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Design, synthesis, and structure–activity relationship (SAR) of *N*-[7-(4-hydroxyphenoxy)-6-methylindan-4-yl]malonamic acids as thyroid hormone receptor β (TRβ) selective agonists

Hiroaki Shiohara [a,*], Tetsuya Nakamura [a], Norihiko Kikuchi [a], Tomonaga Ozawa [a], Akane Matsuzawa [a], Ryuichi Nagano [a], Hideki Ohnota [a], Takahide Miyamoto [b], Kazuo Ichikawa [c], Kiyoshi Hashizume [d]

[a] Central Research Laboratory, Kissei Pharmaceutical Co., Ltd, 4365-1, Kashiwabara, Hotaka, Azumino-city, Nagano 399-8304, Japan
[b] Miyamoto Clinic, 1-6, Ryojima, Matsumoto-city, Nagano 390-0848, Japan
[c] Ichikawa Clinic, 1548-2, Minamiminowa-Village, Kamiina-County, Nagano 399-4598, Japan
[d] Matsumoto Dental University Hospital, Shiojiri-city, Nagano 399-0781, Japan

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ABSTRACT

Highly TRβ selective thyromimetics have several potential therapeutic applications. Based on the novel indane derivative KTA-439 with high receptor (TRβ) and organ (liver) selectivity, a series of thyroid hormone analogues were prepared, in which the isopropyl at the 3′-position was replaced with alkyl and aralkyl moieties of variable lengths and branches. Binding assays for these human TRs and reporter cell assays showed that 2-arylethyl derivatives had higher TRβ selectivity than KTA-439. KTA-574, a representative 2-arylethyl derivative, had TRβ specificity in a binding assay and exhibited full agonism in a reporter cell assay.

1. Introduction

Thyroid hormones (THs) affect the growth, development, and metabolism of most tissues.[1–3] The active endogenous thyroid hormone 3,5,3′-triiodo-L-thyronine (T_3; **1** in Fig. 1) was anticipated to be a potent lipid-lowering agent, although it cannot be used therapeutically for patients with dyslipidemias or those who are obese or have metabolic syndrome because of its side effect of tachycardia.[4]

There are two major subtypes of thyroid hormone receptors (TRs), α (TRα) and β (TRβ), which are encoded for by two different genes.[1] Differential processing of ribonucleic acid (RNA) results in the formation of several isoforms of each gene. TRα$_1$, TRβ$_1$, and TRβ$_2$ isoforms bind to THs and act as ligand-regulated transcription factors.[5] The TRβ$_1$ isoform is prevalent particularly in the liver and to a lesser 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, although 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 heart rate and rhythm) are mediated through the activation of the TRα$_1$ isoform, whereas most of the actions of these hormones on the liver (e.g., lipid-lowering effects) and other tissues are mediated through the activation of the TRβ$_1$ isoform.[8]

Thyromimetics that specifically target TRβ have been shown to reduce plasma cholesterol levels and prevent atherosclerosis by promoting reverse cholesterol transport in an animal model. These compounds may be useful as complements to statin therapy for preventing cardiovascular disease.[8–13] One report suggested that TRβ was a critical TR isoform for T_3-induced proliferation of hepatocytes and pancreatic acinar cells.[14] Recently, a thyroid hormone receptor β subtype-selective thyromimetic was found to be efficacious in both mouse and monkey hair growth models after topical applications.[15] These reports suggested that highly TRβ selective thyromimetics have potential therapeutic applications.

We previously found that novel indane derivatives **2a**–**2e** had higher organ (liver) selectivity than eprotirome (**3**). *N*-[7-(4-Hydroxy-3-isopropylphenoxy)-6-methylindan-4-yl] malonamic acid (KTA-439, **2a**), a representative indane derivative, exhibited higher liver selectivity than **3** in a cholesterol-fed rat model and had the same high human TRβ selectivity as **3** in a binding assay.[16] We sought to improve the TRβ selectivity of **2a**. Thus, in the present study, we investigated the SARs for *N*-[7-(4-hydroxyphenoxy)-6-methylindan-4-yl] malonamic acids. We describe our discovery process for a TRβ-specific agonist.

* Corresponding author. Tel.: +81 (0)263 82 8820; fax: +81 (0)263 82 8827.
E-mail address: hiroaki_shiohara@pharm.kissei.co.jp (H. Shiohara).

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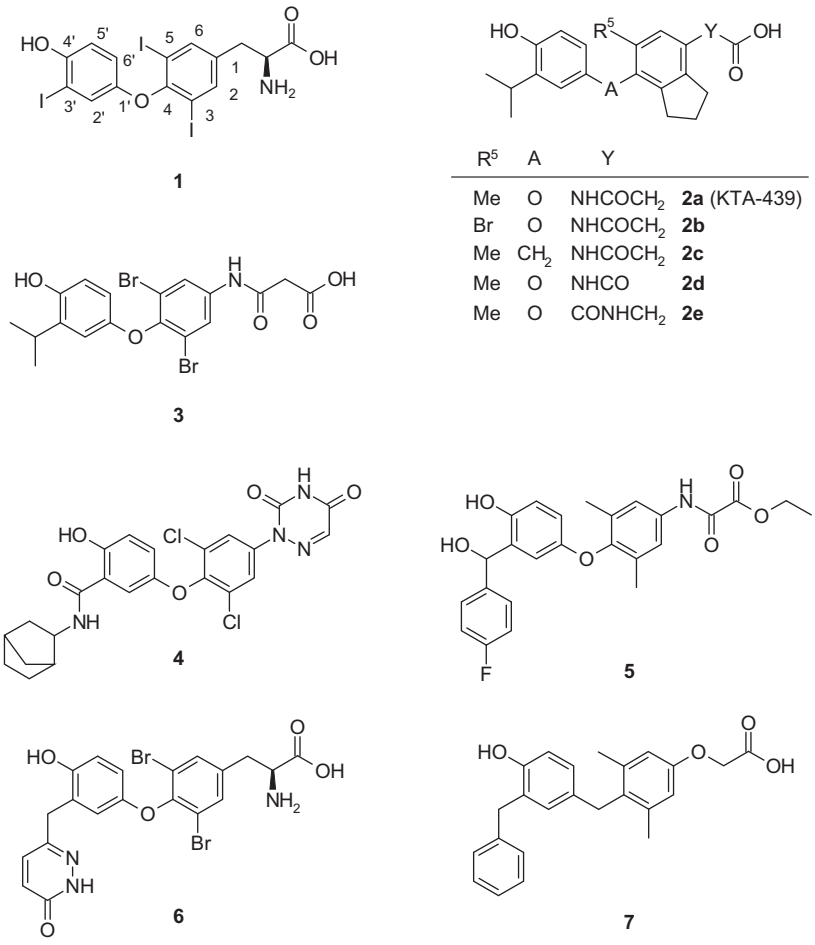


R^5	A	Y	
Me	O	$NHCOCH_2$	**2a** (KTA-439)
Br	O	$NHCOCH_2$	**2b**
Me	CH_2	$NHCOCH_2$	**2c**
Me	O	NHCO	**2d**
Me	O	$CONHCH_2$	**2e**

Figure 1. Structures of T_3 (**1**), previously reported indane derivatives (**2a**–**2e**), eprotirome (**3**), reported benzamide (**4**), axitirome (**5**), L-94901 (**6**), and GC-24 (**7**).

2. Strategy

It has been shown that substituent modifications on the outer ring of the biphenyl ether skeleton can result in enhanced TRβ selectivity. Benzamide **4**[17] with a bulky moiety at its 3′-position reportedly was 105-fold more TRβ-selective compared with TRα, although its amide moiety appeared to be metabolically labile. Liver-selective axitirome (**5**)[18] and L-94901 (**6**)[19] also have steric bulk moieties at their 3′-positions as does TRβ-selective GC-24 (**7**),[20] which has a benzyl moiety at its 3′-position. We speculated that these liver-selective compounds **5** and **6** might also be TRβ selective. Thus, we focused on designing indane derivatives based on **2a**, in which the isopropyl at the 3′-position was replaced with either alkyl, aralkyl including α-OH-4-F-benzyl, or 3-[6-oxo-1, 6-dihydropyridazin-3-yl]methyl.

3. Results and discussion

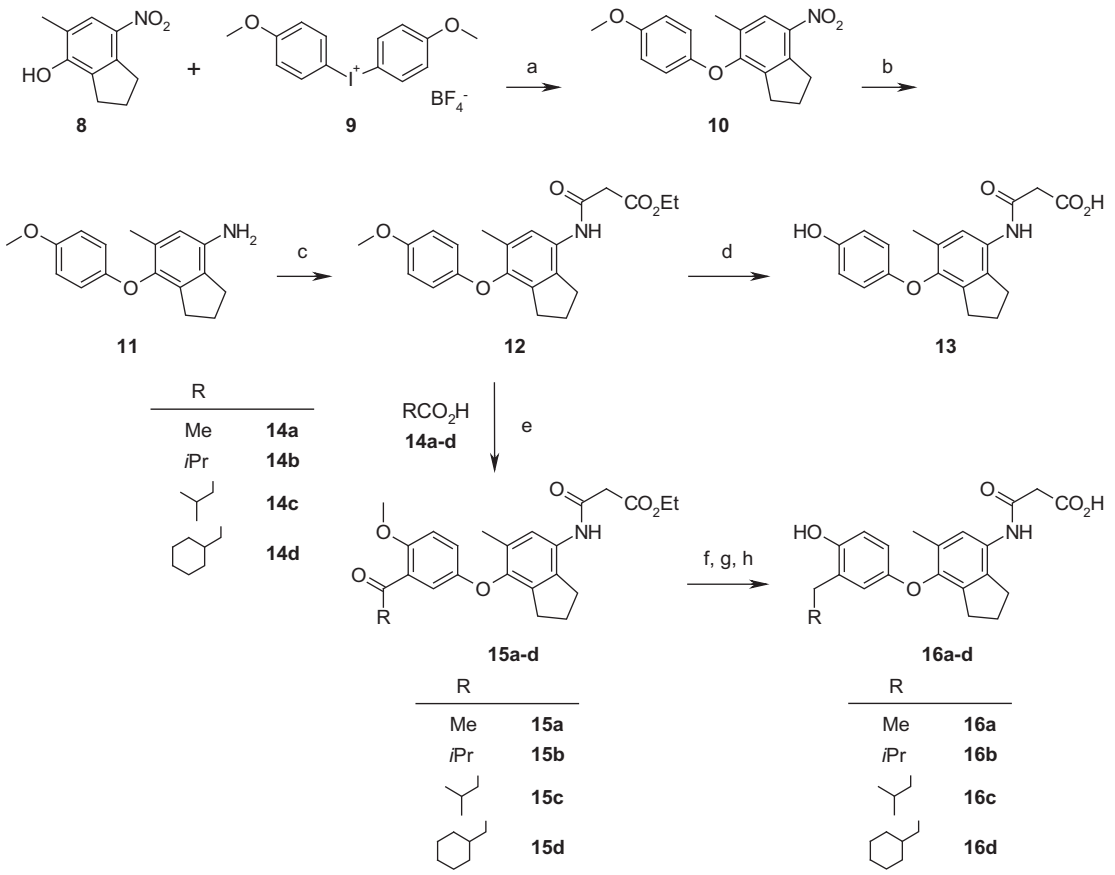
3.1. Synthesis of indane derivatives with alkyl substituents at their 3′-positions

As outlined in Scheme 1, four indane derivatives with alkyl substituents at their 3′-positions were prepared. The nitro compound **8**[16] was coupled with salt **9**[18] to give ether **10**. Nitro group reduction with H_2/Pd gave aniline **11**, which when coupled with ethyl malonyl chloride gave anilide **12**. Demethylation and hydrolysis with BBr_3 gave 3′-H ligand **13**. Dehydrative Friedel–Crafts acylation of **12** with the carboxylic acids **14a–d** in the presence of Tf_2O[21] gave ketones **15a–d**. Demethylation, reduction, and hydrolysis gave the final target ligands **16a–d**.

3.2. In vitro effects on TRs of indane derivatives with an alkyl substituent at their 3′-positions

Table 1 summarizes the results of a radioligand binding assay for *h*TRα and *h*TRβ and a reporter cell assay using COS1 cells stably transfected with *h*TRα or *h*TRβ and a luciferase reporter gene downstream thyroid response element.

The natural ligand T_3 bound to *h*TRα and *h*TRβ with K_i values of 2.29 and 2.33 nM, respectively. The 3′-H compound **13** was weakly, but moderately selective for *h*TRβ compared with *h*TRα in terms of binding. When the hydrogen atom at the 3′-position was replaced with an ethyl and an *i*Pr group (**16a**, **2a**), the binding affinities increased for both isoforms, which resulted in high *h*TRβ selectivity. The *i*Pr compound **2a** was more *h*TRβ-selective than ethyl compound **16a**. Compounds **16b** and **16c**, which had elongated *i*Pr moieties with methylene and ethylene, exhibited high *h*TRβ selectivity. When a cyclohexyl group was added at the 2-ethyl of **16a** (**16d**), the binding affinities increased for both isoforms, resulting in high *h*TRβ selectivity. Compound **13** exhibited partial agonism, whereas the other compounds had full agonism in a reporter cell assay, except for the most bulky **16d** that exhibited full agonism to TRLuc-β and partial agonism to TRLuc-α.



Scheme 1. Synthetic route for preparing **16a–d**. Reagents and conditions: (a) Cu, Et_3N, CH_2Cl_2, 5 days; (b) H_2/Pd-C, EtOAc; (c) $ClCOCH_2CO_2Et$, pyridine, CH_2Cl_2, 0 °C; (d) BBr_3, CH_2Cl_2; (e) Tf_2O, CH_2Cl_2; (f) BCl_3, CH_2Cl_2; (g) Et_3SiH, TFA, CH_2Cl_2; and (h) NaOH, MeOH.

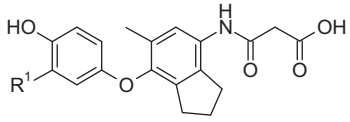
3.3. Synthesis of indane derivatives with *p*-fluorobenzyl and 3-[6-oxo-1,6-dihydropyridazin-3-yl]methyl at their 3′-positions

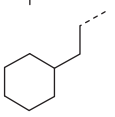
We attempted to synthesize indane derivatives with α-OH-4-F-benzyl moiety in a manner similar to that described for **5**. However, this moiety was so acid labile that the desired acid was decomposed by itself (data not shown). Thus, we prepared a 4-F-benzyl compound rather than a α-OH-4-F-benzyl compound. The preparation of this compound and a 3-[6-oxo-1,6-dihydropyridazin-3-yl] methyl compound is outlined in Scheme 2. Benzylation of known **17** gave benzyl ether **18**, which was treated with $(CF_3CO_2)_3I$ prepared from I_2 to give iodonium salt **19**.[14] Nitro compound **8** was coupled with **19** to give ether **20**. Nitro group reduction and debenzylation of **20** with H_2/Pd gave aniline **21**. Coupling **21** with ethyl malonyl chloride and alkaline hydrolysis gave target ligand **22**. Coupling **8** with known **23**,[22] hydrolysis, and demethylation gave oxopyridazine **24**. Nitro group reduction of **24** gave aniline **25**. Coupling **25** with ethyl malonyl chloride and alkaline hydrolysis gave target ligand **26**.

3.4. Design and synthesis of indane derivatives with an aralkyl moiety at their 3′-positions

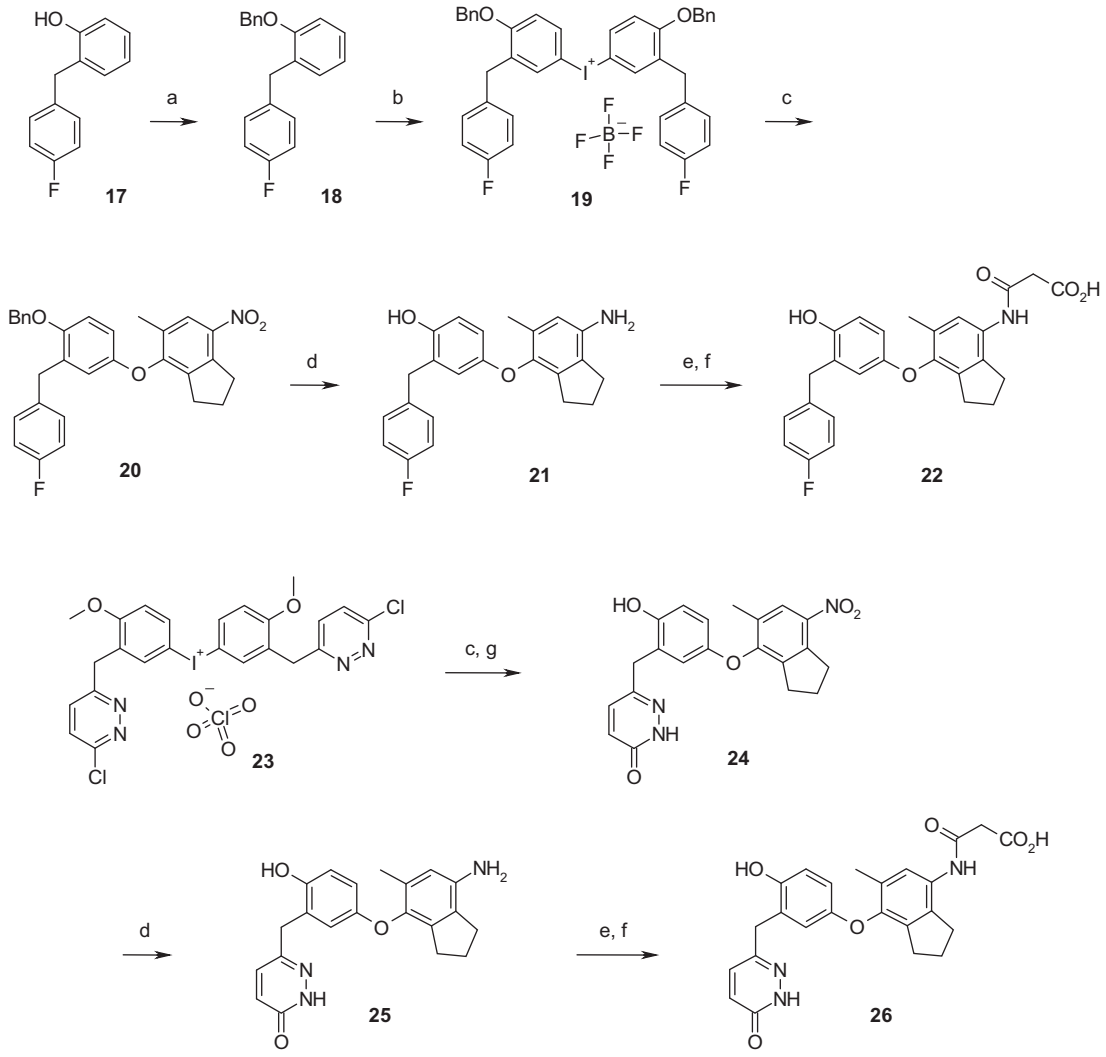
Because indane derivatives with a bulky alkyl moiety at their 3′-positions had high *h*TRβ potency and selectivity, we designed and synthesized other indane derivatives with aralkyl moieties to obtain additional SAR information, as outlined in Scheme 3. Acylation of **12** with carboxylic acids **27a–c** gave ketones **28a–c**. Demethylation of **28a** gave phenol **29**, which was hydrolyzed to give ketone ligand **30**. Reduction of **29** with $NaBH(OAc)_3$ and hydrolysis gave the acid stable α-OH ligand **31**. Demethylation, reduction, and hydrolysis of **28a–c** gave the final target ligands **32a–c**.

Table 1
Thyroid hormone receptor binding affinities (K_i) and reporter cell line potency efficacies (% agonism) of compounds **1**, **2a**, **13**, **16a–c**, and **16d**



Compounds	R^1	K_i[a] (nM)		α/β[b]	% Agonism[c]	
		*h*TRβ	*h*TRα		TRLuc-β	TRLuc-α
1		2.29	2.33	1	100	100
13	H	1662	>10000	>6	62	47
16a	Et	53.6	710	13	99	96
2a[d]	*i*Pr	7.82	172	22	113	110
16b		39.9	1431	36	109	96
16c		31.7	503	16	94	94
16d		17.0	429	25	73	48

[a] Values are means of two experiments. The variability was 25% on average.
[b] Selectivity (K_i *h*TRα)/(K_i *h*TRβ).
[c] Values at 10^{-5} M; T_3 set at 100%.
[d] Ref. 16.



Scheme 2. Synthetic route for preparing **22** and **26**. Reagents and conditions: (a) BnBr, Cs_2CO_3, DMF; (b) (i) $(CF_3CO_2)_3I$, CH_2Cl_2; (ii) $NaBF_4$; MeOH; (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) (i) NaOAc; and (ii) HBr, AcOH.

3.5. In vitro effects of ligands on TRs

The in vitro results for indane derivatives with an aralkyl moiety at their 3′-positions are summarized in Table 2. The 4-F-benzyl ligand **22** had high affinity for *h*TRβ and moderate *h*TRβ selectivity, which was less than that of **5**. Interestingly, although amino acid **6** with a 3-[6-oxo-1,6-dihydropyridazin-3-yl] methyl moiety had high *h*TRα affinity and moderate *h*TRα selectivity, ligand **26** with the same moiety had high *h*TRβ affinity and moderate *h*TRβ selectivity. This suggested that the indane skeleton strongly preferred *h*TRβ over *h*TRα.

When a phenyl group was added at the 2-ethyl of **16a** (**32a**), the binding affinity for *h*TRβ increased slightly and decreased for *h*TRα, which resulted in high *h*TRβ selectivity. Compound **32b** that had an elongated 4-F-benzyl moiety with the methylene of **22** also improved *h*TRβ selectivity. It is noteworthy that this is the first report on *h*TRβ-selective thyromimetics with phenethyl moieties. Substituting the OH group at the α-position of **32a** as in **31** negatively affected both subtypes' affinities. Ketone **30** and the phenylpropyl compound **32c** both exhibited decreased subtype affinity and efficacy. Based on these results, we focused on the 2-arylethyl group at the 3′-position to improve *h*TRβ selectivity.

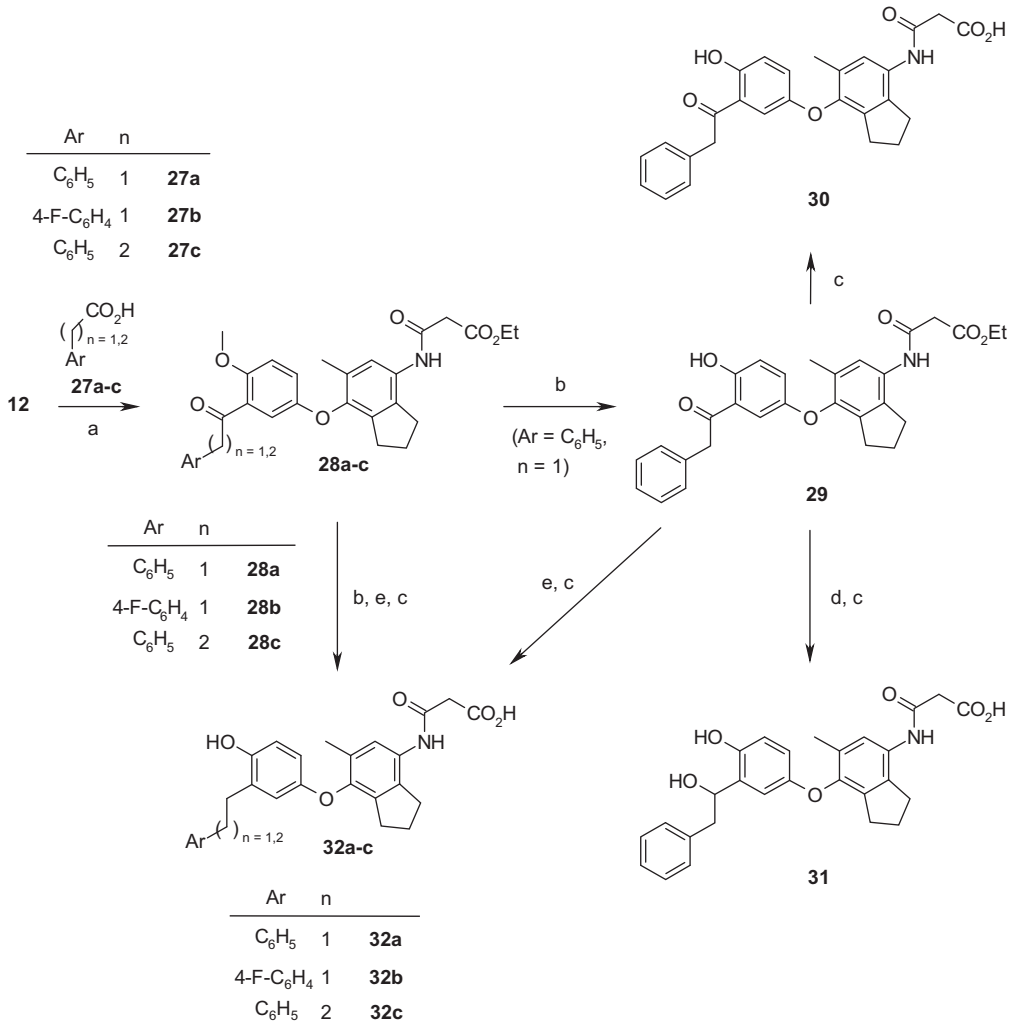
3.6. Design and synthesis of indane derivatives with a 2-arylethyl moiety at their 3′-positions

Finally, we designed and synthesized indane derivatives with a 2-arylethyl moiety to obtain additional SAR information as outlined in Scheme 4. Acylation of **12** with carboxylic acids **33a–e** and reduction gave ethers **34a–e**. Coupling **34a–e** with ethyl malonyl chloride and alkaline hydrolysis gave target ligands **35a–e**.

Dehydrative Friedel–Crafts acylations of **12** with methoxyphenylacetic acids were not successful because these acids reacted with themselves. Thus, we synthesized **40a–c** as follows. Phenyl ether **10** was treated with $Cl_2CHOCH_3/TiCl_4$ to give aldehyde **36**. A Wittig reaction with **37a–c** and reduction of the nitro group and olefin with H_2/Pd gave anilines **38a–c**. Coupling **38a–c** with ethyl malonyl chloride gave esters **39a–c**, which were demethylated and hydrolyzed to give target ligands **40a–c**.

3.7. In vitro effects on TRs of the indane derivatives with a 2-arylethyl moiety at their 3'-positions

The in vitro results for indane derivatives with a 2-arylethyl moiety at their 3′-positions are summarized in Table 3. Introducing



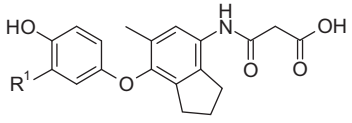
Scheme 3. Synthetic route for preparing **30**, **31,** and **32a–c**. Reagents and conditions: (a) Tf_2O, CH_2Cl_2; (b) BCl_3, CH_2Cl_2; (c) NaOH, MeOH; (d) $NaBH(OAc)_3$, THF; and (e) Et_3SiH, TFA, CH_2Cl_2.

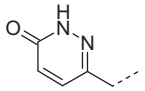
an additional fluorine into the 4-F-phenyl ring at the 2- or 3-position (**35a**, **35b**) was tolerated for both subtypes as compared with **32b**. Introducing chlorine (**35c**, **35d**, **35e**) into the phenyl ring negatively affected the efficacies. These chlorine compounds had *h*TRβ affinity and *h*TRβ selectivity similar to **32a**, but exhibited partial agonism. Interestingly, introducing OH into the phenyl ring at the 2-position greatly improved *h*TRβ selectivity sufficiently to regard **40a** (KTA-574) as a specific *h*TRβ agonist. Introducing OH at the 3- or 4-position also improved *h*TRβ selectivity, but reduced the efficacies (**40b**, **40c**).

4. Modeling

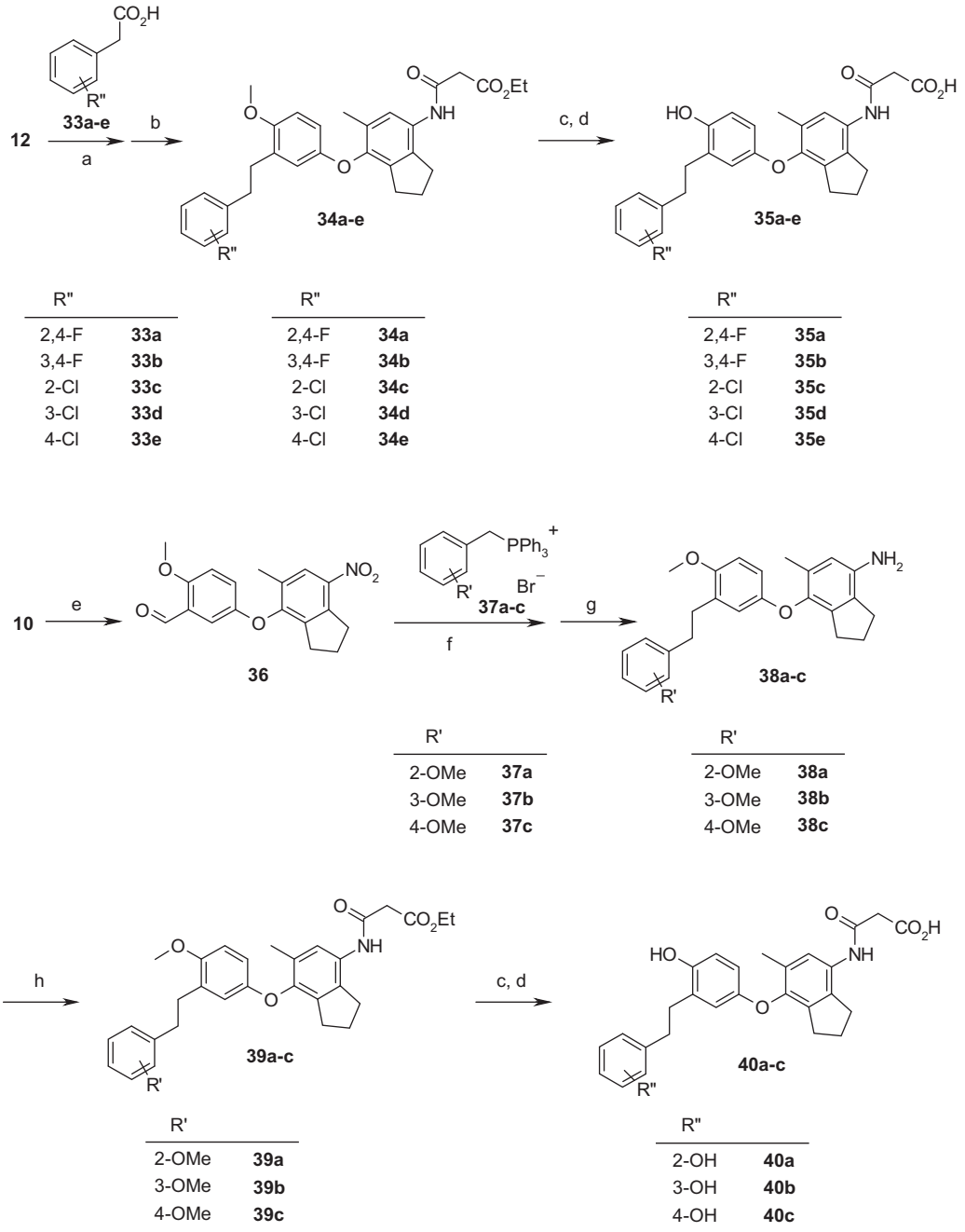
Molecular modeling studies were performed to investigate the cause of the high affinity and selectivity of **40a**. Docking models for **40a** were constructed from the crystal structures of *h*TR–Triac (**41**, Fig. 2) complexes[23] and modified from the crystal structure of an *h*TR–**7** complex.[20] Figure 3 shows the docking model for *h*TRβ with **40a**. This model suggested that interactions occurred between COOH of **40a** and Arg-316/Arg-320 of *h*TRβ and between *CO*NH of **40a** and Asn-331 of *h*TRβ. Other hydrogen bonds were observed between 4′-OH of **40a** and His-435 of *h*TRβ, which was thought to play an important role in agonist activity. These interactions

Table 2
Thyroid hormone receptor binding affinities (K_i) and reporter cell line potency efficacies (% agonism) of compounds **5**, **6**, **22**, **26**, **30**, **31**, **32a**, **32b**, and **32c**



Compounds	R^1	K_i[a] (nM)		α/β[b]	% Agonism[c]	
		*h*TRβ	*h*TRα		TRLuc-β	TRLuc-α
5		2.17	40.0	18	94	104
6		238	8.72	0.04	121	163
22	4-F-$C_6C_4CH_2$	3.70	30.5	8	92	115
26		14.1	91.8	7	79	73
32a	$PhCH_2CH_2$	40.2	1638	41	86	52
32b	4-F-$C_6C_4CH_2CH_2$	8.20	228	28	90	67
31	$PhCH_2CH(OH)$	124	6751	54	68	61
30	$PhCH_2CO$	441	>10000	>23	23	6
32c	$PhCH_2CH_2CH_2$	223	4866	22	15	2

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



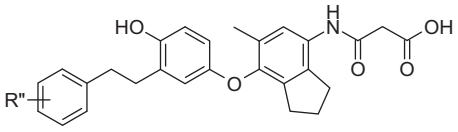
Scheme 4. Synthetic route for preparing **35a–e** and **40a–c**. Reagents and conditions: (a) Tf_2O, CH_2Cl_2; (b) Et_3SiH, TFA, CH_2Cl_2; (c) BBr_3, CH_2Cl_2; (d) NaOH, MeOH; (e) $MeOCHCl_2$, $TiCl_4$, CH_2Cl_2; (f) ^tBuOK, THF ; (g) H_2/Pd-C, EtOAc; and (h) $ClCOCH_2CO_2Et$, pyridine, CH_2Cl_2, 0 °C.

were previously suggested between thyromimetics with malonamic acid and *h*TRβ. Another hydrogen bond was observed between 2-OH of the phenethyl of **40a** and Gly-344 of *h*TRβ (Fig 3a). This interaction may have affected the high affinity with agonist activity, although the same interaction was observed between **40a** and *h*TRα (data not shown). Because the aromatic rings of an indane phenyl ether are closed to aliphatic side chains of non-polar amino residues, we considered the contributions of CH/π interactions.[24,25]

The CHPAI program was used to search for CH/π interactions.[26] Several CH/π interactions were observed between an indane phenyl ether and TRs. Figure 3b shows CH/π interactions between **40a** and Leu-330, Ile-276, Leu-346, Met-442, and Phe-451 of *h*TRβ. Thus, compound **40a** interacted with thyroid hormone receptors through hydrogen bonds and CH/π interactions. However, no differences in interactions were observed in the phenyl ethyl part. The cause of the high selectivity of **40a** remained unclear.

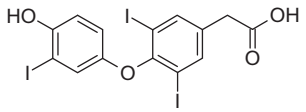
In an X-ray study, Borngraeber et al. showed that the benzyl group at the 3′-position of the distal ring of the *h*TRβ-selective thyromimetic **7** bound to *h*TRβ and bent helices 3 and 11.[20] They concluded that 4 of the 14 side chains responsible for proper registration of helix 12 moved by 1.6–4.0 Å without affecting its position in the protein. It is known that substitutions on hormones can reach toward and alter the position of helix 12, which affects receptor activity. Ligand **7** was accepted because of the flexibility of helix 11 in *h*TRβ. They speculated that helix 11 was better packed in *h*TRα and that changes in the spatial volume near the ligand substitution were probably less tolerated in *h*TRα.

Table 3
Thyroid hormone receptor binding affinities (K_i) and reporter cell line potency efficacies (% agonism) of compounds **32a**, **32b**, **35a–e**, and **40a–c**



Compounds	R″	K_i[a] (nM)		α/β[b]	% Agonism[c]	
		hTRβ	hTRα		TRLuc-β	TRLuc-α
32a	H	40.2	1638	40	86	52
32b	4-F	8.20	228	28	90	67
35a	2,4-F	12.0	201	17	73	49
35b	3,4-F	6.00	186	31	101	45
35c	2-Cl	30.0	814	27	35	11
35d	3-Cl	41.0	1366	33	41	13
35e	4-Cl	40.0	1645	41	40	11
40a(KTA-574)	2-OH	53.5	>10000	>187	81	66[d]
40b	3-OH	81.3	>10000	>123	50	53[d]
40c	4-OH	57.6	>10000	>174	44	25

[a] Values are means of two experiments. The variability was 25% on average.
[b] Selectivity (K_i *h*TRα)/(K_i *h*TRβ).
[c] Values at 10^{-5} M; T_3 set at 100%.
[d] Values at 10^{-4} M; T_3 set at 100%.



41

Figure 2. Structure of Triac (**41**).

Polikarpov et al. performed Molecular Dynamics (MD) simulations of thyroid hormones and suggested the contributions of waters on selectivity, which is the basis of ligand dissociation, and the stabilization of helix 12 in agonist conformation.[23,27–29] This group showed that the TRβ ligand-binding cavity (LBC) was more extensive relative to TRα. Introducing a large group was allowed in TRβ, while it was not allowed in TRα that had a smaller LBC compared with that of TRβ.[30]

We also performed MD simulations for TRs and **40a** to explain receptor selectivity, but obtained no positive results. However, the hypotheses that helix 11 was better packed in *h*TRα and that TRβ LBC was more extensive relative to TRα are supported by our results that the most bulky **16d** in Table 1 exhibited full agonism to TRLuc-β and partial agonism to TRLuc-α.

Based on our results, modeling, and these hypotheses, one reason for the *h*TRβ specificity of **40a** is the following.

When **40a** binds to *h*TRβ, helix 11 is slightly moved. However, this movement is not enough to break the interaction between His-435 and OH of the distal ring of **40a** and is not enough to change the position of helix 12; thus, it exhibits full agonism. The hydrogen bond between Gly-344 and **40a** and the CH/π interaction between Met-442/Phe-451 and **40a** may have affected the high affinity with agonist activity. In contrast, when **40a** attempts to bind to *h*TRα, helix 11 is moved enough to break the interaction between His-435 and OH of the distal ring of **40a** because of the better packing of helix 11 in *h*TRα; thus, **40a** cannot bind to *h*TRα.

When **35c–e**, **40b,** or **40c** binds to *h*TRβ, helix 11 is moved so as to change the position of helix 12 slightly with the interaction between His-435 and OH of the distal ring of ligands; thus, they exhibit partial agonism.

We are confident that the *h*TRβ-specificity of **40a** is explained not only by the type and size of its 3′-position, but also because our indane skeleton strongly prefers *h*TRβ over *h*TRα, as **6** and **26** exhibited opposite selectivity.

5. Conclusion

We designed novel thyromimetics with high receptor (*h*TRβ) selectivity based on the novel indane derivative **2a** in which the isopropyl at the 3′-position was replaced with alkyl and aralkyl moieties of variable lengths and branches. The results of a binding assay for *h*TRs and a reporter cell assay revealed that a previously unreported 2-arylethyl moiety affected higher *h*TRβ selectivity. KTA-574 (**40a**) with the 2-OH-$C_6H_4CH_2CH_2$ moiety at the 3′-position showed *h*TRβ specificity in a binding assay and exhibited full agonism in a reporter cell assay. Both the nature of the *h*TRβ-selective indane skeleton and the size/shape of the 2-OH-$C_6H_4CH_2CH_2$ moiety at the 3′-position contributed to the *h*TRβ specificity of **40a**.

The results of this study should provide useful SAR information for the further design of potent, *h*TRβ-specific, thyromimetics for therapeutic uses and deepen our understanding of thyroid hormone actions.[31]

6. Experimental

6.1. Chemistry: general

Uncorrected melting points were obtained with a Yanako MP-3S Micro melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker Avance II$^+$ 400 or Avance III 600, and chemical shifts were reported in parts per million (δ) downfield from tetramethylsilane used as the internal standard. Peak patterns are shown using the following abbreviations: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Mass spectra (HRMS) were obtained with an Agilent Technologies 6520 Accurate-Mass Q-TOF apparatus. 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 using 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.

6.1.1. 4-(4-Methoxyphenoxy)-5-methyl-7-nitroindane (10)

To a solution of **8** (6.00 g, 31.1 mmol) and **9** (17.0 g, 39.7 mmol) in CH_2Cl_2 (150 mL), copper bronze (2.00 g, 31.5 mmol) and Et_3N (5.6 mL, 40.2 mmol) were added at room temperature. The mixture was stirred at room temperature for 5 days. Insoluble materials were removed by filtration. The filtrate was evaporated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc 1/0–3/1) to give **10** (7.30 g, 79%) as a beige solid. Beige solid; mp 88–89 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.00–2.15 (2H, m), 2.24 (3H, s), 2.60–2.70 (2H, m), 3.30–3.45 (2H, m), 3.77 (3H, s), 6.73 (2H, d, J = 9.1 Hz), 6.81 (2H, d, J = 9.1 Hz), 7.96 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.1, 24.8, 30.3, 34.3, 55.7, 114.9, 116.5, 125.7, 130.8, 139.5, 141.8, 141.8,

150.9, 154.7, 155.0; HRMS calcd for $C_{17}H_{18}NO_4$ $(M+H)^+$ 300.1230, found 300.1231.

6.1.2. [7-(4-Methoxyphenoxy)-6-methylindan-4-yl]amine (11)

To a solution of **10** (1.68 g, 5.61 mmol) in EtOAc (50 mL), 10% Pd/C (56% wet weight with water, 1.37 g, 0.566 mmol) was added. The mixture was stirred overnight under a hydrogen atmosphere at room temperature. Insoluble materials were removed by filtration and washed with EtOAc. The filtrate was evaporated to dryness under reduced pressure to give **11** (1.51 g, 100%) as a beige solid. Beige solid; mp 102–103 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.95–2.15 (5H, m), 2.60–2.80 (4H, m), 3.44 (2H, br s), 3.75 (3H, s), 6.41 (1H, s), 6.65–6.85 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.8, 24.9, 29.7, 30.3, 55.7, 114.6, 115.5, 115.6, 128.4, 129.9, 137.7, 139.0, 142.2, 152.7, 153.9; HRMS calcd for $C_{17}H_{20}NO_2$ $(M+H)^+$ 270.1489, found 270.1485.

6.1.3. Ethyl *N*-[7-(4-methoxyphenoxy)-6-methylindan-4-yl]malonamate (12)

To a solution of **11** (1.30 g, 4.83 mmol) and pyridine (0.585 mL, 7.23 mmol) in CH_2Cl_2 (50 mL), ethyl malonyl chloride (0.680 mL, 5.33 mmol) was added dropwise at 0 °C. The mixture was stirred for 3 h at room temperature. After adding water (20 mL), the mixture was partitioned between water and CH_2Cl_2. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 19/1–0/1) to give **12** (1.21 g, 65%) as a beige solid. Beige solid; mp 113–115 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (3H, t, J = 7.1 Hz), 2.00–2.15 (2H, m), 2.16 (3H, s), 2.60–2.75 (2H, m), 2.80–2.95 (2H, m), 3.49 (2H, s), 3.76 (3H, s), 4.27 (2H, q, J = 7.1 Hz), 6.65–6.85 (4H, m), 7.77 (1H, s), 9.20 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 16.1, 24.9, 30.2, 30.4, 41.2, 55.7, 61.9, 114.6, 115.9, 121.9, 130.0, 130.1, 134.4, 137.4, 146.6, 152.1, 154.2, 162.6, 170.4; HRMS calcd for $C_{22}H_{26}NO_5$ $(M+H)^+$ 384.1805, found 384.1800.

6.1.4. *N*-[7-(4-Hydroxyphenoxy)-6-methylindan-4-yl]malonamic acid (13)

To a solution of **12** (32 mg, 83.5 μmol) in CH_2Cl_2 (1 mL), a 1 M solution of BBr_3 in CH_2Cl_2 (0.500 mL, 0.500 mmol) was added dropwise at −78 °C. The mixture was stirred overnight at room temperature. After adding water, the mixture was partitioned between water and CH_2Cl_2. The organic layer was extracted with a saturated aqueous solution of $NaHCO_3$. The alkaline water layer was washed with EtOAc, acidified with 2 M HCl, and extracted with EtOAc. The organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give **13** (6 mg, 21%) as a white solid. White solid; mp 200–204 °C (dec) (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD = 7/1) δ: 1.95–2.10 (2H, m), 2.15 (3H, s), 2.60–2.70 (2H, m), 2.80–2.90 (2H, m), 3.47 (2H, s), 6.60–6.75 (4H, m), 7.63 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD = 7/1) δ: 16.2, 25.1, 30.5, 30.5, 40.6, 116.1, 116.2, 122.7, 129.7, 130.1, 135.4, 137.7, 147.2, 151.1, 151.6, 164.4, 171.7; HRMS calcd for $C_{19}H_{20}NO_5$ $(M+H)^+$ 342.1336, found 342.1341.

6.1.5. Ethyl *N*-[7-(3-acetyl-4-methoxyphenoxy)-6-methylindan-4-yl]malonamate (15a)

To a solution of **12** (192 mg, 0.501 mmol) and acetic acid (**14a**) (0.043 mL, 0.751 mmol) in CH_2Cl_2 (0.5 mL), trifluoromethanesulfonic anhydride (0.125 mL, 0.762 mmol) was added. The mixture was stirred for 15 h at room temperature. After adding water, the reaction mixture was extracted with CH_2Cl_2. 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 = 19/1–0/1) to give **15a** (29 mg, 14%) as a beige solid. Beige solid; mp 120–122 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (3H, t, J = 7.1 Hz), 2.00–2.10 (2H, m), 2.14 (3H, s), 2.58 (3H, s), 2.60–2.70 (2H, m), 2.85–2.95 (2H, m), 3.49 (2H, s), 3.87 (3H, s), 4.27 (2H, q, J = 7.1 Hz), 6.80–6.90 (2H, m), 7.17 (1H, d, J = 3.0 Hz), 7.79 (1H, s), 9.18 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 16.1, 24.9, 30.2, 30.4, 31.8, 41.2, 56.0, 62.0, 112.9, 116.4, 119.8, 121.9, 129.0, 129.9, 130.4, 134.4, 137.3, 146.1, 151.7, 153.7, 162.6, 170.4, 199.4; HRMS calcd for $C_{24}H_{28}NO_6$ $(M+H)^+$ 426.1911, found 426.1915.

6.1.6. Ethyl *N*-[7-(3-isobutyryl-4-methoxyphenoxy)-6-methylindan-4-yl]malonamate (15b)

The title compound was prepared from **12** and isobutyric acid (**14b**) in a manner similar to that described for **15a** as a white solid (52%). White solid; mp 147–148 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.12 (6H, d, J = 7.0 Hz), 1.34 (3H, t, J = 7.2 Hz), 2.00–2.10 (2H, m), 2.14 (3H, s), 2.65–2.70 (2H, m), 2.85–2.95 (2H, m), 3.43 (1H, heptet, J = 7.0 Hz), 3.49 (2H, s), 3.83 (3H, s), 4.27 (2H, q, J = 7.2 Hz), 6.80–6.85 (2H, m), 6.95–7.00 (1H, m), 7.78 (1H, s), 9.19 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 16.1, 18.5, 24.9, 30.2, 30.4, 40.1, 41.2, 56.1, 61.0, 62.0, 112.6, 116.2, 118.5, 121.9, 129.8, 129.9, 130.4, 134.3, 137.3, 146.1, 151.8, 152.3, 162.6, 170.4, 207.5; HRMS calcd for $C_{26}H_{32}NO_6$ $(M+H)^+$ 454.2224, found 454.2223.

6.1.7. Ethyl *N*-{7-[4-methoxy-3-(3-methylbutyryl)phenoxy]-6-methylindan-4-yl}malonamate (15c)

The title compound was prepared from **12** and 3-methylbutyric acid (**14c**) in a manner similar to that described for **15a** as a pale yellow solid (55%). Pale yellow solid; mp 151–153 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90–1.00 (6H, m), 1.34 (3H, t, J = 7.1 Hz), 2.00–2.10 (2H, m), 2.14 (3H, s), 2.15–2.25 (1H, m), 2.60–2.70 (2H, m), 2.75–2.95 (4H, m), 3.49 (2H, s), 3.84 (3H, s), 4.27 (2H, q, J = 7.1 Hz), 6.80–6.85 (2H, m), 7.05–7.10 (1H, m), 7.78 (1H, s), 9.19 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 16.1, 22.7, 24.9, 25.0, 30.2, 30.4, 41.2, 52.6, 56.0, 62.0, 112.8, 116.2, 119.0, 121.9, 129.9, 130.0, 130.4, 134.3, 137.3, 146.1, 151.8, 152.9, 162.6, 170.4, 202.6; HRMS calcd for $C_{27}H_{34}NO_6$ $(M+H)^+$ 468.2381, found 468.2380.

6.1.8. Ethyl *N*-{7-[3-(2-cyclohexylacetyl)-4-methoxyphenoxy]-6-methylindan-4-yl}malonamate (15d)

The title compound was prepared from **12** and cyclohexylacetic acid (**14d**) in a manner similar to that described for **15a** as a pale yellow solid (72%). Pale yellow solid; mp 154–155 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90–1.30 (5H, m), 1.34 (3H, t, J = 7.1 Hz), 1.60–1.75 (5H, m), 1.80–1.95 (1H, m), 2.00–2.10 (2H, m), 2.14 (3H, s), 2.60–2.70 (2H, m), 2.75–2.95 (4H, m), 3.49 (2H, s), 3.83 (3H, s), 4.27 (2H, q, J = 7.1 Hz), 6.80–6.90 (2H, m), 7.00–7.10 (1H, m), 7.78 (1H, s), 9.19 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 16.1, 24.9, 26.2, 26.3, 30.2, 30.4, 33.4, 34.3, 41.2, 51.3, 56.1, 61.9, 112.8, 116.2, 119.0, 121.9, 129.9, 130.1, 130.4, 134.3, 137.3, 146.1, 151.8, 152.9, 162.6, 170.4, 202.6; HRMS calcd for $C_{30}H_{38}NO_6$ $(M+H)^+$ 508.2694, found 508.2687.

6.1.9. *N*-[7-(3-Ethyl-4-hydroxyphenoxy)-6-methylindan-4-yl]malonamic acid (16a)

To a solution of **15a** (27 mg, 63.5 μmol) in CH_2Cl_2 (2 mL), a 1 M solution of BCl_3 in CH_2Cl_2 (0.20 mL, 0.200 mmol) was added dropwise at 0 °C. The mixture was stirred for 3 days at room temperature. After adding EtOH, the mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel

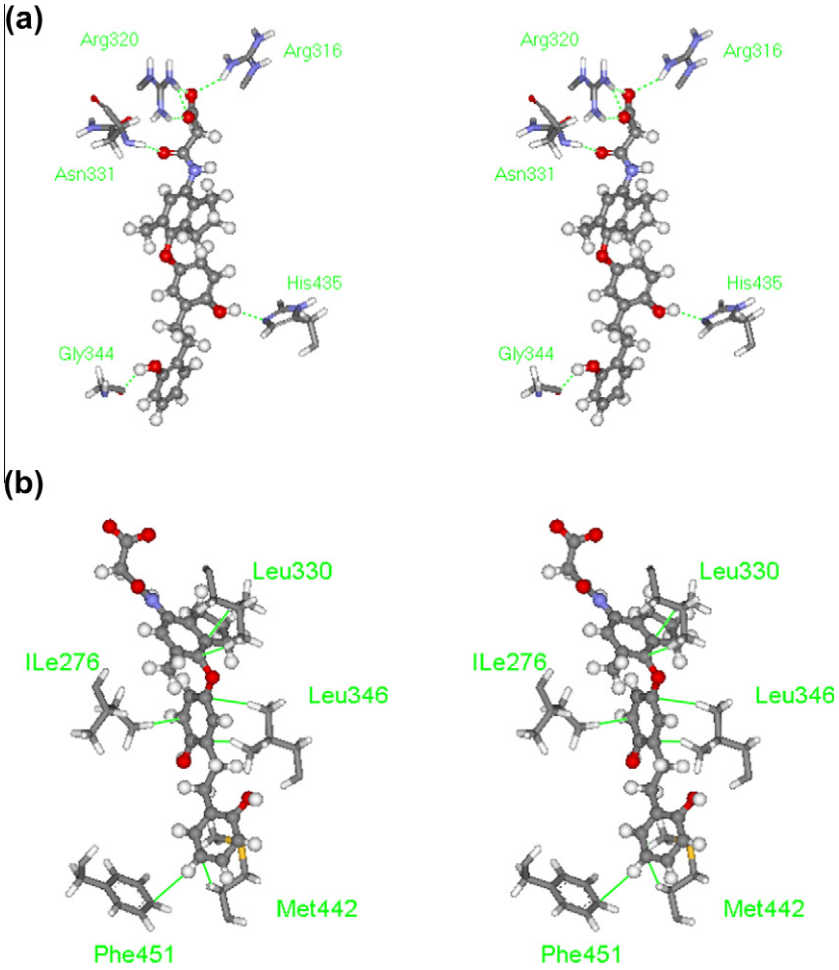


Figure 3. (a, b) Docking model for *h*TRβ with **40a** constructed from the crystal structure of *h*TRβ–**41** complex (PDB code 3JZC[23]), which was modified from the crystal structure of *h*TRβ–**7** complex (PDB code 1Q4X[20]). (a) Hydrogen bonds or polar interactions between *h*TRβ and **40a**. (b) CH/π interactions between *h*TRβ and **40a**.

(eluent: hexane/EtOAc = 19/1–0/1) to give ethyl *N*-[7-(3-acetyl-4-hydroxyphenoxy)-6-methylindan-4-yl]malonamate (25 mg, 96%).

To a solution of ethyl *N*-[7-(3-acetyl-4-hydroxyphenoxy)-6-methylindan-4-yl] malonamate (25 mg, 60.8 μmol) in CH_2Cl_2 (0.3 mL), triethylsilane (0.058 mL, 0.366 mmol) and TFA (0.3 mL) were added. The mixture was stirred overnight at room temperature. After adding an aqueous solution of $NaHCO_3$, the reaction mixture was extracted with CH_2Cl_2. 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 = 19/1–0/1) to give ethyl *N*-[7-(3-ethyl-4-hydroxyphenoxy)-6-methylindan-4-yl]malonamate (10 mg, 41%).

To a solution of ethyl *N*-[7-(3-ethyl-4-hydroxyphenoxy)-6-methylindan-4-yl]malonamate (10 mg, 25.2 μmol) in MeOH (1 mL), an aqueous solution of 1 M NaOH (1 mL) was added. The mixture was stirred for 30 min under an argon atmosphere at 60 °C. After adding 2 M HCl (0.5 mL) at 0 °C, the precipitate was collected to give **16a** (5 mg, 54%) as a white solid. White solid; mp 118–120 °C (dec) (EtOH–H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.07 (3H, t, J = 7.4 Hz), 1.85–2.00 (2H, m), 2.05 (3H, s), 2.46 (2H, q, J = 7.4 Hz), 2.50–2.60 (2H, m), 2.70–2.85 (2H, m), 3.37 (2H, s), 6.30–6.40 (1H, m), 6.50–6.70 (2H, m), 7.38 (1H, s), 8.89 (1H, s), 9.56 (1H, br s), 12.62 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.1, 15.7, 22.8, 24.5, 30.0, 30.5, 43.2, 112.3, 115.3, 115.6, 123.2, 128.2, 130.3, 131.1, 136.0, 136.6, 146.2, 149.4, 150.1, 164.3, 169.5; HRMS calcd for $C_{21}H_{24}NO_5$ $(M+H)^+$ 370.1649, found 370.1650.

6.1.10. *N*-[7-(4-Hydroxy-3-isobutylphenoxy)-6-methylindan-4-yl]malonamic acid (16b)

The title compound was prepared from **15b** in a manner similar to that described for **16a** as a white solid (54%, 3 steps). White solid; mp 152–154 °C (dec) (EtOAc–hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.75–0.90 (6H, m), 1.75–2.00 (3H, m), 2.06 (3H, s), 2.25–2.35 (2H, m), 2.50–2.60 (2H, m), 2.75–2.85 (2H, m), 3.38 (2H, s), 6.35–6.50 (2H, m), 6.60–6.70 (1H, m), 7.38 (1H, s), 8.83 (1H, s), 9.50 (1H, br s), 12.60 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.7, 22.2, 24.5, 27.9, 28.3, 30.0, 30.5, 43.2, 113.0, 115.5, 117.1, 123.2, 128.2, 128.4, 130.3, 136.0, 136.6, 146.3, 149.8, 149.8, 164.3, 169.6; HRMS calcd for $C_{23}H_{28}NO_5$ $(M+H)^+$ 398.1962, found 398.1967.

6.1.11. *N*-{7-[4-Hydroxy-3-(3-methylbutyl)phenoxy]-6-methylindan-4-yl}malonamic acid (16c)

The title compound was prepared from **15c** in a manner similar to that described for **16a** as a white solid (43%, 3 steps). White solid; mp 132–135 °C (dec) (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD = 7/1) δ: 0.90–0.95 (6H, m), 1.40–1.65 (3H, m), 1.95–2.10 (2H, m), 2.15 (3H, s), 2.50–2.70 (4H, m), 2.80–2.90 (2H, m), 3.46 (2H, s), 6.35–6.45 (1H, m), 6.55–6.65 (2H, m), 7.63 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD = 7/1) δ: 16.1, 22.6, 25.0, 28.0, 28.1, 30.3, 30.4, 38.9, 40.3, 112.7, 115.5, 116.8, 122.5, 129.5, 130.0, 130.6, 135.2, 137.6, 147.2, 148.7, 151.4, 164.3, 171.9; HRMS calcd for $C_{24}H_{30}NO_5$ $(M+H)^+$ 412.2118, found 412.2124.

6.1.12. *N*-{7-[3-(2-Cyclohexylethyl)-4-hydroxyphenoxy]-6-methylindan-4-yl}malonamic acid (16d)

The title compound was prepared from **15d** in a manner similar to that described for **16a** as a white solid (56%, 3 steps). White solid; mp 166–167 °C(dec) (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ = 7/1) δ: 0.85–1.00 (2H, m), 1.05–1.35 (4H, m), 1.40–1.50 (2H, m), 1.55–1.80 (5H, m), 2.16 (3H, s), 2.50–2.75 (4H, m), 2.80–2.90 (2H, m), 3.46 (2H, s), 6.35–6.45 (1H, m), 6.55–6.65 (2H, m), 7.63 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$ = 7/1) δ: 16.0, 24.9, 26.3, 26.7, 27.4, 30.2, 30.3, 33.3, 37.2, 37.5, 40.4, 112.7, 115.3, 116.6, 122.4, 129.4, 129.9, 130.7, 135.1, 137.5, 147.1, 148.7, 151.2, 164.3, 171.5; HRMS calcd for $C_{27}H_{34}NO_5$ $(M+H)^+$ 452.2431, found 452.2428.

6.1.13. 1-Benzyloxy-2-(4-fluorobenzyl)benzene (18)

Benzyl bromide (30 mL, 252 mmol) and Cs_2CO_3 (100 g, 307 mmol) were added to a solution of 2-(4-fluorobenzyl)phenol (51.3 g, 254 mmol) in DMF (200 mL), and the mixture was stirred overnight at 80 °C. After adding water, the mixture was extracted with EtOAc. The organic layer was washed with water and brine, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give **18** (66.6 g, 90%) as a colorless oil. Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.98 (2H, s), 5.04 (2H, s), 6.85–7.00 (4H, m), 7.05–7.20 (4H, m), 7.25–7.50 (5H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 35.6, 69.9, 111.7, 114.8, 115.0, 120.8, 127.3, 127.6, 127.8, 128.5, 130.3, 130.3, 130.4, 136.7, 137.1, 156.4; HRMS calcd for $C_{20}H_{18}FO$ $(M+H)^+$ 293.1336, found 293.1336.

6.1.14. Bis[4-benzyloxy-3-(4-fluorobenzyl)phenyl]iodonium tetrafluoroborate (19)

Fuming nitric acid (85 mL, 1980 mmol) was added to Ac_2O (226 mL, 2400 mmol) under ice cooling. Then, iodine (76.1 g, 300 mmol) was added to this reaction mixture. Later, TFA (175 mL, 2250 mmol) was added dropwise. After stirring for 1 h at room temperature, the mixture was evaporated to dryness under reduced pressure at <35 °C. Ac_2O (500 mL) and **18** (391 g, 1337 mmol) were then added to the residue. Later, TFA (100 mL) was added dropwise under ice cooling. After stirring at 4 °C for 4 days, the reaction mixture was evaporated to dryness under reduced pressure at <35 °C. MeOH (1000 mL), an aqueous solution of $K_2S_2O_5$ (100 g/500 mL), and 4 M aqueous $NaBF_4$ (1250 mL) were added in succession to the residue. The mixture was stirred for 2 h. 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 M aqueous solution of $NaBF_4$ (500 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was triturated with diethyl ether. Insoluble material was collected by filtration to give **19** (263 g, 68%) as a white solid. White solid; mp 131–132 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.89 (4H, s), 5.03 (4H, s), 6.80–6.95 (6H, m), 7.00–7.10 (4H, m), 7.20–7.40 (10H, m), 7.60 (2H, d, J = 2.5 Hz), 7.80 (2H, dd, J = 2.5, 8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 35.4, 70.5, 101.3, 115.1, 115.2, 115.3, 127.5, 128.5, 128.7, 130.6, 134.5, 135.2, 135.4, 135.6, 136.4, 159.9; HRMS calcd for $C_{40}H_{32}F_2IO_2$ $(M)^+$ 709.1410, found 709.1398.

6.1.15. 4-[4-Benzyloxy-3-(4-fluorobenzyl)phenoxy]-5-methyl-7-nitroindane (20)

The title compound was prepared from **19** in a manner similar to that described for **10** as a white solid (54%). White solid; mp 106–107 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.00–2.10 (2H, m), 2.22 (3H, s), 2.55–2.65 (2H, m), 3.30–3.40 (2H, m), 3.92 (2H, s), 4.99 (2H, s), 6.52 (1H, dd, J = 3.0, 8.8 Hz), 6.63 (1H, d, J = 3.0 Hz), 6.79 (1H, d, J = 8.8 Hz), 6.85–6.95 (2H, m), 7.05–7.15 (2H, m), 7.25–7.40 (5H, m), 7.94 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.1, 24.8, 30.4, 34.3, 35.5, 70.6, 112.8, 113.6, 114.9, 115.1, 118.3, 125.7, 127.3, 127.9, 128.5, 130.2, 130.3, 130.7, 131.6, 136.1, 137.0, 139.4, 141.8, 150.8, 151.8, 154.6; HRMS calcd for $C_{30}H_{27}FNO_4$ $(M+H)^+$ 484.1919, found 484.1910.

6.1.16. 4-(7-Amino-5-methylindan-4-yloxy)-2-(4-fluorobenzyl) phenol (21)

The title compound was prepared from **20** in a manner similar to that described for **11** as a beige solid (98%). Beige solid; mp 169–170 °C (dec) (EtOAc–hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.80–1.95 (5H, m), 2.40–2.50 (2H, m), 2.55–2.65 (2H, m), 3.77 (2H, s), 4.61 (2H, s), 6.28 (1H, s), 6.35 (1H, dd, J = 3.0, 8.7 Hz), 6.49 (1H, d, J = 3.0 Hz), 6.67 (1H, d, J = 8.7 Hz), 7.00–7.10 (2H, m), 7.15–7.25 (2H, m), 8.97 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.6, 24.3, 29.5, 29.9, 34.4, 112.7, 114.3, 114.6, 115.5, 116.5, 126.9, 128.1, 130.2, 136.2, 137.2, 140.0, 140.9, 148.9, 151.0, 159.3, 161.7; HRMS calcd for $C_{23}H_{23}FNO_2$ $(M+H)^+$ 364.1707, found 364.1721.

6.1.17. *N*-{7-[3-(4-Fluorobenzyl)-4-hydroxyphenoxy]-6-methylindan-4-yl}malonamic acid (22)

Ethyl *N*-{7-[3-(4-fluorobenzyl)-4-hydroxyphenoxy]-6-methylindan-4-yl}malonamate was prepared from **21** in a manner similar to that described for **12**.

To a solution of ethyl *N*-{7-[3-(4-fluorobenzyl)-4-hydroxyphenoxy]-6-methylindan-4-yl}malonamate (2.16 g, 4.52 mmol) in EtOH (30 mL), an aqueous solution of 1 M NaOH (20 mL) was added. The mixture was stirred for 30 min under an argon atmosphere at 60 °C. After adding 1 M HCl (20 mL) at 0 °C, the mixture was extracted twice with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was crystallized from a small amount of EtOH and water to give **22** (40%, 2 steps) as a white solid. White solid; mp 162–164 °C (dec) (EtOH–H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.85–1.95 (2H, m), 2.03 (3H, s), 2.70–2.80 (2H, m), 3.25–3.35 (2H, m), 3.38 (2H, s), 3.79 (2H, s), 6.39 (1H, dd, J = 3.0, 8.7 Hz), 6.54 (1H, d, J = 3.0 Hz), 6.69 (1H, d, J = 8.7 Hz), 7.00–7.10 (2H, m), 7.15–7.25 (2H, m), 7.36 (1H, s), 9.08 (1H, s), 9.48 (1H, s), 12.60 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.7, 24.5, 30.0, 30.5, 34.4, 43.2, 113.2, 114.9, 115.6, 117.0, 123.2, 128.1, 128.4, 130.3, 130.4, 136.0, 136.6, 137.1, 146.2, 149.4, 150.1, 159.7, 161.3, 164.3, 169.6; HRMS calcd for $C_{26}H_{25}FNO_5$ $(M+H)^+$ 450.1711, found 450.1712.

6.1.18. 6-[2-Hydroxy-5-(5-methyl-7-nitroindan-4-yloxy) benzyl]-2*H*-pyridazine-3-one (24)

3-Chloro-6-[2-methoxy-5-(5-methyl-7-nitroindan-4-yloxy) benzyl]pyridazine was prepared from **23** in a manner similar to that described for **10**.

A mixture of 3-chloro-6-[2-methoxy-5-(5-methyl-7-nitroindan-4-yloxy)benzyl]pyridazine (760 mg, 1.78 mmol), sodium acetate (50 mg, 0.610 mmol), and acetic acid (10 mL) was heated for 2 h at reflux temperature under Ar. The reaction mixture was evaporated to dryness under reduced pressure. After adding water, the residue was stirred for 30 min. The mixture was extracted with dichloromethane. 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 to give 6-[2-methoxy-5-(5-methyl-7-nitroindan-4-yloxy)benzyl]-2*H*-pyridazine-3-one (707 mg).

To a solution of 6-[2-methoxy-5-(5-methyl-7-nitroindan-4-yloxy)benzyl]-2*H*-pyridazine-3-one (707 mg) in acetic acid (10 mL) hydrobromic acid (48%, 10 mL) was added. The mixture was heated overnight at reflux temperature under Ar. After adding water, the reaction mixture was extracted with dichloro-

methane. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was crystallized from a small amount of ethyl acetate to give **24** (270 mg, 36%, 3 steps) as a white solid. White solid; mp 246–248 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.00–2.10 (2H, m), 2.22 (3H, s), 2.55–2.70 (2H, m), 3.30–3.40 (2H, m), 3.87 (2H, s), 6.51 (1H, dd, J = 3.0, 8.7 Hz), 6.66 (1H, d, J = 3.0 Hz), 6.73 (1H, d, J = 8.7 Hz), 6.86 (1H, d, J = 9.6 Hz), 7.30 (1H, d, J = 9.6 Hz), 7.97 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.1, 24.8, 30.4, 34.3, 36.1, 115.6, 117.5, 117.7, 124.9, 125.7, 130.7, 131.2, 134.5, 139.4, 141.8, 141.9, 148.0, 149.7, 150.7, 154.5, 160.9; HRMS calcd for $C_{21}H_{20}N_3O_5$ $(M+H)^+$ 394.1397, found 394.1403.

6.1.19. 6-[5-(7-Amino-5-methylindan-4-yloxy)-2-hydroxybenzyl]-2*H*-pyridazine-3-one (25)

The title compound was prepared from **24** in a manner similar to that described for **11** as a beige solid (100%). Beige solid; mp 141–144 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ = 9/1) δ: 1.95–2.10 (5H, m), 2.55–2.75 (4H, m), 3.85 (2H, s), 6.42 (1H, s), 6.52 (1H, dd, J = 2.9, 8.8 Hz), 6.57 (1H, d, J = 2.9 Hz), 6.69 (1H, d, J = 8.8 Hz), 6.85 (1H, d, J = 9.6 Hz), 7.27 (1H, d, J = 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$ = 9/1) δ: 15.7, 24.8, 29.5, 30.2, 35.4, 114.4, 115.8, 116.4, 116.8, 124.5, 128.8, 129.8, 130.0, 134.7, 137.5, 138.6, 142.3, 148.7, 152.0, 161.5; HRMS calcd for $C_{21}H_{22}N_3O_3$ $(M+H)^+$ 364.1656, found 364.1652.

6.1.20. *N*-{7-[4-Hydroxy-3-(6-oxo-1,6-dihydropyridazin-3-ylmethyl)phenoxy]-6-methylindan-4-yl}malonamic acid (26)

The title compound was prepared from **25** in a manner similar to that described for **22** as a white solid (9%, 2 steps). White solid; mp 215–218 °C (dec) (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.85–1.95 (2H, m), 2.04 (3H, s), 2.70–2.80 (2H, m), 3.38 (2H, s), 3.74 (2H, s), 6.45 (1H, dd, J = 3.0, 8.6 Hz), 6.54 (1H, d, J = 3.0 Hz), 6.72 (1H, d, J = 8.6 Hz), 6.79 (1H, d, J = 9.8 Hz), 7.22 (1H, d, J = 9.8 Hz), 7.38 (1H, s), 9.20 (1H, s), 9.52 (1H, br s), 12.73 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.7, 24.5, 30.0, 30.5, 34.3, 43.2, 113.9, 115.8, 117.0, 123.2, 125.3, 128.1, 129.7, 130.5, 134.0, 136.0, 136.6, 146.1, 146.6, 149.6, 150.1, 160.2, 164.4, 169.6; HRMS calcd for $C_{24}H_{24}N_3O_6$ $(M+H)^+$ 450.1660, found 450.1665.

6.1.21. Ethyl *N*-[7-(4-methoxy-3-phenylacetylphenoxy)-6-methylindan-4-yl]malonamate (28a)

The title compound was prepared from **12** and phenylacetic acid (**27a**) in a manner similar to that described for **15a** as a yellow solid (49%). Yellow solid; mp 123–124 °C (EtOAc–hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.33 (3H, t, J = 7.1 Hz), 2.00–2.10 (2H, m), 2.11 (3H, s), 2.55–2.65 (2H, m), 2.80–2.90 (2H, m), 3.49 (2H, s), 3.86 (3H, s), 4.26 (2H, s), 4.27 (2H, q, J = 7.1 Hz), 6.84 (1H, d, J = 9.1 Hz), 6.89 (1H, dd, J = 3.0, 9.1 Hz), 7.06 (1H, d, J = 3.0 Hz), 7.15–7.30 (5H, m), 7.77 (1H, s), 9.18 (1H, br s); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.1, 16.1, 24.9, 30.2, 30.3, 41.2, 50.1, 56.0, 61.9, 112.8, 116.5, 119.8, 121.9, 126.6, 128.3, 128.8, 129.7, 129.8, 130.4, 134.3, 135.1, 137.3, 146.0, 151.8, 153.1, 162.6, 170.4, 199.6; HRMS calcd for $C_{30}H_{32}NO_6$ $(M+H)^+$ 502.2224, found 502.2235.

6.1.22. Ethyl *N*-{7-[3-(4-fluorophenyl)acetyl-4-methoxyphenoxy]-6-methylindan-4-yl}malonamate (28b)

The title compound was prepared from **12** and (4-fluorophenyl)acetic acid (**27b**) in a manner similar to that described for **15a** as a beige solid (55%). Beige solid; mp 134–135 °C (EtOAc–hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.34 (3H, t, J = 7.1 Hz), 2.00–2.10 (2H, m), 2.12 (3H, s), 2.60–2.65 (2H, m), 2.85–2.90 (2H, m), 3.49 (2H, s), 3.88 (3H, s), 4.23 (2H, s), 4.27 (2H, q, J = 7.1 Hz), 6.85 (1H, d, J = 9.0 Hz), 6.90 (1H, dd, J = 3.1, 9.0 Hz), 6.95–7.00 (2H, m), 7.06 (1H, d, J = 3.1 Hz), 7.10–7.20 (2H, m), 7.77 (1H, s), 9.18 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.1, 16.1, 24.9, 30.2, 30.3, 41.2, 49.2, 56.0, 62.0, 112.9, 115.1, 115.2, 116.5, 120.0, 121.9, 128.6, 129.8, 130.5, 130.8, 131.2, 134.3, 137.3, 146.0, 151.8, 153.1, 162.6, 170.4, 199.3; HRMS calcd for $C_{30}H_{31}FNO_6$ $(M+H)^+$ 520.2130, found 520.2124.

6.1.23. Ethyl *N*-{7-[4-methoxy-3-(3-phenylpropionyl)phenoxy]-6-methylindan-4-yl}malonamate (28c)

The title compound was prepared from **12** and 3-phenylpropionic acid (**27c**) in a manner similar to that described for **15a** as a pale yellow solid (76%). Pale yellow solid; mp 107–109 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (3H, t, J = 7.1 Hz), 2.00–2.10 (2H, m), 2.14 (3H, s), 2.60–2.70 (2H, m), 2.85–2.95 (2H, m), 2.99 (2H, t, J = 7.7 Hz), 3.28 (2H, t, J = 7.7 Hz), 3.49 (2H, s), 3.83 (3H, s), 4.27 (2H, q, J = 7.1 Hz), 6.83 (1H, d, J = 9.0 Hz), 6.87 (1H, dd, J = 3.0, 9.0 Hz), 7.13 (1H, d, J = 3.0 Hz), 7.15–7.30 (5H, m), 7.79 (1H, s), 9.20 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 16.1, 24.9, 30.2, 30.4, 30.4, 41.2, 45.3, 56.0, 62.0, 112.8, 116.4, 119.6, 121.9, 125.9, 128.4, 128.5, 129.0, 129.9, 130.5, 134.3, 137.3, 141.7, 146.1, 151.8, 153.3, 162.6, 170.4, 201.2; HRMS calcd for $C_{31}H_{34}NO_6$ $(M+H)^+$ 516.2381, found 516.2381.

6.1.24. Ethyl *N*-[7-(4-hydroxy-3-phenylacetylphenoxy)-6-methylindan-4-yl]malonamate (29)

To a solution of **28a** (83 mg, 0.166 mmol) in CH_2Cl_2 (2 mL), a 1 M solution of BCl_3 in CH_2Cl_2 (0.50 mL, 0.500 mmol) was added dropwise at 0 °C. The mixture was stirred overnight at room temperature. After adding EtOH, the mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 3/1–1/1) to give **29** (49 mg, 61%) as a beige solid. Beige solid; mp 188–190 °C (EtOAc–hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.34 (3H, t, J = 7.1 Hz), 2.00–2.10 (2H, m), 2.09 (3H, s), 2.55–2.65 (2H, m), 2.85–2.95 (2H, m), 3.52 (2H, s), 4.09 (2H, s), 4.28 (2H, q, J = 7.1 Hz), 6.90 (1H, d, J = 9.1 Hz), 7.05 (1H, dd, J = 3.0, 9.1 Hz), 7.09 (1H, s), 7.20–7.35 (5H, m), 7.85 (1H, s), 9.29 (1H, br s), 11.81 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.1, 16.0, 24.8, 30.2, 30.3, 41.1, 45.8, 62.0, 114.5, 118.4, 119.7, 122.0, 125.0, 127.1, 128.8, 129.1, 129.9, 130.6, 133.9, 134.3, 137.3, 145.8, 150.0, 157.7, 162.7, 170.5, 203.4; HRMS calcd for $C_{29}H_{30}NO_6$ $(M+H)^+$ 488.2068, found 488.2079.

6.1.25. *N*-[7-(4-Hydroxy-3-phenylacetylphenoxy)-6-methylindan-4-yl]malonamic acid (30)

To a solution of **29** (12 mg, 0.0246 mmol) in MeOH (1 mL), an aqueous solution of 1 M NaOH (1 mL) was added. The mixture was stirred for 30 min under Ar at 60 °C. After adding 2 M HCl (0.55 mL) at 0 °C, the precipitate was collected to give **30** (10 mg, 89%) as a beige solid. Beige solid; mp 155–156 °C (dec) (EtOH–H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.85–2.00 (2H, m), 2.04 (3H, s), 2.45–2.55 (2H, m), 2.75–2.85 (2H, m), 3.41 (2H, s), 4.29 (2H, s), 6.92 (1H, d, J = 9.0 Hz), 7.01 (1H, dd, J = 3.0, 9.0 Hz), 7.10–7.35 (6H, m), 7.44 (1H, s), 9.54 (1H, br s), 11.27 (1H, s), 12.62 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.6, 24.5, 29.9, 30.5, 43.2, 46.3, 115.4, 119.0, 120.5, 123.4, 123.5, 126.5, 128.1, 128.4, 129.4, 130.8, 134.7, 136.2, 136.6, 145.5, 149.6, 155.2, 164.4, 169.5, 202.4; HRMS calcd for $C_{27}H_{26}NO_6$ $(M+H)^+$ 460.1755, found 460.1759.

6.1.26. *N*-{7-[4-Hydroxy-3-(1-hydroxy-2-phenylethyl)phenoxy]-6-methylindan-4-yl}malonamic acid (31)

To a solution of **29** (19 mg, 0.039 mmol) in THF (10 mL), $NaBH(OAc)_3$ (42 mg, 0.198 mmol) was added. The mixture was stirred overnight at room temperature. After adding water, the

reaction mixture was extracted with 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 = 1/0–0/1) to give ethyl *N*-{7-[4-hydroxy-3-(1-hydroxy-2-phenylethyl)phenoxy]-6-methylindan-4-yl}malonamate (15 mg, 79%). The title compound was prepared from ethyl *N*-{7-[4-hydroxy-3-(1-hydroxy-2-phenylethyl)phenoxy]-6-methylindan-4-yl}malonamate in a manner similar to that described for **30** as a white solid (99%). White solid; mp 105–108 °C (dec) (EtOAc–hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.85–2.00 (2H, m), 2.03 (3H, s), 2.60–2.95 (4H, m), 4.90–5.10 (2H, m), 6.44 (1H, dd, J = 3.0, 8.7 Hz), 6.67 (1H, d, J = 8.7 Hz), 6.71 (1H, d, J = 3.0 Hz), 7.10–7.25 (5H, m), 7.38 (1H, s), 9.08 (1H, br s), 9.59 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.8, 24.5, 30.0, 30.5, 43.3, 43.4, 68.3, 113.1, 113.4, 115.4, 123.1, 125.6, 127.7, 128.2, 129.4, 130.3, 133.1, 135.9, 136.7, 139.6, 146.2, 147.9, 150.1, 164.4, 169.6; HRMS calcd for $C_{27}H_{28}NO_6$ $(M+H)^+$ 462.1911, found 462.1956.

6.1.27. *N*-[7-(4-Hydroxy-3-phenethylphenoxy)-6-methylindan-4-yl]malonamic acid (32a)

The title compound was prepared from **28a** in a manner similar to that described for **16a** as a white solid (35%, 3 steps). White solid; mp 155–156 °C (dec) (EtOH–H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.85–2.00 (2H, m), 2.01 (3H, s), 2.40–2.50 (2H, m), 2.70–2.85 (6H, m), 3.38 (2H, s), 6.38 (1H, dd, J = 3.0, 8.7 Hz), 6.43 (1H, d, J = 3.0 Hz), 6.68 (1H, d, J = 8.7 Hz), 7.10–7.30 (5H, m), 7.36 (1H, s), 8.99 (1H, br s), 9.49 (1H, br s), 12.62 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.7, 24.5, 29.9, 30.5, 31.7, 34.9, 43.2, 112.9, 115.4, 116.6, 123.2, 125.6, 128.0, 128.1, 128.3, 128.6, 130.3, 136.0, 136.6, 141.7, 146.2, 149.6, 149.9, 164.3, 169.6; HRMS calcd for $C_{27}H_{28}NO_5$ $(M+H)^+$ 446.1962, found 446.1944.

6.1.28. *N*-(7-{3-[2-(4-Fluorophenyl)ethyl]-4-hydroxyphenoxy}-6-methylindan-4-yl)malonamic acid (32b)

The title compound was prepared from **28b** in a manner similar to that described for **16a** as a beige solid (46%, 3 steps). Beige solid; mp 82–85 °C (dec) (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD = 7/1) δ: 1.95–2.10 (2H, m), 2.12 (3H, s), 2.55–2.65 (2H, m), 2.75–2.90 (6H, m), 3.48 (2H, s), 6.40–6.50 (2H, m), 6.63 (1H, d, J = 8.6 Hz), 6.85–6.95 (2H, m), 7.05–7.15 (2H, m), 7.64 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD = 7/1) δ: 16.1, 24.9, 30.3, 30.4, 32.5, 34.9, 40.2, 113.5, 114.8, 115.0, 115.7, 117.0, 122.4, 128.9, 129.84, 129.89, 135.0, 137.6, 147.0, 148.6, 131.4, 160.5, 162.1, 164.2, 171.5; HRMS calcd for $C_{27}H_{27}FNO_5$ $(M+H)^+$ 464.1868, found 464.1870.

6.1.29. *N*-{7-[4-Hydroxy-3-(3-phenylpropyl)phenoxy]-6-methylindan-4-yl}malonamic acid (32c)

The title compound was prepared from **28c** in a manner similar to that described for **16a** as a beige solid (33%, 3 steps). Beige solid; mp 111–115 °C (dec) (EtOAc–hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.70–2.00 (4H, m), 2.07 (3H, s), 2.40–2.60 (6H, m), 2.70–2.85 (2H, m), 3.40 (2H, s), 6.43 (1H, dd, J = 2.9, 8.7 Hz), 6.50 (1H, d, J = 2.9 Hz), 6.69 (1H, d, J = 8.7 Hz), 7.05–7.30 (5H, m), 7.41 (1H, s), 8.92 (1H, br s), 9.51 (1H, s), 12.62 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.8, 24.5, 29.2, 30.0, 30.5, 30.8, 34.7, 43.2, 112.9, 115.5, 116.2, 123.2, 125.6, 128.2, 128.2, 128.3, 129.1, 130.4, 136.0, 136.6, 142.0, 146.3, 149.6, 150.1, 164.3, 169.6; HRMS calcd for $C_{28}H_{30}NO_5$ $(M+H)^+$ 460.2118, found 460.2122.

6.1.30. Ethyl *N*-(7-{3-[2-(2,4-difluorophenyl)ethyl]-4-methoxyphenoxy}-6-methylindan-4-yl)malonamate (34a)

Ethyl *N*-{7-[3-(2,4-difluorophenyl)acetyl-4-methoxyphenoxy]-6-methylindan-4-yl}malonamate was prepared from **12** and (2,4-difluorophenyl)acetic acid (**33a**) in a manner similar to that described for **15a** (83%).

To a solution of ethyl *N*-{7-[3-(2,4-difluorophenyl)acetyl-4-methoxyphenoxy]-6-methylindan-4-yl}malonamate (100 mg, 0.186 mmol) in CH_2Cl_2 (0.37 mL), triethylsilane (0.104 mL, 0.651 mmol) and TFA (0.130 mL) were added. The mixture was stirred overnight at room temperature. After adding water, the reaction mixture was extracted with Et_2O. The organic layer was washed with water, a saturated aqueous solution of $NaHCO_3$, and brine. 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 = 5/1) to give **34a** (65 mg, 67%). White solid; mp 105–107 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (3H, t, J = 7.2 Hz), 2.00–2.10 (2H, m), 2.12 (3H, s), 2.55–2.65 (2H, m), 2.75–2.90 (6H, m), 3.49 (2H, s), 3.76 (3H, s), 4.27 (2H, q, J = 7.2 Hz), 6.50 (1H, d, J = 2.9 Hz), 6.53 (1H, dd, J = 2.9, 8.9 Hz), 6.65–6.75 (3H, m), 6.95–7.05 (1H, m), 7.75 (1H, s), 9.18 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 16.1, 24.9, 28.5, 30.2, 30.3, 31.0, 41.2, 55.8, 61.9, 103.2, 103.4, 103.5, 110.5, 110.7, 111.0, 112.9, 117.2, 121.8, 130.0, 130.1, 130.7, 131.2, 134.3, 137.4, 146.6, 151.6, 152.2, 162.6, 170.5; HRMS calcd for $C_{30}H_{32}F_2NO_5$ $(M+H)^+$ 524.2243, found 524.2252.

6.1.31. Ethyl *N*-(7-{3-[2-(3,4-difluorophenyl)ethyl]-4-methoxyphenoxy}-6-methylindan-4-yl)malonamate (34b)

The title compound was prepared from **12** and (3,4-difluorophenyl)acetic acid (**33b**) in a manner similar to that described for **34a** as a white solid (59%, 2 steps). White solid; mp 115–117 °C (EtOAc–hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.34 (3H, t, J = 7.1 Hz), 2.00–2.10 (2H, m), 2.12 (3H, s), 2.55–2.65 (2H, m), 2.75–2.90 (6H, m), 3.50 (2H, s), 3.77 (3H, s), 4.27 (2H, q, J = 7.1 Hz), 6.47 (1H, d, J = 3.0 Hz), 6.56 (1H, dd, J = 3.0, 8.8 Hz), 6.70 (1H, d, J = 8.8 Hz), 6.75–7.05 (3H, m), 7.75 (1H, s), 9.18 (1H, br s); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.1, 16.0, 24.9, 30.2, 30.3, 32.3, 35.0, 41.2, 55.8, 61.9, 111.1, 113.0, 116.6, 116.8, 117.1, 117.2, 117.3, 121.9, 124.3, 130.0, 130.1, 130.5, 134.3, 137.4, 139.0, 146.5, 151.6, 152.1, 162.6, 170.4; HRMS calcd for $C_{30}H_{32}F_2NO_5$ $(M+H)^+$ 524.2243, found 524.2248.

6.1.32. Ethyl *N*-(7-{3-[2-(2-chlorophenyl)ethyl]-4-methoxyphenoxy}-6-methylindan-4-yl)malonamate (34c)

The title compound was prepared from **12** and (2-chlorophenyl)acetic acid (**33c**) in a manner similar to that described for **34a** as a pale yellow solid (74%, 2 steps). Pale yellow solid; mp 111–113 °C (EtOAc–hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.34 (3H, t, J = 7.1 Hz), 2.00–2.10 (2H, m), 2.13 (3H, s), 2.60–2.70 (2H, m), 2.80–2.90 (4H, m), 2.95–3.00 (2H, m), 3.49 (2H, s), 3.76 (3H, s), 4.27 (2H, q, J = 7.1 Hz), 6.51 (1H, dd, J = 3.0, 8.8 Hz), 6.58 (1H, d, J = 3.0 Hz), 6.68 (1H, d, J = 8.8 Hz), 7.05–7.15 (3H, m), 7.30–7.35 (3H, m), 7.76 (1H, s), 9.18 (1H, br s); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.1, 16.1, 24.9, 30.2, 30.4, 30.5, 33.6, 41.2, 55.8, 62.0, 111.0, 112.7, 117.3, 121.8, 126.5, 127.2, 129.3, 130.0, 130.1, 130.6, 131.1, 134.0, 134.2, 137.5, 139.6, 146.6, 151.6, 152.3, 162.6, 170.5; HRMS calcd for $C_{30}H_{33}ClNO_5$ $(M+H)^+$ 522.2042, found 522.2049.

6.1.33. Ethyl *N*-(7-{3-[2-(3-chlorophenyl)ethyl]-4-methoxyphenoxy}-6-methylindan-4-yl)malonamate (34d)

The title compound was prepared from **12** and (3-chlorophenyl)acetic acid (**33d**) in a manner similar to that described for **34a** as a white solid (54%, 2 steps). White solid; mp 135–136 °C (EtOAc–hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.34 (3H, t, J = 7.2 Hz), 2.00–2.10 (2H, m), 2.13 (3H, s), 2.55–2.65 (2H, m), 2.80–2.90 (6H, m), 3.49 (2H, s), 3.77 (3H, s), 4.27 (2H, q, J = 7.2 Hz), 6.51 (1H, d, J = 3.0 Hz), 6.55 (1H, dd, J = 3.0, 8.9 Hz), 6.70 (1H, d, J = 8.9 Hz), 6.95–7.05 (3H, m), 7.10–7.20 (3H, m),

7.75 (1H, s), 9.18 (1H, br s); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.1, 16.1, 24.9, 30.2, 30.3, 32.2, 35.6, 41.2, 55.8, 62.0, 111.1, 112.9, 117.1, 121.9, 125.9, 126.8, 128.7, 129.4, 130.0, 130.1, 130.8, 133.9, 134.3, 137.5, 144.2, 146.5, 151.6, 152.2, 162.6, 170.5; HRMS calcd for $C_{30}H_{33}ClNO_5$ $(M+H)^+$ 522.2042, found 522.2046.

6.1.34. Ethyl *N*-(7-{3-[2-(4-chlorophenyl)ethyl]-4-methoxyphenoxy}-6-methylindan-4-yl)malonamate (34e)

The title compound was prepared from **12** and (4-chlorophenyl)acetic acid (**33e**) in a manner similar to that described for **34a** as a colorless amorphous solid (58%, 2 steps). Colorless amorphous solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.34 (3H, t, J = 7.2 Hz), 2.00–2.10 (2H, m), 2.12 (3H, s), 2.55–2.65 (2H, m), 2.80–2.90 (6H, m), 3.50 (2H, s), 3.77 (3H, s), 4.27 (2H, q, J = 7.2 Hz), 6.48 (1H, d, J = 2.9 Hz), 6.56 (1H, dd, J = 2.9, 8.7 Hz), 6.70 (1H, d, J = 8.7 Hz), 7.00–7.10 (2H, m), 7.15–7.25 (2H, m), 7.75 (1H, s), 9.18 (1H, br s); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.1, 16.1, 24.9, 30.2, 30.3, 32.3, 35.2, 41.2, 55.8, 62.0, 111.1, 113.0, 117.1, 121.9, 128.2, 129.9, 130.0, 130.0, 130.8, 131.4, 134.3, 137.4, 140.5, 146.6, 151.6, 152.1, 162.6, 170.5; HRMS calcd for $C_{30}H_{33}ClNO_5$ $(M+H)^+$ 522.2042, found 522.2045.

6.1.35. *N*-(7-{3-[2-(2,4-Difluorophenyl)ethyl]-4-hydroxyphenoxy}-6-methylindan-4-yl)malonamic acid (35a)

To a solution of **34a** (69 mg, 0.132 mmol) in CH_2Cl_2 (2 mL), a 1 M solution of BBr_3 in CH_2Cl_2 (0.527 mL, 0.527 mmol) was added dropwise at −78 °C. The mixture was stirred overnight at room temperature. After adding EtOH, the mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 1/1) to give ethyl *N*-(7-{3-[2-(2,4-difluorophenyl)ethyl]-4-hydroxyphenoxy}-6-methylindan-4-yl)malonamate (63 mg, 94%).

The title compound was prepared from ethyl *N*-(7-{3-[2-(2,4-difluorophenyl)ethyl]-4-hydroxyphenoxy}-6-methylindan-4-yl) malonamate in a manner similar to that described for **30** as a beige solid (74%). Beige solid; mp 85–88 °C (dec) (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD = 9/1) δ: 1.95–2.10 (2H, m), 2.11 (3H, s), 2.55–2.65 (2H, m), 2.75–2.95 (6H, m), 3.45 (2H, s), 6.40–6.50 (2H, m), 6.60–6.80 (3H, m), 7.00–7.10 (1H, m), 7.61 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD = 9/1) δ: 15.9, 24.9, 28.2, 30.2, 30.9, 40.6, 103.3, 110.7, 113.4, 115.5, 117.0, 122.5, 124.5, 128.7, 129.4, 129.8, 131.3, 135.3, 137.5, 147.1, 149.0, 151.1, 160.2, 161.8, 164.6, 171.7; HRMS calcd for $C_{27}H_{26}F_2NO_5$ $(M+H)^+$ 482.1774, found 482.1779.

6.1.36. *N*-(7-{3-[2-(3,4-Difluorophenyl)ethyl]-4-hydroxyphenoxy}-6-methylindan-4-yl)malonamic acid (35b)

The title compound was prepared from **34b** in a manner similar to that described for **35a** as a beige solid (29%, 2 steps). Beige solid; mp 153–154 °C (dec) (EtOAc–hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.85–2.00 (5H, m), 2.35–2.50 (2H, m), 2.70–2.95 (6H, m), 6.30–6.40 (2H, m), 6.65–6.70 (1H, m), 6.90–7.00 (1H, m), 7.10–7.30 (2H, m), 7.79 (1H, s), 9.04 (1H, s), 12.45 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.6, 24.4, 29.9, 30.5, 31.4, 33.8, 43.2, 113.2, 115.5, 116.6, 116.7, 116.9, 117.0, 117.2, 123.2, 125.0, 128.0, 128.1, 130.3, 135.9, 136.6, 139.4, 146.2, 149.6, 149.9, 164.3, 169.6; HRMS calcd for $C_{27}H_{26}F_2NO_5$ $(M+H)^+$ 482.1774, found 482.1780.

6.1.37. *N*-(7-{3-[2-(2-Chlorophenyl)ethyl]-4-hydroxyphenoxy}-6-methylindan-4-yl)malonamic acid (35c)

The title compound was prepared from **34c** in a manner similar to that described for **35a** as a beige solid (30%, 2 steps). Beige solid; mp 134–138 °C (dec) (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD = 9/1) δ: 1.95–2.10 (2H, m), 2.12 (3H, s), 2.55–2.65 (2H, m), 2.80–2.90 (4H, m), 2.95–3.05 (2H, m), 3.50 (2H, s), 6.43 (1H, dd, J = 2.4, 8.6 Hz), 6.54 (1H, d, J = 2.4 Hz), 6.63 (1H, d, J = 8.6 Hz), 7.05–7.20 (3H, m), 7.30–7.35 (1H, m), 7.63 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD = 9/1) δ: 16.1, 24.9, 30.3, 30.4, 30.5, 33.6, 40.2, 113.3, 115.7, 117.2, 122.4, 122.5, 126.7, 127.4, 128.7, 129.4, 130.0, 130.6, 133.9, 135.0, 137.6, 139.3, 147.0, 148.5, 151.5, 164.2, 171.3; HRMS calcd for $C_{27}H_{27}ClNO_5$ $(M+H)^+$ 480.1572, found 480.1577.

6.1.38. *N*-(7-{3-[2-(3-Chlorophenyl)ethyl]-4-hydroxyphenoxy}-6-methylindan-4-yl)malonamic acid (35d)

The title compound was prepared from **34d** in a manner similar to that described for **35a** as a beige solid (51%, 2 steps). Beige solid; mp 154–155 °C (dec) (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD = 9/1) δ: 1.95–2.10 (2H, m), 2.12 (3H, s), 2.55–2.65 (2H, m), 2.80–2.90 (6H, m), 3.46 (2H, s), 6.40–6.50 (2H, m), 6.60–6.70 (1H, m), 7.00–7.20 (4H, m), 7.63 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD = 9/1) δ: 16.0, 24.9, 30.2, 30.3, 32.2, 35.3, 40.2, 113.4, 115.5, 116.9, 122.4, 125.9, 126.8, 128.6, 128.7, 129.4, 129.4, 129.9, 133.8, 135.1, 137.5, 144.1, 147.0, 148.9, 151.1, 164.3, 171.5; HRMS calcd for $C_{27}H_{27}ClNO_5$ $(M+H)^+$ 480.1572, found 480.1573.

6.1.39. *N*-(7-{3-[2-(4-Chlorophenyl)ethyl]-4-hydroxyphenoxy}-6-methylindan-4-yl)malonamic acid (35e)

The title compound was prepared from **34e** in a manner similar to that described for **35a** as a beige solid (46%, 2 steps). Beige solid; mp 125–128 °C (dec) (EtOAc–hexane); ^{1}H NMR (600 MHz, DMSO-d_6) δ: 1.85–1.95 (2H, m), 1.99 (3H, s), 2.40–2.50 (2H, m), 2.70–2.85 (6H, m), 3.38 (2H, s), 6.36 (1H, d, J = 3.0 Hz), 6.39 (1H, dd, J = 3.0, 8.6 Hz), 6.68 (1H, d, J = 8.6 Hz), 7.10–7.15 (2H, m), 7.25–7.30 (2H, m), 7.36 (1H, s), 9.00 (1H, s), 9.49 (1H, s), 12.62 (1H, br s); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 15.7, 24.5, 29.9, 30.5, 31.5, 34.0, 43.2, 113.1, 115.4, 116.6, 123.2, 127.9, 127.9, 128.0, 128.1, 128.2, 130.3, 136.0, 136.6, 140.6, 146.2, 149.6, 149.9, 164.3, 169.6; HRMS calcd for $C_{27}H_{27}ClNO_5$ $(M+H)^+$ 480.1572, found 480.1540.

6.1.40. 2-Methoxy-5-(5-methyl-7-nitroindan-4-yloxy)benzaldehyde (36)

To a solution of **10** (5.00 g, 16.7 mmol) and dichloromethyl methyl ether (3.02 mL, 33.4 mmoL) in CH_2Cl_2 (50 mL), $TiCl_4$ (42 mg, 0.198 mmol) was added dropwise at 0 °C. The mixture was stirred overnight at room temperature. After adding ice water, 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 triturated with hexane and diethyl ether, and the insoluble material was collected by filtration to give **36** (4.37 g, 80%) as a beige solid. Beige solid; mp 175–176 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.00–2.15 (2H, m), 2.22 (3H, s), 2.64 (2H, t, J = 7.5 Hz), 3.39 (2H, t, J = 7.5 Hz), 3.92 (3H, s), 6.97 (1H, d, J = 9.0 Hz), 7.11 (1H, dd, J = 3.2, 9.0 Hz), 7.15 (1H, d, J = 3.2 Hz), 7.97 (1H, s), 10.41 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.0, 24.8, 30.3, 34.3, 56.2, 113.4, 113.8, 123.5, 125.4, 125.9, 130.7, 139.5, 142.0, 142.1, 150.8, 153.9, 157.5, 189.1; HRMS calcd for $C_{18}H_{18}NO_5$ $(M+H)^+$ 328.1179, found 328.1187.

6.1.41. 7-{4-Methoxy-3-[2-(2-methoxyphenyl)ethyl]phenoxy}-6-methylindan-4-ylamine (38a)

To a solution of (2-methoxybenzyl)triphenylphosphonium bromide (**37a**) (546 mg, 1.30 mmol) in THF (20 mL), KO^{t}Bu (135 mg, 1.20 mmol) was added under Ar at room temperature. After stirring for 15 min, **36** (328 mg, 1.00 mmol) was added to give 4-{4-methoxy-3-[2-(2-methoxyphenyl)vinyl]phenoxy}-5-methyl-7-nitroindane (247 mg, 57%)

To a solution of 4-{4-methoxy-3-[2-(2-methoxyphenyl) vinyl]phenoxy}-5-methyl-7-nitroindane (257 mg, 0.572 mmol) in EtOAc (50 mL), 10% Pd/C (56% wet with water, 200 mg, 0.0827 mmol) was added. The mixture was stirred overnight under a hydrogen atmosphere at room temperature. Insoluble materials were removed by filtration and washed with EtOAc. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 19/1–0/1) to give **38a** (192 mg, 83%) as a colorless amorphous solid. Colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.90–2.15 (5H, m), 2.55–2.92 (8H, m), 3.45 (2H, br s), 3.75 (3H, s), 3.80 (3H, s), 6.40 (1H, d, J = 4.5 Hz), 6.48 (1H, dd, J = 8.8 Hz, 3.0 Hz), 6.62 (1H, d, J = 3.0 Hz), 6.67 (1H, d, J = 8.8 Hz), 6.75–6.95 (2H, m), 7.00–7.25 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.9, 24.9, 29.7, 30.3, 30.4, 30.4, 55.3, 55.9, 110.2, 111.0, 112.0, 115.5, 117.0, 120.3, 126.9, 128.3, 129.9, 130.0, 130.6, 132.1, 137.8, 138.8, 142.3, 152.0, 152.2, 157.5; HRMS calcd for $C_{26}H_{30}NO_3$ $(M+H)^+$ 404.2220, found 404.2219.

6.1.42. 7-{4-Methoxy-3-[2-(3-methoxyphenyl)ethyl]phenoxy}-6-methylindan-4-ylamine (38b)

The title compound was prepared from (3-methoxybenzyl)triphenylphosphonium bromide (**37b**) in a manner similar to that described for **38a** as a colorless amorphous solid (70%, 2 steps). Colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.90–2.15 (5H, m), 2.55–2.95 (8H, m), 3.45 (2H, br s), 3.70–3.85 (6H, m), 6.35–6.90 (7H, m), 7.10–7.25 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.8, 24.9, 29.7, 30.3, 32.4, 36.1, 55.1, 55.9, 111.1, 111.2, 112.4, 114.1, 115.5, 116.9, 121.0, 128.4, 129.1, 129.9, 131.3, 137.7, 138.8, 142.3, 143.9, 151.9, 152.2, 159.5; HRMS calcd for $C_{26}H_{30}NO_3$ $(M+H)^+$ 404.2220, found 404.2215.

6.1.43. 7-{4-Methoxy-3-[2-(4-methoxyphenyl)ethyl]phenoxy}-6-methylindan-4-ylamine (38c)

The title compound was prepared from (4-methoxybenzyl)triphenylphosphonium bromide (**37c**) in a manner similar to that described for **38a** as a colorless amorphous solid (49%, 2 steps). Colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.95–2.15 (5H, m), 2.55–2.95 (8H, m), 3.45 (2H, br s), 3.76 (3H, s), 3.78 (3H, s), 6.40 (1H, s), 6.45–6.55 (2H, m), 6.69 (1H, d, J = 8.7 Hz), 6.75–6.85 (2H, m), 7.00–7.10 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.8, 24.9, 29.6, 30.3, 32.7, 35.1, 55.2, 55.9, 111.1, 112.3, 113.6, 115.5, 116.9, 128.4, 129.4, 129.9, 131.4, 134.4, 137.7, 138.8, 142.3, 151.9, 152.2, 157.7; HRMS calcd for $C_{26}H_{30}NO_3$ $(M+H)^+$ 404.2220, found 404.2218.

6.1.44. Ethyl *N*-(7-{4-methoxy-3-[2-(2-methoxyphenyl) ethyl]phenoxy}-6-methylindan-4-yl)malonamate (39a)

The title compound was prepared from **38a** in a manner similar to that described for **12** as a white solid (80%). White solid; mp 101–102 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (3H, t, J = 7.1 Hz), 1.95–2.10 (2H, m), 2.13 (3H, s), 2.63 (2H, t, J = 7.4 Hz), 2.75–2.95 (6H, m), 3.49 (2H, s), 3.76 (3H, s), 3.79 (3H, s), 4.27 (2H, q, J = 7.1 Hz), 6.49 (1H, dd, J = 3.0, 8.8 Hz), 6.60 (1H, d, J = 3.0 Hz), 6.68 (1H, d, J = 8.8 Hz), 6.75–6.90 (2H, m), 7.00–7.20 (2H, m), 7.75 (1H, s), 9.18 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 16.1, 24.9, 30.2, 30.3, 30.4, 30.4, 41.2, 55.3, 55.9, 61.9, 110.2, 111.0, 112.3, 117.3, 120.2, 121.8, 127.0, 129.9, 130.0, 130.0, 130.5, 132.2, 134.2, 137.5, 146.7, 151.6, 152.3, 157.5, 162.6, 170.4; HRMS calcd for $C_{31}H_{36}NO_6$ $(M+H)^+$ 518.2537, found 518.2532.

6.1.45. Ethyl *N*-(7-{4-methoxy-3-[2-(3-methoxyphenyl) ethyl]phenoxy}-6-methylindan-4-yl)malonamate (39b)

The title compound was prepared from **38b** in a manner similar to that described for **12** as a white solid (78%). White solid; mp 94–95 °C (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (3H, t, J = 7.1 Hz), 1.95–2.10 (2H, m), 2.13 (3H, s), 2.55–2.70 (2H, m), 2.75–2.95 (6H, m), 3.49 (2H, s), 3.77 (3H, s), 3.78 (3H, s), 4.27 (2H, q, J = 7.1 Hz), 6.45–6.60 (2H, m), 6.65–6.80 (4H, m), 7.10–7.25 (1H, m), 7.75 (1H, s), 9.18 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 16.1, 24.9, 30.2, 30.3, 32.4, 36.0, 41.2, 55.1, 55.8, 61.9, 111.1, 111.2, 112.7, 114.1, 117.1, 121.0, 121.8, 129.1, 130.0, 130.0, 131.4, 134.3, 137.5, 143.8, 146.6, 151.6, 152.2, 159.5, 162.6, 170.4; HRMS calcd for $C_{31}H_{36}NO_6$ $(M+H)^+$ 518.2537, found 518.2533.

6.1.46. Ethyl *N*-(7-{4-methoxy-3-[2-(4-methoxyphenyl) ethyl]phenoxy}-6-methylindan-4-yl)malonamate (39c)

The title compound was prepared from **38c** in a manner similar to that described for **12** as a colorless amorphous solid (77%). Colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (3H, t, J = 7.1 Hz), 1.95–2.10 (2H, m), 2.12 (3H, s), 2.55–2.70 (2H, m), 2.75–2.95 (6H, m), 3.50 (2H, s), 3.77 (3H, s), 3.78 (3H, s), 4.27 (2H, q, J = 7.1 Hz), 6.50–6.60 (2H, m), 6.65–6.85 (3H, m), 7.00–7.10 (2H, m), 7.74 (1H, s), 9.20 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 16.1, 24.9, 30.2, 30.4, 32.7, 35.0, 41.2, 55.2, 55.9, 61.9, 111.1, 112.7, 113.6, 117.1, 121.8, 129.4, 130.0, 130.0, 131.5, 134.3, 134.3, 137.5, 146.6, 151.6, 152.2, 157.7, 162.6, 170.4; HRMS calcd for $C_{31}H_{36}NO_6$ $(M+H)^+$ 518.2537, found 518.2535.

6.1.47. *N*-(7-{4-Hydroxy-3-[2-(2-hydroxyphenyl) ethyl]phenoxy}-6-methylindan-4-yl}malonamic acid (40a)

The title compound was prepared from **39a** in a manner similar to that described for **35a** as a beige solid (56%, 2 steps). Beige solid; mp 102–106 °C (dec) (EtOAc–hexane); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD = 7/1) δ: 1.95–2.10 (2H, m), 2.13 (3H, s), 2.60–2.95 (8H, m), 3.49 (2H, s), 6.50–6.60 (2H, m), 6.65–6.80 (3H, m), 7.05–7.15 (2H, m), 7.59 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD = 7/1) δ: 16.1, 25.2, 30.5, 30.6, 30.9, 31.3, 41.0, 113.6, 115.3, 115.9, 116.7, 120.1, 123.2, 127.5, 128.2, 129.6, 130.0, 130.1, 130.2, 136.2, 137.9, 147.5, 149.2, 151.4, 154.8, 165.2, 171.6; HRMS calcd for $C_{27}H_{28}NO_6$ $(M+H)^+$ 462.1911, found 462.1913.

6.1.48. *N*-(7-{4-Hydroxy-3-[2-(3-hydroxyphenyl) ethyl]phenoxy}-6-methylindan-4-yl}malonamic acid (40b)

The title compound was prepared from **39b** in a manner similar to that described for **35a** as a white solid (65%, 2 steps). White solid; mp 150–152 °C (dec) (EtOAc–hexane); ^{1}H NMR (600 MHz, DMSO-d_6) δ: 1.85–1.95 (2H, m), 2.02 (3H, s), 2.45–2.50 (2H, m), 2.65–2.80 (6H, m), 3.39 (2H, s), 6.36 (1H, dd, J = 3.0, 8.6 Hz), 6.47 (1H, d, J = 3.0 Hz), 6.50–6.60 (3H, m), 6.67 (1H, d, J = 8.6 Hz), 6.95–7.05 (1H, m), 7.36 (1H, s), 8.97 (1H, s), 9.16 (1H, s), 12.60 (1H, br s); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 15.7, 24.5, 29.9, 30.5, 31.7, 35.1, 43.2, 112.6, 112.8, 115.2, 115.4, 116.6, 119.0, 123.2, 128.2, 128.8, 129.0, 130.3, 136.0, 136.7, 143.1, 146.2, 149.6, 149.9, 157.2, 164.3, 169.6; HRMS calcd for $C_{27}H_{28}NO_6$ $(M+H)^+$ 462.1911, found 462.1923.

6.1.49. *N*-(7-{4-Hydroxy-3-[2-(4-hydroxyphenyl) ethyl]phenoxy}-6-methylindan-4-yl}malonamic acid (40c)

The title compound was prepared from **39c** in a manner similar to that described for **35a** as a colorless amorphous solid (56%, 2 steps). Colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD = 7/1) δ: 1.95–2.10 (5H, m), 2.55–2.65 (2H, m), 2.75–2.90 (6H, m), 3.48 (2H, s), 6.34 (1H, d, J = 3.0 Hz), 6.49 (1H, dd, J = 3.0, 8.9 Hz), 6.60–6.70 (3H, m), 6.90–7.00 (2H, m), 7.55 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD = 7/1) δ: 15.9, 24.9, 29.6, 30.3, 32.2, 34.6, 40.3, 113.5, 115.0, 115.6, 116.8, 122.6, 122.7, 129.2, 129.4, 129.8, 133.0, 135.3, 137.6, 147.2, 148.8, 151.0, 154.4, 164.5, 171.5; HRMS calcd for $C_{27}H_{28}NO_6$ $(M+H)^+$ 462.1911, found 462.1943.

6.2. Biology

6.2.1. Receptor binding assay

Recombinant *h*TRα$_1$ and *h*TRβ$_1$ were expressed in insect cells.[32] Cell homogenates containing the respective receptors were 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). A 0.5-mL aliquot of the mixture was incubated in a glass tube in an ice bath for 16–48 h. After incubation, 500 μL of an ion-exchange resin (Muromachi Kagaku, Dowex 1-X8, 80 mg/mL, suspended in the buffer indicated above) was added to each test tube and stirred. Stirring was repeated after the resin sedimented at the bottom of the tube, followed by additional stirring. The tubes were centrifuged at 1000 rpm for 5 min at 1 °C using a centrifuge separator (KUBOTA, 8800). An aliquot of the supernatant (500 μL) was transferred to another tube, and radioactivity was measured with a γ-ray detector. The detected radioactivity was proportional to the amount of [^{125}I]-T_3 bound to the soluble thyroid hormone receptor. The amount of recombinant thyroid hormone receptor cell homogenate used in the experiment was in a range for which the radioactivity associated with T_3 binding showed a concentration-dependent increase in the amount of the homogenate.

The K_d value of T_3 to a particular receptor subtype was determined from Scatchard analysis of the binding data obtained with the different [^{125}I]-T_3 levels. Under these experimental conditions, the K_d values of T_3 binding for *h*TRα$_1$ and *h*TRβ$_1$ were 0.268 and 0.304 nM, respectively.

The K_i values of each compound were calculated using the equation

$$K_i\ (\mathrm{nM}) = [IC_{50}]/(1 + K_d/0.95),$$

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

6.2.2. Luciferase reporter gene assay

*h*TRα$_1$[33] and *h*TRβ$_1$[34] were cloned in a mammalian cell expression vector (pCDM8, Promega) as described previously.[35] The luciferase reporter gene was constructed by inserting the thyroid hormone responsive element (5′-GATCCAGGTCATGACCTGGATCC-3′) into a commercial luciferase expression vector (pGL2-promoter, Promega). Each thyroid hormone receptor vector and the luciferase reporter vector were co-transfected into trypsin-digested and suspended COS1 cells using the calcium phosphate-mediated method.[36] These cells were seeded into 96-well multiwell plates and cultured overnight. The following day, thyromimetics (at 10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4} M) were added and culture continued for 1 day. Luciferase activities were determined using a commercial kit (Luciferase Assay System, Promega) and Top count (Packard) on the third day. All thyromimetics showed dose-dependent responses.

6.3. Molecular modeling

A docking model for **40a** was constructed based on the crystal structure of *h*TRβ$_1$ with **41** (PDB code 3JZC[23]). The malonic acid part of **40a** was modeled by keeping the hydrogen bonds that were observed between TRβ and **41**. The phenethyl part of **40a** was modeled with reference to the complex between TRβ and **7,** which had a large substituent next to the hydroxyl group of di-phenyl ether (PDB code 1Q4X[20]).

The constructed model was optimized using CHARMm forcefield implemented in Discovery Studio3.1 (Accelrys Inc., San Diego, CA, USA).[37] Protein structures were optimized by the steepest descent (SD) method at a dielectric constant of $\varepsilon = 4R$ (R: distance). Optimization was performed stepwise. Initially, structures were minimized under conditions that constrained non-hydrogen atoms. Next, the protein backbone atoms were constrained. At the final step, all atoms were minimized with a harmonic atom constraint. The force constants of the harmonic atom constraints gradually decreased from 10.0 to 1.0 kcal/mol Å^2.

CH/π interactions were evaluated using the program CHPI implemented in BioStation Viewer.[26] This program determined the distances and angles between CHs and interacting aromatic rings. This program searched for CH/π interactions based on the distances (<3.05 Å) and angles between CHs and interacting aromatic rings.[38]

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