Indanylacetic Acid Derivatives Carrying 4-Thiazolyl-phenoxy Tail Groups, a New Class of Potent PPAR α/γ/δ Pan Agonists: Synthesis, Structure−Activity Relationship, and In Vivo Efficacy

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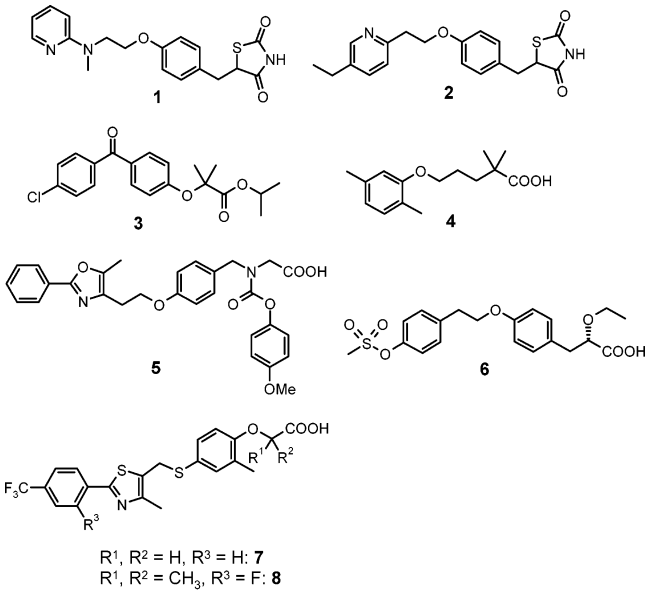
Compounds that simultaneously activate the three peroxisome proliferator-activated receptor (PPAR) subtypes alpha, gamma, and delta hold potential to address the adverse metabolic and cardiovascular conditions associated with diabetes and the metabolic syndrome. We recently identified the indanylacetic acid moiety as a well-tunable PPAR agonist head group. Here we report the synthesis and structure−activity relationship (SAR) studies of novel aryl tail group derivatives that led to a new class of potent PPAR pan agonists. While most of the tail group modifications imparted potent PPAR delta agonist activity, improvement of PPAR alpha and gamma activity required the introduction of new heterocyclic substituents that were not known in the PPAR literature. Systematic optimization led to the discovery of 4-thiazolyl-phenyl derivatives with potent PPAR alpha/gamma/delta pan agonistic activity. The lead candidate from this series was found to exhibit excellent ADME properties and superior therapeutic potential compared to known PPAR gamma activating agents by favorably modulating lipid levels in *h*ApoA1 mice and hyperlipidemic hamsters, while normalizing glucose levels in diabetic rodent models.

Introduction

Diabetes and its associated adverse cardiovascular conditions are increasingly prevalent in the Western society and are considered one of the main threats to human health in the 21st century.[1] The nuclear hormone receptors PPARα[a] and PPARγ are important regulators of lipid and carbohydrate metabolism, and agonists have shown therapeutic benefit for the treatment of diabetes and dyslipidemia.[2−5] PPARγ has been identified as a key regulator for insulin sensitivity, and two PPARγ agonists, rosiglitazone (**1**) and pioglitazone (**2**), have demonstrated clinical success in the treatment of Type 2 diabetes since their introduction in 1999.[6,7] Agonists of PPARα, for example, fenofibrate (**3**) or gemfibrozil (**4**), have been shown to lower plasma lipid, triglyceride, and free fatty acid (FFA) levels and have been in clinical use for the treatment of dyslipidemia since the 1960s. As combined treatment with PPARγ and PPARα agonists has been recognized for its potential to improve insulin resistance and lower triglyceride levels, several companies have been actively pursuing PPARα,γ dual-acting compounds.[8−11] The clinically most extensively investigated candidates muraglitazar[12,13] (**5**) and tesaglitazar[14−16] (**6**) were shown to significantly lower glucose and lipid levels in clinical trials. The role of the third PPAR family member, PPARδ, is just beginning to emerge. Animal studies revealed that activation of PPARδ, for example by the selective PPARδ agonist **7** (GW501516), induces fatty acid catabolism in skeletal muscle and is associated with improved insulin sensitivity, attenuated weight gain, and elevated high-density lipoprotein (HDL) levels.[17−21]



To effectively target insulin resistance/hyperglycemia and associated conditions including dyslipidemia and hypertension (i.e., the metabolic syndrome), the concept of simultaneously activating PPARα, γ, and δ through a single compound has attracted increasing interest over the past few years.[22] A number of PPAR pan agonists have been described in the literature,[23−29] and animal studies with selected compounds suggest benefits over selective PPARγ and PPARα,γ agonists, particularly with respect to their effects on lipid levels and body weight.[22] The clinically most advanced PPAR pan agonist, sodelglitazar (**8**), is currently in phase II clinical trials. Human efficacy and safety evaluation of this first clinical example will be an important step toward validation of this approach.

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[a] Abbreviations: PPAR, peroxisome proliferator-activated receptor; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FFA, free fatty acid; IRBA, insulin receptor binding assay.

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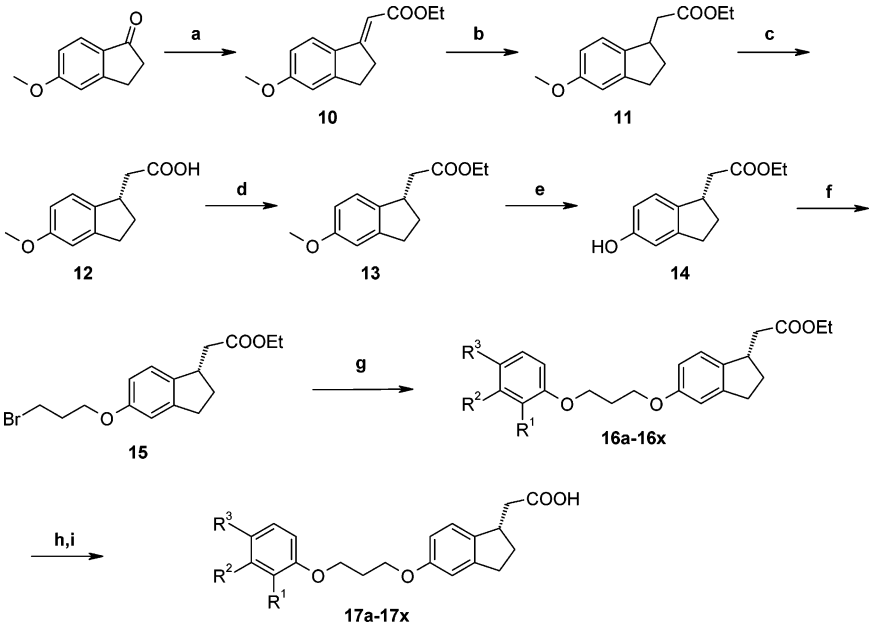
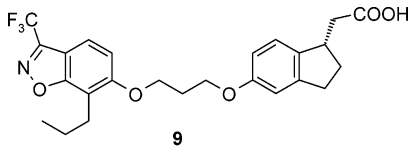
Scheme 1. Synthesis of the Target Compounds[a]



[a] Reagents and conditions: (a) ethyl bromoacetate, zinc, THF; (b) H_2, Pd/C, EtOH; (c) 10−30% lipase PS (amano enzymes), 99% ee 38% (3 steps); (d) TMSCl, EtOH, 99%; (e) $AlCl_3$, EtSH, CH_2Cl_2, 96%; (f) 1,3-dibromopropane, cesium carbonate, DMF, RT, 60%; (g) substituted phenol, Cs_2CO_3, DMF; (h) LiOH, THF, H_2O, MeOH.

We recently described PPARα,γ dual agonists containing the new indanylacetic acid head group.[30] In the course of our SAR studies with this core, we discovered that derivatives lacking a substituent at the α position of the acetic acid moiety show markedly increased PPARδ agonistic activity, however, at the expense of either PPARα or PPARγ agonist activity.[31] While our initial efforts focused on combining the indanylacetic acid moiety with oxazole or thiazole tail groups,[32] we later sought to expand the structural variety of the tail group portion.[33] One of the first derivatives emerging from this effort was compound **9**, which contains an established PPAR agonist benzisoxazole tail portion.[23,34] Compound **9** was a potent full agonist at all three PPAR receptors in vitro but was hampered by unfavorable drug properties, among them poor aqueous solubility (<1 μM).

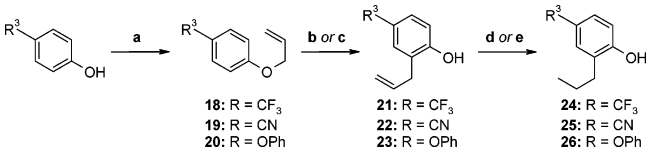


9

*h*PPARα EC_{50} 192 nM
*h*PPARδ EC_{50} 6 nM
IRBA EC_{50} 42 nM

Initial structure−activity relationship (SAR) studies focused on close analogs of **9** having fused ring systems such as benzisoxazoles, benzofurans, and indoles with various substituents.[33] The SAR from these studies suggested that the propyl-substituted trifluoromethylbenzisoxazole group in compound **9** is, among fused ring systems, optimized for PPARγ and PPARα activity (see Supporting Information). Further optimization of the tail group concentrated on substituted aryl rings instead of fused ring systems. This effort led to the discovery of the potent and balanced PPAR triple activating 4-thiazolyl-phenoxy series, the details of which will be described in this account. Optimization within this series culminated in the identification of **34r**, a compound with favorable drug properties and robust in vivo efficacy in a number of therapeutically relevant animal models.

Scheme 2. Synthesis of 2-Propylphenol Derivatives via Claisen Rearrangement[a]



[a] Reagents and conditions: (a) allylbromide, Cs_2CO_3, DMF; (b) 200 °C; (c) BCl_3, CH_2Cl_2; (d) H_2, Pd/C, EtOH; (e) NH^+HCOO^-, Pd/C, EtOH.

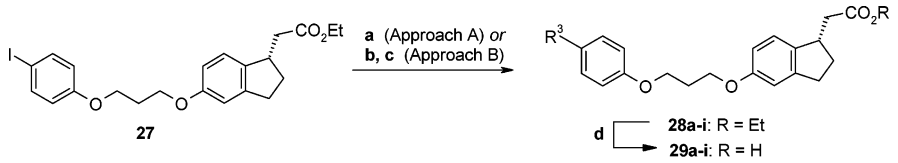
Chemistry

Target compounds **17a**−**17x** were synthesized according to Scheme 1. Reformatsky reaction of 5-methoxyindanone with ethylbromoacetate yielded the exocyclic alkene **10**, which was subsequently hydrogenated to the indanylacetic acid ester **11**. Treatment with lipase PS (Amano enzyme) led to the selective hydrolysis of the (*S*)-enantiomer of ester **11** to its corresponding (*S*)-acid **12**. The absolute configuration was indirectly determined by X-ray crystallography of a derivative containing Evans' oxazolidinone chiral auxiliary (see Supporting Information). Enantiomerically pure **12** was esterified (**13**), demethylated (**14**), and reacted with a 1,3-dibromopropane group to furnish the head-linker fragment **15**. This compound was then coupled with substituted phenols comprising the tail portion to form the ester intermediates **16a**−**16x**, which were hydrolyzed to afford the final compounds **17a**−**17x**.

Tail groups were commercially available, synthesized according to Scheme 2, and modified *after* attachment to the head-linker fragment **15** (Schemes 3−5). Intermediates carrying a propyl chain *ortho* to the phenol OH group were synthesized by allylation of the corresponding phenols, thermal or Lewis acid mediated Claisen rearrangement reaction, and subsequent hydrogenation of the allyl group (Scheme 2).

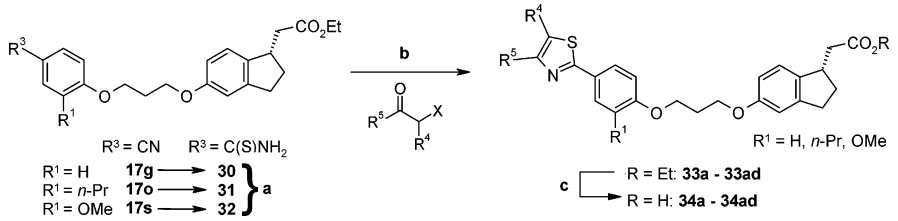
The R^3 group of intermediate **16** was used as a handle to introduce structural diversity, because SAR studies had identified this position as an important structural feature for achieving PPAR pan agonistic activity. Emphasis was placed on the introduction of heterocyclic groups at this position. Such analogs

Scheme 3. Tail Group Modification via Suzuki Coupling Reaction[a]



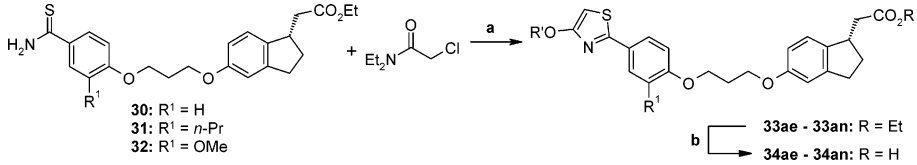
[a] Reagents and conditions: (a) $R^3B(OH)_2$, $PdCl_2(dppf)$, Na_2CO_3, toluene, dioxane; (b) bis(pinacolato)diboron, $PdCl_2(dppf)$, KOAc, DMF, 80 °C; (c) R^3-Br, $PdCl_2(dppf)$, Na_2CO_3, DMF, 80 °C; (d) LiOH, THF, H_2O, MeOH.

Scheme 4. Tail Group Modification via Hantzsch Thiazole Synthesis[a]



[a] Reagents and conditions: (a) H_2S, $HNEt_2$, DMF, rt → 60 °C; (b) α-bromo/chloroketone, EtOH; (c) LiOH, THF, H_2O, MeOH.

Scheme 5. Synthesis of 4-(Alkoxythiazolyl)phenyl Derivatives[a]



[a] Reagents and conditions: (a) R′OH, 70 °C; (b) LiOH, THF, H_2O, MeOH.

were prepared via Suzuki-type coupling chemistry using heterocyclic boronic acids (Scheme 3, approach A) or inverse Suzuki coupling conditions using the borylated scaffold (Scheme 3, approach B).

SAR analysis (vide infra) identified thiazoles as preferred R^3 substituents. Because availability of suitable thiazole building blocks was too limited for generating sufficient diversity through Suzuki coupling chemistry, Hantzsch thiazole synthesis[35] was used to install functionalized thiazoles. Suitable nitrile templates were converted to thioamides that were subsequently reacted with structurally diverse α-bromo/chloro carbonyl building blocks[36] to yield the corresponding thiazoles.[37]

When 2-chloro-*N*,*N*-dimethylacetamide was used as the α-halo carbonyl precursor, Hantzsch reaction in an alcoholic solvent (e.g., EtOH, *i*-PrOH) was accompanied by replacement of the dimethylamino group by the alkoxy group (Scheme 5). This unexpected outcome was utilized to generate a number of analogs with R^5 = alkoxy (**34ae**−**34an**).

Results and Discussion

In Vitro SAR Studies. Compounds were evaluated for human PPARα and human PPARδ in vitro potency using fluorescence resonance energy transfer (FRET) assays. Their PPARα and PPARδ cell potency were measured in cell-based GAL-4 transactivation assays in CV-1 cells either transfected with PPARα or PPARδ ligand binding domain. PPARγ activity was assessed using a cell-based functional assay (IRBA) in mouse 3T3-L1 cells.[38] This assay measures the ability of the test compound to cause an increase in the number of insulin receptors and, hence, is an index of the insulin sensitizing activity.

The SAR studies covered in this account describe variation of the phenyl tail group in combination with a fixed head group, indanylacetic acid, and a fixed 1,3-bis(oxy)-propylidene tether. The indanylacetic acid group had been established in our laboratories as a well-suited head group for modulating activity at the respective PPAR receptor subtypes. Previous studies suggested that the indanylacetic acid group with no further substitution at the α and β positions offers an opportunity to simultaneously address all three PPAR receptor subtypes, α, γ, and δ.[31]

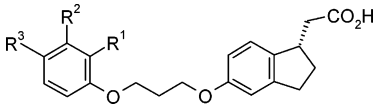
To derive basic SAR information, we started our effort by appending the phenyl tail group with small substituents. As can be seen in Table 1, PPARδ activity was generally high for this series, regardless of the nature of the phenyl substitution. Substitutions at both the 2- and 4-positions (R^1 and R^3, respectively) were found to play an important role for achieving PPARγ as well as PPARα agonistic activities, but the potencies were not satisfactory. The highest PPARα agonistic activities were observed for compounds **17n** and **17r**, indicating that increasing steric bulk of the R^3 substituent, combined with an extended R^1 alkyl or alkoxy chain, held promise for achieving more balanced PPAR pan agonistic activity.

We then turned to analogs bearing larger R^3 substituents. To improve the aqueous solubility of the compounds shown in Table 1 (mostly <5 μM; data not shown), a series of heterocycles were explored. As shown in Table 2, most analogs in this series are potent PPARδ agonists with relatively weak PPARγ or PPARα activity. However, the thiadiazole **17x** showed a markedly better PPAR pan activity profile compared to other heterocyclic variants, stimulating further SAR investigation of similar structure classes.

As a replacement for the thiadiazole group, we continued our optimization efforts with the structurally related thiazole moiety for the advantages of accessibility, feasibility of further derivatization, and drug likeness. The SAR of the previous analog series (Tables 1 and 2) indicated that a propyl/methoxy group in the 2-position of the phenyl tail moiety could further improve the PPARγ activity.

As shown in Table 3, this undertaking led to compounds with significantly improved PPARα and PPARγ activities. For the first time within the class of indanylacetic acids carrying

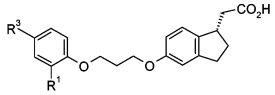
Table 1. In Vitro Activities of Indanylacetic Acid Analogs Containing Substituted Phenyl Tail Groups[a]



no.	R^1	R^2	R^3	*h*PPARα FRET,[b] EC_{50} [nM]	*h*PPARδ FRET,[c] EC_{50} [nM]	IRBA,[d] EC_{50} [nM]
17a	H	H	H	>10,000	44	>10,000
17b	H	H	Et	1,980	8.9	6,200
17c	H	H	CF_3	1,610	4.2	5,580
17d	H	H	OCF_3	6,800	13	1,020
17e	H	H	OMe	>10,000	6.7	3,000
17f	H	H	OEt	>10,000	6.6	940
17g	H	H	CN	5,700	7.3	637
17h	H	H	Ph	>10,000	43	n.d.[e]
17i	H	Me	H	>10,000	56	8,000
17j	H	Me	Me	>10,000	67	>10,000
17k	H	OMe	H	>10,000	117	n.d.[e]
17l	Me	H	Me	9,360	4.6	2,180
17m	*n*-Pr	H	H	>10,000	2.4	1,520
17n	*n*-Pr	H	CF_3	1,140	1.6	303
17o	*n*-Pr	H	CN	3,950	25	570
17p	*n*-Pr	H	OPh	>10,000	1.9	n.d.[e]
17q	OMe	H	Me	>10,000	7.5	1,670
17r	OMe	H	Et	700	2.7	1,650
17s	OMe	H	CN	7,500	14	700
17t	OEt	H	Me	>10,000	2.2	1,240

[a] Reported in vitro values are an average of at least two replicates. [b] PPARα compound activity was assessed by measuring the human PPARα ligand binding domain with the co-activator protein CBP. [c] PPARδ compound activity was assessed by measuring the ligand-dependent association of the human PPARδ ligand binding domain with the co-activator protein TRAP220. [d] PPARγ compound activity was assessed by using the IRBA in mouse 3T3-L1 cells. [e] Not determined.

Table 2. In Vitro Activity of Indanylacetic Acid Analogs Containing 4-Heteroaryl-Substituted Aryl Tail Groups[a]



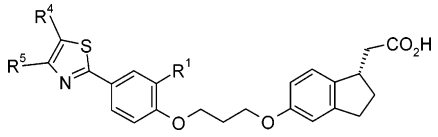
No.	R^1	R^3	*h*PPARα FRET, EC_{50} [nM][b]	*h*PPARδ FRET, EC_{50} [nM][c]	IRBA, EC_{50} [nM][d]	Synthetic approach[e]
17u	H		>10,000	11	555	C
17v	$NHCOCH_3$		9,200	367	5,600	C
17w	Cl		6,850	2230	8,700	C
17x	Me		520	3.4	158	C
29a	H		>10,000	5.9	650	A
29b	H		3,270	3.8	4,100	A
29c	H		6,600	1.5	740	A
29d	H		1,690	2.3	550	A
29e	H		>10,000	43	485	A
29f	H		7,280	11	970	A
29g	H		>10,000	5.6	300	A
29h	H		5,260	2.2	550	B
29i	H		2,900	0.95	1,800	B

[a–d] See corresponding footnotes from Table 1. [e] Compounds were synthesized according to Scheme 3, approaches A or B, or using a preformed heterocycle-substituted phenol building block (approach C).

substituted phenyl tail groups, potent activities at all three receptor subtypes were achieved. The key SAR trends are the following: (1) The in vitro activities of the thiazoles where R^5 is an alkoxy group (e.g., **34al**) and where R^4 and R^5 form a fused cycloalkyl ring (e.g., **34o**−**34q**) are the highest and most balanced within the series. (2) A substituent at the R^1 position is important to achieve PPARγ and especially PPARα activity in most of the examples. However, if R^4 and R^5 form a cycloalkyl ring (especially cyclohexyl, as in **34o**), an R^1 substituent does not appear to be as crucial for achieving potent PPARγ and PPARα activities. (3) In most cases, compounds with an *n*-propyl group in the R^1 position show higher PPARγ and PPARα activities than compounds with a methoxy group in this position.

Further in vitro and in vivo evaluation of these compounds revealed the tetrahydrobenzothiazoles **34o** and **34p** and the dihydropyranothiazole **34r** to have the best overall profiles. To support the interpretation of in vivo efficacy data from different

Table 3. In Vitro Activities of 4-Thiazolylphenyl Analogs[a]



no.	R^4	R^5	R^1	*h*PPARα FRET,[b] EC_{50} [nM]	*h*PPARδ FRET,[c] EC_{50} [nM]	IRBA,[d] EC_{50} [nM]
34a	H	H	*n*-Pr	111	1.6	48
34b			OMe	255	0.58	374
34c	H	Me	OMe	268	2.7	960
34d			H	1,280	4.4	874
34e	H	Et	*n*-Pr	147	11	45
34f			OMe	254	2.5	65
34g	H	*t*-Bu	*n*-Pr	87	11	18
34h	H	CF_3	*n*-Pr	197	3.3	55
34i			OMe	437	2.9	327
34j	Me	Me	H	1,250	2.9	280
34k			OMe	83	4	33
34l			H	112	1.3	1,200
34m			*n*-Pr	328	3.5	94
34n			OMe	53	4.1	116
34o			H	391	2.2	294
34p			*n*-Pr	43	1.9	12
34q			OMe	44	3.3	84
34r			*n*-Pr	101	4.0	42
34s			OMe	328	1.3	181
34t			OMe	526	5.2	214
34u			H	2,530	6.9	480
34v	$COCH_3$	Me	*n*-Pr	175	18	17
34w			OMe	560	3.4	49
34x	$CONMe_2$	Me	*n*-Pr	140	4.4	20
34y			OMe	803	2.1	
34z			H	10,000	218	312
34aa	COOH	Me	*n*-Pr	1,690	46	238
34ab			OMe	10,000	28	1,000
34ac	COOH	CH_2OH	*n*-Pr	6,490	12	891
34ad	H	CH_2CO_2H	*n*-Pr	2,480	4.6	27
34ae	H	OMe	H	5,800	1.3	300
34af			OMe	755	3.0	69
34ag			H	100	1.2	753
34ah	H	OEt	*n*-Pr	105	2	41
34ai			OMe	1,350	3.4	920
34aj	H	O*i*-Pr	*n*-Pr	47	2.3	45
34ak			OMe	180	3	44
34al	Me	OEt	*n*-Pr	61	3.2	34
34am			OMe	150	6	177
34an	Et	OEt	OMe	520	5.4	362

[a–d] See corresponding footnotes from Table 1.

Table 4. Cellular Activities of Selected Analogs Across Species[a]

	PPARα, EC_{50} [nM] (% agonism)			PPARδ, EC_{50} [nM] (% agonism)			IRBA, EC_{50} [nM]	
no.	human	mouse	hamster	human	mouse	hamster	human	mouse
34o	152 (100)	>10 000 (28)	135 (78)	40 (85)	84 (43)	144 (79)	170	294
34p	5 (100)	7700 (79)		2.6 (93)	8.6 (82)		81	12
34r	116 (88)	>10 000 (25)	923 (100)	2.7 (64)	16 (60)	8 (100)	102	42

[a] See corresponding footnote from Table 1.

Table 5. Solubility, CYP450 Inhibition, and Mouse Pharmacokinetic Data of Selected Analogs[a]

no.	aq. solubility,[b] pH 6.8 [μM]	CYP450 inhibition,[c] IC_{50} [μM]	mouse PK[d] (10 mg/kg, p.o.); C_{max} [μM]
34o	31	all >10	20
34p	< 5	all >10	5.1
34r	55	all >10	18

[a] See corresponding footnote from Table 1 [b] Kinetic solubility determined by HPLC; buffered aqueous test solution contained 1% DMSO. [c] Determined for CYP 1A2, 2C8, 2C9, 2D6, and 3A4 by enzyme assays using appropriate fluorescent substrates. [d] Compounds were administered in 0.5% methylcellulose.

animal models, we determined the cellular activities at PPAR subtypes from different species, including cellular activity in the IRBA using human preadipocytes.

As can be seen from Table 4, PPARγ activities from mouse and human cells are comparable for all three compounds. Likewise, no substantial species dependency is seen in the case of PPARδ. However, all compounds show pronounced activity differentiation across species at the PPARα receptor, with significantly higher activity at human and hamster PPARα compared to mouse PPARα. Spot checking of other compounds from Table 3 revealed that the species dependency trends are general for this compound class (data not shown). Selectivities toward the key members of the human nuclear hormone receptor family were also examined. Compounds **34o**, **34p**, and **34r** showed EC_{50} values of >10 μM in a binding assay of the androgen, estrogen, glucocorticoid, and progesterone receptors.

Solubility, cytochrome P450 (CYP450) enzyme inhibition, and mouse pharmacokinetic data of compounds **34o**, **34p**, and **34r** are shown in Table 5. Oral exposure of compound **34p** is significantly lower than those of the other two compounds, which may be at least partly due to its poor aqueous solubility.

Comparison of the in vivo activities of compounds **34o**, **34p**, and **34r** revealed a clear superiority of compound **34r**. Compound **34o** only showed a weak glucose-lowering effect, which is in agreement with its in vitro data (least active among the three compounds in the IRBA). Compound **34p**, despite its excellent in vitro profile, likewise did not reach the overall efficacy profile of compound **34r**, presumably due to its lower oral exposure.

Effects of Compound 34r in *db*/*db* and *h*ApoA1 Mice. Female *db*/*db* mice were dosed once daily for 7 days with 0.3, 1, 3, and 10 mg/kg **34r** and with 1, 3, and 10 mg/kg of rosiglitazone (**1**), respectively. Compound **1** is known to lower glucose levels in this animal model[39] and in man[40] by activating the PPARγ receptor. Both **1** (all doses) and the 1, 3, and 10 mg/kg doses of **34r** significantly and dose-dependently reduced blood glucose levels. The estimated ED_{50} for compound **34r** in this model is 0.4 mg/kg (Figure 1).

To assess the effect of compound **34r** on improving lipid levels, studies in transgenic mice expressing the human apoA1 gene were conducted. This model has proven useful in the assessment of hypolipidemic drugs such as fenofibrate (**3**; PPARα agonist) and **7** (PPARδ agonist). Compound **7** is known to reduce triglyceride levels and raise HDL-cholesterol (HDLc) in mice by activating the PPARδ receptor.[19−21] Male *h*ApoA1 mice were treated with 10 mg/kg of **34r** or 10 mg/kg of **7** for 7 days. Both compounds caused significant dose-dependent reduction in plasma triglycerides and increase in HDLc, and the magnitude of the effects were comparable (Figure 2).

In female *h*ApoA1 mice, the 10 mg/kg dose of **34r** as well as reference compound **7** significantly increased HDLc levels, however compound **34r** was not as efficacious as **7** at the same dose levels. Neither compound showed statistically significant effects on triglyceride levels in this model (data not shown).

In addition to its effects on lipid levels, compound **34r** caused reduction in glucose levels in the *h*ApoA1 mice model to a

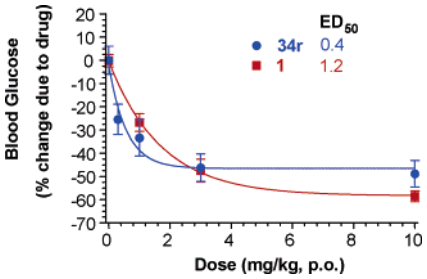


Figure 1. Effects of compound **34r** (0.3, 1, 3, and 10 mg/kg) and rosiglitazone (**1**; 1, 3, and 10 mg/kg) on blood glucose levels in *db*/*db* mice after 8 days of dosing (qd, p.o.).

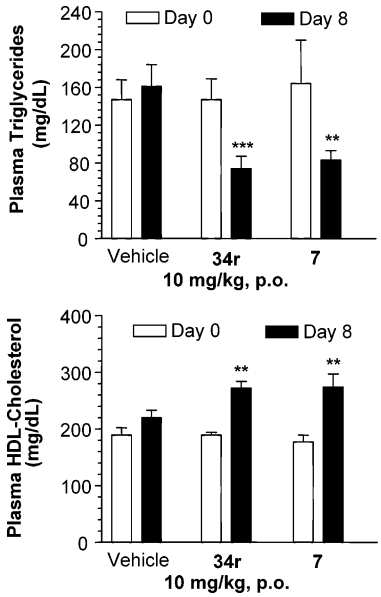


Figure 2. Effects of compound **34r** and **7** (both 10 mg/kg) on plasma triglyceride and HDLc levels in male *h*ApoA1 mice after 7 days of dosing (qd, p.o.). Each bar is the mean ± SEM for 6−8 mice. $^{**}p < 0.01$, $^{***}p < 0.001$ versus vehicle.

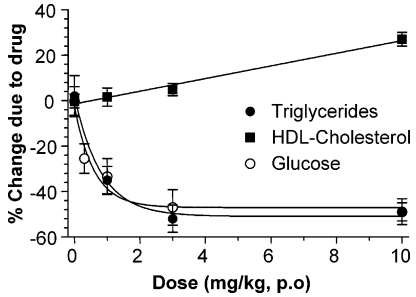


Figure 3. Summary of the effects of compound **34r** (0.3, 1, 3, and 10 mg/kg) on blood glucose levels in *db*/*db* mice and on triglycerides/HDLc in male *h*ApoA1 mice after 8 days of dosing (qd, p.o.).

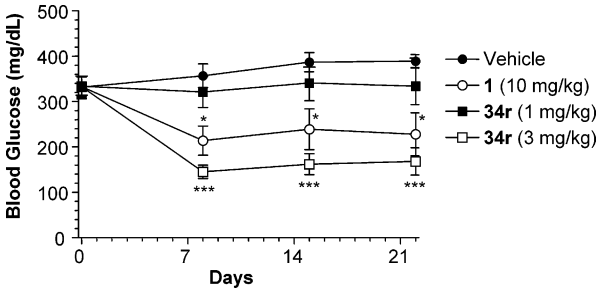


Figure 4. Effects of compound **34r** (1 and 3 mg/kg) and rosiglitazone (**1**; 10 mg/kg) on blood glucose levels in ZDF rats after 21 days of dosing (qd, p.o.). The rats were dosed as described in the Experimental Section. Each bar is the mean ± SEM for 7 rats. $^{**}p < 0.01$, $^{***}p < 0.001$ versus vehicle.

similar extent as seen in the *db*/*db* model (ED_{50} in both models around 0.5 mg/kg). Figure 3 summarizes the combined effects of compound **34r** on glucose, triglyceride, and HDLc levels in female *db*/*db* mice and male *h*ApoA1 mice.

Effects of Compound 34r in Zucker Diabetic Fatty (ZDF) Rats. The ZDF rat is an inbred rat model that, through genetic mutation and a managed diet, closely mimics human adult onset type 2 diabetes and related complications.[41] To assess the glucose lowering effect of compound **34r** versus benchmark, male ZDF rats were dosed once daily for 21 days with 10 mg/kg rosiglitazone (**1**) and 1 and 3 mg/kg of compound **34r**. As shown in Figure 4, compound **34r** (at 3 mg/kg) was significantly more efficacious in lowering glucose levels than **1**. The effects of both **1** and **34r** on plasma triglycerides and HDLc were not pronounced in this model under the chosen starting glucose and lipid levels, however, both compound **34r** (at 1 and 3 mg/kg doses) and **1** (at 10 mg/kg) lowered FFA levels in the same study (data not shown).

Effects of Compound 34r in Fat-Fed Hyperlipidemic Hamsters. Hamsters are considered a good model for the study of plasma lipoprotein regulation due to similarities in lipid metabolism to man. For example, this model has been shown to be highly predictive of the human lipid modulating efficacy of fibrates.[42] Furthermore, cellular activities of compound **34r** at the hamster PPARδ and PPARα receptors are more predictive than murine of the activities at the human receptors (Table 4). Hence, the hamster model was considered a well-suited model for assessing the impact of **34r** on lipid homeostasis with potential utility for predicting the lipid effects of this compound in man.

Fat-fed hyperlipidemic Golden Syrian hamsters were treated with **34r** (10 mg/kg), rosiglitazone (**1**; 10 mg/kg), and fenofibrate (**3**; 100 mg/kg) for two weeks. All compounds, except rosiglitazone, caused significant changes in lipoprotein distribution, characterized by a lowering of vLDL and LDL (low-density

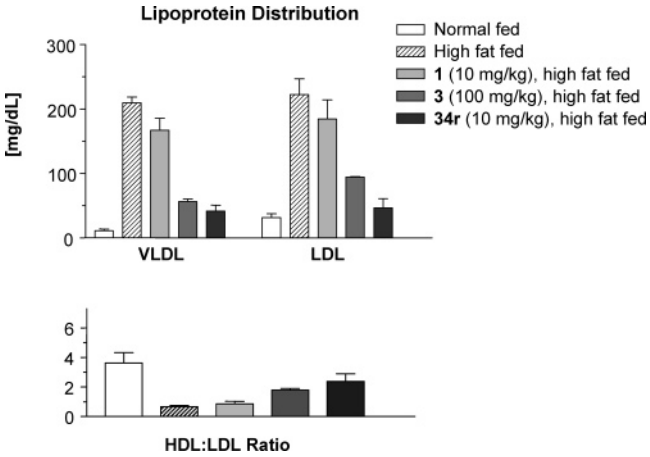


Figure 5. Effects of compound **34r** (10 mg/kg), rosiglitazone (**1**; 10 mg/kg), and fenofibrate (**3**; 100 mg/kg) on lipoprotein distribution in fat-fed hyperlipidemic hamsters after 14 days of dosing (qd, p.o.). Each bar is the mean ± SEM for 10 hamsters.

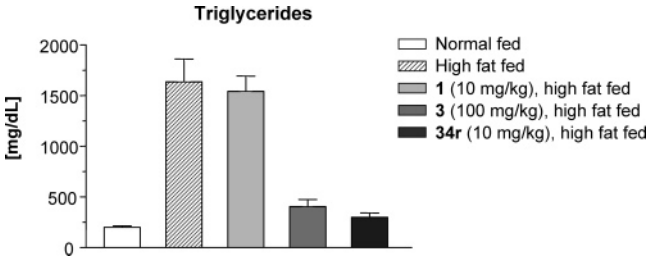


Figure 6. Effects of compound **34r** (10 mg/kg), rosiglitazone (**1**; 10 mg/kg), and fenofibrate (**3**; 100 mg/kg) on triglyceride levels in fat fed hyperlipidemic hamsters after 14 days of dosing (qd, p.o.). Each bar is the mean ± SEM for 10 hamsters.

lipoprotein) and an increase of HDL/LDL ratios (Figure 5). Compound **34r** also lowered triglyceride and total cholesterol levels to a similar or greater extent than that of fenofibrate, whereas rosiglitazone had no effect on lipid levels (Figure 6).

Summary and Conclusion

4-Thiazolylphenyl groups were identified as novel PPAR agonist tail portions. In combination with the recently established indanylacetic acid head group, these compounds were shown to give balanced PPAR $\alpha/\gamma/\delta$ pan agonistic activities in vitro and good selectivities against other nuclear hormone receptor family members, including androgen, estrogen, glucocorticoid, and progesterone receptors. Optimization efforts within the thiazolylphenyl series led to the identification of **34r**, a compound with a good in vitro pharmacology profile and excellent ADME properties. Compound **34r** was found to dose-dependently reduce blood glucose and was significantly more potent than the standard of care agent rosiglitazone in *db*/*db* mice. In ZDF rats, **34r** showed superior glucose-lowering efficacy compared to rosiglitazone. In male *h*ApoA1 mice, **34r** dose-dependently lowered triglyceride and raised HDL cholesterol levels. Compound **34r** also caused a significant change in lipoprotein distribution in fat-fed hyperlipidemic hamsters highlighted by reduction of total cholesterol, increase of the HDL/LDL ratio, and reduction of triglyceride levels. In summary, **34r** displays a highly attractive in vivo pharmacology profile. The magnitude of effects seen in the in vivo experiments is equal or superior to standard of care agents and corroborates earlier reports that PPAR $\alpha/\gamma/\delta$ pan agonists hold potential for the treatment of diabetes and associated dyslipidemia.

Experimental Section

In Vitro Assays. PPARα Activity. (a) PPARα FRET Assay: Activity was assessed by measuring the human PPARα ligand binding domain with the co-activator protein CBP. Europium-labeled anti-GST antibody, streptavidin-labeled APC, biotin-labeled CBP, and PPARα-GST were incubated at rt in buffer in the presence or absence of test compound. Following a 2 h incubation, fluorescence was measured at emission wavelengths of 615 or 655 nm, with excitation at 340 nm.

(b) Cell-Based GAL4 Transactivation Assay for PPARα in CV-1 Cells: CV-1 cells were plated in 96-well plates and incubated overnight at 37 °C in 5% CO_2. Cells were transfected with human PPARα ligand binding domain, pFR LUC DNA, and pRLSV40 DNA using lipofectamine plus. Cells were incubated overnight at 37 °C in 5% CO_2 and treated with test compound or vehicle. Following overnight incubation, cells were assayed for luciferase activity using Dual-Luciferase reporter 1000 assay system.

PPARδ Activity. (a) PPARδ FRET Assay: The same protocol was used as described for the PPARα FRET assay, except substituting PPARα-GST with PPARδ-GST.

(b) Cell-Based GAL4 Transactivation Assay for PPARδ in CV-1 Cells: The same protocol was used as described for the PPARα cell assay, except substituting human PPARα ligand binding domain with human PPARδ ligand binding domain.

PPARγ Activity. PPARγ activity was assessed by using the IRBA in mouse 3T3-L1 cells. This assay measures the ability of test compound to cause an increase in the number of insulin receptors and, hence, is an index of the insulin sensitizing activity. 3T3-L1 cells were seeded in 96-well tissue culture plates using DMEM media containing 10% fetal bovine serum, 1% pen/strep, and 2 mM L-glutamine, and were grown until they were 2 days postconfluent. Cells were then treated for 2 days with medium containing 0.5 μM human IGF-1 and test compound. After treatment, the medium was replaced with medium free of IGF-1 and compound and incubated for 4 days. After washing the cells with buffer, they were incubated with 0.1 nM ^{125}I-insulin and (±)100 nM unlabeled insulin and incubated at rt for 1 h. The cells were then washed 3× with buffer, dissolved with 1 N NaOH, and the amount of radioligand bound measured using a gamma counter.

Selectivity Assays. Binding assays for androgen, progesterone, estrogen, and glucocorticoid receptors were performed using a similar protocol except for the source of the receptor and the ligand used. The androgen receptor was recombinant human expressed in SF9 baculovirus cells (10 μL per well) and ^{3}H-dihydrotestosterone as the radioligand (NEN NET453, use at 1:800 dilution). Nonspecific binding was determined using cold DHT. Estrogen receptor binding was performed using a cytosolic preparation from black Swiss Mouse uteri (20 μL per well) with ^{3}H−O-estradiol, (Amersham TRK 587 at 1:666.7 dilution) and cold estradiol as a nonspecific ligand. Glucocorticoid receptor binding was determined using a cytosol preparation from HUH cells with ^{3}H-dexamethaxone (Amersham TRK 645 at 1:312.5 dilution) and cold dexamethasone as a nonspecific ligand. Progesterone receptor binding was performed using the cytosol from T47D cell line, ^{3}H-progesterone (NEN NEX 381 at 1:1100 dilution), and progesterone as the nonspecific ligand. Briefly, 65 μL of diluted cytosol was added to each well of a 96-well polypropylene plate. An amount equal to 10 μL of 10× test compound, control DMSO (total binding), or 1 μM cold ligand (nonspecific binding) was added next. ^{3}H-ligand in the amount of 25 μL was then added to a final concentration of 10 nM. The assay was incubated overnight at 4 °C. An aliquot of 50 μL of the assay volume was added to a prespun (2 min at 2100 rpm) spin plate (Edge Biosystems catalog no. 31909). The plate was spun for 5 min at 2500 rpm, and the flow through was caught on a Wallac isoplate (catalog no. 1450-514). Scintillant (ScintiSafe or Ultima Gold) in the amount of 175 μL was added, and the plate was allowed to equilibrate for 1 h. Finally, the plate was counted for 1 min in the Wallac Microbeta.

In Vivo Models. Animals. Female *db*/*db* mice and male/female *h*ApoA1 mice were purchased from The Jackson Laboratory (Bar Harbor, ME). Male ZDF rats were purchased from Genetic Models, Inc. (Indianapolis, IN). All animals were purchased at 6 weeks of age and were maintained on standard laboratory rodent chow ad libitum. The *h*ApoA1 mice were used within two weeks of their arrival, whereas the *db*/*db* mice and ZDF rats were maintained on diet for 3−4 and 4−8 weeks, respectively, to ensure that they exhibited hyperglycemia prior to starting the study. The average body weight was 50, 25, and 356 g for the *db*/*db* mice, *h*ApoA1 mice, and the ZDF rats, respectively.

Male Syrian Golden Hamsters (*Mesocricetus auratus*, Lak:LVG-(SYR)BR) were obtained from a Charles River Laboratories barrier or isolator colony. The hamsters were no older than 7 weeks, and the weight was between 120 and 150 g. The animals were fed either a high fat diet (groups 2−10) or rodent chow (group 1) ad libitum for the duration of the study. In addition, a 10% fructose drinking water solution was used for all groups except group 1.

Dosing Regimen. All animals were weighed and tail-bled prior to the start of study. Blood from *db*/*db* mice or ZDF rats was analyzed for glucose levels using either a Beckman Glucose Analyzer 2 (Beckman Instruments, Fullerton, CA) or a Technicon Axon autoanalyzer (Bayer Corporation, Tarrytown, NY). Plasma from *h*ApoA1 mice was analyzed for triglyceride and HDLc levels using the Axon autoanalyzer. The animals were arranged into the appropriate number of groups with each group having the same mean blood glucose levels (*db*/*db* mice and ZDF rats) or plasma triglyceride levels (*h*ApoA1 mice) prior to dosing. All animals were then orally dosed once daily with vehicle (0.5% methylcellulose in water), a positive control compound, or test compound. The *db*/*db* mice were dosed for 7 days, *h*ApoA1 mice for 7 days, and ZDF rats for 21 days. All animals were fed ad libitum throughout the study. Approximately 24 h after the last dose, the animals were weighed and bled again, and the plasma or serum was analyzed for glucose, triglycerides, or HDLc. Livers from the *h*ApoA1 mice were removed and weighed, and the weight was expressed as percent of body weight. All results are expressed as the mean ± SEM for the number of animals indicated in the figure legends.

For the hyperlipidemic hamster studies, on study day 0, hamsters were individually weighed and distributed into one of 10 groups prior to receiving a high fat diet and fructose supplemented water (groups 2−10). All groups (1−10) had similar weight means, ±10% of the average weight of all study animals. On study day 10, animals were individually weighed and had blood collected by a retro-orbital eye bleed, except for four (4) hamsters from group 10, which were dosed with vehicle and then euthanized and bled via a terminal bleed. Blood was prepared as EDTA plasma. After the retro-orbital eye bleed on study day 10, all hamsters were given a daily oral dose (by weight) of either vehicle or one of the test compounds for 14 continuous days. Individual hamster body weights were taken and recorded on study days 0, 4, 10, 17, and 24. No test compound was given at the day of sacrifice (day 24). On study day 24, all animals were submitted to necropsy. Following euthanasia, blood and tissue (liver, skeletal muscle and fat pads) were collected and frozen. Blood was collected into EDTA tubes for plasma preparation and frozen. Plasma samples were analyzed via fast protein liquid chromatography (FPLC) using a published procedure.[43]

Calculation of Percent Change Due to Drug Treatment. To compare the effects of test compound treatment on glucose levels in *db*/*db* mice with its effects on triglyceride levels in *h*ApoA1 mice, it is useful to calculate the percent change in glucose or triglyceride that is due to drug treatment. This takes into account any changes that may have occurred in the vehicle-treated animals during the study. The percent change due to drug treatment is calculated as follows

$$(((T_f/T_i)/(V_f/V_i)) - 1) \times 100$$

where T_f and T_i are the final and initial values of either blood glucose or plasma triglyceride levels in the drug-treated animals, respectively, and V_f and V_i are the same for the vehicle-treated animals. A positive number denotes a drug-induced increase, whereas a negative number denotes a drug-induced decrease.

Statistical Analysis. ANOVA was used to evaluate the effects of positive control drugs and test compound using InStat (GraphPad Software, Inc., San Diego, CA). The Tukey−Kramer Multiple Comparisons Test was used for the parametric ANOVA. Whenever a nonparametric ANOVA was required, the Kruskal−Wallis Test was used. Results were considered significant at $p < 0.05$.

General Chemistry. Purchased reagents and anhydrous solvents were used as received. Air and moisture sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa.

Column chromatography was performed on a Biotage system using 32−63 micron, 60 Å, silica gel pre-packed cartridges.

Purification using preparative reversed-phase HPLC chromatography was accomplished using a Gilson 215 system, using a YMC Pro-C18 AS-342 (150 × 20 mm I.D.) column and 1 mL/min flow rate. Typically, the mobile phase used was a mixture of H_2O (A) and MeCN (B). The water could be mixed or not with 0.1% TFA. A typical gradient was: 0.5 min, 90% A, 10% B; 11.0 min, 0% A, 100% B.

Chiral analytical HPLC experiments were performed using one of the two following methods using a Varian Pro Star 1200. Method A: Chiracel AD column, 4.6 (I.D.) × 250 mm; mobile phase, A, 0.1% TFA in hexanes; B, 0.1% TFA in *i*-PrOH; isocratic, 95% A (5% B), 20 min; flow rate, 1.5 mL/min; UV detection, 284 nm. Method B: Chiracel AD column, 4.6 (I.D.) × 250 mm; mobile phase, A, 0.1% TFA in hexanes; B, 0.1% TFA in *i*-PrOH; isocratic, 95% A (5% B), 25 min; flow rate, 1.0 mL/min; UV detection, 284 nm.

Electron impact mass spectra (EI-MS or GC-MS) were obtained with a Hewlett-Packard 5989A mass spectrometer equipped with a Hewlett-Packard 5890 Gas Chromatograph with a J & W DB-5 column (0.25 μM coating; 30 m × 0.25 mm). The ion source was maintained at 250 °C, and spectra were scanned from 50 to 800 amu at 2 s per scan.

Two different methods were used to obtain HPLC electrospray mass spectra (HPLC ES-MS). HPLC-MS method 1: An Agilent 1100 HPLC system was equipped with an Agilent 1100 autosampler, quaternary pump, and a diode array. The HPLC column used was a Waters Sunfire C-18 column (2.1 × 30 mm, 3.5 μM). The HPLC eluent was directly coupled with a 1:4 split to a Finnigan LTQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 50 to 800 amu using a variable ion time according to the number of ions in the source using positive ion mode. The eluents were A, water with 0.1% formic acid, and B, acetonitrile with 0.1% formic acid. Gradient elution from 10% B to 90% B over 3.0 min at a flow rate of 1.0 mL/min was used with an initial hold of 2.0 min and a final hold at 95% B of 1.0 min. Total run time was 8.0 min.

HPLC-MS method 2: An Agilent 1100 HPLC system was equipped with an Agilent 1100 autosampler, quaternary pump, a variable wavelength detector set at 254 nm. The HPLC column used was a Waters Sunfire C-18 column (2.1 × 30 mm, 3.5 μM). The HPLC eluent was directly coupled without splitting to a Finnigan LCQ DECA ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 140 to 1200 amu using a variable ion time according to the number of ions in the source using positive ion mode. The eluents were A, 2% acetonitrile in water with 0.02% TFA, and B, 2% water in acetonitrile with 0.02% TFA. Gradient elution from 10% B to 90% B over 3.0 min at a flow rate of 1.0 mL/min was used with an initial hold of 1.0 min and a final hold at 95% B of 1.0 min. Total run time was 7.0 min. For consistency in characterization data, the retention time (RT) is reported in min at the apex of the peak, as detected by the UV−vis detector set at 254 nm.

^{1}H NMR spectroscopy was performed on 300 or 400 MHz Varian Mercury-plus as well as Bruker DRX500 spectrometers. The samples were dissolved in deuterated solvents and transferred to 5 mm ID Wilmad NMR tubes. The spectra were acquired at 293 K. The chemical shifts were recorded on the ppm scale and were referenced to the appropriate residual solvent signals, such as 2.49 ppm for DMSO-d_6, 1.93 ppm for CD_3CN, 3.30 ppm for CD_3OD, 5.32 ppm for CD_2Cl_2, and 7.26 ppm for $CDCl_3$.

Ethyl (5-Methoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethanoate (10). To a solution of 5-methoxyindanone (150 g, 0.91 mol) in anhydrous tetrahydrofuran (4.5 L), was added zinc (30 mesh, 103.64 g, 1.59 mol) and copper(I) chloride (4.53 g, 0.045 mol). The suspension was stirred under argon atmosphere and heated under reflux for 15 min; approximately a 25% portion of ethyl bromoacetate (133 mL, 1.18 mol) was added to the refluxing mixture in a slow dropwise fashion. After allowing cooling and stirring for 12 h at rt, TLC showed the presence of desired product. The remainder of ethyl bromoacetate was added dropwise, and the internal temperature was increased to 35 °C. After 4 h, TLC showed complete reaction. After the solids settled to the bottom of the flask, the liquid was siphoned off, leaving a small amount behind to cover the solids. The flask was recharged with 5-methoxyindanone (157.6 g, 1.86 mol total), anhydrous tetrahydrofuran (4.5 L), and zinc (80.92 g, 2.73 mol total). Ethyl bromoacetate (140 mL, 2.36 mol) was added dropwise, and the internal temperature was increased to 35 °C. When the stirred mixture was cooled to rt, TLC showed the reaction to be complete. The solids were allowed to settle and the liquid was siphoned off. The combined reaction solutions were concentrated under reduced pressure to a volume of about 2 L. The liquid was then poured into HCl (1 N aqueous solution, cooled in ice water) to bring the pH to 1. The product was extracted with ethyl acetate (2 × 1 L, 1 × 500 mL). The combined extracts were washed with water (1 L) and brine (1 L), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a dark red oil which solidified gradually (438.3 g; theoretical yield = 432 g). ^{1}H NMR ($CDCl_3$) δ 7.5 (d, 1H), 6.8 (m, 2H), 6.2 (t, 1 H), 4.2 (q, 2H), 3.8 (s, 3H), 3.3 (m, 2H), 3.0 (t, 2H), 1.3 (t, 3H). MS (CI) *m*/*z* 233 $[M + H]^+$.

Ethyl (5-Methoxy-2,3-dihydro-1*H*-inden-1-yl)acetate (11). The crude product **10** was dissolved in absolute ethanol (2.6 L) and hydrogenated at 40 psi of hydrogen over 10% palladium on carbon (21.6 g). Filtration through Celite and concentration of the filtrate afforded the title compound: 433.3 g (99% yield for two steps) as a brown oil. ^{1}H NMR ($CDCl_3$) δ 7.1 (dd, 1H), 6.8 (d, 1H), 6.7 (dd, 1H), 4.2 (q, 2H), 3.8 (s, 3H), 3.5 (m, 1H), 2.9 (m, 2H), 2.7 (dd, 1H), 2.4 (m, 2H), 1.7 (m, 1H), 1.3 (t, 3H). MS (CI) *m*/*z* 235 $[M + H]^+$.

[(1*S*)-5-Methoxy-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (12). A mixture of the crude ester **11** (500 g, 2.13 mol; 87% pure as determined by analytical HPLC) in reagent grade acetone (1 L), a phosphate buffer (2.5 L, pH 7.0, 0.05 M), and water (2.5 L) was treated in one portion with Amano Lipase PS (150 g, Amano Enzymes), and the mixture was stirred vigorously at rt for 12 h. Chiral analytical HPLC analysis (method A) of an aliquot (homogeneous aliquot prepared by dissolving an aliquot in *i*-PrOH followed by filtration) showed one peak corresponding to unreacted *R*-ester and another peak corresponding to desired *S*-acid. Only trace amounts of *S*-ester and *R*-acid were noted. Then HCl (500 mL, 2 N aqueous solution) was added in one portion to the reaction mixture to ensure a pH ∼2, and the mixture was stirred for 20 min. The mixture was filtered and the solids were washed with EtOAc (2 × 500 mL) and then water (500 mL). The combined filtrates were further diluted with EtOAc (1 L), and the layers were stirred together vigorously. Stirring was stopped, and the layers were allowed to separate. The resulting emulsion was broken by the addition of solid NaCl and stirring. The aqueous layer was removed and then extracted with EtOAc (3 × 1 L) in the same fashion. The combined organic extractions were washed with water (4 × 500 mL) and brine and then extracted with Na_2CO_3 (8 × 500 mL, 5% aqueous solution). Chiral analytical HPLC (method A) analysis of the organic layer showed that it contained none of the *S*-enantiomer acid. The combined Na_2CO_3 extracts were washed with EtOAc (2 × 1 L) and then acidified to pH ∼2 by the addition of HCl (2 N aqueous solution). A white solid precipitated, accompanied by CO_2 evolution. The mixture was extracted with EtOAc (3 × 1 L). The combined extracts were washed with water (2 × 1 L) and brine and then dried over Na_2SO_4. Chiral analytical

HPLC (method A) analysis of this solution showed that the material had an ee of 98%. The solvent was evaporated under reduced pressure, giving an oil that solidified upon standing. The title product (172.9 g) was obtained as an off-white solid after vacuum drying, and then this material was recrystallized from boiling hexanes (8.8 L). After cooling for 12 h, light yellow needles were collected via filtration, washed with hexanes (200 mL), and dried under suction. The title product (146.9 g, 38% from crude starting ester) was obtained as light yellow needles after vacuum drying. ^{1}H NMR ($CDCl_3$) δ 7.10 (d, 1H), 6.79 (d, 1H), 6.73 (dd, 1H), 3.79 (s, 3H), 3.55 (m, 1H), 2.89 (m, 2H), 2.79 (dd, 1H), 2.46 (dd, 1H), 2.43 (m, 1H), 1.80 (m, 1H). MS (ESI) *m*/*z* 207 $[M + H]^+$. The absolute configuration was indirectly determined by single-crystal X-ray crystallography of a derivative containing Evans' oxazolidinone chiral auxiliary (see Supporting Information).

Ethyl [(1*S*)-5-Methoxy-2,3-dihydro-1*H*-inden-1-yl]acetate (13). To a solution of the acid **12** (305 g, 1.48 mol) in 4.8 L of absolute EtOH at rt under argon was added chlorotrimethylsilane (413 mL, 3.25 mol) dropwise. After stirring for 12 h, the EtOH was evaporated under reduced pressure, giving a biphasic liquid mixture. This mixture was diluted in ice-water (500 mL) and then extracted with EtOAc (2 × 750 mL). The combined extracts were washed with water (3 × 300 mL) and then with a saturated aqueous solution of $NaHCO_3$ (200 mL). The organic phase was washed once more with water (300 mL) and then brine and dried over Na_2SO_4. The title compound (354 g, quant.) was obtained as a light yellow oil after solvent removal and vacuum drying. ^{1}H NMR ($CDCl_3$) δ 7.07 (d, 1H), 6.78 (d, 1H), 6.71 (dd, 1H), 4.18 (q, 2H), 3.78 (s, 3H), 3.52 (m, 1H), 2.89 (m, 2H), 2.72 (dd, 1H), 2.37 (o, 2H), 1.74 (m, 1H), 1.28 (t, 3H). MS (CI) *m*/*z* 235 $[M + H]^+$.

Ethyl [(1*S*)-5-Hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetate (14). To a cold solution (ice water bath) of **13** (346 g, 1.48 mol) in CH_2Cl_2 (4.2 L) was added $AlCl_3$ (984.6 g, 7.38 mol) portionwise under argon such that the reaction temperature was maintained below 10 °C. The light brown suspension was stirred for 10 min, and then EtSH (546 mL, 7.38 mol) was added dropwise at such a rate that the reaction temperature was maintained below 5 °C. After 2.5 h of stirring below 10 °C, the reaction mixture was slowly poured into 6 L of ice water with strong agitation. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 1 L). The combined CH_2Cl_2 layers were washed with water (2 × 1 L) and then dried over Na_2SO_4. The solvent was removed under reduced pressure, giving a brown oil that was filtered through a pad of silica gel (eluted with 0−10% EtOAc/Hexanes). Fractions were collected, and the title compound (314 g, 96%) was obtained as a thick yellow oil after solvent removal and vacuum drying. ^{1}H NMR ($CDCl_3$) δ 6.92 (d, 1H), 6.62 (d, 1H), 6.55 (dd, 1H), 4.10 (q, 2H), 3.43 (q, 1H), 2.75 (m, 2H), 2.64 (dd, 1H), 2.31 (dd, 1H), 2.29 (m, 1H), 1.67 (m, 1H), 1.20 (t, 3H). MS (CI) *m*/*z* 221 $[M + H]^+$.

Ethyl [(1*S*)-5-(3-Bromopropoxy)-2,3-dihydro-1*H*-inden-1-yl]-acetate (15). To a solution of ethyl [(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetate (0.166 g, 0.754 mmol; **14**) in DMF (0.5 mL, containing 1% v/v of water) were added 1,3-dibromopropane (0.27 mL, 2.64 mmol) and Cs_2CO_3 (0.295 g, 0.905 mmol). The mixture was stirred at rt for 13 h and then at 80 °C for 1 h. Upon cooling to rt, the reaction mixture was concentrated under reduced pressure. The residue was suspended in EtOAc and filtered, and the filter cake was washed with EtOAc. The combined filtrate was dried, concentrated, and purified by silica gel chromatography (100% hexanes to EtOAc/hexane (v/v) 1:19 gradient) to give 153 mg (60%) of the title compound containing minor impurities. This material was used in later steps without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, 1H), 6.78 (s, 1H), 6.70 (dd, 1H), 4.19 (q, 2H), 4.08 (t, 2H), 3.60 (t, 2), 3.58−3.44 (m, 1H), 2.96−2.64 (m, 3H), 2.50−2.21 (m, 4H), 1.93−1.68 (m, 1H), 1.28 (t, 3H).

1-(Allyloxy)-4-(trifluoromethyl)benzene (18). 4-(Trifluoromethyl)phenol (1.50 g, 9.25 mmol), allyl bromide (14.55 g, 12.03 mmol), Cs_2CO_3 (3.62 g, 11.10 mmol), and water (15 drops) were combined in DMF (40 mL), and the mixture was stirred for 12 h. The reaction mixture was then concentrated under reduced pressure, diluted with water, and extracted with EtOAc (2×). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 0.96 g (51%) of the title compound as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (d, 2H), 5.32 (d, 1H), 5.43 (d, 1H), 6.05 (m, 1H), 6.97 (d, 2H), 7.53 (d, 2H).

4-(Allyloxy)benzonitrile (19). 4-Hydroxybenzonitrile (30.0 g, 252 mmol), allyl bromide (39.6 g, 327 mmol), and Cs_2CO_3 (98.5 g, 302 mmol) were dissolved in DMF (900 mL), and water (1 mL) was added. After stirring for 12 h at rt, the reaction mixture was concentrated under reduced pressure, water was added, and the mixture was extracted with EtOAc (2×). The combined organic layers were washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure, yielding 40 g (100%) of the title compound as a white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (d, 2H), 5.34 (d, 1H), 5.43 (d, 1H), 6.03 (m, 1H), 6.96 (d, 2H), 7.58 (d, 2H).

2-Allyl-4-(trifluoromethyl)phenol (21). Under an atmosphere of argon, 1-(allyloxy)-4-(trifluoromethyl)benzene (200 mg, 0.99 mmol; **18**) was dissolved in CH_2Cl_2 (anhydrous, 5 mL) and cooled to 15 °C. Then a solution of boron trichloride (1.04 mL, 1.04 mmol, 1 M in hexane) was added dropwise, and the reaction mixture was stirred for 2 h during which time the reaction mixture was allowed to warm to rt. The mixture was poured onto ice and extracted with EtOAc (2×). The combined organic phases were washed with $NaHCO_3$ (saturated aqueous solution), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the product as a yellow oil. This was used in the next step without further purification.

3-Allyl-4-hydroxybenzonitrile (22). 4-(Allyloxy)benzonitrile (40.0 g, 251.3 mmol; **19**) was heated under argon at 200 °C for 20 h. Upon cooling to rt, the product was purified via silica gel flash chromatography (EtOAc/hexane (v/v) 1:10 → EtOAc/hexane (v/v) 1:4), yielding 27.5 g (69%) of the title compound as a white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (d, 2H), 5.18 (d, 1H), 5.24 (d, 1H), 5.99 (m, 1H), 6.05 (br, 1H), 6.89 (d, 1H), 7.46 (d, 2H).

2-Allyl-4-phenoxyphenol (23). 1-(Allyloxy)-4-phenoxybenzene **(20)**, prepared by using a similar procedure as described for the synthesis of compound **18**, was further converted into the title compound using a similar procedure as described for the preparation of compound **22**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (d, 2H), 4.82 (s, 1H), 5.17 (d, 2H), 5.99 (m, 1H), 6.80 (m, 2H), 6.83 (s, 1H), 6.93 (d, 2H), 7.04 (t, 1H), 7.29 (m, 2H).

2-Propyl-4-(trifluoromethyl)phenol (24). The crude 2-allyl-4-(trifluoromethyl)phenol (**21**) was dissolved in EtOH (5 mL), Pd/C (20 mg, 10%, Fluka) was added, and the mixture was stirred under an atmosphere of hydrogen at rt for 2 h. The catalyst was removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel flash chromatography (EtOAc/hexane (v/v) 1:10). This gave 91 mg (45% over 2 steps) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H), 1.68 (m, 2H), 2.61 (t, 2H), 5.14 (br, 1H), 6.80 (d, 1H), 7.32 (d, 1H), 7.36 (s, 1H).

4-Hydroxy-3-propylbenzonitrile (25). 3-Allyl-4-hydroxybenzonitrile (20.0 g, 126 mmol; **22**) was dissolved in EtOH (320 mL) under argon. Pd/C (80 mg, 10%, Fluka) was added, and the reaction mixture was stirred under a hydrogen atmosphere (1 atm) at rt for 20 h. The catalyst was filtered off and then the reaction mixture was concentrated under reduced pressure, yielding 20.2 g (99%) of the title compound as a slightly greenish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, 3H), 1.63 (m, 2H), 2.56 (m, 2H), 6.86 (d, 1H), 7.30 (m, 2H).

4-Phenoxy-2-propylphenol (26). 2-Allyl-4-phenoxyphenol (**23**; 4.8 g, 21.3 mmol), Pd/C (480 mg, 10%) and ammonium formate (8.03 g, 127.3 mmol) were combined in ethanol (100 mL) under an argon atmosphere and heated to 40 °C. After 1.5 h, the catalyst was filtered off, and the solution was concentrated under reduced pressure and redissolved in EtOAc. The solution was passed through a silica gel plug and concentrated to give the title compound as a yellow oil (4.8 g, 99.9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t,

3H), 1.63 (m, 2H), 2.56 (t, 2H), 4.69 (s, 1H), 6.72 (m, 2H), 6.83 (s, 1H), 6.91 (d, 2H), 7.01 (t, 1H), 7.26 (m, 2H).

((1*S*)-5-{3-[2-Propyl-4-(trifluoromethyl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (16n). Compounds **24** (91 mg, 0.45 mmol) and **15** (149 mg, 0.44 mmol) were dissolved in 6 mL of DMF containing 1 vol % H_2O. Cesium carbonate (171 mg, 0.52 mmol) was added, and the mixture was stirred at 40 °C for 16 h. The DMF was removed under reduced pressure, water was added, and it was extracted (2×) with EtOAc. The combined organic phases were dried with Na_2SO_4, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography using hexanes/EtOAc (20:1) furnished the product as a clear oil in 143 mg (70%) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, 3H), 1.29 (t, 3H), 1.60 (m, 2H), 1.76 (m, 1H), 2.29 (m, 2H), 2.39 (m, 2H), 2.61 (m, 2H), 2.72 (dd, 1H), 2.86 (m, 2H), 4.17 (m, 6H), 6.69 (d, 1H), 6.78 (s, 1H), 6.88 (d, 1H), 7.07 (d, 1H), 7.07 (d, 1H), 7.34 (s, 1H), 7.40 (d, 1H). Compounds **16a**−**16m** and compounds **16o**−**16x** were made using the same procedure as for the preparation of compound **16n** using appropriate starting materials.

((1*S*)-5-{3-[2-Propyl-4-(trifluoromethyl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic Acid (17n). To a solution of compound **16n** (132 mg, 0.28 mmol) in 4 mL of THF/water (3:1) was added LiOH·H_2O (14 mg, 0.34 mmol), and the mixture was stirred at rt for 16 h. The THF was evaporated and more water was added. The aqueous layer was washed with a small amount of ether. The aqueous layer was then acidified with 1 N HCl and extracted (3×) with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated to give 112 mg (90%) of the pure product as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.47 (d, J = 8.55 Hz, 1H), 7.39 (s, 1H), 7.01−7.10 (m, 2H), 6.74 (s, 1H), 6.66 (d, J = 8.24 Hz, 1H), 4.15 (t, J = 5.80 Hz, 2H), 4.02−4.10 (m, 2H), 3.26−3.33 (m, 1H), 2.73−2.80 (m, 1H), 2.68 (ddd, J = 16.02, 7.93, 7.78 Hz, 2H), 2.18−2.26 (m, 2H), 2.11−2.16 (m, J = 5.87, 5.87, 5.87, 5.87 Hz, 2H), 1.55−1.63 (m, 1H), 1.44−1.52 (m, J = 7.39, 7.39, 7.39, 7.39, 7.39 Hz, 4H), 0.81 (t, J = 7.32 Hz, 3H). LC-MS: method 1, RT (min) = 5.66 (no ionization); method 2, RT (min) = 4.39 (no ionization).

Compounds **17a**−**17m** and compounds **17o**−**17x** were made using the same procedure as for the preparation of compound **17n** using appropriate starting materials.

[(1*S*)-5-(3-Phenoxypropoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (17a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.22 (m, 3H), 7.09 (d, 1H), 6.95−6.87 (m, 2H), 6.80 (s, 1H), 6.74 (d, 1H), 4.18−4.08 (m, 4H), 3.51 (m, 1H), 2.88−2.79 (m, 2H), 2.73 (d, 1H), 2.48−2.31 (m, 2H), 2.26−2.17 (m, 2H), 1.87−1.71 (m, 1H). LC-MS: method 2, RT (min) = 3.98 (no ionization).

{**(1*S*)-5-[3-(4-Ethylphenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (17b).** ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.05 (dd, J = 7.93, 4.27 Hz, 3H), 6.80 (d, J = 8.24 Hz, 2H), 6.76 (s, 1H), 6.64−6.69 (m, 1H), 4.03 (t, J = 5.49 Hz, 4H), 3.33 (m, 1H), 2.75−2.81 (m, 1H), 2.69 (dt, J = 15.87, 7.93 Hz, 2H), 2.58 (d, J = 5.80 Hz, 1H), 2.5 (m, 1H), 2.19−2.27 (m, 4H), 2.04−2.11 (m, J = 6.18, 6.18, 6.18, 6.18 Hz, 2H), 1.60 (dd, J = 12.51, 7.63 Hz, 1H), 1.07−1.14 (m, 3H). LC-MS: method 1, RT (min) = 5.37; [M + H]$^+$ 355.0; method 2, RT (min) = 4.07 (no ionization).

((1*S*)-5-{3-[4-(Trifluoromethyl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic Acid (17c). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.22 (d, J = 8.54 Hz, 2H), 6.97−7.06 (m, 3H), 6.75 (s, 1H), 6.66 (d, J = 8.24 Hz, 1H), 4.01−4.10 (m, 4H), 3.25−3.32 (m, 1H), 2.68 (ddd, J = 16.02, 7.93, 7.78 Hz, 1H), 2.5 (m, 1H), 2.18−2.26 (m, 2H), 2.05−2.12 (m, J = 6.18, 6.18, 6.18, 6.18 Hz, 2H), 1.59 (ddd, J = 19.99, 7.93, 7.78 Hz, 1H). LC-MS: method 1, RT (min) = 5.36 (no ionization); method 2, RT (min) = 4.04 (no ionization).

((1*S*)-5-{3-[4-(Trifluoromethoxy)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic Acid (17d). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.21 (d, J = 8.85 Hz, 2H), 6.90−7.07 (m, 3H), 6.74 (s, 1H), 6.65 (d, J = 7.63 Hz, 1H), 3.70−4.10 (m, 4H), 3.28 (m, 1H), 2.62−2.84 (m, 2H), 2.59 (m, 1H), 2.15−2.24 (m, 2H), 1.99−2.14 (m, 2H), 1.58 (dd, J = 12.51, 7.63 Hz, 1H). LC-MS: method 1, RT (min) = 5.38; [M + H]$^+$ 410.9; method 2, RT (min) = 4.06 (no ionization).

{**(1*S*)-5-[3-(4-Methoxyphenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (17e).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, 1H), 6.84−6.70 (m, 6H), 4.17−4.05 (m, 4H), 3.76 (s, 3H), 3.51 (m, 1H), 2.90−2.77 (m, 2H), 2.50−2.35 (m, 2H), 2.25−2.17 (m, 2H), 1.85−1.70 (m, 1H). LC-MS: method 2, RT (min) = 3.18; [M + H]$^+$ 356.9.

{**(1*S*)-5-[3-(4-Ethoxyphenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (17f).** ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.04 (d, J = 8.24 Hz, 1H), 6.76−6.82 (m, 4H), 6.75 (s, 1H), 6.66 (d, J = 7.02 Hz, 1H), 4.01 (dt, J = 16.78, 6.10 Hz, 4H), 3.89 (q, J = 7.02 Hz, 2H), 3.26−3.33 (m, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 15.87, 7.93 Hz, 1H), 2.5 (m, 1H), 2.18−2.26 (m, 2H), 2.01−2.08 (m, J = 6.10, 6.10, 6.10, 6.10 Hz, 2H), 1.55−1.63 (m, 1H), 1.18−1.26 (m, 3H). LC-MS: method 1, RT (min) = 5.17; [M + H]$^+$ 371.1; method 2, RT (min) = 3.85; [M + H]$^+$ 371.2.

{**(1*S*)-5-[3-(4-Cyanophenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (17g).** ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.59 (d, J = 8.54 Hz, 1H), 7.50 (s, 1H), 7.02−7.10 (m, 2H), 6.74 (s, 1H), 6.65 (d, J = 7.93 Hz, 1H), 4.16 (t, J = 5.95 Hz, 2H), 4.06 (t, J = 6.10 Hz, 2H), 3.25−3.33 (m, 1H), 2.73−2.80 (m, 1H), 2.68 (dt, J = 15.79, 7.82 Hz, 1H), 2.18−2.26 (m, 2H), 2.09−2.16 (m, J = 5.95, 5.95, 5.95, 5.95 Hz, 2H), 1.55−1.63 (m, 1H), 1.42−1.50 (m, J = 7.32, 7.32, 7.32, 7.32, 7.32 Hz, 2H), 0.80 (t, J = 7.32 Hz, 3H). LC-MS: method 1, RT (min) = 5.30; [M + H]$^+$ 393.9; method 2, RT (min) = 3.98; [M + H]$^+$ 394.1.

{**(1*S*)-5-[3-(Biphenyl-4-yloxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (17h).** ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.54 (dd, J = 7.63, 5.80 Hz, 4H), 7.38 (t, J = 7.63 Hz, 2H), 7.26 (t, J = 7.17 Hz, 1H), 7.05 (d, J = 8.24 Hz, 1H), 6.99 (d, J = 8.54 Hz, 2H), 6.77 (s, 1H), 6.64−6.72 (m, 1H), 4.12 (t, J = 6.10 Hz, 2H), 4.06 (t, J = 6.10 Hz, 2H), 3.26−3.33 (m, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 15.79, 7.82 Hz, 1H), 2.5 (m, 1H), 2.17−2.26 (m, 2H), 2.06−2.14 (m, J = 6.03, 6.03, 6.03, 6.03 Hz, 2H), 1.54−1.63 (m, 1H). LC-MS: method 1, RT (min) = 5.44; [M + H]$^+$ 403.1; method 2, RT (min) = 4.13 (no ionization).

{**(1*S*)-5-[3-(3-Methylphenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (17i).** ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.10 (t, J = 7.78 Hz, 1H), 7.04 (d, J = 8.24 Hz, 1H), 6.75 (s, 1H), 6.64−6.71 (m, 4H), 4.00−4.06 (m, 4H), 3.27−3.33 (m, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 15.87, 7.93 Hz, 1H), 2.5 (m, 1H), 2.18−2.26 (m, 5H), 2.03−2.10 (m, J = 6.03, 6.03, 6.03, 6.03 Hz, 2H), 1.55−1.63 (m, 1H). LC-MS: method 1, RT (min) = 5.22; [M + H]$^+$ 341.1; method 2, RT (min) = 3.91; [M + H]$^+$ 341.3.

{**(1*S*)-5-[3-(3,4-Dimethylphenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (17j).** ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.04 (d, J = 8.24 Hz, 1H), 6.96 (d, J = 8.24 Hz, 1H), 6.75 (s, 1H), 6.64−6.69 (m, 2H), 6.60 (dd, J = 8.09, 1.98 Hz, 1H), 4.01 (q, J = 6.71 Hz, 4H), 3.32 (s, 1H), 3.25−3.32 (m, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 15.95, 8.05 Hz, 2H), 2.5 (m, 1H), 2.18−2.26 (m, 2H), 2.11 (s, 3H), 2.03−2.09 (m, 5H), 1.55−1.63 (m, 1H). LC-MS: method 1, RT (min) = 5.33; [M + H]$^+$ 355.0; method 2, RT (min) = 4.01 (no ionization).

{**(1*S*)-5-[3-(3-Methoxyphenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (17k).** ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.12 (t, J = 8.09 Hz, 1H), 7.04 (d, J = 8.24 Hz, 1H), 6.75 (s, 1H), 6.66 (d, J = 7.93 Hz, 1H), 6.42−6.49 (m, 3H), 4.04 (q, J = 6.31 Hz, 4H), 3.67 (s, 3H), 3.25−3.33 (m, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 15.87, 7.93 Hz, 1H), 2.5 (m, 1H), 2.18−2.26 (m, 2H), 2.03−2.10 (m, J = 6.10, 6.10, 6.10, 6.10 Hz, 2H), 1.55−1.63 (m, 1H). LC-MS: method 1, RT (min) = 5.07; [M + H]$^+$ 357.1; method 2, RT (min) = 3.75; [M + H]$^+$ 357.2.

{**(1*S*)-5-[3-(2,4-Dimethylphenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (17l).** ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.04 (d, J = 7.93 Hz, 1H), 6.85−6.92 (m, 2H), 6.73−6.79 (m, 2H), 6.66 (d, J = 7.63 Hz, 1H), 3.99−4.08 (m, 4H), 3.26−3.33 (m, 1H), 2.74−2.81 (m, 1H), 2.68 (dt, J = 15.95, 8.05 Hz, 2H), 2.18−2.26 (m, 2H), 2.14 (s, 3H), 2.04−2.11 (m, 5H), 1.55−1.63

(m, 1H). LC-MS: method 1, RT (min) = 5.39; $[M + H]^+$ 355.0; method 2, RT (min) = 4.08 (no ionization).

{(1*S*)-5-[3-(2-Propylphenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (17m). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.02−7.11 (m, 3H), 6.89 (d, J = 7.93 Hz, 1H), 6.80 (t, J = 7.32 Hz, 1H), 6.74 (s, 1H), 6.66 (d, J = 8.24 Hz, 1H), 4.06 (dt, J = 11.67, 5.91 Hz, 4H), 3.26−3.33 (m, 1H), 2.73−2.80 (m, 2H), 2.65−2.72 (m, 2H), 2.5 (m, 1H), 2.18−2.26 (m, 3H), 2.07−2.13 (m, J = 6.03, 6.03, 6.03, 6.03 Hz, 2H), 1.59 (dd, J = 12.21, 7.63 Hz, 1H), 1.42−1.50 (m, J = 7.40, 7.40, 7.40, 7.40 Hz, 2H), 0.80 (t, J = 7.32 Hz, 3H). LC-MS: method 1, RT (min) = 5.50; $[M + H]^+$ 369.0; method 2, RT (min) = 4.20 (no ionization).

{(1*S*)-5-[3-(4-Cyano-2-propylphenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (17o). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.70 (d, J = 8.85 Hz, 2H), 7.02−7.09 (m, 4H), 6.75 (s, 1H), 6.63−6.69 (m, 1H), 4.16 (t, J = 6.10 Hz, 3H), 4.03 (t, J = 6.10 Hz, 3H), 3.29 (dt, J = 14.27, 7.06 Hz, 2H), 2.74−2.80 (m, 2H), 2.65−2.73 (m, 2H), 2.17−2.26 (m, 4H), 2.08−2.15 (m, J = 6.03, 6.03, 6.03, 6.03 Hz, 3H), 1.54−1.63 (m, 2H). LC-MS: method 1, RT (min) = 4.97; $[M + H]^+$ 351.9; method 2, RT (min) = 3.62; $[M + H]^+$ 352.1.

{(1*S*)-5-[3-(4-Phenoxy-2-propylphenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (17p). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.28 (t, J = 7.78 Hz, 2H), 6.98−7.05 (m, 3H), 6.92 (d, J = 9.16 Hz, 1H), 6.84 (d, J = 7.93 Hz, 1H), 6.73−6.78 (m, 3H), 6.65 (d, J = 8.54 Hz, 1H), 4.02−4.09 (m, 4H), 2.98−3.40 (m, 1H), 2.75−2.85 (m, 4H), 2.50 (m, 1H), 2.59−2.72 (m, 2H), 2.17−2.24 (m, 2H), 2.08−2.12 (m, 2H), 1.58 (m, 1H), 1.40−1.48 (m, 2H), 0.78 (t, J = 7.32 Hz, 3H). LC-MS: method 1, RT (min) = 5.84; $[M + H]^+$ 460.9; method 2, RT (min) = 4.54; $[M + H]^+$ 461.5.

{(1*S*)-5-[3-(2-Methoxy-4-methylphenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (17q). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.04 (d, J = 8.24 Hz, 1H), 6.71−6.80 (m, 3H), 6.59−6.67 (m, 2H), 4.01 (dt, J = 19.23, 6.10 Hz, 4H), 3.67 (s, 3H), 3.26−3.33 (m, J = 7.48, 7.25, 7.13, 7.13 Hz, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 15.79, 7.82 Hz, 1H), 2.5 (m, 1H), 2.16−2.25 (m, 5H), 2.00−2.08 (m, J = 6.18, 6.18, 6.18, 6.18 Hz, 3H), 1.55−1.63 (m, 1H). LC-MS: method 1, RT (min) = 5.09; $[M + H]^+$ 371.1; method 2, RT (min) = 3.75; $[M + H]^+$ 371.2.

{(1*S*)-5-[3-(4-Ethyl-2-methoxyphenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (17r). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.04 (d, J = 8.24 Hz, 1H), 6.81 (d, J = 7.93 Hz, 1H), 6.75 (s, 2H), 6.65 (t, J = 8.85 Hz, 2H), 4.02 (dt, J = 16.40, 6.14 Hz, 4H), 3.68 (s, 3H), 3.30 (ddd, J = 14.27, 7.48, 7.25 Hz, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 15.95, 8.05 Hz, 1H), 2.5 (m, 1H), 2.18−2.26 (m, 2H), 2.01−2.08 (m, J = 6.18, 6.18, 6.18, 6.18 Hz, 2H), 1.54−1.63 (m, 2H), 1.06−1.14 (m, 3H). LC-MS: method 1, RT (min) = 5.20; $[M + H]^+$ 385.0; method 2, RT (min) = 3.89; $[M + H]^+$ 385.4.

{(1*S*)-5-[3-(4-Cyano-2-methoxyphenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (17s). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.30−7.37 (m, 2H), 7.02−7.11 (m, 2H), 6.74 (s, 1H), 6.65 (d, J = 7.93 Hz, 1H), 4.14 (t, J = 5.80 Hz, 2H), 4.03 (t, J = 5.95 Hz, 2H), 3.75 (s, 3H), 3.27−3.33 (m, 1H), 2.74−2.80 (m, 1H), 2.68 (dt, J = 15.87, 7.93 Hz, 1H), 2.5 (m, 1H), 2.17−2.26 (m, 2H), 2.08−2.16 (m, J = 6.03, 6.03, 6.03, 6.03 Hz, 2H), 1.55−1.63 (m, 1H). LC-MS: method 1, RT (min) = 4.88; $[M + H]^+$ 382.0; method 2, RT (min) = 3.44; $[M + H]^+$ 382.2.

{(1*S*)-5-[3-(2-Ethoxy-4-methylphenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (17t). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.04 (d, J = 8.55 Hz, 1H), 6.80 (d, J = 7.93 Hz, 1H), 6.74 (s, 1H), 6.72 (s, 1H), 6.59−6.67 (m, 2H), 3.98−4.06 (m, 4H), 3.92 (q, J = 6.92 Hz, 2H), 3.26−3.34 (m, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 15.87, 7.93 Hz, 1H), 2.5 (m, 1H), 2.20−2.26 (m, 2H), 2.17 (s, 3H), 2.04 (qd, J = 6.15, 5.95 Hz, 2H), 1.55−1.63 (m, 1H), 1.18−1.25 (m, 3H). LC-MS: method 1, RT (min) = 5.21; $[M + H]^+$ 385.1; method 2, RT (min) = 3.88; $[M + H]^+$ 385.4.

((1*S*)-5-{3-[4-(1*H*-1,2,4-Triazol-1-yl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic Acid (17u). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.07 (s, 1H), 7.69 (d, J = 8.85 Hz, 2H), 7.02−7.09 (m, 3H), 6.76 (s, 1H), 6.64−6.71 (m, 1H), 4.13 (t, J = 6.26 Hz, 2H), 4.06 (t, J = 6.26 Hz, 2H), 3.30 (ddd, J = 14.57, 7.63, 7.40 Hz, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 15.87, 7.93 Hz, 1H), 2.5 (m, 1H), 2.18−2.27 (m, 3H), 2.07−2.15 (m, J = 6.18, 6.18, 6.18, 6.18 Hz, 2H), 1.55−1.63 (m, 1H). LC-MS: method 1, RT (min) = 4.74; $[M + H]^+$ 394.2; method 2, RT (min) = 3.34; $[M + H]^+$ 394.2.

((1*S*)-5-{3-[2-(Acetylamino)-4-(1*H*-1,2,3-triazol-1-yl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic Acid (17v). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.58 (s, 1H), 8.46 (s, 1H), 7.87 (s, 1H), 7.43−7.50 (m, 1H), 7.20 (d, J = 8.85 Hz, 1H), 7.05 (d, J = 8.24 Hz, 1H), 6.77 (s, 1H), 6.68 (d, J = 8.24 Hz, 1H), 4.22 (t, J = 5.95 Hz, 2H), 4.12 (t, J = 6.10 Hz, 2H), 3.27−3.33 (m, 1H), 2.74−2.81 (m, 1H), 2.69 (ddd, J = 15.72, 7.78, 7.63 Hz, 1H), 2.5 (m, 1H), 2.17−2.26 (m, 4H), 2.08 (s, 3H), 1.55−1.63 (m, 1H). LC-MS: method 1, RT (min) = 4.58; $[M + H]^+$ 451.2; method 2, RT (min) = 3.19; $[M + H]^+$ 451.2.

((1*S*)-5-{3-[2-Chloro-4-(4*H*-1,2,4-triazol-4-yl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic Acid (17w). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.08 (s, 1H), 7.55 (d, J = 8.54 Hz, 1H), 7.46 (d, J = 2.14 Hz, 2H), 7.24 (dd, J = 8.54, 2.14 Hz, 1H), 7.04 (d, J = 8.24 Hz, 1H), 6.76 (s, 1H), 6.66 (d, J = 7.93 Hz, 1H), 4.28 (t, J = 5.95 Hz, 2H), 4.08 (t, J = 6.10 Hz, 2H), 3.29 (dt, J = 14.34, 7.17 Hz, 1H), 2.74−2.80 (m, 1H), 2.68 (dt, J = 15.87, 7.93 Hz, 2H), 2.20−2.24 (m, 2H), 2.16 (dt, J = 11.90, 5.95 Hz, 2H), 1.55−1.63 (m, 1H). LC-MS: method 1, RT (min) = 4.72; $[M + H]^+$ 428.2; method 2, RT (min) = 3.31; $[M + H]^+$ 428.3.

[(1*S*)-5-(3-{2-Methyl-4-[3-(trifluoromethyl)-1,2,4-thiadiazol-5-yl]phenoxy}propoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (17x). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.89 (d, J = 8.54 Hz, 1H), 7.86 (s, 1H), 7.13 (d, J = 8.54 Hz, 1H), 7.05 (d, J = 8.24 Hz, 1H), 6.77 (s, 1H), 6.68 (d, J = 7.93 Hz, 1H), 4.21 (t, J = 5.80 Hz, 2H), 4.09 (t, J = 6.10 Hz, 2H), 3.30 (dt, J = 14.65, 7.32 Hz, 1H), 2.74−2.81 (m, 1H), 2.69 (ddd, J = 16.02, 7.93, 7.78 Hz, 2H), 2.55−2.63 (m, 1H), 2.15−2.24 (m, 7H), 1.55−1.63 (m, 1H). LC-MS: method 1, RT (min) = 5.62; $[M + H]^+$ 493.1; method 2, RT (min) = 4.32; $[M + H]^+$ 493.0.

Ethyl {(1*S*)-5-[3-(4-Iodophenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (27). To a mixture of 4-iodophenol (512 mg, 2.33 mmol) and intermediate **15** (794 mg, 2.33 mmol) in 40 mL of DMF (containing 1% water) was added powdered Cs_2CO_3 (1137 mg, 3.49 mmol), and the mixture was stirred at rt for 16 h. EtOAc was added to the mixture, and the solid residue was removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (5% EtOAc in Hex) to give the pure product (248 mg, 22%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, 2H), 7.06 (d, 1H), 6.80 (s, 1H), 6.72−6.64 (m, 3H), 4.23−4.06 (m, 6H), 3.58−3.46 (m, 1H), 2.94−2.78 (m, 2H), 2.72 (dd, 1H), 2.43−2.35 (m, 2H), 2.28−2.20 (m, 2H), 1.80−1.69 (m, 1H), 1.18 (t, 3H).

Ethyl ((1*S*)-5-{3-[4-(3-Thienyl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (28a; Approach A). To a solution of thiophene-3-boronic acid (53 mg, 0.42 mmol), ethyl {(1*S*)-5-[3-(4-iodophenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (**27**; 50 mg, 0.10 mmol) in toluene (1.8 mL) and 1,4-dioxane (0.45 mL) was added $PdCl_2(dppf)\cdot CH_2Cl_2$ (7.6 mg, 0.01 mmol), and argon was passed through the mixture for 30 min. Then Na_2CO_3 (2 N aqueous solution, 0.50 mL) was added, and the mixture was heated to 75 °C for 48 h. The reaction was cooled to rt and extracted with EtOAc (2×). The combined organic phases were washed with $NaHCO_3$ (saturated aqueous solution), dried, filtered, and concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel to give 33 mg (73%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, 2H), 7.40−7.31 (m, 3H), 7.06 (d, 1H), 6.97 (d, 2H), 6.80 (s, 1H), 6.72 (dd, 1H), 4.24−4.10 (m, 6H), 3.60−3.48 (m, 1H), 2.98−2.90 (m, 2H), 2.72 (dd, 1H), 2.46−2.36 (m, 2H), 2.36−2.23 (m, 2H), 1.85−1.70 (m, 1H), 1.30 (t, 3H). Compounds **28b**−**28g** were synthesized using the same procedure as for the preparation of compound **28a** using appropriate starting materials.

Ethyl ((1*S*)-5-{3-[4-(6-Methyl-2-pyridinyl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (28h; Approach B). To a

solution of ethyl{(1*S*)-5-[3-(4-iodophenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (**27**; 70 mg, 0.15 mmol) in DMF (1 mL) was added bis(pinacolato)diboron (41 mg, 0.16 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (11 mg, 0.01 mmol), and KOAc (43 mg, 0.44 mmol). Argon was passed through the solution, and the reaction mixture was heated at 80 °C for 2 h and then cooled to rt. More $PdCl_2$(dppf)·CH_2Cl_2 (5 mg, 0.005 mmol) was added, followed by the addition of 2-bromo-6-methylpyridine (50 mg, 0.29 mmol) and Na_2CO_3 (2 M aqueous solution, 0.37 mL). The reaction mixture was heated to 80 °C for 12 h and then cooled to rt, diluted with HCl (1 N aqueous solution), and extracted with EtOAc. The combined organic phases were dried, filtered, and concentrated under reduced pressure. Purification by preparative thin layer chromatography (EtOAc/hexanes 2:3) gave 286 mg (40%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 2H), 7.73−7.62 (m, 1H), 7.62−7.52 (m, 1H), 7.16−6.96 (m, 4H), 6.83 (s, 1H), 6.52 (d, 1H), 4.28−4.04 (m, 6H), 3.52−3.38 (m, 1H), 2.96−2.63 (m, 3H), 2.54 (s, 3H), 2.48−2.12 (m, 4H), 1.82−1.62 (m, 1H), 1.23 (t, 3H). Compound **28i** was synthesized using the same procedure as for the preparation of compound **28h** using appropriate starting materials.

((1*S*)-5-{3-[4-(3-Thienyl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic Acid (29a). To a solution of compound **28a** (24 mg, 0.05 mmol) in 1.6 mL of THF/water (3:1) was added LiOH·H_2O (3 mg, 0.07 mmol), and the mixture was stirred at rt for 16 h. The THF was evaporated and more water was added. The aqueous layer was washed with a small amount of ether. The aqueous layer was then acidified with 1 N HCl and extracted 3× with EtOAc. The combined organic layers were dried ($MgSO_4$), concentrated, and subjected to preparative HPLC purification to give 6.5 mg (29%) of the pure product. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.66 (s, 1H), 7.53−7.61 (m, 3H), 7.44 (d, J = 4.88 Hz, 1H), 7.06 (d, J = 8.24 Hz, 1H), 6.94 (d, J = 8.55 Hz, 2H), 6.77 (s, 1H), 6.68 (d, J = 7.32 Hz, 1H), 4.04−4.12 (m, 4H), 3.32 (d, J = 3.05 Hz, 1H), 2.78 (d, J = 4.27 Hz, 1H), 2.66−2.75 (m, 1H), 2.5 (m, 1H), 2.19−2.27 (m, 2H), 2.08−2.14 (m, 2H), 1.60 (d, J = 4.88 Hz, 1H). LC-MS: method 1, RT (min) = 5.40; $[M + H]^+$ 409.0; method 2, RT (min) = 3.97 (no ionization). Compounds **29b**−**29i** were synthesized using the same procedure as for the preparation of compound **29a** using appropriate starting materials.

((1*S*)-5-{3-[4-(3-Furyl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid (29b). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.46 (d, J = 8.55 Hz, 1H), 7.04 (d, J = 8.24 Hz, 1H), 6.99 (td, J = 8.47, 3.51 Hz, 1H), 6.91 (d, J = 8.54 Hz, 1H), 6.81−6.87 (m, 1H), 6.73−6.80 (m, 1H), 6.67 (d, J = 8.24 Hz, 1H), 4.13 (d, J = 15.87 Hz, 1H), 4.06 (dt, J = 18.84, 5.99 Hz, 4H), 3.26−3.33 (m, 2H), 2.90−2.97 (m, 1H), 2.74−2.81 (m, 2H), 2.69 (dt, J = 16.10, 7.97 Hz, 1H), 2.18−2.27 (m, 2H), 2.06−2.14 (m, 2H), 1.72 (s, 1H), 1.59 (ddd, J = 19.99, 7.93, 7.78 Hz, 1H). LC-MS: method 1, RT (min) = 5.24; $[M + H]^+$ 393.1; method 2, RT (min) = 3.88 (no ionization).

((1*S*)-5-{3-[4-(1*H*-Indol-6-yl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic Acid (29c). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 7.69 (s, 1H), 7.52 (d, J = 8.54 Hz, 2H), 7.39 (d, J = 8.24 Hz, 1H), 7.26−7.34 (m, 2H), 7.06 (d, J = 8.54 Hz, 1H), 6.97 (d, J = 8.54 Hz, 2H), 6.78 (s, 1H), 6.69 (d, J = 6.71 Hz, 1H), 6.41 (s, 1H), 4.05−4.14 (m, 4H), 3.33 (d, J = 2.75 Hz, 1H), 2.76−2.82 (m, 1H), 2.70 (dt, J = 15.79, 7.82 Hz, 1H), 2.60 (dd, J = 15.41, 5.65 Hz, 1H), 2.19−2.28 (m, 2H), 2.09−2.16 (m, J = 6.03, 6.03, 6.03, 6.03 Hz, 2H), 1.60 (dd, J = 12.21, 7.63 Hz, 1H). LC-MS: method 1, RT (min) = 5.26; $[M + H]^+$ 442.1; method 2, RT (min) = 3.93; $[M + H]^+$ 442.5.

{(1*S*)-5-[3-(4-Pyridin-3-ylphenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (29d). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.78 (s, 1H), 7.98 (d, J = 7.93 Hz, 1H), 7.61 (d, J = 8.54 Hz, 2H), 7.41 (dd, J = 7.78, 4.73 Hz, 1H), 7.01−7.07 (m, 3H), 6.76 (s, 1H), 6.63−6.71 (m, 1H), 4.13 (t, J = 6.10 Hz, 2H), 4.06 (t, J = 6.10 Hz, 2H), 3.26−3.33 (m, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 15.95, 8.05 Hz, 1H), 2.5 (m, 1H), 2.18−2.27 (m, 3H), 2.12 (qd, J = 6.00, 5.80 Hz, 3H), 1.54−1.63 (m, 1H). LC-MS: method 1, RT (min) = 4.43; $[M + H]^+$ 404.2; method 2, RT (min) = 2.98; $[M + H]^+$ 404.3.

((1*S*)-5-{3-[4-(4-Methoxypyridin-3-yl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic Acid (29e). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.35 (d, J = 2.14 Hz, 1H), 7.89 (dd, J = 8.54, 2.44 Hz, 1H), 7.52 (d, J = 8.54 Hz, 2H), 7.05 (d, J = 8.24 Hz, 1H), 6.99 (d, J = 8.54 Hz, 2H), 6.83 (d, J = 8.54 Hz, 1H), 6.76 (s, 1H), 6.67 (d, J = 8.24 Hz, 1H), 4.03−4.13 (m, 4H), 3.83 (s, 3H), 3.26−3.33 (m, 1H), 2.94 (s, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 16.10, 7.97 Hz, 2H), 2.17−2.26 (m, 3H), 2.07−2.15 (m, 2H), 1.54−1.63 (m, 1H). LC-MS: method 1, RT (min) = 5.28; $[M + H]^+$ 434.2; method 2, RT (min) = 3.84; $[M + H]^+$ 434.4.

{(1*S*)-5-[3-(4-Pyrimidin-5-ylphenoxy)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic Acid (29f). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.08 (s, 1H), 9.03 (s, 2H), 7.70 (d, J = 8.55 Hz, 2H), 7.06 (t, J = 8.09 Hz, 3H), 6.77 (s, 1H), 6.67 (d, J = 7.93 Hz, 1H), 4.11−4.17 (m, 2H), 4.06 (t, J = 6.10 Hz, 2H), 3.30 (dt, J = 14.42, 7.29 Hz, 1H), 2.75−2.81 (m, 1H), 2.69 (dt, J = 15.95, 8.05 Hz, 1H), 2.5 (m, 1H), 2.18−2.27 (m, 2H), 2.09−2.16 (m, J = 6.10, 6.10, 6.10, 6.10 Hz, 2H), 1.55−1.63 (m, 1H). LC-MS: method 1, RT (min) = 4.82; $[M + H]^+$ 405.2; method 2, RT (min) = 3.43; $[M + H]^+$ 405.2.

((1*S*)-5-{3-[4-(2,4-Dimethoxypyrimidin-5-yl)phenoxy]propoxy-2,3-dihydro-1*H*-inden-1-yl)acetic Acid (29g). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.25 (s, 1H), 7.39 (d, J = 8.54 Hz, 2H), 7.05 (d, J = 8.24 Hz, 1H), 6.96 (d, J = 8.54 Hz, 2H), 6.76 (s, 1H), 6.67 (d, J = 8.24 Hz, 1H), 4.11 (t, J = 6.10 Hz, 2H), 4.05 (t, J = 5.95 Hz, 2H), 3.88 (s, 6H), 3.26−3.33 (m, 1H), 2.74−2.81 (m, 1H), 2.65−2.73 (m, 1H), 2.5 (m, 1H), 2.18−2.26 (m, 2H), 2.07−2.14 (m, J = 6.03, 6.03, 6.03, 6.03 Hz, 2H), 1.59 (dd, J = 12.36, 7.78 Hz, 1H). LC-MS: method 1, RT (min) = 5.12; $[M + H]^+$ 465.2; method 2, RT (min) = 3.55; $[M + H]^+$ 465.3.

((1*S*)-5-{3-[4-(6-Methyl-2-pyridinyl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic Acid (29h). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.94 (d, J = 8.54 Hz, 2H), 7.76 (s, 1H), 7.66 (d, J = 7.63 Hz, 1H), 7.18 (d, J = 7.02 Hz, 1H), 7.00−7.08 (m, 3H), 6.77 (s, 1H), 6.68 (d, J = 8.24 Hz, 1H), 4.14 (t, J = 6.10 Hz, 2H), 4.03−4.11 (m, 3H), 3.26−3.33 (m, 1H), 2.94 (s, 1H), 2.77 (d, J = 3.66 Hz, 2H), 2.65−2.74 (m, 2H), 2.18−2.26 (m, 2H), 2.07−2.15 (m, 2H), 1.55−1.63 (m, 1H), 1.18 (s, 1H), 1.12 (t, J = 7.48 Hz, 1H). LC-MS: method 1, RT (min) = 4.32; $[M + H]^+$ 418.2; method 2, RT (min) = 2.91; $[M + H]^+$ 418.3.

[(1*S*)-5-(3-{4-[5-(Trifluoromethyl)pyridin-2-yl]phenoxy}propoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid (29i). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.15 (d, J = 8.54 Hz, 1H), 8.03−8.10 (m, 3H), 7.06 (d, J = 8.54 Hz, 2H), 7.04 (s, 1H), 6.77 (s, 1H), 6.68 (d, J = 7.02 Hz, 1H), 4.16 (t, J = 6.10 Hz, 2H), 4.02−4.12 (m, 3H), 3.30 (dt, J = 14.42, 7.29 Hz, 1H), 2.74−2.81 (m, 1H), 2.69 (ddd, J = 16.02, 7.93, 7.78 Hz, 1H), 2.5 (m, 1H), 2.18−2.26 (m, 2H), 2.07−2.16 (m, 2H), 1.55−1.63 (m, 1H), 1.18 (s, 1H). LC-MS: method 1, RT (min) = 5.49; $[M + H]^+$ 472.2; method 2, RT (min) = 4.16; $[M + H]^+$ 472.3.

Ethyl ((1*S*)-5-{3-[4-(Aminocarbonothioyl)-2-propylphenoxy]-propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (31). To a solution of ethyl {(1*S*)-5-[3-(4-cyano-2-propylphenoxy) propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (**17o**, 1.2 g, 2.9 mmol) in anhydrous DMF (15 mL) under argon at rt was passed H_2S gas at a moderate rate for 20 min. Then a solution of diethylamine (0.3 g, 4.3 mmol) in DMF (3 mL) was added in one portion, and the reaction mixture was stirred at 60 °C for 3 h. Upon completion, the reaction was cooled to rt and argon was passed through the reaction mixture for 1 h to remove residual H_2S. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel flash chromatography (EtOAc/hexane (v/v) = 1:1) to give 0.9 g (76%) of the title compound as a yellow solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.94 (t, 3H), 1.31 (t, 3H), 1.52−1.64 (m, 2H), 1.65−1.80 (m, 1H), 2.20−2.44 (m, 4H), 2.58−2.95 (m, 5H), 3.38−3.61 (m, 1H), 4.16−4.21 (m, 4H), 4.26 (t, 2H), 6.69 (d, 1H), 6.80 (s, 1H), 6.95 (d, 1H), 7.09 (d, 1H), 7.79 (d, 1H), 7.84 (s, 1H).

Ethyl ((1*S*)-5-{3-[4-(Aminocarbonothioyl)-2-methoxyphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (32). Into a

solution of ethyl {(1*S*)-5-[3-(4-cyano-2-methoxyphenoxy) propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (2.2 g, 5.4 mmol; **17s**) in DMF (anhydrous, 20 mL) under argon at rt was passed H_2S gas at a moderate rate for 30 min. A solution of diethylamine (0.8 g, 8.1 mmol) in DMF (5 mL) was added in one portion, and the reaction was stirred at 60 °C for 3 h. Then the reaction was cooled to rt and argon was passed through the reaction mixture for 1 h to remove residual H_2S. The reaction mixture was then concentrated under reduced pressure and the residue was purified by silica gel flash chromatography (EtOAc/hexane (v/v) = 1:1) to afford 1.9 g (81%) of the title compound as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (t, 3H), 1.60−1.68 (m, 1H), 2.15−2.22 (m, 2H), 2.23−2.34 (m, 1H), 2.38 (q, 1H), 2.70−2.86 (m, 3H), 3.38−3.44 (m, 1H), 3.80 (s, 3H), 4.05−4.16 (m, 4H), 4.19 (t, 2H), 6.70 (d, 1H), 6.80 (s, 1H), 6.97 (d, 1H), 7.06 (d, 1H), 7.56−7.64 (m, 2H), 9.33−9.40 (s, 1H), 9.65 (s, 1H).

Ethyl ((1*S*)-5-{3-[4-(Aminocarbonothioyl)phenoxy]propoxy-2,3-dihydro-1*H*-inden-1-yl)acetate (30). The title product was synthesized using the same procedure as for the preparation of compound **31** using appropriate starting materials. ^{1}H NMR (400 MHz, CD_3OD) δ 7.92 (dd, 2H), 7.14 (d, 1H), 6.96 (dd, 2H), 6.82 (m, 1H), 6.76 (m, 1H), 4.20−4.28 (m, 2H), 4.11−4.19 (m, 4H), 3.40−3.57 (m, 1H), 2.69−2.96 (m, 3H), 2.28−2.44 (m, 2H), 2.20−2.27 (q, 2H), 1.72−1.80 (m, 1H), 1.21−1.30 (t, 3H).

Ethyl ((1*S*)-5-{3-[2-methoxy-4-(1,3-thiazol-2-yl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (33b). Ethyl ((1*S*)-5-{3-[4-(aminocarbonothioyl)-2-methoxyphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (1.00 g, 2.3 mmol; **32**) and bromoacetaldehyde diethyl acetal (1.78 g, 9.2 mmol) were dissolved in EtOH (30 mL) and water (2 drops) was added. The mixture was heated at 70 °C for 18 h, and then the reaction mixture was cooled to rt and concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/hexane (v/v) = 1:1) gave 610 mg (58%) of the title compound as a clear oil. LC-MS (method 2): RT (min) = 3.81; $[M + H]^+$ 468.1.

Ethyl ((1*S*)-5-{3-[4-(4-Ethyl-1,3-thiazol-2-yl)-2-propylphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (33e). A solution of ethyl ((1*S*)-5-{3-[4-(aminocarbonothioyl)-2-propylphenoxy]-propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (90 mg, 0.2 mmol; **31**) and 1-bromo-2-butanone (35.8 mg, 0.24 mmol) in EtOH (anhydrous, 8 mL) was heated at 70 °C for 6 h. The reaction mixture was cooled to rt and then concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/hexane (v/v) 1:2) gave 42 mg (42%) of the title compound as a clear oil. LC-MS (method 2): RT (min) = 4.85; $[M + H]^+$ 508.2.

Ethyl ((1*S*)-5-{3-[4-(1,3-Benzothiazol-2-yl)-2-methoxyphenoxy] propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (33t). A slurry of 2-aminothiophenol (357 mg, 2.85 mmol) in polyphosphoric acid (14.0 g) was heated to 110 °C and 4-hydroxy-3-methoxybenzoic acid (480 mg, 2.85 mmol) was added. After 2 h, the reaction mixture was cooled to rt. The mixture was poured carefully into ice cold water, and the solution was neutralized with KOH (3 M aqueous solution). The aqueous phase was extracted with EtOAc (2×). The combined organic layers were washed with Na_2CO_3 (1 M aqueous solution), HCl (1 M aqueous solution), and water, dried, and concentrated under reduced pressure. Purification by silica gel chromatography gave 22 mg of the intermediate 4-(1,3-benzothiazol-2-yl)-2-methoxyphenol as an oil. This intermediate was coupled with compound **15** as described for the preparation of compound **16n** to give the title compound as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, 1H), 7.86 (d, 1H), 7.70 (s, 1H), 7.58 (m, 1H), 7.48 (m, 1H), 7.37 (m, 1H), 7.06 (d, 1H), 6.96 (d, 1H), 6.81 (s, 1H), 6.72 (d, 1H), 4.34−4.24 (m, 2H), 4.24−4.12 (m, 4H), 4.00 (s, 3H), 3.58−3.48 (m, 1H), 2.95−2.80 (m, 2H), 2.72 (dd, 1H), 2.44−2.28 (m, 4H), 1.84−1.68 (m, 1H), 1.28 (t, 3H).

Ethyl ((1*S*)-5-{3-[4-(4-Isopropoxy-1,3-thiazol-2-yl)-2-methoxyphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (33ak). A solution of ethyl ((1*S*)-5-{3-[4-(aminocarbonothioyl)-2-methoxyphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (500 mg, 1.1 mmol; **32**) and 2-chloro-*N*,*N*-dimethylacetamide (800 mg, 6.6 mmol) in *i*-PrOH (anhydrous, 15 mL) was stirred at 70 °C for 8 h. The reaction was cooled to rt and concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/hexane (v/v) = 1:2) gave 292 mg (49%) of the title compound as a yellow oil. LC-MS (method 2): RT (min) = 4.27; $[M + H]^+$ 526.1.

Compound **33a** was synthesized using a similar procedure as described for the preparation of compound **33b**. Compounds **33c**, **33d**, **33f**−**33s**, and **33u**−**33ad** were made using a similar procedure as described for the preparation of compound **33e**. Among those, compounds **33z**−**33ad** were prepared as derivatives having R^1 or R^2 = COOMe or COOEt. Compounds **33ae**−**33aj** and **33al**−**33an** were synthesized using a similar procedure as described for compound **33ak**.

Compounds **34a**−**34an** were synthesized using the ester hydrolysis procedure described for the preparation of compound **17n**.

[(1*S*)-5-{3-[2-Propyl-4-(1,3-thiazol-2-yl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34a). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.78 (d, J = 3.36 Hz, 1H), 7.69 (d, J = 8.54 Hz, 1H), 7.66 (s, 1H), 7.59 (s, 1H), 7.04 (t, J = 8.39 Hz, 2H), 6.75 (s, 1H), 6.67 (d, J = 7.32 Hz, 1H), 4.14 (t, J = 5.80 Hz, 2H), 4.08 (t, J = 6.10 Hz, 2H), 3.30 (dt, J = 14.27, 7.06 Hz, 1H), 2.74−2.81 (m, 1H), 2.69 (ddd, J = 16.02, 7.93, 7.78 Hz, 1H), 2.5 (m, 1H), 2.18−2.26 (m, 4H), 2.11−2.16 (m, J = 5.87, 5.87, 5.87, 5.87 Hz, 2H), 1.59 (dd, J = 12.36, 7.48 Hz, 1H), 1.47−1.55 (m, J = 7.32, 7.32, 7.32, 7.32 Hz, 2H), 0.83 (t, J = 7.32 Hz, 3H). LC-MS: method 1, RT (min) = 5.50; $[M + H]^+$ 452.2; method 2, RT (min) = 4.12; $[M + H]^+$ 452.3.

[(1*S*)-5-{3-[2-Methoxy-4-(1,3-thiazol-2-yl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34b). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.79 (s, 1H), 7.61 (d, J = 3.05 Hz, 1H), 7.45 (s, 1H), 7.04 (d, J = 8.24 Hz, 2H), 6.76 (s, 1H), 6.67 (s, 1H), 4.12 (t, J = 6.10 Hz, 2H), 4.05 (t, J = 5.95 Hz, 2H), 3.79 (s, 3H), 3.29 (m, 1H), 2.80 (m, 1H), 2.70 (m, 1H), 2.50 (m, 1H), 2.24 (m, 2H), 2.08−2.16 (m, 2H), 1.59 (s, 1H). LC-MS: method 1, RT (min) = 4.98; $[M + H]^+$ 440.2; method 2, RT (min) = 3.64; $[M + H]^+$ 440.2.

[(1*S*)-5-{3-[2-Methoxy-4-(4-methyl-1,3-thiazol-2-yl)phenoxy]-propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34c). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.40 (s, 1H), 7.37 (d, J = 8.54 Hz, 1H), 7.16 (s, 1H), 7.03 (t, J = 9.31 Hz, 2H), 6.76 (s, 1H), 6.67 (d, J = 8.24 Hz, 1H), 4.12 (t, J = 6.10 Hz, 2H), 4.05 (t, J = 5.95 Hz, 2H), 3.78 (s, 4H), 3.26−3.33 (m, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 15.79, 7.82 Hz, 1H), 2.5 (m, 1H), 2.35 (s, 2H), 2.18−2.26 (m, 2H), 2.08−2.15 (m, J = 6.03, 6.03, 6.03, 6.03 Hz, 2H), 1.55−1.63 (m, 1H). LC-MS: method 1, RT (min) = 5.09; $[M + H]^+$ 454.2; method 2, RT (min) = 3.68; $[M + H]^+$ 454.3.

[(1*S*)-5-{3-[4-(4-Ethyl-1,3-thiazol-2-yl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34d). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.79 (d, J = 8.54 Hz, 2H), 7.15 (s, 1H), 6.98−7.06 (m, 3H), 6.76 (s, 1H), 6.67 (d, J = 7.32 Hz, 1H), 4.13 (t, J = 6.10 Hz, 3H), 4.05 (t, J = 6.10 Hz, 2H), 3.30 (dt, J = 14.34, 7.17 Hz, 1H), 2.74−2.81 (m, 1H), 2.66−2.73 (m, 3H), 2.5 (m, 1H), 2.18−2.26 (m, 2H), 2.08−2.15 (m, J = 6.03, 6.03, 6.03, 6.03 Hz, 2H), 1.55−1.63 (m, 1H), 1.20 (t, J = 7.63 Hz, 3H). LC-MS: method 1, RT (min) = 5.41; $[M + H]^+$ 438.2; method 2, RT (min) = 4.01; $[M + H]^+$ 438.3.

[(1*S*)-5-{3-[4-(4-Ethyl-1,3-thiazol-2-yl)-2-propylphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34e). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.65 (d, J = 8.55 Hz, 1H), 7.62 (s, 1H), 7.05 (d, J = 8.39 Hz, 1H), 7.02 (d, J = 8.39 Hz, 1H), 6.75 (s, 1H), 6.64−6.69 (m, 1H), 4.06−4.15 (m, 4H), 3.26−3.33 (m, 1H), 2.74−2.81 (m, 1H), 2.65−2.72 (m, 3H), 2.5 (m, 1H), 2.18−2.26 (m, 2H), 2.13 (qd, J = 6.00, 5.80 Hz, 2H), 1.55−1.63 (m, 1H), 1.50 (qt, J = 7.40, 7.21 Hz, 3H), 1.20 (t, J = 7.48 Hz, 3H), 0.83 (t, J = 7.32 Hz, 3H). LC-MS: method 1, RT (min) = 5.84; $[M + H]^+$ 480.3; method 2, RT (min) = 4.20; $[M + H]^+$ 480.3.

[(1*S*)-5-{3-[4-(4-Ethyl-1,3-thiazol-2-yl)-2-methoxyphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34f). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.40 (s, 1H), 7.38 (d, J = 8.55 Hz, 1H), 7.18 (s, 1H), 7.04 (t, J = 8.55 Hz, 2H), 6.76 (s, 1H), 6.64−6.71 (m, 1H), 4.12 (t, J = 5.95 Hz, 2H), 4.05 (t, J = 5.95 Hz, 2H), 3.78 (s, 3H), 3.37 (s, 1H), 3.27−3.33 (m, 2H), 2.75−2.84 (m, 1H), 2.67−

2.75 (m, 4H), 2.5 (m, 1H), 2.18−2.26 (m, 2H), 2.08−2.16 (m, 2H), 1.59 (dd, J = 12.21, 7.63 Hz, 1H), 1.21 (t, J = 7.48 Hz, 3H). LC-MS: method 1, RT (min) = 5.24; $[M + H]^+$ 468.2; method 2, RT (min) = 3.60; $[M + H]^+$ 468.3.

[(1*S*)-5-{3-[4-(4-*tert*-Butyl-1,3-thiazol-2-yl)-2-propylphenoxy]propoxy}-2,3-dihydro-1*H*-1-inden-1-yl]acetic Acid (34g). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.60 (d, J = 1.83 Hz, 1H), 7.05 (d, J = 8.39 Hz, 1H), 7.02 (d, J = 8.39 Hz, 1H), 6.75 (s, 1H), 6.63−6.69 (m, 1H), 4.06−4.15 (m, 4H), 3.30 (s, 1H), 2.73−2.81 (m, 1H), 2.69 (d, J = 7.93 Hz, 1H), 2.5 (m, 1H), 2.18−2.26 (m, 2H), 2.10−2.18 (m, 2H), 1.59 (d, J = 4.58 Hz, 1H), 1.46−1.55 (m, 2H), 1.28 (s, 10H), 1.09−1.15 (m, 1H), 1.06 (s, 3H), 0.81−0.89 (m, 4H). LC-MS: method 1, RT (min) = 6.17; $[M + H]^+$ 508.3; method 2, RT (min) = 4.81; $[M + H]^+$ 508.4.

[(1*S*)-5-(3-{2-Propyl-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenoxy}propoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34h). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.74 (d, J = 8.55 Hz, 1H), 7.68 (d, J = 1.53 Hz, 1H), 7.02−7.09 (m, 2H), 6.75 (s, 1H), 6.67 (d, J = 7.93 Hz, 1H), 4.16 (t, J = 5.80 Hz, 2H), 4.09 (t, J = 6.10 Hz, 2H), 3.26−3.33 (m, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 16.10, 7.97 Hz, 1H), 2.5 (m, 1H), 2.18−2.26 (m, 4H), 2.12−2.17 (m, J = 5.95, 5.95, 5.95, 5.95 Hz, 2H), 1.59 (dd, J = 12.21, 7.63 Hz, 1H), 1.48−1.55 (m, 2H), 0.83 (t, J = 7.32 Hz, 3H). LC-MS: method 1, RT (min) = 5.83; $[M + H]^+$ 520.2; method 2, RT (min) = 4.51; $[M + H]^+$ 520.4.

[(1*S*)-5-(3-{2-Methoxy-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenoxy}propoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34i). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.48 (d, J = 8.24 Hz, 1H), 7.42 (s, 1H), 7.07 (d, J = 8.24 Hz, 1H), 7.05 (d, J = 8.24 Hz, 1H), 6.76 (s, 1H), 6.68 (s, 1H), 4.15 (t, J = 5.95 Hz, 2H), 4.05 (t, J = 5.95 Hz, 2H), 3.81 (s, 3H), 3.27−3.33 (m, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 15.87, 7.93 Hz, 1H), 2.5 (m, 1H), 2.18−2.26 (m, 2H), 2.10−2.16 (m, 2H), 1.55−1.63 (m, 1H). LC-MS: method 1, RT (min) = 5.34; $[M + H]^+$ 508.1; method 2, RT (min) = 3.98; $[M + H]^+$ 508.3.

[(1*S*)-5-{3-[4-(4,5-Dimethyl-1,3-thiazol-2-yl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34j). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.71 (d, J = 8.85 Hz, 2H), 7.06 (d, J = 8.24 Hz, 1H), 6.98 (d, J = 8.85 Hz, 2H), 6.77 (s, 1H), 6.68 (d, J = 6.71 Hz, 1H), 4.13 (t, J = 6.10 Hz, 2H), 4.06 (t, J = 6.10 Hz, 2H), 3.28 (d, J = 3.97 Hz, 2H), 2.77 (d, J = 8.24 Hz, 1H), 2.65−2.74 (m, 1H), 2.31 (s, 3H), 2.19−2.27 (m, 5H), 2.07−2.15 (m, 3H), 1.60 (dd, J = 12.51, 7.32 Hz, 1H). LC-MS: method 1, RT (min) = 5.28; $[M + H]^+$ 438.2; method 2, RT (min) = 3.80; $[M + H]^+$ 438.3.

[(1*S*)-5-{3-[4-(4,5-Dimethyl-1,3-thiazol-2-yl)-2-methoxyphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34k). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.34 (s, 1H), 7.28 (d, J = 8.24 Hz, 1H), 6.98−7.06 (m, 2H), 6.76 (s, 1H), 6.64−6.71 (m, 1H), 4.11 (t, J = 6.10 Hz, 2H), 4.05 (t, J = 6.10 Hz, 2H), 3.77 (s, 3H), 3.30 (ddd, J = 14.27, 7.48, 7.25 Hz, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 15.79, 7.82 Hz, 1H), 2.5 (m, 1H), 2.30 (s, 3H), 2.18−2.27 (m, 5H), 2.07−2.15 (m, J = 6.14, 6.14, 6.03, 5.80 Hz, 2H), 1.54−1.63 (m, 1H). LC-MS: method 1, RT (min) = 5.17; $[M + H]^+$ 468.2; method 2, RT (min) = 3.68; $[M + H]^+$ 468.3.

[(1*S*)-5-{3-[4-(5,6-Dihydro-4*H*-cyclopenta[*d*]^{1,3}thiazol-2-yl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34l). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.74 (d, J = 8.55 Hz, 2H), 7.05 (d, J = 8.24 Hz, 1H), 6.99 (d, J = 8.85 Hz, 2H), 6.77 (s, 1H), 6.67 (d, J = 8.24 Hz, 1H), 4.13 (t, J = 6.10 Hz, 2H), 4.05 (t, J = 6.10 Hz, 2H), 3.36 (m, 1H), 2.85 (t, J = 6.87 Hz, 4H), 2.69−2.78 (m, 5H), 2.19−2.27 (m, 2H), 2.12 (qd, J = 6.00, 5.80 Hz, 2H), 1.59 (dd, J = 12.21, 7.63 Hz, 1H). LC-MS: method 1, RT (min) = 5.44; $[M + H]^+$ 450.2; method 2, RT (min) = 4.06; $[M + H]^+$ 450.3.

[(1*S*)-5-{3-[4-(5,6-Dihydro-4*H*-cyclopenta[*d*]^{1,3}thiazol-2-yl)-2-propylphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34m). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.56−7.63 (m, 2H), 6.98−7.07 (m, 2H), 6.76 (s, 1H), 6.67 (d, J = 7.93 Hz, 1H), 4.06−4.15 (m, 4H), 3.35 (d, J = 3.05 Hz, 1H), 2.85 (t, J = 6.87 Hz, 3H), 2.69−2.78 (m, 5H), 2.5 (m, 1H), 2.19−2.26 (m, 4H), 2.10−2.17 (m, J = 5.99, 5.99, 5.87, 5.65 Hz, 2H), 1.59 (dd, J = 12.21, 7.63 Hz, 1H), 1.47−1.55 (m, 2H), 0.84 (t, J = 7.32 Hz, 3H). LC-MS: method 1, RT (min) = 5.87; $[M + H]^+$ 492.3; method 2, RT (min) = 4.47; $[M + H]^+$ 492.4.

[(1*S*)-5-{3-[4-(5,6-Dihydro-4*H*-cyclopenta[*d*]^{1,3}thiazol-2-yl)-2-methoxyphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34n). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.38 (s, 1H), 7.33 (d, J = 8.24 Hz, 1H), 7.04 (d, J = 8.24 Hz, 1H), 7.02 (d, J = 8.24 Hz, 1H), 6.76 (s, 1H), 6.67 (d, J = 7.63 Hz, 1H), 4.11 (t, J = 6.10 Hz, 3H), 4.05 (t, J = 6.10 Hz, 3H), 3.78 (s, 4H), 2.85 (t, J = 6.87 Hz, 2H), 2.69−2.78 (m, 5H), 2.18−2.26 (m, 2H), 2.11 (dq, J = 6.41, 6.21 Hz, 3H), 1.54−1.63 (m, 1H). LC-MS: method 1, RT (min) = 5.32; $[M + H]^+$ 480.2; method 2, RT (min) = 3.97; $[M + H]^+$ 480.4.

[(1*S*)-5-{3-[4-(4,5,6,7-Tetrahydro-1,3-benzothiazol-2-yl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34o). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.72 (d, J = 8.54 Hz, 2H), 7.04 (d, J = 8.24 Hz, 1H), 6.98 (d, J = 8.85 Hz, 2H), 6.76 (s, 1H), 6.67 (d, J = 7.32 Hz, 1H), 4.09−4.17 (m, 2H), 4.05 (t, J = 6.10 Hz, 2H), 3.30 (ddd, J = 14.27, 7.48, 7.25 Hz, 1H), 2.74−2.80 (m, 1H), 2.65−2.73 (m, 5H), 2.5 (s, 1H), 2.18−2.26 (m, 2H), 2.08−2.15 (m, J = 6.03, 6.03, 6.03, 6.03 Hz, 2H), 1.76 (m, 4H), 1.55−1.63 (m, 1H). LC-MS: method 1, RT (min) = 5.52; $[M + H]^+$ 464.2; method 2, RT (min) = 4.01; $[M + H]^+$ 464.4.

[(1*S*)-5-{3-[2-Propyl-4-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34p). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.56−7.63 (m, 2H), 7.06 (d, J = 8.24 Hz, 1H), 6.99 (d, J = 8.55 Hz, 1H), 6.76 (s, 1H), 6.67 (d, J = 7.02 Hz, 1H), 4.06−4.15 (m, 4H), 3.31 (d, J = 3.36 Hz, 1H), 2.73−2.81 (m, 2H), 2.65−2.73 (m, 5H), 2.60 (dd, J = 15.41, 5.95 Hz, 1H), 2.5 (m, 1H), 2.19−2.27 (m, 2H), 2.10−2.17 (m, 2H), 1.77 (s, 4H), 1.60 (dd, J = 12.51, 7.63 Hz, 1H), 1.46−1.55 (m, J = 7.32, 7.32, 7.32, 7.32 Hz, 2H), 0.84 (t, J = 7.32 Hz, 3H). LC-MS: method 1, RT (min) = 5.94; $[M + H]^+$ 506.3; method 2, RT (min) = 4.34; $[M + H]^+$ 506.4.

[(1*S*)-5-{3-[2-Methoxy-4-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34q). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.36 (s, 1H), 7.30 (d, J = 8.24 Hz, 1H), 7.06 (d, J = 8.24 Hz, 1H), 7.1 (d, J = 8.24 Hz, 1H), 6.76 (s, 1H), 6.68 (d, J = 8.24 Hz, 1H), 4.12 (t, J = 6.10 Hz, 2H), 4.06 (t, J = 6.10 Hz, 2H), 3.78 (s, 3H), 3.33 (d, J = 3.05 Hz, 1H), 2.77 (dd, J = 8.24, 4.88 Hz, 1H), 2.70 (dd, J = 16.17, 6.10 Hz, 5H), 2.5 (m, 1H), 2.19−2.26 (m, 2H), 2.08−2.15 (m, J = 6.03, 6.03, 6.03, 6.03 Hz, 2H), 1.77 (s, 5H), 1.60 (dd, J = 12.36, 7.78 Hz, 1H). LC-MS: method 1, RT (min) = 5.36; $[M + H]^+$ 494.2; method 2, RT (min) = 3.94; $[M + H]^+$ 494.3.

[(1*S*)-5-{3-[4-(6,7-Dihydro-5*H*-pyrano[2,3-*d*]^{1,3}thiazol-2-yl)-2-propylphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34r). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.55 (d, J = 8.54 Hz, 1H), 7.51 (s, 1H), 6.97−7.06 (m, 2H), 6.74 (s, 1H), 6.66 (d, J = 7.93 Hz, 1H), 4.15−4.21 (m, 2H), 4.05−4.14 (m, 4H), 3.26−3.33 (m, 1H), 2.75 (dd, J = 8.39, 5.04 Hz, 2H), 2.68 (t, J = 6.10 Hz, 3H), 2.5 (s, 1H), 2.18−2.26 (m, 4H), 2.09−2.16 (m, 2H), 1.89−1.96 (m, 2H), 1.58 (s, 1H), 1.45−1.53 (m, 2H), 0.82 (t, J = 7.32 Hz, 3H). LC-MS: method 1, RT (min) = 5.67; $[M + H]^+$ 508.3; method 2, RT (min) = 4.30; $[M + H]^+$ 508.6. Anal. ($C_{29}H_{33}NO_5S$) C, H, N.

[(1*S*)-5-{3-[4-(6,7-Dihydro-5*H*-pyrano[2,3-*d*]^{1,3}thiazol-2-yl)-2-methoxyphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34s). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.27−7.34 (m, 1H), 7.05 (d, J = 8.24 Hz, 1H), 7.03 (d, J = 8.24 Hz, 1H), 6.76 (s, 1H), 6.67 (d, J = 7.93 Hz, 1H), 4.15−4.22 (m, 2H), 4.11 (t, J = 6.10 Hz, 2H), 4.04 (t, J = 5.95 Hz, 2H), 3.73−3.80 (m, 3H), 3.37 (s, 1H), 3.26−3.33 (m, 1H), 2.74−2.81 (m, 1H), 2.65−2.72 (m, 3H), 2.5 (s, 1H), 2.18−2.26 (m, 2H), 2.07−2.15 (m, 2H), 1.89−1.96 (m, 2H), 1.55−1.63 (m, 1H). LC-MS: method 1, RT (min) = 5.16; $[M + H]^+$ 496.2; method 2, RT (min) = 3.83; $[M + H]^+$ 496.6.

[(1*S*)-5-{3-[4-(1,3-Benzothiazol-2-yl)-2-methoxyphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34t). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.65−7.71 (m, 2H), 7.53 (d, J = 8.54 Hz, 1H), 7.07 (d, J = 8.24 Hz, 1H), 6.75 (s, 1H), 6.66 (d, J = 7.93 Hz, 1H), 4.15−4.20 (m, 2H), 4.11 (t, J = 5.80 Hz, 2H), 3.35 (s, 3H), 3.17 (t, J = 5.65 Hz, 2H), 2.95 (s, 1H), 2.77 (dd, J = 8.24, 4.88 Hz,

1H), 2.64−2.73 (m, 2H), 2.59 (s, 1H), 2.39 (s, 1H), 2.20−2.29 (m, 4H), 1.60 (s, 1H), 1.20 (t, J = 7.17 Hz, 3H). LC-MS: method 1, RT (min) = 4.20 (no ionization); method 2, RT (min) = 2.96 (no ionization).

[(1*S*)-5-{3-[4-(5-Acetyl-4-methyl-1,3-thiazol-2-yl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic Acid (34u). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.89 (d, J = 8.85 Hz, 2H), 7.04 (d, J = 8.55 Hz, 3H), 6.76 (s, 1H), 6.68 (s, 1H), 6.66 (d, J = 1.53 Hz, 1H), 4.16 (t, J = 6.10 Hz, 2H), 4.05 (t, J = 6.10 Hz, 2H), 3.26−3.33 (m, J = 7.17, 7.17, 7.17, 7.17 Hz, 1H), 2.74−2.81 (m, 1H), 2.68 (td, J = 16.40, 8.70 Hz, 4H), 2.5 (m, 1H), 2.18−2.26 (m, 2H), 2.09−2.15 (m, J = 6.14, 6.14, 6.03, 5.80 Hz, 5H), 1.55−1.63 (m, 1H). LC-MS: method 1, RT (min) = 5.24; [M + H]$^+$ 466.2; method 2, RT (min) = 3.79; [M + H]$^+$ 466.4.

[(1*S*)-5-{3-[4-(5-Acetyl-4-methyl-1,3-thiazol-2-yl)-2-propylphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic Acid (34v). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.73−7.79 (m, 1H), 7.71 (d, J = 1.83 Hz, 1H), 7.05 (dd, J = 8.39, 5.04 Hz, 2H), 6.75 (s, 1H), 6.64−6.69 (m, 1H), 4.16 (t, J = 5.80 Hz, 2H), 4.08 (t, J = 6.10 Hz, 2H), 3.37 (s, 1H), 3.30 (d, J = 7.02 Hz, 2H), 2.74−2.80 (m, 2H), 2.62−2.72 (m, 3H), 2.5 (m, 4H), 2.18−2.26 (m, 2H), 2.11−2.17 (m, 2H), 1.55−1.63 (m, 1H), 1.46−1.55 (m, 3H), 0.83 (t, J = 7.32 Hz, 3H). LC-MS: method 1, RT (min) = 5.64; [M + H]$^+$ 508.3; method 2, RT (min) = 4.26; [M + H]$^+$ 508.3.

[(1*S*)-5-{3-[4-(5-Acetyl-4-methyl-1,3-thiazol-2-yl)-2-methoxyphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic Acid (34w). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.51 (d, J = 8.24 Hz, 1H), 7.46 (s, 1H), 7.07 (d, J = 8.39 Hz, 1H), 7.05 (d, J = 8.39 Hz, 2H), 6.76 (s, 1H), 6.66 (s, 1H), 4.15 (t, J = 6.10 Hz, 3H), 4.05 (t, J = 6.10 Hz, 2H), 3.80 (s, 3H), 3.27−3.33 (m, 1H), 2.74−2.81 (m, 1H), 2.63−2.72 (m, 4H), 2.5 (m, 1H), 2.18−2.26 (m, 2H), 2.09−2.16 (m, 2H), 1.55−1.63 (m, 1H). LC-MS: method 1, RT (min) = 5.10; [M + H]$^+$ 496.2; method 2, RT (min) = 3.59; [M + H]$^+$ 496.3.

[(1*S*)-5-(3-{4-[5-(Dimethylcarbamoyl)-4-methyl-1,3-thiazol-2-yl]-2-propylphenoxy}propoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34x). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.66 (d, J = 8.54 Hz, 1H), 7.63 (s, 1H), 7.03 (t, J = 8.54 Hz, 2H), 6.75 (s, 1H), 6.66 (d, J = 8.24 Hz, 1H), 4.14 (t, J = 5.80 Hz, 2H), 4.08 (t, J = 6.10 Hz, 2H), 3.26−3.34 (m, 1H), 2.95 (s, 6H), 2.74−2.80 (m, 1H), 2.65−2.72 (m, 1H), 2.5 (m, 1H), 2.30 (s, 3H), 2.18−2.26 (m, 4H), 2.10−2.16 (m, 2H), 1.59 (dd, J = 12.21, 7.63 Hz, 1H), 1.46−1.54 (m, 2H), 0.82 (t, J = 7.17 Hz, 3H). LC-MS: method 1, RT (min) = 5.27; [M + H]$^+$ 537.3; method 2, RT (min) = 3.92; [M + H]$^+$ 537.4.

[(1*S*)-5-(3-{4-[5-(Dimethylcarbamoyl)-4-methyl-1,3-thiazol-2-yl]-2-methoxyphenoxy}propoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34y). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.37−7.43 (m, 2H), 7.04 (d, J = 8.24 Hz, 2H), 6.75 (s, 1H), 6.64−6.70 (m, 1H), 4.13 (t, J = 5.95 Hz, 2H), 4.05 (t, J = 5.95 Hz, 2H), 3.78 (s, 3H), 3.26−3.33 (m, 1H), 2.95 (s, 6H), 2.74−2.81 (m, 1H), 2.65−2.72 (m, 1H), 2.5 (m, 1H), 2.31 (s, 3H), 2.17−2.26 (m, 2H), 2.08−2.15 (m, 2H), 1.58 (dd, J = 12.36, 7.48 Hz, 1H). LC-MS: method 1, RT (min) = 4.81; [M + H]$^+$ 525.2; method 2, RT (min) = 3.44; [M + H]$^+$ 525.4.

2-[4-(3-{[(1*S*)-1-(Carboxymethyl)-2,3-dihydro-1*H*-inden-5-yl]-oxy}propoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic Acid (34z). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.86 (d, J = 8.85 Hz, 2H), 7.04 (t, J = 8.39 Hz, 3H), 6.77 (s, 1H), 6.68 (dd, J = 8.24, 1.22 Hz, 1H), 4.16 (t, J = 5.95 Hz, 2H), 4.06 (t, J = 6.10 Hz, 2H), 3.36 (s, 1H), 2.75−2.82 (m, 1H), 2.69 (dt, J = 16.10, 7.97 Hz, 1H), 2.55−2.63 (m, 3H), 2.5 (m, 1H), 2.19−2.27 (m, 2H), 2.09−2.16 (m, J = 6.03, 6.03, 6.03, 6.03 Hz, 2H), 1.56−1.63 (m, 1H). LC-MS: method 1, RT (min) = 5.00; [M + H]$^+$ 468.2; method 2, RT (min) = 3.64; [M + H]$^+$ 468.3.

2-[4-(3-{[(1*S*)-1-(Carboxymethyl)-2,3-dihydro-1*H*-inden-5-yl]-oxy}propoxy)-3-propylphenyl]-4-methyl-1,3-thiazole-5-carboxylic Acid (34aa). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.73 (d, J = 8.85 Hz, 1H), 7.68 (d, J = 1.53 Hz, 1H), 7.04 (d, J = 6.41 Hz, 2H), 7.03 (s, 1H), 6.75 (s, 1H), 6.67 (s, 1H), 4.15 (t, J = 5.65 Hz, 2H), 4.08 (t, J = 5.95 Hz, 2H), 3.27−3.33 (m, 1H), 2.86−2.96 (m, 1H), 2.74−2.81 (m, 2H), 2.65−2.72 (m, 2H), 2.55−2.63 (m, 4H), 2.18−2.26 (m, 2H), 2.11−2.17 (m, 2H), 1.54−1.63 (m, 1H), 1.46−1.54 (m, 2H), 1.12 (t, J = 7.48 Hz, 1H), 0.83 (t, J = 7.32 Hz, 4H). LC-MS: method 1, RT (min) = 5.28; [M + H]$^+$ 510.2; method 2, RT (min) = 3.90; [M + H]$^+$ 510.3.

2-[4-(3-{[(1*S*)-1-(Carboxymethyl)-2,3-dihydro-1*H*-inden-5-yl]-oxy}propoxy)-3-methoxyphenyl]-4-methyl-1,3-thiazole-5-carboxylic Acid (34ab). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.47 (d, J = 8.24 Hz, 1H), 7.44 (s, 1H), 7.01−7.08 (m, 2H), 6.76 (s, 1H), 6.67 (d, J = 8.24 Hz, 1H), 4.14 (t, J = 6.10 Hz, 2H), 4.05 (t, J = 6.10 Hz, 2H), 3.80 (s, 3H), 3.26−3.34 (m, 1H), 2.74−2.81 (m, 1H), 2.69 (ddd, J = 16.02, 7.93, 7.78 Hz, 1H), 2.60 (s, 3H), 2.18−2.26 (m, 3H), 2.12 (qd, J = 6.00, 5.80 Hz, 2H), 1.59 (ddd, J = 19.99, 7.93, 7.78 Hz, 1H). LC-MS: method 1, RT (min) = 4.89; [M + H]$^+$ 498.2; method 2, RT (min) = 3.46; [M + H]$^+$ 498.2.

2-[4-(3-{[(1*S*)-1-(Carboxymethyl)-2,3-dihydro-1*H*-inden-5-yl]-oxy}propoxy)-3-propylphenyl]-4-(hydroxymethyl)-1,3-thiazole-5-carboxylic Acid (34ac). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.73 (d, J = 8.54 Hz, 1H), 7.64 (s, 1H), 6.98−7.06 (m, 2H), 6.75 (s, 1H), 6.66 (d, J = 7.93 Hz, 1H), 4.14 (t, J = 5.65 Hz, 2H), 4.07 (t, J = 6.10 Hz, 2H), 3.5 (m, 2H), 3.30 (dt, J = 14.42, 7.29 Hz, 2H), 2.74−2.80 (m, 1H), 2.68 (dt, J = 15.87, 7.93 Hz, 1H), 2.5 (m, 1H), 2.18−2.26 (m, 4H), 2.10−2.16 (m, J = 5.87, 5.87, 5.87, 5.87 Hz, 2H), 1.54−1.63 (m, 1H), 1.44−1.52 (m, J = 7.63, 7.48, 7.48, 7.48, 7.48 Hz, 2H), 0.78−0.85 (m, 3H). LC-MS: method 1, RT (min) = 5.01 (no ionization); method 2, RT (min) = 3.69; [M + H]$^+$ 526.4.

{2-[4-(3-{[(1*S*)-1-(Carboxymethyl)-2,3-dihydro-1*H*-inden-5-yl]oxy}propoxy)-3-propylphenyl]-1,3-thiazol-4-yl}acetic Acid (34ad). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.65 (d, J = 8.54 Hz, 1H), 7.61 (s, 1H), 7.33 (s, 1H), 7.05 (d, J = 8.39 Hz, 1H), 7.02 (d, J = 8.39 Hz, 1H), 6.75 (s, 1H), 6.67 (d, J = 7.93 Hz, 1H), 4.06−4.15 (m, 4H), 3.70 (s, 2H), 3.26−3.33 (m, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 15.87, 7.93 Hz, 1H), 2.5 (m, 1H), 2.18−2.26 (m, 4H), 2.10−2.16 (m, 2H), 1.55−1.63 (m, 1H), 1.46−1.54 (m, J = 7.36, 7.36, 7.36, 7.36, 7.17 Hz, 2H), 0.83 (t, J = 7.17 Hz, 3H). LC-MS: method 1, RT (min) = 5.17; [M + H]$^+$ 510.2; method 2, RT (min) = 3.76; [M + H]$^+$ 510.3.

[(1*S*)-5-{3-[4-(4-Methoxy-1,3-thiazol-2-yl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34ae). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.69−7.78 (m, 1H), 6.97−7.06 (m, 3H), 6.76 (s, 1H), 6.67 (d, J = 8.24 Hz, 1H), 4.13 (t, J = 6.10 Hz, 3H), 3.99−4.07 (m, 3H), 3.79 (s, 2H), 3.26−3.33 (m, 1H), 2.74−2.81 (m, 1H), 2.69 (ddd, J = 15.95, 7.86, 7.63 Hz, 1H), 2.18−2.26 (m, 3H), 2.08−2.15 (m, 2H), 1.59 (dt, J = 19.91, 7.74 Hz, 1H). LC-MS: method 1, RT (min) = 5.21; [M + H]$^+$ 440.2; method 2, RT (min) = 3.86; [M + H]$^+$ 440.4.

[(1*S*)-5-{3-[2-Methoxy-4-(4-methoxy-1,3-thiazol-2-yl)phenoxy]-propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34af). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.33−7.38 (m, 2H), 7.04 (t, J = 9.46 Hz, 2H), 6.77 (s, 1H), 6.68 (d, J = 8.24 Hz, 1H), 6.46 (s, 1H), 4.09−4.17 (m, 2H), 4.06 (t, J = 5.95 Hz, 2H), 3.75−3.82 (m, 6H), 3.32 (m, 1H), 2.75−2.82 (m, 1H), 2.70 (dt, J = 15.87, 7.93 Hz, 1H), 2.5 (m, 1H), 2.19−2.27 (m, 2H), 2.08−2.16 (m, J = 5.99, 5.99, 5.87, 5.65 Hz, 2H), 1.56−1.64 (m, 1H). LC-MS: method 1, RT (min) = 5.07; [M + H]$^+$ 470.2; method 2, RT (min) = 3.77; [M + H]$^+$ 470.2.

[(1*S*)-5-{3-[4-(4-Ethoxy-1,3-thiazol-2-yl)phenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34ag). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.75 (d, J = 8.54 Hz, 2H), 6.98−7.06 (m, 3H), 6.76 (s, 1H), 6.64−6.71 (m, 1H), 6.41 (s, 1H), 4.14 (t, J = 6.10 Hz, 2H), 4.03−4.10 (m, 4H), 3.30 (ddd, J = 14.19, 7.32, 7.17 Hz, 1H), 2.74−2.81 (m, 1H), 2.69 (ddd, J = 15.95, 7.86, 7.63 Hz, 1H), 2.5 (m, 1H), 2.18−2.26 (m, 2H), 2.08−2.15 (m, 2H), 1.55−1.63 (m, 1H), 1.30 (t, J = 6.87 Hz, 3H). LC-MS: method 1, RT (min) = 5.32; [M + H]$^+$ 454.2; method 2, RT (min) = 4.05; [M + H]$^+$ 454.6.

[(1*S*)-5-{3-[4-(4-Ethoxy-1,3-thiazol-2-yl)-2-propylphenoxy]-propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34ah). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.61 (d, J = 8.54 Hz, 1H), 7.57 (s, 1H), 7.04 (d, J = 8.39 Hz, 1H), 7.01 (d, J = 8.39 Hz, 1H), 6.75 (s, 1H), 6.66 (d, J = 6.41 Hz, 1H), 6.39 (s, 1H), 4.13 (t, J = 5.80 Hz, 2H),

4.03−4.10 (m, 4H), 3.29 (m, 1H), 2.84 (m, 1H), 2.73−2.82 (m, 2H), 2.63−2.72 (m, 3H), 2.57 (m, 1H), 2.20−2.26 (m, 2H), 2.09−2.16 (m, 2H), 1.61 (m, 1H), 1.45−1.53 (m, 2H), 1.30 (t, J = 6.87 Hz, 3H), 0.83 (t, J = 7.32 Hz, 3H). LC-MS: method 1, RT (min) = 5.74; $[M + H]^+$ 496.3; method 2, RT (min) = 4.41; $[M + H]^+$ 496.5.

[(1*S*)-5-{3-[4-(4-Ethoxy-1,3-thiazol-2-yl)-2-methoxyphenoxy]-propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34ai). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.32−7.40 (m, 2H), 7.03 (t, J = 9.16 Hz, 2H), 6.76 (s, 1H), 6.64−6.71 (m, 1H), 6.42 (s, 1H), 4.12 (t, J = 6.10 Hz, 2H), 4.03−4.08 (m, 4H), 3.74−3.81 (m, 3H), 3.30 (dt, J = 14.27, 7.06 Hz, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 15.79, 7.82 Hz, 1H), 2.5 (m, 1H), 2.18−2.26 (m, 2H), 2.11 (qd, J = 6.00, 5.80 Hz, 2H), 1.59 (ddd, J = 19.99, 7.93, 7.78 Hz, 1H), 1.30 (t, J = 7.02 Hz, 3H). LC-MS: method 1, RT (min) = 5.23; $[M + H]^+$ 484.2; method 2, RT (min) = 3.73; $[M + H]^+$ 484.2.

[(1*S*)-5-{3-[4-(4-Isopropoxy-1,3-thiazol-2-yl)-2-propylphenoxy]-propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34aj). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.64−7.71 (m, 1H), 6.98−7.06 (m, 2H), 6.74 (s, 1H), 6.66 (d, J = 5.80 Hz, 1H), 4.09−4.18 (m, 3H), 4.07 (s, 2H), 3.37 (s, 1H), 3.30 (d, J = 7.32 Hz, 2H), 2.89−2.96 (m, 1H), 2.77 (s, 1H), 2.75 (d, J = 4.27 Hz, 1H), 2.64−2.72 (m, 2H), 2.18−2.26 (m, 2H), 2.09−2.17 (m, 2H), 1.54−1.63 (m, 1H), 1.48 (d, J = 7.32 Hz, 2H), 1.26 (d, J = 5.80 Hz, 1H), 1.21 (dd, J = 9.92, 6.26 Hz, 1H), 1.12 (t, J = 7.48 Hz, 1H), 0.76−0.84 (m, 4H). LC-MS: method 1, RT (min) = 4.81; $[M + H]^+$ 412.1; method 2, RT (min) = 3.44; $[M + H]^+$ 412.3.

[(1*S*)-5-{3-[4-(4-Isopropoxy-1,3-thiazol-2-yl)-2-methoxyphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34ak). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.31−7.36 (m, 2H), 7.04 (d, J = 8.85 Hz, 1H), 7.02 (d, J = 8.85 Hz, 1H), 6.76 (s, 1H), 6.67 (d, J = 8.24 Hz, 1H), 6.43 (s, 1H), 4.62 (dt, J = 11.98, 6.07 Hz, 1H), 4.12 (t, J = 6.10 Hz, 2H), 4.05 (t, J = 5.95 Hz, 2H), 3.78 (s, 3H), 3.26−3.33 (m, 1H), 2.74−2.81 (m, 1H), 2.69 (dt, J = 15.87, 7.93 Hz, 1H), 2.5 (m, 1H), 2.18−2.26 (m, 2H), 2.08−2.15 (m, J = 6.03, 6.03, 6.03, 6.03 Hz, 2H), 1.55−1.64 (m, 1H), 1.26 (d, J = 6.10 Hz, 6H). LC-MS: method 1, RT (min) = 5.33; $[M + H]^+$ 498.2; method 2, RT (min) = 4.04; $[M + H]^+$ 498.3.

[(1*S*)-5-{3-[4-(4-Ethoxy-5-methyl-1,3-thiazol-2-yl)-2-propylphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34al). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.56 (d, J = 8.54 Hz, 1H), 7.51 (d, J = 1.53 Hz, 1H), 6.98−7.06 (m, 2H), 6.75 (s, 1H), 6.66 (d, J = 8.24 Hz, 1H), 4.25 (q, J = 6.82 Hz, 2H), 4.05−4.14 (m, 4H), 3.26−3.33 (m, 1H), 2.74−2.80 (m, 2H), 2.68 (ddd, J = 15.72, 7.78, 7.63 Hz, 2H), 2.5 (m, 1H), 2.19−2.26 (m, 2H), 2.10−2.17 (m, 5H), 1.55−1.63 (m, 1H), 1.45−1.53 (m, 2H), 1.21−1.27 (m, 3H), 0.78−0.85 (m, 3H). LC-MS: method 1, RT (min) = 6.14; $[M + H]^+$ 510.3; method 2, RT (min) = 4.72; $[M + H]^+$ 510.4.

[(1S)-5-{3-[4-(4-Ethoxy-5-methyl-1,3-thiazol-2-yl)-2-methoxyphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34am). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.30 (m, 2H), 7.04 (d, J = 8.54 Hz, 1H), 7.02 (d, J = 8.54 Hz, 1H), 6.71 (s, 1H), 6.62 (d, J = 9.46 Hz, 1H), 4.26 (d, J = 6.71 Hz, 2H), 4.11 (m, 2H), 4.03 (m, 2H), 3.77 (m, 3H), 3.35 (m, 1H), 2.7 (m, 1H), 2.6 (m, 1H), 2.5 (m, 1H), 2.26 (m, 2H), 2.17 (s, 3H), 2.10 (m, 2H), 1.54 (m, 1H), 1.25 (t, J = 7.02 Hz, 3H). LC-MS: method 1, RT (min) = 5.51; $[M + H]^+$ 498.2; method 2, RT (min) = 4.23 (no ionization).

[(1*S*)-5-{3-[4-(4-Ethoxy-5-ethyl-1,3-thiazol-2-yl)-2-methoxyphenoxy]propoxy}-2,3-dihydro-1*H*-inden-1-yl]acetic Acid (34an). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.28−7.34 (m, 2H), 7.05 (d, J = 8.24 Hz, 1H), 7.03 (d, J = 8.24 Hz, 1H), 6.76 (s, 1H), 6.67 (d, J = 7.93 Hz, 1H), 4.26 (q, J = 7.02 Hz, 2H), 4.11 (t, J = 5.95 Hz, 2H), 4.05 (t, J = 6.10 Hz, 2H), 3.74−3.80 (m, 3H), 3.30 (dt, J = 14.34, 7.17 Hz, 1H), 2.74−2.81 (m, 1H), 2.69 (ddd, J = 15.95, 7.86, 7.63 Hz, 1H), 2.5 (m, 1H), 2.18−2.26 (m, 3H), 2.07−2.15 (m, J = 5.99, 5.99, 5.87, 5.65 Hz, 3H), 1.55−1.63 (m, 1H), 1.21−1.28 (m, 3H), 1.13 (t, J = 7.32 Hz, 3H). LC-MS: method 1, RT (min) = 5.65; $[M + H]^+$ 512.3; method 2, RT (min) = 4.21; $[M + H]^+$ 512.3.

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Supporting Information Available: Determination of the absolute configuration of compound **12**. In vitro activities of fused ring tail group derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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