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Novel Bisaryl Substituted Thiazoles and Oxazoles as Highly Potent and Selective Peroxisome Proliferator-Activated Receptor δ Agonists

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The discovery, synthesis, and optimization of compound **1** from a high-throughput screening hit to highly potent and selective peroxisome proliferator-activated receptor δ (PPARδ) agonists are reported. The synthesis and structure−activity relationship in this series are described in detail. On the basis of a general schematic PPAR pharmacophore model, scaffold **1** was divided into headgroup, linker, and tailgroup and successively optimized for PPAR activation using in vitro PPAR transactivation assays. A (2-methylphenoxy)acetic acid headgroup, a flexible linker, and a five-membered heteroaromatic center ring with two hydrophobic aryl substituents were required for efficient and selective PPARδ activation. The fine-tuning of these aryl substituents led to an array of highly potent and selective compounds such as compound **38c**, displaying an excellent pharmacokinetic profile in mouse. In an in vivo acute dosing model, selected members of this array were shown to induce the expression of pyruvate dehydrogenase kinase-4 (PDK4) and uncoupling protein-3 (UCP3), genes that are known to be involved in energy homeostasis and regulated by PPARδ in skeletal muscle.

Introduction

Lack of physical exercise and caloric imbalance are two hallmarks of the sedentary lifestyle common in Western societies. This has led to a rise in metabolic diseases of nearly epidemic proportions. According to the World Health Organization, the incidence of type 2 diabetes will likely exceed an alarming 200 million cases by year 2010.[1,2] The metabolic syndrome encompasses type 2 diabetes and has emerged as a term that generally defines the presence of conditions associated with the imbalance of lipid and/or glucose homeostasis, such as obesity, insulin resistance, dyslipidemia, and hypertension.[3] The metabolic syndrome has also been identified as a strong predictor of cardiovascular disease and atherosclerosis, which in turn may lead to myocardial infarction and cerebral stroke, events that rank among the leading causes of mortality in Western societies.

The peroxisome proliferator-activated receptors (PPARs[a]) are key regulators of genes involved in energy homeostasis and as such provide excellent targets for the potential treatment of diseases associated with the metabolic syndrome.[4−11] The PPARs are lipid-activated transcription factors belonging to the nuclear receptor superfamily and comprise three distinct subtypes: PPARα, PPARγ, and PPARδ(β). PPARα is highly expressed in tissues with high fatty acid oxidation and upon stimulation increases high-density lipoprotein cholesterol (HDL-C) synthesis, promotes reverse cholesterol transport, induces cellular uptake of fatty acids, and reduces triglycerides.[12,13] The fibrate class of hypolipidemic drugs are synthetic PPARα ligands.[14,15] PPARγ plays a critical role in the differentiation of preadipocytes to adipocytes, promotes lipid storage, and enhances glucose disposal into peripheral tissues.[16,17] A group of marketed insulin sensitizers called the thiazolidinediones (TZDs) are agonists for PPARγ.[18,19]

The physiological role of the third isoform PPARδ remained elusive mainly because of the lack of selective ligands. There are currently no PPARδ drugs on the market. The emergence of fairly selective synthetic agonists such as GW501516 and their utilization in appropriate in vitro and in vivo models have revealed that PPARδ may also play an important role in lipid absorption, transport, and metabolism.[20−24] GW501516, when dosed once a day orally at 0.1−3 mg/kg in male obese rhesus monkeys, increased HDL-C up to 80% while reducing triglyceride levels by 50% in a dose dependent manner. Low-density lipoprotein cholesterol (LDL-C) (−30%) and insulin (−50%) were also affected without any change in fasting glucose levels.[25] PPARδ is ubiquitously expressed and is activated by long-chain fatty acids and by prostacyclin.[26] Increased intake of long-chain fatty acids leads to an increase in circulating fatty acids and fat accumulation in several tissues, resulting in an imbalance of metabolic parameters and onset of insulin

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[a] Abbreviations: PPAR, peroxisome proliferator-activated receptor; SAR, structure−activity relationship; PDK4, pyruvate dehydrogenase kinase-4; UCP3, uncoupling protein-3; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TZD, thiazolidinedione; HTS, high throughput screen; DBD, DNA-binding domain; LBD, ligand binding domain; RXR, retinoid X receptor; HG, headgroup; TA, transactivation; FRET, fluorescence resonance energy transfer; PCR, polymerase chain reaction; PK, pharmacokinetics.

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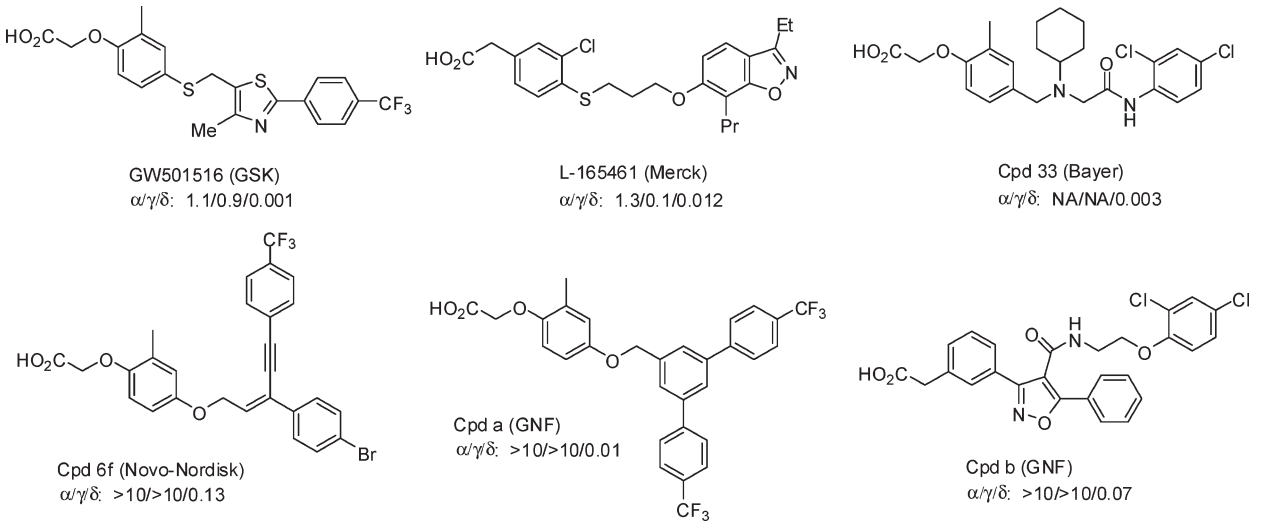


Figure 1. PPARδ agonists with reported EC_{50} values in the transactivation assay of the three PPAR subtypes (in μM).

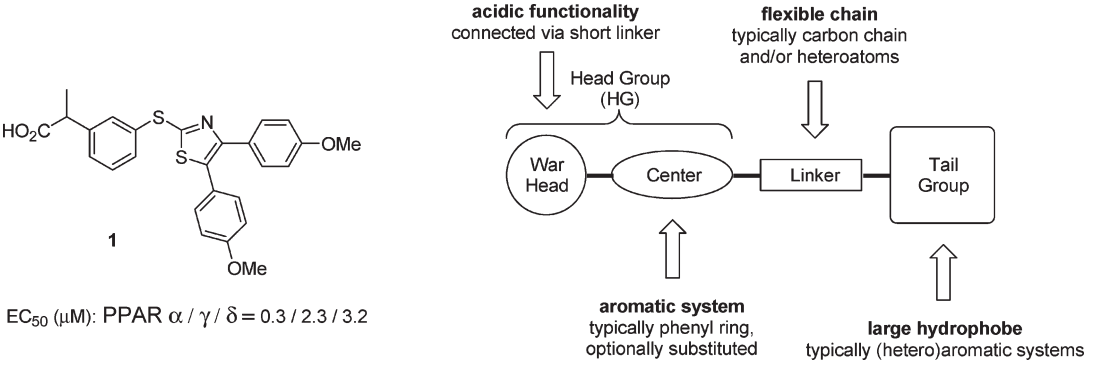


Figure 2. Initial hit compound **1** derived from HTS (left) and the general schematic structural features of PPAR agonists (right).

resistance. PPARδ may act as a sensor for these fatty acids and may help to normalize these parameters by regulating fatty acid uptake, β-oxidation, energy uncoupling, and the number of oxidative myofibers.[27−29] PPARδ has also been implicated in several developmental aspects, which is reflected in the high mortality and phenotype of knockout animals.[30] The role of PPARδ in the development of intestinal tumors is still a matter of debate.[31,32]

In addition to GW501516, a number of small-molecule agonists for PPARδ have been identified and reported,[33] including L-165461, as part of a benzisoxazole series disclosed by a research group at Merck displaying moderate selectivity (Figure 1).[34] Compounds from both series have been extensively used by several research laboratories in various in vitro and in vivo studies, but the results from these studies cannot be exclusively attributed to effects on the PPARδ subtype due to their significant cross-activity to PPARα and PPARγ. During the course of our efforts reported in this publication, researchers at Bayer and Novo-Nordisk published PPARδ agonists without any detectable cross-reactivity to the other subtypes.[35,36] However, to date there are no in vivo studies reported with these compounds, and in the case of the Bayer compound the authors noted extensive metabolism of the cyclohexyl moiety that limits the use of this compound in in vivo studies. We recently reported two novel scaffolds as PPARδ selective agonists, but despite reasonable exposure in rodents at low doses, the overall poor physicochemical properties proved to be an impediment to further in depth analysis of the compounds.[37,38] Therefore, novel PPARδ agonists with an improved selectivity profile and with improved physicochemical properties leading to an adequate in vivo profile are needed to further elucidate the pharmacology of this receptor.

In an effort to identify novel structures with PPARδ agonist activity, we performed a high throughput screen (HTS) of approximately 1 million compounds using a cell-based transactivation assay. Hits were defined as compounds that induced luciferase activity in cells transiently transfected with a luciferase reporter gene plasmid containing the GAL4 binding element and a chimeric plasmid consisting of the yeast GAL4 DNA-binding domain (DBD) fused to the ligand binding domain (LBD) of PPARδ (GAL4-PPARδ). Approximately 1000 compounds were selected that displayed luciferase activities at least half the levels of that induced by GW501516. These primary hits were evaluated for selectivity against GAL4-PPARα, GAL4-PPARγ, and GAL4-RXR. On the basis of their relative potency, their lack of activity on RXR, and their chemical structure, a set of ∼100 molecules were selected and reconfirmed. Compound **1** (Figure 2) was among the identified and reconfirmed hits. The molecule could be divided into a headgroup, linker, and a tailgroup, a general structural feature that is frequently observed for PPAR agonists.

As a nonselective PPAR agonist, compound **1** showed moderate activity on all three PPAR subtypes. Although not nearly as potent, the hit stood out in displaying

a comparable efficacy (~80%) for PPARδ activation when compared to GW501516 (100%), which was used as the PPARδ standard in this assay. This indicates that compound **1** has the potential to act as a full agonist of the PPARδ subtype, one of the main criteria for our lead compounds. Compound **1** also possesses a novel bisarylthiazole tailgroup, making it a promising starting point for medicinal chemistry optimization.

Results and Discussion

Chemistry and SAR. Research groups at Merck and GSK have previously reported PPARδ-selective agonists that display optimized headgroups for this subtype.[39,40] Our initial strategy was to enhance the potency and selectivity of compound **1** for the PPARδ subtype by linking the reported headgroups with our novel tail piece. Thus, intermediate headgroups **50**−**55** were synthesized according to the literature (Figure 3),[33,39,41,42] and were connected to the bisarylthiazole portion of compound **1** through a variety of different linkers to create a series of hybrid structures (Scheme 1).

The commercially available ketone **2** was brominated to give bromoketone **3**. Compound **3** was cyclized with ammonium dithiocarbamate at elevated temperatures to yield the mercaptothiazole intermediate **4**. The ammonium dithiocarbamate was freshly prepared by passing ammonia through a solution of carbon disulfide.[43] The headgroup intermediates **50** and **51** were alkylated with excess alkyl dibromide[44] to give the corresponding bromides **5a**−**c** and **6a**−**c**, respectively. These and the methylene chlorides **54** and **55** were then reacted with intermediate **4** under basic conditions. The intermediate esters were hydrolyzed to give final compounds **7a**−**c**, **8a**−**c**, **9**, and **10**.

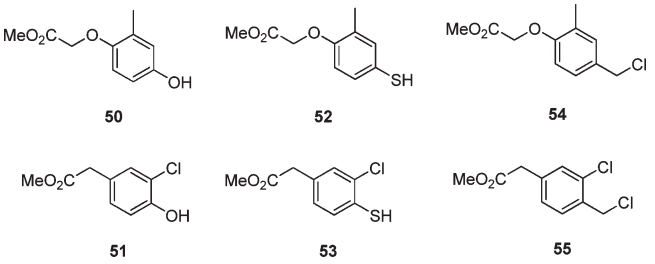
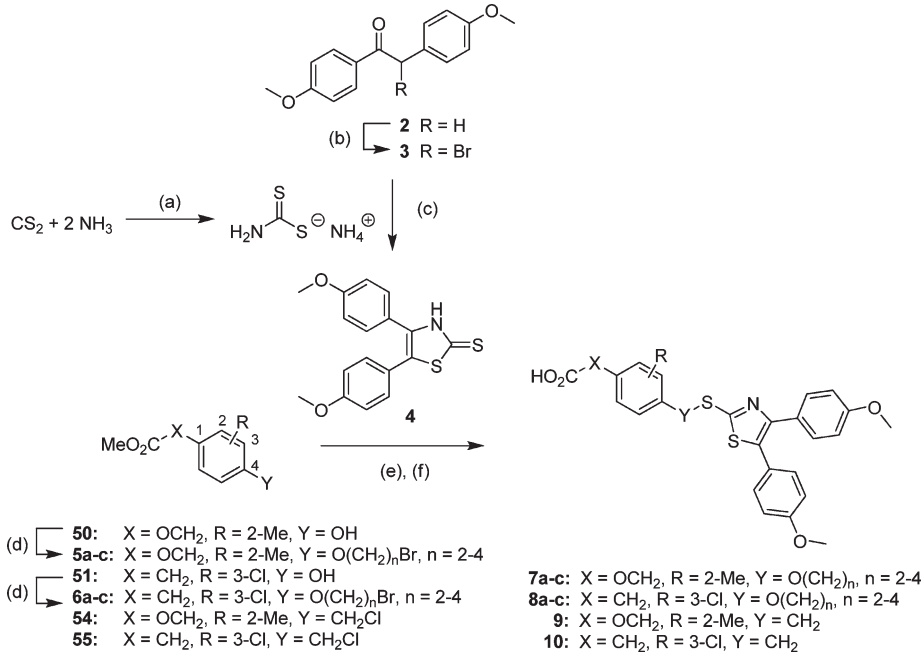


Figure 3. Intermediate headgroups **50**−**55** used to enhance potency and selectivity for PPARδ.

Different synthetic routes, depicted in Scheme 2, were employed in order to obtain hybrid compounds with shorter linkers. The first route started by reacting bromoketone **3** with potassium rhodanide. The intermediate thiocyanate was closed to the 2-chlorothiazole **11** by treatment with HCl (g).[45] High temperature condensation with headgroups **52** and **53** under basic conditions followed by saponification yielded sulfur-linked compounds **12** and **13**. Alternatively, bromoketone **3** was reacted with ethyl thiooxamate in a Hantsch type cyclization.[46,47] Then the carboxylate was reduced with $LiAlH_4$ to give the thiazole alcohol **14**. The corresponding oxazole alcohol **15** was synthesized by esterification of commercially available *p*-methoxybenzoin with bromoacetic acid in the presence of dicyclohexylcarbodiimide (DCC) and *N*-dimethylaminopyridine (DMAP), followed by ring closure to the oxazole using ammonium acetate and hydrolysis under basic conditions.[48] Both alcohols **14** and **15** could be converted to the final products **16**−**22** by Mitsunobu coupling with the headgroups **50**−**53** and subsequent saponification of the ester intermediates.

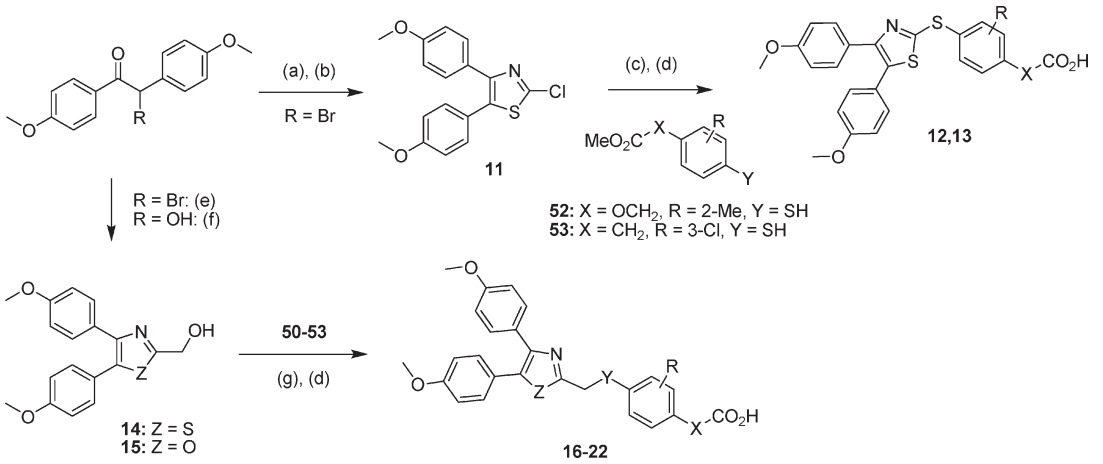
All analogues were assessed for their PPAR modulator activities using the standard Gal4 chimera cell-based reporter assays as described above. The experimental data shown in Table 1 indicate the importance of linker type and linker length for both potency and selectivity of PPAR activation. For compounds containing longer linkers, such as in compounds **7a**−**c** and **8a**−**c**, marginal PPARα and PPARγ activity but no PPARδ activity was observed.

Scheme 1. Synthetic Scheme for Thiothiazoles **7**−**10**[a]



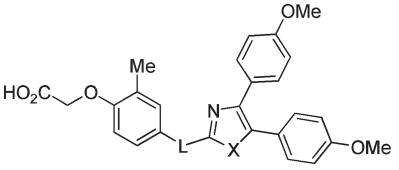
[a] Reagents: (a) THF, 10 °C, 2 h, 94%; (b) Br_2, $CHCl_3$, room temp, 0.5 h, 88%; (c) EtOH, 60 °C, 3 h, 96%; (d) $Br(CH_2)_nBr$ (n = 2−4), Cs_2CO_3, acetone, 50 °C, 8 h, 66−82%; (e) **4**, NaOEt, EtOH, room temp, 12 h; (f) LiOH, THF, H_2O, 60 °C, 12 h, 57−83% over two steps.

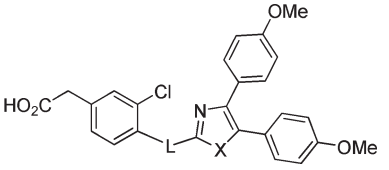
Scheme 2. Synthesis of Thiazoles and Oxazoles **12**−**22**[a]



[a] Reagents: (a) KSCN, acetone, reflux, 8 h, 94%; (b) HCl (gas), EtOAc, room temp, 6 h, 50%; (c) NaOEt, EtOH, reflux 5 h; (d) LiOH, H_2O, THF, room temp, 24 h, 60−72% over two steps; (e) (i) ethyl thiooxamate, EtOH, reflux, 12 h, 81%; (ii) $LiAlH_4$, THF, room temp, 1 h, 79%; (f) (i) bromoacetic acid, DCC, DMAP, DCM, room temp, 18 h, 74%, (ii) NH_4OAc, AcOH, reflux, 2 h, 76%, (iii) K_2CO_3, MeCN, reflux, 2 h, 80%; (g) **50**−**53**, PPh_3, DEAD, DCM, room temp, 12 h, 50−63% over two steps.

Table 1. Cell-Based Transactivation Activity of PPAR Subtypes for Compounds with Various Headgroups and Linkers





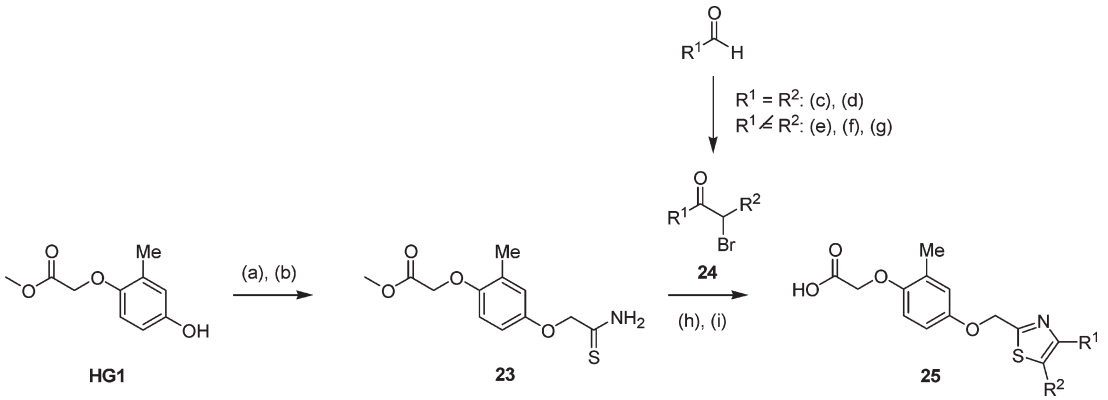
for above-left structure						for above-right structure					
			PPAR EC_{50} (μM) (% efficacy[a])						PPAR EC_{50} (μM) (% efficacy[a])		
compd	linker L	X	α	γ	δ	compd	linker L	X	α	γ	δ
7c	-O-$(CH_2)_4$-S-	S	2.37 (89)	6.36 (39)	> 10	**8c**	-O-$(CH_2)_4$-S-	S	0.80 (65)	2.56 (57)	> 10
7b	-O-$(CH_2)_3$-S-	S	5.25 (62)	6.89 (47)	> 10	**8b**	-O-$(CH_2)_3$-S-	S	0.84 (66)	4.61 (52)	> 10
7a	-O-$(CH_2)_2$-S-	S	5.35 (64)	5.66 (26)	> 10	**8a**	-O-$(CH_2)_2$-S-	S	1.06 (61)	5.87 (41)	> 10
9	-CH_2-S-	S	> 10	> 10	5.67 (28)	**10**	-CH_2-S-	S	> 10	> 10	3.30 (58)
12	-S-	S	> 10	> 10	1.41 (56)	**13**	-S-	S	> 10	> 10	6.36 (22)
16	-O-CH_2-	S	> 10	> 10	0.10 (75)	**17**	-O-CH_2-	S	> 10	> 10	0.81 (47)
18	-S-CH_2-	S	> 10	> 10	0.47 (59)	**19**	-S-CH_2-	S	> 10	> 10	0.03 (55)
20	-O-CH_2-	O	> 10	> 10	0.12 (73)	**21**	-S-CH_2-	O	> 10	> 10	0.25 (54)
22	-S-CH_2-	O	> 10	> 10	0.66 (69)						

[a] The % efficacy is calculated relative to response to reference compounds (100%). Reference compounds used for % efficacy calculation: PPARα, KRP297; PPARγ, rosiglitazone; PPARδ, GW501516.

Shorter linkers as in compounds **9**−**22** led to the desired selective PPARδ activity. In the hydroquinone headgroup series (Table 1, left), the optimal linker was oxomethylene (compound **16**). A sulfur linked compound (compound **12**) as in the initial hit resembles a similar linker length, but this compound was markedly less potent and efficacious probably because of its reduced flexibility. The analysis of a recently solved cocrystal structure suggests that a flexible linker is crucial for efficient PPAR activation.[26] A simple reversal of the thio−methylene linker (compound **18**) to the methylene−thio linker (entry **9**) resulted in a significant loss of activity. This observation suggests that not only linker length but also changes in the electronic properties of the adjacent aromatic systems play a major role in influencing PPAR activity. When the shorter phenyl acetate headgroup was used (Table 1, right), the optimal linker was thio−methylene (compound **19**), which leads to an overall similar distance between the carboxylate and the hydrophobic tail piece when compared to compound **16**. In this series, the disadvantage of having a sulfur atom next to the heterocycle seems to be even more pronounced (compounds **10**, **13**). When the tailgroup heterocycle was changed from a thiazole to an oxazole ring, the activity of the derived compounds followed a similar trend (compounds **20**−**22**). Because of its repeated display of significantly higher efficacy, the hydroquinone series was chosen over the phenylacetate series for further optimization. It is worth noting that a series of imidazole analogues (X = NR) were also prepared (synthesis not shown), all of which failed to show any PPAR activity.

After the initial optimization of headgroup and linker in our hybrid molecules, we turned our attention to the heteroaromatic tail moiety. In order to quickly access thiazole analogues bearing various substituents, we first transformed headgroup **50** to the thioamide intermediate **23** via sulfurization of a nitrile intermediate (Scheme 3).[49]

Scheme 3. Initial Exploration of Thiazole Tail via Hantsch Condensation[a]



[a] Reagents: (a) chloroacetonitrile, MeCN, Cs_2CO_3, 2 h, room temp, 94%; (b) thioacetamide, HCl, dioxane, DMF, 100 °C, 12 h, 62%; (c) KCN, EtOH, refux, 7 h, 65−90%; (d) DDQ, PPh_3, *n*-Bu_4NBr, DCM, room temp, 2 h, 30−40%; (e) TMSCN, ZnI_2, DCM, 0 °C, 2 h, then room temp 12 h, 85−95%; (f) LDA, $ArCH_2Br$, THF, −78 °C, 2 h, then room temp 15 h, 40−60%; (g) pyridinium tribromide, DCM, room temp, 2 h, 75−92%; (h) EtOH, 180 °C, microwave, 5 min; (i) LiOH, H_2O, THF, room temp, 2 h, 53−90% over two steps.

Thioacetamide was used as the sulfur source, as it was found to be easier to handle and afforded higher yields than the more commonly used hydrogen sulfide or diethyl dithiophosphate procedures.[50] The thioamide **23** was condensed with a wide range of α-bromoketones **24** and saponified to give thiazoles of general formula **25**. Some α-bromoketones or their nonbrominated ethanone precursors were commercially available. When both R^1 and R^2 were aryl groups, we employed an Umpolung type synthesis route similar to the benzoin synthesis.[51] Condensation of two arylaldehyde molecules in the presence of cyanide gave the "symmetric" ($R^1 = R^2$) α-hydroxyketone. Transformation of alcohol to bromide using tetrabutylammonium bromide and DDQ gave α-bromoketones **24**. For $R^1 \neq R^2$, the arylaldehyde was first reacted with trimethylsilyl cyanide in the presence of zinc iodide. The stable silanyloxy−acetonitrile intermediate was isolated, then deprotonated with lithium diisopropylamide (LDA) and quenched with a benzyl bromide.[52] The resulting unsymmetric ($R^1 \neq R^2$) 1,2-diarylethanone was brominated using pyridinium tribromide to yield α-bromoketones **24**.[53]

More than 150 analogues were synthesized according to Scheme 3. The activities of selected representatives are depicted in Table 2. The amide analogues **25b** were prepared by bromination and subsequent condensation of *β*-ketoamides, and ethers such as **25m** were prepared by condensation of the corresponding α-bromomethylacetates with intermediates **24** followed by alkylation of the hydroxy group (syntheses not shown). Any combination of unsubstituted phenyl as R^1 or R^2 with hydrogen, alkylamides, or ethers (compounds **25a**,**b**,**l**,**m**) resulted in inactive compounds. The same result was obtained when both R^1 and R^2 were unsubstituted phenyls (**25r**). Once the phenyl rings were substituted on either R^1 or R^2, moderate activity was observed on the PPAR receptors. Only compounds with para-substitution showed significant activity. Any ortho, meta, or multiple substituents on the phenyl rings obliterated activity (data not shown). Any charged or highly polar substituents were not tolerated, in agreement with the overall hydrophobic nature of the binding pocket.[26,54] By comparing series **25c**−**e** to series **25n**−**p**, one can observe a divergent preference for the nature of the substituents on the phenyl rings of both R^1 and R^2. This finding is further supported by comparing the activities of the compound pairs **25j**,**u** and **25k**,**v**. Generally, the activities of this scaffold for PPARδ activation are optimal when both R^1 and R^2 are aryl rings. Each series experiences more than a 10-fold increase in activity when substituting sterically similar but electronically different groups on the phenyl ring of R^1 or R^2. Evidently, the aryl ring of R^1 strongly preferred an electron-donating substituent such as a methoxy group, and the aryl ring of R^2 preferred an electron-withdrawing substituent such as a chloride. Electron-withdrawing groups on both aryl rings were tolerated (compounds **25i**,**t**) but were not as active as the unsymmetric analogues.

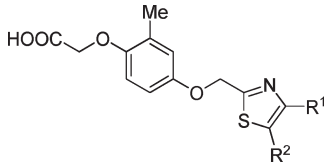
In addition to the electronic effects, there also was a strong steric component to the SAR. Even extended aromatic systems such as biphenyls (**25f**) or naphthyls (data not shown) were tolerated. The retention of activity of compound **25s**, which bears a biphenyl substituent on both R^1 and R^2, is consistent with the substantial size (> 1000 $Å^3$) of the PPAR ligand binding pocket seen in the reported crystal structures.[54]

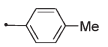
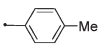
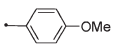
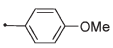
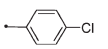
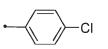
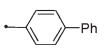
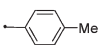
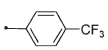
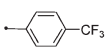
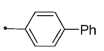
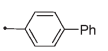
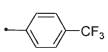
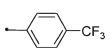
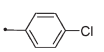
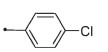
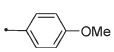
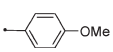
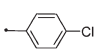
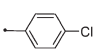
One interesting observation from this survey was that the thiazole positions 4 and 5 of these analogues were not equivalent as might be expected if the thiazole ring was merely holding the aryl groups in the right geometry to fit the receptor binding pocket, despite the difference in size of the sulfur versus the nitrogen atom. Another surprising observation was the high activity of **25q** which has a 3-pyridyl substituent at R^1. Combining these results with the earlier finding that a methoxy group on the substituent at this side of the molecule (R^1) was preferred, we hypothesized that one or more of the heteroatoms in and around the thiazole ring are likely involved in the binding event.

In general, most compounds were selective for PPARδ with only a few showing limited cross-activity to PPARα (compounds **25d**,**f**). These results were supportive of our strategy to optimize the linker length and tail substituents in combination with previously described headgroups for the generation of highly PPARδ-selective compounds.

The methodologies described in Scheme 3 were crucial to get a first impression of the characteristics and SAR within the thiazole unit of our scaffold. There are only a limited number of diphenylethanones commercially available, and the formation of α-bromoketones through the nonsymmetric benzoin condensation route lacked the scope and seviceability to quickly generate a wide range of diverse

Table 2. Selected SAR Results of the Initial Tailgroup Survey



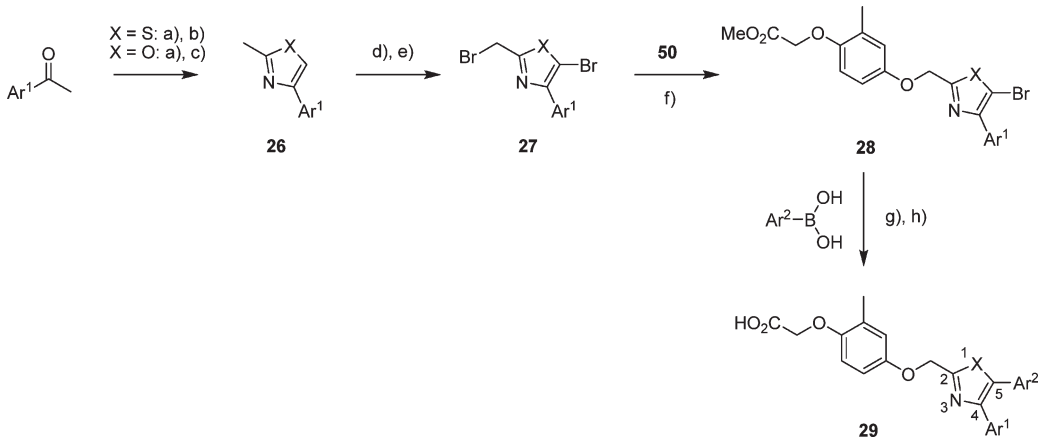
			PPAR EC_{50} (μM) (% efficacy[a])						PPAR EC_{50} (μM) (% efficacy)		
Cpd	R^1	R^2	α	γ	δ	Cpd	R^1	R^2	α	γ	δ
25a		H, Alkyl	>10	>10	>10	**25l**	Alkyl		>10	>10	>10
25b		CONHR	>10	>10	>10	**25 m**	OR		>10	>10	>10
25c		H	>10	>10	>10	**25n**	Me		>10	>10	6.32 (65)
25d		H	4.08 (5)	>10	4.06 (43)	**25o**	Me		>10	>10	>10
25e		H	>10	>10	4.71 (84)	**25p**	Me		>10	>10	0.32 (86)
25f		H	0.48 (42)	>10	0.34 (42)	**25q**			>10	>10	0.19 (82)
25g		H	>10	>10	1.39 (98)	**25r**			>10	>10	>10
25h		Me	>10	>10	2.40 (64)	**25s**			>10	>10	0.13 (71)
25i			>10	>10	0.35 (58)	**25t**			>10	>10	0.51 (61)
25j			>10	>10	0.19 (78)	**25u**			>10	>10	2.62 (62)
25k			>10	>10	5.90 (41)	**25v**			>10	>10	0.13 (79)

[a] The % efficacy is calculated relative to response to reference compounds (100%). Reference compounds used for % efficacy calculation: PPARα, KRP297; PPARγ, rosiglitazone; PPARδ, GW501516.

analogues. Alternative strategies had to be explored that allowed us to specifically address either position 4 or position 5 on the heteroaromatic ring and to utilize a general and robust diversifying step late in the synthetic route. Scheme 4 shows an efficient route for the rapid exploration of position 5 in the thiazole (oxazole) ring. After bromination of the aryl acetate with pyridinium tribromide, the heterocycle was formed by condensation with either thioamide or acetamide to give thiazoles or oxazoles of the general structure **26**. Position 5 of the heterocycle was then brominated using bromine in acidic media, followed by radical bromination of the methyl group in position 2 using *N*-bromosuccinimide to yield dibromide **27**.[55] Alternatively, position 5 of the ester precursor to compound **25** (R^2 = H, Scheme 3) could also be brominated as long as R_1 did not contain electron-withdrawing or extended aromatic substituents. In the latter cases, bromination was observed in the aryl ring of the headgroup. After substitution of dibromide **27** with headgroup **50**, intermediate **28** was subjected to microwave-mediated Suzuki coupling conditions in the presence of various arylboronic acids.[56,57] Final products **29** were obtained by saponification of the ester precursors.

The wide scope of the Suzuki coupling gave us the opportunity for a detailed investigation and optimization of position 5 in the heteroaromatic ring. The results for Ar^1 = *p*-methoxyphenyl are summarized in Table 3. Consistent with the findings of Table 2, thiazoles (X = S) with aryl groups bearing electron-withdrawing substituents in position 5 (compounds **29a**,**b**,**e**) generally showed increased potency over electron-donating substituents (compound **18**). A more in depth survey of hydrophobic substituents led to several interesting findings. The unusually high efficacy of compound **29i** having a *n*-propyl substitution was remarkable, whereas a *tert*-butyl group (compound **29j**) proved

Scheme 4. Synthesis of Diaryl Thiazoles and Oxazoles Allowing Rapid Exploration of Position 5[a]



[a] Reagents: (a) pyridinium tribromide, DCM, room temp, 1 h, 50−90%; (b) thioamide, EtOH, reflux, 2 h, 37−75%; (c) acetamide, 150 °C, 2 h, 55−70%; (d) Br_2, HOAc, DCM, room temp, 2 h, 70−85%; (e) NBS, AIBN, CCl_4, 55 °C, 24 h, 35−70%; (f) Cs_2CO_3, MeCN, room temp, 2 h, 41−60%; (g) $Pd(PPh_3)_4$, DME, EtOH, Na_2CO_3 (aq), 170 °C, 5 min; (h) 1 N LiOH, THF, room temp, 6 h, 67−90% over two steps.

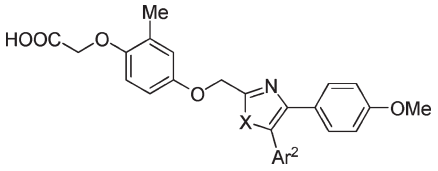
to be too bulky even for the large hydrophobic PPAR ligand binding pocket. Extended aromatic systems as Ar^2 (compounds **29k**,**m**−**p**) were among the most potent compounds in this series with the exception of compound **29l**, which most likely led to a steric clash with the ligand binding pocket. Heterocycles such as pyridines and pyrimidines or five-membered heterocycles were not well tolerated (exemplified by compound **29g**) with the exception of the 3-quinolyl substituent in compound **29n**. Any attempt to decorate Ar^2 with two or more substituents led to a significant loss of activity (e.g., compounds **29h**,**q**). The substitution pattern clearly showed a preference in the order of para (compound **29b**) > meta (compound **29c**) ≫ ortho (compound **29d**). In general the oxazole analogues (X = O, compounds **29aa**−**ah**) followed the trends observed for the thiazoles (X = S). Remarkably, none of the analogues in this series had any detectable cross-activity to the other PPAR subtypes.

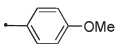
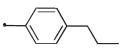
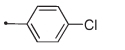
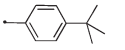
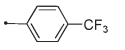
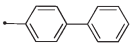
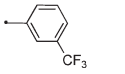
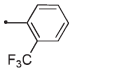
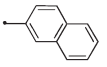
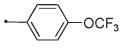
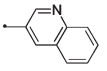
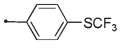
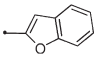
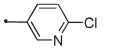
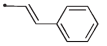
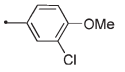
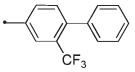
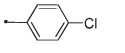
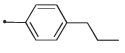
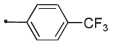
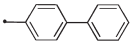
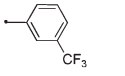
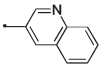
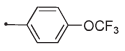
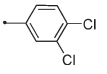
Switching the diversifying step from position 5 to position 4 proved to be more challenging (Scheme 5). Gaining access to the common intermediate **30** (analogous to intermediate **26** in Scheme 4) required simultaneous exploration of several synthetic routes. The first route employed hydroboration of ethyl ethynyl ether followed by in situ palladium mediated cross-coupling with an aryl halide.[58] The resulting ethoxyethene was brominated in EtOH to give intermediate **31**, which can be viewed as a stable equivalent to the bromoketone intermediates used in Schemes 3 and 4 but with switched bromide and keto functionalities. Hantsch cyclization of the in situ formed α-bromoaldehyde of **31** led to heterocycle **30**. Alternatively, intermediate **30** (X = S) was obtained directly via cross-coupling of 2-methylthiazole with aryl halides in the presence of copper iodide using conditions previously reported for imidazoles,[59] although with rather modest yields. In a third route, a diazo transfer reaction of aryl acetates and freshly prepared methanesulfonylazide[60,61] led to intermediate **32**, which was cyclized with acetonitrile in a 1,3-dipolar cycloaddition to give intermediate **30** (X = O). The remainder of the synthetic route was accomplished similar to Scheme 4: double bromination of intermediate **30** to dibromide **33**, followed by substitution with **50** led to intermediate **34**. Intermediate **34** was diversified by Suzuki cross-coupling with various boronic acids and saponified to yield final compounds **35**.

The results obtained in Table 3 enabled us to focus on a few optimal substituents at position 5 of the thiazole (oxazole) such as substituents displaying electron-withdrawing and/or hydrophobic properties. Table 4 lists examples that have a fixed *p*-OCF_3-phenyl substitution in position 5. A similar survey was performed for other substituents in position 5 such as biphenyl or *p*-propylphenyl. The activities of these compounds showed the same general trends as the ones observed in Table 4. A hydrophobic and/or electron-withdrawing substituent in position 4 (compounds **35a**,**b**) led to a 5- to 10-fold decrease in activity. Consistent with earlier results, multiple and/or meta substitution (compounds **35c**,**d**) tended to be less potent. Exceptions were the alkylenedioxobenzene substituents in compounds **35l**−**n** which retained good potency and showed excellent efficacy. A linear extension of the alkoxy group from methoxy to butoxy (compounds **29e**, **35e**−**g**) was tolerated but did not improve activity. On the other hand, α-branched alkoxy groups (compounds **35h**,**i**,**k**) significantly enhanced potencies, compound **35h** representing the first single digit nanomolar compound in this series.

The generally high hydrophobicity of the analogues described so far could potentially lead to cytotoxic liabilities or bioavailability problems due to lack of solubility. To address these potential issues, we continued to optimize position 5 with the goal to incorporate more hydrophilic substituents to lower the clogP value (> 7) of compounds in this series. Highly solubilizing or polar groups such as charged species or sulfones were not tolerated (data not shown), as already mentioned, not surprising given the overall hydrophobic nature of both the receptor ligand binding pocket and the endogenous lipid ligands. Also, incorporation of sulfonamides or amides such as in compound **35s** or benzoxazolones (compound **35t**) and related heterocycles led to a substantial decrease in activity. It became apparent that we had to optimize within a small window of hydrophilicity tolerated by the ligand binding pocket. Anilines (compounds **35o**−**r**) were mostly well tolerated but did not significantly improve the physicochemical properties of the molecules. At most, an aniline type morpholino group (compound **35r**) maintained the compound activity fairly well while decreasing the clogP value of the compound (clogP = 6.3). A similar

Table 3. Optimization of Position 5 in the Thiazole/Oxazole Ring (Ar^1 = *p*-OMe-phenyl)



			PPAR EC_{50} / μM (% efficacy[a])						PPAR EC_{50} / μM (% efficacy)		
Cpd	X	Ar^2	α	γ	δ	Cpd	X	Ar^2	α	γ	δ
18	S		>10	>10	0.10 (75)	**29i**	S		>10	>10	0.51 (112)
29a	S		>10	>10	0.06 (78)	**29j**	S		>10	>10	0.72 (54)
29b	S		>10	>10	0.04 (71)	**29k**	S		>10	>10	0.01 (71)
29c	S		>10	>10	0.07 (67)	**29l**	S		>10	>10	>10
29d	S		>10	>10	>10	**29m**	S		>10	>10	0.02 (72)
29e	S		>10	>10	0.02 (70)	**29n**	S		>10	>10	0.08 (110)
29f	S		>10	>10	0.15 (75)	**29o**	S		>10	>10	0.05 (86)
29g	S		>10	>10	0.88 (88)	**29p**	S		>10	>10	0.11 (70)
29h	S		>10	>10	0.13 (68)	**29q**	S		>10	>10	0.25 (65)
29aa	O		>10	>10	0.05 (83)	**29ae**	O		>10	>10	0.01 (90)
29ab	O		>10	>10	0.01 (79)	**29af**	O		>10	>10	0.01 (70)
29ac	O		>10	>10	0.65 (69)	**29ag**	O		>10	>10	0.11 (89)
29ad	O		>10	>10	0.01 (79)	**29ah**	O		>10	>10	0.07 (74)

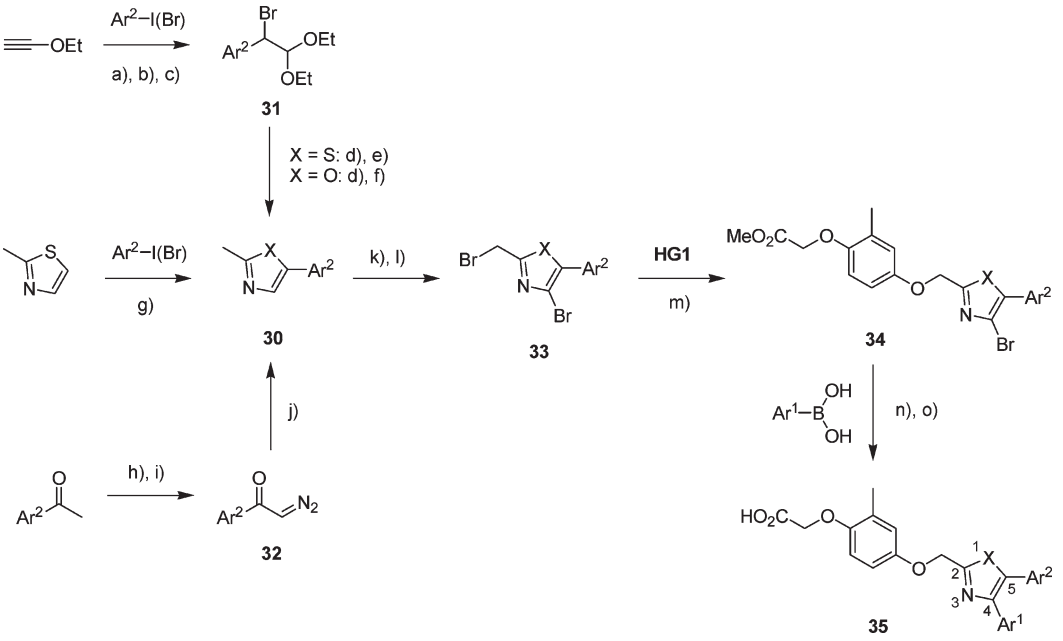
[a] The % efficacy is calculated relative to response to reference compounds (100%). Reference compounds used for % efficacy calculation: PPARα, KRP297; PPARγ, rosiglitazone; PPARδ, GW501516.

decrease in clogP was observed in the "reverse" amide series **35u**−**w**. Unfortunately, the very potent representatives of this series (compounds **35v**,**w**) were also starting to show cross-activity to the other PPAR subtypes.

The survey of thiazoles (X = S) presented in Table 4 was repeated with the oxazole (X = O) analogues. In general, the oxazoles followed the same trends as the thiazoles (data not shown). A few subtle differences can be noted and are represented in Table 4 by compounds **35aa**−**ad**: the oxazole analogues tended to be more potent but also showed a higher degree of cross-activity within the PPAR subtypes when compared to their thiazole counterparts.

The incorporation of heteroatoms into the aryl substituent leads to a further decrease of hydrophobicity in the series. Since compound **25q** in Scheme 2 contained a pyridine as Ar^1 and showed good activity, a logical follow-up was to combine this feature with the findings of Tables 3 and 4 to generate compound series **38**. When the corresponding

Scheme 5. Synthesis of Diaryl Thiazoles and Oxazoles Allowing Rapid Exploration of Position 4[a]



[a] Reagents: (a) BH_3, THF, 2 h; (b) $Pd(OAc)_2$, PPh_3, NaOH, THF, reflux, 15 h, 40−60%; (c) *N*-bromosuccinimide, EtOH, room temp, 2 h, 70−80%; (d) Ac_2O, AcCl, NaOAc, $CHCl_3$, 60 °C, 5 h, 90−100%; (e) thioacetamide, EtOH, 180 °C, microwave, 5 min, 50−60%; (f) acetamide, 150 °C, 2 h, 65−80%; (g) 2-methylthiazole, Cs_2CO_3, CuI, $Pd(OAc)_2$, PPh_3, DMF, 140 °C, 24 h, 15−25%; (h) LiHMDS, THF, −78 °C, then $CF_3CO_2CH_2CF_3$, 20 min; (i) methanesulfonyl azide, NEt_3, H_2O, MeCN, room temp, 1 h, 43−93% over two steps; (j) $AlCl_3$, MeCN; (k) Br_2, DCM, room temp, 1 h, 65−80%; (l) NBS, AIBN, CCl_4, 75 °C, 12 h, 66−79%; (m) Cs_2CO_3, MeCN, room temp, 2 h, 80−100%; (n) $Pd(PPh_3)_4$, DME, EtOH, Na_2CO_3 (aq), 170 °C, 5 min; (o) 1 N LiOH, THF, room temp, 6 h, 67−90% over two steps.

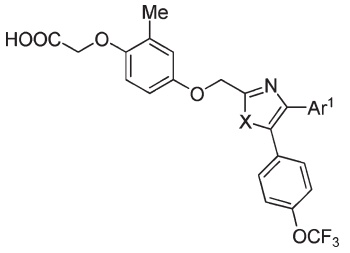
boronic acids were not commercially available, we synthesized the building blocks according to Scheme 6. Aromatic nucleophilic substitution to intermediate **36** was followed by lithiation and quenching with triisopropyl borate[62,63] to yield compounds of the general formula **37**. Indeed, the use of pyridine-3-boronic acids and 5-pyrimidine-5-boronic acids in the Suzuki coupling step of Scheme 5 led to compounds with high potency and efficacy for PPAR activation. The in vitro activities and a comparison of thiazoles versus oxazoles are summarized in Table 5. Both series showed outstanding ability for PPARδ activation, especially in conjunction with additional substituents from the prior optimization efforts (compounds **38c**−**h**, **38ac**−**ah**). Having nitrogens in any other position in the aryl ring than the one displayed in Table 5 led to inactive compounds (data not shown). The oxazoles again were more potent in the PPARδ transactivation assay but also had considerably more cross-activity to PPARα and PPARγ.

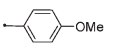
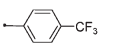
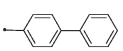
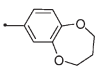
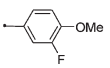
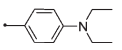
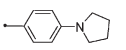
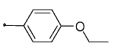
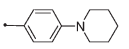
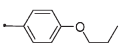
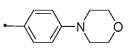
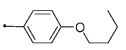
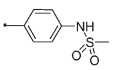
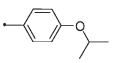
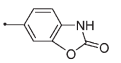
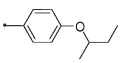
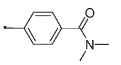
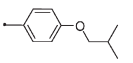
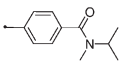
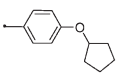
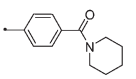
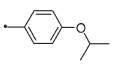
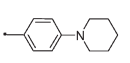
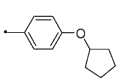
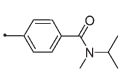
In parallel with the optimization of the bisarylthiazole tailpiece, a survey of acidic headgroups was conducted. The synthesis to their ester precursors was described previously.[42,64−69] These esters were coupled with bromide **39** using Cs_2CO_3 in acetonitrile and hydrolyzed to give final products **40** (Scheme 7). Intermediate **39** was synthesized following the general procedures described in Scheme 4, with the exception that the Suzuki coupling with 4-trifluoromethylphenylboronic acid was done directly after bromination of the thiazole ring.

A number of interesting results are listed in Table 6. The bare *p*-phenoxyacetic acid was active (compound **40a**), whereas meta (compound **40b**) and ortho (compound **40c**) orientations were not tolerated for PPAR activation. Adding a geminal dimethyl group (compound **40d**) had little effect on PPARδ activity, while adding an ethoxy group (compound **40e**) as commonly seen with PPARα/γ dual agonists[66] led to activity across all PPAR subtypes, although with quite low efficacies. An alkyl substitution (methyl, propyl) within the phenyl ring (compounds **29b**, **40f**) as in **50** led to a dramatic >25-fold increase in activity over compound **40a**. Changing the position of the methyl group in the phenyl ring (compound **40g**) caused a ∼100-fold drop in activity. The decrease in activity of analogue **40h** can be explained by the increase in linker length when incorporating sulfur instead of oxygen (cf. compound **20**, Table 1). The substitution of the oxygen closer to the carboxylate warhead with a methylene group (compound **40i**) did not lead to any improvements. Replacing the methyl group with a trifluoromethyl group (compound **40j**) was fairly well tolerated. Several attempts to enclose the methyl group into a bicyclic system (compound **40k**−**o**) gave compounds with lower PPAR activity compared to compound **29b**. The loss of activity of compound **40n** can be explained by the requirement of the acidic warhead to reach out of plane orthogonally to the center phenyl ring in order to form the crucial contacts with the AF-2 helix of the receptor.[26] Phenylacetic acid analogues (compounds **40p**−**s**) were also tolerated and gave good results when phenyl substituents and linker length were reoptimized (compound **40s**) as explained earlier (cf. compound **17**, Table 1). In summary, none of the various headgroups employed in this survey was able to increase PPARδ agonist activity when compared to **50**.

Biology. Our optimization efforts described above generated a collection of approximately 100 PPARδ-selective compounds with activities of <25 nM potency and >80% efficacy. Representative examples can be found in Table 7. The compounds displayed similar activities when comparing their ability to bind and induce activation of the ligand binding domain of PPARδ in a cell-based Gal4-DBD-based

Table 4. Optimization of Position 4 in the Thiazole/Oxazole Ring (Ar^2 = *p*-OCF_3-phenyl)



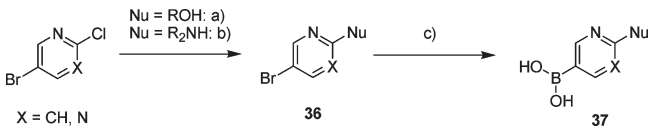
			PPAR EC_{50} (μM) (% efficacy[a])						PPAR EC_{50} (μM) (% efficacy)		
Cpd	X	Ar^1	α	γ	δ	Cpd	X	Ar^1	α	γ	δ
29e	S		>10	>10	0.023 (70)	**35l**	S		>10	>10	0.031 (103)
35a	S		>10	>10	0.331 (73)	**35m**	S		>10	>10	0.017 (81)
35b	S		>10	>10	0.160 (70)	**35n**	S		>10	>10	0.013 (81)
35c	S		>10	>10	0.056 (79)	**35o**	S		>10	>10	0.030 (77)
35d	S		>10	>10	0.120 (82)	**35p**	S		>10	>10	0.410 (74)
35e	S		>10	>10	0.032 (88)	**35q**	S		5.20 (9)	>10	0.052 (79)
35f	S		>10	>10	0.035 (86)	**35r**	S		>10	>10	0.045 (93)
35g	S		>10	>10	0.026 (85)	**35s**	S		>10	>10	0.775 (57)
35h	S		>10	>10	0.007 (78)	**35t**	S		>10	>10	0.544 (67)
35i	S		>10	>10	0.018 (87)	**35u**	S		>10	>10	0.023 (68)
35j	S		>10	>10	0.063 (92)	**35v**	S		0.69 (65)	1.20 (32)	0.002 (97)
35k	S		>10	>10	0.010 (94)	**35w**	S		1.59 (55)	1.56 (26)	0.006 (77)
35aa	O		2.60 (43)	>10	0.003 (84)	**35ab**	O		1.15 (43)	>10	0.018 (83)
35ac	O		0.91 (56)	>10	0.004 (92)	**35ad**	O		0.70 (49)	0.60 (48)	0.001 (86)

[a] The % efficacy is calculated relative to response to reference compounds (100%). Reference compounds used for % efficacy calculation: PPARα, KRP297; PPARγ, rosiglitazone; PPARδ, GW501516.

luciferase reporter gene assay [transactivation (TA) assay] and their ability to induce a conformational change in the LBD of PPARδ to recruit a coactivator peptide [fluorescence resonance energy transfer (FRET) assay] in a cell-free system. The ability of the compounds to activate a rodent (mouse) PPARδ receptor was comparable to the human PPARδ activities. In general, the compounds were well tolerated in cellular assays up to 10 μM and were cytotoxic only when tested at high concentrations (>30 μM), as indicated by the reduction of TA activity at high compound concentrations. This moderate cytotoxicity was also observed in hepatocytes and bone marrow cells again only at high compound concentrations (>50 μM) for some compounds and appeared to decrease with decreasing

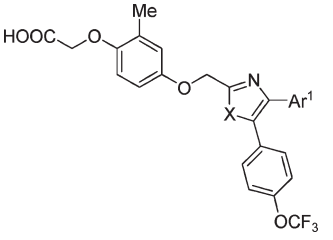
lipophilicity of the compounds. The same trend was observed for their potential to nonselectively inhibit transmembrane receptors in a cell-free setting when tested against a panel of GPCRs and ion channels (data not shown). These observations led to the hypothesis that the highly lipophilic compounds in this series probably have membrane-disruptive, detergent-like properties at critical micelle concentrations.[70] A subset of compounds was further characterized for in vivo phamacokinetics, and compounds showing reasonable oral exposure were evaluated in an acute dosing in vivo model using C57BL/6 mice. The compounds chosen for in vivo evaluation had >90% parent remaining after 2 h of incubation with mouse liver microsomes except compound **46** and were well tolerated in both the pharmacokinetic and acute efficacy studies. The solubility and oral exposure was clearly affected by the nature of the substituents on the thiazole/oxazole core, with the slight trend toward less hydrophobic substituents accounting for better oral exposure. As reported previously,[21,27,71,72] PPARδ regulates lipid metabolism by increasing fatty acid metabolism in peripheral tissues, particularly in skeletal muscle, and by promoting energy uncoupling in fat and muscle. To assess the in vivo effects of PPARδ-selective compounds, real-time PCR gene expression studies were performed on samples of relevant metabolic tissues collected from mice dosed with our compounds. Briefly, C57BL6 mice were treated with either vehicle or compound once daily orally at 10 mg/kg for 3 days and skeletal muscle, liver, and adipose tissues were

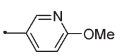
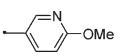
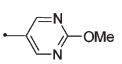
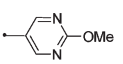
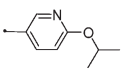
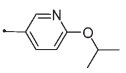
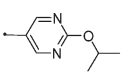
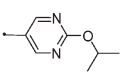
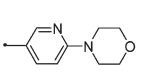
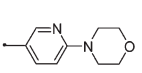
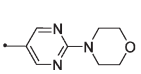
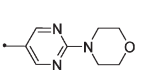
Scheme 6. Synthesis of Heterocyclic Boronic Acid Building Blocks[a]



[a] Reagents: (a) NaH, ROH, reflux, 15 h, 75−80%; (b) R_2NH, K_2CO_3, MeCN, reflux, 5 h, 75−80%; (c) *n*-BuLi, diethyl ether, −78 °C, 2 h, then $B(O^iPr)_3$, 2 h, 60−77%.

Table 5. Optimization of Position 4 in the Thiazole/Oxazole Ring (Ar^2 = *p*-OCF_3-phenyl) Continued



			PPAR EC_{50} (μM) (% efficacy[a])						PPAR EC_{50} (μM) (% efficacy)		
Cpd	X	Ar^1	α	γ	δ	Cpd	X	Ar^1	α	γ	δ
38a	S		>10	>10	0.068 (88)	**38aa**	O		>10	>10	0.007 (75)
38b	S		>10	>10	0.059 (95)	**38ab**	O		>10	>10	0.055 (75)
38c	S		>10	>10	0.017 (94)	**38ac**	O		>10	>10	0.008 (82)
38d	S		>10	>10	0.034 (89)	**38ad**	O		>10	>10	0.014 (77)
38e	S		>10	>10	0.008 (100)	**38ae**	O		0.79 (70)	2.49 (20)	0.003 (96)
38f	S		>10	>10	0.006 (101)	**38af**	O		0.16 (82)	0.98 (24)	0.001 (90)
38g	S		>10	>10	0.018 (84)	**38ag**	O		1.20 (46)	2.49 (20)	0.002 (94)
38h	S		1.99 (38)	>10	0.003 (89)	**38ah**	O		0.41 (69)	1.03 (27)	0.001 (99)

[a] The % efficacy is calculated relative to response to reference compounds (100%). Reference compounds used for % efficacy calculation: PPARα, KRP297; PPARγ, rosiglitazone; PPARδ, GW501516.

Scheme 7. Exploration of Headgroup SAR[a]

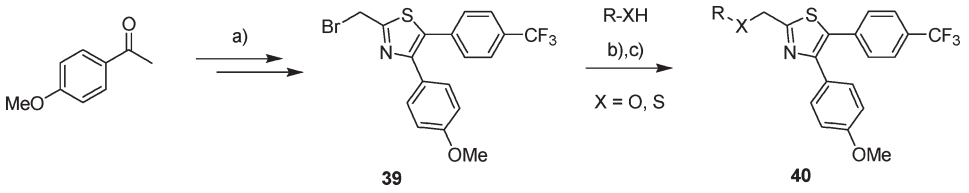
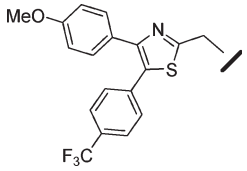
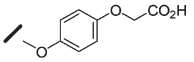
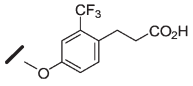
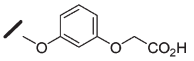
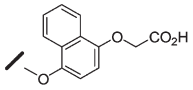
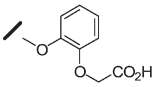
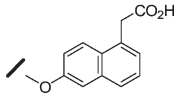
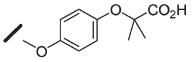
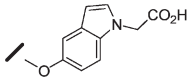
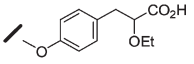
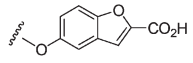
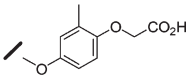
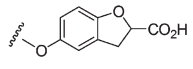
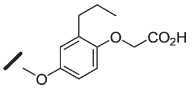
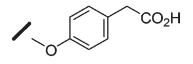
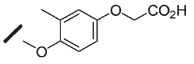
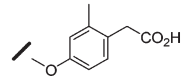
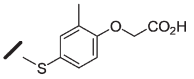
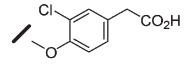
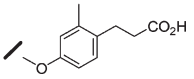
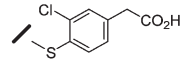


Table 6. Selected SAR of the Headgroup Survey

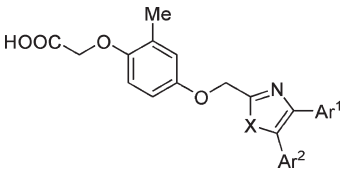


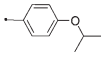
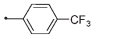
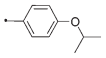
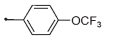
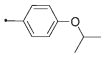
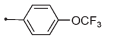
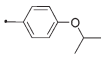
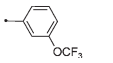
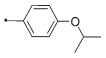
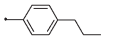
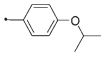
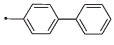
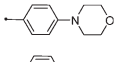
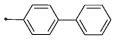
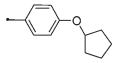
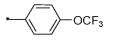
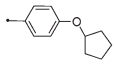
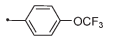
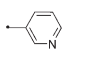
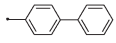
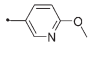
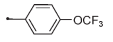
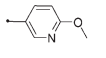
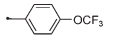
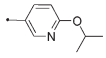
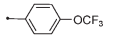
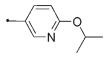
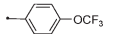
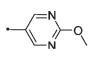
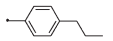
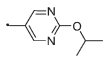
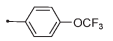
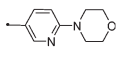
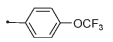
Cpd	R	PPAR EC_{50} (μM) (% efficacy[a]) α	γ	δ	Cpd	R	PPAR EC_{50} (μM) (% efficacy) α	γ	δ
40a		>10	>10	0.93 (69)	**40j**		>10	>10	0.38 (54)
40b		>10	>10	>10	**40k**		>10	>10	2.93 (26)
40c		>10	>10	>10	**40l**		>10	>10	0.74 (32)
40d		>10	>10	1.20 (52)	**40m**		>10	>10	0.34 (55)
40e		1.09 (37)	1.31 (23)	1.87 (20)	**40n**		>10	>10	>10
29b		>10	>10	0.04 (71)	**40o**		>10	>10	0.46 (36)
40f		>10	>10	0.02 (70)	**40p**		>10	>10	1.30 (54)
40g		>10	>10	2.26 (37)	**40q**		>10	>10	0.14 (47)
40h		>10	>10	0.23 (68)	**40r**		>10	>10	0.48 (56)
40i		>10	>10	0.14 (65)	**40s**		>10	>10	0.062 (65)

[a] The % efficacy is calculated relative to response to reference compounds (100%). Reference compounds used for % efficacy calculation: PPARα, KRP297; PPARγ, rosiglitazone; PPARδ, GW501516.

collected for quantitative real-time PCR analysis of PPARδ-regulated genes. The fold induction of two PPARδ-regulated genes, PDK4 (pyruvate dehydrogenase kinase-4, a key enzyme in glucose metabolism) and UCP3 (uncoupling protein-3, involved in energy uncoupling), in skeletal muscle is summarized in Table 7. As shown, compounds in this series showed in vivo up-regulation of the skeletal muscle PDK4 and UCP3 gene expression at the RNA levels. Compounds in this series also regulated expression of some additional PPARδ-regulated genes involved in fatty acid oxidation and energy metabolism in skeletal muscle, liver, and adipose tissues (data not shown).

Table 7. In Vitro Human and Mouse PPARδ Activities,[a] in Vivo PK Properties, and Acute Dosing in Vivo Gene Induction Results of Representative Examples



					in vitro			*in vivo*					
cpd	X	Ar^1	Ar^2	clogP[c]	TA hPPARδ EC_{50} in μM (% efficacy)[a]	TA mPPARδ EC_{50} in μM (% efficacy)[a]	FRET hPPARδ EC_{50} in μM (% efficacy)[a]	$AUC_{0\text{-}24h}$ (h*nM)	$t_{1/2}$ (h)	C_{max} (μM)	F (%)	UCP3 (fold ind)[d]	PDK4 (fold ind)
41	S			7.40	0.011 (88)	0.020 (83)	0.016 (155)	37326	3.9	2.8	70	1.7 ± 0.9	1.1 ± 0.7
35h	S			7.63	0.008 (81)	0.026 (82)	0.010 (120)	54097	9.0	3.7	88	2.4 ± 0.5*	1.9 ± 0.6*
35aa	O			6.96	0.002 (91)[b]	0.009 (88)	0.013 (108)	104075	5.1	7.8	129	2.2 ± 1.1*	2.3 ± 1.9**
42	S			7.63	0.009 (87)	0.046 (71)	0.016 (120)	20306	3.2	2.4	49	1.9 ± 0.8*	1.7 ± 0.9*
43	S			8.06	0.011 (90)	0.017 (89)	0.013 (127)	-	-	-	-	-	-
44	S			8.39	0.009 (80)[b]	0.029 (87)	0.010 (75)	-	-	-	-	2.4 ± 1.2*	1.5 ± 0.7
45	S			7.11	0.018 (81)[b]	0.072 (77)	0.014 (67)	31924	5.1	2.7	30	2.5 ± 1.2	1.4 ± 0.8
35k	S			8.26	0.011 (91)	0.031 (88)	0.015 (97)	16130	7.6	1.2	19	2.8 ± 1.2*	1.9 ± 0.9*
35ac	O			7.59	0.004 (90)[b]	0.009 (97)	0.012 (103)	23275	3.1	2.4	35	2.5 ± 0.9*	2.1 ± 0.7*
46	O			5.48	0.008 (76)[b]	0.030 (83)	0.006 (94)	814	4.0	0.4	10	-	-
38c	S			6.18	0.017 (94)	0.090 (79)	0.012 (143)	195686	4.6	17.3	140	2.5 ± 0.8*	1.9 ± 0.7*
38ac	O			5.53	0.007 (84)	0.097 (85)	0.010 (91)	96776	2.5	13.7	89	1.4 ± 0.2*	1.2 ± 0.2**
38e	S			7.02	0.009 (100)	0.013 (86)	0.012 (138)	62855	10.8	4.7	72	2.9 ± 1.5*	1.9 ± 0.7*
38ae	O			6.37	0.003 (95)[b]	0.007 (99)	0.014 (102)	95801	5.3	9.1	144	2.5 ± 1.3*	1.5 ± 0.9
47	O			5.14	0.009 (96)[b]	0.030 (87)	0.010 (121)	6415	2.7	2.2	41	2.5 ± 1.8**	2.0 ± 1.0*
38f	S			6.18	0.006 (83)	0.010 (85)	0.014 (126)	20053	2.3	3.5	88	1.5 ± 0.7	1.6 ± 0.8
38ag	O			4.76	0.002 (94)[b]	0.005(100)	-	1946	3.8	0.7	18	-	-
GW501516				6.79	0.005 (100)[b]	0.077 (100)	0.006 (155)	29795	4.4	3.9		3.2 ± 2.2*	2.5 ± 1.1*

[a] The % efficacy is calculated relative to response to reference compounds (100%). Reference compounds used for % efficacy calculation: TA assay, GW501516; FRET assay, L165041. [b] Detectable cross-activity to PPARα. [c] clogP values were calculated using the program cLogP 4.0 developed by BioByte, Inc. of Claremont, CA. [d] Gene expression data are reported as fold change ± SEM ($n = 5-6$ mice/group) relative to the vehicle control. Student's t test was used for the statistical analysis. The symbol ∗ indicates $p < 0.01$ relative to vehicle control, and ∗∗ indicates $P < 0.05$ relative to vehicle control.

Conclusions

In conclusion, we described the discovery and synthesis of a novel series of selective PPARδ agonists. The structure−activity relationships of the headgroup, linker, and tailgroup moieties were thoroughly investigated. The compound series was gradually optimized on the basis of transactivation activities and resulted in several examples with an improved PPAR subtype selectivity and an improved pharmacokinetic profile compared to prior disclosed PPARδ agonists. The requirement of a flexible linker in the series for improved potency was in line with the general agonist model known in the PPAR field, as was the overall hydrophobic character of the heteroaromatic tailgroup. While thiazoles followed the trend of being more selective over the other PPAR subtypes, the oxazole analogues were generally more potent but less selective for PPARδ activation. The five-membered heteroaromatic center ring required two aryl substituents for high potency, efficacy, and selectivity for PPARδ activation. The aryl substituents were not interchangable and had to be optimized individually, suggesting that the center heteroaromatic ring is involved in the binding event. The aryl ring in position 5 of the heterocycle was optimal when para-substituted with an electron-withdrawing and/or hydrophobic substituent. The aryl ring in position 4 was amenable to slightly more hydrophilic features. Within the series, optimal physicochemical parameters were achieved when substituting position 4 with pyridines or pyrimidines displaying *p*-alkoxy or amino substituents. A survey of various headgroups was conducted on the scaffold but did not lead to any improvements over the initially selected (2-methylphenoxy)acetic acid. Compounds with good to excellent pharmacokinetic properties, such as compound **38c**, demonstrated in vivo regulation of genes involved in energy homeostasis in relevant metabolic tissues when dosed acutely in C57Bl/6 mice. Several compounds are currently undergoing additional evaluation to further elucidate the role of PPARδ in glucose and lipid metabolism and to assess the potential of developing this series for diseases associated with the metabolic syndrome.

Experimental Section

Chemistry. Nuclear magnetic resonance (^{1}H NMR) spectra were obtained with a Bruker Avance spectrometer operating at 400 MHz with a QNP 5 mm probe. Chemical shifts are given in parts per million (δ, ppm) and are referenced to the solvent in which they were run. Microwave reactions were performed in an Emrys optimizer (Biotage AB). Wattage was automatically adjusted to maintain the desired temperature. Flash column chromatography was performed using silica gel (Merck grade 9385, 230−400 mesh, 60 Å (Aldrich)) or on an ISCO Combiflash system Sg100c using Redisep normal phase disposable columns (Teledyne ISCO, Lincoln NE). For compound elution, a gradient of either MeOH/DCM or EtOAc/hexanes was used as the mobile phase. Preparative reverse phase high pressure liquid chromatography (HPLC) was performed on an automated Gilson HPLC system using an Ultro C18 Guard column, 50 mm × 50 mm i.d. (Peeke Scientific, Redwood City, CA) and an XTerra Prep MS C18, 10 μm, 250 mm × 50 mm i.d., part number 186001083 (Waters Corp., Milford, MA). A flow rate of 100 mL/min, λ = 220 nm, and a gradient of mobile phases A (0.05% TFA in H_2O) and B (0.035% TFA in MeCN) were used to purify selected compounds. The purity of final compounds was assessed on the basis of analytical HPLC, and the results were greater 95% unless specified otherwise (Agilent 1100 HPLC stack and 1946 MSD mass spectrometer. The HPLC uses a Waters Atlantis dC18 50 mm × 2.1 mm, 5 μm column, with mobile phases A (H_2O + 0.05% TFA) and B (ACN + 0.035% TFA). The data were acquired in positive mode with the ESI source probe at 4000 V, drying gas flow of 12 L/min, nebulizer pressure of 60 psig, and drying gas temperature of 350 °C.

High resolution mass spectroscopy (HRMS) analysis was performed using the following system: an eight-channel pipetter was used to flush 10 μL of a solution of 80% MeCN/0.2% AcOH into each well of the sample plate containing varying amounts of compound in DMSO. After the liquid was mixed by aspirating and dispensing 3×, an aliquot of 10 μL was taken and diluted into 100 μL of 80% MeCN/0.2% AcOH. Solutions were analyzed by flow-injecting 3 μL of the diluted samples with an autosampler (Agilent Technologies, Palo Alto, CA) into a 50 μL/min stream of 80% MeCN/0.2% AcOH delivered by an HPLC pump (Agilent Technologies, Palo Alto, CA) into the ESI source of an LTQOrbitrap mass spectrometer (ThermoElectron, San Jose, CA). Centroid data were recorded for 2 min at 30 000 resolution on the Orbitrap analyzer. The signal was integrated for 30 s across the "plug" profile of the eluting samples using the Xcalibur software package (ThermoElectron, San Jose, CA) to obtain the accurate mass values of the samples.

Reference compounds were obtained using previously disclosed synthetic procedures: 2-[2-methyl-4-([4-methyl-2-[4-(trifluoromethyl)phenyl)-1,3-thiazol-5-yl]methylsulfanyl]phenoxy]-acetic acid (GW501516);[41] [4-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propoxy]phenoxy]acetic acid (L165041);[73] 5-[2,4-dioxothiazolidin-5-yl)methyl]-2-methoxy-*N*-[[(4-trifluoromethyl)-phenyl]methyl]benzamide (KRP297).[74] (*RS*)-5-[4-(2-[Methyl-(pyridin-2-yl)amino]ethoxy)benzyl]thiazolidine-2,4-dione (Rosiglitazone) was obtained by extraction (aqueous $NaHCO_3$, EtOH) from commercially available Avandia tablets (Pharmaceutical Buyers International Inc.).

2-Bromo-1,2-bis(4-methoxyphenyl)ethanone (3). To a solution of desoxyanisoin **2** (10 g, 39.0 mmol) in anhydrous $CHCl_3$ (200 mL) was added bromine (2.4 mL, 46.8 mmol) dropwise. After the addition was complete (indicated by a color change to red), the solvent was removed in vacuo, the remainder was triturated with diethyl ether, and the precipitated product was filtered to give **3** (11.5 g, 88%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ = 7.98 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.72 (s, 1H), 3.83 (s, 3H), 3.75 (s, 3H). MS *m*/*z* 255.4 $[M + H]^+$.

4,5-Bis(4-methoxyphenyl)-3*H*-thiazole-2-thione (4). 2-Bromo-1,2-bis(4-methoxyphenyl)ethanone **3** (3.0 g, 8.9 mmol) and ammonium dithiocarbamate (1.5 g, 13.4 mmol, prepared according to WO 9837074) were dissolved in EtOH (50 mL) and heated to 60 °C for 3 h. The solvent was then partially removed in vacuo and the precipitate filtered and recrystallized from EtOH to yield **4** (2.8 g, 96%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ = 7.26 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 3.77 (s, 3H). MS *m*/*z* 330.2 $[M + H]^+$.

[4-(2-Bromoethoxy)-2-methylphenoxy]acetic Acid Methyl Ester (5a). (4-Hydroxy-2-methylphenoxy)acetic acid methyl ester (**50**, 0.5 g, 2.8 mmol), 1,2-dibromoethane (2.4 mL, 27.7 mmol), and Cs_2CO_3 (4.5 g, 13.9 mmol) were suspended in dry acetone. The mixture was heated to reflux overnight. The reaction mixture was cooled to room temperature and filtered, and the solvent was removed in vacuo. The remainder was purified by chromatography (silica, DCM/MeOH gradient) to afford **5a** (0.7 g, 82%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.77 (s, 1H), 6.66 (m, 2H), 4.60 (s, 2H), 4.23 (t, *J* = 7.6 Hz, 2H), 3.80 (s, 3H), 3.60 (t, *J* = 7.6 Hz, 2H), 2.27 (s, 3H). MS *m*/*z* 303.2 $[M + H]^+$.

(4-{2-[4,5-Bis(4-methoxyphenyl)thiazol-2-ylsulfanyl]ethoxy}-2-methylphenoxy)acetic Acid (7a). [4-(2-Bromoethoxy)-2-methylphenoxy]acetic acid methyl ester **5a** (91 mg, 0.30 mmol) was added dropwise to a solution of NaOMe (23 mg, 0.33 mmol) and

intermediate **4** in EtOH (5 mL). After the mixture was stirred at room temperature for 24 h the solvent was removed in vacuo to afford crude (4-{2-[4,5-bis(4-methoxyphenyl)thiazol-2-ylsulfanyl]-ethoxy}-2-methylphenoxy)acetic acid methyl ester, which was dissolved in THF (3 mL). A solution of 1 M LiOH in H_2O (0.6 mL) was added, and the mixture was stirred overnight at room temperature. Then the mixture was acidified with 1 M HCl, EtOAc (10 mL) was added, and the organic layer was washed with H_2O (3 × 5 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified on reverse phase HPLC to afford **7a** (115 mg, 77%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ = 7.34 (d, J = 8.9 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.73−6.64 (m, 3H), 4.56 (s, 2H), 4.29 (t, J = 6.4 Hz), 3.79 (s, 3H), 3.78 (s, 3H), 3.57 (t, J = 6.4 Hz, 2H), 2.18 (s, 3H). MS m/z 538.4 $[M + H]^+$. HRMS calcd for $C_{28}H_{28}NO_6S_2$ $[M + H]^+$ 538.1353; found 538.1344.

Compounds **7b**−**10** were prepared following the synthetic procedure of **7a** using the appropriate headgroups **50**−**55** and dibromoalkanes.

2-(4-(3-(4,5-Bis(4-methoxyphenyl)thiazol-2-ylthio)propoxy)-2-methylphenoxy)acetic Acid (7b). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.34 (d, J = 8.9 Hz, 2H), 7.14 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.9 Hz, 2H), 6.73−6.63 (m, 3H), 4.55 (s, 2H), 4.06 (t, J = 5.9 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.42 (t, J = 7.0 Hz, 2H), 2.23 (m, 2H), 2.18 (s, 3H). MS m/z 552.4 $[M + H]^+$. HRMS calcd for $C_{29}H_{30}NO_6S_2$ $[M + H]^+$ 552.1509; found 552.1508.

2-(4-(4-(4,5-Bis(4-methoxyphenyl)thiazol-2-ylthio)butoxy)-2-methylphenoxy)acetic Acid (7c). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.34 (d, J = 8.9 Hz, 2H), 7.16 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.9 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 6.72−6.61 (m, 3H), 4.56 (s, 2H), 3.95 (t, J = 6.0 Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.31 (t, J = 7.2 Hz, 2H), 2.19 (s, 3H), 2.01−1.89 (m, 4H). MS m/z 566.4 $[M + H]^+$. HRMS calcd for $C_{30}H_{32}NO_6S_2$ $[M + H]^+$ 566.1666; found 566.1669.

2-(4-(2-(4,5-Bis(4-methoxyphenyl)thiazol-2-ylthio)ethoxy)-3-chlorophenyl)acetic Acid (8a). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.37−6.82 (m, 11H), 4.42 (t, J = 6.4 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.66 (t, J = 6.4 Hz, 2H), 3.50 (s, 2H). MS m/z 542.3 $[M + H]^+$. HRMS calcd for $C_{27}H_{25}ClNO_5S_2$ $[M + H]^+$ 542.0857; found 542.0855.

2-(4-(3-(4,5-Bis(4-methoxyphenyl)thiazol-2-ylthio)propoxy)-3-chlorophenyl)acetic Acid (8b). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.35−6.80 (m, 11H), 4.19 (t, J = 5.8 Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.55 (s, 2H), 3.47 (t, J = 7.0 Hz, 2H), 2.30 (m, 2H). MS m/z 556.4 $[M + H]^+$. HRMS calcd for $C_{28}H_{27}ClNO_5S_2$ $[M + H]^+$ 556.1014; found 556.1020.

2-(4-(4-(4,5-Bis(4-methoxyphenyl)thiazol-2-ylthio)butoxy)-3-chlorophenyl)acetic Acid (8c). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.36−6.80 (m, 11H), 4.10 (t, J = 5.7 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.51 (s, 2H), 3.36 (t, J = 7.1 Hz, 2H), 2.08−1.98 (m, 4H). MS m/z 570.4 $[M + H]^+$. HRMS calcd for $C_{29}H_{29}ClNO_5S_2$ $[M + H]^+$ 570.1170; found 570.1182.

{4-[4,5-Bis(4-methoxyphenyl)thiazol-2-ylsulfanylmethyl]-2-methylphenoxy}acetic Acid (9). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44 (d, J = 8.8 Hz, 2H), 7.24−7.18 (m, 4H), 6.86−6.80 (m, 4H), 6.66 (d, J = 8.4 Hz, 1H), 5.30 (s, 2H), 4.67 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 2,27 (s, 3H). MS m/z 508.1 $[M + H]^+$. HRMS calcd for $C_{27}H_{26}NO_5S_2$ $[M + H]^+$ 508.1247; found 508.1249.

2-(4-((4,5-Bis(4-methoxyphenyl)thiazol-2-ylthio)methyl)-3-chlorophenyl)acetic Acid (10). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51−7.45 (m, 3H), 7.35 (d, J = 1.2 Hz, 1H), 7.22 (s, 1H), 7.20 (s, 1H), 7.13 (dd, J = 1.2 Hz, J = 8.0 Hz, 1H), 4.57 (s, 2H), 3.802 (s, 3H), 3.809 (s, 3H), 3.62 (s, 2H). MS m/z 512.0 $[M + H]^+$. HRMS calcd for $C_{26}H_{23}ClNO_4S_2$ $[M + H]^+$ 512.0752; found 512.0752.

2-Chloro-4,5-bis(4-methoxyphenyl)thiazole (11). 2-Bromo-1,2-bis(4-methoxyphenyl)ethanone **3** (500 mg, 1.49 mmol) and potassium rhodanide (145 mg, 1.49 mmol) were heated to reflux in acetone (20 mL) for 8 h. The mixture was cooled, diluted with H_2O (50 mL), extracted with EtOAc (3 × 50 mL), and washed with brine (30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give crude 1,2-bis-(4-methoxyphenyl)-2-thiocyanatoethanone, which was dissolved in EtOAc (100 mL). Then HCl gas was bubbled through the solution for 2 h. The mixture was neutralized with aqueous NaOH to pH 6, extracted with EtOAc (3 × 50 mL), and washed sequentially with H_2O (30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica, EtOAc/hexane gradient) to afford **11** (230 mg, 50%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 (d, J = 9.0 Hz, 2H), 7.25 (d, J = 9.3 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 9.3 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 3H). MS m/z 332.3 $[M + H]^+$.

{4-[4,5-Bis(4-methoxyphenyl)thiazol-2-ylsulfanyl]-2-methylphenoxy}acetic Acid (12). 52 (28 mg, 0.131 mmol), intermediate **11** (40 mg, 0.131 mmol), and NaOEt (18 mg, 0.262 mmol) were dissolved in EtOH (1 mL) and heated to reflux for 6 h. The mixture was acidified with aqueous 1 N HCl (1 mL) and extracted with EtOAc (2 × 4 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated to provide crude {4-[4,5-bis(4-methoxyphenyl)thiazol-2-ylsulfanyl]-2-methylphenoxy}acetic acid ethyl ester, which was then dissolved in THF (1 mL) and 1 N LiOH (200 μL) and stirred at room temperature for 2 h. The mixture was acidified with aqueous HCl, extracted with EtOAc (2 × 4 mL), dried ($MgSO_4$), filtered, concentrated, and purified on reverse phase HPLC to afford **12** (12 mg, 18%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.33 (d, 8.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 6.70 (m, 5H), 4.65 (s, 2H), 3.71 (s, 3H), 3.69 (s, 3H), 2.22 (s, 3H). MS m/z 494.4 $[M + H]^+$. HRMS calcd for $C_{26}H_{24}NO_5S_2$ $[M + H]^+$ 494.1091; found 494.1089.

2-(4-(4,5-Bis(4-methoxyphenyl)thiazol-2-ylthio)-3-chlorophenyl)-acetic Acid (13). The compound was prepared according to the procedure for **12** starting with **53** instead of **52**. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (d, J = 8.0 Hz, 1H), 7.44 (s, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.4 Hz, 4H), 3.77 (s, 6H), 3.64 (s, 2H). MS m/z 498.3 $[M + H]^+$. HRMS calcd for $C_{26}H_{24}NO_5S_2$ $[M + H]^+$ 498.0595; found 498.0595.

[4,5-Bis(4-methoxyphenyl)thiazol-2-yl]methanol (14). A solution of 2-bromo-1,2-bis(4-methoxyphenyl)ethanone **3** (3.0 g, 9.0 mmol) and ethyl thiooxamate (1.2 g, 9.0 mmol) in anhydrous EtOH (20 mL) was heated to reflux for 12 h. The solvent was removed in vacuo and the remainder was purified by flash column chromatography (silica, EtOAc/hexane gradient) to afford 4,5-bis(4-methoxyphenyl)thiazole-2-carboxylic acid ethyl ester (2.7 g, 81%) as a colorless wax: ^{1}H NMR (400 MHz, CD_3OD) δ = 7.39 (d, J = 8.9 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.45 (q, J = 7.1, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H). MS m/z 370.4 $[M + H]^+$.

4,5-Bis(4-methoxyphenyl)thiazole-2-carboxylic acid ethyl ester (1.0 g, 2.7 mmol) was dissolved in dry THF (20 mL) and cooled to 0 °C. A solution of 1 M lithium aluminum hydride in THF (4 mL, 4.1 mmol) was added dropwise via cannula, and the mixture was stirred at 0 °C for 1 h. Sodium sulfate decahydrate (1.3 g, 4.1 mmol) was added slowly, and the mixture was stirred an additional 1 h at room temperature. The suspension was then filtered over Celite, dried ($MgSO_4$), and concentrated. The concentrate was purified by flash column chromatography (silica, EtOAc/hexane gradient) to yield **14** (0.7 g, 79%) as a yellow oil: ^{1}H NMR (400 MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 3.96 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H). MS m/z 328.4 $[M + H]^+$.

2-Hydroxymethyl-4,5-bis(4-methoxyphenyl)oxazole (15). A mixture of anisoin (1.00 g, 3.49 mmol), bromoacetic acid

(0.53 g, 3.84 mmol), 1,3-dicyclohexycarbodiimide (0.88 g, 4.23 mmol), DMAP (21.5 mg, 0.17 mmol), and DCM (25 mL) was stirred for 16 h at room temperature under nitrogen. Then the mixture was filtered, concentrated, and purified by flash column chromatography (silica, EtOAc/hexane gradient) to give bromoacetic acid 1,2-bis(4-methoxyphenyl)-2-oxoethyl ester (1.02 g, 74%) as a slightly yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 6.90−6.84 (m, 5H), 4.03−3.96 (m, 2H), 3.82 (s, 3H), 3.77 (s, 3H). MS m/z 393.2 $[M + H]^+$.

A solution of the previously prepared ester (393 mg, 1.00 mmol) and NH_4OAc (384 mg, 5.0 mmol) in AcOH (6 mL) was heated to reflux for 90 min. The mixture was poured into H_2O (15 mL) and extracted with DCM (30 mL). The organic layer was dried ($MgSO_4$), filtered, and purified by flash chromatography (silica, EtOAc/hexane gradient) to afford 2-(bromomethyl)-4,5-bis(4-methoxyphenyl)oxazole (283 mg, 76%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58−7.50 (m, 4H), 6.90 (d, J = 8.0 Hz, 4H), 5.22 (s, 2H), 3.83 (s, 6H). MS m/z 374.1 $[M + H]^+$.

A mixture of the bromomethyl intermediate (75.0 mg, 0.20 mmol), K_2CO_3 (110.4 mg, 0.80 mmol), and MeCN (5 mL) was heated to reflux for 2 h. The mixture was diluted with H_2O, then extracted with EtOAc (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give **15** (50 mg, 80%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 5.2 Hz, 1H), 6.82 (d, J = 5.2 Hz, 2H), 4.72 (s, 2H), 3.77 (s, 6H). MS m/z 312.1 $[M + H]^+$.

{4-[4,5-Bis(4-methoxyphenyl)thiazol-2-ylmethoxy]-2-methylphenoxy}acetic Acid (16). Intermediate **14** (25 mg, 0.08 mmol), **50** (18 mg, 0.09 mmol), and triphenylphosphine (30 mg, 0.11 mmol) were dissolved in dry DCM (1 mL) and cooled to 0 °C. Diethyl azodicarboxylate (24 μL, 0.15 mmol) was added slowly, and the solution was stirred at room temperature overnight. The solvent was removed in vacuo, and the residue was dissolved in THF (1 mL). Then a solution of 1 M LiOH in H_2O (0.2 mL) was added and the mixture was stirred at room temperature for 2 h. The mixture was acidified with 1 M HCl and extracted with EtOAc (10 mL). The organic layer was washed with H_2O (5 mL), dried ($MgSO_4$), filtered, concentrated, and purified on reverse phase HPLC to afford **16** (23 mg, 63%) as a colorless glass: ^{1}H NMR (400 MHz, CD_3OD) δ = 7.36 (d, J = 8.9 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 6.91−6.75 (m, 7H), 5.30 (s, 2H), 4.62 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 2.25 (s, 3H). MS m/z 492.4 $[M + H]^+$. HRMS calcd for $C_{27}H_{26}NO_6S$ $[M + H]^+$ 492.1476; found 492.1474.

Compounds **17**−**22** were prepared following the synthetic procedure of **16** using the appropriate headgroups **50**−**55** and intermediate **14** or **15**.

2-(4-((4,5-Bis(4-methoxyphenyl)thiazol-2-yl)methoxy)-3-chlorophenyl)acetic Acid (17). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74−6.80 (m, 11H), 5.43 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.57 (s, 2H). MS m/z 496.3 $[M + H]^+$. HRMS calcd for $C_{26}H_{23}ClNO_5S$ $[M + H]^+$ 496.0980; found 496.0981.

2-(4-((4,5-Bis(4-methoxyphenyl)thiazol-2-yl)methylthio)-2-methylphenoxy)acetic Acid (18). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74−6.63 (m, 11H), 4.62 (s, 2H), 4.35 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.23 (s, 3H). MS m/z 508.4 $[M + H]^+$. HRMS calcd for $C_{27}H_{26}NO_5S_2$ $[M + H]^+$ 508.1247; found 508.1241.

2-(4-((4,5-Bis(4-methoxyphenyl)thiazol-2-yl)methylthio)-3-chlorophenyl)acetic Acid (19). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74−6.78 (m, 11H), 4.51 (s, 2H), 3.79 (s, 3H), 3.79 (s, 3H), 3.58 (s, 2H). MS m/z 512.3 $[M + H]^+$. HRMS calcd for $C_{26}H_{23}ClNO_4S_2$ $[M + H]^+$ 512.0752; found 512.0756.

{4-[4,5-Bis(4-methoxyphenyl)oxazol-2-ylmethoxy]-2-methylphenoxy}acetic Acid (20). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.40−7.37 (m, 4H), 6.81−6.87 (m, 5H), 6.74−6.66 (m, 2H), 5.04 (s, 2H), 4.52 (s, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 2.16 (s, 3H). MS m/z 476.1 $[M + H]^+$. HRMS calcd for $C_{27}H_{26}NO_7$ $[M + H]^+$ 476.1704; found 476.1701.

2-(4-((4,5-Bis(4-methoxyphenyl)oxazol-2-yl)methylthio)-3-chlorophenyl)acetic acid (21). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.47 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 1.6 Hz, 1H), 7.30 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.12 (dd, J = 2.0 Hz, J = 8.0 Hz, 1H), 6.79−6.85 (m, 4H), 4.21 (s, 2H), 3.72 (s, 6H), 3.52 (s, 2H). MS m/z 496.0 $[M + H]^+$. HRMS calcd for $C_{26}H_{23}ClNO_5S$ $[M + H]^+$ 496.0980; found 496.0981.

2-(4-((4,5-Bis(4-methoxyphenyl)oxazol-2-yl)methylthio)-2-methylphenoxy)acetic Acid (22). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.29 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.8 Hz, 1H), 7.13 (s, 1H), 6.86−6.81 (m, 4H), 6.67 (d, J = 8.4 Hz, 1H), 4.58 (s, 2H), 4.01 (s, 2H), 3.73 (s, 6H), 2.01 (s, 3H). MS m/z 492.1 $[M + H]^+$. HRMS calcd for $C_{27}H_{26}NO_6S$ $[M + H]^+$ 492.1476; found 492.1472.

(2-Methyl-4-thiocarbamoylmethoxyphenoxy)acetic Acid Methyl Ester (23). 50 (1.64 g, 8.3 mmol) and chloroacetonitrile (0.55 mL, 8.7 mmol) were dissolved in MeCN (30 mL). Cs_2CO_3 (5.4 g, 16.7 mmol) was added, and the mixture was stirred for 2 h at room temperature. Insoluble salts were filtered and washed with EtOAc. Then the filtrate was concentrated to give an oil which crystallized under vacuum to give (4-cyanomethoxy-2-methylphenoxy)acetic acid methyl ester (1.84 g, 94%) as a pale-yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.76 (s, 1H), 6.67 (s, 1H), 6.60 (d, J = 8.5 Hz, 1H), 4.62 (s, 2H), 4.54 (s, 2H), 3.73 (s, 3H), 2.21 (s, 3H). MS m/z 236.3 $[M + H]^+$.

(4-Cyanomethoxy-2-methylphenoxy)acetic acid methyl ester (1.75 g, 7.45 mmol) and thioacetamide (1.12 g, 14.9 mmol) were dissolved in DMF (120 mL). A 4 M HCl solution and 1,4-dioxane (20 mL) was added, and the mixture was stirred at 100 °C overnight. The mixture was diluted with saturated $NaHCO_3$, extracted with EtOAc, and washed subsequently with H_2O (4 × 100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was triturated with DCM (5 mL) and hexanes (5 mL) and collected by filtration to afford **23** (1.24 g, 62%) as a beige solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.84 (d, J = 2.9 Hz, 1H), 6.78 (d, J = 8.9 Hz, 1H), 6.71 (dd, J = 3.0, 8.9 Hz, 1H), 4.75 (s, 2H), 4.67 (s, 2H), 4.04 (s, 1H), 3.69 (s, 3H), 2.18 (s, 3H). MS m/z 270.3 $[M + H]^+$.

General Procedures to Intermediate 24. Method A: From Aldehyde ($R^1 = R^2$), Exemplified by 2-Bromo-1,2-bis(4-chlorophenyl)ethanone. 4-Chlorobenzaldehyde (0.57 g, 2.04 mmol) was dissolved in EtOH (8 mL). A solution of KCN (18.0 mg, 0.27 mmol) in H_2O (4 mL) was added and the mixture was heated at reflux for 7 h, then cooled, extracted with EtOAc (50 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (diethyl ether/hexane gradient) to give 1,2-bis(4-chlorophenyl)-2-hydroxyethanone (0.57 g, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 (m, 2H), 7.39 (m, 2H), 7.31 (m, 2H), 7.25 (m, 2H), 5.88 (s, 1H), 4.50 (bro. 1H). MS m/z 262.9 $[M - OH]^+$.

To a solution of 2,3-dichloro-5,6-dicyanobenzoquinone (242 mg, 1.07 mmol) and triphenylphosphine (280 mg, 1.07 mmol) in DCM (5 mL) was added tetrabutylammonium bromide (344 mg (1.07 mmol) and 1,2-bis(4-chlorophenyl)-2-hydroxyethanone (200 mg, 0.71 mmol). The solution was stirred for 1.5 h at room temperature, then concentrated and purified by flash column chromatography (silica, EtOAc/hexane gradient) to give 2-bromo-1,2-bis(4-chlorophenyl)ethanone (85 mg, 0.25 mmol, 35%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (d, J = 8.8 Hz, 2H), 7.40−7.35 (m, 4H), 7.29 (d, J = 8.4 Hz, 2H), 6.17 (s, 1H). MS m/z 343.0 $[M + H]^+$.

Method B: From Aldehyde ($R^1 \neq R^2$), Exemplified by 2-Bromo-1-(4-chlorophenyl)-2-phenylethanone. 4-Chlorobenzaldehyde (4.2 g, 30.4 mmol) and trimethylsilyl cyanide (3.0 g, 30.4 mmol) were dissolved in DCM (50 mL). The solution was cooled to 0 °C, and then zinc iodide (43 mg, 1.13 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 16 h at

room temperature. Then it was concentrated, suspended in diethyl ether, and filtered through activated charcoal. The filtrate was dried ($MgSO_4$) and concentrated to give (4-chlorophenyl)trimethylsilanyloxyacetonitrile (6.6 g, 90%): MS m/z 214.1 $[M - CN]^+$.

(4-Chlorophenyl)trimethylsilanyloxyacetonitrile (906 mg, 3.78 mmol) was dissolved in THF (8 mL) and added dropwise into a solution of 2 M LDA (1.89 mL, 3.78 mmol) in THF (4 mL) at −78 °C. The reaction mixture was stirred for 30 min followed by addition a solution of benzyl bromide (0.65 g, 3.78 mmol) in THF (2 mL) at −78 °C. The mixture was allowed to warm to room temperature and stirred for 18 h. Then it was diluted with H_2O (10 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was dissolved in MeOH (10 mL), 1 M H_2SO_4 (4 mL) was added, and the mixture was stirred at room temperature for 12 h. Then the pH of the mixture was adjusted to 10 by adding 1 N NaOH, followed by extraction with EtOAc (3 × 20 mL). The organic layers were combined, washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to give 1-(4-chlorophenyl)-2-phenylethanone. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.8 Hz, 2H), 7.33 (m, 2H), 7.25 (m, 3H), 4.26 (s, 2H). MS m/z 231.1 $[M + H]^+$.

1-(4-Chlorophenyl)-2-phenylethanone (100 mg, 0.4 mmol) and pyridinium tribromide (126 mg, 0.4 mmol) were dissolved in DCM (2 mL) and stirred at room temperature for 1 h. The solution was concentrated to give 2-bromo-1-(4-chlorophenyl)-2-phenylethanone. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, J = 8.4 Hz, 2H), 7.51 (m, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.38 (s, 1H), 7.36 (m, 1H), 6.31 (s, 1H). MS m/z 308.0 $[M + H]^+$.

[2-Methyl-4-(4-phenylthiazol-2-ylmethoxy)phenoxy]acetic Acid (25a, R^2 = H). 2-Bromo-1-phenylethanone (26 mg, 0.13 mmol) and (2-methyl-4-thiocarbamoylmethoxyphenoxy)acetic acid methyl ester **23** (34 mg, 0.13 mmol) were dissolved in EtOH (1 mL) and subjected to microwave irradiation (180 °C) for 5 min. The mixture was concentrated, then dissolved in a mixture of THF (1 mL) and H_2O (0.5 mL). $LiOH \cdot H_2O$ (54 mg, 0.64 mmol) was added. The mixture was stirred for 2 h at room temperature, then acidified with 1 N HCl and extracted with EtOAc (5 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified on reverse phase HPLC to afford [2-methyl-4-(4-phenylthiazol-2-ylmethoxy)phenoxy]acetic acid **25a** (35 mg, 76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 (m, 2H), 7.45 (s, 1H), 7.38 (m, 2H), 7.30 (m, 1H), 6.83 (d, J = 2.9 Hz, 1H), 6.73 (dd, J = 3.1, 8.9 Hz, 1H), 6.64 (d, J = 8.8 Hz, 1H), 5.29 (s, 2H), 4.51 (s, 2H), 2.22 (s, 3H). MS m/z 356.4 $[M + H]^+$. HRMS calcd for $C_{19}H_{18}NO_4S$ $[M + H]^+$ 356.0951; found 356.0957.

[4-(4-Ethyl-5-phenylthiazol-2-ylmethoxy)-2-methylphenoxy]acetic Acid (25b, R^1 = Ethyl). 1-Bromo-1-phenylbutan-2-one (29 mg, 0.13 mmol) and (2-methyl-4-thiocarbamoylmethoxyphenoxy)acetic acid methyl ester **23** (34 mg, 0.13 mmol) were dissolved in EtOH (1 mL) and subjected to microwave irradiation (180 °C) for 5 min. The mixture was concentrated, then dissolved in a mixture of THF (1 mL) and H_2O (0.5 mL). $LiOH \cdot H_2O$ (54 mg, 0.64 mmol) was added. The mixture was stirred for 2 h at room temperature, then acidified with 1 N HCl and extracted with EtOAc (5 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified on reverse phase HPLC to afford [4-(4-ethyl-5-phenylthiazol-2-ylmethoxy)-2-methylphenoxy]acetic acid **25b** (34 mg, 68%): ^{1}H NMR (400 MHz, CD_3OD) δ = 7.27−7.23 (m, 2H), 7.18−7.14 (m, 3H), 6.83 (d, J = 2.4 Hz, 1H), 6.76−6.71 (m, 2H), 5.19 (s, 2H), 4.60 (s, 2H), 4.05 (s, 2H), 2.40 (s, 3H), 2.22 (s, 3H). MS m/z 384.1 $[M + H]^+$. HRMS calcd for $C_{21}H_{22}NO_4S$ $[M + H]^+$ 384.1264; found 384.1266.

[2-Methyl-4-(4-phenyl-5-phenylcarbamoylthiazol-2-ylmethoxy)-phenoxy]acetic Acid (25c, R = Ph). 2-Benzoylacetanilide (267 mg, 1.11 mmol) and *N*-bromosuccinimide (218 mg, 1.23 mmol) were dissolved in carbon tetrachloride (5 mL) and stirred at room temperature for 1 h. The mixture was poured into H_2O (5 mL), extracted with DCM (10 mL), dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica, EtOAc/hexane gradient) to give 2-bromo-3-oxo-3,*N*-diphenylpropionamide (270 mg, 76%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.78 (s, 1H), 8.06 (d, J = 8.6 Hz, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.54 (m, 4H), 7.37 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.17 (t, J = 7.4 Hz, 1H), 5.70 (s, 1H). MS m/z 318.2 $[M + H]^+$.

(2-Methyl-4-thiocarbamoylmethoxyphenoxy)acetic acid methyl ester **23** (63 mg, 0.234 mmol) and 2-bromo-3-oxo-3,*N*-diphenylpropionamide (78 mg, 0.245 mmol) were dissolved in a mixture of EtOH (2 mL) and piperidine (4 μL). The reaction mixture was subjected to microwave irradiation (180 °C) for 3 min. The mixture was diluted with H_2O (5 mL), extracted with EtOAc (8 mL), and washed with brine (5 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified on reverse phase HPLC to give the [2-methyl-4-(5-phenylbenzooxazol-2-ylmethoxy)phenoxy]acetic acid methyl ester. The ester was dissolved in THF (1 mL). Then 1 N LiOH (200 μL) was added and the mixture was stirred at room temperature for 2 h. Then it was acidified with 1 M HCl, extracted with EtOAc (10 mL), dried ($MgSO_4$), filtered, concentrated, and purified on reverse phase HPLC to afford **25c** (14 mg, 12%) as a yellow solid: ^{1}H NMR (400 MHz, DMSO) δ = 6.89 (s, 1H), 6.79 (d, J = 2.8 Hz, 1H), 6.68 (m, 4H), 5.70 (m, 6H), 5.51 (s, 2H), 5.21 (s, 2H), 4.56 (s, 2H), 4.54 (s, 2H), 2.11 (s, 3H), 2.09 (s, 3H). MS m/z 475.3 $[M + H]^+$. HRMS calcd for $C_{26}H_{23}N_2O_5S$ $[M + H]^+$ 475.1322; found 475.1322.

[4-(4-Methoxy-5-phenylthiazol-2-ylmethoxy)-2-methylphenoxy]-acetic Acid (25d, R = Me). (2-Methyl-4-thiocarbamoylmethoxyphenoxy)acetic acid methyl ester **23** (50 mg, 0.186 mmol) and methyl α-bromophenyl acetate (44 μL, 0.278 mmol) were dissolved in toluene (5 mL) and pyridine (60 μL, 0.742 mmol) and heated to 100 °C for 12 h. The mixture was diluted with H_2O (10 mL), extracted with EtOAc (10 mL), and washed with brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified on reverse phase HPLC to afford [4-(4-hydroxy-5-phenylthiazol-2-ylmethoxy)-2-methylphenoxy]acetic acid methyl ester (27 mg, 40%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (d, J = 7.6 Hz, 2H), 7.29 (m, 3H), 6.82 (d, J = 3.1 Hz, 1H), 6.71 (dd, J = 3.0, 8.6 Hz, 1H), 6.59 (d, J = 8.9 Hz, 1H), 5.16 (s, 2H), 4.52 (s, 2H), 3.71 (s, 3H), 2.21 (s, 3H). MS m/z 386.4 $[M + H]^+$.

[4-(4-Hydroxy-5-phenylthiazol-2-ylmethoxy)-2-methylphenoxy]acetic acid methyl ester (14 mg, 0.036 mmol), K_2CO_3 (15 mg, 0.109 mmol), and methyl iodide (5.7 μL, 0.091 mmol) were stirred together in DMF (1 mL) at room temperature for 1 h. The mixture was diluted with H_2O (5 mL), extracted with EtOAc (8 mL), and washed with H_2O (3 × 5 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give crude [4-(4-methoxy-5-phenylthiazol-2-ylmethoxy)-2-methylphenoxy]acetic acid methyl ester, which was dissolved in THF (1 mL). Then 1 N LiOH (200 μL) was added and the reaction mixture was stirred at room temperature for 1 h. Then it was acidified with 1 M HCl, extracted with EtOAc (10 mL), dried ($MgSO_4$), filtered, concentrated, and purified on reverse phase HPLC to afford **25d** (4 mg, 29%) as a white solid: ^{1}H NMR (400 MHz, DMSO) δ = 7.60 (d, J = 8.5 Hz, 2H), 7.29 (t, J = 7.6 Hz, 2H), 7.16 (d, J = 7.4 Hz, 1H), 6.82 (d, J = 2.8 Hz, 1H), 6.70 (dd, J = 3.0, 8.8 Hz, 1H), 6.63 (d, J = 8.8 Hz, 1H), 5.14 (s, 2H), 4.57 (s, 2H), 4.03 (s, 3H), 2.22 (s, 3H). MS m/z 386.4 $[M + H]^+$. HRMS calcd for $C_{20}H_{20}NO_5S$ $[M + H]^+$ 386.1057; found 386.1060.

Compounds **25e−v** were prepared following the synthetic procedures of **25a,b** using the appropriate intermediate **24**.

[2-Methyl-4-(4-*p*-tolylthiazol-2-ylmethoxy)phenoxy]acetic Acid (25e). ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ = 8.06 (d, J = 1.3 Hz, 1H), 7.85 (d, J = 7.0 Hz, 2H), 7.26 (d, J = 7.0 Hz, 2H), 6.94 (s, 1H), 6.84 (d, J = 8.9 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 5.40 (s, 2H), 4.62 (s, 2H), 2.34 (s,3H), 2.18 (s, 3H). MS m/z 370.4 $[M + H]^+$. HRMS calcd for $C_{20}H_{20}NO_4S$ $[M + H]^+$ 370.1108; found 370.1114.

2-(4-((4-(4-Methoxyphenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (25f). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (d, J = 8.8 Hz, 2H), 7.32 (s, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 2.9 Hz, 1H), 6.73 (dd, J = 3.0, 8.9 Hz, 1H), 6.65 (d, J = 8.8 Hz, 1H), 5.30 (s, 2H), 4.53 (s, 2H), 3.81 (s, 3H), 2.24 (s, 3H). MS m/z 386.4 $[M + H]^+$. HRMS calcd for $C_{20}H_{20}NO_5S$ $[M + H]^+$ 386.1057; found 386.1063.

{4-[4-(4-Chlorophenyl)thiazol-2-ylmethoxy]-2-methylphenoxy}acetic Acid (25g). ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ = 8.21 (s, 1H), 7.99 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 3.0 Hz, 1H), 6.84 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.77 (d, J = 8.9 Hz, 1H), 5.41 (s, 2H), 4.62 (s, 2H), 2.18 (s, 3H). MS m/z 390.3 $[M + H]^+$. HRMS calcd for $C_{19}H_{17}ClNO_4S$ $[M + H]^+$ 390.0562; found 390.0568.

[2-Methyl-4-(4-methyl-5-*p*-tolylthiazol-2-ylmethoxy)phenoxy]acetic Acid (25h). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.31−7.20 (m, 4H), 6.85 (d, J = 2.8 Hz, 1H), 6.77−6.69 (m, 2H), 5.22 (s, 2H), 4.56 (s, 2H), 2.35 (s, 3H), 2.27 (s, 3H), 2.11 (s, 3H). MS m/z 384.1 $[M + H]^+$. HRMS calcd for $C_{21}H_{22}NO_4S$ $[M + H]^+$ 384.1264; found 384.1267.

{4-[5-(4-Methoxyphenyl)-4-methylthiazol-2-ylmethoxy]-2-methylphenoxy}acetic Acid (25i). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.43 (s, 1H), 3.82 (s, 3H), 2.31 (s, 3H). MS m/z 400.1 $[M + H]^+$. HRMS calcd for $C_{21}H_{22}NO_5S$ $[M + H]^+$ 400.1213; found 400.1217.

{4-[5-(4-Chlorophenyl)-4-methylthiazol-2-ylmethoxy]-2-methylphenoxy}acetic Acid (25j). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.48−7.43 (m, 4H), 6.86 (d, J = 2.8 Hz, 1H), 6.77−6.69 (m, 2H), 5.24 (s, 2H), 4.56 (s, 2H), 2.36 (s, 3H), 2.11 (s, 3H). MS m/z 404.0 $[M + H]^+$. HRMS calcd for $C_{20}H_{19}ClNO_4S$ $[M + H]^+$ 404.0718; found 404.0723.

[4-(4-Biphenyl-4-ylthiazol-2-ylmethoxy)-2-methylphenoxy]acetic Acid (25k). ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ = 8.20 (d, J = 1.4 Hz, 1H), 7.99−8.07 (m, 2H), 7.78−7.72 (m. 4H), 7.50−7.48 (m, 2H), 7.40−7.38 (m, 1H), 6.96 (s, 1H), 6.86 (d, J = 8.9 Hz, 1H), 6.78 (d, J = 8.9 Hz, 1H), 5.43 (s, 2H), 4.63 (s, 2H), 2.19 (s, 3H). MS m/z 432.4 $[M + H]^+$. HRMS calcd for $C_{25}H_{22}NO_4S$ $[M + H]^+$ 432.1264; found 432.1269.

{2-Methyl-4-[4-(4-trifluoromethylphenyl)thiazol-2-ylmethoxy]-phenoxy}acetic Acid (25l). ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ = 8.37 (s, 1H), 8.18 (d, J = 8.2 Hz, 2H), 7.81 (d, J = 8.3 Hz, 2H), 6.94 (d, J = 3.0 Hz, 1H), 6.84 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.76 (d, J = 8.9 Hz, 1H), 5.42 (s, 2H), 4.61 (s, 2H), 2.17 (s, 3H). MS m/z 424.3 $[M + H]^+$. HRMS calcd for $C_{20}H_{17}F_3NO_4S$ $[M + H]^+$ 424.0825; found 424.0829.

{2-Methyl-4-[5-methyl-4-(4-trifluoromethylphenyl)thiazol-2-ylmethoxy]phenoxy}acetic Acid (25m). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.85 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 6.76 (dd, J = 3.0, 8.9 Hz, 1H), 6.69 (d, J = 8.9 Hz, 1H), 5.27 (s, 2H), 4.56 (s, 2H), 2.95 (s, 3H), 2.11 (s, 3H). MS m/z 438.3 $[M + H]^+$. HRMS calcd for $C_{21}H_{19}F_3NO_4S$ $[M + H]^+$ 438.0982; found 438.0980.

[2-Methyl-4-(4-pyridin-3-yl-5-*p*-tolylthiazol-2-ylmethoxy)-phenoxy]acetic Acid (25n). ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ = 8.64 (d, J = 1.7 Hz, 1H), 8.54 (dd, J = 1.4 Hz, J = 4.8 Hz, 1H), 7.91 (d, J = 8.0 Hz), 7.47 (dd, J = 5.0 Hz, J = 7.9 Hz, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 3.0 Hz, 1H), 6.87 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.41 (s, 2H), 4.64 (s, 2H), 2.34 (s, 3H), 2.19 (s, 3H). MS m/z 447.4 $[M + H]^+$.

[4-(4,5-Diphenylthiazol-2-ylmethoxy)-2-methylphenoxy]acetic Acid (25o). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 (m, 2H), 7.23 (m, 8H), 6.82 (d, J = 2.9 Hz, 1H), 6.69 (dd, J = 3.0, 8.9 Hz, 1H), 6.61 (d, J = 8.9 Hz, 1H), 5.26 (s, 2H), 4.53 (s, 2H), 2.20 (s, 3H). MS m/z 432.4 $[M + H]^+$. HRMS calcd $C_{25}H_{22}NO_4S$ $[M + H]^+$ 432.1264; found 432.1266.

2-(4-((4,5-Bis(4-biphenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (25p). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.66−7.57 (m, 10H), 7.43−7.36 (m, 6H), 7.32−7.26 (m, 2H), 6.91 (d, J = 3.2 Hz, 1H), 6.84−6.73 (m, 2H), 5.33 (s, 2H), 4.58 (s, 2H), 2.20 (s, 3H). MS m/z 584.2 $[M + H]^+$.

2-(4-((4,5-Bis(4-(trifluoromethyl)phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (25q). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.71 (d, J = 8.4 Hz, 2H), 7.65 (s, 4H), 7.56 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 2.8 Hz, 1H), 6.87−6.77 (m, 2H), 5.39 (s, 2H), 4.63 (s, 2H), 2.27 (s, 3H). MS m/z 568.0 $[M + H]^+$. HRMS calcd $C_{27}H_{20}F_6NO_4S$ $[M + H]^+$ 568.1012; found 568.1011.

{4-[4,5-Bis(4-chlorophenyl)thiazol-2-ylmethoxy]-2-methylphenoxy}acetic Acid (25r). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.45 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.34−7.30 (m, 4H), 6.91 (d, J = 2.8 Hz, 1H), 6.85−6.76 (m, 2H), 5.34 (s, 2H), 4.62 (s, 2H), 2.26 (s, 3H). MS m/z 501.0 $[M + H]^+$. HRMS calcd $C_{25}H_{20}Cl_2NO_4S$ $[M + H]^+$ 500.0485; found 500.0488.

{4-[4-(4-Methoxyphenyl)-5-phenylthiazol-2-ylmethoxy]-2-methylphenoxy}acetic Acid (25s). ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ = 7.40−7.34 (m, 7H), 6.96 (d, J = 3.0 Hz, 1H), 6.87 (m, 3H), 6.78 (d, J = 8.9 Hz, 1H), 5.38 (s, 2H), 4.63 (s, 2H), 3.74 (s, 3H), 2.19 (s, 3H). MS m/z 462.4 $[M + H]^+$. HRMS calcd $C_{26}H_{24}NO_5S$ $[M + H]^+$ 462.1370; found 462.1372.

{4-[5-(4-Methoxyphenyl)-4-phenylthiazol-2-ylmethoxy]-2-methylphenoxy}acetic Acid (25t). ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ = 7.47−7.26 (m, 7H), 6.95 (m, 3H), 6.87 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.38 (s, 2H), 4.63 (s, 2H), 3.77 (s, 3H), 2.19 (s, 3H). MS m/z 462.4 $[M + H]^+$. HRMS calcd $C_{26}H_{24}NO_5S$ $[M + H]^+$ 462.1370; found 462.1373.

{4-[4-(4-Chlorophenyl)-5-phenylthiazol-2-ylmethoxy]-2-methylphenoxy}acetic Acid (25u). ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ = 7.46−7.31 (m, 9H), 6.96 (d, J = 3.0 Hz, 1H), 6.87 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.40 (s, 2H), 4.63 (s, 2H), 2.19 (s, 3H). MS m/z 466.3 $[M + H]^+$. HRMS calcd $C_{25}H_{21}ClNO_4S$ $[M + H]^+$ 466.0875; found 466.0880.

{4-[5-(4-Chlorophenyl)-4-phenylthiazol-2-ylmethoxy]-2-methylphenoxy}acetic Acid (25v). ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ = 7.47−7.30 (m, 9H), 6.96 (d, J = 3.0 Hz, 1H), 6.87 (dd, J = 3.0 Hz, J = 8.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.40 (s, 2H), 4.64 (s, 2H), 2.19 (s, 3H). MS m/z 466.3 $[M + H]^+$. HRMS calcd $C_{25}H_{21}ClNO_4S$ $[M + H]^+$ 466.0875; found 466.0880.

General Procedures to Intermediate 26. Method A: X = S, Exemplified by 4-(4-Methoxyphenyl)-2-methylthiazole). 1-(4-Methoxyphenyl)ethanone (200 mg, 1.33 mmol) and pyridinium tribromide (425 mg, 1.33 mmol) were dissolved in DCM (5 mL), and the mixture was stirred for 1 h at room temperature. The mixture was diluted with 1 N HCl (10 mL), extracted with DCM, and washed with brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give crude 2-bromo-1-(4-methoxyphenyl)-ethanone which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (d, J = 9.2 Hz, 2H), 6.96 (d, J = 9.2 Hz, 2H), 4.40 (s, 2H), 3.89 (s, 3H). MS m/z 229.0 $[M + H]^+$.

2-Bromo-1-(4-methoxyphenyl)ethanone (25 g, 109 mmol) and thioacetamide (9.0 g, 120 mmol) were dissolved in EtOH (60 mL) and heated to reflux for 2 h. The solvent was removed in vacuo to afford crude 4-(4-methoxyphenyl)-2-methylthiazole. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, J = 8.8 Hz, 2H), 6.99 (s, 1H), 6.76 (d, J = 8.8 Hz, 2H), 3.66 (s, 3H), 2.58 (s, 3H). MS m/z 206.1 $[M + H]^+$.

Method B: X = O, Exemplified by 4-(4-Methoxyphenyl)-2-methyloxazole). 2-Bromo-1-(4-methoxyphenyl)ethanone (20.0 g, 87.3 mmol) and acetamide (15.5 g, 262.0 mmol) were heated to 150 °C for 2 h. The mixture was cooled to room temperature, diluted with EtOAc, and washed successively with saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica, EtOAc/hexane gradient) to give 4-(4-methoxyphenyl)-2-methyloxazole (10.3 g, 62%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 (s, 1H), 7.56 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 3.76 (s, 3H), 2.44 (s, 3H). MS m/z 190.1 $[M + H]^+$.

General Procedure to Intermediate 27 (X = S), Exemplified by 5-Bromo-2-(bromomethyl)-4-(4-methoxyphenyl)thiazole. 4-(4-Methoxyphenyl)-2-methylthiazole (872 mg, 4.25 mmol) was

dissolved in DCM (10 mL). Then bromine (240 μL, 4.67 mmol) was added and the mixture was stirred at room temperature for 2 h. The mixture was diluted with saturated $NaHCO_3$, extracted with DCM, and washed with brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give 5-bromo-4-(4-methoxyphenyl)-2-methylthiazole as a white solid (1.15 g, 96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 3.26 (s, 3H). MS m/z 283.9 $[M + H]^+$.

N-Bromosuccinimide (69 mg, 0.39 mmol) was added to a solution of 5-bromo-4-(4-methoxyphenyl)-2-methylthiazole (100 mg, 0.35 mmol) in carbon tetrachloride (10 mL). The above solution was stirred at room temperature for 15 h. Then the mixture was washed successively with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica, EtOAc/hexane gradient) to give 5-bromo-2-(bromomethyl)-4-(4-methoxyphenyl)thiazole (74 mg, 58%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.62 (s, 2H), 3.78 (s, 3H). MS m/z 361.8 $[M + H]^+$.

5-Bromo-2-(bromomethyl)-4-(4-methoxyphenyl)oxazole (27, X = O). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 4.46 (s, 2H), 3.85 (s, 3H). MS m/z 347.9 $[M + H]^+$.

General Procedure to Intermediate 28, Exemplified by Ethyl 2-(4-((5-Bromo-4-(4-methoxyphenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetate. A mixture of 5-bromo-2-bromomethyl-4-(4-methoxyphenyl)thiazole (2.87 g, 7.92 mmol), **50** (1.24 g of ethyl ester, 6.34 mmol), and Cs_2CO_3 (3.01 g, 9.48 mmol) in MeCN (200 mL) was stirred at room temperature for 2 h. The mixture was filtered, then concentrated and purified by flash column chromatography (silica, EtOAc/hexane gradient) to give ethyl 2-(4-((5-bromo-4-(4-methoxyphenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetate (3.38 g, 86%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (d, J = 6.8 Hz, 1H), 7.79 (d, J = 6.8 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 3.0 Hz, 1H), 6.67 (dd, J = 3.0, 8.9 Hz, 1H), 6.59 (d, J = 8.8 Hz, 1H), 5.20 (s, 2H), 4.51 (s, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 2.22 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H). MS m/z 492.2 $[M + H]^+$.

Methyl 2-(4-((5-Bromo-4-(4-methoxyphenyl)oxazol-2-yl)methoxy)-2-methylphenoxy)acetate (28, X = O). The compound was prepared following the synthetic procedure to the thiazole **28** (X = S). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 (d, J = 9.8 Hz, 2H), 6.90 (d, J = 9.8 Hz, 2H), 6.80 (d, J = 3.2 Hz, 1H), 6.71 (m, 1H), 6.58 (m, 1H), 4.99 (s, 2H), 4.52 (s, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 2.20 (s, 3H). MS m/z 463.0 $[M + H]^+$.

2-(4-((5-(4-Chlorophenyl)-4-(4-methoxyphenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (29a). A mixture of {4-[5-bromo-4-(4-methoxyphenyl)thiazol-2-ylmethoxy]-2-methylphenoxy}acetic acid methyl ester (30.0 mg, 0.064 mmol), 4-chlorophenylboronic acid (20 mg, 0.13 mmol), tetrakis(triphenylphosphine)palladium (8 mg, 0.006 mmol), K_2CO_3 (36 mg, 0.26 mmol), 1,4-dioxane (1 mL), EtOH (0.4 mL), and H_2O (0.2 mL) in a sealed vial was heated to 120 °C and stirred at this temperature overnight. The reaction mixture was cooled to room temperature. Then THF (1 mL) and LiOH (200 μL of 1 N) were added and the mixture was stirred at room temperature for 2 h. The reaction mixture was acidified with 1 M HCl, extracted with EtOAc (10 mL), dried ($MgSO_4$), filtered, concentrated, and purified on reverse phase HPLC to afford **29a** (15 mg, 45%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 3.2, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H), 4.63 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS m/z 496.3 $[M + H]^+$. HRMS calcd $C_{26}H_{23}ClNO_5S$ $[M + H]^+$ 496.0980; found 496.0984.

Compounds **29b**−**ah** were prepared following the synthetic procedure of **29a** using the appropriate bromothiazole or bromooxazole intermediates and boronic acids.

2-(4-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (29b). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 3.0 Hz, 1H), 6.77 (d, J = 8.8 Hz, 2H), 6.71 (dd, J = 3.0, 8.9 Hz, 1H), 6.64 (d, J = 8.8 Hz, 1H), 5.26 (s, 2H), 4.56 (s, 2H), 3.74 (s, 3H), 2.21 (s, 3H). MS m/z 530.3 $[M + H]^+$. HRMS calcd $C_{27}H_{23}F_3NO_5S$ $[M + H]^+$ 530.1244; found 530.1244.

2-(4-((5-(3-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (29c). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 (s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 2.8 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 3.2, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 4.64 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS m/z 530.4 $[M + H]^+$. HRMS calcd $C_{27}H_{23}F_3NO_5S$ $[M + H]^+$ 530.1244; found 530.1241.

2-(4-((5-(2-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (29d). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.93 (dd, J = 1.6, 8.8 Hz, 1H), 7.85 (m, 1H), 7.74 (m, 1H), 7.56 (dd, J = 1.6, 8.0 Hz, 1H), 7.27 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 2.8 Hz, 1H), 6.88 (dd, J = 3.2, 8.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 1H), 5.43 (s, 2H), 4.65 (s, 2H), 3.71 (s, 3H), 2.19 (s, 3H). MS m/z 530.2 $[M + H]^+$. HRMS calcd $C_{27}H_{23}F_3NO_5S$ $[M + H]^+$ 530.1244; found 530.1243.

{4-[4-(4-Methoxyphenyl)-5-(4-trifluoromethoxyphenyl)thiazol-2-ylmethoxy]-2-methylphenoxy}acetic Acid (29e). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.1 Hz, 2H), 6.82 (d, J = 2.9 Hz, 1H), 6.76 (d, J = 8.8 Hz, 2H), 6.71 (dd, J = 2.8, 8.8 Hz, 1H), 6.63 (d, J = 8.9 Hz, 1H), 5.25 (s, 2H), 4.56 (s, 2H), 3.75 (s, 3H), 2.21 (s, 3H). MS m/z 530.2 $[M + H]^+$. HRMS calcd $C_{27}H_{23}F_3NO_6S$ $[M + H]^+$ 546.1193; found 546.1193.

2-(4-((4-(4-Methoxyphenyl)-5-(4-(trifluoromethylthio)phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (29f). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.57 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 2.4 Hz, 1H), 6.80 (d, J = 8.8 Hz, 2H), 6.76−6.54 (m, 2H), 5.25 (s, 2H), 4.53 (s, 2H), 3.70 (s, 3H), 2.16 (s, 3H). MS m/z 562.1 $[M + H]^+$. HRMS calcd $C_{27}H_{23}F_3NO_5S_2$ $[M + H]^+$ 562.0965; found 562.0963.

2-(4-((5-(6-Chloropyridin-3-yl)-4-(4-methoxyphenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (29g). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.40 (d, J = 2.4 Hz, 1H), 7.57 (dd, J = 2.4, 8.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 2.8 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.65 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS m/z 497.0 $[M + H]^+$. HRMS calcd $C_{25}H_{22}ClN_2O_5S$ $[M + H]^+$ 497.0933; found 497.0933.

2-(4-((5-(3-Chloro-4-methoxyphenyl)-4-(4-methoxyphenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (29h). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 2.4 Hz, 1H), 7.15 (dd, J = 2.0, 8.4 Hz, 1H), 6.89 (d, J = 2.8 Hz, 1H), 6.84 (m, 3H), 6.76 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.32 (s, 2H), 4.63 (s, 2H), 3.94 (s, 3H), 3.82 (s, 3H), 2.28 (s, 3H). MS m/z 526.3 $[M + H]^+$. HRMS calcd $C_{27}H_{25}ClNO_6S$ $[M + H]^+$ 526.1086; found 526.1085.

2-(4-((4-(4-Methoxyphenyl)-5-(4-propylphenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (29i). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28−7.05 (m, 6H), 6.82 (d, J = 2.8 Hz, 1H), 6.77−6.66 (m, 4H), 5.22 (s, 2H), 4.52 (s, 2H), 3.69 (s, 3H), 2.49 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.58−1.52 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H). MS m/z 504.2 $[M + H]^+$. HRMS calcd $C_{29}H_{30}NO_5S$ $[M + H]^+$ 504.1839; found 504.1839.

2-(4-((5-(4-*tert*-Butylphenyl)-4-(4-methoxyphenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (29j). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 2.4 Hz, 1H), 6.86

(d, J = 8.8 Hz, 2H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.44 (s, 2H), 4.63 (s, 2H), 3.83 (s, 3H), 2.28 (s, 3H), 1.31 (s, 9H). MS m/z 518.4 $[M + H]^+$. HRMS calcd $C_{30}H_{32}NO_5S$ $[M + H]^+$ 518.1996; found 518.1996.

2-(4-((5-(4-Biphenyl)-4-(4-methoxyphenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (29k). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (d, J = 7.6 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.41 (m, 7H), 6.91 (d, J = 2.8 Hz, 1H), 6.85 (d, J = 8.4 Hz, 2H), 6.79 (dd, J = 2.4, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.64 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H). MS m/z 538.4 $[M + H]^+$. HRMS calcd $C_{32}H_{28}NO_5S$ $[M + H]^+$ 538.1683; found 538.1684.

2-(4-((4-(4-Methoxyphenyl)-5-(naphthalen-1-yl)thiazol-2-yl)-methoxy)-2-methylphenoxy)acetic Acid (29l). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (m, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.48 (m, 3H), 7.40 (m, 1H), 7.33 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 2.8 Hz, 1H), 6.82 (dd, J = 2.8, 8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 6.64 (d, J = 8.9 Hz, 2H), 5.42 (s, 2H), 4.65 (s, 2H), 3.69 (s, 3H), 2.30 (s, 3H). MS m/z 512.1 $[M + H]^+$. HRMS calcd $C_{30}H_{26}NO_5S$ $[M + H]^+$ 512.1527; found 512.1526.

2-(4-((4-(4-Methoxyphenyl)-5-(naphthalen-3-yl)thiazol-2-yl)-methoxy)-2-methylphenoxy)acetic Acid (29m). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (s, 1H), 7.76 (m, 3H), 7.49 (m, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.34 (dd, J = 1.6, 8.4 Hz, 1H), 6.92 (d, J = 2.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.39 (s, 2H), 4.64 (s, 2H), 3.80 (s, 3H), 2.29 (s, 3H). MS m/z 512.1 $[M + H]^+$. HRMS calcd $C_{30}H_{26}NO_5S$ $[M + H]^+$ 512.1527; found 512.1528.

2-(4-((4-(4-Methoxyphenyl)-5-(quinolin-3-yl)thiazol-2-yl)-methoxy)-2-methylphenoxy)acetic Acid (29n). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.86 (d, J = 2.0 Hz, 1H), 8.24 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.77 (m, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.63 (s, 2H), 3.77 (s, 3H), 2.27 (s, 3H). MS m/z 513.0 $[M + H]^+$. HRMS calcd $C_{29}H_{25}N_2O_5S$ $[M + H]^+$ 513.1479; found 513.1471.

2-(4-((5-(Benzofuran-2-yl)-4-(4-methoxyphenyl)thiazol-2-yl)-methoxy)-2-methylphenoxy)acetic Acid (29o). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.48 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 7.6 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 3.2 Hz, 1H), 6.73 (dd, J = 3.2, 8.8 Hz, 1H), 6.72 (s, 1H), 6.64 (d, J = 8.8 Hz, 1H), 5.28 (s, 2H), 4.48 (s, 2H), 3.71 (s, 3H), 2.10 (s, 3H). MS m/z 502.3 $[M + H]^+$. HRMS calcd $C_{28}H_{24}NO_6S$ $[M + H]^+$ 502.1319; found 502.1313.

2-(4-((4-(4-Methoxyphenyl)-5-styrylthiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (29p). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.54 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 7.6 Hz, 2H), 7.24 (m, 2H), 7.20 (m, 2H), 7.02 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 16.0 Hz, 1H), 6.88 (d, J = 2.8 Hz, 1H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.31 (s, 2H), 4.56 (s, 2H), 3.76 (s, 3H), 2.12 (s, 3H). MS m/z 488.4 $[M + H]^+$. HRMS calcd $C_{28}H_{26}NO_5S$ $[M + H]^+$ 488.1527; found 488.1521.

2-(4-((5-(4-Phenyl-3-(trifluoromethyl)phenyl)-4-(4-methoxyphenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (29q). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.59 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.34−7.30 (m, 5H), 7.25−7.21 (m, 3H), 6.85−6.82 (m, 3H), 6.77−6.68 (m, 2H), 5.26 (s, 2H), 4.53 (s, 2H), 3.71 (s, 3H), 2.17 (s, 3H). MS m/z 606.1 $[M + H]^+$. HRMS calcd $C_{33}H_{27}F_3NO_5S$ $[M + H]^+$ 606.1557; found 606.1558.

2-(4-((5-(4-Chlorophenyl)-4-(4-methoxyphenyl)oxazol-2-yl)-methoxy)-2-methylphenoxy)acetic Acid (29aa). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.49(d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.79−6.69 (m, 2H), 5.09 (s, 2H), 4.55 (s, 2H), 3.75 (s, 3H), 2.16 (s, 3H). MS m/z 480.1 $[M + H]^+$. HRMS calcd $C_{26}H_{23}ClNO_6$ $[M + H]^+$ 480.1209; found 480.1209.

2-(4-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-oxazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (29ab). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.67−7.59(m, 4H), 7.43 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.79−6.69 (m, 2H), 5.10 (s, 2H), 4.53 (s, 2H), 3.75 (s, 3H), 2.17 (s, 3H). MS m/z 514.1 $[M + H]^+$. HRMS calcd $C_{27}H_{23}F_3NO_6$ $[M + H]^+$ 514.1472; found 514.1470.

{4-[4-(4-Methoxyphenyl)-5-(3-trifluoromethylphenyl)oxazol-2-ylmethoxy]-2-methylphenoxy}acetic Acid (29ac). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 (s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.42 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 2.8, 1H), 6.78 (dd, J = 3.0 Hz, 9.0 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.09 (s, 2H), 4.52 (s, 2H), 3.74 (s, 3H), 2.16 (s, 3H). MS m/z 514.1 $[M + H]^+$. HRMS calcd $C_{27}H_{23}F_3NO_6$ $[M + H]^+$ 514.1472; found 514.1470.

2-(4-((4-(4-Methoxyphenyl)-5-(4-(trifluoromethoxy)phenyl)-oxazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (29ad). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.59 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 9.2 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.79−6.68 (m, 2H), 5.08 (s, 2H), 4.53 (s, 2H), 3.75 (s, 3H), 2.17 (s, 3H). MS m/z 530.0 $[M + H]^+$. HRMS calcd $C_{27}H_{23}F_3NO_7$ $[M + H]^+$ 530.1421; found 530.1416.

2-(4-((4-(4-Methoxyphenyl)-5-(4-propylphenyl)oxazol-2-yl)-methoxy)-2-methylphenoxy)acetic Acid (29ae). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.41−7.35 (m, 4H), 7.11 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 2.4 Hz, 1H), 6.76−6.65 (m, 2H), 5.03 (s, 2H), 4.51 (s, 2H), 3.72 (s, 3H), 2.50 (t, J = 7.6 Hz, 2H), 2.15 (s, 3H), 1.59−1.50 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H). MS m/z 488.2 $[M + H]^+$. HRMS calcd $C_{29}H_{30}NO_6$ $[M + H]^+$ 488.2068; found 488.2068.

{4-[5-Biphenyl-4-yl-4-(4-methoxyphenyl)oxazol-2-ylmethoxy]-2-methylphenoxy}acetic Acid (29af). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.63−7.57 (m, 6H), 7.49−7.47 (m, 2H), 7.38 (t, J = 7.4 Hz, 2H), 7.28 (t, J = 7.6 Hz, 1H), 6.93−6.91 (m, 2H), 6.87 (d, J = 2.8 Hz, 1H), 6.79−6.69 (m, 2H), 5.11 (s, 2H), 4.54 (s, 2H), 3.75 (s, 3H), 2.17 (s, 3H). MS m/z 522.2 $[M + H]^+$. HRMS calcd $C_{32}H_{28}NO_6$ $[M + H]^+$ 522.1911; found 522.1910.

2-(4-((4-(4-Methoxyphenyl)-5-(quinolin-3-yl)oxazol-2-yl)-methoxy)-2-methylphenoxy)acetic Acid (29ag). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.94(s, 1H), 8.61 (s, 1H), 8.01−7.95 (m, 2H), 7.80−7.63 (m, 2H), 7.53 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 3.2 Hz, 1H), 6.83−6.70 (m, 2H), 5.17 (s, 2H), 4.56 (s, 2H), 3.76 (s, 3H), 2.17 (s, 3H). MS m/z 497.2 $[M + H]^+$. HRMS calcd $C_{29}H_{25}N_2O_6$ $[M + H]^+$ 497.1707; found 497.1703.

2-(4-((5-(3,4-Dichlorophenyl)-4-(4-methoxyphenyl)oxazol-2-yl)-methoxy)-2-methylphenoxy)acetic Acid (29ah). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.65 (d, J = 2.0 Hz, 1H), 7.52−7.40 (m, 4H), 6.95 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 2.8 Hz, 1H), 6.80−6.69 (m, 2H), 5.11 (s, 2H), 4.54 (s, 2H), 3.76 (s, 3H), 2.16 (s, 3H). MS m/z 514.1 $[M + H]^+$. HRMS calcd $C_{26}H_{22}Cl_2NO_6$ $[M + H]^+$ 514.0819; found 514.0820.

General Procedures to Intermediate 30. Method A: X = S, Exemplified by 2-Methyl-5-(4-(trifluoromethoxy)phenyl)thiazole. Ethyl ethynyl ether (6.0 g, 85.6 mmol) was dissolved in THF (100 mL) at 0 °C. Then borane−tetrahydronfuran complex (1 M in THF, 28.5 mL, 28.5 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 2 h at room temperature. The resulting solution was added to a mixture of 1-iodo-4-trifluoromethoxybenzene (20.5 g, 71.33 mmol), triphenylphosphine (598 mg, 2.28 mmol), palladium(II) acetate (128 mg, 0.57 mmol), and sodium hydroxide (8.5 g, 214 mmol) in THF (200 mL). The reaction mixture was heated to reflux for 15 h, then cooled, diluted with EtOAc (1000 mL), washed with saturated $NaHCO_3$, brine, and H_2O. The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica, EtOAc/hexane gradient) to give 1-(2-ethoxyvinyl)-4-trifluoromethoxybenzene as a white solid (4.6 g, 28%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 12.8 Hz, 1H), 5.98 (d, J = 13.2 Hz, 1H), 4.08 (q, J = 7.0 Hz, 2H), 1.50 (t, J = 7.0 Hz, 3H). MS m/z 233.1 $[M + H]^+$.

1-(2-Ethoxyvinyl)-4-trifluoromethoxybenzene (4.6 g, 19.8 mmol) was dissolved in a mixture of EtOH/THF, 4:1 (150 mL). Then NBS (3.52 g, 19.8 mmol) was added. The mixture was stirred at room temperature for 2 h, then concentrated and purified by flash column chromatography (silica, EtOAc/hexane gradient) to give 1-(1-bromo-2,2-diethoxyethyl)-4-trifluoromethoxybenzene **31** as a white solid (5.9 g, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 4.95 (d, J = 6.4 Hz, 1H), 4.83 (d, J = 6.0 Hz, 1H), 3.84−3.77 (m, 1H), 3.71−3.61 (m, 2H), 3.50−3.43 (m, 1H), 1.29 (t, J = 7.0 Hz, 3H), 1.09 (t, J = 7.0 Hz, 3H). MS m/z 277.0 $[M - Br]^+$.

1-(1-Bromo-2,2-diethoxyethyl)-4-trifluoromethoxybenzene **31** (1.00 g, 2.80 mmol) was dissolved in $CHCl_3$ (3 mL). Then Ac_2O (286 mg, 2.80 mmol), $NaOAc \cdot 3H_2O$ (228 mg, 1.68 mmol), and AcCl (153 mg, 1.97 mmol) were added successively and the mixture was stirred at 50 °C for 5 h. The mixture was diluted with DCM (50 mL) and washed with saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give crude bromo-(4-trifluoromethoxyphenyl)-acetaldehyde (793 mg, 100%). This aldehyde (793 mg, 2.80 mmol) and thioacetamide (211 mg, 2.80 mmol) were dissolved in EtOH (8 mL), and the mixture was stirred at 90 °C for 15 h. The solution was diluted with EtOAc (50 mL) and washed with saturated $NaHCO_3$ (30 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica, EtOAc/hexane gradient) to give 2-methyl-5-(4-trifluoromethoxyphenyl)thiazole as a white solid (442 mg, 61%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 (s, 1H), 7.46 (m, 2H), 7.18 (m, 2H), 2.68 (s, 3H). MS m/z 260.0 $[M + H]^+$.

Method B: X = S, Exemplified by 5-(4-Biphenyl)-2-methylthiazole. 4-Iodobiphenyl (40.0 g, 171.6 mmol) was dissolved in DMF (800 mL). Then 2-methylthiazole (8.50 g, 85.5 mmol), triphenylphosphine (3.6 g, 13.73 mmol), cesium carbonate (55.9 g, 171.6 mmol), and palladium(II) acetate (3.01 g, 13.7 mmol) were added successively. The reaction mixture was stirred at 140 °C for 24 h, then filtered through Celite 545. The filter was washed with saturated aqueous K_2CO_3 and EtOAc. The filtrate was diluted with EtOAc and washed with saturated $NaHCO_3$, H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica, EtOAc/hexane gradient) to give 5-biphenyl-4-yl-2-methylthiazole (7.62 g, 18%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (s, 1H), 7.51−7.56 (m, 5H), 4.28−7.41 (m, 4H), 2.69 (s, 3H). MS m/z 252.0 $[M + H]^+$.

Method C: X = O, Exemplified by 5-(4-trifluoromethoxyphenyl)-2-methyloxazole. 1,1,1,3,3,3-Hexamethyldisilazane (8.93 g, 55.35 mmol) was dissolved in THF (50 mL) and cooled to 0 °C. *n*-Butyllithium (2.5 M in hexanes, 21.55 mL, 53.88 mmol) was added dropwise, and the resulting solution was stirred for 10 min at 0 °C. Then it was cooled to −78 °C. 4′-(Trifluoromethoxy)acetophenone (10.0 g, 48.98 mmol) in THF (64 mL) was added dropwise over 30 min and stirred for another 45 min at −78 °C. Then 2,2,2-trifluoroethyltrifluoroacetate (11.43 g, 58.78 mmol) was added rapidly. The mixture was stirred for 20 min at −78 °C. Then it was poured into 5% HCl (200 mL) and extracted with diethyl ether (2 × 100 mL). The organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in MeCN (50 mL), and then H_2O (0.88 mL, 48.98 mmol) and triethylamine (7.43 g, 73.47 mmol) were added. Freshly prepared methanesulfonyl azide (8.98 g, 73.47 mmol) in MeCN (16 mL) was added over 30 min at room temperature. [Methanesulfonyl azide was prepared from the following procedure: Methanesulfonyl chloride (8.85 g, 73.47 mmol) was dissolved in acetone (50 mL). Then sodium azide (7.56 g, 116.0 mmol) was added over 30 min, and the mixture was stirred for 1.5 h at room temperature. The solution was filtered, washed with acetone, and concentrated.] The reaction mixture was stirred for 1 h and then concentrated. The residue was diluted with diethyl ether (200 mL), washed with 10% NaOH (3 × 50 mL), then with brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica, EtOAc/hexane gradient) to give 2-diazo-4′-trifluoromethoxyacetophenone **32** (7.93 g, 70%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 5.89 (s, 1H). MS m/z 203.0 $[M + H - N_2]^+$.

Aluminum chloride (19.6 g, 146.8 mmol) was added in portions into anhydrous MeCN (200 mL) under argon. 2-Diazo-4′-trifluoromethoxyacetophenone **32** (16.89 g, 73.4 mmol) in MeCN (200 mL) was added dropwise over 30 min at room temperature under nitrogen. The mixture was stirred for 45 min at room temperature. Then it was poured into ditheyl ether (500 mL). The solution was carefully quenched with 0.2 N HCl, then basified with 1 N NaOH to pH 9−10 and extracted with diethyl ether (3 × 200 mL). The combined organic layers were washed with H_2O (100 mL) and brine (50 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica, EtOAc/hexane gradient) to give 2-methyl-5-(4-trifluoromethoxyphenyl)oxazole (14.0 g, 78%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H), 7.13 (s, 1H), 2.46 (s, 3H). MS m/z 244.0 $[M + H]^+$.

General Procedure to Intermediate 33 (X = S), Exemplified by 4-Bromo-2-(bromomethyl)-5-(4-(trifluoromethoxy)phenyl)thiazole. 2-Methyl-5-(4-(trifluoromethoxy)phenyl)thiazole (1.0 g, 3.68 mmol) was dissolved in $CHCl_3$ (100 mL). Then bromine (245 μL, 4.77 mmol) was added and the mixture was stirred at room temperature for 15 h. The solution was diluted with DCM (100 mL) and washed with saturated $NaHCO_3$ (50 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give crude product, which was purified by flash column chromatography (diethyl ether/hexane gradient) to give 4-bromo-2-methyl-5-(4-(trifluoromethoxy)phenyl)thiazole as a colorless oil (730 mg, 56%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (m, 2H), 7.21 (m, 2H), 2.67 (s, 3H). MS m/z 337.90 $[M + H]^+$.

N-Bromosuccinimide (504 mg, 2.83 mmol) was added to a solution of 4-bromo-2-methyl-5-(4-trifluoromethoxyphenyl)-thiazole (730 mg, 2.16 mmol) in carbon tetrachloride (50 mL). The above solution was stirred at 75 °C for 18 h. The solution was diluted with DCM (50 mL) and washed with saturated $NaHCO_3$ (50 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (diethyl ether/hexane gradient) to give 4-bromo(2-bromomethyl)-5-(4-(trifluoromethoxy)phenyl)thiazole (486 mg, 54%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (m, 2H), 7.23 (m, 2H), 4.63 (s, 2H). MS m/z 416.8 $[M + H]^+$.

4-Bromo-2-bromomethyl-5-(4-trifluoromethoxyphenyl)oxazole (33, X = O). The compound was prepared following the synthetic procedure to thiazole **33** (X = S). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (d, 2H, J = 8.6 Hz), 7.25 (d, 2H, J = 8.6 Hz), 4.41 (s, 3H). MS m/z 399.8 $[M + H]^+$.

General Procedure to Intermediate 34 (X = S), Exemplified by Methyl 2-(4-((4-Bromo-5-(4-(trifluoromethoxy)phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetate. A mixture of 4-bromo-(2-bromomethyl)-5-(4-(trifluoromethoxy)phenyl)thiazole (486 mg, 1.16 mmol), **50** (227 mg, 1.16 mmol), and Cs_2CO_3 (756 mg, 2.32 mmol) in MeCN (20 mL) was stirred at room temperature for 2 h. The mixture was filtered, then concentrated and purified by flash column chromatography (silica, EtOAc/hexane gradient) to give methyl 2-(4-((4-bromo-5-(4-(trifluoromethoxy)phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetate (586 mg, 95%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (m, 2H), 7.28 (m, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.74(dd, J = 3.2 Hz, J = 8.8 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 5.28 (s, 2H), 4.61 (s, 2H), 3.80 (s, 3H), 2.29 (s, 3H). MS m/z 532.0 $[M + H]^+$.

{4-[4-Bromo-5-(4-trifluoromethoxyphenyl)oxazol-2-ylmethoxy]-2-methylphenoxy}acetic Acid Methyl Ester (34, X = O). The compound was prepared following the synthetic procedure to thiazole **34** (X = S). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 3.2 Hz, 1H),

6.70 (m, 1H), 6.59 (m, 1H), 5.03 (s, 2H), 4.53 (s, 2H), 3.72 (s, 3H), 3.72 (s, 3H), 2.21 (s, 3H). MS m/z 516.9 $[M + H]^+$.

2-(4-((4-(4-(Trifluoromethyl)phenyl)-5-(4-(trifluoromethoxy)-phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35a). A mixture of methyl 2-(4-((4-bromo-5-(4-(trifluoromethoxy)-phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetate **34** (30.0 mg, 0.056 mmol), 4-trifluoromethylphenylboronic acid (20 mg, 0.10 mmol), tetrakis(triphenylphosphine)palladium (7.9 mg, 0.006 mmol), K_2CO_3 (35.8 mg, 0.26 mmol), 1,4-dioxane (1 mL), EtOH (0.4 mL), and H_2O (0.2 mL) in a sealed vial was heated to 120 °C and stirred at this temperature overnight. The reaction mixture was cooled to room temperature. Then THF (1 mL) and LiOH (200 μL of 1 N) were added and stirred at room temperature for 2 h. The mixture was acidified with 1 M HCl, extracted with EtOAc (10 mL), dried ($MgSO_4$), filtered, concentrated, and purified on reverse phase HPLC to afford **35a** (27.7 mg, 85%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 3.2 Hz, 1H), 6.79 (dd, J = 3.2, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.65 (s, 2H), 2.30 (s, 3H). MS m/z 584.0 $[M + H]^+$. HRMS calcd $C_{27}H_{20}F_6NO_5S$ $[M + H]^+$ 584.0961; found 584.0961.

Compounds **35b**−**ad** were prepared following the synthetic procedure of **35a** using the appropriate bromothiazole or bromooxazole intermediates and boronic acids.

2-(4-((4-(4-Biphenyl)-5-(4-(trifluoromethoxy)phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35b). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 (d, J = 7.2 Hz, 2H), 7.56 (s, 4H), 7.44 (t, J = 7.2 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 2.8 Hz, 1H), 6.79 (dd, J = 2.8, 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.64 (s, 2H), 2.30 (s, 3H). MS m/z 592.4 $[M + H]^+$. HRMS calcd $C_{32}H_{25}F_3NO_5S$ $[M + H]^+$ 592.1401; found 592.1401.

2-(4-((4-(3-Fluoro-4-methoxyphenyl)-5-(4-(trifluoromethoxy)-phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35c). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 (d, J = 8.4 Hz, 2H), 7.21 (m, 3H), 6.89 (m, 2H), 6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.65 (s, 2H), 3.90 (s, 3H), 2.29 (s, 3H). MS m/z 564.3 $[M + H]^+$. HRMS calcd $C_{27}H_{22}F_4NO_6S$ $[M + H]^+$ 564.1099; found 564.1099.

2-(4-((4-(3-Methoxyphenyl)-5-(4-(trifluoromethoxy)phenyl)-thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35d). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.18−7.11 (m, 3H), 6.93−6.88 (m, 2H), 6.82 (d, J = 2.8 Hz, 1H), 6.80−6.66 (m, 3H), 5.25 (s, 2H), 4.52 (s, 2H), 3.57 (s, 3H), 2.16 (s, 3H). MS m/z 546.1 $[M + H]^+$. HRMS calcd $C_{27}H_{23}F_3NO_6S$ $[M + H]^+$ 546.1193; found 546.1194.

2-(4-((4-(4-Ethoxyphenyl)-5-(4-(trifluoromethoxy)phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35e). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.36−7.16 (m, 6H), 6.85 (d, J = 2.8 Hz, 1H), 6.79−6.68 (m, 4H), 5.26 (s, 2H), 4.54 (s, 2H), 3.97−3.91 (m, 2H), 2.16 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H). MS m/z 560.2 $[M + H]^+$. HRMS calcd $C_{28}H_{25}F_3NO_6S$ $[M + H]^+$ 560.1349; found 560.1348.

2-(4-((4-(4-Propoxyphenyl)-5-(4-(trifluoromethoxy)phenyl)-thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35f). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 2.8 Hz, 1H), 6.79−6.67 (m, 4H), 5.24 (s, 2H), 4.53 (s, 2H), 3.84 (t, J = 6.4 Hz, 2H), 2.16 (s, 3H), 1.72−1.67 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). MS m/z 574.1 $[M + H]^+$. HRMS calcd $C_{29}H_{27}F_3NO_6S$ $[M + H]^+$ 574.1506; found 574.1507.

2-(4-((4-(4-Butoxyphenyl)-5-(4-(trifluoromethoxy)phenyl)-thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35g). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 2.8 Hz, 1H), 6.79−6.67 (m, 4H), 5.24 (s, 2H), 4.53 (s, 2H), 3.88 (t, J = 6.4 Hz, 2H), 2.16 (s, 3H), 1.68−1.64 (m, 2H), 1.44−1.38 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H). MS m/z 588.1 $[M + H]^+$. HRMS calcd $C_{30}H_{29}F_3NO_6S$ $[M + H]^+$ 588.1662; found 588.1665.

{4-[4-(4-Isopropoxyphenyl)-5-(4-trifluoromethoxyphenyl)thiazol-2-ylmethoxy]-2-methylphenoxy}acetic Acid (35h). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 2.8 Hz, 1H), 6.78−6.67 (m, 4H), 5.24 (s, 2H), 4.53 (s, 2H), 4.51 (m, 1H), 2.16 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H). MS m/z 574.2 $[M + H]^+$. HRMS calcd $C_{29}H_{27}F_3NO_6S$ $[M + H]^+$ 574.1506; found 574.1505.

2-(4-((4-(4-*sec*-Butoxyphenyl)-5-(4-(trifluoromethoxy)phenyl)-thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35i). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 2.8 Hz, 1H), 6.77−6.67 (m, 4H), 5.24 (s, 2H), 4.52 (s, 2H), 4.30−4.25 (m, 1H), 2.16 (s, 3H), 1.62−1.52 (m, 2H), 1.18 (d, J = 6.0 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H). MS m/z 588.1 $[M + H]^+$. HRMS calcd $C_{30}H_{29}F_3NO_6S$ $[M + H]^+$ 588.1662; found 588.1664.

2-(4-((4-(4-Isobutoxyphenyl)-5-(4-(trifluoromethoxy)phenyl)-thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35j). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 2.8 Hz, 1H), 6.80−6.66 (m, 4H), 5.24 (s, 2H), 4.49 (s, 2H), 3.66 (d, J = 6.4 Hz, 2H), 2.19 (s, 3H), 2.01−1.91 (m, 1H), 0.94 (s, 3H), 0.93 (s, 3H). MS m/z 588.1 $[M + H]^+$. HRMS calcd $C_{30}H_{29}F_3NO_6S$ $[M + H]^+$ 588.1662; found 588.1663.

2-(4-((4-(4-(Cyclopentyloxy)phenyl)-5-(4-(trifluoromethoxy)-phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35k). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.38 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 2.8 Hz, 1H), 6.79−6.69 (m, 4H), 5.27 (s, 2H), 4.73 (m, 1H), 4.54 (s, 2H), 2.16 (s, 3H), 1.86−1.54 (m, 8H). MS m/z 600.1 $[M + H]^+$. HRMS calcd $C_{31}H_{29}F_3NO_6S$ $[M + H]^+$ 600.1662; found 600.1664.

2-(4-((4-(Benzo[*d*][1,3]dioxol-5-yl)-5-(4-(trifluoromethoxy)-phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35l). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.94 (m, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.77 (m, 2H), 6.70 (d, J = 8.8 Hz, 1H), 5.97 (s, 2H), 5.33 (s, 2H), 4.64 (s, 2H), 2.29 (s, 3H). MS m/z 560.3 $[M + H]^+$. HRMS calcd $C_{27}H_{21}F_3NO_7S$ $[M + H]^+$ 560.0985; found 560.0984.

2-(4-((4-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-(4-(trifluoromethoxy)phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35m). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 2.0 Hz, 1H), 6.90 (m, 2H), 6.77 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 8.8 Hz, 1H), 5.31 (s, 2H), 4.63 (s, 2H), 4.26 (m, 4H), 2.28 (s, 3H). MS m/z 574.1 $[M + H]^+$. HRMS calcd $C_{28}H_{23}F_3NO_7S$ $[M + H]^+$ 574.1142; found 574.1138.

2-(4-((4-(3,4-Dihydro-2*H*-benzo[*b*][1,4]dioxepin-8-yl)-5-(4-(trifluoromethoxy)phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)-acetic Acid (35n). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.34 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 8.97 (d, J = 2.0 Hz, 2H), 6.90−6.77 (m, 3H), 6.75−6.67 (m, 2H), 5.24 (s, 2H), 4.53 (s, 2H), 4.09−4.02 (q, 4H), 2.16 (s, 3H), 2.08−2.03 (m, 2H). MS m/z 588.1 $[M + H]^+$. HRMS calcd $C_{29}H_{25}F_3NO_7S$ $[M + H]^+$ 588.1299; found 588.1299.

2-(4-((4-(4-(Diethylamino)phenyl)-5-(4-(trifluoromethoxy)-phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35o). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.50 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.14 (bs, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.76−6.67 (m, 2H), 5.26 (s, 2H), 4.53 (s, 2H), 3.51 (q, J = 7.2 Hz, 4H), 2.16 (s, 3H), 1.05 (t, J = 7.0 Hz, 6H). MS m/z 587.2 $[M + H]^+$. HRMS calcd $C_{30}H_{30}F_3N_2O_5S$ $[M + H]^+$ 587.1822; found 587.1820.

2-(4-((4-(4-(Pyrrolidin-1-yl)phenyl)-5-(4-(trifluoromethoxy)-phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35p). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.33 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.81 (d, J = 2.8 Hz, 1H), 6.74−6.65 (m, 2H), 6.50 (d, J = 8.8 Hz, 2H), 5.21 (s, 2H), 4.52 (s, 2H), 3.21 (t, J = 5.4 Hz, 4H), 2.15 (s, 3H), 1.95−1.90

(m, 4H). MS m/z 585.2 $[M + H]^+$. HRMS calcd $C_{30}H_{28}F_3N_2O_5S$ $[M + H]^+$ 585.1666; found 585.1663.

2-(4-((4-(4-(Piperidin-1-yl)phenyl)-5-(4-(trifluoromethoxy)phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35q). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.51 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.76−6.67 (m, 2H), 5.27 (s, 2H), 4.54 (s, 2H), 3.42 (t, J = 5.4 Hz, 4H), 2.17 (s, 3H), 1.87−1.82 (m, 4H), 1.68−1.64 (m, 2H). MS m/z 599.2 $[M + H]^+$. HRMS calcd $C_{31}H_{30}F_3N_2O_5S$ $[M + H]^+$ 599.1822; found 599.1818.

2-(4-((4-(4-Morpholinophenyl)-5-(4-(trifluoromethoxy)phenyl)-thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35r). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.77 (dd, J = 2.8, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.33 (s, 2H), 4.63 (s, 2H), 3.93 (m, 4H), 3.27 (m, 4H), 2.28 (s, 3H). MS m/z 601.2 $[M + H]^+$. HRMS calcd $C_{30}H_{28}F_3N_2O_6S$ $[M + H]^+$ 601.1615; found 601.1615.

2-(4-((4-(4-(Methylsulfonamide)phenyl)-5-(4-(trifluoromethoxy)-phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35s). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.36−7.32 (m, 4H), 7.20 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.76−6.67 (m, 2H), 5.25 (s, 2H), 4.52 (s, 2H), 2.89 (s, 3H), 2.16 (s, 3H). MS m/z 609.1 $[M + H]^+$. HRMS calcd $C_{27}H_{24}F_3N_2O_7S_2$ $[M + H]^+$ 609.0972; found 609.0972.

2-(4-((4-(6-Benzo[d]oxazol-2(3*H*)-one)-5-(4-(trifluoromethoxy)-phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35t). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.64 (s, 1H), 8.13 (m, 2H), 7.49 (m, 2H), 7.33 (br s, 3H), 7.26 (d, J = 8.4 Hz, 1H), 7.03 (dd, J = 4.0, 8.0 Hz, 1H), 6.95 (s, 1H), 6.88 (m, 1H), 6.79 (dd, J = 3.2, 8.8 Hz, 1H), 5.41 (s, 2H), 4.63 (s, 2H), 2.30 (s, 3H). MS m/z 573.2 $[M + H]^+$. HRMS calcd $C_{27}H_{20}F_3N_2O_7S$ $[M + H]^+$ 573.0938; found 573.0936.

2-(4-((4-(4-(*N*,*N*-Dimethyl)benzamide)-5-(4-(trifluoromethoxy)-phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35u). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.48 (d, J = 8.4 Hz, 2H), 7.37−7.30 (m, 4H), 7.20 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.77−6.68 (m, 2H), 5.28 (s, 2H), 4.53 (s, 2H), 3.01 (s, 3H), 2.92 (s, 3H), 2.17 (s, 3H). MS m/z 587.1 $[M + H]^+$. HRMS calcd $C_{29}H_{26}F_3N_2O_6S$ $[M + H]^+$ 587.1458; found 587.1457.

2-(4-((4-(4-(*N*-Isopropyl-*N*-methyl)benzamide)-5-(4-(trifluoromethoxy)phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35v). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.52 (d, J = 8.0 Hz, 2H), 7.41−7.28 (m, 4H), 7.24 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 3.2 Hz, 1H), 6.82−6.73 (m, 2H), 5.32 (s, 2H), 4.58 (s, 2H), 3.95−3.86 (m, 1H), 2.89−2.88 (m, 3H), 2.22 (s, 3H), 1.25−1.12 (m, 6H). MS m/z 615.2 $[M + H]^+$. HRMS calcd $C_{31}H_{30}F_3N_2O_6S$ $[M + H]^+$ 615.1772; found 615.1772.

2-(4-((4-(4-((Piperidin-1-yl)methanone)phenyl)-5-(4-(trifluoromethoxy)phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35w). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.57 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 2.8 Hz, 1H), 6.86−6.77 (m, 2H), 5.37 (s, 2H), 4.63 (s, 2H), 3.70(bs, 2H), 3.39 (bs, 2H), 2.26 (s, 3H), 1.72−1.54 (m, 6H). MS m/z 627.1 $[M + H]^+$. HRMS calcd $C_{32}H_{30}F_3N_2O_6S$ $[M + H]^+$ 627.1772; found 627.1777.

2-(4-((4-(4-Isopropoxyphenyl)-5-(4-(trifluoromethoxy)phenyl)-oxazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35aa). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.69 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 3.2 Hz, 1H), 6.87−6.77 (m, 2H), 5.18 (s, 2H), 4.69 (m, 1H), 4.59 (s, 2H), 2.26 (s, 3H), 1.35 (d, J = 6.0 Hz, 6H). MS m/z 558.2 $[M + H]^+$. HRMS calcd $C_{29}H_{27}F_3NO_7$ $[M + H]^+$ 558.1734; found 558.1733.

2-(4-((4-(4-(Piperidin-1-yl)phenyl)-5-(4-(trifluoromethoxy)-phenyl)oxazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35ab). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.73−7.68 (m, 4H), 7.50 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 2.8 Hz, 1H), 6.88−6.77 (m, 2H), 5.20 (s, 2H), 4.63 (s, 2H), 3.56−3.53 (m, 4H), 2.26 (s, 3H), 1.98−1.75 (m, 6H). MS m/z 583.2 $[M + H]^+$. HRMS calcd $C_{31}H_{30}F_3N_2O_6$ $[M + H]^+$ 583.2051; found 583.2047.

2-(4-((4-(4-(Cyclopentyloxy)phenyl)-5-(4-(trifluoromethoxy)-phenyl)oxazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35ac). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.59 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.77−6.67 (m, 2H), 5.08 (s, 2H), 4.87−4.75 (m, 1H), 4.48 (s, 2H), 2.16 (s, 3H), 1.96−1.58 (m, 8H). MS m/z 584.1 $[M + H]^+$. HRMS calcd $C_{31}H_{29}F_3NO_7$ $[M + H]^+$ 584.1891; found 584.1887.

2-(4-((4-(4-(*N*-Isopropyl-*N*-methyl)benzamide)-5-(4-(trifluoromethoxy)phenyl)oxazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (35ad). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.61−7.58 (m, 4H), 7.40−7.31 (m, 2H), 7.25 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 3.2 Hz, 1H), 6.78−6.67 (m, 2H), 5.10 (s, 2H), 4.52 (s, 2H), 3.97−3.84 (m, 1H), 2.86−2.78 (m, 3H), 2.15 (s, 3H), 1.19−1.09 (m, 6H). MS m/z 599.2 $[M + H]^+$. HRMS calcd $C_{31}H_{30}F_3N_2O_7$ $[M + H]^+$ 599.1927; found 599.1928.

General Procedures to Intermediate 36. Method A: Nu = ROH, Exemplified by 2-Isopropoxy-5-bromopyridine. NaH (5.2 g, 130 mmol) was suspended in isopropanol (50 mL). The reaction mixture was stirred for 30 min at 60 °C. After the gas evolution ceased, 2-chloro-5-bromopyridine (10.0 g, 52 mmol) dissolved in isopropanol (100 mL) was added and the mixture was heated to reflux for 24 h. Then the solvent was removed in vacuo, and the residue was diluted with H_2O and extracted into EtOAc (2 × 40 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated to afford 2-isopropoxy-5-bromopyridine (8.4 g, 75%) as a light-brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10 (d, J = 2.5 Hz, 1H), 7.54 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.52 (d, J = 8.8 Hz, 1H), 5.17 (m, 1H), 1.26 (d, J = 6.2 Hz, 6H). MS m/z 215.9 $[M + H]^+$.

Method B: Nu = R_2NH, Exemplified by 5-Bromo-2-morpholinopyrimidine. Morpholine (5.4 mL, 62.4 mmol) was dissolved in MeCN (250 mL). K_2CO_3 (8.6 g, 62.4 mmol) was added, and the mixture was stirred at room temperature for 1 h. Then 2-chloro-5-bromopyrimidine (10.0 g, 52 mmol) was added, and the mixture was heated to reflux for 5 h. The reaction mixture was concentrated, and the residue was taken up in H_2O (100 mL) and extracted with EtOAc (2 × 100 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to afford 5-bromo-2-morpholinopyrimidine (10.1 g, 80%) as a light-brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.24 (s, 2H), 3.69 (m, 8H). MS m/z 243.9 $[M + H]^+$.

General Procedure to Intermediate 37, Exemplified by 2-Isopropoxy-5-pyridineboronic Acid. 2-Isopropoxy-5-bromopyridine (0.65 g, 3 mmol) was dissolved in diethyl ether (10 mL) and cooled to −78 °C under argon. *n*-Butyllithium (1.6 M in hexane, 2.81 mL, 4.5 mmol) was added dropwise, and the mixture was stirred at −78 °C for 2 h. Triisopropyl borate (1.72 mL, 7.5 mmol) was added, and the mixture was stirred for 2 h at −78 °C. The mixture was warmed to room temperature, quenched with H_2O (20 mL), and stirred overnight at room temperature. The diethyl ether was removed in vacuo, and the aqueous layer was adjusted to pH 10 (with 2 M NaOH) and washed with diethyl ether. Then the aqueous layer was adjusted to pH 3 (with 48% aq. HBr) and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to afford 2-isopropoxy-5-pyridineboronic acid (0.42 g, 77%) as a colorless glass. ^{1}H NMR could not be obtained. MS m/z 182.1 $[M + H]^+$.

Compounds **38a**−**ah** were prepared following the synthetic procedure of **35a** using the appropriate bromothiazole or bromooxazole intermediates and boronic acids.

2-(4-((4-(Pyridin-3-yl)-5-(4-(trifluoromethoxy)phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (38a). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.68 (s, 1H), 8.55 (d, J = 5.2 Hz, 1H), 8.11 (dd, J = 1.8 Hz, J = 8.2 Hz, 1H), 7.60−7.56 (m, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 2.8 Hz, 1H),

6.81−6.70 (m, 2H), 5.34 (s, 2H), 4.56 (s, 2H), 2.16 (s, 3H). MS m/z 516.9 $[M + H]^+$. HRMS calcd $C_{25}H_{20}F_3N_2O_5S$ $[M + H]^+$ 517.1040; found 517.1036.

2-(4-((4-(Pyrimidin-5-yl)-5-(4-(trifluoromethoxy)phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (38b). ^{1}H NMR (400 MHz, CD_3OD) δ = 9.24 (s, 1H), 8.98 (s, 2H), 7.71 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 2.8 Hz, 1H), 7.02−6.90 (m, 2H), 5.56 (s, 2H), 4.67 (s, 2H), 2.39 (s, 3H). MS m/z 518.1 $[M + H]^+$. HRMS calcd $C_{24}H_{19}F_3N_3O_5S$ $[M + H]^+$ 518.0992; found 518.0987.

{4-[4-(6-Methoxypyridin-3-yl)-5-(4-trifluoromethoxyphenyl)-thiazol-2-ylmethoxy]-2-methylphenoxy}acetic Acid (38c). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.13 (d, J = 2.0 Hz, 1H), 7.72 (dd, J = 2.4 Hz, J = 8.4 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.77−6.68 (m, 3H), 5.27 (s, 2H), 4.54 (s, 2H), 3.83 (s, 3H), 2.17 (s, 3H). MS m/z 547.1 $[M + H]^+$. HRMS calcd $C_{26}H_{22}F_3N_2O_6S$ $[M + H]^+$ 547.1145; found 547.1142.

2-(4-((4-(2-Methoxypyrimidin-5-yl)-5-(4-(trifluoromethoxy)-phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (38d). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.53 (s, 2H), 7.44 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.77−6.68 (m, 2H), 5.29 (s, 2H), 4.54 (s, 2H), 3.93 (s, 3H), 2.17 (s, 3H). MS m/z 548.1 $[M + H]^+$. HRMS calcd $C_{25}H_{21}F_3N_3O_6S$ $[M + H]^+$ 548.1098; found 548.1093.

2-(4-((4-(6-Isopropoxypyridin-3-yl)-5-(4-(trifluoromethoxy)-phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (38e). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.48 (m, 1H), 7.77 (m, 1H), 7.32−7.16 (m, 5H), 6.80−6.64 (m, 3H), 5.31 (m, 2H), 5.25 (s, 2H), 4.58 (s, 2H), 3.77 (m, 4H), 2.21 (s, 3H), 1.38 (d, J = 6.1 Hz, 6H). MS m/z 575.1 $[M + H]^+$. HRMS calcd $C_{28}H_{26}F_3N_2O_6S$ $[M + H]^+$ 575.1458; found 575.1452.

2-(4-((4-(2-Isopropoxypyrimidin-5-yl)-5-(4-(trifluoromethoxy)-phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (38f). MS m/z 576.1 $[M + H]^+$. HRMS calcd $C_{27}H_{25}F_3N_3O_6S$ $[M + H]^+$ 576.1411; found 576.1408.

2-(4-((4-(6-Morpholinopyridin-3-yl)-5-(4-(trifluoromethoxy)-phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (38g). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.39 (d, J = 2.1 Hz, 1H), 7.83 (m, 1H), 7.51−7.35 (m, 4H), 6.99−6.82 (m, 4H), 5.41 (s, 2H), 4.77 (s, 2H), 3.98 (m, 4H), 3.79 (m, 4H), 2.40 (s, 3H). MS m/z 602.2 $[M + H]^+$. HRMS calcd $C_{29}H_{26}F_3N_3O_6S$ $[M + H]^+$ 602.1567; found 602.1564.

2-(4-((4-(2-Morpholinopyrimidin-5-yl)-5-(4-(trifluoromethoxy)-phenyl)thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (38h). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.48 (s, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.89 (s, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.71 (d, J = 7.3 Hz, 1H), 5.32 (s, 2H), 4.64 (s, 2H), 3.82 (m, 4H), 3.78 (m, 4H), 2.29 (s, 3H). MS m/z 603.3 $[M + H]^+$. HRMS calcd $C_{28}H_{26}F_3N_4O_6S$ $[M + H]^+$ 603.1520; found 603.1517.

2-(4-((4-(Pyridin-3-yl)-5-(4-(trifluoromethoxy)phenyl)oxazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (38aa). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.89 (bs, 1H), 8.69 (bs, 1H), 8.13 (d, J = 7.6 Hz, 1H), 7.81 (d, J = 8.8 Hz, 2H), 7.61−7.52 (m, 3H), 7.05 (d, J = 2.0 Hz, 1H), 6.99−6.88 (m, 2H), 5.33 (s, 2H), 4.73 (s, 2H), 2.33 (s, 3H). MS m/z 501.1 $[M + H]^+$. HRMS calcd $C_{25}H_{20}F_3N_2O_6$ $[M + H]^+$ 501.1268; found 501.1270.

2-(4-((4-(Pyrimidin-5-yl)-5-(4-(trifluoromethoxy)phenyl)oxazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (38ab). ^{1}H NMR (400 MHz, CD_3OD) δ = 9.09 (s, 1H), 8.92 (s, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 2.4 Hz, 1H), 6.81−6.70 (m, 2H), 5.17 (s, 2H), 4.55 (s, 2H), 2.16 (s, 3H). MS m/z 502.1 $[M + H]^+$. HRMS calcd $C_{24}H_{19}F_3N_3O_6$ $[M + H]^+$ 502.1221; found 502.1212.

2-(4-((4-(6-Methoxypyridin-3-yl)-5-(4-(trifluoromethoxy)-phenyl)oxazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (38ac). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.28 (d, J = 2.4 Hz, 1H), 7.79 (dd, J = 2.4 Hz, J = 8.8 Hz, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.81−6.68 (m, 3H), 5.11 (s, 2H), 4.54 (s, 2H), 3.85 (s, 3H), 2.16 (s, 3H). MS m/z 531.1 $[M + H]^+$. HRMS calcd $C_{26}H_{22}F_3N_2O_7$ $[M + H]^+$ 531.1374; found 531.1373.

2-(4-((4-(2-Methoxypyrimidin-5-yl)-5-(4-(trifluoromethoxy)-phenyl)oxazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (38ad). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.66 (s, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.77−6.66 (m, 2H), 5.11 (s, 2H), 4.53 (s, 2H), 3.96 (s, 3H), 2.15 (s, 3H). MS m/z 532.1 $[M + H]^+$. HRMS calcd $C_{25}H_{21}F_3N_3O_7$ $[M + H]^+$ 532.1326; found 532.1322.

{4-[4-(6-Isopropoxypyridin-3-yl)-5-(4-trifluoromethoxyphenyl)-oxazol-2-ylmethoxy]-2-methylphenoxy}acetic Acid (38ae). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.36 (d, J = 2.4 Hz, 1H), 7.90 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 7.70 (d, J = 9.2 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 3.2 Hz, 1H), 6.88−6.77 (m, 3H), 5.28 (m, 1H), 5.20 (s, 2H), 4.63 (s, 2H), 2.26 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H). MS m/z 558.9 $[M + H]^+$. HRMS calcd $C_{28}H_{26}F_3N_2O_7$ $[M + H]^+$ 559.1687; found 559.1681.

2-(4-((4-(2-Isopropoxypyrimidin-5-yl)-5-(4-(trifluoromethoxy)-phenyl)oxazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (38af). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.75 (s, 2H), 7.96 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 6.90−6.68 (m, 3H), 5.32 (m, 1H), 5.16 (s, 2H), 4.64 (s, 2H), 2.28 (s, 3H), 1.42 (d, J = 6.2 Hz, 6H). MS m/z 560.2 $[M + H]^+$. HRMS calcd $C_{27}H_{25}F_3N_3O_7$ $[M + H]^+$ 560.1639; found 560.1635.

2-(4-((4-(6-Morpholinopyridin-3-yl)-5-(4-(trifluoromethoxy)-phenyl)oxazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (38ag). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.36 (s, 1H), 7.37 (dd, J = 2.2 Hz, J = 9.0 Hz, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 6.91−6.68 (m, 3H), 5.15 (s, 2H), 4.64 (s, 2H), 3.89 (m, 4H), 3.72 (m, 4H), 2.26 (s, 3H). MS m/z 586.3 $[M + H]^+$. HRMS calcd $C_{29}H_{27}F_3N_3O_7$ $[M + H]^+$ 586.1796; found 586.1791.

2-(4-((4-(2-Morpholinopyrimidin-5-yl)-5-(4-(trifluoromethoxy)-phenyl)oxazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (38ah). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (s, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.00 (d, J = 8.3 Hz, 2H), 6.64−6.43 (m, 3H), 4.90 (s, 2H), 4.38 (s, 2H), 3.61 (m, 4H), 3.55 (m, 4H), 2.02 (s, 3H). MS m/z 587.2 $[M + H]^+$. HRMS calcd $C_{28}H_{26}F_3N_4O_7$ $[M + H]^+$ 587.1748; found 587.1747.

2-Bromomethyl-4-(4-methoxyphenyl)-5-(4-trifluoromethylphenyl)thiazole (39). 2-Bromo-1-(4-methoxyphenyl)ethanone (25.0 g, 109 mmol) and thioacetamide (9.0 g, 120 mmol) were dissolved in EtOH (60 mL) and heated to reflux for 2 h. The mixture was concentrated to give crude 4-(4-methoxyphenyl)-2-methylthiazole, which was dissolved in DCM (300 mL). Bromine (6.20 mL, 120 mmol) was added, and the mixture was heated at 40 °C for 3 h. The mixture was diluted with saturated $NaHCO_3$ (100 mL), extracted into DCM, and washed with brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give 5-bromo-4-(4-methoxyphenyl)-2-methylthiazole (31.0 g, quant). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 3.26 (s, 3H). MS m/z 283.9 $[M + H]^+$.

5-Bromo-4-(4-methoxyphenyl)-2-methylthiazole (4 g, 14.1 mmol), 4-trifluoromethylphenylboronic acid (3.2 g, 16.9 mmol), and sodium carbonate (4.5 g, 42.3 mmol) were dissolved in a mixture of H_2O (12.6 mL), EtOH (9.3 mL), and 1,2-dimethoxyethane (37.8 mL) in a sealed tube. $Pd(PPh_3)_4$ (490 mg, 0.42 mmol) was added, and the mixture was subjected to microwave irradiation (170 °C, 10 min). Then the mixture was diluted with H_2O (50 mL), extracted into EtOAc (200 mL), and washed with brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica, EtOAc/hexane gradient) to afford 4-(4-methoxyphenyl)-2-methyl-5-(4-trifluoromethylphenyl)thiazole (3.66 g, 74%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 2.77 (s, 3H). MS m/z 350.0 $[M + H]^+$.

4-(4-Methoxyphenyl)-2-methyl-5-(4-trifluoromethylphenyl)-thiazole (3.66 g, 10.5 mmol) and *N*-bromosuccinimide (2.05 g, 11.5 mmol) were dissolved in carbon tetrachloride (60 mL) and heated to 50 °C. Azo-bis-isobutyronitrile (172 mg, 1.0 mmol) was dissolved in carbon tetrachloride (10 mL) and added dropwise to the reaction mixture. Then it was heated to 60 °C for 16 h. The reaction mixture was diluted with saturated $NaHCO_3$, extracted into DCM, and washed with brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (silica, EtOAc/hexane gradient) to afford **39** (2.6 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 4.69 (s, 2H), 3.74 (s, 3H). MS m/z 428.0 $[M + H]^+$.

2-(4-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-thiazol-2-yl)methoxy)phenoxy)acetic Acid (40a). Methyl 2-(4-hydroxyphenoxy)acetate (21 mg, 0.12 mmol) and 2-bromomethyl-4-(4-methoxyphenyl)-5-(4-trifluoromethylphenyl)-thiazole **39** (0.034 g, 0.079 mmol) were dissolved in MeCN (1.5 mL). Cesium carbonate (0.047 g, 0.14 mmol) was added, and the mixture was vigorously stirred at room temperature for 3 h. The reaction mixture was acidified with 1 N HCl (5 mL), then extracted with DCM, dried ($MgSO_4$), and concentrated to give the ester as an oil. The ester was dissolved in THF (3 mL), treated with 1 N LiOH (0.3 mL), and stirred at room temperature for 6 h. Then the reaction mixture was acidified with 1 N HCl (5 mL), extracted with EtOAc (10 mL), dried ($MgSO_4$), filtered, concentrated, and purified on reverse phase HPLC to afford **40a** (56 mg, 92%) as an off-white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 9.1 Hz, 2H), 6.89 (d, J = 9.1 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.35 (s, 2H), 4.62 (s, 2H), 3.83 (s, 3H). MS m/z 516.3 $[M + H]^+$. HRMS calcd $C_{26}H_{21}F_3NO_5S$ $[M + H]^+$ 516.1087; found 516.1086.

Compounds **40b**−**s** were prepared according to the procedure for **40a**, using the appropriate phenol or thiophenol headgroups.

2-(3-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-thiazol-2-yl)methoxy)phenoxy)acetic Acid (40b). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.0 Hz, 1H), 6.66 (dd, J = 2.8, 8.8 Hz, 1H), 6.60 (d, J = 8.8 Hz, 1H), 5.39 (s, 2H), 4.65 (s, 2H), 3.82 (s, 3H). MS m/z 516.3 $[M + H]^+$. HRMS calcd $C_{26}H_{21}F_3NO_5S$ $[M + H]^+$ 516.1087; found 516.1084.

2-(2-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-thiazol-2-yl)methoxy)phenoxy)acetic Acid (40c). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 7.10 (dd, J = 2.0 Hz, 8.8 Hz, 1H), 7.01 (m, 3H), 6.85 (d, J = 8.8 Hz, 2H), 5.49 (s, 2H), 4.71 (s, 2H), 3.81 (s, 3H). MS m/z 516.3 $[M + H]^+$. HRMS calcd $C_{26}H_{21}F_3NO_5S$ $[M + H]^+$ 516.1087; found 516.1083.

2-(4-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)thiazol-2-yl)methoxy)phenoxy)-2-methylpropanoic Acid (40d). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 6.92 (s, 4H), 6.84 (d, J = 8.8 Hz, 2H), 5.34 (s, 2H), 3.81 (s, 3H), 1.52 (s, 6H). MS m/z 544.4 $[M + H]^+$. HRMS calcd $C_{28}H_{25}F_3NO_5S$ $[M + H]^+$ 544.1401; found 544.1397.

2-Ethoxy-3-(4-(5-(4-(trifluoromethyl)phenyl)-4-(4-methoxyphenyl)thiazol-2-yl)methoxyphenyl)propanoic Acid (40e). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.42 (s, 2H), 4.08 (dd, J = 7.6, 4.4 Hz, 1H), 3.83 (s, 3H), 3.61 (m, 1H), 3.47 (m, 1H), 3.10 (dd, J = 14.4, 4.4 Hz, 1H), 2.98 (dd, J = 14.4, 7.6 Hz, 1H), 1.18 (t, J = 7.2 Hz, 3H). MS m/z 558.1 $[M + H]^+$. HRMS calcd $C_{29}H_{27}F_3NO_5S$ $[M + H]^+$ 558.1557; found 558.1555.

{4-[4-(4-Methoxyphenyl)-5-(4-trifluoromethylphenyl)thiazol-2-ylmethoxy]-2-propylphenoxy}acetic Acid (40f). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 3.0 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 6.79 (dd, J = 3.0, 9.0 Hz, 1H), 6.71 (d, J = 9.0 Hz, 1H), 5.37 (s, 2H), 4.63 (s, 2H), 3.82 (s, 3H), 2.63 (t, J = 7.6 Hz, 2H), 1.63 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H). MS m/z 558.2 $[M + H]^+$. HRMS calcd $C_{29}H_{27}F_3NO_5S$ $[M + H]^+$ 558.1557; found 558.1555.

2-(4-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-thiazol-2-yl)methoxy)-3-methylphenoxy)acetic Acid (40g). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.84 (m, 2H), 6.71 (dd, J = 3.2, 8.8 Hz, 1H), 5.36 (s, 2H), 4.63 (s, 2H), 3.82 (s, 3H), 2.31 (s, 3H). MS m/z 530.1 $[M + H]^+$. HRMS calcd $C_{27}H_{23}F_3NO_5S$ $[M + H]^+$ 530.1244; found 530.1243.

2-(4-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-thiazol-2-yl)methylthio)-2-methylphenoxy)acetic Acid (40h). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.05 (m, 4H), 6.58 (d, J = 8.8 Hz, 2H), 6.41 (d, J = 8.4 Hz, 1H), 4.41 (s, 2H), 4.16 (s, 2H), 3.56 (s, 3H), 2.01 (s, 3H). MS m/z 546.3 $[M + H]^+$. HRMS calcd $C_{27}H_{23}F_3NO_4S_2$ $[M + H]^+$ 546.1015; found 546.1017.

3-(4-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-thiazol-2-yl)methoxy)-2-methylphenyl)propanoic Acid (40i). ^{1}H NMR (400 MHz, CD_3CN) δ = 7.64 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 2.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 6.83 (dd, J = 2.8, 8.4 Hz, 1H), 5.36 (s, 2H), 3.78 (s, 3H), 2.83 (t, J = 7.2 Hz, 2H), 2.52 (t, J = 7.2 Hz, 2H), 2.29 (s, 3H). MS m/z 528.2 $[M + H]^+$. HRMS calcd $C_{28}H_{25}F_3NO_4S$ $[M + H]^+$ 528.1451; found 528.1451.

3-(4-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-thiazol-2-yl)methoxy)-2-(trifluoromethyl)phenyl)propanoic Acid (40j). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 7.34 (s, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.15 (dd, J = 8.4, 2.8 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 5.41 (s, 2H), 3.82 (s, 3H), 3.10 (t, J = 7.6 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H). MS m/z 568.1 $[M + H]^+$. HRMS calcd $C_{27}H_{20}F_6NO_4S$ $[M + H]^+$ 582.1169; found 582.1169.

2-(1-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-thiazol-2-yl)methoxy)naphthalen-4-yloxy)acetic Acid (40k). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (m, 1H), 8.27 (m, 1H), 7.59 (m, 4H), 7.48 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.6 Hz, 1H), 6.70 (d, J = 8.6 Hz, 1H), 5.51 (s, 2H), 4.83 (s, 2H), 3.83 (s, 3H). MS m/z 566.4 $[M + H]^+$. HRMS calcd $C_{30}H_{23}F_3NO_5S$ $[M + H]^+$ 566.1244; found 566.1243.

2-(2-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-thiazol-2-yl)methoxy)naphthalen-5-yl)acetic Acid (40l). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (d, J = 10.0 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.49 (d, J = 8.3 Hz, 2H), 7.36 (m, 5H), 7.23 (m, 3H), 6.79 (d, J = 8.8 Hz, 2H), 5.44 (s, 2H), 3.99 (s, 2H), 3.75 (s, 3H). MS m/z 550.2 $[M + H]^+$. HRMS calcd $C_{30}H_{23}F_3NO_4S$ $[M + H]^+$ 550.1295; found 550.1291.

2-(5-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-thiazol-2-yl)methoxy)-1*H*-indol-1-yl)acetic Acid (40m). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 7.18−6.91 (m, 4H), 6.79 (d, J = 8.8 Hz, 2H), 6.45 (d, J = 3.1 Hz, 2H), 5.36 (s, 2H), 4.81 (s, 2H), 3.76 (s, 3H). MS m/z 539.1 $[M + H]^+$. HRMS calcd $C_{28}H_{22}F_3N_2O_4S$ $[M + H]^+$ 539.1247; found 539.1246.

5-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)thiazol-2-yl)methoxy)benzofuran-2-carboxylic Acid (40n). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (s, 1H), 7.49 (d, J = 8.8 Hz, 1H),

7.44 (d, J = 7.6 Hz, 1H), 7.33 (m, 4H), 7.22 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 8.4 Hz, 2H), 5.79 (s, 2H), 3.90 (s, 3H). MS m/z 526.1 $[M + H]^+$. HRMS calcd $C_{27}H_{19}F_3NO_5S$ $[M + H]^+$ 526.0931; found 526.0924.

5-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)thiazol-2-yl)methoxy)-2,3-dihydrobenzofuran-2-carboxylic Acid (40o). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 6.4 Hz, 2H), 6.92−6.84 (m, 5H), 5.43 (s, 2H), 5.25 (dd, J = 6.4, 10.4 Hz, 1H), 3.83 (s, 3H), 3.62 (dd, J = 10.8, 16.0 Hz, 1H), 3.41 (dd, J = 5.6, 16.0 Hz, 1H). MS m/z 528.0 $[M + H]^+$. HRMS calcd $C_{27}H_{21}F_3NO_5S$ $[M + H]^+$ 528.1087; found 528.1082.

2-(4-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)thiazol-2-yl)methoxy)phenyl)acetic Acid (40p). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 10.0 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 5.40 (s, 2H), 3.82 (s, 3H), 3.62 (s, 2H). MS m/z 500.3 $[M + H]^+$. HRMS calcd $C_{26}H_{21}F_3NO_4S$ $[M + H]^+$ 500.1138; found 500.1135.

2-(4-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-thiazol-2-yl)methoxy)-2-methylphenyl)acetic Acid (40q). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.4 Hz, 1H), 6.90 (m, 1H), 6.85 (m, 3H), 5.40 (s, 2H), 3.82 (s, 3H), 3.64 (s, 2H), 1.32 (s, 3H). MS m/z 514.1 $[M + H]^+$. HRMS calcd $C_{27}H_{23}F_3NO_4S$ $[M + H]^+$ 514.1295; found 514.1294.

2-(4-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-thiazol-2-yl)methoxy)-3-chlorophenyl)acetic Acid (40r). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 2.0 Hz, 1H), 7.16 (dd, J = 2.0, 8.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 5.46 (s, 2H), 3.82 (s, 3H), 3.59 (s, 2H). MS m/z 534.3 $[M + H]^+$. HRMS calcd $C_{26}H_{20}ClF_3NO_4S$ $[M + H]^+$ 534.0749; found 534.0751.

2-(4-((5-(4-(Trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-thiazol-2-yl)methylthio)-3-chlorophenyl)acetic Acid (40s). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 (d, J = 8.0 Hz, 2H), 7.29 (m, 6H), 7.06 (dd, J = 1.6, 8.0 Hz, 1H), 6.76 (d, J = 8.8 Hz, 2H), 4.44 (s, 2H), 3.73 (s, 3H), 3.52 (s, 2H). MS m/z 550.3 $[M + H]^+$. HRMS calcd $C_{26}H_{20}ClF_3NO_3S_2$ $[M + H]^+$ 550.0520; found 550.0522.

The syntheses of compounds **41**−**47** in Table 7 are according to the general synthetic procedures described above, and analytical data for these compounds are listed below. Analytical data for entries **35h**, **35aa**, **35k**, **35ac**, **38c**, **38ac**, **38e**, **38ae**, **38f**, and **38ag** are listed above.

2-(4-((5-(4-(Trifluoromethyl)phenyl)-4-(4-isopropoxyphenyl)-thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (41). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 2.8 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.90 (dd, J = 2.8, 8.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 5.41 (s, 2H), 4.67 (m, 3H), 2.32 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H). MS m/z 558.2 $[M + H]^+$. HRMS calcd $C_{29}H_{27}F_3NO_5S$ $[M + H]^+$ 558.1557; found 558.1551.

2-(4-((4-(4-Isopropoxyphenyl)-5-(3-(trifluoromethoxy)phenyl)-thiazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (42). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.47 (t, J = 8.0 Hz, 1H), 7.39−7.34 (m, 3H), 7.26−7.24 (m, 1H), 7.17 (s, 1H), 6.94 (d, J = 3.2 Hz, 1H), 6.89−6.78 (m, 4H), 5.35 (s, 2H), 4.64 (s, 2H), 4.62 (m, 1H), 2.27 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H). MS m/z 574.2 $[M + H]^+$. HRMS calcd $C_{29}H_{27}F_3NO_6S$ $[M + H]^+$ 574.1506; found 574.1509.

2-(4-((4-(4-Isopropoxyphenyl)-5-(4-propylphenyl)thiazol-2-yl)-methoxy)-2-methylphenoxy)acetic Acid (43). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.26 (d, J = 8.8 Hz, 2H), 7.13−7.04 (m, 4H), 6.81 (d, J = 2.8 Hz, 1H), 6.74−6.66 (m, 2H), 5.21 (s, 2H), 4.52 (s, 2H), 4.51−4.46 (m, 1H), 2.49 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.57−1.51 (m, 2H), 1.21 (d, J = 6.0 Hz, 6H), 0.85 (t, J = 7.4 Hz, 3H). MS m/z 532.2 $[M + H]^+$. HRMS calcd $C_{31}H_{34}NO_5S$ $[M + H]^+$ 532.2152; found 532.2155.

2-(4-((4-(4-Isopropoxyphenyl)-5-(4-biphenyl)thiazol-2-yl)-methoxy)-2-methylphenoxy)acetic Acid (44). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.61−7.57 (m, 4H), 7.40−7.35 (m, 6H), 7.29 (t, J = 6.8 Hz, 1H), 6.88 (d, J = 2.8 Hz, 1H), 6.80−6.71 (m, 4H), 5.28 (s, 2H), 4.56 (s, 2H), 4.53 (m, 1H), 2.17 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H). MS m/z 566.2 $[M + H]^+$. HRMS calcd $C_{29}H_{27}F_3NO_6S$ $[M + H]^+$ 566.1996; found 566.1994.

2-(4-((4-(4-Morpholinophenyl)-5-(4-biphenyl)thiazol-2-yl)-methoxy)-2-methylphenoxy)acetic Acid (45). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 (d, J = 8.4 Hz, 2H), 7.47 (t, J = 8.4 Hz, 4H), 7.37 (t, J = 7.6 Hz, 2H), 7.30 (m, 3H), 7.04 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 2.8 Hz, 1H), 6.70 (dd, J = 2.8, 8.8 Hz, 1H), 6.61 (d, J = 8.8 Hz, 1H), 5.27 (s, 2H), 4.55 (s, 2H), 3.90 (m, 4H), 3.26 (m, 4H), 2.20 (s, 3H). MS m/z 593.2 $[M + H]^+$. HRMS calcd $C_{35}H_{33}N_2O_5S$ $[M + H]^+$ 593.2105; found 593.2103.

2-(4-((5-(4-Biphenyl)-4-(pyridin-3-yl)oxazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (46). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.89 (bs, 1H), 8.64 (bs, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.80−7.56 (m, 7H), 7.49 (t, J = 7.4 Hz, 2H), 7.40 (t, J = 7.0 Hz, 1H), 6.96 (d, J = 2.8 Hz, 1H), 6.91−6.79 (m, 2H), 5.25 (s, 2H), 4.64 (s, 2H), 2.24 (s, 3H). MS m/z 493.0 $[M + H]^+$. HRMS calcd $C_{30}H_{25}N_2O_6$ $[M + H]^+$ 493.1758; found 493.1755.

2-(4-((4-(2-Methoxypyrimidin-5-yl)-5-(4-propylphenyl)oxazol-2-yl)methoxy)-2-methylphenoxy)acetic Acid (47). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.66 (s, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.77−6.67 (m, 2H), 5.09 (s, 2H), 4.53 (s, 2H), 3.95 (s, 3H), 2.56 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.61−1.55 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H). MS m/z 490.2 $[M + H]^+$. HRMS calcd $C_{27}H_{28}N_3O_6$ $[M + H]^+$ 490.1973; found 490.1969.

Biology. Transactivation Reporter Gene Assay. GAL4-hPPARαLBD, GAL4-hPPARγLBD, and GAL4-hPPARδLBD constructs were as described previously. The reporter construct, pG5-Luc was purchased from Promega (catalog no. E2440) and contains five copies of GAL4 binding sites followed by a TATA box and the firefly luciferase gene. 293T cells were grown to 60−70% confluence prior to transfection in 10% FBS DMEM + 1% Antibiotic-Antimycotic. Briefly, cells were washed with PBS (pH 7.2) and trypsinized. The cells were subsequently resuspended in 5% charcoal−dextran treated FBS (Hyclone catalog no. SH30068.03) in DMEM medium. Cells were then transfected in suspension using 9 μL of Fugene6 + 3 μg of DNA (1:3 ratio of GAL4-hPPAR/pg5-Luc) per 1×10^6 cells. Then 5000 cells/well were plated in 384-well format. Following 6 h of incubation, cells were treated with compounds diluted to a 1× final concentration (final DMSO concentration was 1%). Plates were incubated for 18−20 h at 37 °C, after which the cells were lysed with Britelite reagent (Perkin-Elmer, catalog no. 6016979) diluted to 60% with distilled H_2O, and the plates were read on the CLIPR (Molecular Devices, Sunnyvale CA). Data were obtained in quadruplicate, two replicate data points from one transfection and two from another transfection performed on separate days. Data for each day were averaged and normalized to the DMSO control using Microsoft Excel. Coefficients of variation (CVs) were <15% across two plates within the same day. EC_{50} values were generated using Graphpad Prism, version 4, using the sigmoidal dose response with variable slope equation. The bottom was fit to a normalized value of 1 (DMSO control). The % efficacy was calculated on the basis of the highest normalized activity of GW501516 for the PPARδ assay, rosiglitazone for the PPARγ assay, or KRP-927 for the PPARα assay, which represented 100% efficacy in each case.

Fluorescence Resonance Energy Transfer (FRET) Assay. The binding of a ligand to a nuclear receptor induces a conformational change that leads to increased or decreased binding of transcriptional coactivator and/or corepressor molecules. A coactivator-dependent receptor ligand assay (CARLA), which measures PPAR ligand-dependent coactivator recruitment in

the TR_FRET format, was used to measure the binding of and activation by PPAR ligands to the human PPARα LBD, PPARγLBD, and PPARδ LBD. EC_{50} values were obtained as mean values ± SEM from three independent measurements and calculated with XLfit. The efficacy response is calculated relative to the "*y*-range" or efficacy response of GW501516 (set as 100%).

In Vivo Acute Dosing Induced Gene Assay. C57BL/6 male mice (age 8−9 weeks, Charles River Labs) were treated orally by gavage once daily with the compounds at 10 mg/kg or with vehicle (0.5% carboxymethylcellulose (CMC), 2% Tween-80) for 3 days. On the fourth day and 4 h after the last dose was administered, mice were euthanized. Samples of skeletal muscle (quadriceps), liver, and adipose tissues were collected from the five to six mice in each treatment group, rapidly frozen in liquid nitrogen and stored at −80 °C. Total RNA was isolated from the tissues, and SYBR Green quantitative real-time-PCR was performed on an ABI PRISM 7900HT sequence detection system (Applied Biosystems). For each sample, the quantity of the target gene and the endogenous reference GAPDH was determined to obtain a normalized target value. Data were analyzed using SDS 2.0 software (Applied Biosystems). The data are expressed as fold change ± SEM relative to the vehicle control.

Pharmacokinetic Studies. The 5- to 6-week-old male Balb/c mice were obtained from Jackson Laboratory (Bar Harbor, ME). The animal weights at the time of compound administration were 20−25 g. The test compounds were formulated in 0.5% CMC suspension and dosed orally at 10 mg/kg via gavage. Blood samples in mice (n = 3) were drawn serially at five sampling times within 24 h after dosing. Plasma concentrations of these compounds were quantified utilizing a liquid chromatography/mass spectrometry (LC/MS/MS) assay. Pharmacokinetic parameters were calculated by noncompartmental regression analysis using Winnonlin 4.0 software (Pharsight, Mountain View, CA).

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