 by Tsuneo Hirano, for UNIX machines, *JCPE Newsletter*, **1989**, *1*(2), 36.