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Discovery of novel indane derivatives as liver-selective thyroid hormone receptor β (TRβ) agonists for the treatment of dyslipidemia

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ABSTRACT

Thyromimetics that specifically target TRβ have been shown to reduce plasma cholesterol levels and avoid atherosclerosis through the promotion of reverse cholesterol transport in an animal model. We designed novel thyromimetics with high receptor (TRβ) and organ (liver) selectivity based on the structure of eprotirome (**3**) and molecular modeling. We found that indane derivatives are potent and dual-selective thyromimetics expected to avoid hypothyroidism in some tissues as well as heart toxicity. KTA-439 (**29**), a representative indane derivative, showed the same high human TRβ selectivity in a binding assay as **3** and higher liver selectivity than **3** in a cholesterol-fed rat model.

1. Introduction

Thyroid hormones (THs) affect growth, development, and metabolism in practically all tissues.[1–3] An excess quantity of circulating TH, commonly referred to as hyperthyroidism, results in increased heart rate, body temperature, osteoporosis, muscle fatigue, changes in mental state, and dramatic reductions in circulating cholesterol levels and body weight. THs are expected to be potent lipid-lowering agents, but they cannot be used therapeutically in patients with dyslipidemia, obesity, or metabolic syndrome mainly because of the side effect of tachycardia.[4]

There are two major THs: thyroxine (T_4; **1** in Fig. 1) and 3,5,3′-triiodo-L-thyronine (T_3; **2**). They exert their actions by binding to nuclear thyroid hormone receptors (TRs) in the nucleus. There are two major subtypes of TRs, α (TRα) and β (TRβ), expressed from two different genes.[1] Differential processing of ribonucleic acid (RNA) results in the formation of several isoforms from each gene. The TRα$_1$, TRβ$_1$, and TRβ$_2$ isoforms bind THs and act as ligand-regulated transcription factors.[5] The TRβ$_1$ isoform is prevalent particularly in the liver, and to a lower degree, in the heart.[6] The TRβ$_2$ isoform is expressed in the hypothalamus, anterior pituitary gland, and the developing brain.[1,7] The TRα$_1$ isoform is also widely distributed, but its levels are generally lower than those of the TRβ$_1$ isoform. The literature suggests that most of the effects of THs on the heart (particularly on the rate and rhythm) are mediated through activation of the TRα$_1$ isoform, whereas most of the actions of the hormones on the liver (e.g., lipid-lowering effect) and other tissues are mediated through activation of the TRβ$_1$ isoform.[8]

Thyromimetics that specifically target TRβ have been shown to reduce plasma cholesterol levels and avoid atherosclerosis through the promotion of reverse cholesterol transport in an animal model. Such compounds may be useful as a complement to statin therapy in the prevention of cardiovascular disease.[8–11] However, TRβ activation can be expected to reduce thyroid-stimulating hormone (TSH) levels and thereby reduce the endogenous production of thyroid hormones. A reduction in TSH levels and subsequent reduction in T_4 may paradoxically cause hypothyroidism in some tissues. Most of the selective analogs are known to reduce TSH and/or T_4 levels at therapeutic doses.[12] A derivative of malonamic acid, eprotirome (KB2115; **3**) (Karo Bio), is a thyroid hormone analog with minimal uptake in non-hepatic tissues compared with T_3. It has a modestly higher affinity for TRβ than for TRα. In a 2-week clinical trial, **3** was reported to reduce serum levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoprotein B without evident side effects. However, in a 12-week study, serum total and free T_4 levels were modestly decreased in patients who received eprotirome therapy.[13–15]

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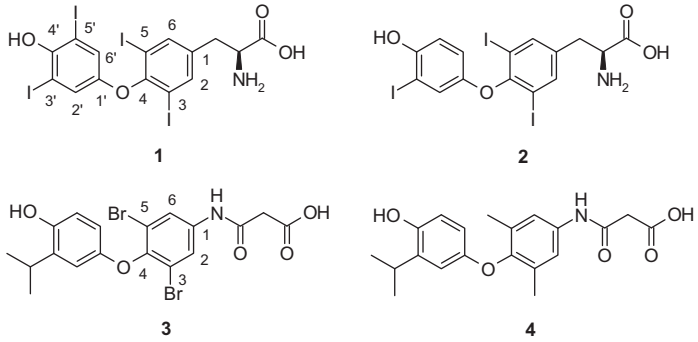


Figure 1. Structures of T_4 (**1**), T_3 (**2**), eprotirome (**3**), and the reported thyroid hormone ligand (**4**).

We investigated novel thyromimetics that showed high receptor (TRβ) and organ (liver) selectivity to avoid hypothyroidism as well as heart toxicity. In the present study, we describe the discovery process and investigate the structure–activity relationships (SARs) of novel indane derivatives.

2. Strategy

We designed the compounds based on **3** because it showed modestly high TRβ selectivity in vitro and modest liver selectivity in a clinical trial.[14,15] The mechanism of liver selectivity is uncertain. Yokoyama et al. reported that some compounds with high potency for the nucleus and with significantly lower binding affinity to the membrane showed separation of lipid-lowering effects from cardiac effects in rats.[16] However, it was uncertain whether these compounds also showed separation of lipid-lowering effects from the negative feedback of T_4. Conversely, TRβ potency and selectivity can be evaluated in vitro. Hence, we first evaluated TRβ selectivity in vitro and then evaluated liver selectivity in vivo using synthesized compounds.

3. Results and discussion

3.1. First design of the target

Only one amino acid is different from *h*TRα and *h*TRβ in the hormone-binding pocket (Ser-277 vs Asn-331, respectively).[17] The crystal structures of *h*TRs bound to T_3 revealed that hydrogen bonds were formed between the Arg-228α/282β of *h*TRs and COOH of T_3 but not between the Ser-277α/Asn-331β of *h*TRs and T_3 (Fig. 2a, b).[18]

A docking model of **3** was constructed from the crystal structure of *h*TRβ–T_3 complex (Fig. 2c). The docking model suggested the possibility that interactions occur between NH of **3** and Asn-331 of *h*TRβ and between COOH of **3** and Arg-266α/320β but not between NH of **3** and Ser-277 of *h*TRα. We supposed that these different interactions affect the *h*TRβ selectivity of **3**, which was higher than that of T_3. The model also suggested that the *h*TRβ–ligand complex showed an unoccupied space in the binding cavity next to the 2-position of **3** (Fig. 2d). Filling of this space was expected to stabilize the complex. Hence, we first decided to synthesize new malonamic acid derivatives with a substituent at the 2-position.[19]

3.2. Synthesis of malonamic acids with a substituent at the 2-position

Two malonamic acid derivatives with a substituent at the 2-position were prepared, as outlined in Scheme 1. Benzylation of the commercially available **5** gave the benzyl ether **6**, which was treated with $(CF_3CO_2)_3I$ **7** prepared from I_2 following a previously reported method[16] to give bis(4-benzyloxy-3-isopropylphenyl) iodonium BF_4^- **8**. Commercially available 2,3,6-trisubstituted phenols **9** and **10** were nitrated with $NaNO_2$/TFA and HNO_3/CH_2Cl_2 to give the nitrophenols **11** and **12**, which were coupled with the salt **8** to give the diphenyl ethers **13** and **14**, respectively. Nitro group reduction of **13** with H_2/Pt gave the aniline **15**, which was coupled with ethyl malonyl chloride to give the anilide **16**. Debenzylation of **16** with TFA/H_2O/Me_2S (95/5/10) gave the ester **17**,[20] which was hydrolyzed to give the final target ligand **18**. Nitro group reduction and debenzylation of **14** with H_2/Pd gave the aniline **19**. The coupling and hydrolysis of **19** as described above gave the malonamic acid **20**.

3.3. Synthesis of malonamic acids with fused rings

We prepared malonamic acids in which an additional ring was fused to the inner ring between the 2-position and 3-position, as outlined in Scheme 2. Known **22a**,[21] **23**,[22] and 5-bromoindan-4-ol **22b**, which was prepared from the known indan-4-ol **21**, were nitrated with HNO_3/CH_2Cl_2 to give **24a**, **25**, and **24b**, respectively. The nitro compounds **24a**, **24b**, and **25** were coupled with the salt **8** to give the ethers **26a**, **26b**, and **27**, respectively. Nitro group reduction and debenzylation of **26a** with H_2/Pd gave the aromatic amine **28**. Coupling and hydrolysis of **28** as described above gave the target compound **29**. Nitro group reduction of **26b** and **27** with H_2/Pt gave the aromatic amines **30** and **31**, which were coupled with ethyl malonyl chloride to give the amides **32** and **33**, respectively. Debenzylation and alkaline hydrolysis of **32** and **33** gave the fused compounds **34** and **35**, respectively.

3.4. In vitro effects of the ligands on TRs

The results of a radioligand binding assay for *h*TRα and *h*TRβ as well as a reporter cell assay employing COS1 cells stably transfected with *h*TRα or *h*TRβ and the luciferase reporter gene downstream the thyroid response element are summarized in Table 1. The natural ligand T_3 (**2**) bound to *h*TRα and *h*TRβ with K_i of 2.29 and 2.33 nM, respectively. Compound **3** was found to be selective for *h*TRβ over *h*TRα with regard to binding. When the bromine atom was replaced with methyl groups (compound **4**[13]), binding affinities decreased for both isoforms, thereby resulting in high *h*TRβ selectivity. Substitution of the methyl group at the 2-position of **4** as in **20** did not affect affinity and selectivity. The trihalogenated compound **18** also showed similar affinity and selectivity to **3**. Interestingly, the indane compounds in which the alkyl ring was fused on the inner ring between the 2-position and 3-position (**29**, **34**) showed high affinity for *h*TRβ and selectivity for *h*TRβ over *h*TRα. However, the 5,6,7,8-tetrahydronaphthalene compound **35** showed lower affinity for *h*TRβ, resulting in diminished selectivity. All compounds displayed full agonism in the reporter cell assay.

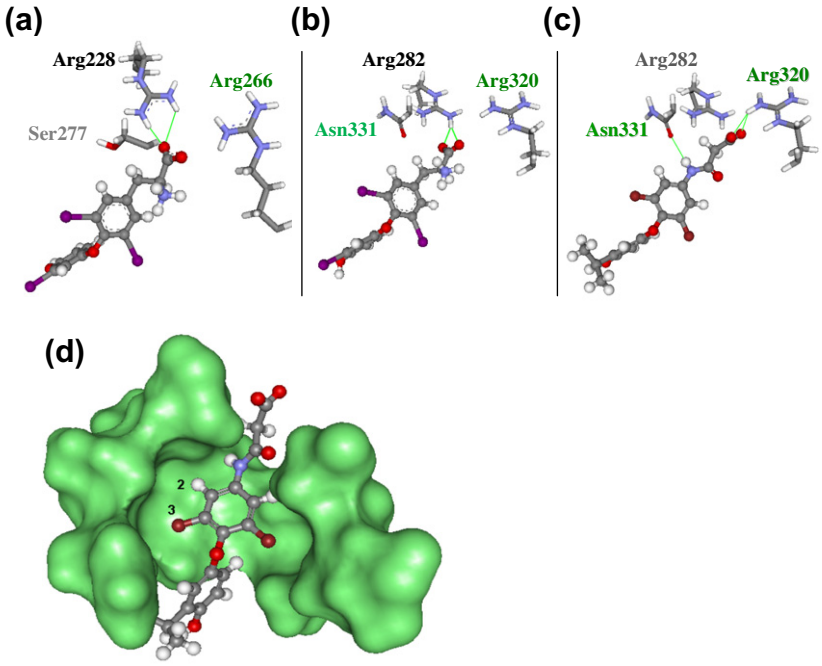
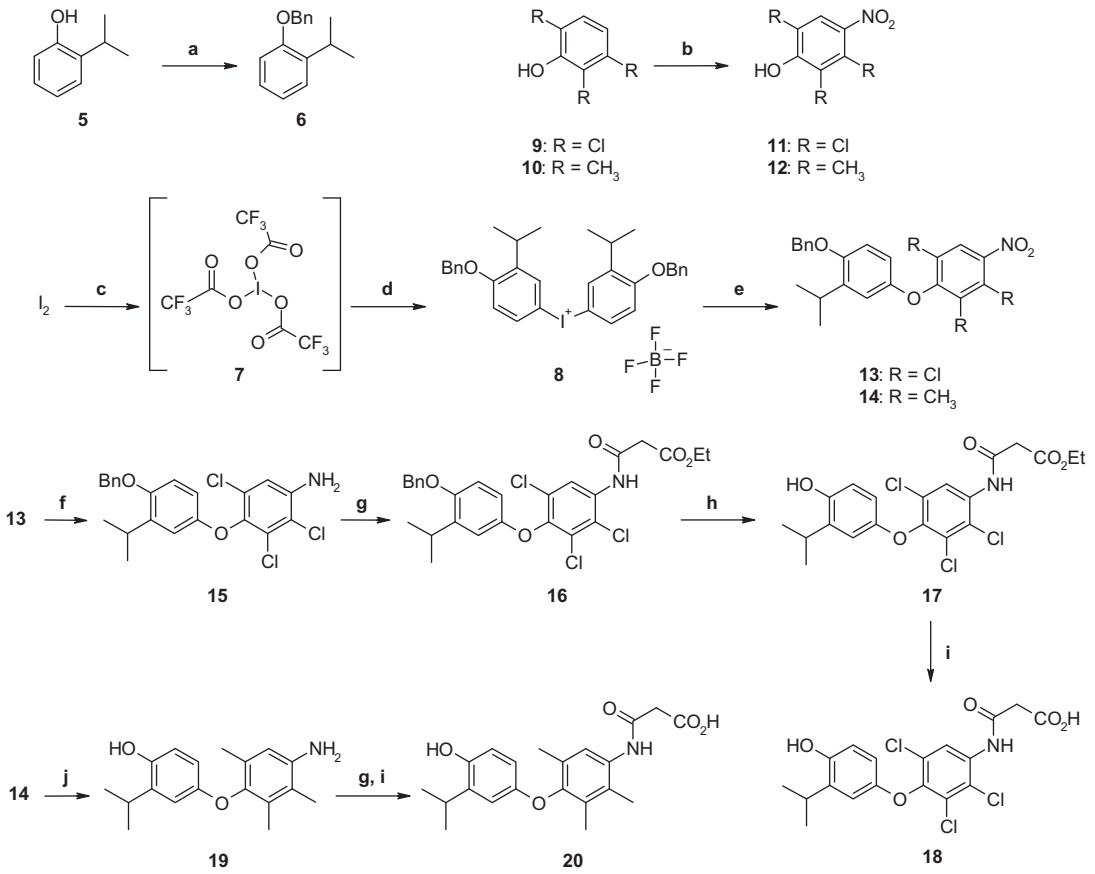
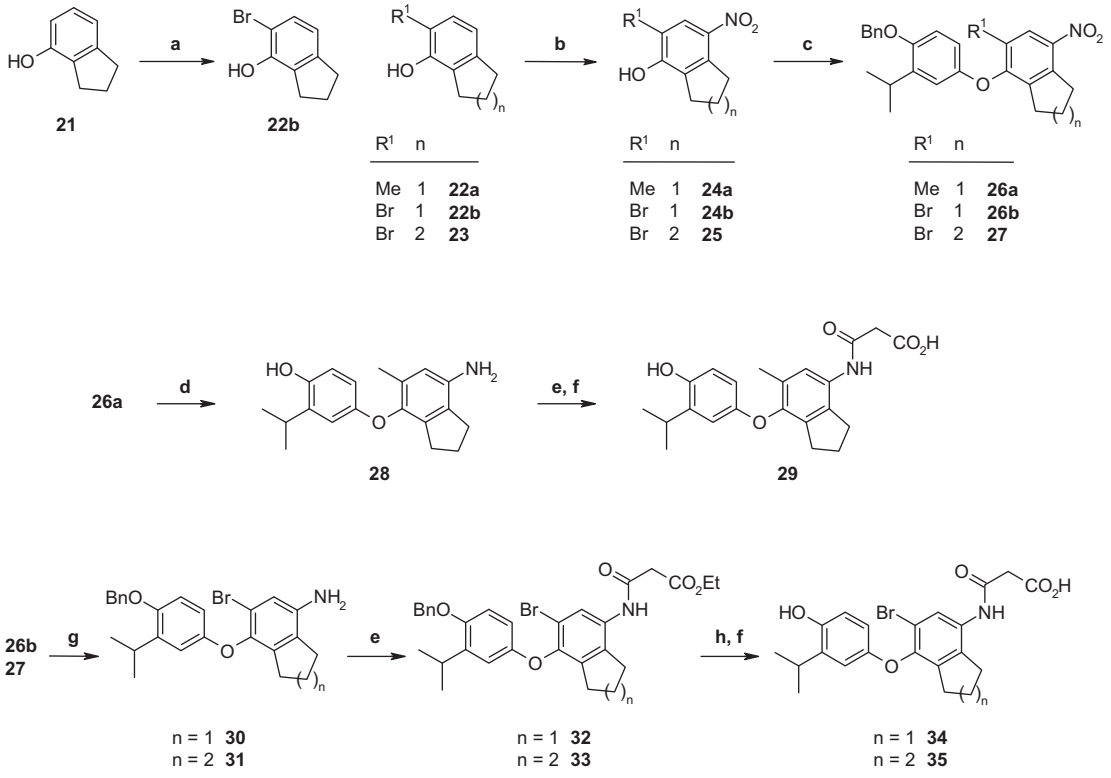


Figure 2. (a), (b) Interactions observed in the published crystallographic structures of ligand binding domain (LBD)–ligand complexes. (a) T_3 and *h*TRα and (PDB code 2H79), (b) T_3 and *h*TRβ (PDB code 3GWS). Hydrogen bonds or polar interactions are observed between COOH of T_3 and Arg-228α/282β of *h*TRs but not between T_3 and Ser-277α/Asn-331β of *h*TRs.[18] (c), (d) The docking model of *h*TRβ with eprotirome (**3**) constructed from the crystal structure of *h*TRβ–T_3 complex. (PDB code 3GWS). (c) Interactions between **3** and *h*TRβ. Hydrogen bonds are possible between NH of **3** and Asn-331β and between COOH of **3** and Arg-320β. (d) The *h*TRβ–ligand complex showed an unoccupied space in the binding cavity next to the 2-position of **3**.



Scheme 1. Synthetic route for the preparation of **18** and **20**. Reagents and conditions: (a) BnBr, K_2CO_3, CH_3CN; (b) (R = Cl) $NaNO_2$, TFA; (R = CH_3) HNO_3, CH_2Cl_2; (c) HNO_3 (fuming), TFA; (d) (i) **6**, CH_2Cl_2; (ii) $NaBF_4$, MeOH; (e) **11** or **12**, Cu, Et_3N, CH_2Cl_2, 5 days; (f) H_2/PtO_2, EtOAc; (g) $ClCOCH_2CO_2Et$, pyridine, CH_2Cl_2, 0 °C; (h) TFA/H_2O/Me_2S (95/5/10); (i) NaOH, MeOH; (j) H_2/Pd-C, EtOAc.



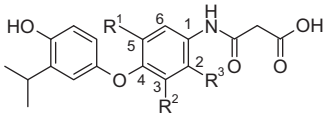
Scheme 2. Synthetic route for the preparation of **29**, **34**, and **35**. Reagents and conditions: (a) *N*-Bromosuccinimide, iPr_2NH, CH_2Cl_2, 0 °C; (b) HNO_3, AcOH; (c) **8**, Cu, Et_3N, CH_2Cl_2, 5 days; (d) H_2/Pd-C, EtOAc; (e) $ClCOCH_2CO_2Et$, pyridine, CH_2Cl_2, 0 °C; (f) NaOH, MeOH; (g) H_2/PtO_2, EtOAc; (h) $TFA/H_2O/Me_2S$ (95/5/10).

3.5. Next design: synthesis of indane derivatives with other acids and spacers

The previously unknown indane derivatives were found to have high *h*TRβ potency and selectivity. Hence, we synthesized other indane derivatives with other acids and ring spacers to obtain further SAR information, as outlined in Scheme 3. The aromatic amine **28** was condensed with diethyl oxalate to give the oxamate **36**, which was hydrolyzed to give the oxamic acid **37**. Coupling of **28** with ethyl (chlorosulfonyl)acetate followed by hydrolysis gave the sulfamoylacetic acid **38**. Nitro group reduction of **26a** with H_2/Pt gave the aromatic amine **39** from which the carboxylic acid **40** was prepared by diazotization, iodization, palladium-catalyzed cyanation, and alkaline hydrolysis. Coupling with glycine ethyl ester gave the amide **41**. Debenzylation of **41** with $TFA/H_2O/Me_2S$ (95/5/10) gave the deprotected product **42**, which was hydrolyzed to give the carbonylaminoacetic acid **43**.

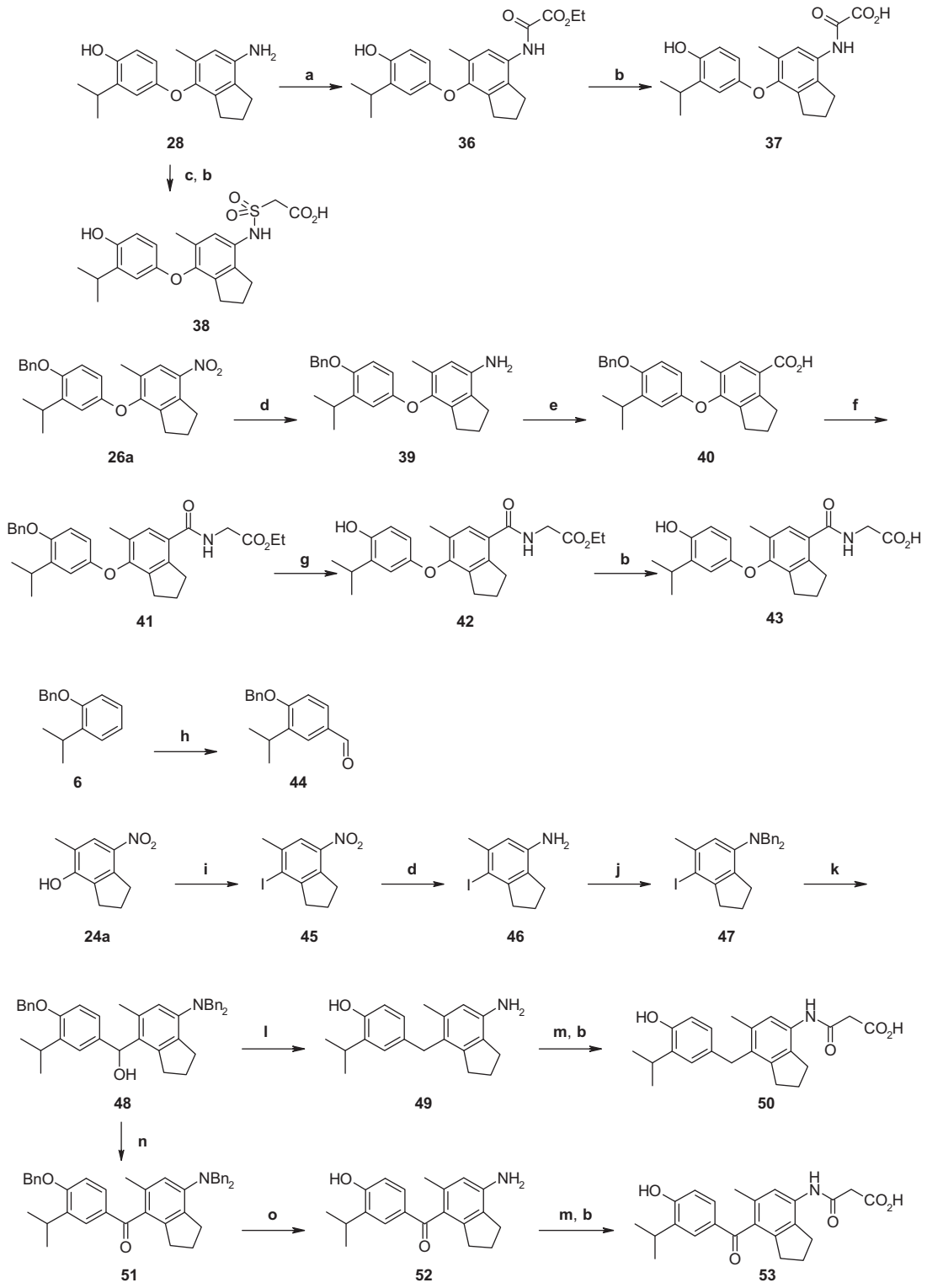
The benzyl ether **6** was treated with $Cl_2CHOCH_3/TiCl_4$ to give the aldehyde **44**. Triflation of the nitro compound **24a** with Tf_2O followed by iodization gave the iodoindane **45**. Nitro group reduction of **45** with H_2/Pt gave the aromatic amine **46**, which was benzylated to give **47**. The aldehyde **44** was coupled with a lithiated compound from the iodide **47** to give the biaryl alcohol **48**, which was hydrogenolyzed to give the biarylmethane **49**. Coupling

Table 1
Thyroid hormone receptor binding affinities (K_i) and reporter cell line potency efficacies (% agonism) of compounds **2–4**, **18**, **20**, **29**, **34**, and **35**



Compound	R^1	R^2	R^3	K_i (nM)[a]		α/β[b]	% Agonism[c]	
				*h*TRβ	*h*TRα		TRLuc-β	TRLuc-α
2				2.29	2.33	1	100	100
3	Br	Br	H	0.43	9.60	22	111	98
4	Me	Me	H	10.0	147	15	180	107
18	Cl	Cl	Cl	1.54	24.4	16	108	120
20	Me	Me	Me	20.3	195	10	123	95
29	Me	$CH_2CH_2CH_2$		7.80	172	22	113	110
34	Br	$CH_2CH_2CH_2$		1.19	69.3	58	93	106
35	Br	$CH_2(CH_2)_2CH_2$		301	300	1	115	124

[a] Values are means of two experiments. On average, the variability was 25%.
[b] Selectivity (K_i *h*TRα)/(K_i *h*TRβ).
[c] Values at 10^{-5} M; T_3 as 100%.



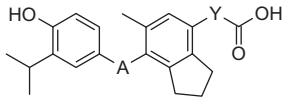
Scheme 3. Synthetic route for the preparation of **37**, **38**, **43**, **50**, and **53**. Reagents and conditions: (a) $(CO_2Et)_2$, 110 °C; (b) NaOH, MeOH; (c) $ClSO_2CH_2CO_2Et$, pyridine, CH_2Cl_2, 0 °C; (d) H_2/PtO_2, EtOAc; (e) (i) $NaNO_2$, ii) KI, (iii) $Zn(CN)_2$, $Pd(dba)_2$, DPPF, NMP, 80 °C, (iv) NaOH, EtOH, reflux; (f) $NH_2CH_2CO_2Et$ HCl, EDCI, HOBt, Et_3N, DMF; (g) TFA/H_2O/Me_2S (95/5/10); (h) Cl_2CHOCH_3, $TiCl_4$; (i) (i) Tf_2O; (ii) KI; (j) BnBr, Cs_2CO_3, DMF; (k) (i) ^tBuLi, THF, −100 °C; (ii) **44**; (l) H_2/Pd-C, HCl, EtOH, 50 °C; (m) $ClCOCH_2CO_2Et$, pyridine, CH_2Cl_2, 0 °C; (n) MnO_2, CH_2Cl_2; (o) H_2/Pd-C, THF.

between compound **49** and ethyl malonyl chloride and hydrolysis as described above gave the carboxylic acid **50**. Oxidation of the alcohol **48** with MnO_2 gave the ketone **51**. Hydrogenolysis of **51** provided the aromatic amine **52**, which was coupled with ethyl malonyl chloride and hydrolyzed to give **53**.

3.6. In vitro effects of indane derivatives with other acids and spacers on TRs

The in vitro results of indane derivatives are summarized in Table 2. The oxamic acid **37**, which has COOH at a shorter distance

Table 2
Thyroid hormone receptor binding affinities (K_i) and reporter cell line potency efficacies (% agonism) of compounds **29**, **37**, **38**, **43**, **50**, and **53**



Compound	A	Y	K_i (nM)[a]		α/β[b]	% Agonism[c]	
			*h*TRβ	*h*TRα		TRLuc-β	TRLuc-α
29	O	$NHCOCH_2$	7.80	172	22	113	110
37	O	NHCO	2.59	2.45	1	105	95
43	O	$CONHCH_2$	15.1	127	8	99	114
38	O	$NHSO_2CH_2$	213	1246	6	93	81
50	CH_2	$NHCOCH_2$	19.7	154	8	90	98
53	C=O	$NHCOCH_2$	59.0	Nt[d]	–	115	64

[a] Values are means of two experiments. On average, the variability was 25%.
[b] Selectivity (K_i *h*TRα)/(K_i *h*TRβ).
[c] Values at 10^{-5} M; T_3 as 100%.
[d] Nt = not tested.

Table 3
ED values and the potency ratio for **2**, **3**, **29**, **34**, **37**, **43**, and **50** in a cholesterol-fed rat model[a]

Compound	ED_{50} Chol (nmol/kg)	ED_{30} T_4 (nmol/kg)	T_4/Chol[b]
2 (T_3)	5.95	1.87	0.31
3 (Eprotirome)	9.06	25.0	2.8
29 (KTA-439)	21.9	611	28
34	105	997	9.5
37	2.80	85.2	30
43	111	2030	18
50	30.0	388	13

[a] Subcutaneous administration for 2 days. $n = 3$.
[b] Ratio (ED_{30} T_4)/(ED_{50} Chol).

from the inner ring than the malonamic acid **29**, showed improved *h*TRβ potency but no *h*TRβ selectivity. The carbonylaminoacetic acid **43**, which has an inverse CONH to **29**, showed reduced *h*TRβ selectivity. These results suggested that the interaction between COOH of the ligand and Arg-320β plays a central role in *h*TRβ selectivity and that the interaction between NH of the ligand and Asn-331β plays a peripheral role. The COOH–Arg-320β interaction might be more favorable than the COOH–Arg-266α interaction when the ligand has COOH at a similar distance from the inner ring to **29**/**43**. The sulfamoylacetic acid **38**, which replaced NHCO of **29** with $NHSO_2$ and was expected to have a similar COOH–Arg-320β interaction and NH–Asn-331β interaction, showed decreased *h*TRβ potency but slightly retained *h*TRβ selectivity. The methylene compound **50**, which replaced the O-ring spacer of **29** with CH_2 and was also expected to have similar interactions, showed slightly decreased hTRβ potency and selectivity. The ketone **53** also showed decreased *h*TRβ potency. All compounds displayed full agonism in the reporter cell assay. From the results detailed above, we concluded that an indane malonamic acid with an O-ring spacer was the best form with regard to *h*TRβ potency and selectivity.

3.7. In vivo effects of the ligands on a cholesterol-fed rat model

The cholesterol- and T_4-lowering effects of the new compounds were assessed in a cholesterol-fed rat model via subcutaneous administration. The in vivo results are summarized in Table 3. The data are shown as ED_{50} for cholesterol (dose causing 50% greater lowering from the vehicle) and ED_{30} for T_4. The natural ligand T_3 reduced cholesterol and T_4 levels. The potency ratio (obtained by dividing ED_{30} of T_4 by ED_{50} of cholesterol) showed that T_4 lowering was more severe than cholesterol lowering. T_3 effects cholesterol lowering at the liver and T_4 lowering at the pituitary gland. Eprotirome **3** showed similar cholesterol lowering as observed with T_3 and improved the potency ratio; this indicates that **3** was more liver selective than T_3. Surprisingly, **29** and **34** were more selective than **3** for cholesterol lowering versus T_4 lowering. In all compounds, the most potent cholesterol-lowering effect was observed with **37**, which also showed highest liver selectivity (although it was non-selective for *h*TRβ over *h*TRα). Moreover, **43** and **50** showed more liver selectivity than **3**. The results detailed above indicated that the novel indane derivatives were more liver selective than T_3 and **3**.

4. Conclusion

We designed novel thyromimetics with high receptor (TRβ) and organ (liver) selectivity based on the structure of eprotirome (**3**) and molecular modeling. We found that indane derivatives are potent and dual-selective thyromimetics expected to avoid hypothyroidism. The interaction between COOH of the ligand and Arg-320β plays a central role in *h*TRβ selectivity, and the indane structure is the key for high liver selectivity. KTA-439 (**29**), a representative indane derivative, showed the same high human TRβ selectivity in a binding assay as **3** and higher liver selectivity than **3** in a cholesterol-fed rat model.

We expect the novel indane derivatives to be a new generation of thyromimetics for the treatment of dyslipidemia and to have an improved therapeutic window between the lowering of cholesterol and T_4.

5. Experimental

5.1. Chemistry: general

Melting points were taken on a Yanako MP-3S Micro melting point apparatus and were uncorrected. ^1H and ^{13}C NMR spectra were recorded using Bruker Avance II$^+$ 400 or Avance III 600 instruments, and chemical shifts were reported in parts per million (δ) downfield from tetramethylsilane as the internal standard. Peak patterns were shown using the following abbreviations: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. The mass spectra (HRMS) were obtained using an Agilent Technologies 6520 Accurate-Mass Q-TOF instrument. Silica gel $60F_{254}$-precoated glass plates from Merck KgaA or aminopropyl silica gel (APS)-precoated NH plates from Fuji Silysia Chemical Ltd were used for thin layer chromatography (TLC). Flash or medium-pressure liquid chromatography (MPLC) was performed on silica gel BW-350 from Fuji Silysia Chemical Ltd or APS Daisogel IR-60 (particle size, 25–40 μM) from Daiso Co., Ltd. All reagents and solvents were commercially available unless otherwise indicated. Purchased reagents and solvents were used without further purification unless otherwise noted.

5.1.1. 1-Benzyloxy-2-isopropylbenzene (6)

Benzyl bromide (75.2 mL, 632 mmol) and K_2CO_3 (107 g, 774 mmol) were added to a solution of 2-isopropylphenol (87.2 g, 640 mmol) in acetonitrile (500 mL), and the mixture was refluxed for 29 h. The reaction mixture was evaporated under reduced pressure to dryness. After adding water, the mixture was extracted with EtOAc. The organic layer was washed with 1 M NaOH, water, and brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give **6** (142 g, 98%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.24 (6H, d, J = 6.9 Hz), 3.42 (1H, heptet, J = 6.9 Hz), 5.08 (2H, s), 6.88–6.97 (2H, m), 7.12–7.17 (1H, m), 7.22–7.25 (1H, m), 7.30–7.47 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.7, 26.8, 69.9, 111.7, 120.9, 126.1, 126.5, 127.1, 127.7, 128.5, 137.4, 137.6, 155.9; HRMS calcd for $C_{16}H_{19}O$ $(M+H)^+$ 227.1430, found 227.1429.

5.1.2. Bis-(4-benzyloxy-3-isopropylphenyl)iodonium tetrafluoroborate (8)

Fuming nitric acid (80.8 mL, 1754 mmol) was added to Ac_2O (201 mL, 2130 mmol) under ice cooling. Then, iodine (67.4 g, 266 mmol) was added to this reaction mixture. Later, TFA (154 mL, 1999 mmol) was added dropwise. After stirring at room temperature for 1 h, the mixture was evaporated under reduced pressure at <35 °C to dryness. Ac_2O (250 mL) and **6** (141 g, 623 mmol) were then added to the residue. Later, TFA (50 mL) was added dropwise under ice cooling. After stirring at 4 °C for 16 h, the reaction mixture was evaporated under reduced pressure at <35 °C to dryness. MeOH (500 mL), an aqueous solution of potassium metabisulfite (50 g/250 mL), and a 4.5 mol/L aqueous solution of $NaBF_4$ (700 mL) were added to the residue, successively. The mixture was stirred for 30 min. After the precipitate was aggregated, the supernatant was decanted. The residue was dissolved in CH_2Cl_2 (1000 mL), and the organic layer was washed with a 4.5 mol/L aqueous solution of $NaBF_4$ (250 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The residue was triturated with diethyl ether. The insoluble material was collected by filtration to give **8** (146 g, 92%) as a beige solid. Beige solid; mp 152–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20 (12H, d, J = 6.9 Hz), 3.35 (2H, heptet, J = 6.9 Hz), 5.11 (4H, s), 6.95 (2H, d, J = 8.9 Hz), 7.26–7.53 (10H, m), 7.69 (2H, d, J = 2.4 Hz), 7.78 (1H, dd, J = 2.4, 8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.2, 27.5, 70.4, 103.0, 115.1, 127.2, 128.3, 128.8, 132.8, 134.5, 135.8, 142.6, 159.3; HRMS calcd for $C_{32}H_{34}IO_2$ $(M)^+$ 577.1598, found 577.1591.

5.1.3. 2,3,6-Trichloro-4-nitrophenol (11)

To a mixture of 2,3,6-trichlorophenol (3.58 g, 18.1 mmol) and trifluoroacetic acid (TFA) (15 mL), sodium nitrite (4.02 g, 58.2 mmol) was added in small portions. After stirring at room temperature overnight, the mixture was added to ice water (100 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was crystallized from a small amount of EtOAc and hexane to give **11** (3.28 g, 75%) as a beige solid. Beige solid; mp 147–149 °C (dec) (EtOAc–hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.28 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 120.4, 123.1, 125.0, 125.5, 139.7, 154.9; HRMS calcd for $C_6HCl_3NO_3$ $(M-H)^-$ 239.9027, found 239.9029.

5.1.4. 2,3,6-Trimethyl-4-nitrophenol (12)

To a solution of 2,3,6-trimethylphenol (4.61 g, 33.8 mmol) in CH_2Cl_2 (50 mL), nitric acid (60%, 3.10 mL, 40.7 mmol) was added in small portions at 40 °C. After refluxing for 20 min, the mixture was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The residue was crystallized from a small amount of CH_2Cl_2 and hexane to give **12** (2.01 g, 33%) as a beige solid. Beige solid; mp 99–101 °C (CH_2Cl_2–hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.18 (3H, s), 2.21 (3H, s), 2.32 (3H, s), 7.58 (1H, s), 9.41 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.6, 15.6, 16.3, 122.4, 124.1, 124.8, 130.4, 142.4, 157.2; HRMS calcd for $C_9H_{12}NO_3$ $(M+H)^+$ 182.0812, found 182.0811.

5.1.5. 2-(4-Benzyloxy-3-isopropylphenoxy)-1,3,4-trichloro-5-nitrobenzene (13)

To a mixture of **11** (2.45 g, 10.1 mmol) and **8** (7.36 g, 11.1 mmol) in CH_2Cl_2 (35 mL), copper bronze (1.99 g, 31.3 mmol) and ET_3N (2.0 mL, 14.3 mmol) were added at room temperature. The mixture was stirred at room temperature for 5 days. The insoluble materials were removed by filtration. The filtrate was evaporated under reduced pressure to dryness. The residue was purified by column chromatography on silica gel (eluent:hexane/EtOAc 1/0–3/1) to give **13** (3.09 g, 65%) as a beige solid. Beige solid; mp 80–83 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22 (6H, d, J = 6.9 Hz), 3.39 (1H, heptet, J = 6.9 Hz), 5.03 (2H, s), 6.42 (1H, dd, J = 3.1, 8.8 Hz), 6.78 (1H, d, J = 8.8 Hz), 6.89 (1H, d, J = 3.1 Hz), 7.29–7.57 (5H, m), 7.95 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.5, 27.2, 70.6, 111.6, 112.3, 112.8, 114.4, 115.6, 125.0, 127.1, 127.9, 128.6, 128.8, 132.3, 137.3, 139.7, 145.5, 150.1, 152.2; HRMS calcd for $C_{22}H_{19}Cl_3NO_4$ $(M+H)^+$ 466.0374, found 466.0357.

5.1.6. 2-(4-Benzyloxy-3-isopropylphenoxy)-1,3,4-trimethyl-5-nitrobenzene (14)

The title compound was prepared from **12** in a manner similar to that described for **13** as a white solid (65%). White solid; mp 85–87 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20 (6H, d, J = 6.9 Hz), 2.14 (3H, s), 2.15 (3H, s), 2.41 (3H, s), 3.38 (1H, heptet, J = 6.9 Hz), 5.01 (2H, s), 6.28 (1H, dd, J = 3.1, 8.8 Hz), 6.74 (1H, d, J = 8.8 Hz), 6.79 (1H, d, J = 3.1 Hz), 7.28–7.47 (5H, m), 7.58 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.4, 15.8, 16.5, 22.6, 27.1, 70.7, 110.9, 112.6, 113.6, 124.4, 127.1, 127.8, 128.5, 130.3, 130.8, 133.1, 137.5, 139.6, 147.5, 151.0, 151.4, 154.5; HRMS calcd for $C_{25}H_{28}NO_4$ $(M+H)^+$ 406.2013, found 406.2011.

5.1.7. 4-(4-Benzyloxy-3-isopropylphenoxy)-2,3,5-trichloro phenylamine (15)

PtO_2 (38 mg, 0.167 mmol) was added to a solution of **13** (0.790 mg, 1.69 mmol) in EtOAc (30 mL). The mixture was stirred under a hydrogen atmosphere at room temperature for 2 h. Insoluble materials were removed by filtration. The filtrate was evaporated under reduced pressure to dryness to give **15** (0.740 g, 100%) as a colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.70–1.94 (4H, m), 2.04 (6H, s), 2.68–2.95 (4H, m), 3.47 (2H, s), 4.96 (2H, s), 6.02–6.12 (1H, m), 6.38–6.54 (3H, m), 7.20–7.50 (5H,m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.6, 27.2, 70.6, 111.1, 112.3, 113.9, 114.0, 115.6, 117.0, 127.1, 127.7, 128.3, 128.5, 137.6, 139.2, 139.9, 141.5, 151.4, 151.4; HRMS calcd for $C_{22}H_{21}Cl_3NO_2$ $(M+H)^+$ 436.0632, found 436.0631.

5.1.8. Ethyl *N*-[4-(4-benzyloxy-3-isopropylphenoxy)-2,3,5-tri chlorophenyl]malonamate (16)

To a solution of **15** (132 mg, 0.302 mmol) and pyridine (0.046 mL, 0.361 mmol) in CH_2Cl_2 (5 mL), ethyl malonyl chloride (0.046 mL, 0.361 mmol) was added dropwise at 0 °C. The mixture was stirred at room temperature for 3 h. After adding 1 M HCl (5 mL), the reaction mixture was extracted with EtOAc. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 19/1–1/1) to give **16** (157 mg, 94%) as a colorless amorphous solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.21 (6H, d, J = 6.9 Hz), 1.35 (3H, t, J = 7.1 Hz), 3.36 (1H, heptet, J = 6.9 Hz), 3.56 (2H, s), 4.31 (2H, q, J = 7.1 Hz), 5.02 (2H, s), 6.41 (1H, dd, J = 3.1, 8.9 Hz), 6.76 (1H, d, J = 8.9 Hz), 6.87 (1H, d, J = 3.1 Hz), 7.29–7.47 (5H, m), 8.60 (1H, s), 10.06 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.1, 22.5, 27.2, 41.4, 62.3, 70.6, 111.3, 112.3, 112.8, 114.0, 120.7, 121.7, 127.2, 127.8, 128.5, 129.3, 133.1, 137.5, 139.3, 144.6, 150.9, 151.6, 163.3, 169.7; HRMS calcd for $C_{27}H_{27}Cl_3NO_5$ $(M+H)^+$ 550.0949, found 550.0951.

5.1.9. Ethyl *N*-[2,3,5-trichloro-4-(4-hydroxy-3-isopropylphen oxy)phenyl]malonamate (17)

16 (153 mg, 0.278 mmol) was dissolved in a mixed solvent of TFA/water /Me_2S (95/5/10, 3 mL). The mixture was allowed to stand at room temperature overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 19/1–0/1) to give **17** (97 mg, 76%) as a colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (6H, d, J = 6.9 Hz), 1.35 (3H, t, J = 7.1 Hz), 3.18 (1H, heptet, J = 6.9 Hz), 3.56 (2H, s), 4.30 (2H, q, J = 7.1 Hz), 4.88 (1H, s), 6.37 (1H, dd, J = 3.0, 8.7 Hz), 6.63 (1H, d, J = 8.7 Hz), 6.81 (1H, d,

J = 3.0 Hz), 8.58 (1H, s), 10.07 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.4, 27.4, 41.4, 62.3, 112.0, 113.9, 115.7, 120.8, 121.8, 128.6, 129.3, 133.0, 136.2, 144.7, 148.3, 150.9, 163.4, 169.7; HRMS calcd for $C_{20}H_{21}Cl_3NO_5$ $(M+H)^+$ 460.0480, found 460.0490.

5.1.10. *N*-[2,3,5-Trichloro-4-(4-hydroxy-3-isopropylphenoxy) phenyl]malonamic acid (18)

To a solution of **17** (74 mg, 161 mmol) in MeOH (5 mL), an aqueous solution of 1 M NaOH (5 mL) was added. The mixture was stirred under an argon atmosphere at 50 °C for 30 min. After adding 1 M HCl (5 mL) and brine (10 mL), the mixture was extracted twice with EtOAc (10 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH = 1/0–9/1) to give **18** (32 mg, 46%) as a white solid. White solid; mp 143–146 °C (dec) (EtOH–H_2O); ^{1}H NMR (600 MHz, DMSO-d_6) δ: 1.13 (6H, d, J = 6.9 Hz), 3.15 (1H, heptet, J = 6.9 Hz), 6.30 (1H, dd, J = 3.0, 8.7 Hz), 6.68 (1H, d, J = 8.7 Hz), 6.72 (1H, d, J = 3.0 Hz), 8.53 (1H, br s), 9.16(1H, br s), 12.95 (1H, br s); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 22.3, 26.6, 43.9, 111.2, 112.9, 115.3, 120.6, 121.7, 126.9, 128.3, 134.9, 135.8, 142.8, 149.2, 149.8, 168.7, 169.8; HRMS calcd for $C_{18}H_{17}Cl_3NO_5$ $(M+H)^+$ 432.0167, found 432.0176.

5.1.11. 4-(4-Amino-2,3,6-trimethylphenoxy)-2-isopropylphenol (19)

To a solution of **14** (10.9 g, 27.0 mmol) in EtOAc (100 mL), 10% Pd/C (50% wet with water, 10.5 g, 4.93 mmol) was added. The mixture was stirred under a hydrogen atmosphere at room temperature overnight. Insoluble materials were removed by filtration and washed with CH_2Cl_2/MeOH. The filtrate was evaporated under reduced pressure to dryness to give **19** (7.51 g, 97%) as a beige solid. Beige solid; mp 180–182 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD) δ: 1.20 (6H, d, J = 6.8 Hz), 2.02 (3H, s), 2.05 (3H, s), 2.08 (3H, s), 3.20 (1H, heptet, J = 6.8 Hz), 6.23 (1H, dd, J = 3.0, 8.7 Hz), 6.52 (1H, d, 8.7 Hz), 6.73 (1H, d, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ: 13.1, 13.2, 16.4, 22.6, 27.2, 111.1, 113.1, 115.3, 115.5, 120.3, 129.2, 130.6, 136.2, 140.6, 144.4, 147.4, 152.5; HRMS calcd for $C_{18}H_{24}NO_2$ $(M+H)^+$ 286.1802, found 286.1803.

5.1.12. *N*-[4-(4-Hydroxy-3-isopropylphenoxy)-2,3,5-trimethyl phenyl]malonamic acid (20)

Ethyl *N*-[4-(4-hydroxy-3-isopropylphenoxy)-2,3,5-trimethylphenl]malonamate was prepared from **19** in a manner similar to that described for **16**. The title compound was obtained from ethyl *N*-[4-(4-hydroxy-3-isopropylphenoxy)-2,3,5-trimethylphenyl]malonamate in a manner similar to that described for **18** as a beige solid (41%, two steps). Beige solid; mp 95–98 °C (dec) (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD) δ: 1.19 (6H, d, J = 6.9 Hz), 2.07 (6H, s), 2.18 (3H, s), 3.24 (1H, heptet, J = 6.9 Hz), 3.49 (2H, s), 6.21 (1H, dd, J = 3.0, 8.6 Hz), 6.63 (1H, d, J = 8.6 Hz), 6.71 (1H, d, J = 3.0 Hz), 7.40 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ: 13.3, 14.2, 16.5, 22.5, 27.2, 40.3, 111.3, 113.3, 115.4, 124.4, 129.1, 129.4, 131.1, 131.2, 136.4, 147.8, 149.5, 151.8, 165.0, 171.4; HRMS calcd for $C_{21}H_{26}NO_5$ $(M+H)^+$ 372.1805, found 372.1806.

5.1.13. 5-Bromoindan-4-ol (22b)

Diisopropylamine (2.55 mL, 18.1 mmol) was added to a solution of **21** (24.2 g, 180 mmol) in CH_2Cl_2 (200 mL). To this solution, *N*-bromosuccinimide (32.1 g, 180 mmol) was added in small portions under ice cooling, and the mixture was stirred at room temperature overnight. Dilute H_2SO_4 (pH 1, 200 mL) was added to the reaction mixture, and the mixture was separated. The organic layer was washed with water and brine, successively, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent:hexane/EtOAc = 1/0–1/1) to give **22b** (31.1 g, 81%) as a white solid. White solid; mp 66–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.05–2.16 (2H, m), 2.83–2.95 (4H, m), 5.45 (1H, s), 6.69 (1H, d, J = 8.0 Hz), 7.22 (1H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.2, 21.7, 22.6, 25.0, 26.7, 27.2, 70.6, 111.0, 112.4, 113.9, 114.8, 126.9, 127.2, 127.8, 25.4, 29.9, 33.1, 107.3, 117.7, 129.8, 131.1, 146.5, 148.4; HRMS calcd for C_9H_8BrO $(M-H)^-$ 210.9764, found 210.9765.

5.1.14. 5-Methyl-7-nitroindan-4-ol (24a)

To a solution of **22a**[21] (8.68 g, 58.6 mmol) in AcOH (80 mL), nitric acid (60%, 4.50 mL, 59.1 mmol) was added over 5 min under ice cooling. After stirring for 5 min at 0 °C, the mixture was stirred at room temperature. The solvent was removed under reduced pressure. The residue was crystallized from a small amount of CH_2Cl_2 and hexane to give **24a** (2.19 g, 19%) as a beige solid. Beige solid; mp 172–174 °C (EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.15–2.25 (2H, m), 2.29 (3H, s), 2.85–2.95 (2H, m), 3.55–3.45 (2H, m), 5.19 (1H, br s), 7.90 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.3, 24.8, 28.8, 34.8, 122.9, 126.0, 131.0, 138.7, 141.8, 155.2; HRMS calcd for $C_{10}H_{12}NO_3$ $(M+H)^+$ 194.0812, found 194.0808.

5.1.15. 5-Bromo-7-nitroindan-4-ol (24b)

The title compound was prepared from **22b** in a manner similar to that described for **24a** as a beige solid (34%). Beige solid; mp 148–149 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.13–2.26 (2H, m), 2.95–3.02 (2H, m), 3.36–3.43 (2H, m), 6.04 (1H, s), 8.25 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.6, 30.0, 34.8, 107.6, 127.0, 133.2, 139.1, 143.9, 153.2; HRMS calcd for $C_9H_9BrNO_3$ $(M+H)^+$ 257.9760, found 257.9754.

5.1.16. 2-Bromo-4-nitro-5,6,7,8-tetrahydronaphthalen-1-ol (25)

The title compound was prepared from **23**[22] in a manner similar to that described for **24a** as a beige solid (60%). Beige solid; mp 95–96 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.70–1.90 (4H, m), 2.70–2.80 (2H, m), 2.95–3.05 (2H, m), 6.03 (1H, s), 8.06 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.3, 21.9, 24.5, 27.2, 106.1, 126.0, 127.2, 135.2, 143.1, 153.9; HRMS calcd for $C_{10}H_9BrNO_3$ $(M-H)^-$ 269.9771, found 269.9772.

5.1.17. 4-(4-Benzyloxy-3-isopropylphenoxy)-5-methyl-7-nitroindane (26a)

The title compound was prepared from **24a** in a manner similar to that described for **13** as a white solid (68%). White solid; mp 86–87 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20 (6H, d, J = 6.9 Hz), 2.05 (2H, t, J = 7.5 Hz), 2.25 (3H, s), 2.64 (2H, t, J = 7.6 Hz), 3.30–3.50 (3H, m), 5.03 (2H, s), 6.44 (1H, dd, J = 8.8, 3.1 Hz), 6.70–6.90 (2H, m), 7.25–7.50 (5H, m), 7.96 (1H, d, J = 0.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.1, 22.6, 24.9, 27.0, 30.4, 34.3, 70.7, 112.5, 112.7, 114.5, 125.7, 127.2, 127.8, 128.5, 130.7, 137.4, 139.3, 139.5, 141.6, 141.8, 151.1, 151.3, 154.8; HRMS calcd for $C_{26}H_{28}NO_4$ $(M+H)^+$ 418.2013, found 418.2012.

5.1.18. 4-(4-Benzyloxy-3-isopropylphenoxy)-5-bromo-7-nitroindane (26b)

The title compound was prepared from **24b** in a manner similar to that described for **13** as a pale yellow solid (19%). Pale yellow solid; mp 117–118 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20 (6H, d, J = 6.9 Hz), 2.02–2.11 (2H, m), 2.63–2.70 (2H, m), 3.32–3.43 (3H, m), 5.05 (2H, s), 6.49 (1H, dd, J = 3.0, 8.8 Hz), 6.78 (1H, d, J = 8.8 Hz), 6.86 (1H, d, J = 3.0 Hz), 7.30–7.47 (5H, m), 8.34 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.6, 24.7, 27.1, 31.0, 34.4, 70.6, 112.5, 113.1, 114.7, 115.1, 127.2, 127.8, 128.1, 128.6, 137.3, 139.5, 140.7, 142.0, 143.6, 150.5, 151.8, 153.6; HRMS calcd for $C_{25}H_{23}BrNO_4$ $(M-H)^-$ 480.0816, found 480.0817.

5.1.19. 5-(4-Benzyloxy-3-isopropylphenoxy)-6-bromo-8-nitro-1,2,3,4-tetrahydronaphthalene (27)

The title compound was prepared from **25** in a manner similar to that described for **13** as a beige solid (19%). Beige solid; mp 65–

67 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21 (6H, d, J = 6.9 Hz), 1.65–1.80 (4H, m), 2.60–2.70 (2H, m), 2.90–3.00 (2H, m), 3.36 (1H, heptet, J = 6.9 Hz), 5.02 (2H, s), 6.35 (1H, dd, J = 3.1, 8.9 Hz), 6.76 (1H, d, J = 8.9 Hz), 6.83 (6H, d, J = 3.1 Hz), 7.25–7.45 (5H, m), 8.05 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.2, 21.7, 22.6, 25.0, 26.7, 27.2, 70.6, 111.0, 112.4, 113.9, 114.8, 126.9, 127.2, 127.8, 128.5, 134.1, 136.0, 137.5, 139.6, 146.9, 150.5, 151.5, 153.6; HRMS calcd for $C_{26}H_{27}BrNO_4$ $(M+H)^+$ 498.1101, found 498.1076.

5.1.20. 4-(7-Amino-5-methylindan-4-yloxy)-2-isopropylphenol (28)

The title compound was prepared from **26a** in a manner similar to that described for **19** as a beige solid (100%). Beige solid; mp 174–175 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD) δ: 1.19 (6H, d, J = 6.9 Hz), 1.98–2.10 (2H, m), 2.08 (3H, s), 2.62–2.74 (4H, m), 3.22 (1H, heptet, J = 6.9 Hz), 6.33 (1H, dd, J = 3.0, 8.7 Hz), 6.43 (1H, s), 6.57 (1H, d, J = 8.7 Hz), 6.73 (1H, d, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ: 16.1, 22.6, 25.2, 27.1, 30.7, 30.8, 54.2, 112.2, 113.9, 115.4, 124.3, 128.2, 130.6, 136.6, 138.6, 139.0, 148.5, 148.7, 151.3, 165.6; HRMS calcd for $C_{19}H_{24}NO_2$ $(M+H)^+$ 298.1802, found 298.1805.

5.1.21. *N*-[7-(4-Hydroxy-3-isopropylphenoxy)-6-methylindan-4-yl]malonamic acid (29)

The title compound was prepared from **28** in a manner similar to that described for **20** as a white solid (80%). White solid; mp 122–125 °C (dec) (EtOH–H_2O); ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD) δ: 1.19 (6H, d, J = 7.0 Hz), 1.95–2.10 (2H, m), 2.16 (3H, s), 2.60–2.70 (2H, m), 2.80–2.90 (2H, m), 3.22 (1H, heptet, J = 7.0 Hz), 3.48 (2H, s), 6.33 (1H, dd, J = 3.0, 8.8 Hz), 6.59 (1H, d, J = 8.8 Hz), 6.75 (1H, d, J = 3.0 Hz), 7.64 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD) δ: 16.1, 22.5, 25.0, 27.1, 30.3, 30.4, 40.4, 112.2, 113.8, 115.4, 122.4, 129.5, 130.0, 135.1, 136.3, 137.5, 147.2, 148.0, 151.7, 164.2, 171.6; HRMS calcd for $C_{22}H_{26}NO_5$ $(M+H)^+$ 384.1805, found 384.1801.

5.1.22. 7-(4-Benzyloxy-3-isopropylphenoxy)-6-bromoindan-4-ylamine (30)

The title compound was prepared from **26b** in a manner similar to that described for **15** as a white solid (100%). White solid; mp 86–89 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.19 (6H, d, J = 6.9 Hz), 2.00–2.10 (2H, m), 2.64–2.71 (4H, m), 3.36 (1H, heptet, J = 6.9 Hz), 3.53 (2H, br s), 5.00 (2H, s), 6.45 (1H, dd, J = 3.0, 8.8 Hz), 6.75 (1H, d, J = 8.8 Hz), 6.77 (1H, s), 6.85 (1H, d, J = 3.0 Hz), 7.27–7.46 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.7, 24.7, 27.1, 29.8, 30.9, 70.7, 111.8, 112.5, 114.1, 114.8, 117.0, 127.2, 127.7, 128.5, 130.3, 137.7, 138.9, 139.3, 140.1, 140.9, 150.8, 152.1; HRMS calcd for $C_{25}H_{27}BrNO_2$ $(M+H)^+$ 452.1220, found 452.1229.

5.1.23. 4-(4-Benzyloxy-3-isopropylphenoxy)-3-bromo-5,6,7,8-tetrahydronaphthalen-1-ylamine (31)

The title compound was prepared from **27** in a manner similar to that described for **15** as a white solid (88%). White solid; mp 199–201 °C (EtOAc–hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.20 (6H, d, J = 7.0 Hz), 1.60–1.85 (4H, m), 2.35–2.45 (2H, m), 2.50–2.60 (2H, m), 3.36 (1H, heptet, J = 7.0 Hz), 3.55 (2H, s), 5.00 (2H, s), 6.39 (1H, dd, J = 2.8, 8.8 Hz), 6.74 (1H, d, J = 8.8 Hz), 6.81 (1H, s), 6.83 (1H, d, J = 2.8 Hz), 7.25–7.50 (5H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 21.9, 22.2, 22.7, 24.3, 24.7, 27.1, 70.6, 110.9, 112.4, 113.6, 114.4, 115.8, 122.8, 127.2, 127.7, 128.5, 133.6, 137.8, 139.0, 141.8, 142.3, 150.7, 152.1; HRMS calcd for $C_{26}H_{29}BrNO_2$ $(M+H)^+$ 466.1376, found 466.1371.

5.1.24. Ethyl *N*-[6-bromo-7-(4-hydroxy-3-isopropylphenoxy) indan-4-yl]malonamate (32)

The title compound was prepared from **30** in a manner similar to that described for **16** as a beige solid (100%). Beige solid; mp 112–114 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20 (6H, d, J = 7.0 Hz), 1.34 (3H, t, J = 7.3 Hz), 2.00–2.15 (2H, m), 2.65–2.75 (2H, m), 2.80–2.95 (2H, m), 3.37 (1H, heptet, J = 7.0 Hz), 3.50 (2H, s), 4.27 (2H, q, J = 7.3 Hz), 5.01 (2H, s), 6.46 (1H, dd, J = 3.0, 9.0 Hz), 6.75 (1H, d, J = 9.0 Hz), 6.86 (1H, d, J = 3.0 Hz), 8.26 (1H, br s), 9.37 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.6, 24.8, 27.1, 30.3, 31.0, 40.9, 62.1, 70.7, 112.2, 112.5, 114.4, 114.8, 123.5, 127.2, 127.7, 128.5, 131.1, 135.9, 137.6, 138.8, 139.1, 145.4, 151.1, 151.5, 162.7, 170.5; HRMS calcd for $C_{30}H_{33}BrNO_5$ $(M+H)^+$ 566.1537, found 566.1540.

5.1.25. Ethyl *N*-[4-(4-benzyloxy-3-isopropylphenoxy)-3-bromo-5,6,7,8-tetrahydronaphthalen-1-yl]malonamate (33)

The title compound was prepared from **31** in a manner similar to that described for **16** as a white solid (64%). White solid; mp 121–122 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21 (6H, d, J = 6.8 Hz), 1.34 (3H, t, J = 7.3 Hz), 1.60–1.85 (4H, m), 2.55–2.70 (4H, m), 3.37 (1H, heptet, J = 6.8 Hz), 3.52 (2H, s), 4.28 (2H, q, J = 6.8 Hz), 5.00 (2H, s), 6.38 (1H, dd, J = 3.0, 8.8 Hz), 6.74 (1H, d, J = 8.8 Hz), 6.84 (1H, d, J = 3.0 Hz), 7.25–7.50 (5H, m), 8.21 (1H, s), 9.32 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 21.7, 22.1, 22.6, 24.7, 24.7, 27.1, 41.1, 62.1, 70.6, 111.0, 112.4, 113.8, 114.6, 123.8, 127.2, 127.7, 128.5, 129.0, 133.2, 133.7, 137.7, 139.2, 146.7, 150.9, 151.4, 162.9, 170.6; HRMS calcd for $C_{31}H_{35}BrNO_5$ $(M+H)^+$ 580.1693, found 580.1700.

5.1.26. *N*-[6-Bromo-7-(4-hydroxy-3-isopropylphenoxy)indan-4-yl]malonamic acid (34)

Ethyl *N*-[6-bromo-7-(4-hydroxy-3-isopropylphenoxy)indan-4-yl]malonamate was prepared from **32** in a manner similar to that described for **17**. The title compound was obtained from ethyl *N*-[6-bromo-7-(4-hydroxy-3-isopropylphenoxy)indan-4-yl]malonamate in a manner similar to that described for **18** as a white solid (32%, 2 steps). White solid; mp 182–184 °C (dec) (EtOH–H_2O); ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD) δ: 1.19 (6H, d, J = 6.8 Hz), 1.95–2.10 (2H, m), 2.60–2.75 (2H, m), 2.80–2.90 (2H, m), 3.23 (1H, heptet, J = 6.8 Hz), 3.48 (2H, s), 6.38 (1H, dd, J = 3.0, 8.7 Hz), 6.62 (1H, d, J = 8.7 Hz), 6.77 (1H, d, J = 3.0 Hz), 8.10 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ: 22.8, 25.1, 27.3, 30.7, 31.3, 40.8, 113.0, 114.5, 114.8, 115.6, 124.5, 130.9, 136.8, 137.2, 139.2, 146.2, 149.1, 151.1, 164.8, 171.9; HRMS calcd for $C_{21}H_{21}BrNO_5$ $(M-H)^-$ 446.0609, found 446.0613.

5.1.27. *N*-[3-Bromo-4-(4-hydroxy-3-isopropylphenoxy)-5,6,7,8-tetrahydronaphthalen-1-yl]malonamic acid (35)

The title compound was obtained from **33** in a manner similar to that described for **34** as a white solid (86%). White solid; mp 124–126 °C (dec) (EtOH–H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.12 (6H, d, J = 7.0 Hz), 1.55–1.75 (4H, m), 2.45–2.65 (4H, m), 3.15 (1H, heptet, J = 7.0 Hz), 3.43 (2H, s), 6.21 (1H, dd, J = 3.0, 8.8 Hz), 6.65 (6H, d, J = 8.8 Hz), 6.67 (1H, d, J = 3.3 Hz), 7.69 (1H, s), 8.96 (1H, s), 9.51 (1H, s), 12.70 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.3, 21.4, 22.3, 24.2, 24.4, 26.5, 43.1, 110.9, 112.6, 113.0, 115.3, 125.7, 132.1, 133.1, 133.7, 135.7, 146.3, 149.1, 149.5, 164.9, 169.5; HRMS calcd for $C_{22}H_{25}BrNO_5$ $(M+H)^+$ 462.0911, found 462.0896.

5.1.28. Ethyl *N*-[7-(4-hydroxy-3-isopropylphenoxy)-6-methylindan-4-yl]oxamate (36)

Diethyl oxalate (1.35 g, 9.20 mmol) was added to **28** (274 mg, 0.920 mmol), and the mixture was stirred under an argon

atmosphere at 110 °C for 2 h. The reaction mixture was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 19/1–0 /1) to give **36** (318 mg, 87%) as a white solid. White solid; mp 117–119 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21 (6H, d, J = 6.9 Hz), 1.44 (3H, t, J = 7.1 Hz), 2.00–2.15 (2H, m), 2.17 (3H, s), 2.60–2.75 (2H, m), 2.80–2.95 (2H, m), 3.10–3.25 (1H, m), 4.42 (2H, q, J = 7.1 Hz), 4.65–4.85 (1H, br s), 6.35 (1H, dd, J = 8.6, 3.0 Hz), 6.60 (1H, d, J = 8.6 Hz), 6.76 (1H, d, J = 3.0 Hz), 7.78 (1H, s), 8.69 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 16.2, 22.5, 25.0, 27.3, 30.1, 30.4, 63.7, 112.3, 113.9, 115.8, 121.8, 128.6, 130.4, 134.6, 136.0, 137.8, 147.4, 147.6, 152.0, 153.7, 161.2; HRMS calcd for $C_{23}H_{28}NO_5$ $(M+H)^+$ 398.1962, found 398.1966.

5.1.29. *N*-[7-(4-Hydroxy-3-isopropylphenoxy)-6-methylindan-4-yl]oxamic acid (37)

The title compound was obtained from **36** in a manner similar to that described for **18** as a white solid (86%). White solid; mp 143–144 °C (EtOH–H_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22 (6H, d, J = 7.0 Hz), 2.00–2.15 (2H, m), 2.20 (3H, s), 2.65–2.75 (2H, m), 2.85–2.95 (2H, m), 3.17 (1H, heptet, J = 7.0 Hz), 6.36 (1H, dd, J = 3.0, 8.5 Hz), 6.60 (1H, d, J = 8.5 Hz), 6.76 (1H, d, J = 3.0 Hz), 7.74 (1H, s), 8.78 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.2, 22.5, 25.0, 27.3, 30.0, 30.5, 112.4, 113.9, 115.8, 121.6, 127.7, 130.6, 135.0, 136.1, 138.1, 147.4, 148.2, 151.9, 154.6, 160.1; HRMS calcd for $C_{21}H_{24}NO_5$ $(M+H)^+$ 370.1649, found 370.1649.

5.1.30. [7-(4-Hydroxy-3-isopropylphenoxy)-6-methylindan-4-ylsulfamoyl]acetic acid (38)

Ethyl [7-(4-hydroxy-3-isopropylphenoxy)-6-methylindan-4-ylsulfamoyl]acetate was prepared from **28** and ethyl (chlorosulfonyl)acetate in a manner similar to that described for **16**. The title compound was obtained from ethyl [7-(4-hydroxy-3-isopropylphenoxy)-6-methylindan-4-ylsulfamoyl]acetate in a manner similar to that described for **18** as a beige solid (65%, 2 steps). Beige solid; mp 139–143 °C (dec) (EtOH–H_2O); ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD) δ: 1.15 (6H, d, J = 6.8 Hz), 1.90-2.05 (2H, m), 2.11 (3H, s), 2.55-2.65 (2H, m), 2.85-2.95 (2H, m), 3.21 (1H, heptet, J = 6.8 Hz), 4.00 (2H, s), 6.28 (1H, dd, J = 3.0, 8.8 Hz), 6.59 (1H, d, J = 8.8 Hz), 6.70 (1H, d, J = 3.0 Hz), 7.11 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ: 16.1, 22.6, 25.2, 27.1, 30.7, 30.8, 54.2, 112.2, 113.9, 115.4, 124.3, 128.2, 130.6, 136.6, 138.6, 139.0, 148.5, 148.7, 151.3, 165.6; HRMS calcd for $C_{21}H_{26}NO_6S$ $(M+H)^+$ 420.1475, found 420.1459.

5.1.31. 7-(4-Benzyloxy-3-isopropylphenoxy)-6-methylindan-4-ylamine (39)

The title compound was obtained from **26a** in a manner similar to that described for **15** as a beige solid (79%). Beige solid; mp 78–80 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.19 (6H, d, J = 6.9 Hz), 1.98–2.10 (2H, m), 2.08 (3H, s), 2.63–2.75 (4H, m), 3.36 (1H, heptet, J = 6.9 Hz), 3.45 (2H, br s), 5.00 (2H, s), 6.41 (1H, s), 6.41 (1H, dd, J = 3.0, 8.9 Hz), 6.73 (1H, d, J = 8.9 Hz), 6.81 (1H, d, J = 3.0 Hz), 7.27–7.45 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.9, 22.7, 25.0, 27.1, 29.7, 30.3, 70.8, 111.4, 112.6, 113.8, 115.5, 127.2, 127.7, 128.4, 128.5, 129.9, 137.7, 137.8, 138.8, 138.9, 142.3, 150.3, 152.9; HRMS calcd for $C_{26}H_{30}NO_2$ $(M+H)^+$ 388.2271, found 388.2271.

5.1.32. 7-(4-Benzyloxy-3-isopropylphenoxy)-6-methylindan-4-carboxylic acid (40)

Concentrated HCl (50 mL), water (100 mL), and toluene (60 mL) were added to **39** (6.78 g, 17.5 mmol). The mixture was heated to form a hydrochloride salt and then cooled using an ice bath. After adding an aqueous solution of $NaNO_2$ (1.33 g, 19.2 mmol) in water (20 mL), the mixture was stirred under ice cooling for 5 min. After adding an aqueous solution of KI (29.0 g, 175 mmol) in water (50 mL), the reaction mixture was stirred at room temperature for 10 min and then at 100 °C for 10 min. After adding an aqueous solution of sodium sulfite (4 g/40 mL) under ice cooling, the reaction mixture was extracted with EtOAc. The organic layer was washed with water, a saturated aqueous solution of $NaHCO_3$, and brine, successively, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give a crude iodo compound. The mixture of the crude product (8.89 g), $Zn(CN)_2$ (1.45 g, 12.3 mmol), bis(dibenzylidenacetone)palladium (200 mg, 0.348 mmol), 1,1′-bis(diphenylphosphino)ferrocene (400 mg, 0.721 mmol), and 1-methyl-2-pyrrolidone (30 mL) was stirred under an argon atmosphere at 80 °C overnight. The mixture was partitioned between water and EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 1/0–1/1) to give a crude cyano compound. NaOH (9.42 g, 236 mmol) was added to a solution of the crude product (6.69 g) in EtOH (50 mL). The reaction mixture was refluxed under an argon atmosphere for 3 days and evaporated under reduced pressure to dryness. The residue was neutralized with 1 M HCl. After adding water, the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The residue was crystallized from a small amount of CH_2Cl_2 and hexane to give **40** (4.17 g, 57%) as a beige solid. Beige solid; mp 154–155 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20 (6H, d, J = 6.9 Hz), 1.97–2.10 (2H, m), 2.22 (3H, s), 2.59–2.68 (2H, m), 3.26–3.34 (2H, m), 3.38 (1H, heptet, J = 6.9 Hz), 5.02 (2H, s), 6.44 (1H, dd, J = 3.0, 8.8 Hz), 6.76 (1H, d, J = 8.8 Hz), 6.82 (1H, d, J = 3.0 Hz), 7.30–7.50 (5H, m), 7.86 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.9, 22.7, 25.0, 27.0, 29.9, 34.2, 70.7, 112.3, 112.7, 114.4, 121.5, 127.2, 127.8, 128.5, 129.3, 132.6, 137.6, 137.9, 139.3, 148.7, 151.0, 151.5, 154.4, 171.3; HRMS calcd for $C_{27}H_{29}O_4$ $(M+H)^+$ 417.2060, found 417.2067.

5.1.33. Ethyl {[7-(4-benzyloxy-3-isopropylphenoxy)-6-methylindan-4-carbonyl]amino}acetate (41)

To a solution of **40** (1.15 g, 2.76 mmol) in DMF (15 mL), HOBt (423 mg, 2.76 mmol), EDCI (795 mg, 4.14 mmol), glycine ethyl ester HCl (578 mg, 4.14 mmol), and ET_3N (1.15 mL, 8.28 mmol) were added under ice cooling. The reaction mixture was stirred at room temperature for 2 days. After adding 1 M HCl, the reaction mixture was extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 19/1–1/1) to give **41** (1.32 g, 95%) as a beige solid. Beige solid; mp 100–102 °C (EtOAc–hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.20 (6H, d, J = 6.9 Hz), 1.33 (3H, t, J = 7.1 Hz), 1.97–2.07 (2H, m), 2.20 (3H, s), 2.58–2.66 (2H, m), 3.16–3.21 (2H, m), 3.37 (1H, heptet, J = 6.9 Hz), 4.24 (2H, d, J = 4.9 Hz), 4.27 (2H, q, J = 7.1 Hz), 5.02 (2H, s), 6.42 (1H, dd, J = 3.0, 8.8 Hz), 6.47 (1H, t, J = 4.9 Hz), 6.75 (1H, d, J = 8.8 Hz), 6.80 (1H, d, J = 3.0 Hz), 7.30–7.46 (6H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.2, 15.9, 22.7, 25.5, 27.1, 29.9, 33.2, 41.9, 61.7, 70.7, 112.1, 112.7, 114.2, 127.1, 127.2, 127.7, 128.5, 129.0, 129.4, 137.6, 138.1, 139.2, 143.8, 150.9, 151.7, 152.3, 168.3, 170.3; HRMS calcd for $C_{31}H_{36}NO_5$ $(M+H)^+$ 502.2588, found 502.2597.

5.1.34. Ethyl {[7-(4-hydroxy-3-isopropylphenoxy)-6-methylindan-4-carbonyl]amino}acetate (42)

The title compound was obtained from **41** in a manner similar to that described for **17** as a beige amorphous solid (53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21 (6H, d, J = 6.9 Hz), 1.32 (3H, t, J = 7.1 Hz), 1.97–2.07 (2H, m), 2.18 (3H, s), 2.57–2.64 (2H, m),

3.13–3.23 (3H, m), 4.24 (2H, d, J = 5.0 Hz), 4.27 (2H, q, J = 7.1 Hz), 4.98 (1H, s), 6.33 (1H, dd, J = 3.0, 8.6 Hz), 6.49 (1H, t, J = 5.0 Hz), 6.59 (1H, d, J = 8.6 Hz), 6.75 (1H, d, J = 3.0 Hz), 7.43 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 15.9, 22.5, 25.5, 27.3, 29.9, 33.2, 41.9, 61.7, 112.6, 114.0, 115.8, 127.1, 129.0, 129.4, 136.1, 138.1, 143.8, 147.5, 151.7, 152.3, 168.3, 170.3; HRMS calcd for $C_{24}H_{30}NO_5$ $(M+H)^+$ 412.2118, found 412.2125.

5.1.35. {[7-(4-Hydroxy-3-isopropylphenoxy)-6-methylindan-4-carbonyl]amino}acetic acid (43)

The title compound was obtained from **42** in a manner similar to that described for **18** as a white solid (79%). White solid; mp 145–147 °C (EtOAc–hexane); ^{1}H NMR (600 MHz, DMSO-d_6) δ: 1.11 (6H, d, J = 7.0 Hz), 1.85–1.95 (2H, m), 2.13 (3H, s), 2.45–2.55 (2H, m), 3.00–3.10 (2H, m), 3.16 (1H, heptet, J = 7.0 Hz), 3.88 (2H, d, J = 5.8 Hz), 6.31 (1H, dd, J = 3.0, 8.7 Hz), 6.66 (1H, d, J = 8.7 Hz), 6.67 (1H, d, J = 3.0 Hz), 7.42 (1H, s), 8.41 (1H, t, J = 5.8 Hz), 8.99 (1H, br s); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 15.6, 22.3, 24.9, 26.5, 29.5, 32.5, 41.1, 112.4, 113.4, 115.4, 127.6, 127.8, 128.7, 135.6, 136.8, 144.0, 149.1, 149.9, 151.4, 167.5, 171.4; HRMS calcd for $C_{22}H_{26}NO_5$ $(M+H)^+$ 384.1805, found 384.1808.

5.1.36. 4-Benzyloxy-3-isopropylbenzaldehyde (44)

To a solution of **6** (2.27 g, 10.0 mmol) and dichloromethyl methyl ether (1.80 mL, 20.0 mmol) in CH_2Cl_2 (30 mL), $TiCl_4$ (2.20 mL, 20.0 mmol) was added dropwise under ice cooling with stirring. The reaction mixture was stirred at room temperature under an argon atmosphere for 3.5 h. After adding ice water (300 mL), the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and brine, successively, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 1/0–1/1) to give **44** (1.75 g, 69%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.27 (6H, d, J = 6.9 Hz), 3.42 (1H, heptet, J = 6.9 Hz), 5.18 (2H, s), 7.01 (1H, d, J = 8.4 Hz), 7.33–7.47 (5H, m), 7.69 (1H, dd, J = 2.1, 8.4 Hz), 7.80 (1H, d, J = 2.1 Hz), 9.88 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 22.4, 26.9, 70.2, 111.3, 127.2, 127.4, 128.2, 128.7, 129.9, 130.4, 136.4, 138.3, 161.1, 191.4; HRMS calcd for $C_{17}H_{19}O_2$ $(M+H)^+$ 255.1380, found 255.1385.

5.1.37. 4-Iodo-5-methyl-7-nitroindane (45)

To a solution of **24a** (2.78 g, 14.4 mmol) and pyridine (3.15 mL, 38.9 mmol) in CH_2Cl_2 (20 mL), Tf_2O (3.15 mL, 18.7 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 25 min. After adding water and 1 M HCl, the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give a crude product (4.40 g). LiI (2.20 g, 14.5 mmol) was added to a solution of the crude product (1.09 g, 3.35 mmol) in DMF (3 mL). The mixture was stirred under an argon atmosphere at 140 °C for 14 h. After adding water, the reaction mixture was extracted with EtOAc. The organic layer was washed with a 1 M NaOH, water, and brine, successively, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give **45** (0.949 mg, 87%, 2 steps) as a beige solid. Beige solid; mp 115–116 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.12–2.20 (2H, m), 2.51 (3H, s), 3.00–3.06 (2H, m), 3.52–3.57 (2H, m), 7.84 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.3, 27.9, 35.6, 40.3, 108.5, 122.1, 137.2, 141.3, 153.2, 168.4; HRMS calcd for $C_{10}H_{11}INO_2$ $(M+H)^+$ 303.9829, found 303.9835.

5.1.38. 7-Iodo-6-methylindan-4-ylamine (46)

The title compound was obtained from **45** in a manner similar to that described for **15** as a beige solid (90%). Beige solid; mp 103–104 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.90–2.05 (2H, m), 2.20 (3H, s), 2.70–2.85 (4H, m), 5.18 (2H, br s), 6.42 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.8, 27.2, 31.0, 40.0, 83.2, 114.0, 125.9, 138.2, 143.8, 148.3; HRMS calcd for $C_{10}H_{13}IN$ $(M+H)^+$ 274.0087, found 274.0091.

5.1.39. Dibenzyl(7-iodo-6-methylindan-4-yl)amine (47)

To a solution of **46** (1.70 g, 6.22 mmol) in DMF (15 mL), Cs_2CO_3 (4.46 g, 13.7 mmol) and benzyl bromide (1.63 mL, 13.7 mmol) were added. The mixture was stirred at room temperature overnight. The mixture was partitioned between water and EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was crystalized from a small amount of EtOAc and hexane to give **47** (1.16 g, 41%) as a white solid. White solid; mp 124–125 °C (EtOAc–hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.02–2.10 (2H, m), 2.29 (3H, s), 2.89–2.94 (2H, m), 3.12–3.16 (2H, m), 4.18 (4H, s), 6.60 (1H, s), 7.19–7.31 (10H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 24.3, 28.0, 33.9, 40.1, 55.4, 91.8, 119.5, 127.0, 128.2, 128.3, 134.3, 138.5, 139.4, 147.6, 150.4; HRMS calcd for $C_{24}H_{25}IN$ $(M+H)^+$ 454.1026, found 454.1030.

5.1.40. (4-Benzyloxy-3-isopropylphenyl)-(7-dibenzylamino-5-methylindan-4-yl)methanol (48)

To a solution of **47** (585 mg, 1.29 mmol) in dry THF (10 mL), a 1.48 mol/L solution of t-BuLi in n-pentane (1.30 mL, 1.89 mmol) was added at −100 °C. The mixture was stirred for 15 min. The solution of **44** (328 mg, 1.29 mmol) in THF (5 mL) was added. The reaction mixture was stirred at ambient temperature for 15 min and then warmed to room temperature. After adding a saturated aqueous solution of NH_4Cl and brine, the mixture was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on APS (eluent: hexane/EtOAc =19/1–1/1) to give **48** (536 mg, 71%) as a colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.14–1.21 (6H, m), 1.90–2.05 (3H, m), 2.17 (3H, s), 2.65–2.72 (1H, m), 2.90–2.96 (3H, m), 3.34–3.43 (1H, m), 4.20 (4H, s), 5.06 (2H, s), 6.10–6.14 (1H, m), 6.53 (1H, s), 6.82 (1H, d, J = 8.5 Hz), 6.94–6.98 (1H, m), 7.15–7.45 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.1, 22.7, 25.9, 27.0, 31.7, 32.8, 55.3, 70.1, 72.1, 111.3, 120.9, 124.2, 126.8, 127.1, 127.7, 128.2, 128.3, 128.5, 128.7, 130.8, 134.7, 135.2, 135.3, 136.9, 137.6, 138.8, 145.0, 147.0, 154.7; HRMS calcd for $C_{41}H_{44}NO_2$ $(M+H)^+$ 582.3367, found 582.3365.

5.1.41. 4-(7-Amino-5-methylindan-4-ylmethyl)-2-isopropylphenol (49)

To a solution of **48** (100 mg, 0.172 mmol) in EtOH (10 mL), 2 M HCl (1 mL) and 10% Pd/C (50% wet with water, 40 mg, 0.0188 mmol) were added. The mixture was stirred under a hydrogen atmosphere at 50 °C overnight. Insoluble materials were removed by filtration. The filtrate was evaporated under reduced pressure to dryness. After adding a saturated aqueous solution of $NaHCO_3$ and brine, the mixture was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc) to give **49** (16 mg, 32%) as a white solid. White solid; mp 160–162 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.12 (6H, d, J = 7.0 Hz), 1.85–2.00 (2H, m), 2.06 (3H, s), 2.55–2.75 (4H, m), 3.16 (1H, heptet, J = 7.0 Hz), 4.52 (2H, br s), 6.27 (1H, s), 6.55 (1H, dd, J = 1.8, 8.3 Hz), 6.63 (1H, d, J = 8.3 Hz), 6.88 (1H, d, J = 1.8 Hz), 8.93 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.2, 22.5, 24.3, 26.5, 29.5, 31.9, 34.3, 114.2, 114.7, 123.1, 124.9, 125.3, 125.6, 131.2, 133.6, 134.2, 141.9, 143.6, 152.1; HRMS calcd for $C_{20}H_{26}NO$ $(M+H)^+$ 296.2009, found 296.2003.

5.1.42. *N*-[7-(4-Hydroxy-3-isopropylbenzyl)-6-methylindan-4-yl]malonamic acid (50)

The title compound was obtained from **49** in a manner similar to that described for **20** as a white solid (93%). White solid; mp 162–165 °C (dec) (EtOH–H_2O); ^{1}H NMR (600 MHz, DMSO-d_6) δ: 1.11 (6H, d, J = 7.0 Hz), 1.90–2.00 (2H, m), 2.15 (3H, s), 2.75–2.85 (4H, m), 3.12 (1H, heptet, J = 7.0 Hz), 3.79 (2H, s), 6.50–6.65 (2H, m), 6.85–6.95 (1H, m), 7.29 (1H, s), 8.98 (1H, s), 9.40 (1H, s), 12.51 (1H, br s); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 19.2, 22.5, 24.4, 26.4, 30.5, 31.8, 34.6, 43.2, 114.8, 122.2, 125.3, 125.8, 129.9, 131.6, 131.7, 133.2, 133.8, 134.1, 144.1, 152.3, 164.2, 169.6; HRMS calcd for $C_{23}H_{28}NO_4$ (M+H)$^+$ 382.2013, found 382.2015.

5.1.43. (4-Benzyloxy-3-isopropylphenyl)-(7-dibenzylamino-5-methylindan-4-yl)methanone (51)

Manganese (IV) oxide (2.98 g, 34.2 mmol) was added to a solution of **48** (497 mg, 0.854 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 3 days. Insoluble materials were removed by filtration. The filtrate was evaporated under reduced pressure to dryness to give **51** (436 mg, 88%) as a pale yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.24 (6H, d, J = 6.9 Hz), 1.93–2.03 (2H, m), 2.06 (3H, s), 2.59–2.67 (2H, m), 2.92–2.99 (2H, m), 3.39 (1H, heptet, J = 6.9 Hz), 4.28 (4H, s), 5.14 (2H, s), 6.54 (1H, s), 6.88 (1H, d, J = 8.6 Hz), 7.22–7.46 (15H, m), 7.53 (1H, dd, J = 2.1, 8.6 Hz), 7.83 (1H, d, J = 2.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.7, 22.5, 26.0, 27.0, 32.0, 32.4, 55.0, 70.1, 110.7, 119.3, 126.9, 127.1, 127.7, 128.0, 128.2, 128.3, 128.7, 129.9, 130.2, 130.9, 133.3, 133.9, 136.7, 137.6, 138.6, 143.8, 148.4, 160.2, 198.8; HRMS calcd for $C_{41}H_{42}NO_2$ (M+H)$^+$ 580.3210, found 580.3201.

5.1.44. (7-Amino-5-methylindan-4-yl)-(4-hydroxy-3-isopropylphenyl)methanone (52)

To a solution of **51** (436 mg, 0.752 mmol) in THF (100 mL), 10% Pd/C (50% wet with water, 436 mg, 0.205 mmol) was added. The mixture was stirred under a hydrogen atmosphere at room temperature overnight. Insoluble materials were removed by filtration and washed with CH_2Cl_2/MeOH. The filtrate was evaporated under reduced pressure to dryness to give **52** (136 mg, 58%) as a pale yellow solid. Pale yellow solid; mp 220–223 °C (THF–CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$+CD_3OD) δ: 1.22 (6H, d, J = 6.9 Hz), 1.97–2.05 (2H, m), 2.10 (3H, s), 2.58–2.73 (4H, m), 3.27 (1H, heptet, J = 6.9 Hz), 6.40 (1H, s), 6.73 (1H, d, J = 8.4 Hz), 7.43 (1H, dd, J = 2.1, 8.4 Hz), 7.74 (1H, d, J = 2.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$+CD_3OD) δ: 19.6, 22.4, 25.1, 27.0, 29.0, 32.5, 114.7, 114.7, 126.4, 127.6, 128.7, 130.1, 130.3, 135.2, 135.4, 143.0, 143.7, 159.6, 199.7; HRMS calcd for $C_{20}H_{24}NO_2$ (M+H)$^+$ 310.1802, found 310.1803.

5.1.45. *N*-[7-(4-Hydroxy-3-isopropylbenzoyl)-6-methylindan-4-yl]malonamic acid (53)

The title compound was obtained from **52** in a manner similar to that described for **20** as a white solid (57% 2 steps). White solid; mp 162–165 °C (dec) (EtOH–H_2O); ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD) δ: 1.22 (6H, d, J = 6.9 Hz), 1.98–2.07 (2H, m), 2.15 (3H, s), 2.64–2.69 (2H, m), 2.83–2.90 (2H, m), 3.27 (1H, heptet, J = 6.9 Hz), 3.50 (2H, s), 6.73 (1H, d, J = 8.3 Hz), 7.37 (1H, dd, J = 1.9, 8.3 Hz), 7.73 (1H, s), 7.78 (1H, d, J = 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ: 19.3, 22.2, 24.9, 26.9, 29.6, 32.0, 40.4, 114.7, 120.6, 128.2, 129.0, 130.3, 132.1, 133.4, 133.6, 134.0, 135.7, 142.6, 160.0, 164.5, 171.5, 198.9; HRMS calcd for $C_{23}H_{26}NO_5$ (M+H)$^+$ 396.1805, found 396.1813.

5.2. Biology

5.2.1. Receptor binding assay

Recombinant *h*TRα_1 and *h*TRβ_1 were expressed in insect cells.[23] Each cell homogenate containing the respective receptors was mixed with appropriate concentrations of test compounds. L-3,5,3′-[^{125}I]-triiodothyronine ([^{125}I]-T_3, 0.95 nM, 160 Ci/mmol, [^{125}I]-T_3(NEN) was diluted with L-3,5,3′-triiodothyronine (Sigma) in a buffer containing 0.4 M KC1, 1 mM $MgCl_2$, 10 mM Tris–HCl, and 1 mM dithiothreitol (pH 8.0). Each 0.5 mL of the mixture was incubated in a glass tube in an ice bath for 16–48 h. At the end of incubation, 500 μL of an ion-exchange resin (Muromachi Kagaku, Dowex 1-X8, 80 mg/mL, suspended in the abovementioned buffer) was added to each test tube and stirred. Stirring was repeated after sedimentation of the resin at the bottom of the tube, followed by further stirring. The tubes were centrifuged at 1000 rpm for 5 min at 1 °C using a centrifuge separator (KUBOTA, 8800). A portion of the supernatant (500 μL) was transferred to another tube, and the radioactivity was measured using a γ-ray detector. The radioactivity detected reflected the quantity of [^{125}I]-T_3 bound to the soluble thyroid hormone receptor. The amount of the recombinant thyroid hormone receptor cell homogenate in the experiment was used in a range in which the radioactivity of T_3 binding showed a concentration-dependent increase in the amount of the homogenate.

The K_d value of T_3 to the respective receptor subtype was determined according to the Scatchard analysis of the binding data obtained in the various [^{125}I]-T_3 levels. The K_d values of T_3 to *h*TRα_1 and *h*TRβ_1 were 0.268 nM and 0.304 nM, respectively, under these experimental conditions.

The K_i values of each compound were calculated using the following equation: $K_i(\mathrm{nM}) = [\mathrm{IC}_{50}]/(1 + K_d/0.95)$.

where IC_{50} represents the concentration of the compound that inhibits [^{125}I]-T_3 binding by 50%.

5.2.2. Luciferase reporter gene assay

*h*TRα_1[24] and *h*TRβ_1[25] were cloned into a mammalian cell expression vector (pCDM8, Promega) as described previously.[26] The luciferase reporter gene was constructed by inserting the thyroid hormone responsive element (5′-GATCCAGGTCATGACCTGGATCC-3′) into the commercial luciferase expression vector (pGL2-promoter, Promega). Each thyroid hormone receptor vector and the luciferase reporter vector were cotransfected into trypsin-digested and suspended COS1 cells using the calcium phosphate-mediated method.[27] The cells were seeded into 96-well multiwell plates and cultured overnight. On the next day, thyromimetics were added to the culture and cultured for 1 day. Luciferase activities were measured using a commercial kit (Luciferase Assay System, Promega) and Top count (Packard) on the third day.

5.2.3. Cholesterol- and T_4-lowering activities

High-cholesterol diets (CE2, 1.5% cholesterol, 0.5% cholic acid, CLEA Japan) were fed to 5-week-old male Wistar rats for 1 week beforehand. Test compounds (3–30,000 nmol/kg) dissolved in a vehicle containing 5% ethanol (Wako Pure Chemical) and 0.5% sodium carboxymethylcellulose (Wako Pure Chemical) were subcutaneously (5 mL/kg) administered to the rats once daily for 2 days. The rats were continuously fed the high-cholesterol diets during the treatment. On the next day of dosing (i.e., the final day of dosing), whole blood was collected from the abdominal aorta under ether anesthesia. Serum was obtained by centrifugation of clotted blood.

Serum cholesterol levels were determined using a commercial kit (Cholesterol C-test Wako, Wako Pure Chemical). The mean serum cholesterol level in rats fed a normal diet (CLEA Japan, CE2) was subtracted from that in vehicle-treated rats fed a high-cholesterol diet, and the difference was regarded to be 100%. The dosage that lowered the serum cholesterol level by 50% is shown as ED_{50} in Table 3.

Serum T_4 levels were determined using a commercial kit (T_4 'Eiken', Eiken Chemical). The mean serum T_4 level in rats fed a normal

diet (CLEA Japan, CE2) was subtracted from that in vehicle-treated rats fed a high-cholesterol diet, and the difference was regarded to be 100%. The dosage that lowered the serum T_4 level by 30% is shown as ED_{30} in Table 3.

5.3. Molecular modeling

Coordinates of hTRα_1 and hTRβ_1 were retrieved from the Protein Data Bank (PDB); the PDB codes are 2H79 and 3GWS, respectively.[18] The docking model of **3** was constructed from the crystal structure observed in the complex between hTRβ_1 and T_3 (PDB code: 3GWS) using Discovery Studio 3.1 (Accelrys Inc., San Diego, CA, USA).[28]

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