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Discovery of LSZ102, a Potent, Orally Bioavailable Selective Estrogen Receptor Degrader (SERD) for the Treatment of Estrogen Receptor Positive Breast Cancer

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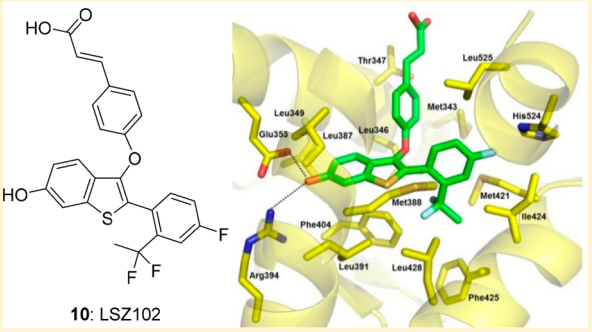
Supporting Information

ABSTRACT: In breast cancer, estrogen receptor alpha (ERα) positive cancer accounts for approximately 74% of all diagnoses, and in these settings, it is a primary driver of cell proliferation. Treatment of ERα positive breast cancer has long relied on endocrine therapies such as selective estrogen receptor modulators, aromatase inhibitors, and selective estrogen receptor degraders (SERDs). The steroid-based anti-estrogen fulvestrant (**5**), the only approved SERD, is effective in patients who have not previously been treated with endocrine therapy as well as in patients who have progressed after receiving other endocrine therapies. Its efficacy, however, may be limited due to its poor physicochemical properties. We describe the design and synthesis of a series of potent benzothiophene-containing compounds that exhibit oral bioavailability and preclinical activity as SERDs. This article culminates in the identification of LSZ102 (**10**), a compound in clinical development for the treatment of ERα positive breast cancer.



INTRODUCTION

Despite recent advances in early detection and treatment, breast cancer remains the second leading cause of cancer mortality among women in the United States, accounting for an estimated 40 290 deaths in 2015 alone.[1] Although it is often generalized as a single disease, breast cancer is classified in a clinical setting by its molecular subtype, arising from the characterization of three key biomarkers. The presence or absence of the receptors estrogen and progesterone leads to a hormone receptor classification (HR+/HR−), and increased or decreased levels of human epidermal growth factor receptor 2 (HER2) lead to a HER2 protein classification (HER2+/HER2−). Nearly 74% of breast cancers demonstrate high expression of estrogen receptor alpha (ERα), a nuclear hormone receptor directly implicated in the progression of HR+ cancers.[2] This ligand-inducible transcription factor binds physiological ligands such as 17β-estradiol and induces an activating conformational change in the receptor, leading to an increase or decrease in the expression of genes that contribute to breast cancer pathogenesis.[3]

In patients with ERα positive breast cancer, treatment has long relied on endocrine therapies such as tamoxifen (**1**, and its active metabolite **2**)[4] and anastrozole (**3**),[5] both of which prevent ligand-dependent activation of ER transcriptional activity (Figure 1). Tamoxifen (**1**), which until recently was the primary standard of care for such patients, functions as a selective estrogen receptor modulator (SERM), effectively blocking the binding of estrogens to the receptor and limiting its effects in breast tissue. Women treated with this therapy often respond

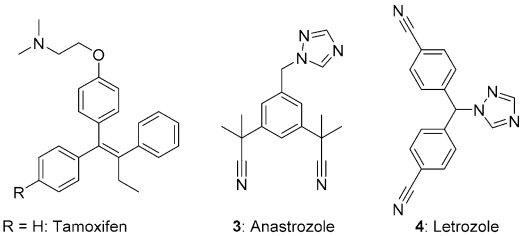


Figure 1. Structures of tamoxifen, its bioactive metabolite 4-hydroxytamoxifen, and aromatase inhibitors anastrazole and letrozole.

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positively,[3] but *de novo* and acquired resistance in these patients, ultimately leading to disease progression, remains a significant medical challenge. Although the specific mechanism through which ERα positive tumors develop resistance to tamoxifen is not fully understood,[6] aromatase inhibitors (AIs) such as letrozole (**4**),[7] in addition to their use as frontline therapies, have shown clinical efficacy in such refractory cancers.[8] In contrast to tamoxifen, aromatase inhibitors owe their activity to the reduction in the production of estrogens, more specifically by inhibiting the enzyme responsible for the key biosynthetic step in the formation of these mitogenic molecules.[9] Unfortunately, these inhibitors are also subject to therapeutic resistance and can eventually lead to disease relapse.[10] In such settings, selective estrogen receptor degraders (SERDs) distinguish themselves by their ability to induce receptor degradation, which may overcome mechanisms of resistance to AIs and SERMs. The only such degrader currently approved for the treatment of ER positive breast cancer is the SERD fulvestrant (**5**).[11,12]

This steroid-based anti-estrogen both binds and accelerates the degradation of the estrogen receptor by inducing a denaturing structural change within the receptor,[13] a mechanism found to be clinically effective in endocrine treated patients whose disease has progressed. Fulvestrant (**5**) efficacy may be limited, however, by its poor physicochemical properties. Due to poor oral bioavailability, fulvestrant is administered intramuscularly into the gluteal area in two 5 mL injections once monthly.[14] Although it is efficacious,[12] this dosing regimen does not appear sufficient to fully occupy the receptor.[15] It was with this shortcoming in mind that we sought to address the liabilities of fulvestrant by designing an orally available compound that retained the desirable degradative properties.

The nonsteroidal estrogen antagonist GW-5638 (**6**) and its more active metabolite GW-7604 (**7**), although designed to address the tissue-dependent antagonism observed with tamoxifen,[16] have also been found to induce receptor degradation, a property we sought to maintain in our efforts (Figure 2).[17] We speculated that it should be possible to combine a nonsteroidal core, such as the benzothiophene found in arzoxifene (**8**), with an appropriately selected side chain, such as the carboxylic acid moiety found in GW-7604 (**7**), and that doing so should allow for the preparation of a SERD with the desired orally available profile. It should be noted that a similar approach was undertaken in the identification of clinical candidate GDC-0810 (**9**),[18] although further development was ultimately halted.[19] Herein, we describe the design and synthesis of a series of potent benzothiophene-containing compounds that exhibit oral bioavailability and preclinical activity as SERDs. This article culminates in the identification of LSZ102 (**10**), a clinical agent currently in Phase I/Ib trials for the treatment of ERα positive breast cancer.

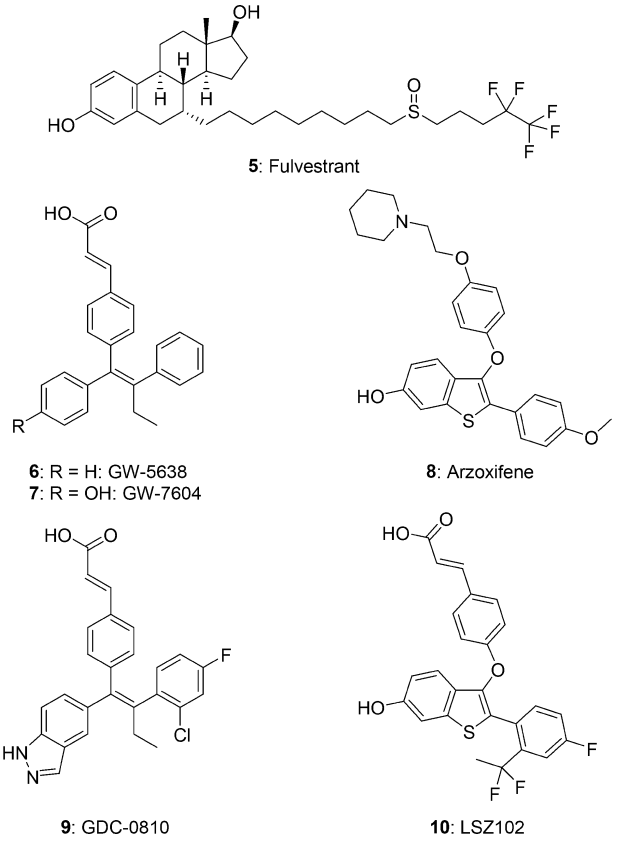

Figure 2. Structures of fulvestrant, GW-5638, active metabolite GW-7604, arzoxifene, GDC-0810, and **10** (LSZ102).

CHEMISTRY

The chemistry efforts toward LSZ102 (**10**) involved the preparation of a number of analogues accessed through varying synthetic routes, all of which are outlined in the following schemes and Supporting Information. The first of this series, ether linked compound **16** and its saturated analogue **17**, were prepared starting with commercially available 6-methoxy-2-(4-ethoxyphenyl)-benzo[*b*]thiophene (**11**) as outlined in Scheme 1. The route to both analogues began with selective bromination of the benzothiophene starting material by treatment of **11** with *N*-bromosuccinamide in THF to afford the desired brominated intermediate as the only observed product in 97% yield after an aqueous wash.[20] Oxidation of this intermediate to the corresponding sulfoxide **12**, necessary for the subsequent displacement reaction, was accomplished by H_2O_2 mediated oxidation in the presence of trifluoroacetic acid.[21] This process furnished **12** in 88% yield with no observed formation of the undesired, overoxidized sulphone intermediate, and it set the stage for the S_NAr reaction with 4-bromophenol. Thus, introduction of the phenyl ether functionality was achieved by treatment of **12** with 4-bromophenol in the presence of NaH (87% yield). The sulfoxide functionality, having served its purpose, was then removed via reduction with $LiAlH_4$ to afford bromo-benzothiophene **13** in 91% yield. Heck reaction with bromide **13** allowed for installation of the carboxylic acid functionality found in both **16** and **17**. Standard coupling conditions [Et_3N, $Pd(PPh_3)_2Cl_2$] with *tert*-butyl acrylate as the alkene partner afforded fully protected ether intermediate **15** in 63% yield. Global deprotection with BBr_3 at 0 °C gave the final cinnamic acid containing compound **16** (53% yield). Alternatively, intermediate **15** could also be subjected to reductive conditions (H_2, 10% Pd/C, quantitative) followed by BBr_3 mediated deprotection to afford the corresponding propanoic acid derivative **17** (31% yield).

Imidazole analogues **18** and **19** were obtained in a similar two-step Heck coupling sequence from bromide **13**. In this case, demethylation of **13** allowed for direct access to the final compounds via Heck coupling of the corresponding bromide **14** and bypassed the need for a final BBr_3 deprotection step. Thus, as outlined with the earlier analogues, treatment of **13** with BBr_3 at 0 °C afforded des-methyl **14**, which was subsequently treated with either 4-vinyl-1-methyl or *tert*-butyl 4-vinyl-1*H*-imidazole-1-carboxylate imidazole under standard coupling conditions [Et_3N, $Pd(PPh_3)_2Cl_2$] to afford both compounds in

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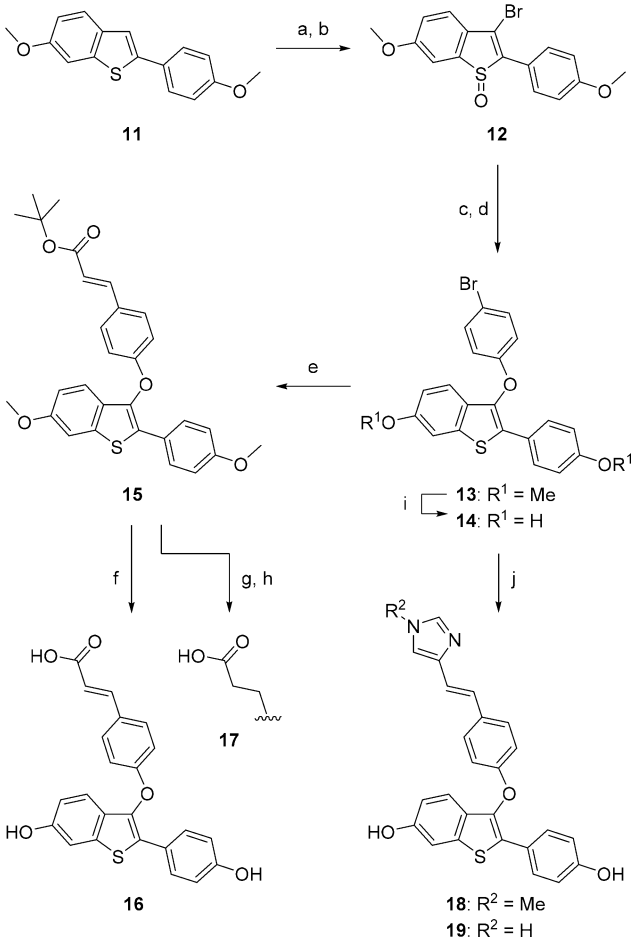
Scheme 1. Synthesis of Ether-Linked Benzothiophene Analogues[a]

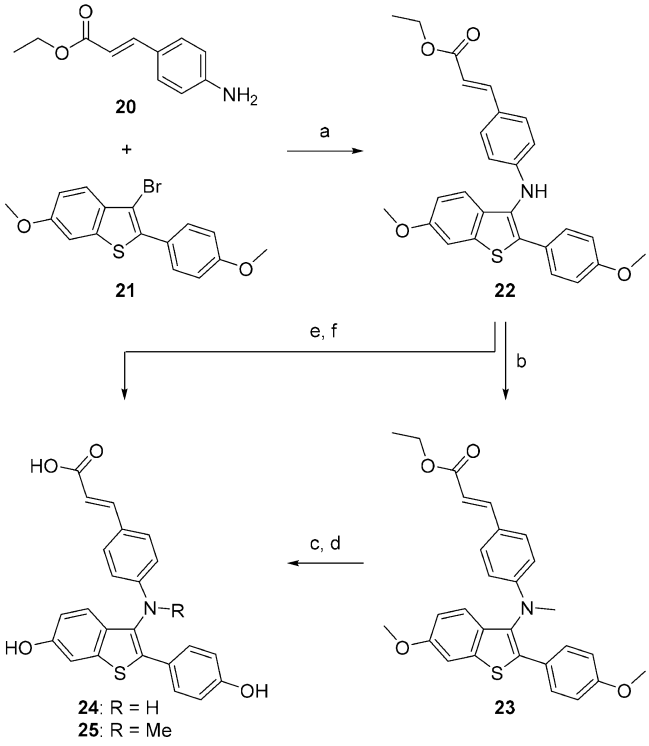


[a]Reagents and conditions: (a) *N*-bromosuccinimide, THF, 0 → 25 °C, 97%; (b) H_2O_2, TFA, CH_2Cl_2, 88%; (c) 4-bromophenol, NaH, DMF, 87%; (d) $LiAlH_4$, THF, 0 °C, 91%; (e) *tert*-butyl acrylate, Et_3N, $Pd(PPh_3)_2Cl_2$, DMF, 120 °C, 63%; (f) BBr_3 (1.0 M in heptane), CH_2Cl_2, 0 °C, 53%; (g) H_2 (balloon), 10% Pd/C, CH_2Cl_2/MeOH (4:1), 99%; (h) BBr_3 (1.0 M in heptane), CH_2Cl_2, 0 °C, 31%; (i) BBr_3 (1.0 M in heptane), CH_2Cl_2, 77%; (j) for **18**: 4-vinyl-1-methyl imidazole, Et_3N, $Pd(PPh_3)_2Cl_2$, DMF, 150 °C, 58%; for **19**: *tert*-butyl 4-vinyl-1*H*-imidazole-1-carboxylate, Et_3N, $Pd(PPh_3)_2Cl_2$, DMF, 150 °C, 15%. THF = tetrahydrofuran, TFA = trifluoroacetic acid, DMF = *N*, *N*-dimethylformamide.

modest yields (58 and 15% yield, respectively). It should be noted that in the case of **19**, the *tert*-butyl carbamate protected imidazole moiety was deprotected under the elevated temperatures of the Heck reaction.

The preparation of amine-linked compounds **24** and **25** differed slightly from that of the ether-linked compounds and is outlined in Scheme 2. Beginning with bromide intermediate **21**, an intermediate from Scheme 1, a Buchwald−Hartwig amination gave a modest yield of fully protected amine **22** (15% yield). Subjection of intermediate **22** to NaH in the presence of excess methyl iodide resulted in methylated amine **23** (36% yield) en route to final compound **25**. Two-step deprotection of this material was accomplished by treatment with BBr_3 to first remove the methyl ether groups, followed by LiOH mediated ester hydrolysis, which gave the methyl amine-linked compound **25** (21% overall yield). The desmethyl analogue **24** was also accessed through intermediate **22**; this time simple

Scheme 2. Synthesis of Amine-Linked Compounds 24 and 25[a]



[a]Reagents and conditions: (a) ethyl 4-aminocinnamate, K_3PO_4, RuPhos palladacycle, 1,4-dioxane, 120 °C, 15%; (b) methyl iodide, NaH, DMF, 36%; (c) BBr_3 (1.0 M in heptane), CH_2Cl_2, 0 °C; (d) LiOH, EtOH, 21% (two steps); (e) BBr_3 (1.0 M in heptane), CH_2Cl_2, 0 °C; (f) NaOH, EtOH, 22% (two steps). DMF = *N*, *N*-dimethylformamide.

treatment with BBr_3 at 0 °C was followed by treatment with NaOH to afford the final amine compound **24** (22% overall yield).

Ketone-linked analogue **29** similarly began with commercially available benzothiophene **11** (Scheme 3). Friedel−Crafts acylation of **11** with 4-bromobenzoyl chloride (**26**) gave bromide **27** in 96% yield and allowed for a very similar end-game sequence to be used for the preparation of **29**. As previously outlined with the ether analogues in Scheme 1, Heck coupling of **27** with *tert*-butyl acrylate afforded the fully protected keto intermediate **28**. Global deprotection with BBr_3 at 0 °C yielded the final cinnamic acid containing compound **29**.

The synthesis of the direct aryl-linked analogue **33** is outlined in Scheme 4. Beginning again with brominated benzothiophene intermediate **21**, Suzuki coupling with methyl 4-boronocinnamate **30** under standard conditions gave a 65% yield of methyl ester **31**. As before, two-step deprotection of this intermediate began by treatment of **31** with BBr_3 at 0 °C (46% yield) and was followed by LiOH promoted ester hydrolysis, which afforded **33** in 88% yield.

Amide analogues **35a−e** were prepared in one of two methods: either direct HATU mediated coupling with **16** (see Scheme 1 for synthesis) or by stepwise coupling with intermediate **34** followed by methyl ether cleavage (Scheme 5). In the case of compounds **35a−d**, treatment of **16** (or **34** in the case of **35b**) with the corresponding amine (methylamine, NH_4Cl, or ethanolamine) under standard HATU coupling conditions (HATU, DIEA) led directly to the final compounds.

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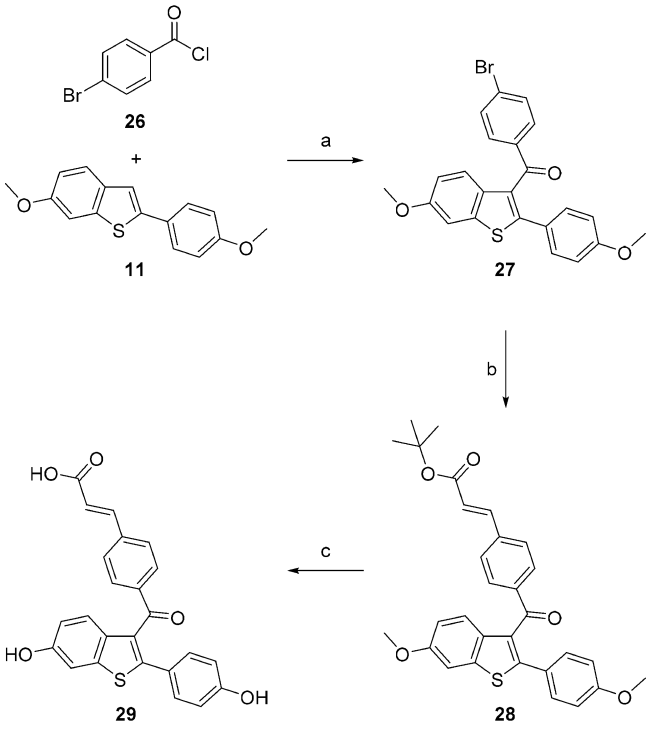
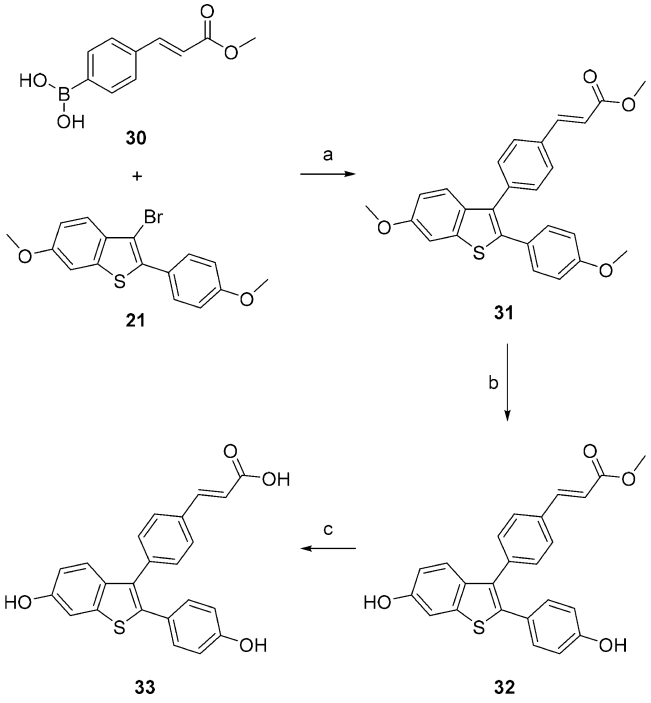
Scheme 3. Synthesis of Ketone-Linked Compound 29[a]



[a]Reagents and conditions: (a) $AlCl_3$, CH_2Cl_2, 0 → 25 °C, 96%; (b) *tert*-butyl acrylate, Et_3N, $Pd(PPh_3)_2Cl_2$, DMF, 120 °C, 88%; (c) BBr_3 (1.0 M in CH_2Cl_2), CH_2Cl_2, 0 °C, 42%. DMF = *N*,*N*-dimethylformamide.

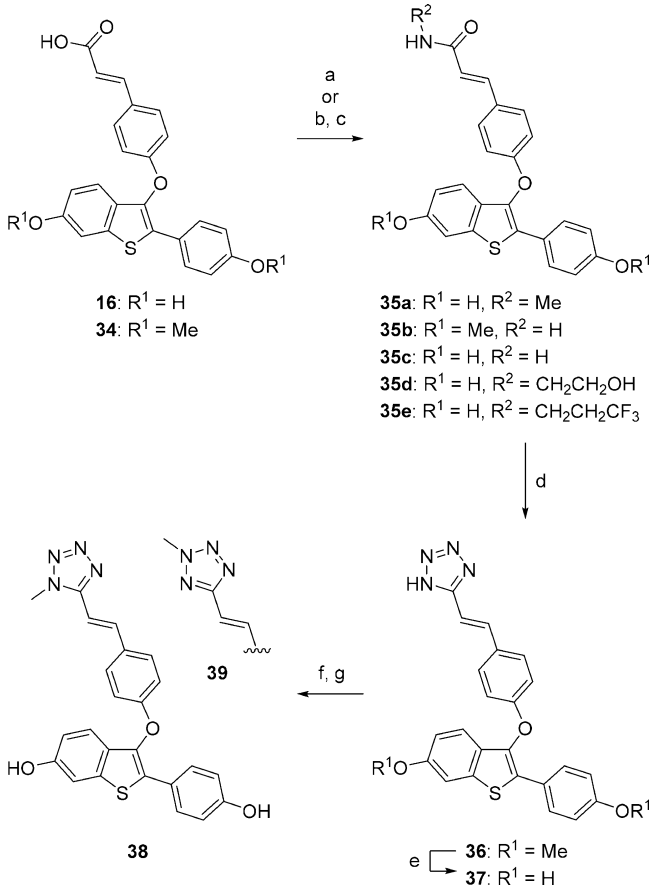
Scheme 4. Synthesis of Compound 33[a]



[a]Reagents and conditions: (a) Na_2CO_3, $Pd(PPh_3)_4$, dimethoxyethane/water (4:1), 100 °C, 65%; (b) BBr_3 (1.0 M in heptane), CH_2Cl_2, 0 °C, 46%; (c) LiOH (2.0 N aqueous), THF/water (4:1), 60 °C, 88%. THF = tetrahydrofuran

For compound **35e**, HATU mediated coupling afforded the methyl ether protected material, which was unmasked in the presence of BBr_3 to give the final compound (62% overall yield).

Scheme 5. Synthesis of Ether-Linked Compounds 35a−e and Tetrazoles 37−39[a]



[a]Reagents and conditions: (a) R^1 = H for **35a**, **35c**, and **35d** and R^1 = Me for **35b**, HATU, DIEA, DMF, 30−80%; (b) R^1 = Me for **35e**, HATU, DIEA, DMF, 72%; (c) BBr_3, CH_2Cl_2, 86%; (d) Bu_2SnO, $TMSN_3$, dimethoxyethane, 180 °C, 83%; (e) BBr_3, CH_2Cl_2, 40%; (f) methyl iodide, K_2CO_3, DMF, 91% (combined yield of both 1- and 2-methyl tetrazole); (g) BBr_3, CH_2Cl_2, 32−35%. HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, DIEA = *N*,*N*-diisopropylethylamine, DMF = *N*,*N*-dimethylformamide, Me = methyl, Bu = butyl, TMS = trimethysilyl.

In a similar fashion, tetrazole compounds **37**−**39** were prepared from primary amide intermediate **35b**. Reaction of **35b** with dibutyltin oxide and trimethylsilylazide resulted in conversion to the corresponding tetrazole **36** (83% yield), which was then either directly deprotected or further methylated. Deprotection of **36** with BBr_3, as outlined with previous benzothiophene analogues, yielded tetrazole **37** in 40% yield. Subjection of intermediate **36** to K_2CO_3 and excess methyl iodide led to a mixture of the 1- and 2-methyl substituted tetrazole intermediates, which were separated by column chromatography and subjected to BBr_3 to afford both **38** and **39** (35 and 32% yield, respectively).

The exploration of substituted phenyl linkers, outlined in Scheme 6, was accomplished in much the same manner as previously outlined (Scheme 1) with the variability arising from the phenol displacement partner. Sulfoxide **12** was once again employed as an activated bromide intermediate for displacement. Reaction of **12** with the appropriately substituted hydroxycinnamate (see Supporting Information for synthesis

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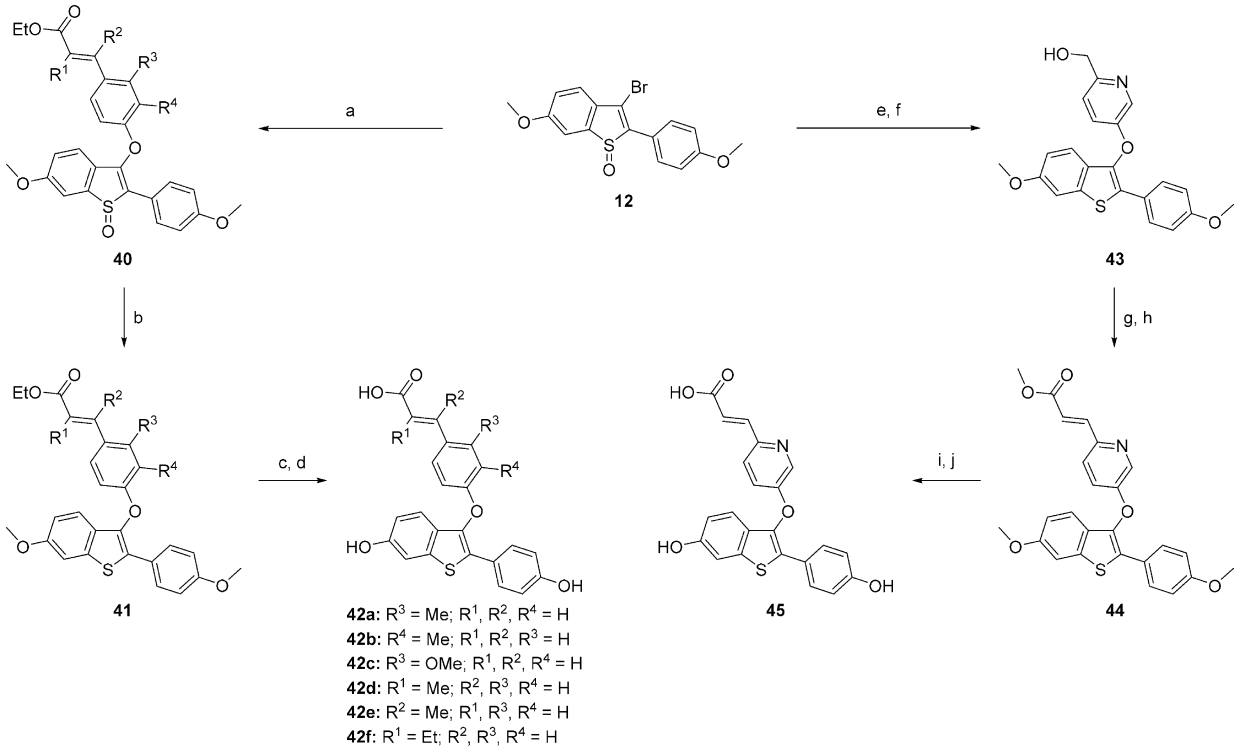
Scheme 6. Synthesis of Linker-Substituted Compounds[a]



[a]Reagents and conditions: (a) NaH, DMF, 43−86%; (b) TMSCl, PPh_3, THF, 75 °C, 65−98%; (c) BBr_3, CH_2Cl_2, 0 °C, 16−93% (**42d** was obtained directly from this step); (d) LiOH (2 N aqueous), EtOH, 41−80% (for **42a−c** and **42e−f**); (e) 5-hydroxypyridine-2-carboxylate, NaH, DMF, 80 °C, 52%; (f) $LiAlH_4$, THF, 0 °C, 93%; (g) MnO_2, CH_2Cl_2; (h) methyl 2-triphenylphosphoranylidene)acetate, CH_2Cl_2, 32% (2 steps); (i) BBr_3, CH_2Cl_2; (j) LiOH, THF/water (1:1), 9% (two steps). Ac = acetate, DMF = *N*,*N*-dimethylformamide, TMS = trimethylsilyl, Ph = phenyl, THF = tetrahydrofuran.

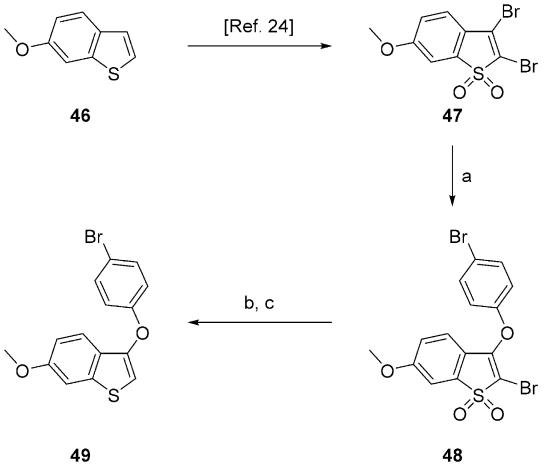
of hydroxycinnamates) under basic conditions (NaH) gave the corresponding ether intermediate **40** (43−86% yield). Reduction of the sulfoxide functionality was achieved by treatment with TMS-Cl/PPh_3, which led to the protected benzothiophene intermediate **41** (65−98% yield).[22,23] As before, stepwise deprotection of this intermediate (**41**) was accomplished by reaction with BBr_3 followed by basic hydrolysis (LiOH) to afford the final analogues **42a−f** in good to modest yields over the two steps.

Pyridine analogue **45** was accessed through a slightly modified route, but again, it began with bromide displacement using intermediate **12**. Reaction of benzothiophene **12** with 5-hydroxypyridine-2-carboxylate in the presence of NaH (52% yield) was followed by reduction of the carboxylate moiety with $LiAlH_4$ to give alcohol **43** (93% yield). MnO_2 promoted oxidation to the corresponding aldehyde, and subsequent Wittig olefination afforded protected cinnamate **44** (32% overall yield). Deprotection of the methyl ethers (BBr_3) followed by ester hydrolysis (LiOH) gave the final compound **45** in 9% overall yield.

An approach to 2-substituted benzothiophenes where diversity is introduced at the 2-position late in the synthesis was achieved by the synthesis of key intermediate **49**, outlined in Scheme 7. Synthesis of dibromo intermediate **47** was accomplished as previously reported in the literature.[24] Ether formation by addition of 4-bromophenol to **47** in the presence of Cs_2CO_3 afforded **48** in 98% yield. Reduction of the pendant thiophene bromide in **48** was achieved by addition of $NaBH_4$ (97% yield) and followed by DIBAL-H reduction of the dioxide functionality to afford the key benzothiophene intermediate **49** (84% yield).

As shown in Scheme 8, Heck coupling of intermediate **49** with either methyl acrylate or *tert*-butyl acrylate afforded the protected benzothiophene intermediates **50a** and **50b** (61−66% yield), which were poised for further functionalization. The final synthesis of analogues **53d−r** and **10** was accomplished

Scheme 7. Synthesis of Key Intermediate 49[a]



[a]Reagents and conditions: (a) 4-bromophenol, Cs_2CO_3, THF, 98%; (b) $NaBH_4$, DMSO/MeOH (3:1), 97%; (c) DIBAL-H, THF, 75 °C, 84%. THF = tetrahydrofuran, DMSO = dimethyl sulfoxide, DIBAL-H = diisobutylaluminum hydride.

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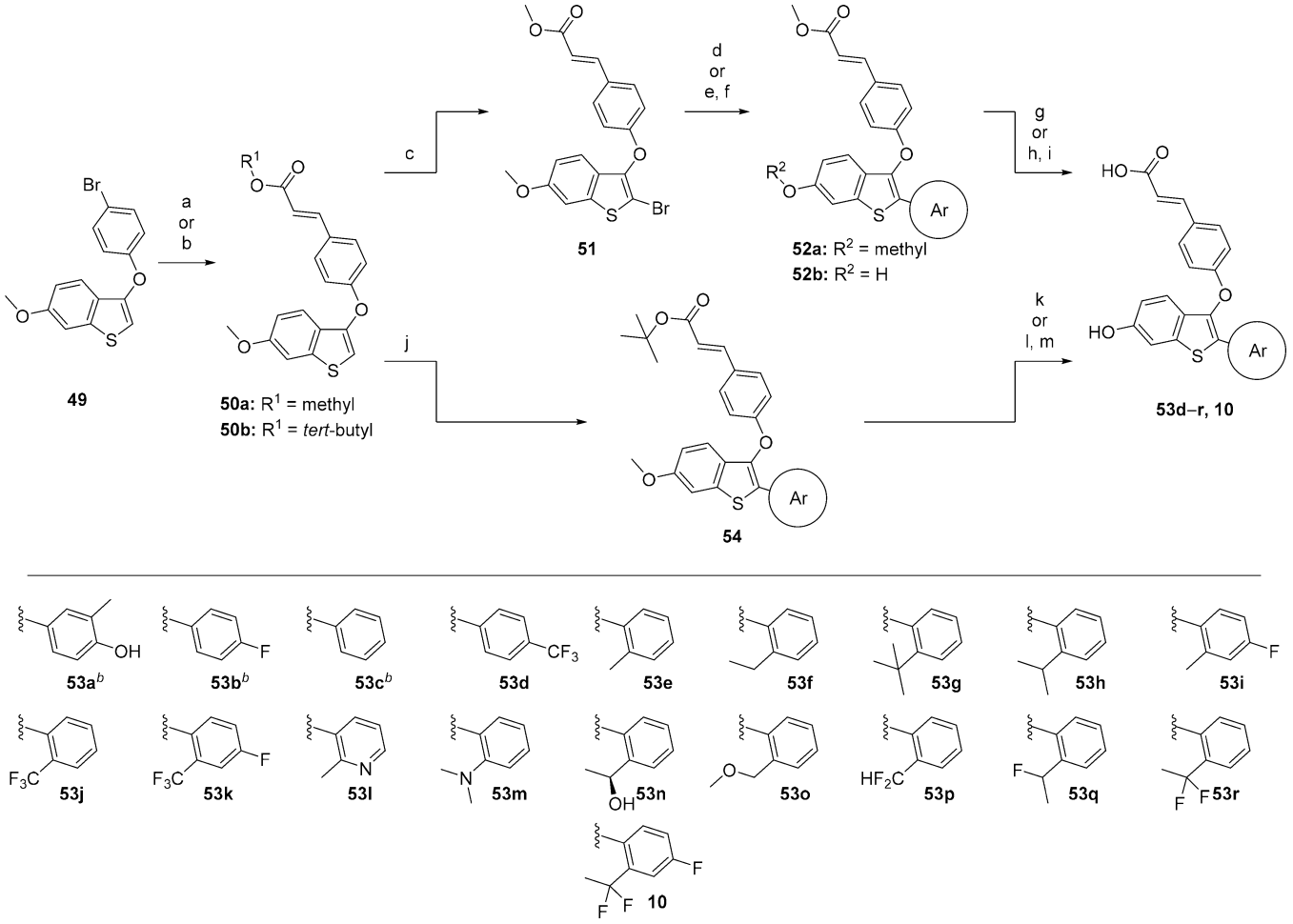
Scheme 8. Synthesis of Phenyl-Substituted Benzothiophene Analogues 53d−r and LSZ102 (10)[a]



[a]Reagents and conditions: (a) methyl acrylate, Et_3N, $Pd(PPh_3)_2Cl_2$, DMF, 120 °C, 61%; (b) *tert*-butyl acrylate, Et_3N, $Pd(PPh_3)_2Cl_2$, DMF, 120 °C, 66%; (c) *N*-bromosuccinimide, THF, 90%; (d) 2-(methoxymethyl)benzeneboronic acid, $Pd(dppf)Cl_2$, K_2CO_3, DME, 110 °C, 79% (only **53o** was made in this manner); (e) BBr_3 (1.0 M in heptane), CH_2Cl_2, 45%; (f) boronic acid/ester, $Pd(dppf)Cl_2$, K_2CO_3, DME, 110 °C, 42−87%; (g) LiOH, MeOH/water (3:1), 11−70%; (h) LiOH, MeOH, 55% (compound **53o** only); (i) thiophenol, K_2CO_3, *N*-methyl-2-pyrrolidone, 190 °C, 6% (compound **53o** only); (j) K_2CO_3, trimethylacetic acid, BrettPhos palladacycle (first generation), DMA, 150 °C, 39−97%; (k) BBr_3 (1.0 M in heptane), CH_2Cl_2, 0 °C, 20−66%; (l) thiophenol, K_2CO_3, *N*-methyl-2-pyrrolidone, 200 °C, 22−77%; (m) HCl (4 N in 1,4-dioxane), THF, 50 °C, 19−34%. [b]Compounds **53a−c** were synthesized in a similar sequence to Scheme 6; for full details see Supporting Information. DMF = *N*, *N*-dimethylformamide, THF = tetrahydrofuran, dppf = 1,1′-bis(diphenylphosphino)ferrocene, DME = 1,2-dimethoxyethane, DMA = *N*, *N*-dimethylacetamide.

using one of two major pathways, the first of which involved rebromination of intermediate **50a** by treatment with *N*-bromosuccinamide to afford brominated intermediate **51** in 90% yield. This material was then either subjected directly to Suzuki coupling conditions in the case of **53o** or partially deprotected with BBr_3 to furnish the intermediate methyl-ester phenol (45% yield). This brominated methyl-ester intermediate (structure not shown) was then paired with appropriate boronic acids or boronate esters, under standard reaction conditions [$Pd(dppf)Cl_2$, K_2CO_3], to give the corresponding ester-protected intermediates in good yields (42−87%). Intermediate **52a**, which was only encountered for compound **53o**, was then subjected to LiOH mediated hydrolysis of the pendant methyl ester followed by thiophenol cleavage of the methyl ether, affording **53o** in 3% yield over the two-step process. For compounds **53m,q,r** and **10**, obtained through Suzuki coupling of the partially protected methyl-ester phenol intermediate (structure not shown), a final LiOH mediated hydrolysis furnished the final compounds in 11−70% yield. Alternatively, intermediate **50b** was also directly subjected to C−H activation conditions (K_2CO_3, trimethylacetic acid, BrettPhos palladacycle first generation) with corresponding halogens to yield intermediates **54** in good overall yield (39−97%). Subsequent deprotection of both the *tert*-butyl ester as well as the methyl ether functionalities was achieved in either a direct BBr_3 mediated reaction or a stepwise fashion and afforded final compounds **53d−l**, **53n**, and **53p**.

A select number of substituted benzothiophenes were made by introducing the desired 2-phenyl moiety in the first step. Thus, BrettPhos palladacycle mediated C−H functionalization of 6-methoxybenzo[*b*] thiophene (**46**) in the presence of the corresponding phenyl bromide afforded the desired 2-substitued-benzothiophenes, which were further functionalized en route to final compounds **53a−c** (for details, see Supporting Information).

RESULTS AND DISCUSSION

As mentioned earlier, the efforts leading to the discovery of LSZ102 (**10**) centered around the hypothesis that it would be

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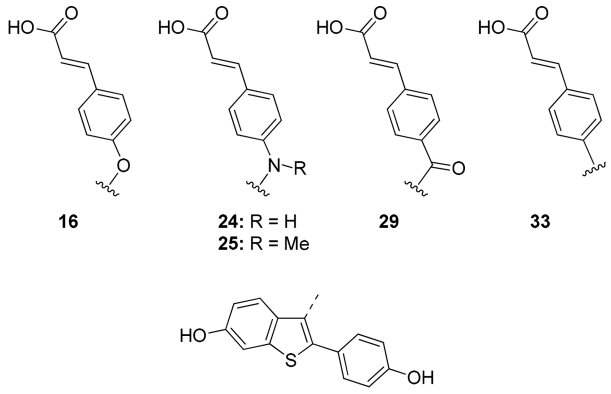
possible to combine a nonsteroidal benzothiophene core with an appropriate side chain, such as the carboxylic acid functionality found in GW-7604 (**7**). In doing so, we thought it should be possible to obtain a candidate that retained the selective degrader functionality while imparting a more pharmaceutical friendly profile that would allow for oral administration. Although we did explore alternative nonsteroidal replacements for the fulvestrant core, one of which is outlined in our earlier publication,[17] for the purposes of this article we will focus on our work with the benzothiophenes. As outlined in Figure 3, our earliest investigation in to the benzothiophene



entry	ERα transcription IC_{50} (nM)	% ERα remaining	clogD
fulvestrant	3.4	18	7.3
tamoxifen	1,605	90	6.8
4-hydroxytamoxifen	3	94	6.2
16	748	41	5.8
24	> 10,000	44	5.9
25	3,400	30	6.3
29	> 10,000	76	5.5
33	> 10,000	60	5.6

Figure 3. Benzothiophene-based linker exploration.

scaffold included the preparation of a number of linkers through which the benzothiophene was ultimately connected to our cinnamic acid side chain. As shown in the table, these compounds varied from the ether and amine tethers shown in compounds **16** and **24**–**25**, respectively, to the carbonyl connection of **29** or even the direct C–C bond tether shown in compound **33**.

In order to characterize the aforementioned compounds, we utilized a number of *in vitro* assays, allowing us to quantify both the anti-estrogen activity and the ability to degrade ERα. Anti-estrogen activity was evaluated with an estrogen-responsive reporter gene in ER+ MCF-7 breast cancer cells (ERα transcription IC_{50}) (Figure 3). Degradation of ERα was measured using an in-cell western protocol with two distinct setups, both of which involved treatment of MCF-7 cells with compound for 18 h followed by fixation and processing for in-cell visualization using an anti-ERα antibody that monitored the amount of receptor remaining. The first in-cell western assay assessed the remaining ERα levels when compounds were added at 10 μM (% ERα remaining). A follow-up assay was used for compounds inducing significant receptor degradation to determine the concentration of test compound at which half of the ERα receptor level remained (ERα degradation IC_{50}). Synthesized compounds were also benchmarked against known ERα modulators/degraders with the most common metric being fulvestrant and tamoxifen/4-hydroxytamoxifen. This allowed us to characterize our early prototype compounds both from an anti-estrogen (i.e., antagonist) perspective as well as their ability to degrade the ERα receptor.

Evaluating the compounds outlined in Figure 3 set the context for our further exploration into the benzothiophene scaffold. As expected, tamoxifen and 4-hydroxytamoxifen were not effective in degrading the receptor at 10 μM with 90 and 94% ERα remaining, respectively. Fulvestrant clearly stands out in terms of both its ERα antagonistic potency as well as its ability to efficiently degrade the receptor (18% ERα remaining at 10 μM); however, the notably high clogD no doubt contributes to its limited pharmacokinetic profile. These initial compounds (**16**, **24**, **25**, **29**, **33**) generally appeared to reduce the lipophilicity as compared to fulvestrant, which gave some early indication that they were reasonable medicinal chemistry starting points. Taking a further look at the *in vitro* data in Figure 3, we see that ether-linked compound **16** was both active as an ERα antagonist (ERα transcription IC_{50} = 748 nM) and efficient in reducing receptor levels at 10 μM with 41% ERα remaining. Compounds **24** and **25** both were able to degrade the ERα receptor comparably to **16** at 10 μM (44 and 30% versus 41% ERα remaining) but demonstrated less antagonistic activity than **16**. Compounds **29** and **33** were poor ERα antagonists and degraders; therefore, the ether-linked benzothiophene **16** was ultimately selected for further optimization.

Having selected benzothiophene **16** as our lead compound for further optimization, we hypothesized it might be possible to further improve its degradative properties by tuning the cinnamic acid functionality. Table 1 outlines these results and begins with a look at the saturated propionic acid analogue **17**, which was prepared to probe the necessity of the α,β-unsaturation found in the parent compound (**16**). Propionic acid **17** was found to be nearly equipotent as an ERα antagonist (ERα transcription IC_{50} = 457 nM) but slightly less effective as an ERα degrader (58% ERα remaining), suggesting that the rigidity of the cinnamic acid moiety found in **17** is favorable. Taking a further look into the optimization of the carboxylic acid functionality, we investigated a number of amide-containing analogues. All four of the amides shown in Table 1 (**35a,c**–**e**) demonstrated improved antagonistic activity when compared to **16** (ERα IC_{50} values = 10–55 nM); however, they are nearly equivalent to the parent compound when comparing their efficacy in degrading ER at 10 μM (40–48% ERα remaining). Primary amide **35c** demonstrated that the carboxylic acid moiety is not alone in its ability to effectively degrade ERα (48% ERα remaining), and secondary amides **35a,d,e** followed up on this with equally comparable ERα remaining values. Unfortunately, the amide analogues were found to be less soluble than the parent cinnamic acid (**16**), and for this reason, they were not pursued further. Tetrazole **37** and its methylated analogues **38** and **39**, although improved as antagonists, did not appreciably improve the level of ERα degradation achieved (33–76% ERα remaining at 10 μM). Imidazole **19** and methylimidazole **18** were improved as antagonists (ERα IC_{50} values of 53 and 125 nM, respectively) but were again equally effective as degraders when compared to **16**. Furthermore, as was observed with the amide analogues discussed earlier, the imidazole compounds were significantly less soluble than the parent. Given this data, we prioritized the cinnamic acid functionality of **16** as our ERα degradation functionality and sought to improve its antagonistic properties with further modification.

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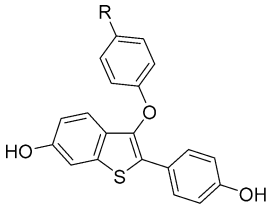
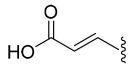
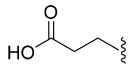
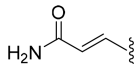
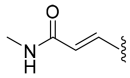
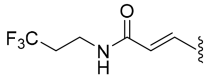
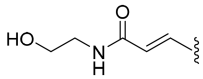
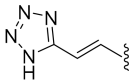
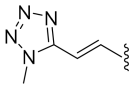
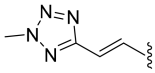
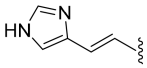
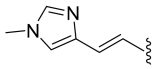
Table 1. Effects of Carboxylic Acid Replacements



cmpd.	R	solubility at pH 6.8 (mM)	ERα transcription IC_{50} (nM)	% ERα remaining	ERα degradation IC_{50} (nM)
16		0.34	748	41	26
17		> 1	457	58	31
35c		<0.005	40	48	n.d.[a]
35a		<0.005	53	40	58
35e		<0.005	10	45	1
35d		0.011	55	47	n.d.[a]
37		0.19	219	76	n.d.[a]
38		n.d.[a]	1	39	60
39		n.d.[a]	3	33	34
19		<0.005	53	39	11
18		0.009	125	47	17

[a]n.d. = not determined.

Replacement of the central core ring was investigated as outlined in Table 2 and began with the introduction of a pyridine ring (**45**). This substitution had a slightly positive effect on the ability to degrade ERα (26% ERα remaining) but led to a decrease in ERα antagonistic activity (ERα transcription IC_{50} = 7750 nM). Similarly, methyl and methoxy substitutions around this ring were explored (**42a−c**), but again, although this was tolerated from a standpoint of effecting degradation of the ERα (27−37% ERα remaining), the modifications, at best, led to a retention of ERα antagonistic potency as compared to **16**, and in the case of methoxy compound **42c**, they lead to a nearly 7-fold drop in potency. Table 3 shows similar results for compounds **42d−f**, in which we explored direct substitution on the double bond. In all cases, it was shown that substitution, while tolerated from a potency perspective as an antagonist (ERα transcription IC_{50}'s = 216−886 nM), did not lead to any marked improvements in the ability to effect ERα degradation (33−42% ERα remaining). For this reason, further functionalization around the cinnamic acid moiety of the compounds was not pursued, and the unsubstituted cinnamic acid **16** remained the frontrunner.

With *in vitro* potency beginning to focus in on key compound functionality, we evaluated a number of our early analogues for their pharmacokinetic (PK) properties (Table 4) to assess what, if any, pharmacokinetic liabilities these compounds might have. Oral dosing of a 3 mg/kg solution of **16** in Sprague−Dawley rats gave our first look into the PK properties of this structural class and showed rather low bioavailability (6%) as well as low peak plasma concentration (C_{max} po = 80 nM) and high clearance (54 mL/min/kg). Our first attempt to improve this profile focused around the introduction of proximal substitution to the potentially metabolic labile phenolic functionality on the right-hand half of **16**. This led to the preparation of methyl-substituted **53a**, which, although slightly improved in our *in vitro* potency assays (ERα transcription IC_{50} = 327 nM, 26% ERα remaining), did not prove advantageous from a

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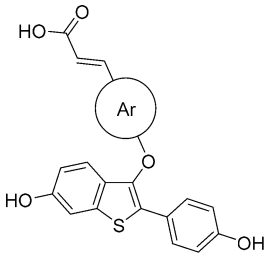
Table 2. Effect of Variation of Linker Substituents



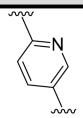
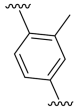
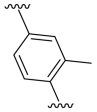
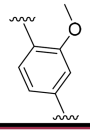
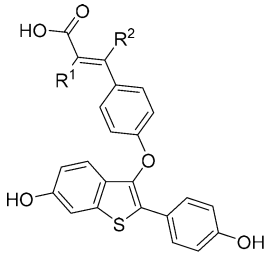
cmpd.	Ar	ERα transcription IC_{50} (nM)	% ERα remaining
45		7,750	26
42a		1,270	27
42b		1,030	37
42c		5,020	35

Table 3. Cinnamic Acid Substitution



cmpd.	R^1	R^2	ERα transcription IC_{50} (nM)	% ERα remaining
42d	Me	H	886	33
42e	H	Me	316	42
42f	Et	H	216	35

pharmacokinetic perspective (oral bioavailability = 2% and clearance = 46 mL/min/kg in C57BL/6 mice). The methoxy variant **53s**, although not explored in a pharmacokinetic setting, did lead to an interesting conclusion from the *in vitro* potency data. **53s** was equipotent as an antagonist (ERα transcription IC_{50} = 647 nM) and more efficient as an estrogen receptor degrader at 10 μM (18% ERα remaining), demonstrating that the free phenol functionality was not required to maintain activity in either setting. This finding set up our exploration for alternative functionality at the 4-position and ultimately led to the preparation of compound **53b**, a *para*-fluoro substituted analogue with only slightly reduced potency (ERα transcription IC_{50} = 1823 nM) that maintained the degradative properties at 10 μM (26% ERα remaining). Additionally, this compound led to an improvement in the bioavailability and clearance in both mouse and rat species (oral bioavailability = 19 and 33% and clearance = 22 and 24 mL/min/kg, respectively). Finally, the 4-CF_3 substituted analogue **53d** further improved the pharmacokinetic profile while maintaining activity in both of our key *in vitro* potency assays, leading to an antagonist analogue equipotent to parent compound **16**, with reduced clearance in mice and rats (clearance = 6 and 30 mL/min/kg, respectively) and increased bioavailability (oral bioavailability = 28 and 74%, respectively).

As these early pharmacokinetic studies were being run, we were also working to improve the potency of parent compound **16** and came across an interesting effect through which we were able to markedly improve our antagonistic activity as well as the potency as an ERα degrader. Although unsubstituted phenyl analogue **53c** is a promising lead, its ERα potency (ERα transcription IC_{50} = 2306 nM; Table 5) is slightly decreased from that of the phenolic parent compound **16**. As we began exploring substitution around this aromatic ring, we found that introduction of an *ortho*-methyl group, as seen with compound **53e**, led to a rather notable 26-fold improvement in antagonistic activity (ERα transcription IC_{50} = 89 nM) and 7-fold increase in potency as a degrader (ERα degrader IC_{50} = 4 nM). Incrementally increasing the size of the substituent to the ethyl group (**54f**) led to a further modest potency improvement (ERα transcription IC_{50} = 36 nM), whereas substantially increasing the size to a *tert*-butyl group (**53g**) had no further positive effect on activity (ERα transcription IC_{50} = 36 nM). However, introduction of an *ortho* isopropyl (**53h**) did demonstrate that further improvement was possible, leading to an increase in potency (ERα transcription IC_{50} = 6 nM) and a very potent ERα degrader (ERα degrader IC_{50} = 0.4 nM with 13% ERα remaining).

Interestingly, during the course of our study, this *ortho*-substituted pattern and its effect on potency on the ER has, to our knowledge, only been reported by Katzenellenbogen et al. during their exploration of modified 2,3-diarylindenes.[25,26] In their work, a methyl group introduced to a 2-phenyl substituent in the *ortho* position to its attachment to the indene nucleus increased binding affinity 11-fold over the unsubstituted system. Upon further investigation with our benzothiophene analogues, we found that the *ortho*-substitution pattern leading to this potency increase was torsionally constraining the compounds and organizing the 2-aryl ring almost perpendicular to the plane of the benzothiophene core (Table 5). A comparison of the torsion angles in the energy-minimized conformation of the ligands unbound to the receptor and the conformation found in the bound state to the ligand-binding domain of ERα suggests that preorganization of the 2-aryl ring might, in combination with increased hydrophobic interactions within the ligand-binding pocket, contribute to the observed potency increase.

In a final push to optimize the benzothiophene analogues, and based both on the pharmacokinetic data outlined in Table 4 with the *ortho* effect observed in Table 5, we set out to combine these two advantageous structural features. As such, preparation of compound **53i** demonstrated that the two functionalities could indeed be combined to afford a compound with both suitable pharmacokinetic properties (clearance = 33 mL/min/kg and oral bioavailability = 34%) as well as increased transcriptional activity (ERα transcription IC_{50} = 78 nM) as compared to the desmethyl parent **53b** (ERα transcription IC_{50} = 1823 nM, Table 4). As a replacement for the isopropyl moiety found in **53h**, *ortho*-CF_3 analogue **53j** was only slightly less potent (ERα transcription IC_{50} = 23 nM) than **53h** (Table 6), likely owing to its similar size as compared to the isopropyl group. *Para*-substitution of this compound gave rise to **53k**, which again demonstrated good transcriptional inhibitory activity (ERα transcription IC_{50} = 12 nM) while also showing suitable oral bioavailability (oral bioavailability = 30%) and peak plasma

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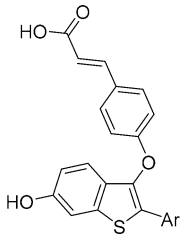
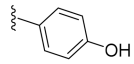
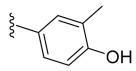
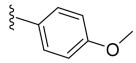
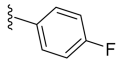
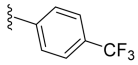
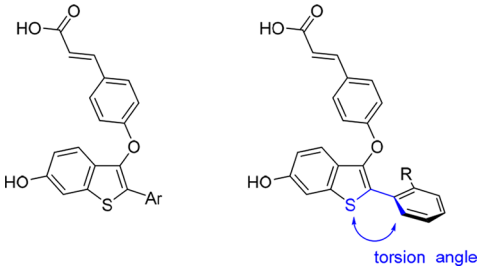
Table 4. Potency and Pharmacokinetic Parameters of Benzothiophene Analogues 16 and 53a,b,d,s



cmpd.	Ar	ERα transcription IC_{50} (nM)	% ERα remaining	Mouse[a] clearance (mL/min/kg)	Mouse[a] C_{max} po (nM)	Mouse[a] oral F (%)	Rat[a] clearance (mL/min/kg)	Rat[a] C_{max} po (nM)	Rat[a] oral F (%)
16		748	41	n.d.[b]	n.d.[b]	n.d.[b]	54	80	6
53a		327	26	46	46	2	n.d.[b]	n.d.[b]	n.d.[b]
53s		647	18	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]
53b		1,823	26	22	505	19	24	847	33
53d		941	18	6	1,380	28	30	985	74

[a]Dose: 1 mg/kg iv, 3 mg/kg po. Formulation = solution. Vehicle **16**: PBS solution containing 5% 0.1 N NaOH/10% PEG300/25% (of 20% Solutol) and 1 N HCl for pH adjustment; **53a,b,d**: PBS solution containing 2 equiv of 0.1 N NaOH/10% PEG300/25% (of 20% Cremophore) and 1 N HCl for pH adjustment. [b]n.d. = not determined. F = bioavailability.

Table 5. Discovering the *Ortho* Effect



cmpd.	Ar	ERα transcription IC_{50} (nM)	% ERα remaining	ERα degradation IC_{50} (nM)	torsion angle bound[a]	torsion angle unbound[b]
53c		2,306	23	26	49°	53°
53e		89	20	4	72°	80°
53f		36	23	1	n.d.[c]	n.d.[c]
53g		36	22	1	n.d.[c]	n.d.[c]
53h		6	13	0.4	82°	82°

[a]Torsion angle between the 2-aryl ring and benzothiophene core was measured from the ligand bound to the ligand-binding domain of ERα. [b]Torsion angle between the 2-aryl ring and benzothiophene core was calculated from molecular mechanics for the unbound conformation. [c]n.d. = not determined.

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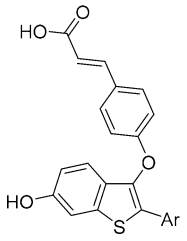
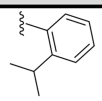
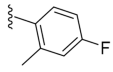
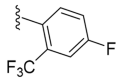
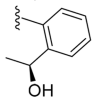
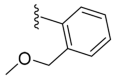
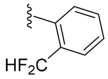
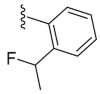
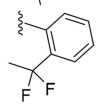
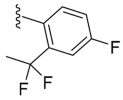
Table 6. Optimizing the *Ortho* Effect and the Corresponding Pharmacokinetic Data



cmpd.	Ar	ERα transcription IC_{50} (nM)	% ERα remaining	ERα degradation IC_{50} (nM)	Mouse[a] clearance (mL/min/kg)	Mouse[a] C_{max} po (nM)	Mouse[a] oral F (%)
53h		6	13	0.4	15	1,176	13
53i		78	19	4	33	925	34
53j		23	17	1	n.d.[b]	n.d.[b]	n.d.[b]
53k		12	24	1	18	1,501	30
53l		669	12	5.4	n.d.[b]	n.d.[b]	n.d.[b]
53m		124	11	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]
53n		179	22	6	n.d.[b]	n.d.[b]	n.d.[b]
53o		123	14	3	n.d.[b]	n.d.[b]	n.d.[b]
53p		52	17	4.2	n.d.[b]	n.d.[b]	n.d.[b]
53q		25	17	0.3	n.d.[b]	n.d.[b]	n.d.[b]
53r		11	15	0.2	14	187	5
10		6	17	0.2	28	492	12
9		24	15	0.5	16	1239	42

[a]Dose: 1 mg/kg iv, 3 mg/kg po. Formulation = solution. Vehicle **53h,i,k**: PBS solution containing 2 equiv of 0.1 N NaOH/10% PEG300/25% (of 20% Cremophore) and 1 N HCl for pH adjustment; **53r**: PBS solution containing 1 N NaOH/10% PEG300/25% (of 20% Cremophore); **10**: PBS solution containing 1 equiv of 1 N NaOH/10% PEG300/25% (of 20% Cremophore) and 1 N HCl for pH adjustment; **9**: PBS solution containing 3% 1 N NaOH/15% PEG200/50% (of 20% Cremophore) and 1 N HCl for pH adjustment. [b]n.d. = not determined. F = bioavailability.

concentration (C_{max} po = 1501 nM). In an attempt to further reduce lipophilicity and introduce some polarity, compounds **53l–o** were prepared, each having obvious structural similarities to the parent compound **53h**. While all four analogues were efficient degraders at 10 μM (11–22% ERα remaining), they were all less active than the parent when compared in the transcriptional assay (ERα transcription IC_{50} = 123–669 nM), leading us to the conclusion that polarity is not well tolerated in this part of the molecule. As a final approach to optimize potency, a variety of fluorinated analogues were prepared in an attempt to both optimize activity and minimize any metabolic liabilities that might arise from moving forward with an isopropyl substituent. To that end, compounds **53p–r** and **10** were prepared, leading to a slight increase in activity from **53p** to **53q**

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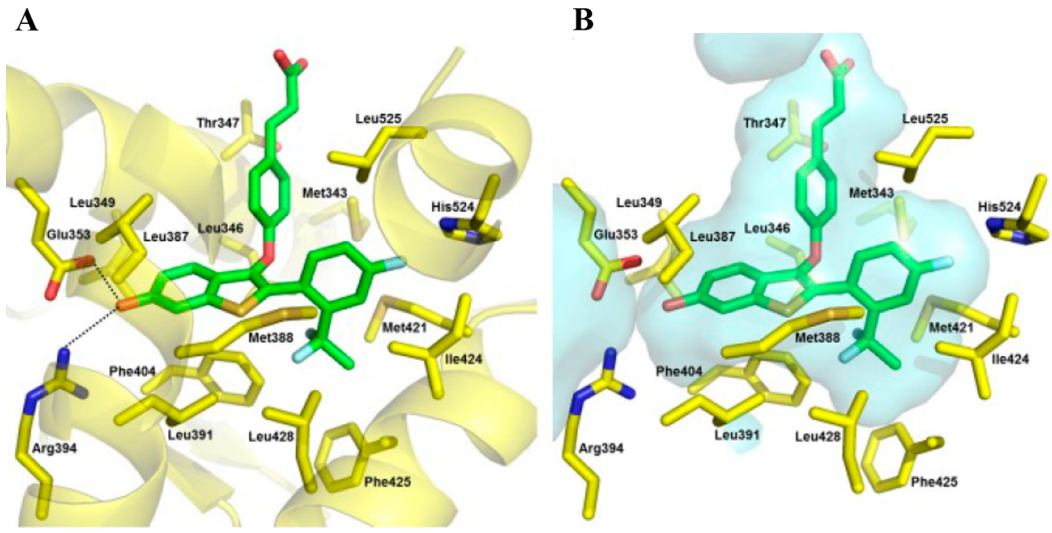

Figure 4. (A) Binding pocket of ERα in complex with **10** (PDB code: 6B0F) highlighting residues that form the ligand-binding pocket. (B) van der Waals excluded surface of the ligand-binding pocket.

(ERα transcription IC_{50} = 52 and 25 nM, respectively) and a further increase upon introduction of the difluoroethyl moiety found in **53r** (ERα transcription IC_{50} = 11 nM). Finally, combining the difluoroethyl group with the *para*-fluoro group found in the earlier analogues resulted in **10**. Whereas **53r** had unsatisfactory pharmacokinetic properties, most notably a low oral bioavailability of 5% in C57BL/6 mice, **10** showed an acceptable PK profile with 12% oral bioavailability and at the same time was our most potent ERα antagonist and degrader.

Crystallography was used to gain a structural understanding of how the difluoroethyl substitution of **10** influences ligand binding. The structure of ERαLDB (301−553) in complex with **10** (PDB code: 6B0F) was solved to 2.86 Å. The overall fold of the ERαLBD structure compares well with that of the previously described structures[27] with an rmsd value of 0.486 Å when including main chain atoms from residues 310−525 of chain A with those same atoms of ERαLBD bound to raloxifene (PDB code: 1ERR). Consistent with ERα structures that contain ligands with a hydroxyl moiety on the A-ring is the hydrogen bonding network among residues Arg394 and Glu353 and this hydroxyl group. Aside from these interactions, the remainders occur within the largely hydrophobic core of the ligand binding domain (LBD). The A/B-rings of **10** are positioned between Phe404 on one side of the pocket and Leu387 on the other and make additional interactions with Leu349, Met388, and Leu391, whereas the D-ring is within van der Waals distances to Met421, Ile424, and Leu525. The difluoroethyl forces a repositioning of Phe425 to further increase the volume of the ligand-binding pocket as compared to an E2 (PDB code: 1ERE) or GW5638 (PDB code: 1R5K) bound structure. This same repositioning mimics that seen in the structure of ERα in complex with raloxifene. The induced pocket is defined by additional interactions with Phe404, Phe425, Leu428, and Met421 (Figure 4A). A van der Waals excluded surface was generated using PyMOL[28] to demonstrate the ability of **10** to adequately fill the available space within the LBD (Figure 4B).

Pharmacokinetics and Pharmacodynamics of 10. *In Vitro Characterization of 10.* ERα degradation observed in the in-cell assay format was confirmed by western blot analysis and shown to be proteosome-mediated (Figure 5). Compound **10** as well as fulvestrant and the previously reported tetrahydroisoquinolone **40**[17] induces significant degradation of ERα after 24 h

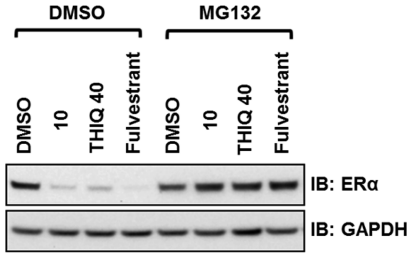

Figure 5. Proteasome-dependent ERα degradation by **10**. Western blot analysis of the effect of **10**, THIQ 40, and fulvestrant (10 μM, 24 h) on ERα levels with or without MG132 pretreatment for 24 h. IB = immunoblot.

when given as a 10 μM solution to MCF-7 cells. However, simultaneous incubation with MG132, a pan-proteasome inhibitor, rescues ERα degradation, suggesting that degradation of ERα is mediated through this process.

Evaluation of dose-dependent ERα degradation in an in-cell western assay is shown in Figure 6, demonstrating, as expected,

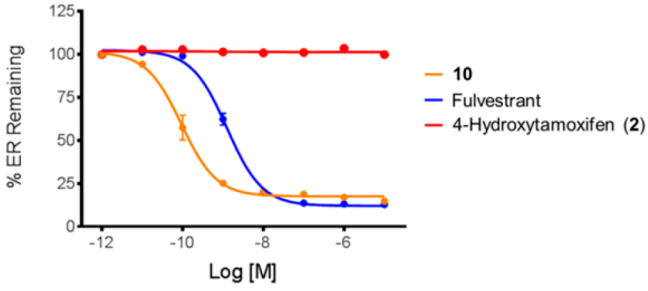

Figure 6. Measurement of ERα reduction by **10**, fulvestrant, and 4-hydroxytamoxifen (**2**) in MCF-7 cells grown in 10% charcoal dextran-stripped serum supplemented media. For the in-cell western, cells were incubated with compounds for 18 h followed by fixation and processing to determine the amount of ERα protein remaining.

that 4-hydroxytamoxifen did not induce degradation, consistent with its reported profile.[29] In this format, compound **10** was found to be more potent (ERα degradation IC_{50} = 0.2 nM) than fulvestrant (ERα degradation IC_{50} = 1.2 nM). As shown in Figure 6, fulvestrant and compound **10** cannot fully degrade

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ERα in MCF-7 cells even at saturating biochemical concentrations. The remaining low levels of ERα might not be accessible in the cell to proteolytic degradation of the compounds and result in a low level of remaining ER.[30] The residual pool of ER may be bound to a multiprotein complex in the nuclear compartment and be slow to turn over or exported from the nucleus.

Next, we evaluated the anti-proliferative effect of **10** in ER positive estradiol dependent MCF-7 cells over a dose response of compound. We observed robust inhibition of cell proliferation in MCF-7 cells upon incubation with **10** with a half-inhibitory concentration of 1.7 nM (Figure 7). Fulvestrant and

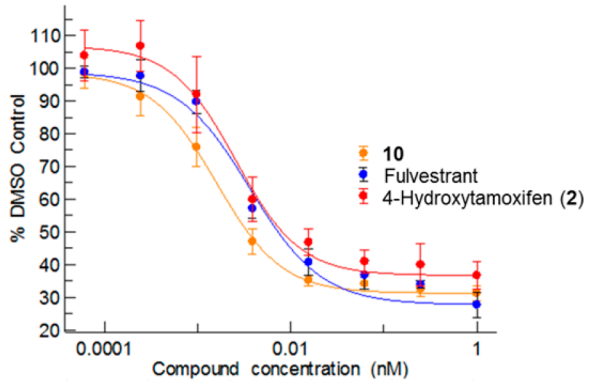

Figure 7. Proliferation of MCF-7 cells. Cells were incubated in RPMI (without phenol red) plus 10% charcoal dextran-stripped serum and treated with compounds in the presence of 0.1 nM estradiol for 6 days. Cell viability was determined by CellTiter-Glo assay. IC_{50} values were calculated using the XLfit software and are defined as the inflection point of the fitted inhibition curves. RPMI = Roswell Park Memorial Institute.

4-hydroxytamoxifen had IC_{50} values of 4.4 and 9.9 nM, respectively, significantly higher than that of **10**. The more potent effect of **10** on cellular proliferation suggests that its superior potency as an ER degrader over fulvestrant translates into more potent anti-profilerative activity.

To further determine the effect of **10** on ER-mediated gene transcription, we developed an MCF-7 cell line that stably expresses a 3× ERE-luciferase reporter. Our data demonstrated that **10** effectively inhibited the estrogen-induced activation of the ERE-luciferase reporter using charcoal-stripped serum treated with E2 (Figure 8A). The IC_{50}'s of **10** and fulvestrant were similar (0.3 and 0.2 nM, respectively), whereas the IC_{50} of 4-hydroxytamoxifen was 10-fold higher at 2 nM.

One challenge with using a 3× ERE reporter gene is that the signal is greatly amplified above physiological levels normally seen in the cell. To address this issue, we also measured the activity of **10** on the canonical endogenous ER target gene GREB1. Interestingly, we found that fulvestrant this time had the most robust inhibition on mRNA levels with an IC_{50} of 3.8 nM, whereas **10** had an IC_{50} of 8.9 nM, which was similar to that of 4-hydroxytamoxifen (IC_{50} of 10.2 nM) (Figure 8B). Although it is not clear why there is a potency difference between fulvestrant and **10** to inhibit GREB1 expression, it could be unique features of promoters of ER target genes that confer more or less activity to the two degrader compounds.

*In Vivo Characterization of **10**.* To evaluate the anti-tumor activity of **10**, efficacy was assessed in the MCF-7 human breast cancer xenograft model in mice supplemented with estradiol pellets to support robust tumor growth. Treatment of the mice with **10** once daily at 20 mg/kg resulted in significant tumor

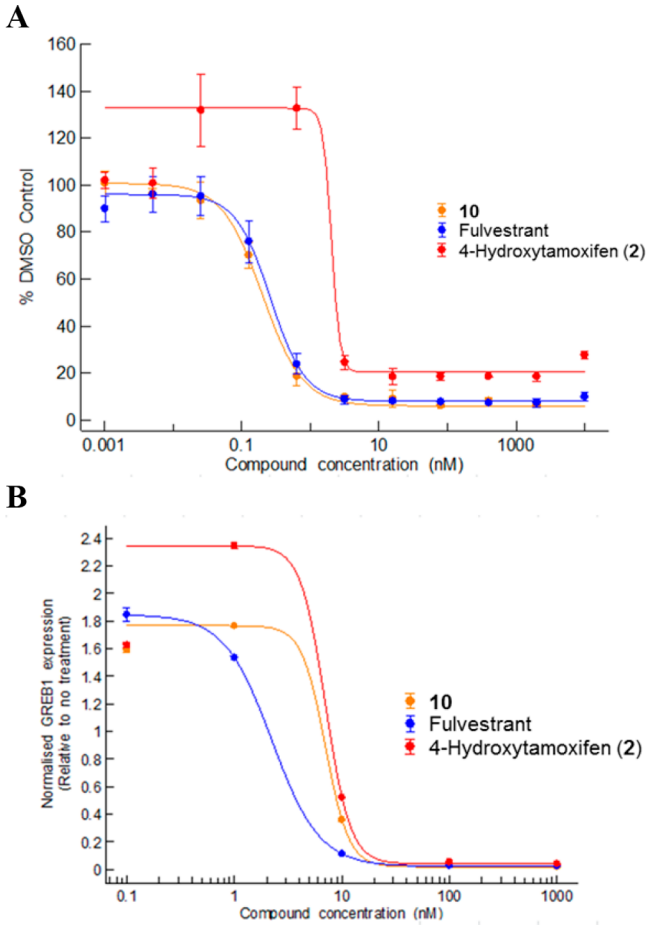

Figure 8. Inhibition of ER-mediated gene transcription by **10**. MCF-7-EREluc and MCF-7 cells were incubated in phenol-red free RPMI plus 10% charcoal dextran-stripped serum and treated with compounds in the presence of 0.1 nM E2 for 24 h. (A) Cell luciferase signal from MCF-7-EREluc was measured using Bright-Glo assay and normalized to DMSO control. (B) mRNA of ER target gene GREB1 from treated MCF-7 cells was quantified by TaqMan assay.

growth inhibition as compared to the control group treated with vehicle alone, resulting in tumor stasis (mean change in tumor volume of **10** vs control = $\%\Delta T/\Delta C$ of 2.4% on day 48, $p < 0.05$). Plasma samples collected on day 19 after treatment started showed an exposure of **10** of 3230 nM·h by AUC with a maximal concentration of 1068 nM. Tamoxifen and fulvestrant, used as controls, induced statistically significant tumor stasis and a growth inhibition of $\%\Delta T/\Delta C$ of 24%, respectively (Figure 9A). Tumors were collected and processed for mRNA and protein isolation from the end of the efficacy study on day 48 post-implantation at 7 h post last treatment to assess pharmacodynamics marker changes. Consistent with its anti-tumor efficacy, **10**, as well as the tamoxifen and fulvestrant controls, strongly inhibited transcription of the ER-regulated target gene for progesterone receptor (Figure 9B). The two SERD compounds fulvestrant and **10** also showed a marked reduction in ER levels in the tumors, with 67 and 63% inhibition as compared to the untreated control, respectively (Figure 9C).

*Pharmacokinetic Characterization of **10** in Advanced Preclinical Species.* Pharmacokinetic parameters of **10** were finally evaluated in rats and dogs to assess if sufficient exposure for toxicological studies could be achieved (Table 7). Dosing of 3 mg/kg solution of **10** in male Sprague–Dawley rats resulted in 33% bioavailability and a dose-normalized exposure of 620 nM·h.

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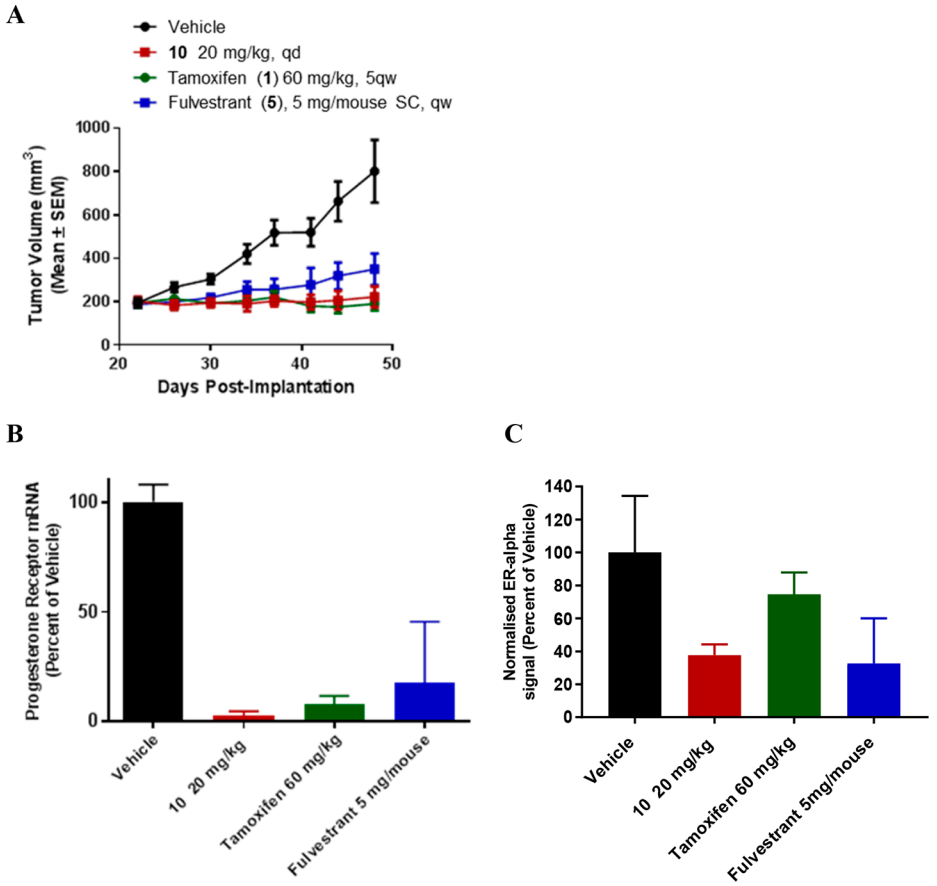

Figure 9. Anti-tumor efficacy of **10** in the ER+ human breast cancer MCF-7 xenograft model. Tumors were established in female NSG mice by injection of 10^7 cells into the axillary mammary fat pad area of each mouse. Mice were implanted with 0.72 mg estradiol/90-day release pellets several days prior to cell implantation. When tumors reached an average of 200 mm^3, mice were randomized according to tumor volume into treatment groups (n = 8). Test agents were administered at the dose levels and schedules indicated. **10** or its vehicle alone was orally administred once daily, and tamoxifen was orally administered 5 times a week. Fulvestrant was administered subcutaneously (sc) once a week (5 mg/mouse). (A) Tumor volumes of treatment groups vs days post randomization. $p < 0.05$, ANOVA, Holm−Sidak posthoc test, versus vehicle control. Inhibition of progesterone receptor mRNA levels as analyzed by RT-PCR (B) and ER protein levels as analyzed by quantification of a western blot (C) as compared to the vehicle control at the end of the efficacy study at 7 h post last dose are shown.

Table 7. Pharmacokinetic Parameters for 10 in Advanced Preclinical Species

species	dose (iv/po, mg/kg)	formulation	clearance (mL/min/kg)	C_{max} po dn[a] (nM)	AUC_{0-t} iv dn[a] (nMh)	AUC_{0-t} po dn[a] (nM·h)	V_{ss} (L/kg)	$t_{1/2}$ for elimination (h)	oral F[b] (%)
SD[c] rat	1/3	solution[d]	19	240	1849	620	0.9	1.4	33
WH[e] rat	−/30	suspension[f]		1259		2117			
	−/100	suspension[f]		513		1940			
	−/300	suspension[f]		334		3405			
beagle dog	0.3/10	solution[g]	5	268	7713	962	0.3	4.1	12
	−/30	suspension[f]		123		624			

[a]dn = dose normalized. [b]F = bioavailability. [c]SD = Sprague−Dawley. [d]Vehicle: PBS containing 1 equiv of 1 N NaOH/10% PEG300/25% (of 20% Solutol) and 1 N HCl for pH adjustment. [e]WH = Wistar Han. [f]Vehicle: 0.5% methyl cellulose and 0.1% Tween 80. [g]Vehicle: PBS containing 5% NaOH/20% PEG300/5% Solutol.

A separate study in female Wistar Han rats dosing amorphous **10** in suspension in a dose escalating study demonstrated dose proportional exposure from 30 to 100 mg/kg. Increased dosing to 300 mg/kg lead to an over proportional exposure by AUC, whereas C_{max} was under proportional with dose. In dogs, a low clearance of 5 mL/min/kg (15% of hepatic blood flow) was measured, and oral administration yielded a biovailalability of 12% and good exposure (e.g., the 10 mg/kg dose in dogs resulted in an exposure roughly 3-fold higher than the fully efficacious exposure required in the mouse xenograft model, seen in Figure 9A, from a 20 mg/kg dose: 9625 versus 3230 nM·h). Dosing of a suspension to dogs resulted in a small drop in exposure with a dose-normalized exposure of ~2/3 of the exposure seen with solution dosing.

CONCLUSIONS

Chemistry optimization resulted in benzothiophene-based compound **10** (LSZ102), which was found to be a potent ERα antagonist and degrader. Substitution at the *ortho* position of the 2-aryl ring proved to be crucial to achieve high potency, and substitution at the *para* position was beneficial for the

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pharmacokinetic properties. **10** is a very potent ERα degrader, as shown in western assays, inducing a proteosome-mediated proteolysis of the receptor. **10** exhibited robust anti-tumor efficacy and inhibition of PD markers in a MCF-7 human breast cancer model at well-tolerated dose level and together with its acceptable exposure upon oral administration is an attractive compound for study in a clinical setting. **10** is currently being evaluated in advanced or metastatic ERα+ breast cancer in a Phase I/Ib trial.[31] Preliminary results from this study indicate that oral single-agent LSZ102 appears well-tolerated, with a manageable safety profile.[32]

EXPERIMENTAL SECTION

General Chemical Methods. Starting materials, reagents, and solvents were obtained from commercial sources and used as received. THF and diethyl ether were anhydrous grade. Compound **47** was prepared as described in ref 24. Progress of the reactions was monitored by analytical LC/MS using an Agilent 1100 series with UV detection at 214 and 254 nm and an electrospray mode (ESI) coupled with a waters ZQ single quad mass detector. Progress of the reactions was also monitored by analytical LC/MS using an Waters Classic AcQuity UPLC with UV detection at 214 and 254 nm and an electrospray mode (ESI) coupled with a waters SQ single quad mass detector. Analytical thin-layer chromatography (TLC) was carried out on S-2 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and ethanolic *p*-anisaldehyde, aqueous ammonium cerium nitrate/ammonium molybdate, or basic aqueous potassium permanganate as developing agent. Purification of intermediates and final products was carried out on a normal phase using an ISCO CombiFlash system and prepacked SiO_2 cartridges eluted with optimized gradients of either ethyl acetate/heptane mixture or methanol/dichloromethane as described. Preparative high pressure liquid chromatography (HPLC) was performed on a Waters instrument. Systems were run with the described acetonitrile/water gradient with an *n*-propanol, NH_4OH, or TFA modifier as described. Preparative SFC was perform a Thar-80 with UV detection based collection. Analytical chiral SFC was performed on a Waters/Thar SFC Investigator, with UV and MS detection. All compounds where biological data are presented have >95% purity as determined by HPLC. NMR spectra were recorded on a Bruker Ultrashield 400 plus instrument. Chemical shifts (δ) are reported in parts per million (ppm) relative to deuterated solvent as the internal standard ($CDCl_3$ 7.26 ppm, DMSO-d_6 2.50 ppm, CD_3OD 3.31 ppm), and coupling constants (*J*) are in hertz (Hz). Peak multiplicities are expressed as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), multiplet (m), and broad (br).

*(E)-3-(4-((2-(2-(1,1-Difluoroethyl)-4-fluorophenyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl)acrylic Acid (**10**).* To a solution of (*E*)-3-(4-((2-bromo-6-hydroxybenzo[*b*]thiophen-3-yl)-oxy)phenyl)acrylic acid (1.8 g, 4.60 mmol, see procedure **53m** for synthesis) in 1,4-dioxane (10 mL) and water (4 mL) were added 2-(2-(1,1-difluoroethyl)-4-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.633 g, 9.20 mmol, see Supporting Information for synthesis), K_2CO_3 (3.179 g, 23.00 mmol), and XPhos Pd cycle (340 mg, 0.460 mmol). The resulting mixture was heated to 150 °C under microwave irradiation for 45 min, after which time the reaction was filtered to remove solids. The filtrate was diluted with DCM and acidified by addition of sat. aq. citric acid solution. The phases were separated, and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude material was purified by reverse phase HPLC (basic conditions, 0.1% NH_4OH in CH_3CN/H_2O), and the fractions were treated with 1 N HCl to pH 5 and diluted with DCM. The organic layer was collected and concentrated *in vacuo* to afford (*E*)-3-(4-((2-(2-(1,1-difluoroethyl)-4-fluorophenyl)-6-hydroxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylic acid (1.6 g, 3.40 mmol, 74% yield) as a pale orange solid. ^1H NMR (400 MHz, CD_3OD) δ ppm = 1.80 (t, *J* = 18.44 Hz, 3H), 6.23 (d, *J* = 16.17 Hz, 1H), 6.71−6.81 (m, 3H), 7.03 (td, *J* = 8.21, 2.78 Hz, 1H), 7.08−7.14 (m, 2H), 7.22−7.32 (m, 2H), 7.37 (d, *J* = 8.59 Hz, 2H), 7.47 (d, *J* = 16.17 Hz, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ ppm = −84.91, −113.27. ^{13}C NMR (150 MHz, DMSO-d_6) δ ppm = 25.36, 107.69, 113.49, 114.99, 115.87, 116.75, 117.59, 121.62, 121.95, 122.33, 123.59, 124.3, 128.59, 129.89, 135.66, 137.92, 139.56, 140.48, 143.03, 155.95, 158.74, 161.88, 167.54. HRMS ESI *m/z* 471.0865 $[M + H]^+$.

*3-Bromo-6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene 1-Oxide (**12**).* Step 1: To a 500 mL round-bottom flask containing 6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (22 g, 81 mmol) in THF (250 mL) at 0 °C was added *N*-bromosuccinamide (15 g, 84 mmol). The reaction mixture was stirred at 0 °C for 60 min and then allowed to warm to room temperature and stirred for an additional 2 h. Upon completion, the reaction mixture was concentrated to 50% volume and quenched with sat. aq. sodium thiosulfate solution. The resulting solution was extracted with diethyl ether 3×, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford 3-bromo-6-methoxy-2-(4-methoxyphenyl)-benzo[*b*]thiophene (27.5 g, 97% yield). ^1H NMR (400 MHz, $CDCl_3$) δ ppm = 7.63 (d, *J* = 9.1 Hz, 1H), 7.55−7.61 (m, 2H), 7.19 (d, *J* = 2.5 Hz, 1H), 6.96−7.02 (m, 1H), 6.87−6.95 (m, 2H), 3.81 (s, 3H), 3.79 (s, 3H). LC/MS ESI *m/z* 350.1 $[M + H]^+$.

Step 2: To a solution of 3-bromo-6-methoxy-2-(4-methoxyphenyl)-benzo[*b*]thiophene (4 g, 11.45 mmol) in CH_2Cl_2 (20 mL) at room temperature was added trifluoroacetic acid (20 mL) dropwise; the reaction went from orange to dark brown in color. Upon addition, the resulting mixture was stirred at room temperature for 10 min and then hydrogen peroxide (30% wt aq., 1.58 mL, 16.47 mmol) was added dropwise. After 90 min at room temperature, the reaction mixture was quenched with sodium bisulfite (1.71 g, 16.47 mmol) followed by 3.0 mL of water. The resulting suspension was stirred vigorously for 15 min and then concentrated *in vacuo* to remove CH_2Cl_2 and most of the trifluoroacetic acid. The residue was partitioned between CH_2Cl_2 (40 mL) and sat. aq. $NaHCO_3$ solution (40 mL) and separated. The organic layer was collected, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography (SiO_2, 1−40% EtOAc/heptane) to afford 3-bromo-6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene 1-oxide (4.6 g, 88% yield) as an orange solid. ^1H NMR (400 MHz, CD_3OD) δ ppm = 7.51−7.65 (m, 2H), 7.37−7.51 (m, 2H), 7.08 (dd, *J* = 2.27, 8.34 Hz, 1H), 6.79−6.96 (m, 2H), 3.74 (s, 3H), 3.68 (s, 3H). LC/MS ESI *m/z* 367.1 $[M + H]^+$.

*3-(4-Bromophenoxy)-6-methoxy-2-(4-methoxyphenyl)benzo[b]-thiophene (**13**).* Step 1: To a solution of 4-bromophenol (469 mg, 2.71 mmol) in DMF (3 mL) was added sodium hydride (60% suspension in oil, 108 mg, 2.71 mmol); the resulting mixture was allowed to stir for 10 min at room temperature. To the solution was added 3-bromo-6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene 1-oxide (900 mg, 2.46 mmol) as a solid. The reaction was heated to 80 °C for 18 h. Upon completion, the reaction was cooled to room temperature, quenched with water, and diluted with CH_2Cl_2. The organic phase was collected (phase separator) and concentrated *in vacuo* to afford the crude product. The crude material was purified by column chromatography (SiO_2, 0−60% EtOAc/heptane) to afford 3-(4-bromophenoxy)-6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene 1-oxide (980 mg, 87% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm = 7.70−7.78 (m, 2H), 7.53 (d, *J* = 2.02 Hz, 1H), 7.41 (d, *J* = 8.59 Hz, 2H), 6.90−7.06 (m, 6H), 3.91 (s, 3H), 3.83 (s, 3H). LC/MS ESI *m/z* 459.1 $[M + H]^+$.

Step 2: A solution of 3-(4-bromophenoxy)-6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene 1-oxide (970 mg, 2.12 mmol) in THF (5 mL) was cooled to 0 °C. To the cooled solution was added $LiAlH_4$ (129 mg, 3.39 mmol) in one portion. The reaction mixture was stirred at 0 °C for 30 min, after which the mixture was poured into 1.0 M aq. $NaHSO_4$ solution and extracted with CH_2Cl_2. The organic layer was collected (phase separator) and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography (SiO_2, 0−30% EtOAc/heptane) to afford 3-(4-bromophenoxy)-6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (850 mg, 91% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm = 3.83 (s, 3H), 3.90 (s, 3H),

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6.80–6.99 (m, 5H), 7.22–7.32 (m, 2H), 7.32–7.44 (m, 2H), 7.65 (d, J = 9.09 Hz, 2H). LC/MS ESI m/z 443.4 $[M + H]^+$.

*3-(4-Bromophenoxy)-2-(4-hydroxyphenyl)benzo[b]thiophen-6-ol (**14**).* To a 30 mL vial containing 3-(4-bromophenoxy)-6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (100 mg, 0.23 mmol) in CH_2Cl_2 (1 mL) was added BBr_3 (1.0 M in hexanes, 0.680 mL, 0.68 mmol), and the reaction mixture was stirred for 1 h at room temperature. Upon completion, the reaction was quenched with 4 mL of MeOH and stirred for 10 min. The mixture was the concentrated *in vacuo* onto silica gel, and the crude material was purified by column chromatography (SiO_2, 1–100% EtOAc/heptane) to afford 3-(4-bromophenoxy)-2-(4-hydroxyphenyl)benzo[b]thiophen-6-ol (72 mg, 77% yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.47–7.57 (m, 2H), 7.35–7.45 (m, 2H), 7.20 (d, J = 2.02 Hz, 1H), 7.16 (d, J = 8.59 Hz, 1H), 6.73–6.90 (m, 5H). LC/MS ESI m/z 414.3 $[M + H]^+$.

*(E)-tert-Butyl 3-(4-((6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)phenyl)acrylate (**15**).* To a solution of 3-(4-bromophenoxy)-6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (79 mg, 0.18 mmol) in DMF (1.7 mL) was added triethylamine (0.125 mL, 0.90 mmol) followed by *tert*-butyl acrylate (0.184 mL, 1.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18.9 mg, 0.03 mmol). The mixture was then subjected to microwave irradiation for 1 h at 120 °C, after which the reaction was diluted with water (15 mL) and extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine (30 mL), passed through a phase separator to remove water, and concentrated *in vacuo* to give the crude product as an orange oil which was purified by column chromatography (SiO_2, 0–50% EtOAc/heptane) to give (*E*)-*tert*-butyl 3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo-[b]thiophen-3-yl)oxy)phenyl)acrylate as a pale yellow oil (55 mg, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.44 (s, 9H), 3.71 (s, 3H), 3.78 (s, 3H), 6.13 (d, J = 15.66 Hz, 1H), 6.76–6.83 (m, 3H), 6.86 (m, J = 8.59 Hz, 2H), 7.14–7.19 (m, 2H), 7.31 (m, J = 8.59 Hz, 2H), 7.42 (d, J = 16.17 Hz, 1H), 7.54 (d, J = 8.59 Hz, 2H). LC/MS ESI m/z 433.5 $[M - t\text{-Bu} + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)oxy)phenyl)acrylic Acid (**16**).* To a solution of (*E*)-*tert*-butyl 3-(4-((6-methoxy-2-(4-methoxyphenyl)-benzo[b]thiophen-3-yl)oxy)phenyl)-acrylate (40 mg, 0.08 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C was added BBr_3 (1.0 M in CH_2Cl_2, 0.33 mL, 0.33 mmol) dropwise; a solid immediately precipitated from the solution. The resulting mixture was stirred at 0 °C for 100 min, after which the reaction was quenched by addition of sat. aq. $NaHCO_3$ (4 mL) solution and a white precipitate was observed. The aqueous layer was then extracted with 5% MeOH/EtOAc (4 × 12 mL), and the combined organic layers were passed through a phase separator to remove water and concentrated *in vacuo* to afford the crude product, which was dissolved in MeOH (2 mL) and purified by reverse phase HPLC (neutral conditions, 3% 1-propanol in 1–100% CH_3CN/H_2O) to afford (*E*)-3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)oxy)phenyl)acrylic acid (17.5 mg, 53% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 6.32 (d, J = 16.17 Hz, 1H), 6.75 (d, J = 8.59 Hz, 2H), 6.78–6.82 (m, 1H), 6.92 (d, J = 8.59 Hz, 2H), 7.15 (d, J = 8.59 Hz, 1H), 7.19 (d, J = 2.02 Hz, 1H), 7.44–7.53 (m, 4H), 7.59 (d, J = 16.17 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 108.96, 115.81, 116.74, 117.08, 118.19, 122.74, 124.88, 127.78, 128.31, 129.92, 130.36, 131.21, 138.23, 139.68, 145.54, 157.25, 158.75, 161.04, 171.00. HRMS ESI m/z 405.0790 $[M + H]^+$.

*3-(4-((6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)oxy)phenyl)propanoic Acid (**17**).* Step 1: To a solution of *tert*-butyl (*E*)-3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)-oxy)phenyl)acrylate (27 mg, 0.055 mmol) in 4:1 MeOH:CH_2Cl_2 (2.5 mL) was added palladium on carbon (10 wt %, 0.6 mg). The reaction vessel was evacuated and purged with hydrogen, and the mixture was stirred vigorously under a hydrogen atmosphere (balloon) at room temperature for 18 h. The solution was then purged with nitrogen, and the catalyst was removed by filtration though a pad of Celite and washed with CH_2Cl_2. The resulting solution was concentrated *in vacuo* to afford crude *tert*-butyl 3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)phenyl)propanoate (27 mg, 99% yield), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.41 (s, 9H), 2.50 (t, J = 7.83 Hz, 2H), 2.86 (t, J = 7.83 Hz, 2H), 3.81 (s, 3H), 3.88 (s, 3H), 6.85–6.92 (m, 5H), 7.08 (d, J = 8.59 Hz, 2H), 7.25–7.28 (m, 2H), 7.67 (d, J = 8.59 Hz, 2H). LC/MS ESI m/z 491.3 $[M + H]^+$.

Step 2: To a solution of *tert*-butyl 3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)phenyl)propanoate (27 mg, 0.055 mmol) in CH_2Cl_2 (1.7 mL) at 0 °C was added BBr_3 (1.0 M in CH_2Cl_2, 0.220 mL, 0.220 mmol) dropwise (the reaction turned brown in color, and a solid immediately precipitated from the solution). The resulting mixture was stirred at 0 °C for 1 h, after which the reaction was quenched with ice water (3.0 mL) and allowed to warm to room temperature with vigorous stirring. The resulting mixture was concentrated *in vacuo*, dissolved in MeOH (2 mL), and then purified by reverse phase HPLC (neutral conditions, 3% 1-propanol in 1–100% CH_3CN/H_2O) to afford 3-(4-((6-hydroxy-2-(4-hydroxyphenyl)-benzo-[b]thiophen-3-yl)oxy)phenyl)propanoic acid (7 mg, 31% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 2.54 (t, J = 7.58, 2H), 2.85 (t, J = 7.58 Hz, 2H), 6.72–6.79 (m, 3H), 6.82 (d, J = 8.59 Hz, 2H), 7.08–7.19 (m, 4H), 7.52 (d, J = 8.59 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 31.36, 37.08, 108.87, 115.58, 116.53, 116.65, 122.98, 125.21, 127.42, 128.67, 129.85, 130.75, 136.13, 138.16, 140.39, 157.06, 157.79, 158.56, 177.04. HRMS ESI m/z 407.0943 $[M + H]^+$.

*(E)-2-(4-Hydroxyphenyl)-3-(4-(2-(1-methyl-1H-imidazol-4-yl)-vinyl)phenoxy)-benzo[b]thiophen-6-ol (**18**).* The title compound was prepared as a white solid in 58% yield from 3-(4-bromophenoxy)-2-(4-hydroxyphenyl)benzo[b]thiophen-6-ol and 4-vinyl-1-methyl imidazole using the procedure described for the synthesis of **15**. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 3.82 (s, 3H), 6.57–6.74 (m, 3H), 6.75–6.93 (m, 3H), 6.98–7.14 (m, 3H), 7.32–7.54 (m, 5H), 8.73 (s, 1H). LC/MS ESI m/z 441.3 $[M + H]^+$.

*(E)-3-(4-(2-(1H-Imidazol-4-yl)vinyl)phenoxy)-2-(4-hydroxyphenyl)benzo[b]thiophen-6-ol (**19**).* The title compound was prepared as a white solid in 15% yield from 3-(4-bromophenoxy)-2-(4-hydroxyphenyl)benzo[b]thiophen-6-ol and *tert*-butyl 4-vinyl-1*H*-imidazole-1-carboxylate using the procedure described for the synthesis of **15**. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.57 (s, 1H), 7.43 (d, J = 8.59 Hz, 2H), 7.30 (d, J = 8.59 Hz, 2H), 6.96–7.14 (m, 3H), 6.74–6.96 (m, 4H), 6.53–6.74 (m, 3H). LC/MS ESI m/z 427.3 $[M + H]^+$.

*(E)-Ethyl 3-(4-((6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)amino)phenyl)acrylate (**22**).* To a large microwave vial (10–20 mL) were added 3-bromo-6-methoxy-2-(4-methoxyphenyl)-benzo[b]thiophene (350 mg, 1.00 mmol), ethyl 4-aminocinnamate (383 mg, 2.00 mmol), and K_3PO_4 (425 mg, 2.00 mmol). 1,4-Dioxane (6.0 mL) was then added followed by chloro-(2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2-aminoethyl)phenyl]-palladium(II) methyl-*tert*-butyl ether adduct (RuPhos palladacycle, 73.0 mg, 0.10 mmol), and the reaction was subjected to microwave irradiation at 120 °C for 3 h. Upon completion, the reaction mixture was transferred to round-bottom flask with EtOAc and concentrated *in vacuo*. The resulting material was partitioned between water and EtOAc and separated; the aqueous layer was then further extracted with EtOAc (3×), and the combined organic layers were passed through a phase separator to remove water and concentrated *in vacuo*. The crude material was purified by column chromatography (SiO_2, 0–30% EtOAc/heptane) to afford (*E*)-ethyl 3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)amino)phenyl)acrylate (69.0 mg, 15% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.21–1.26 (m, 3H), 3.76 (s, 3H), 3.85 (s, 3H), 4.15 (q, J = 7.07 Hz, 2H), 6.24 (d, J = 16.17 Hz, 1H), 6.58 (d, J = 8.59 Hz, 2H), 6.94–7.01 (m, 3H), 7.34 (d, J = 8.59 Hz, 1H), 7.41 (d, J = 8.59 Hz, 2H), 7.48 (d, J = 15.66 Hz, 1H), 7.53 (d, J = 2.02 Hz, 1H), 7.58 (d, J = 9.09 Hz, 2H), 8.25 (s, 1H). LC/MS ESI m/z 460.3 $[M + H]^+$.

*(E)-Ethyl 3-(4-((6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)(methyl)amino)phenyl)acrylate (**23**).* To a solution of (*E*)-ethyl 3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[b]-thiophen-3-yl)amino)phenyl)acrylate (69.0 mg, 0.15 mmol) in DMF (6.0 mL) at room temperature was added NaH (60% suspension in oil, 139 mg, 3.48 mmol). After 15 min, methyl iodide (0.272 mL, 4.35 mmol) was added, and the resulting solution was allowed to stir at room temperature for 45 min, after which time the reaction was quenched

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with brine and diluted with water. The resulting solution was then extracted with EtOAc (3×), and the combined organic layers were washed with brine (2×), passed through a phase separator, and concentrated *in vacuo* to afford the crude product which was purified by reverse phase HPLC (neutral conditions, 3% 1-propanol in 1−100% CH_3CN/H_2O) to afford ((*E*)-ethyl 3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)(methyl)amino)phenyl)acrylate (25.5 mg, 36% yield) as a white solid. LC/MS ESI *m*/*z* 474.3 $[M + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)-amino)phenyl)acrylic Acid (**24**).* Step 1: To a solution of (*E*)-ethyl 3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)amino)-phenyl)acrylate (200 mg, 0.44 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C was added BBr_3 (1.0 M in CH_2Cl_2, 1.74 mL, 1.74 mmol) dropwise. After 2 h at 0 °C, the reaction was quenched with water and extracted with 10% 2-propanol/CH_2Cl_2; the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude ethyl (*E*)-3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)amino)phenyl)acrylate, which was used without further purification. LC/MS ESI *m*/*z* 432.2 $[M + H]^+$.

Step 2: To a solution of crude ethyl (*E*)-3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)amino)phenyl)acrylate (70.5 mg, 0.163 mmol) in EtOH (1.0 mL) at room temperature was added LiOH (2 N aq., 1.0 mL, 12.24 mmol); the reaction was allowed to stir at room temperature for 18 h, after which time the reaction was quenched with 4 N HCl until pH ∼ 3 and then extracted with EtOAc (2×). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product, which was purified by reverse phase HPLC (neutral conditions, 3% 1-propanol in 1−100% CH_3CN/H_2O) to afford (*E*)-3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)amino)phenyl)acrylic acid (38.1 mg, 22% yield over two steps). ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 6.19 (d, *J* = 15.66 Hz, 1H), 6.63 (d, *J* = 8.59 Hz, 2H), 6.75 (d, *J* = 15.66 Hz, 2H), 6.82 (dd, *J* = 8.59, 2.02 Hz, 1H), 7.19 (d, *J* = 2.02 Hz, 1H), 7.28−7.38 (m, 3H), 7.42−7.50 (m, 2H), 7.54 (d, *J* = 15.66 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 108.63, 113.87, 114.83, 115.37, 116.62, 123.79, 125.27, 126.31, 128.36, 130.56, 131.12, 132.38, 133.83, 139.35, 147.22, 151.32, 156.77, 158.65, 171.79. HRMS ESI *m*/*z* 404.0945 $[M + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)-(methyl)amino)phenyl)acrylic Acid (**25**).* Step 1: To a solution of (*E*)-ethyl 3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)-(methyl)amino)phenyl)acrylate (25.5 mg, 0.05 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added BBr_3 (1.0 M in CH_2Cl_2, 0.215 mL, 0.21 mmol) dropwise. After 4 h at 0 °C, the reaction was quenched with sat. aq. $NaHCO_3$ and extracted with 5% MeOH/EtOAc; the combined organic layers were passed through a phase separator and concentrated *in vacuo* to afford crude (*E*)-ethyl 3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)(methyl)amino)phenyl)-acrylate, which was used without further purification. LC/MS ESI *m*/*z* 446.5 $[M + H]^+$.

Step 2: To a solution of crude (*E*)-ethyl 3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)(methyl)amino)phenyl)-acrylate (25 mg, 0.06 mmol) in EtOH (1.5 mL) at room temperature was added LiOH (2 N aq., 0.168 mL, 0.34 mmol); the reaction was allowed to stir at room temperature for 18 h, after which time the reaction was quenched with 1 N HCl (4 mL) and concentrated *in vacuo* to remove EtOH. The resulting suspension was extracted with 5% MeOH/EtOAc (3×), dried, and concentrated *in vacuo* to give the crude product, which was purified by reverse phase HPLC (neutral conditions, 3% 1-propanol in 1−100% CH_3CN/H_2O) to afford (*E*)-3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)(methyl)-amino)phenyl)acrylic acid (4.98 mg, 0.01 mmol, 21% yield over two steps) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 3.12 (s, 3H), 6.11 (d, *J* = 15.66 Hz, 1H), 6.56 (d, *J* = 8.59 Hz, 2H), 6.65 (d, *J* = 9.09 Hz, 2H), 6.69 (dd, *J* = 8.59, 2.02 Hz, 1H), 6.98 (d, *J* = 8.59 Hz, 1H), 7.11 (d, *J* = 2.02 Hz, 1H), 7.24 (d, *J* = 9.09 Hz, 2H), 7.30 (d, *J* = 9.09 Hz, 2H), 7.48 (d, *J* = 16.17 Hz, 1H). HRMS ESI *m*/*z* 418.1065 $[M + H]^+$.

*(4-Bromophenyl)(6-methoxy-2-(4-methoxyphenyl)benzo[b]-thiophen-3-yl)methanone (**27**).* To a solution of 6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (350 mg, 1.295 mmol) in CH_2Cl_2 (11 mL) at 0 °C was added 4-bromobenzoyl chloride (284 mg, 1.295 mmol) followed by $AlCl_3$ (190 mg, 1.424 mmol). The resulting mixture was allowed to warm to room temperature, and after 3.5 h, it was quenched by addition of potassium sodium tartrate and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude material, which was purified by column chromatography (SiO_2, 0−30% EtOAc/heptane) to afford (4-bromophenyl)(6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)methanone as a yellow solid (562 mg, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 3.77 (s, 3H), 3.91 (s, 3H), 6.76 (d, *J* = 9.09 Hz, 2H), 6.98−7.04 (m, 1H), 7.30 (d, *J* = 8.59 Hz, 2H), 7.34 (d, *J* = 2.02 Hz, 1H), 7.41 (d, *J* = 8.59 Hz, 2H), 7.59−7.64 (m, 3H). LC/MS ESI *m*/*z* 455.0 $[M + H]^+$.

*tert-Butyl (E)-3-(4-(6-Methoxy-2-(4-methoxyphenyl)benzo[b]-thiophene-3-carbonyl)phenyl)acrylate (**28**).* The title compound was prepared as a yellow solid in 88% yield from (4-bromophenyl)-(6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)methanone and *tert*-butyl acrylate using the procedure described for the synthesis of **15**. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.54 (s, 9H), 3.74 (s, 3H), 3.91 (s, 3H), 6.36 (d, *J* = 16.17 Hz, 1H), 6.74 (d, *J* = 9.09 Hz, 2H), 6.98−7.03 (m, 1H), 7.31 (d, *J* = 8.59 Hz, 2H), 7.34 (d, *J* = 2.53 Hz, 1H), 7.38 (d, *J* = 8.59 Hz, 2H), 7.50 (d, *J* = 16.17 Hz, 1H), 7.64 (d, *J* = 9.09 Hz, 1H), 7.75 (d, *J* = 8.08 Hz, 2H). LC/MS ESI *m*/*z* 501.3 $[M + H]^+$.

*(E)-3-(4-(6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene-3-carbonyl)phenyl)acrylic Acid (**29**).* To a solution of *tert*-butyl (*E*)-3-(4-(6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene-3-carbonyl)-phenyl)acrylate (41 mg, 0.092 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C was added BBr_3 (1.0 M in CH_2Cl_2, 0.37 mL, 0.37 mmol) dropwise; the resulting mixture was stirred at 0 °C for 75 min, after which the reaction was quenched by addition of sat. aq. $NaHCO_3$ (4 mL) solution, reacidifed to pH 3 with conc. HCl. The aqueous layer was then extracted with 5% MeOH/EtOAc (4 × 12 mL). The combined organic layers were passed through a phase separator to remove water and concentrated *in vacuo* to afford the crude product, which was dissolved in MeOH (2 mL) and purified by reverse phase HPLC (neutral conditions, 3% 1-propanol in 1−100% CH_3CN/H_2O) to afford (*E*)-3-(4-(6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophene-3-carbonyl)phenyl)-acrylic acid (16.1 mg, 42% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 6.54 (d, *J* = 15.66 Hz, 1H), 6.66 (d, *J* = 8.59 Hz, 2H), 6.88 (dd, *J* = 8.84, 2.27 Hz, 1H), 7.16 (d, *J* = 8.59 Hz, 2H), 7.32−7.40 (m, 2H), 7.50 (d, *J* = 16.17 Hz, 1H), 7.59−7.64 (m, 2H), 7.65−7.70 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 107.20, 115.41, 115.73, 122.61, 123.54, 123.61, 128.31, 129.04, 129.86, 130.12, 132.07, 137.77, 138.94, 139.37, 141.99, 142.81, 155.59, 158.07, 167.41, 193.18. HRMS ESI *m*/*z* 417.0786 $[M + H]^+$.

*Methyl (E)-3-(4-(6-Methoxy-2-(4-methoxyphenyl)benzo[b]-thiophen-3-yl)phenyl)acrylate (**31**).* To a solution of 3-bromo-6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (200 mg, 0.573 mmol) in 4:1 dimethoxyethane:water (5.0 mL) was added (*E*)-(4-(3-methoxy-3-oxoprop-1-en-1-yl)phenyl)boronic acid (130 mg, 0.630 mmol), Pd-$(PPh_3)_4$ (33.1 mg, 0.029 mmol), and Na_2CO_3 (121 mg, 1.145 mmol). The mixture was then subjected to microwave irradiation for 1 h at 100 °C, after which the reaction was diluted with water and extracted with CH_2Cl_2 (3×). The combined organic layers were concentrated *in vacuo* to give the crude product, which was purified by column chromatography (SiO_2, 0−20% EtOAc/heptane) to give methyl (*E*)-3-(4-(6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)phenyl)-acrylate (160 mg, 65% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 3.80 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 6.48 (d, *J* = 16.17 Hz, 1H), 6.80 (d, *J* = 9.09 Hz, 2H), 6.97 (dd, *J* = 9.09, 2.53 Hz, 1H), 7.23 (d, *J* = 8.59 Hz, 2H), 7.33−7.40 (m, 3H), 7.45 (d, *J* = 8.59 Hz, 1H), 7.56 (d, *J* = 8.08 Hz, 2H), 7.74 (d, *J* = 16.17 Hz, 1H). LC/MS ESI *m*/*z* 431.3 $[M + H]^+$.

*Methyl (E)-3-(4-(6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]-thiophen-3-yl)phenyl)acrylate (**32**).* To a solution of methyl (*E*)-3-(4-(6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)phenyl)-acrylate (150 mg, 0.348 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added BBr_3 (1.0 M in heptane, 1.394 mL, 1.394 mmol), and the reaction

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mixture was stirred for 2 h. Upon completion, the reaction was quenched by addition of sat. aq. $NaHCO_3$ solution, extracted with CH_2Cl_2 (2×), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product. The crude material was purified by column chromatography (SiO_2, 10−100% EtOAc/heptane) to give methyl (*E*)-3-(4-(6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]-thiophen-3-yl)phenyl)acrylate (65 mg, 46% yield) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 3.75 (s, 3H), 6.63 (d, J = 16.17 Hz, 1H), 6.68 (d, J = 8.59 Hz, 2H), 6.87 (dd, J = 8.84, 2.27 Hz, 1H), 7.07 (d, J = 8.59 Hz, 2H), 7.27 (d, J = 8.59 Hz, 1H), 7.29 (d, J = 2.02 Hz, 1H), 7.32 (d, J = 8.08 Hz, 2H), 7.70 (d, J = 16.17 Hz, 1H), 7.75 (d, J = 8.08 Hz, 2H), 9.48 (d, J = 13.64 Hz, 2H). HRMS ESI m/z 403.0985 $[M + H]^+$.

*(E)-3-(4-(6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)-phenyl)acrylic Acid (**33**).* To a solution of methyl (*E*)-3-(4-(6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)phenyl)acrylate (60 mg, 0.149 mmol) in 4:1 THF:MeOH (5.0 mL) at room temperature was added LiOH (2 N aq., 1.0 mL, 13.42 mmol); the reaction was warmed to 60 °C and stirred. After 2 h, the mixture was cooled to room temperature and concentrated *in vacuo* to remove organics. The remaining aqueous layer was acidified with concentrated HCl, and the resulting precipitate was filtered, washed with cold water, and dried under vacuum overnight to afford (*E*)-3-(4-(6-hydroxy-2-(4-hydroxyphenyl)-benzo[*b*]thiophen-3-yl)phenyl)acrylic acid (51 mg, 88% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 6.56 (d, J = 16.17 Hz, 1H), 6.68 (d, J = 8.59 Hz, 2H), 6.86 (dd, J = 8.59, 2.02 Hz, 1H), 7.05 (d, J = 8.59 Hz, 2H), 7.26−7.35 (m, 4H), 7.62 (d, J = 16.17 Hz, 1H), 7.73 (d, J = 8.08 Hz, 2H), 9.66 (br d, J = 11.12 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 107.22, 114.93, 115.57, 119.51, 123.27, 124.31, 128.69, 130.42, 130.45, 130.61, 132.99, 133.23, 136.05, 137.36, 139.20, 143.45, 155.31, 157.29, 167.74. HRMS ESI m/z 389.0845 $[M + H]^+$.

*(E)-3-(4-((6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)phenyl)acrylic Acid (**34**).* Step 1: To a solution of (*E*)-methyl 3-(4-hydroxyphenyl)acrylate (190 mg, 1.07 mmol) in DMF (5 mL) was added sodium hydride (60% suspension in oil, 42.7 mg, 1.07 mmol). The resulting mixture was allowed to stir for 10 min at room temperature, after which 3-bromo-6-methoxy-2-(4-methoxyphenyl)benzo-[*b*]thiophene 1-oxide (300 mg, 0.82 mmol) was added, as a solid. The reaction was heated to 80 °C for 18 h, and upon completion, it was cooled to room temperature, quenched with water, and diluted with CH_2Cl_2. The organic phase was collected, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography (SiO_2, 0−80% EtOAc/heptane) to afford (*E*)-methyl 3-(4-((6-methoxy-2-(4-methoxyphenyl)-1-oxidobenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate (370 mg, 97% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 7.75 (d, J = 9.09 Hz, 2H), 7.65 (d, J = 15.66 Hz, 1H), 7.54 (d, J = 2.02 Hz, 1H), 7.43−7.52 (m, J = 9.09 Hz, 2H), 7.07−7.16 (m, J = 8.59 Hz, 2H), 6.98−7.07 (m, 1H), 6.93 (d, J = 9.09 Hz, 3H), 6.35 (d, J = 16.17 Hz, 1H), 3.91 (s, 3H), 3.82 (d, J = 1.52 Hz, 6H). LC/MS ESI m/z 463.4 $[M + H]^+$.

Step 2: To a 30 mL vial containing (*E*)-methyl 3-(4-((6-methoxy-2-(4-methoxyphenyl)-1-oxidobenzo[*b*]thiophen-3-yl)oxy)phenyl)-acrylate (200 mg, 0.43 mmol) were added THF (5 mL), triphenylphosphine (420 mg, 1.60 mmol), and TMS-Cl (0.553 mL, 4.32 mmol). The reaction was heated to 75 °C for 18 h, after which time the mixture was cooled to room temperature, quenched with sat. aq. $NaHCO_3$, and diluted with DCM. The organic phase was collected, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography (SiO_2, 0−60% EtOAc/heptane) to afford (*E*)-methyl 3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)-acrylate (110 mg, 57% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 7.58−7.73 (m, 3H), 7.38−7.50 (m, J = 8.59 Hz, 2H), 7.28 (t, J = 2.27 Hz, 2H), 6.96−7.05 (m, J = 8.59 Hz, 2H), 6.85−6.96 (m, 3H), 6.32 (d, J = 15.66 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H). LC/MS ESI m/z 447.0 $[M + H]^+$.

Step 3: To a 30 mL vial containing (*E*)-methyl 3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate (110 mg, 0.25 mmol) were added THF (2.00 mL), MeOH (1.00 mL), H_2O (1.00 mL), and LiOH (29.5 mg, 1.23 mmol). The resulting mixture was stirred at room temperature for 60 min, after which the reaction was concentrated *in vacuo*, diluted with water, and acidified to pH 2 with 6 M HCl, causing a precipitate to form. The mixture was diluted with 20 mL of CH_2Cl_2 and 2 mL of MeOH, and the organic layer was collected, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford (*E*)-3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)acrylic acid (98 mg, 92% yield) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.51−7.69 (m, 5H), 7.43 (d, J = 2.02 Hz, 1H), 7.25 (d, J = 9.09 Hz, 1H), 6.88−7.02 (m, 5H), 6.37 (d, J = 15.66 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H). LC/MS ESI m/z 433.0 $[M + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)-oxy)phenyl)-N-methylacrylamide (**35a**).* To a solution of (*E*)-3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)-acrylic acid (97 mg, 0.240 mmol) in 10:1 THF:DMF (4.4 mL) were added HATU (137 mg, 0.360 mmol) and DIEA (0.209 mL, 1.199 mmol), and the mixture was stirred for 10 min, after which time methylamine hydrochloride was added (48.6 mg, 0.720 mmol) and the mixture was stirred at room temperature for 6 h. The reaction was quenched with water and diluted with EtOAc, the layers were separated, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product. The material was dissolved in MeOH (2 mL) and purified by reverse phase HPLC (neutral conditions, 3% 1-propanol in 1−100% CH_3CN/H_2O) to afford (*E*)-3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]-thiophen-3-yl)oxy)phenyl)-*N*-methylacrylamide (80.6 mg, 80% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 2.66−2.71 (m, 3H), 6.43 (d, J = 15.66 Hz, 1H), 6.69−6.86 (m, 3H), 6.90−7.00 (m, 2H), 7.10 (d, J = 8.59 Hz, 1H), 7.26 (d, J = 2.02 Hz, 1H), 7.33 (d, J = 15.66 Hz, 1H), 7.42−7.55 (m, 4H), 7.75−7.87 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 25.71, 108.13, 115.05, 115.71, 115.93, 120.68, 121.40, 122.43, 125.59, 126.01, 128.34, 129.41, 129.48, 135.98, 137.60, 137.85, 155.90, 157.45, 158.14, 165.55. HRMS ESI m/z 418.1102 $[M + H]^+$.

*(E)-3-(4-((6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)phenyl)acrylamide (**35b**).* In a 30 mL vial, (*E*)-3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)-acrylic acid (98 mg, 0.23 mmol) was dissolved in DMF (2 mL). The vial was charged with HATU (129 mg, 0.34 mmol) and DIEA (0.119 mL, 0.68 mmol), and the mixture was stirred for 10 min. A color change from pale orange to a dark orange was observed. To the solution was added NH_4Cl (24.24 mg, 0.45 mmol), and the reaction mixture was stirred for 30 min at room temperature. The reaction was quenched with sat. aq. NH_4Cl and diluted with DCM. The organic phase was collected (phase separator) and concentrated to afford the crude product. The crude material was purified by column chromatography (SiO_2, 1−10% MeOH/DCM) to afford (*E*)-3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)acrylamide (77 mg, 79% yield) as an off-white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 8.00 (s, 4H), 7.59−7.70 (m, 2H), 7.45−7.55 (m, 2H), 7.42 (d, J = 2.02 Hz, 1H), 7.24 (d, J = 8.59 Hz, 1H), 6.84−7.02 (m, 4H), 6.52 (d, J = 15.66 Hz, 1H), 3.88 (s, 2H), 3.79 (s, 3H). LC/MS ESI m/z 432.3 $[M + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)-oxy)phenyl)acrylamide (**35c**).* The title compound was prepared in 34% yield from (*E*)-3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]-thiophen-3-yl)oxy)phenyl)acrylic acid and NH_4Cl using the procedure described for the synthesis of **35a**. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 6.48 (d, J = 15.66 Hz, 1H), 6.73−6.76 (m, 1H), 6.76−6.78 (m, 1H), 6.80 (dd, J = 8.84, 2.27 Hz, 1H), 6.89−6.98 (m, 2H), 7.16 (d, J = 8.59 Hz, 1H), 7.19 (d, J = 2.02 Hz, 1H), 7.42−7.55 (m, 5H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 108.97, 115.81, 116.74, 117.06, 119.91, 122.75, 124.90, 127.74, 128.32, 129.92, 130.59, 130.89, 138.23, 139.73, 142.20, 157.27, 158.75, 160.74, 171.31. HRMS ESI m/z 404.0944 $[M + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)-oxy)phenyl)-N-(2-hydroxyethyl)acrylamide (**35d**).* The title compound was prepared in 30% yield from (*E*)-3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)acrylic acid and

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ethanolamine using the procedure described for the synthesis of **35a**. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 3.41 (t, J = 5.56 Hz, 2H), 3.65 (t, J = 5.81 Hz, 2H), 6.47 (d, J = 15.66 Hz, 1H), 6.71−6.77 (m, 2H), 6.79 (dd, J = 8.59, 2.02 Hz, 1H), 6.88−6.96 (m, 2H), 7.15 (d, J = 9.09 Hz, 1H), 7.18 (d, J = 2.02 Hz, 1H), 7.42−7.54 (m, 5H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 43.29, 61.78, 109.12, 116.07, 116.90, 117.05, 120.35, 122.68, 124.70, 127.55, 128.07, 129.88, 130.68, 130.77, 138.24, 139.70, 141.23, 157.87, 159.18, 160.67, 169.27. HRMS ESI m/z 448.1205 $[M + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)-oxy)phenyl)-N-(3,3,3-trifluoropropyl)acrylamide (**35e**).* Step 1: To a 30 mL vial containing (*E*)-3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo-[*b*]thiophen-3-yl)oxy)phenyl)acrylic acid (41 mg, 0.10 mmol) was added DMF (3 mL), followed by 3,3,3-trifluoropropan-1-amine (13.94 mg, 0.12 mmol), HATU (54.1 mg, 0.14 mmol), and DIEA (0.050 mL, 0.28 mmol). The mixture was stirred at room temperature for 30 min, after which the reaction was quenched with sat. aq. NH_4Cl and diluted with DCM. The organic phase was collected (phase separator) and concentrated *in vacuo* onto silica gel. The crude material was purified by column chromatography (SiO_2, 0−30% EtOAc/heptane) to afford (*E*)-3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)-*N*-(3,3,3-trifluoropropyl)acrylamide (38 mg, 72% yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.64 (d, J = 9.09 Hz, 2H), 7.45−7.56 (m, 3H), 7.42 (d, J = 2.02 Hz, 1H), 7.25 (d, J = 8.59 Hz, 1H), 6.90−7.02 (m, 5H), 6.47 (d, J = 15.66 Hz, 1H), 3.88 (s, 3H), 3.74−3.85 (m, 3H), 3.54 (t, J = 7.07 Hz, 2H), 2.34−2.56 (m, 2H). LC/MS ESI m/z 528.3 $[M + H]^+$.

Step 2: To a 30 mL vial containing (*E*)-3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)-*N*-(3,3,3-trifluoropropyl)acrylamide (38 mg, 0.07 mmol) in CH_2Cl_2 (1 mL) was added BBr_3 (1 M in heptane, 0.072 mL, 0.07 mmol), and the reaction was stirred at room temperature for 1 h. The reaction was quenched with 4 mL of MeOH and stirred for 10 min at room temperature, after which time the resulting mixture was concentrated to 50% volume and the crude product was purified by reverse phase HPLC (acidic conditions, 0.1% TFA in 1−100% CH_3CN/H_2O) to afford (*E*)-3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)-*N*-(3,3,3-trifluoropropyl)acrylamide (31 mg, 86% yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.40−7.63 (m, 5H), 7.21 (d, J = 2.02 Hz, 1H), 7.15 (d, J = 8.59 Hz, 1H), 6.88−6.98 (m, 2H), 6.68−6.87 (m, 3H), 6.45 (d, J = 15.66 Hz, 1H), 3.54 (t, J = 7.07 Hz, 2H), 2.46 (tq, J = 6.82, 10.95 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 34.18, 34.46, 108.96, 115.80, 116.74, 117.08, 119.92, 122.75, 124.90, 126.74, 127.75, 128.33, 129.48, 129.92, 130.59, 130.84, 138.23, 139.73, 141.60, 157.25, 158.75, 160.73, 169.07. LC/MS ESI m/z 500.4 $[M + H]^+$.

*(E)-5-(4-((6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)styryl)-1H-tetrazole (**36**).* To a microwave vial, (*E*)-3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)-acrylamide (75 mg, 0.174 mmol) and Bu_2SnO (4.33 mg, 0.02 mmol) were suspended in dimethoxyethane (3 mL). The vial was charged with $TMSN_3$ (0.023 mL, 0.17 mmol), and the reaction was heated for 60 min at 180 °C under microwave irradiation. The reaction mixture was filtered to remove solids and concentrated onto silica gel. The crude material was purified by column chromatography (SiO_2, 1−20% MeOH/DCM) to afford (*E*)-5-(4-((6-methoxy-2-(4-methoxyphenyl)-benzo[*b*]thiophen-3-yl)oxy)styryl)-1*H*-tetrazole (66 mg, 83% yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.45−7.61 (m, 5H), 7.32 (d, J = 2.02 Hz, 1H), 7.15 (d, J = 9.09 Hz, 1H), 6.98 (d, J = 16.67 Hz, 1H), 6.86−6.93 (m, 2H), 6.78−6.86 (m, 3H), 3.78 (s, 3H), 3.69 (s, 3H). LC/MS ESI m/z 457.4 $[M + H]^+$.

*(E)-3-(4-(2-(1H-Tetrazol-5-yl)vinyl)phenoxy)-2-(4-hydroxyphenyl)-benzo[b]thiophen-6-ol (**37**).* The title compound was prepared as a pale yellow solid in 40% yield from (*E*)-5-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)styryl)-1*H*-tetrazole using the procedure described for the synthesis of **14**. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.45−7.56 (m, 3H), 7.38−7.45 (m, 2H), 7.10 (d, J = 2.02 Hz, 1H), 7.06 (d, J = 8.59 Hz, 1H), 6.98 (d, J = 16.17 Hz, 1H), 6.84−6.92 (m, J = 9.09 Hz, 2H), 6.70 (dd, J = 2.02, 8.59 Hz, 1H), 6.61−6.67 (m, 2H). LC/MS ESI m/z 429.2 $[M + H]^+$.

*(E)-2-(4-Hydroxyphenyl)-3-(4-(2-(1-methyl-1H-tetrazol-5-yl)-vinyl)-phenoxy)benzo[b]thiophen-6-ol (**38**) and (E)-2-(4-Hydroxyphenyl)-3-(4-(2-(2-methyl-2H-tetrazol-5-yl)vinyl)-phenoxy)benzo-[b]thiophen-6-ol (**39**).* Step 1: To a 30 mL vial containing (*E*)-5-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)styryl)-2*H*-tetrazole (15 mg, 0.03 mmol) in DMF (2 mL) were added with iodomethane (2.260 μL, 0.04 mmol) and K_2CO_3 (13.62 mg, 0.10 mmol), and the reaction was stirred at room temperature for 18 h. The reaction was quenched with sat. aq. NH_4Cl (15 mL) and extracted with CH_2Cl_2 (25 mL). The organic phase was collected (phase separator) and concentrated *in vacuo* to afford the crude product. The crude product was purified by reverse phase HPLC (neutral conditions, 3% 1-propanol in 1−100% CH_3CN/H_2O) to afford (*E*)-5-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)styryl)-1-methyl-1*H*-tetrazole (8 mg, 0.08 mmol, 52% yield) and (*E*)-5-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)styryl)-2-methyl-2*H*-tetrazole (6 mg, 0.01 mmol, 39% yield) both as a white solids.

(E)-5-(4-((6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)styryl)-1-methyl-1H-tetrazole. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.48−7.60 (m, 3H), 7.39−7.48 (m, 2H), 7.30 (d, J = 2.02 Hz, 1H), 7.14 (d, J = 9.09 Hz, 1H), 6.95 (d, J = 16.67 Hz, 1H), 6.77−6.90 (m, 5H), 4.24 (s, 3H), 3.76 (s, 3H), 3.68 (s, 3H). LC/MS ESI m/z 471.4 $[M + H]^+$.

(E)-5-(4-((6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)styryl)-2-methyl-2H-tetrazole. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.75 (d, J = 16.17 Hz, 1H), 7.59−7.70 (m, 4H), 7.43 (d, J = 2.02 Hz, 1H), 7.27 (d, J = 8.59 Hz, 1H), 7.09 (d, J = 16.17 Hz, 1H), 6.97−7.05 (m, 2H), 6.90−6.97 (m, 3H), 4.14 (s, 3H), 3.89 (s, 3H), 3.80 (s, 3H). LC/MS ESI m/z 471.4 $[M + H]^+$.

Step 2 for preparation of **38**: The title compound was prepared as a white solid in 35% yield from (*E*)-5-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)styryl)-1-methyl-1*H*-tetrazole using the procedure described for the synthesis of **14**. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.52 (d, J = 16.67 Hz, 1H), 7.38−7.48 (m, 4H), 7.09 (d, J = 2.02 Hz, 1H), 7.06 (d, J = 8.59 Hz, 1H), 6.96 (d, J = 16.67 Hz, 1H), 6.81−6.90 (m, 2H), 6.61−6.73 (m, 3H), 4.24 (s, 3H). LC/MS ESI m/z 443.3 $[M + H]^+$.

Step 2 for preparation of **39**: The title compound was prepared as a white solid in 32% yield from (*E*)-5-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)styryl)-2-methyl-2*H*-tetrazole using the procedure described for the synthesis of **14**. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.64 (d, J = 16.17 Hz, 1H), 7.51−7.59 (m, J = 8.59 Hz, 2H), 7.37−7.47 (m, J = 8.59 Hz, 2H), 7.10 (d, J = 2.02 Hz, 1H), 7.07 (d, J = 8.59 Hz, 1H), 6.97 (d, J = 16.17 Hz, 1H), 6.88 (d, J = 8.59 Hz, 2H), 6.61−6.76 (m, 3H), 4.03 (s, 3H). LC/MS ESI m/z 443.3 $[M + H]^+$.

*(E)-Ethyl 3-(4-((6-Methoxy-2-(4-methoxyphenyl)-1-oxidobenzo-[b]thiophen-3-yl)oxy)-2-methylphenyl)acrylate (**40a**).* The title compound was prepared in 54% yield from 3-bromo-6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene 1-oxide and ethyl (*E*)-3-(4-hydroxy-2-methylphenyl)acrylate (see Supporting Information for synthesis) using the procedure described for the synthesis of **34**, step 1. LC/MS ESI m/z 491.3 $[M + H]^+$.

*(E)-Ethyl 3-(4-((6-Methoxy-2-(4-methoxyphenyl)-1-oxidobenzo-[b]thiophen-3-yl)oxy)-3-methylphenyl)acrylate (**40b**).* The title compound was prepared in 43% yield from 3-bromo-6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene 1-oxide and ethyl (*E*)-3-(4-hydroxy-3-methylphenyl)acrylate (see Supporting Information for synthesis) using the procedure described for the synthesis of **34**, step 1. LC/MS ESI m/z 491.3 $[M + H]^+$.

*(E)-Ethyl 3-(2-Methoxy-4-((6-methoxy-2-(4-methoxyphenyl)-1-oxidobenzo[b]thiophen-3-yl)oxy)phenyl)acrylate (**40c**).* The title compound was prepared in 54% yield from 3-bromo-6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene 1-oxide and ethyl (*E*)-3-(4-hydroxy-2-methoxyphenyl)acrylate (see Supporting Information for synthesis) using the procedure described for the synthesis of **34**, step 1. LC/MS ESI m/z 507.3 $[M + H]^+$.

*(E)-Ethyl 3-(4-((6-Methoxy-2-(4-methoxyphenyl)-1-oxidobenzo-[b]thiophen-3-yl)oxy)phenyl)-2-methyl acrylate (**40d**).* The title compound was prepared in 86% yield from 3-bromo-6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene 1-oxide and (*E*)-ethyl 3-(4-

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hydroxyphenyl)-2-methyl acrylate (see Supporting Information for synthesis) using the procedure described for the synthesis of **34**, step 1. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.35 (t, J = 7.07 Hz, 3H), 2.09 (d, J = 1.52 Hz, 3H), 3.81 (s, 3H), 3.90 (s, 3H), 4.28 (q, J = 7.07 Hz, 2H), 6.91 (d, J = 8.59 Hz, 2H), 6.94 (dd, J = 8.59, 2.53 Hz, 1H), 7.05−7.12 (m, 3H), 7.33 (d, J = 8.59 Hz, 2H), 7.52 (d, J = 2.53 Hz, 1H), 7.60 (s, 1H), 7.73 (d, J = 9.09 Hz, 2H). LC/MS ESI m/z 491.3 $[M + H]^+$.

*Methyl (E)-3-(4-((6-Methoxy-2-(4-methoxyphenyl)-1-oxidobenzo[b]thiophen-3-yl)oxy)phenyl)but-2-enoate (**40e**).* The title compound was prepared in 67% yield from 3-bromo-6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene 1-oxide and methyl (*E*)-3-(4-hydroxyphenyl)but-2-enoate (see Supporting Information for synthesis) using the procedure described for the synthesis of **34**, step 1. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.48−7.61 (m, 3H), 7.34−7.45 (m, 2H), 6.94−7.16 (m, 4H), 6.77−6.89 (m, 2H), 6.00 (d, J = 1.52 Hz, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 3.62 (s, 3H), 2.42 (s, 3H). LC/MS ESI m/z 478.4 $[M + H_2O]^+$.

*Ethyl (E)-2-(4-((6-Methoxy-2-(4-methoxyphenyl)-1-oxidobenzo[b]thiophen-3-yl)oxy)benzylidene)butanoate (**40f**).* The title compound was prepared in 76% yield from 3-bromo-6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene 1-oxide and ethyl (*E*)-2-(4-hydroxybenzylidene)butanoate (see Supporting Information for synthesis) using the procedure described for the synthesis of **34**, step 1. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 1.02 (t, J = 7.58 Hz, 3H), 1.22 (t, J = 7.07 Hz, 3H), 2.39 (q, J = 7.58 Hz, 2H), 3.68 (s, 3H), 3.81 (s, 3H), 4.14 (q, J = 7.07 Hz, 2H), 6.78−6.85 (m, 2H), 6.99−7.11 (m, 4H), 7.25 (d, J = 8.59 Hz, 2H), 7.45 (s, 1 H), 7.48−7.57 (m, 3H). LC/MS ESI m/z 505.0 $[M + H]^+$.

*Ethyl (E)-3-(4-((6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)-2-methylphenyl)acrylate (**41a**).* The title compound was prepared in 78% yield from (*E*)-ethyl 3-(4-((6-methoxy-2-(4-methoxyphenyl)-1-oxidobenzo[b]thiophen-3-yl)oxy)-2-methylphenyl)acrylate using the procedure described for the synthesis of **34**, step 2.

*Ethyl (E)-3-(4-((6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)-3-methylphenyl)acrylate (**41b**).* The title compound was prepared in 67% yield from (*E*)-ethyl 3-(4-((6-methoxy-2-(4-methoxyphenyl)-1-oxidobenzo[b]thiophen-3-yl)oxy)-3-methylphenyl)acrylate using the procedure described for the synthesis of **34**, step 2. LC/MS ESI m/z 475.3 $[M + H]^+$.

*Ethyl (E)-3-(2-Methoxy-4-((6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)phenyl)acrylate (**41c**).* The title compound was prepared in 76% yield from (*E*)-ethyl 3-(2-methoxy-4-((6-methoxy-2-(4-methoxyphenyl)-1-oxidobenzo[b]thiophen-3-yl)oxy)-phenyl)acrylate using the procedure described for the synthesis of **34**, step 2. LC/MS ESI m/z 491.3 $[M + H]^+$.

*(E)-Ethyl 3-(4-((6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)phenyl)-2-methyl acrylate (**41d**).* The title compound was prepared in 77% yield from (*E*)-ethyl 3-(4-((6-methoxy-2-(4-methoxyphenyl)-1-oxidobenzo[b]thiophen-3-yl)oxy)phenyl)-2-methyl acrylate using the procedure described for the synthesis of **34**, step 2. LC/MS ESI m/z 475.3 $[M + H]^+$.

*Methyl (E)-3-(4-((6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)phenyl)but-2-enoate (**41e**).* The title compound was prepared in 65% yield from methyl (*E*)-3-(4-((6-methoxy-2-(4-methoxyphenyl)-1-oxidobenzo[b]thiophen-3-yl)oxy)phenyl)but-2-enoate using the procedure described for the synthesis of **34**, step 2. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.52−7.65 (m, 2H), 7.27−7.38 (m, 2H), 7.13−7.23 (m, 2H), 6.84−6.93 (m, 2H), 6.75−6.84 (m, 3H), 6.01 (d, J = 1.52 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.66 (s, 3H), 2.46 (d, J = 1.01 Hz, 3H). LC/MS ESI m/z 461.2 $[M + H]^+$.

*Ethyl (E)-2-(4-((6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)benzylidene)butanoate (**41f**).* The title compound was prepared as a white solid in 98% yield from ethyl (*E*)-2-(4-((6-methoxy-2-(4-methoxyphenyl)-1-oxidobenzo[b]thiophen-3-yl)oxy)-benzylidene)butanoate using the procedure described for the synthesis of **34**, step 2. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.15 (t, J = 7.58 Hz, 3H), 1.34 (t, J = 7.07 Hz, 3H), 2.54 (q, J = 7.24 Hz, 2H), 3.81 (s, 3H), 3.88 (s, 3H), 4.26 (q, J = 7.07 Hz, 2H), 6.90 (d, J = 8.59 Hz, 3H), 6.98 (d, J = 9.09 Hz, 2H), 7.25−7.29 (m, 2H), 7.31 (d, J = 8.59 Hz, 2H), 7.57 (s, 1H), 7.66 (d, J = 9.09, 2H). LC/MS ESI m/z 489.1 $[M + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)oxy)-2-methylphenyl)acrylic Acid (**42a**).* Step 1: To a solution of ethyl (*E*)-3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)-2-methylphenyl)acrylate in CH_2Cl_2 (3.0 mL) at 0 °C was added BBr_3 (1 M in hexanes, 0.697 mL, 0.697 mmol), and the resulting mixture was stirred for 1 h at 0 °C. Upon completion, the reaction was quenched with water and extracted with CH_2Cl_2. The combined organic layers were washed with sat. aq. $NaHCO_3$, dried over anhyhdrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography (SiO_2, 0−30% EtOAc/heptane) to afford ethyl (*E*)-3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)oxy)-2-methylphenyl)acrylate (78 mg, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.34 (t, J = 7.07 Hz, 3H), 2.36 (s, 3H), 4.27 (q, J = 7.07 Hz, 2H), 4.77 (br s, 2H), 6.25 (d, J = 16.17 Hz, 1H), 6.74−6.87 (m, 5H), 7.22−7.26 (m, 2H), 7.45 (d, J = 8.59 Hz, 1H), 7.56−7.63 (m, 2H), 7.89 (d, J = 15.66 Hz, 1H). HRMS ESI m/z 447.1245 $[M + H]^+$.

Step 2: To a solution of ethyl (*E*)-3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)oxy)-2-methylphenyl)acrylate (51 mg, 0.114 mmol) in EtOH (1.0 mL) at room temperature was added LiOH (2 N aq., 0.4 mL, 0.800 mmol); the reaction was allowed to stir at room temperature for 18 h, after which time the reaction was quenched with 4 N HCl until pH ∼ 3 and then extracted with EtOAc (2×). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product, which was purified by reverse phase HPLC (neutral conditions, 3% 1-propanol in 1−100% CH_3CN/H_2O) to afford (*E*)-3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)oxy)-2-methylphenyl)acrylic acid (30 mg, 63% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 2.34 (s, 3H), 6.26 (d, J = 16.17 Hz, 1H), 6.61−6.90 (m, 5H), 7.08−7.32 (m, 2H), 7.41−7.65 (m, 3H), 7.90 (d, J = 16.17 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 20.06, 108.95, 114.79, 115.78, 116.73, 118.50, 118.77, 122.77, 124.94, 127.70, 128.40, 128.95, 129.51, 129.89, 138.19, 139.69, 141.43, 143.11, 157.23, 158.72, 160.76, 170.88. HRMS ESI m/z 417.0779 $[M - H]^-$.

*(E)-3-(4-((6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)oxy)-3-methylphenyl)acrylic Acid (**42b**).* Step 1: The intermediate was prepared in 77% yield from ethyl (*E*)-3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)-3-methylphenyl)acrylate using the procedure described for the synthesis of **42a**, step 1. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 1.29 (t, J = 7.07 Hz, 3H), 2.50 (s, 3H), 4.21 (q, J = 7.07 Hz, 2H), 6.33 (d, J = 16.17 Hz, 1H), 6.50 (d, J = 8.08 Hz, 1H), 6.75 (d, J = 8.59 Hz, 2H), 6.79 (dd, J = 8.59, 2.02 Hz, 1H), 7.09 (d, J = 8.59 Hz, 1H), 7.16−7.22 (m, 2H), 7.44−7.52 (m, 3H), 7.57 (d, J = 16.17 Hz, 1H). HRMS ESI m/z 447.1278 $[M + H]^+$.

Step 2: The title compound was prepared in 80% yield from ethyl (*E*)-3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)-oxy)-3-methylphenyl)acrylate using the procedure described for the synthesis of **42a**, step 2. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 2.38−2.63 (m, 3H), 6.30 (d, J = 16.17 Hz, 1H), 6.50 (d, J = 8.59 Hz, 1H), 6.73−6.77 (m, 2H), 6.79 (dd, J = 8.59, 2.02 Hz, 1H), 7.09 (d, J = 8.59 Hz, 1H), 7.15−7.24 (m, 2H), 7.42−7.53 (m, 3H), 7.57 (d, J = 16.17 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 16.58, 108.96, 114.86, 115.82, 116.74, 117.61, 122.61, 124.98, 127.57, 128.17, 128.32, 128.73, 129.80, 130.01, 132.25, 138.24, 139.87, 146.05, 157.25, 158.74, 159.14, 170.94. HRMS ESI m/z 417.0782 $[M - H]^-$.

*(E)-3-(4-((6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)oxy)-2-methoxyphenyl)acrylic Acid (**42c**).* Step 1: The intermediate was prepared in 16% yield from ethyl (*E*)-3-(2-methoxy-4-((6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)phenyl)-acrylate using the procedure described for the synthesis of **42a**, step 1. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 1.28 (t, J = 7.07 Hz, 3H), 3.75 (s, 3H), 4.20 (q, J = 7.07 Hz, 2H), 6.39 (d, J = 16.17 Hz, 1H), 6.46 (dd, J = 8.59, 2.53 Hz, 1H), 6.64 (d, J = 2.02 Hz, 1H), 6.76 (d, J = 8.59 Hz, 2H), 6.81 (dd, J = 8.59, 2.02 Hz, 1H), 7.14−7.23 (m, 2H), 7.40 (d, J = 8.59 Hz, 1H), 7.49 (d, J = 9.09 Hz, 2H), 7.84 (d, J = 16.17 Hz, 1H). HRMS ESI m/z 463.1185 $[M + H]^+$.

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Step 2: The title compound was prepared in 52% yield from ethyl (*E*)-3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)-oxy)-2-methoxyphenyl)acrylate using the procedure described for the synthesis of **42a**, step 2. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 3.75 (s, 3H), 6.38 (d, *J* = 16.17 Hz, 1H), 6.46 (dd, *J* = 8.59, 2.02 Hz, 1H), 6.65 (d, *J* = 2.02 Hz, 1H), 6.75−6.79 (m, 2H), 6.79−6.84 (m, 1H), 7.19 (dd, *J* = 5.31, 3.28 Hz, 2H), 7.41 (d, *J* = 8.59 Hz, 1H), 7.47−7.54 (m, 2H), 7.84 (d, *J* = 16.17 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 56.31, 100.56, 108.64, 108.94, 115.82, 116.77, 117.95, 119.07, 122.76, 124.88, 127.81, 128.34, 129.96, 131.35, 138.17, 139.57, 141.09, 157.23, 158.75, 161.43, 162.40, 171.64. LC/MS ESI *m*/*z* 435.1 $[M + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)-oxy)phenyl)-2-methylacrylic Acid (**42d**).* The title compound was prepared in 34% yield from (*E*)-ethyl 3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)-2-methyl acrylate using the procedure described for the synthesis of **16**. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 2.07 (d, *J* = 1.52 Hz, 3 H), 6.78 (d, *J* = 9.09 Hz, 2 H), 6.82 (dd, *J* = 8.59, 2.02 Hz, 1H), 6.97 (d, *J* = 8.59 Hz, 2H), 7.16−7.22 (m, 2H), 7.38 (d, *J* = 9.09 Hz, 2H), 7.53 (d, *J* = 9.09 Hz, 2H), 7.63 (s, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 14.43, 108.95, 115.77, 116.64, 116.73, 122.80, 124.97, 127.71, 128.41, 128.57, 129.91, 131.63, 132.86, 138.23, 139.47, 139.85, 157.21, 158.71, 159.42, 172.54. HRMS ESI *m*/*z* 419.0872 $[M + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)-oxy)phenyl)but-2-enoic Acid (**42e**).* Step 1: The intermediate was prepared in 33% yield from methyl (*E*)-3-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)but-2-enoate using the procedure described for the synthesis of **42a**, step 1. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.35−7.46 (m, 4H), 7.01−7.11 (m, 2H), 6.79−6.89 (m, 2H), 6.62−6.71 (m, 3H), 6.02 (d, *J* = 1.52 Hz, 1H), 3.60 (s, 3H), 2.41 (s, 3H). LC/MS ESI *m*/*z* 431.4 $[M - H]^-$.

Step 2: The title compound was prepared in 41% yield from methyl (*E*)-3-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)-oxy)phenyl)but-2-enoate using the procedure described for the synthesis of **42a**, step 2. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.42 (d, *J* = 9.09 Hz, 2H), 7.27−7.34 (m, *J* = 8.59 Hz, 2H), 7.00−7.13 (m, 2H), 6.75−6.82 (m, *J* = 9.09 Hz, 2H), 6.61−6.72 (m, 3H), 6.05 (s, 1H), 2.25 (d, *J* = 1.01 Hz, 3H). LC/MS ESI *m*/*z* 417.4 $[M - H]^-$.

*(E)-2-(4-((6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)-oxy)benzylidene)butanoic Acid (**42f**).* Step 1: The intermediate was prepared in 68% yield from ethyl (*E*)-2-(4-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)benzylidene)butanoate using the procedure described for the synthesis of **42a**, step 1. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 1.14 (t, *J* = 7.33 Hz, 3H), 1.33 (t, *J* = 7.33 Hz, 3H), 2.54 (q, *J* = 7.24 Hz, 2H), 4.25 (q, *J* = 7.07 Hz, 2H), 6.71−6.85 (m, 3H), 6.92−7.01 (m, 2H), 7.12−7.25 (m, 2H), 7.36 (m, 2H), 7.49−7.63 (m, 3H). LC/MS ESI *m*/*z* 461.0 $[M + H]^+$.

Step 2: The title compound was prepared in 70% yield from ethyl (*E*)-2-(4-((6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)-oxy)benzylidene)butanoate using the procedure described for the synthesis of **42a**, step 2. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 1.15 (t, *J* = 7.33 Hz, 3H), 2.53 (q, *J* = 7.24 Hz, 2H), 6.71−6.85 (m, 3H), 6.92−7.01 (m, 2H), 7.12−7.24 (m, 2H), 7.36 (m, *J* = 9.09 Hz, 2H), 7.48−7.64 (m, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 14.22, 21.79, 108.95, 115.77, 116.73, 116.74, 122.81, 124.97, 127.70, 128.42, 129.92, 131.43, 132.39, 135.37, 138.23, 138.88, 139.86, 157.21, 158.71, 159.49, 172.30. LC/MS ESI *m*/*z* 433.0 $[M + H]^+$.

*(5-((6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)-pyridin-2-yl)methanol (**43**).* Step 1: To a solution of methyl 5-hydroxypyridine-2-carboxylate (0.273 g, 1.78 mmol) in DMF (6.84 mL) at room temperature was added sodium hydride (60% suspension in oil, 0.043 g, 1.78 mmol), and the resulting mixture was stirred at room temperature for 30 min. After 30 min at room temperature, 3-bromo-6-methoxy-2-(4-methoxyphenyl)benzothiophene 1-oxide (0.5 g, 1.37 mmol) was added and the reaction was heated to 80 °C for 18 h. Upon completion, the reaction was cooled to room temperature, quenched with water, and extracted with CH_2Cl_2. The organic layers were combined, passed through a phase separator, and concentrated *in vacuo* to give the crude product, which was purified by column chromatography (SiO_2, 0−75% EtOAc/heptane) to afford methyl 5-((6-methoxy-2-(4-methoxyphenyl)-1-oxidobenzo[*b*]thiophen-3-yl)-oxy)picolinate (314 mg, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 3.73 (s, 3H), 3.84 (s, 3H), 3.90−3.92 (m, 3H), 6.79−6.86 (m, 2H), 6.91 (dd, *J* = 8.59, 2.53 Hz, 1H), 7.03 (d, *J* = 8.59 Hz, 1H), 7.0 (dd, *J* = 8.59, 3.03 Hz, 1H), 7.48 (d, *J* = 2.53 Hz, 1H), 7.55−7.60 (m, 2H), 7.95 (d, *J* = 8.59 Hz, 1H), 8.55 (d, *J* = 2.02 Hz, 1H). LC/MS ESI *m*/*z* 438.2 $[M + H]^+$.

Step 2: To a solution of methyl 5-((6-methoxy-2-(4-methoxyphenyl)-1-oxidobenzo[*b*]thiophen-3-yl)oxy)picolinate (0.314 g, 0.718 mmol) in THF (5.98 mL) at 0 °C was added $LiAlH_4$ (1.0 M in THF, 2.153 mL, 2.15 mmol) dropwise, and the reaction was stirred at 0 °C for 1 h. Upon completion, the reaction was quenched with water and sat. aq. potassium sodium tartrate, and the resulting mixture was stirred for 30 min and then extracted with EtOAc (3×). The organic layers were combined, passed through a phase separator, and concentrated *in vacuo* to afford crude (5-((6-methoxy-2-(4-methoxyphenyl)-benzo[*b*]thiophen-3-yl)oxy)pyridin-2-yl)methanol (0.266 g, 93% yield), which was used without further purification. LC/MS ESI *m*/*z* 394.2 $[M + H]^+$.

*(E)-Methyl 3-(5-((6-methoxy-2-(4-methoxyphenyl)benzo[b]-thiophen-3-yl)oxy)pyridin-2-yl)acrylate (**44**).* Step 1: To a solution of (5-((6-methoxy-2-(4-methoxyphenyl)-benzo[*b*]thiophen-3-yl)oxy)-pyridin-2-yl)methanol (0.266 g, 0.676 mmol) in CH_2Cl_2 (3.38 mL) was added manganese dioxide (1.176 g, 13.52 mmol), and the reaction was stirred at room temperature for 48 h. Upon completion, the reaction was was filtered over Celite and concentrated *in vacuo* to afford crude 5-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)picolinaldehyde, which was used without further purification. LC/MS ESI *m*/*z* 392.2 $[M + H]^+$.

Step 2: To a solution of 5-((6-methoxy-2-(4-methoxyphenyl)-benzo[*b*]thiophen-3-yl)oxy)picolinaldehyde (0.265 g, 0.68 mmol) in CH_2Cl_2 (3.38 mL) at 0 °C was added methyl 2-(triphenylphosphoranylidene)acetate (0.543 g, 1.63 mmol), and the reaction was stirred at room temperature for 18 h. Upon completion, the mixture was concentrated *in vacuo* to afford crude material, which was purified by column chromatography (SiO_2, 0−25% EtOAc/heptanes) to afford (*E*)-methyl 3-(5-((6-methoxy-2-(4-methoxyphenyl)-benzo[*b*]thiophen-3-yl)oxy)pyridin-2-yl)acrylate (96 mg, 32% yield over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 3.70−3.75 (m, 6H), 3.79−3.83 (m, 3H), 6.70 (d, *J* = 15.66 Hz, 1H), 6.77−6.88 (m, 3H), 7.02 (dd, *J* = 8.59, 3.03 Hz, 1H), 7.17 (s, 1H), 7.18−7.22 (m, 2H), 7.48−7.59 (m, 3H), 8.42 (d, *J* = 2.53 Hz, 1H). LC/MS ESI *m*/*z* 448.3 $[M + H]^+$.

*(E)-3-(5-((6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)-oxy)pyridin-2-yl)acrylic Acid (**45**).* Step 1: To a solution of (*E*)-methyl 3-(5-((6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)oxy)-pyridin-2-yl)acrylate (0.096 g, 0.215 mmol) in DCM (2.145 mL) at room temperature was added BBr_3 (1.0 M in heptane, 0.858 mL, 0.86 mmol), and the reaction was stirred at room temperature for 30 min. Upon completion, the reaction was quenched with MeOH (2.0 mL), stirred for 10 min at room temperature, concentrated *in vacuo* onto silica gel, and purified by column chromatography (SiO_2, 0−20% MeOH/DCM) to afford (*E*)-methyl 3-(5-((6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)oxy)pyridin-2-yl)acrylate. LC/MS ESI *m*/*z* 420.3 $[M + H]^+$.

Step 2: To a solution of (*E*)-methyl 3-(5-((6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)oxy)pyridin-2-yl)acrylate (0.118 g, 0.28 mmol) in THF (2.00 mL) and water (2.00 mL) was added lithium hydroxide (1.0 M aq., 0.844 mL, 0.84 mmol), and the reaction was stirred at room temperature for 2 h. Upon completion, the reaction was quenched with water, diluted with CH_2Cl_2, and acidified to pH 1 with 1 N HCl. The mixture was extracted with DCM (3×), and the combined organic layers were passed through a phase separator and concentrated *in vacuo* to afford the crude product, which was purified by reverse phase HPLC (acidic conditions, 3% TFA in 10−100% CH_3CN/H_2O) to afford (*E*)-3-(5-((6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)oxy)pyridin-2-yl)acrylic acid (14 mg, 9% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 6.66 (d, *J* = 15.66 Hz, 1H), 6.77−6.81 (m, 2H), 6.84 (dd, *J* = 8.59,

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2.02 Hz, 1H), 7.17 (d, J = 8.59 Hz, 1H), 7.22 (dd, J = 8.59, 3.03 Hz, 1H), 7.31 (d, J = 2.02 Hz, 1H), 7.44−7.49 (m, 2H), 7.52 (d, J = 15.66 Hz, 1H), 7.64 (d, J = 8.59 Hz, 1H), 8.45 (d, J = 2.53 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 108.24, 115.22, 116.02, 121.19, 121.25, 122.06, 122.41, 125.42, 125.78, 125.98, 128.50, 136.12, 137.11, 138.90, 142.31, 146.81, 154.18, 156.03, 157.60, 167.42. LC/MS ESI m/z 406.2 $[M + H]^+$.

*2-Bromo-3-(4-bromophenoxy)-6-methoxybenzo[b]thiophene 1,1-Dioxide (**48**).* To a solution of 2,3-dibromo-6-methoxybenzo[b]-thiophene 1,1-dioxide (2.50 g, 7.06 mmol) in THF (100 mL) at room temperature were added 4-bromophenol (1.344 g, 7.77 mmol) and Cs_2CO_3 (6.90 g, 21.19 mmol). The mixture was stirred at room temperature for 18 h, after which time the reaction was quenched with water and diluted with CH_2Cl_2. The organic layer was collected (phase separator) and concentrated to provide 2-bromo-3-(4-bromophenoxy)-6-methoxybenzo[b]thiophene 1,1-dioxide (3.10 g, 98% yield) as a white solid, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 3.83 (s, 3H), 6.92−7.03 (m, 3H), 7.25−7.35 (m, 2H), 7.39−7.50 (m, 2H). LC/MS ESI m/z 446.9 $[M + H]^+$.

*3-(4-Bromophenoxy)-6-methoxybenzo[b]thiophene (**49**).* Step 1: To a solution of 2-bromo-3-(4-bromophenoxy)-6-methoxy-benzo[b]-thiophene 1,1-dioxide (3.10 g, 6.95 mmol) in MeOH (10 mL) and DMSO (30 mL) was added $NaBH_4$ (0.789 g, 20.85 mmol). The mixture was stirred at room temperature for 3 h, after which time the reaction was quenched with water and diluted with CH_2Cl_2. The organic layer was collected (phase separator) and concentrated to provide 3-(4-bromophenoxy)-6-methoxybenzo[b]thiophene 1,1-dioxide (2.47 g, 97% yield) as an off white solid, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 3.85 (s, 3H), 5.38 (s, 1H), 7.02−7.08 (m, 3H), 7.22 (d, J = 2.53 Hz, 1H), 7.47−7.60 (m, 3H). LC/MS ESI m/z 367.0 $[M + H]^+$.

Step 2: To a solution of 3-(4-bromophenoxy)-6-methoxybenzo[b]-thiophene 1,1-dioxide (2.47 g, 6.73 mmol) in THF (90 mL) was added DIBAL-H (1.0 M in CH_2Cl_2, 33.6 mL, 33.6 mmol) in one portion. The mixture was heated to 75 °C for 2 h, after which time the reaction was cooled to room temperature and quenched with EtOAc (32.9 mL, 336 mmol). The resulting solution was stirred for 10 min before carefully adding 75 mL of water and potassium sodium tartrate (33.100 g, 117 mmol). The mixture was vigorously stirred for 10 min and diluted with 75 mL of EtOAc. The organic layer was collected, dried with anhydrous $MgSO_4$, and concentrated *in vacuo* to afford 3-(4-bromophenoxy)-6-methoxybenzo[b]thiophene (1.9 g, 84% yield) as a white solid, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 3.81 (s, 3H), 6.46 (s, 1H), 6.90 (d, J = 9.09 Hz, 3H), 7.16−7.22 (m, 1H), 7.31−7.40 (m, 2H), 7.46 (d, J = 9.09 Hz, 1H). LC/MS ESI m/z 336.8 $[M + H]^+$.

*(E)-Methyl 3-(4-((6-methoxybenzo[b]thiophen-3-yl)oxy)phenyl)-acrylate (**50a**).* To a microwave vial, 3-(4-bromophenoxy)-6-methoxybenzo[b]thiophene (500 mg, 1.49 mmol), methyl acrylate (770 mg, 8.95 mmol), and $Pd(PPh_3)_2Cl_2$ (157 mg, 0.22 mmol) were suspended in DMF (12 mL) and triethylamine (1.039 mL, 7.46 mmol). The reaction was heated for 60 min at 120 °C under microwave irradiation. The reaction mixture was diluted with CH_2Cl_2 and water. The organic layer was collected (phase separator) and concentrated to obtain the crude product. The crude material was purified by column chromatography (SiO_2, 1−20% EtOAc/heptane) to afford (*E*)-methyl 3-(4-((6-methoxybenzo[b]thiophen-3-yl)oxy)phenyl)acrylate (311 mg, 0.91 mmol, 61% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.46 (s, 3H), 3.73 (s, 3H), 6.28 (d, J = 16.17 Hz, 1H), 6.59 (s, 1H), 6.90 (dd, J = 8.59, 2.02 Hz, 1H), 7.00 (d, J = 8.59 Hz, 2H), 7.21 (d, J = 2.02 Hz, 1H), 7.37−7.48 (m, 3H), 7.59 (d, J = 16.17 Hz, 1H). LC/MS ESI m/z 341.1 $[M + H]^+$.

*(E)-tert-Butyl 3-(4-((6-methoxybenzo[b]thiophen-3-yl)oxy)-phenyl)acrylate (**50b**).* To a microwave vial, 3-(4-bromophenoxy)-6-methoxybenzo[b]thiophene (4 g, 11.93 mmol), *tert*-butyl acrylate (10.49 mL, 71.6 mmol), and $Pd(PPh_3)_2Cl_2$ (1.256 g, 1.79 mmol) were suspended in DMF (12 mL) and triethylamine (8.32 mL, 59.7 mmol). The reaction was heated for 60 min at 120 °C under microwave irradiation. The reaction mixture was diluted with DCM and water. The organic layer was collected (phase separator) and concentrated to obtain the crude product. The crude material was purified by column chromatography (SiO_2, 1−20% EtOAc/heptane) to afford (*E*)-*tert*-butyl 3-(4-((6-methoxybenzo[b]thiophen-3-yl)oxy)phenyl)acrylate (3 g, 66% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 7.45−7.63 (m, 4H), 7.27−7.33 (m, 1H), 7.03−7.13 (m, 2H), 6.99 (dd, J = 8.8, 2.3 Hz, 1H), 6.66 (s, 1H), 6.30 (d, J = 16.2 Hz, 1H), 3.90 (s, 3H), 1.55 (s, 9H). LC/MS ESI m/z 383.0 $[M + H]^+$.

*(E)-Methyl 3-(4-((2-Bromo-6-methoxybenzo[b]thiophen-3-yl)-oxy)phenyl)acrylate (**51**).* To a solution (*E*)-methyl 3-(4-((6-methoxybenzo[b]thiophen-3-yl)oxy)phenyl)acrylate (310 mg, 0.911 mmol) in THF (11 mL) at room temperature was added *N*-bromosuccinimide (170 mg, 0.956 mmol). The resulting solution was stirred vigorously at room temperature for 2 h, after which time the reaction was quenched by addition of sat. aq. sodium thiosulfate solution and extracted with EtOAc (3×). The combined organic layers were dried over anhydrous MgSO4, filtered, and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (SiO_2, 0−40% EtOAc/heptane) to afford (*E*)-methyl 3-(4-((2-bromo-6-methoxybenzo[b]thiophen-3-yl)oxy)phenyl)acrylate (343 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 7.65 (d, J = 16.0 Hz, 1H), 7.46 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.9 Hz, 1H), 7.20 (d, J = 2.2 Hz, 1H), 6.95 (d, J = 8.7 Hz, 2H), 6.91 (dd, J = 8.8, 2.2 Hz, 1H), 6.31 (s, 1H), 3.86 (s, 3H), 3.79 (s, 3H). LC/MS ESI m/z 420.9 $[M + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-(4-hydroxy-3-methylphenyl)benzo[b]-thiophen-3-yl)oxy)phenyl)acrylic Acid (**53a**).* The title compound was prepared using a similar procedure to that described for the synthesis of **34**; see Supporting Information for synthesis. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 2.14 (s, 3H), 6.35 (d, J = 15.66 Hz, 1H), 6.69 (d, J = 8.59 Hz, 1H), 6.79 (dd, J = 8.59, 2.53 Hz, 1H), 6.89−7.00 (m, 2H), 7.15 (d, J = 8.59 Hz, 1H), 7.18 (d, J = 2.02 Hz, 1H), 7.33 (dd, J = 8.34, 2.27 Hz, 1H), 7.39 (d, J = 1.52 Hz, 1H), 7.49−7.55 (m, 2H), 7.60 (d, J = 16.17 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 16.45 108.95, 115.75, 115.87, 117.07, 118.01, 122.65, 124.71, 126.17, 127.26, 128.02, 128.41, 130.27, 131.09, 131.21, 138.19, 139.54, 145.66, 156.88, 157.17, 161.12, 170.93. HRMS ESI m/z 419.0915 $[M + H]^+$.

*(E)-3-(4-((2-(4-Fluorophenyl)-6-hydroxybenzo[b]thiophen-3-yl)-oxy)phenyl)acrylic Acid (**53b**).* The title compound was prepared using a similar procedure to that described for the synthesis of **34**; see Supporting Information for synthesis. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 6.35 (d, J = 16.17 Hz, 1H), 6.82 (dd, J = 8.84, 2.27 Hz, 1H), 6.95 (d, J = 8.59 Hz, 2H), 7.05−7.13 (m, 2H), 7.19 (d, J = 8.59 Hz, 1H), 7.22 (d, J = 2.02 Hz, 1H), 7.53 (d, J = 8.59 Hz, 2H), 7.60 (d, J = 16.17 Hz, 1H), 7.66−7.73 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 108.85, 116.02, 116.64, 116.86, 116.98, 118.09, 123.09, 125.95, 127.77, 130.32, 130.40, 131.14, 138.62, 140.95, 145.40, 157.64, 160.69, 162.38, 164.84, 170.66. HRMS ESI m/z 406.0675 $[M + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-phenylbenzo[b]thiophen-3-yl)oxy)-phenyl)-acrylic Acid (**53c**).* The title compound was prepared using a similar procedure to that described for the synthesis of **34**; see Supporting Information for synthesis. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 6.28 (d, J = 16.17 Hz, 1H), 6.79 (dd, J = 8.59, 2.02 Hz, 1H), 6.83−6.93 (m, 2H), 7.09−7.30 (m, 5H), 7.38 (d, J = 8.59 Hz, 2H), 7.54 (d, J = 16.17 Hz, 1H), 7.59−7.68 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 108.98, 116.09, 117.11, 118.11, 123.19, 127.27, 128.07, 128.52, 129.03, 130.01, 130.46, 131.25, 133.63, 138.85, 141.16, 145.61, 157.72, 160.94, 170.80. HRMS ESI m/z 389.0834 $[M + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-(4-(trifluoromethyl)phenyl)benzo[b]-thiophen-3-yl)oxy)phenyl)acrylic Acid (**53d**).* Step 1: To a 5 mL microwave vial was added a solution of (*E*)-*tert*-butyl 3-(4-((6-methoxybenzo[b]thiophen-3-yl)oxy)phenyl)acrylate (50 mg, 0.13 mmol) in anhydrous DMA (1.5 mL), followed by 1-bromo-4-(trifluoromethyl)benzene (35.3 mg, 0.16 mmol), 1-bromo-4-fluorobenzene (448 mg, 2.56 mmol), chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2′,4′,6′-tri-i-propyl-1,1′-biphenyl][2-(2-aminoethyl)-phenyl]palladium(II) (BrettPhos palladacycle first generation, 10.4 mg, 0.013 mmol), trimethylacetic acid (40.1 mg, 0.392 mmol), and potassium carbonate (54.2 mg, 0.392 mmol). The microwave vial was

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sealed, purged, and backfilled with nitrogen. The reaction mixture subjected to microwave irradiation for 2 h at 150 °C. Upon completion, the reaction was diluted with EtOAc and washed with water and brine. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give a red brown residue, which was purified by column chromatography (SiO_2, 0−30% EtOAc/heptane) to afford (*E*)-*tert*-butyl 3-(4-((6-methoxy-2-(4-(trifluoromethyl)phenyl)benzo[*b*]thiophen-3 yl)oxy)phenyl)acrylate (59.4 mg, 86% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 1.42−1.61 (m, 9H), 3.77−3.98 (m, 3H), 6.31 (d, *J* = 15.66 Hz, 1H), 6.87−7.04 (m, 3H), 7.28 (d, *J* = 9.09 Hz, 1H), 7.46 (d, *J* = 2.53 Hz, 1H), 7.47−7.57 (m, 3H), 7.65 (d, *J* = 8.08 Hz, 2H), 7.89 (d, *J* = 8.08 Hz, 2H). LC/MS ESI *m*/*z* 471.4 $[M + H]^+$.

Step 2: To a 2-dram vial containing (*E*)-*tert*-butyl 3-(4-((6-methoxy-2-(4-(trifluoromethyl)phenyl)benzo[*b*]thiophen-3 yl)oxy)-phenyl)acrylate (59.4 mg, 0.113 mmol) in anhydrous DCM (1.5 mL) at 0 °C was added BBr_3 (1.0 M in DCM, 451 μL, 0.451 mmol) dropwise. The resulting mixture was stirred at 0 °C for 1 h, after which the reaction was quenched with 3 drops of water, diluted with DCM, and extracted with sat. aq. $NaHCO_3$ (added a few drops of 2-propanol). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford the curde material, which was purified by reverse phase HPLC (neutral conditions, 3% 1-propanol in 10−100% CH_3CN/H_2O) to afford (*E*)-3-(4-((6-hydroxy-2-(4-(trifluoromethyl)-phenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)acrylic acid (33.8 mg, 66% yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 6.36 (d, *J* = 16.17 Hz, 1H), 6.78−6.89 (m, 1H), 6.98 (d, *J* = 8.59 Hz, 2H), 7.17−7.30 (m, 2H), 7.51−7.70 (m, 5H), 7.88 (d, *J* = 8.08 Hz, 2H). HRMS ESI *m*/*z* 457.0710 $[M + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-(o-tolyl)benzo-[b]thiophen-3-yl)oxy)-phenyl)acrylic Acid (**53e**).* Step 1: The intermediate was prepared in 97% yield from (*E*)-*tert*-butyl 3-(4-((6-methoxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate and 1-bromo-2-methylbenzene using the procedure described for the synthesis of **53d**, step 1. LC/MS ESI *m*/*z* 417.3 $[M - t\text{-Bu} + H]^+$.

Step 2: The title compound was prepared in 52% yield from *tert*-butyl (*E*)-3-(4-((6-methoxy-2-(*o*-tolyl)benzo[*b*]thiophen-3-yl)oxy)-phenyl)acrylate using the procedure described for the synthesis of **53d**, step 2. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 2.35 (s, 3H), 6.34 (d, *J* = 15.66 Hz, 1H), 6.76−6.82 (m, 2H), 6.84 (dd, *J* = 8.84, 2.27 Hz, 1H), 7.13 (d, *J* = 8.08 Hz, 1H), 7.16−7.38 (m, 8H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 20.82, 108.88, 115.93, 117.13, 117.85, 123.05, 126.63, 126.83, 127.13, 129.92, 130.11, 130.93, 131.45, 132.18, 132.30, 139.10, 140.03, 141.62, 145.69, 157.37, 161.29, 170.82. HRMS ESI *m*/*z* 403.0995 $[M + H]^+$.

*(E)-3-(4-((2-(2-Ethylphenyl)-6-hydroxybenzo[b]thiophen-3-yl)-oxy)phenyl)-acrylic Acid (**53f**).* Step 1: The intermediate was prepared in 89% yield from (*E*)-*tert*-butyl 3-(4-((6-methoxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate and 1-bromo-2-ethylbenzene using the procedure described for the synthesis of **53d**, step 1. LC/MS ESI *m*/*z* 431.4 $[M - t\text{-Bu} + H]^+$.

Step 2: The title compound was prepared in 42% yield from *tert*-butyl (*E*)-3-(4-((2-(2-ethylphenyl)-6-methoxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate using the procedure described for the synthesis of **53d**, step 2. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 1.14 (t, *J* = 7.58 Hz, 3H), 2.73 (q, *J* = 7.58 Hz, 2H), 6.34 (d, *J* = 15.66 Hz, 1H), 6.79 (d, *J* = 8.59 Hz, 2H), 6.85 (dd, *J* = 8.59, 2.02 Hz, 1H), 7.09−7.17 (m, 1H), 7.22 (d, *J* = 2.02 Hz, 1H), 7.23−7.30 (m, 5H), 7.34 (d, *J* = 9.09 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 16.08, 27.78, 108.83, 115.84, 117.03, 123.17, 124.87, 126.41, 126.75, 127.14, 129.89, 130.02, 130.15, 131.52, 131.63, 132.59, 139.94, 140.50, 141.92, 145.42, 157.28, 160.35, 175.75. HRMS ESI *m*/*z* 417.1148 $[M + H]^+$.

*(E)-3-(4-((2-(2-(tert-Butyl)phenyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl)-acrylic Acid (**53g**).* Step 1: The intermediate was prepared in 53% yield from (*E*)-*tert*-butyl 3-(4-((6-methoxybenzo[*b*]-thiophen-3-yl)oxy)phenyl)acrylate and 1-bromo-2-(*tert*-butyl)benzene using the procedure described for the synthesis of **53d**, step 1. LC/MS ESI *m*/*z* 459.4 $[M - t\text{-Bu} + H]^+$.

Step 2: The title compound was prepared in 20% yield from *tert*-butyl (*E*)-3-(4-((2-(2-(*tert*-butyl)phenyl)-6-methoxybenzo[*b*]-thiophen-3-yl)oxy)phenyl)acrylate using the procedure described for the synthesis of **53d**, step 2. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 1.37 (s, 6H), 3.09 (s, 2H), 6.40 (d, *J* = 15.66 Hz, 1H), 6.71 (dd, *J* = 8.59, 2.02 Hz, 1H), 6.79 (d, *J* = 8.59 Hz, 2H), 6.98 (d, *J* = 2.02 Hz, 1H), 7.04 (d, *J* = 8.59 Hz, 1H), 7.16−7.23 (m, 1H), 7.28 (t, *J* = 7.58 Hz, 2H), 7.35 (d, *J* = 16.17 Hz, 1H), 7.37−7.41 (m, 2H), 7.44 (d, *J* = 9.09 Hz, 2H). HRMS ESI *m*/*z* 445.1465 $[M + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-(2-isopropylphenyl)benzo[b]thiophen-3-yl)oxy)phenyl)acrylic Acid (**53h**).* Step 1: The intermediate was prepared in 85% yield from (*E*)-*tert*-butyl 3-(4-((6-methoxybenzo[*b*]-thiophen-3-yl)oxy)phenyl)acrylate and 1-bromo-2-isopropylbenzene using the procedure described for the synthesis of **53d**, step 1. LC/MS ESI *m*/*z* 445.0 $[M - t\text{-Bu} + H]^+$.

Step 2: The title compound was prepared in 35% yield from *tert*-butyl (*E*)-3-(4-((2-(2-isopropylphenyl)-6-methoxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate using the procedure described for the synthesis of **53d**, step 2. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 1.16 (d, *J* = 6.57 Hz, 6H), 3.23 (m, 1H), 6.31 (d, *J* = 15.66 Hz, 1H), 6.82−6.88 (m, 3H), 7.09−7.15 (m, 1H), 7.22−7.38 (m, 5H), 7.45 (d, *J* = 8.59 Hz, 2H), 7.57 (d, *J* = 16.17 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 24.68, 31.65, 108.86, 115.94, 117.17, 117.84, 123.05, 126.62, 126.82, 126.88, 126.95, 130.05, 130.46, 130.78, 130.95, 132.51, 139.99, 141.70, 145.69, 150.19, 157.33, 161.41, 170.83. HRMS ESI *m*/*z* 431.1309 $[M + H]^+$.

*(E)-3-(4-((2-(4-Fluoro-2-methylphenyl)-6-hydroxybenzo[b]-thiophen-3-yl)oxy)phenyl)-acrylic Acid (**53i**).* Step 1: The intermediate was prepared in 95% yield from (*E*)-*tert*-butyl 3-(4-((6-methoxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate and 1-bromo-4-fluoro-2-methylbenzene using the procedure described for the synthesis of **53d**, step 1. LC/MS ESI *m*/*z* 435.3 $[M - t\text{-Bu} + H]^+$.

Step 2: The title compound was prepared in 63% yield from *tert*-butyl (*E*)-3-(4-((2-(4-fluoro-2-methylphenyl)-6-methoxybenzo[*b*]-thiophen-3-yl)oxy)phenyl)acrylate using the procedure described for the synthesis of **53d**, step 2. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 2.35 (s, 3H), 6.32 (d, *J* = 15.66 Hz, 1H), 6.81−6.92 (m, 4H), 6.98 (dd, *J* = 9.60, 2.53 Hz, 1H), 7.24 (d, *J* = 2.02 Hz, 1H), 7.27 (d, *J* = 8.59 Hz, 1H), 7.31 (dd, *J* = 8.59, 5.56 Hz, 1H), 7.42−7.49 (m, 2H), 7.56 (d, *J* = 16.17 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 20.87, 108.89, 113.59, 113.80, 116.02, 117.15, 117.80, 117.93, 118.02, 123.10, 125.36, 127.00, 130.98, 134.01, 134.10, 140.04, 142.05, 145.65, 157.49, 161.22, 163.09, 165.54, 170.79. HRMS ESI *m*/*z* 421.0911 $[M + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-(2-(trifluoromethyl)-phenyl)benzo[b]-thiophen-3-yl)oxy)phenyl)-acrylic Acid (**53j**).* Step 1: The intermediate was prepared in 78% yield from (*E*)-*tert*-butyl 3-(4-((6-methoxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate and 1-bromo-2-(trifluoromethyl)benzene using the procedure described for the synthesis of **53d**, step 1. LC/MS ESI *m*/*z* 471.4 $[M - t\text{-Bu} + H]^+$.

Step 2: The title compound was prepared in 59% yield from *tert*-butyl (*E*)-3-(4-((6-methoxy-2-(2-(trifluoromethyl)phenyl)benzo[*b*]-thiophen-3-yl)oxy)phenyl)acrylate using the procedure described for the synthesis of **53d**, step 2. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 6.32 (d, *J* = 15.66 Hz, 1H), 6.78−6.91 (m, 3H), 7.16−7.28 (m, 2H), 7.45 (d, *J* = 9.09 Hz, 2H), 7.49−7.62 (m, 4H), 7.70−7.81 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 108.68, 116.11, 117.42, 118.06, 123.27, 123.39, 126.27, 127.53, 127.58, 127.63, 127.68, 130.27, 130.48, 130.93, 131.33, 131.38, 131.63, 132.95, 135.09, 140.31, 143.10, 145.59, 157.67, 161.24, 170.82. HRMS ESI *m*/*z* 457.0702 $[M + H]^+$.

*(E)-3-(4-((2-(4-Fluoro-2-(trifluoromethyl)-phenyl)-6-hydroxy-benzo[b]thiophen-3-yl)oxy)phenyl)acrylic Acid (**53k**).* Step 1: The intermediate was prepared in 94% yield from (*E*)-*tert*-butyl 3-(4-((6-methoxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate and 1-bromo-4-fluoro-2-(trifluoromethyl)benzene using the procedure described for the synthesis of **53d**, step 1. LC/MS ESI *m*/*z* 489.3 $[M - t\text{-Bu} + H]^+$.

Step 2: The title compound was prepared in 36% yield from *tert*-butyl (*E*)-3-(4-((2-(4-fluoro-2-(trifluoromethyl)phenyl)-6-methoxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate using the procedure described for the synthesis of **53d**, step 2. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 6.37 (d, *J* = 15.66 Hz, 1H), 6.84−6.92 (m, 3H), 7.15 (d, *J* = 8.59 Hz, 1H), 7.35 (d, *J* = 2.02 Hz, 1H), 7.49 (d, *J* = 16.17 Hz, 1H), 7.53−7.62 (m, 3H), 7.68 (dd, *J* = 8.59, 5.56 Hz, 1H),

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7.75 (dd, J = 9.35, 2.78 Hz, 1H), 9.92 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 107.90, 114.31, 114.36, 114.56, 114.61, 115.34, 116.02, 117.79, 119.51, 119.72, 120.06, 122.11, 123.67, 125.64, 128.81, 130.08, 136.27, 136.36, 138.24, 141.46, 143.19, 156.32, 158.84, 160.64, 163.12, 167.73. HRMS ESI m/z 475.0634 $[M + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-(2-methylpyridin-3-yl)benzo[b]thiophen-3-yl)oxy)phenyl)acrylic Acid (**53l**).* Step 1: The intermediate was prepared in 78% yield from (*E*)-*tert*-butyl 3-(4-((6-methoxybenzo[*b*]-thiophen-3-yl)oxy)phenyl)acrylate and 3-bromo-2-methylpyridine using the procedure described for the synthesis of **53d**, step 1. LC/MS ESI m/z 474.0 $[M + H]^+$.

Step 2: The title compound was prepared in 52% yield from *tert*-butyl (*E*)-3-(4-((6-methoxy-2-(2-methylpyridin-3-yl)benzo[*b*]-thiophen-3-yl)oxy)phenyl)acrylate using the procedure described for the synthesis of **53d**, step 2. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 8.56 (d, J = 5.6 Hz, 1H), 8.34 (d, J = 8.0 Hz, 1H), 7.69 (t, J = 7.1 Hz, 1H), 7.56 (d, J = 16.0 Hz, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.7 Hz, 1H), 7.31 (d, J = 2.1 Hz, 1H), 6.97−6.86 (m, 3H), 6.33 (d, J = 16.0 Hz, 1H), 2.76 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 20.05, 108.89, 116.73, 117.26, 118.40, 118.73, 123.79, 125.26, 125.98, 130.89, 131.10, 132.65, 140.92, 143.31, 144.47, 145.14, 148.01, 155.36, 158.52, 160.45, 170.34. HRMS ESI m/z 404.0941 $[M + H]^+$.

*(E)-3-(4-((2-(2-(Dimethylamino)phenyl)-6-hydroxybenzo[b]-thiophen-3-yl)oxy)phenyl)acrylic Acid (**53m**).* Step 1: To a solution of (*E*)-methyl 3-(4-((2-bromo-6-methoxybenzo[*b*]thiophen-3-yl)oxy)-phenyl)acrylate (3.0 g, 7.15 mmol) in CH_2Cl_2 (5 mL) at room temperature was added BBr_3 (1.0 M in heptane, 14.31 mL, 14.31 mmol) dropwise. The resulting mixture was stirred at room temperature for 2 h, after which time the reaction was cooled to 0 °C and carefully quenched by addition of sat. aq. $NaHCO_3$ solution. The mixture was diluted with CH_2Cl_2 (100 mL) and MeOH (10 mL) to solubilize all solids and then acidified by addition of sat. aq. citric acid solution. The phases were separated, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (SiO_2, 0−100% EtOAc/heptane) to afford (*E*)-methyl 3-(4-((2-bromo-6-hydroxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate (1.3 g, 45% yield) as a pale yellow solid and (*E*)-3-(4-((2-bromo-6-hydroxybenzo[*b*]-thiophen-3-yl)oxy)phenyl)acrylic acid (1.1 g, 39% yield) as an orange solid.

(E)-Methyl 3-(4-((2-Bromo-6-hydroxybenzo[b]thiophen-3-yl)oxy)-phenyl)acrylate. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 3.76 (s, 3H), 6.43 (d, J = 16.17 Hz, 1H), 6.82 (dd, J = 8.84, 2.27 Hz, 1H), 6.90−6.97 (m, 2H), 7.17 (d, J = 2.02 Hz, 1H), 7.22 (d, J = 8.59 Hz, 1H), 7.53−7.62 (m, 2H), 7.65 (d, J = 15.66 Hz, 1H). LC/MS ESI m/z 406.8 $[M + H]^+$.

(E)-3-(4-((2-Bromo-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl)-acrylic Acid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 6.38 (d, J = 16.17 Hz, 1H), 6.82 (dd, J = 8.59, 2.02 Hz, 1H), 6.89−6.97 (m, 2H), 7.17 (d, J = 2.02 Hz, 1H), 7.23 (d, J = 8.59 Hz, 1H), 7.53−7.60 (m, 2H), 7.63 (d, J = 15.66 Hz, 1H). LC/MS ESI m/z 392.8 $[M + H]^+$.

Step 2: To a solution of (*E*)-methyl 3-(4-((2-bromo-6-hydroxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate (75 mg, 0.185 mmol) in dimethoxyethane (1.0 mL) were added (2-(dimethylamino)-phenyl)boronic acid (91 mg, 0.370 mmol), Pd(dppf)Cl_2 (13.54 mg, 0.019), and 4 N aqueous K_2CO_3 solution (0.370 mL, 0.740 mmol). The mixture was subjected to microwave irradiation for 20 min at 110 °C, after which the reaction was quenched with brine and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product. The crude material was purified by column chromatography (SiO_2, 0−100% EtOAc/heptane) to afford methyl (*E*)-3-(4-((2-(2-(dimethylamino)phenyl)-6-hydroxybenzo[*b*]thiophen-3-yl)-oxy)phenyl)acrylate (72 mg, 87% yield). LC/MS ESI m/z 446.4 $[M + H]^+$.

Step 3: To a solution of (*E*)-3-(4-((2-(2-(dimethylamino)phenyl)-6-hydroxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate (72 mg, 0.162 mmol) in MeOH (3.0 mL) at room temperature was added 2 N aqueous K_2CO_3 solution (0.646 mL, 1.293 mmol), and the resulting mixture was stirred at room temperature for 16 h. Upon completion, the reaction was concentrated *in vacuo*, water (5 mL) was added, and the aqueous layer was acidified to pH ∼ 1 by addition of 1 N aqueous HCl. The aqueous layer was then extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude product. The crude material was purified by reverse phase HPLC (acidic conditions, 3% TFA in 10−100% CH_3CN/H_2O) to afford (*E*)-3-(4-((2-(2-(dimethylamino)phenyl)-6-hydroxybenzo[*b*]-thiophen-3-yl)oxy)phenyl)acrylic acid (14.3 mg, 20% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.73−7.45 (m, 6H), 7.41−7.26 (m, 3H), 6.94−6.86 (m, 3H), 6.33 (d, J = 15.9 Hz, 1H), 3.10 (s, 6H). HRMS ESI m/z 432.1279 $[M + H]^+$.

*(S,E)-3-(4-((6-Hydroxy-2-(2-(1-hydroxyethyl)phenyl)benzo[b]-thiophen-3-yl)oxy)phenyl)acrylic Acid (**53n**).* Step 1: The intermediate was prepared in 39% yield from (*E*)-*tert*-butyl 3-(4-((6-methoxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate and (*S*)-1-(2-bromophenyl)ethanol using the procedure described for the synthesis of **53d**, step 1. LC/MS ESI m/z 520.5 $[M + H_2O]^+$.

Step 2: To a solution of *tert*-butyl (*S*,*E*)-3-(4-((2-(2-(1-hydroxyethyl)phenyl)-6-methoxybenzo[*b*]thiophen-3-yl)oxy)phenyl)-acrylate (59.8 mg, 0.119 mmol) in *N*-methyl-2-pyrrolidone (1.0 mL) were added thiophenol (0.018 mL, 0.178 mmol) and K_2CO_3 (16.4 mg, 0.119 mmol). The resulting mixture was subjected to microwave irradiation at 200 °C for 1 h, after which time the reaction was diluted with EtOAc and brine, the layers were separated, and the aqueous layer was further extracted with EtOAc (1×). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*, and the crude material was purified by column chromatography (SiO_2, 0−100% EtOAc/heptane) to afford *tert*-butyl (*S*,*E*)-3-(4-((6-hydroxy-2-(2-(1-hydroxyethyl)phenyl)benzo[*b*]thiophen-3-yl)-oxy)phenyl)acrylate (12.8 mg, 22% yield). LC/MS ESI m/z 487.5 $[M - H]^-$.

Step 3: To a solution of *tert*-butyl (*S*,*E*)-3-(4-((6-hydroxy-2-(2-(1-hydroxyethyl)phenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate (12.8 mg, 0.026 mmol) in THF (0.7 mL) at room temperature was added 4.0 N HCl in 1,4-dioxane (200 μL, 0.800 mmol); the resulting mixture was warmed to 80 °C for 18 h. Upon completion, the reaction was quenched by addition of sat. aq. $NaHCO_3$ and extracted with EtOAc (3×). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*, and the crude material was purified by reverse phase HPLC (neutral conditions, 3% 1-propanol in 10−100% CH_3CN/H_2O) to afford (*S*,*E*)-3-(4-((6-hydroxy-2-(2-(1-hydroxyethyl)phenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)acrylic acid (3.9 mg, 34% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 1.37 (d, J = 6.57 Hz, 3H), 5.16 (q, J = 6.57 Hz, 1H), 6.32 (d, J = 15.66 Hz, 1H), 6.82−6.90 (m, 3H), 7.17−7.25 (m, 3H), 7.26−7.31 (m, 1H), 7.35−7.41 (m, 1H), 7.45 (d, J = 9.09 Hz, 2H), 7.54 (d, J = 15.66 Hz, 1H), 7.63 (d, J = 7.58 Hz, 1H). LC/MS ESI m/z 431.4 $[M - H]^-$.

*(E)-3-(4-((6-Hydroxy-2-(2-(methoxymethyl)phenyl)benzo[b]-thiophen-3-yl)oxy)phenyl)acrylic Acid (**53o**).* Step 1: To a solution of (*E*)-methyl 3-(4-((2-bromo-6-methoxybenzo[*b*]thiophen-3-yl)oxy)-phenyl)acrylate (100 mg, 0.238 mmol) in 1,2-dimethoxyethane (3.0 mL) was added (2-(methoxymethyl)phenyl)boronic acid (79 mg, 0.477 mmol), Pd(dppf)Cl_2 (17.5 mg, 0.024 mmol), and Na_2CO_3 (2.0 N aqueous, 0.358 mL, 0.715 mmol). The resulting mixture was subjected to microwave irradiation at 100 °C for 20 min, after which time the reaction was diluted with EtOAc, anhydrous Na_2SO_4 was added, and the reaction was filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (SiO_2, 0−20% EtOAc/heptane) to afford (*E*)-methyl 3-(4-((6-methoxy-2-(2-(methoxymethyl)phenyl)-benzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate (86.6 mg, 79% yield). LC/MS ESI m/z 478.0 $[M + H_2O]^+$.

Step 2: To a solution of (*E*)-methyl 3-(4-((6-methoxy-2-(2-(methoxymethyl)phenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate (86.6 mg, 0.188 mmol) in MeOH (3.0 mL) was added LiOH (2.0 N aqueous, 0.564 mL, 1.128 mmol). The resulting mixture was stirred at room temperature for 48 h, after which time the reaction was brought to pH 7 by addition of 1 N HCl; the neutralized reaction was then concentrated *in vacuo* to afford (*E*)-3-(4-((6-methoxy-2-(2-

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(methoxymethyl)phenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)acrylic acid (45.9 mg, 55% yield). LC/MS ESI *m/z* 447.0 $[M + H]^+$.

Step 3: To a solution of (*E*)-3-(4-((6-methoxy-2-(2-(methoxymethyl)phenyl)benzo[*b*]thiophen-3-yl)oxy)phenyl)acrylic acid (45.9 mg, 0.103 mmol) in *N*-methyl-2-pyrrolidone (1.0 mL) were added thiophenol (0.016 mL, 0.154 mmol) and K_2CO_3 (14.21 mg, 0.103 mmol). The resulting mixture was subjected to microwave irradiation at 200 °C for 90 min, after which time the reaction was diluted with EtOAc and filtered. The filtrate was concentrated *in vacuo*, and the crude material was purified by reverse phase HPLC (basic conditions, 0.1% NH_4OH in CH_3CN/H_2O) to afford (*E*)-3-(4-((6-hydroxy-2-(2-(methoxymethyl)phenyl)benzo[*b*]thiophen-3-yl)oxy)-phenyl)acrylic acid (3.0 mg, 6% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.47 (d, *J* = 7.7 Hz, 1H), 7.40−7.31 (m, 4H), 7.31−7.21 (m, 4H), 6.86 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 2H), 6.35 (d, *J* = 15.9 Hz, 1H), 4.53 (s, 2H), 3.29 (s, 3H). HRMS ESI *m/z* 433.1099 $[M + H]^+$.

*(E)-3-(4-((2-(2-(Difluoromethyl)phenyl)-6-hydroxybenzo[b]-thiophen-3-yl)oxy)phenyl)acrylic Acid (**53p**).* Step 1: The intermediate was prepared in 79% yield from (*E*)-*tert*-butyl 3-(4-((6-methoxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate and 1-bromo-2-(difluoromethyl)benzene using the procedure described for the synthesis of **53d**, step 1. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.51 (s, 9H), 3.91 (s, 3H), 6.19 (d, *J* = 16.17 Hz, 1H), 6.82 (d, *J* = 8.59 Hz, 2H), 6.94 (t, *J* = 55.06, 1H), 6.98 (dd, *J* = 8.84, 2.27 Hz, 1H), 7.30−7.35 (m, 3H), 7.37 (d, *J* = 8.59 Hz, 1H), 7.40−7.51 (m, 4H), 7.69−7.76 (m, 1H).

Step 2: To a solution of (*E*)-*tert*-butyl 3-(4-((2-(2-(difluoromethyl)-phenyl)-6-methoxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate (133 mg, 0262 mmol) in *N*-methyl-2-pyrrolidone (1.5 mL) were added thiophenol (0.040 mL, 0.392 mmol) and K_2CO_3 (36.1 mg, 0.262 mmol). The resulting mixture was subjected to microwave irradiation at 200 °C for 1 h, after which time the reaction was quenched by addition of water and extracted with EtOAc (2×). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*, and the resulting crude material was purified by column chromatography (SiO_2, 0−20% EtOAc/heptane) to afford (*E*)-*tert*-butyl 3-(4-((2-(2-(difluoromethyl)phenyl)-6-hydroxybenzo[*b*]thiophen-3-yl)oxy)-phenyl)acrylate (100 mg, 77% yield). LC/MS ESI *m/z* 495.1 $[M + H]^+$.

Step 3: To a solution of (*E*)-*tert*-butyl 3-(4-((2-(2-(difluoromethyl)-phenyl)-6-hydroxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate (100 mg, 0.202 mmol) in 1,4-dioxane (3.0 mL) was added 4.0 M aq. HCl (0.202 mL, 0.809 mmol). The resulting mixture was warmed to 50 °C and stirred at that temperature for 2 h, after which time the reaction was quenched by addition of sat. aq. $NaHCO_3$ and extracted with EtOAc (3×). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*, and the resulting crude material was purified by reverse phase HPLC (basic conditions, 0.1% NH_4OH in CH_3CN/H_2O) to afford (*E*)-3-(4-((2-(2-(difluoromethyl)-phenyl)-6-hydroxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylic acid (16.7 mg, 19% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.72−7.64 (m, 1H), 7.54−7.42 (m, 4H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.33−7.24 (m, 2H), 7.00 (d, *J* = 55.2 Hz, 1H), 6.88 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.81 (d, *J* = 8.9 Hz, 2H), 6.30 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 108.89, 112.32, 114.66, 116.38, 117.01, 117.19, 118.99, 123.09, 123.43, 126.65, 126.92, 126.97, 127.02, 130.52, 130.60, 130.87, 131.91, 132.92, 140.42, 142.46, 144.90, 157.90, 160.86, 171.36. HRMS ESI *m/z* 439.0776 $[M + H]^+$.

*(E)-3-(4-((2-(2-(1-Fluoroethyl)phenyl)-6-hydroxybenzo[b]-thiophen-3-yl)oxy)phenyl)acrylic Acid (**53q**).* Step 1: The intermediate was prepared in 42% yield from (*E*)-methyl 3-(4-((2-bromo-6-hydroxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate and 2-(2-(1-fluoroethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (see Supporting Information for synthesis) using the procedure described for the synthesis of **53m**, step 2. HRMS ESI *m/z* 449.4 $[M + H]^+$.

Step 2: The title compound was prepared in 11% yield from methyl (*E*)-3-(4-((2-(2-(1-fluoroethyl)phenyl)-6-hydroxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate using the procedure described for the synthesis of **42a**, step 2. ^{1}H NMR (400 MHz, CD_3OD) δ ppm = 7.56 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.51 (d, *J* = 15.9 Hz, 1H), 7.47−7.38 (m, 3H), 7.36−7.23 (m, 4H), 6.87 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.32 (d, *J* = 16.0 Hz, 1H), 5.88 (dq, *J* = 46.9, 6.3 Hz, 1H), 1.54 (dd, *J* = 23.6, 6.4 Hz, 3H). HRMS ESI *m/z* 435.1024 $[M + H]^+$.

*(E)-3-(4-((2-(2-(1,1-Difluoroethyl)phenyl)-6-hydroxybenzo[b]-thiophen-3-yl)oxy)phenyl)acrylic Acid (**53r**).* Step 1: The intermediate was prepared in 70% yield from (*E*)-methyl 3-(4-((2-bromo-6-hydroxybenzo[*b*]thiophen-3-yl)oxy)phenyl)acrylate 2-(2-(2-fluoropropan-2-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (see Supporting Information for synthesis) using the procedure described for the synthesis of **53m**, step 2. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 7.63−7.56 (m, 2H), 7.44−7.38 (m, H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 4.1 Hz, 2H), 7.28−7.24 (m, 2H), 6.90−6.81 (m, 3H), 6.28 (d, *J* = 16.1 Hz, 1H), 3.78 (s, 3H), 1.91 (t, *J* = 18.4 Hz, 3H).

Step 2: The title compound was prepared in 47% yield from methyl (*E*)-3-(4-((2-(2-(2-fluoropropan-2-yl)phenyl)-6-hydroxybenzo[*b*]-thiophen-3-yl)oxy)phenyl)acrylate using the procedure described for the synthesis of **42a**, step 2. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 9.94 (s, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.54−7.42 (m, 4H), 7.32 (d, *J* = 2.1 Hz, 1H), 7.10 (d, *J* = 8.7 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.84 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.36 (d, *J* = 16.0 Hz, 1H), 1.94 (t, *J* = 18.9 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ ppm = 26.45, 26.74, 27.04, 108.68, 115.93, 117.40, 117.81, 123.23, 125.73, 126.26, 127.00, 127.08, 127.16, 130.13, 130.31, 130.46, 130.95, 134.74, 139.43, 139.68, 139.93, 140.16, 142.24, 145.75, 157.40, 161.29, 170.71. HRMS ESI *m/z* 453.0919 $[M + H]^+$.

*(E)-3-(4-((6-Hydroxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)oxy)phenyl)acrylic Acid (**53s**).* The title compound was prepared using a similar procedure to that described for the synthesis of **34**; see Supporting Information for synthesis. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.64 (d, *J* = 8.59 Hz, 2H), 7.55−7.62 (m, 2H), 7.51 (d, *J* = 16.17 Hz, 1H), 7.30 (d, *J* = 2.02 Hz, 1H), 7.13 (d, *J* = 8.59 Hz, 1H), 6.90−7.04 (m, 4H), 6.83 (dd, *J* = 2.02, 8.59 Hz, 1H), 6.38 (d, *J* = 16.17 Hz, 1H), 3.75 (s, 3H). LC/MS ESI *m/z* 417.5 $[M - H]^-$.

Cell Culture. MCF-7 cells were routinely maintained in RPMI 1640 medium (Invitrogen) with 10% fetal bovine serum (FBS) (Invitrogen). To deplete growth factors from cells, MCF-7 cells were cultured in phenol red-free RPMI medium with 10% charcoal-stripped FBS (CSS medium; Invitrogen) for 3 days before the assay.

MCF-7 ERE Reporter Gene Assays. *Transient Transfection Assay.* MCF-7 cells were maintained in Dulbecco's modified Eagle's Medium (DMEM)/F12 supplemented with 8% fetal bovine serum (FBS). Cells were seeded in 96-well plates and transfected with an estrogen responsive reporter gene (7×-TK-ERE-Luc) and Renilla-luc (to monitor cellular toxicity) using Lipofectin reagent (Invitrogen), as described in the manufacturer's instructions. After overnight incubation, cells were treated with hormone for 24 h. Cells were then lysed and quantified for luciferase activity using dual luciferase reagent.

ERE-Luciferase Reporter Stable Cell Line Assay. Growth factors depleted MCF-7 ERE-luc cells were seeded (10 000 cells/well) in 96-well plates in CSS medium. After overnight incubation, cells were treated with compounds in the presence of estradiol (0.1 nM) for 24 h. Cells were then lysed and quantified for luciferase activity using Bright-Glo assay.

In-Cell Western To Detect ER Protein Levels. MCF-7 cells were cultured in CDT growth medium (DMEM/F12 phenol red-free media (Gibco, cat. no. 21041) supplemented with 10% charcoal dextran-stripped serum (Gemini Bio-Products, cat. no. 100-119) 72 h prior to plating cells. The cells were seeded in 100 μL of CDT growth medium at a density of 30 000 cells/well in a black, clear-bottom 96-well assay plate (Greiner, cat. no. 655090) and incubated for 24−36 h at 37 °C with 5% CO_2. For **10**, 4-hydroxytamoxifen, and fulvestrant treatment, 11 μL of 10× compound was added to each well in a seven-point, 1:10 dilution series (CSS growth media; normalized for a final assay concentration of 0.1% DMSO), starting at 10 μM, and incubated for 18−24 h at 37 °C with 5% CO_2. DMSO and fulvestrant were used to determine the baseline for maximal response and ERα degradation, respectively. To fix cells, media was first decanted by inversion, followed immediately by the addition of 100 μL/well of 3.7% formaldehyde (Sigma, cat. no. F8775) in PBS (Gibco, cat. no. 20012),

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and the cells were incubated for 20 min at room temperature. Cells were then blocked with 50 μL/well of blocking buffer (PBS pH 7.4, 3% goat serum (Life Technologies, cat. no. 16210072), 1% BSA (Sigma, cat. no. A7906), 0.1% cold fish skin gelatin (Sigma, cat. no. G7041), 0.1% Triton X-100 (OmniPur, cat. no. 9410)) for 2 h with shaking at room temperature or at 4 °C overnight. Blocking buffer was then decanted, and 40 μL of ERα primary antibody (Santa Cruz, cat. no. SC543) at 1:3000 in blocking buffer diluted 1:3 with PBS was added to each well, excluding negative control wells used for background subtraction, sealed with film, and incubated at 4 °C overnight. To remove primary antibody, cells were washed three times with 100 μL/well PBS + 0.1% Tween (AMRESCO, cat. no. 0777) (PBST) for 5 min each. 40 μL of polyclonal anti-rabbit IgG (H+L) CF770 antibody (Biotium, cat. no. 20078) at 1:2000 and DRAQ5 DNA stain (Thermo Scientific, cat. no. 62251) at 1:10 000 in blocking buffer diluted 1:3 with PBS was then added to each well and incubated at room temperature with shaking for 2 h. To remove secondary antibody, cells were washed three times with 100 μL/well of PBST for 5 min each. To minimize Tween autofluorescence signaling, the cells were washed once with 100 μL/well of PBS. To prevent drying during detection, 100 μL/well PBS was then added to each well. For detection, the integrated intensities of ERα (700 channel) and DNA stain (800 channel) were measured using a LI-COR Odyssey (LI-COR Biosciences, Lincoln, NE). Data was then normalized by dividing the integrated intensities of the 700 channel (ER) by the integrated intensities of the 800 channel (DNA). Background subtraction was carried out by subtracting the average of the normalized negative control wells (no primary antibody) from all normalized experimental values. Percent response of normalized/background subtracted data was then calculated by dividing each experimental value by the average of the DMSO control values (% response = (value experimental/value DMSO control) × 100). Dose−response curves, IC_{50}, and percent ERα remaining values were generated using GraphPad Prism v6.02 software (GraphPad, San Diego, CA).

MCF-7 Proliferation Assay. Growth factor-depleted MCF-7 cells were seeded (10 000 cells/well) in 96-well plates in CSS medium. After overnight incubation, cells were treated with compounds in the presence of estradiol (0.1 nM) for 6 days. Cell viability was then measured by CellTiter Glo assay (Promega).

***In Vivo* Efficacy in the MCF-7 Breast Cancer Xenograft Model in Mice.** Mice were handled in accordance with Novartis IACUC regulations and guidelines. Female athymic nude mice were used for tumor xenograft studies. Time released 17-β estradiol pellets (0.36 mg E2, 90-day release; Innovative Research of America) were subcutaneously implanted into mice 2 days prior to tumor implantation. MCF-7 cells were grown in EMEM growth medium supplemented with 10% FBS and human insulin (Sigma-Aldrich cat. no. I9278) at 5% CO_2, 37 °C. Trypsinized cells were pelleted and resuspended in 50% HBSS and 50% Matrigel at 10^7 cells/mL. MCF-7 cells were subcutaneously injected (200 μL/animal) in the right axillary mammary fat pad area. Tumor volume ($width^2 \times length \times \pi/6$) and body weights were measured twice weekly. When tumors reached an average volume of ~200 mm^3, mice were randomized into groups and treatment began. Animals were orally administered vehicle alone or 20 mg/kg **10** daily or 60 mg/kg tamoxifen 5 days per week. Fulvestrant was administered subcutaneously at 5 mg/mouse (corresponds to roughly 250 mg/kg) once weekly, providing a slow release from the depot in the subcutis. The formulations of these three reagents are as follows: 10% ethanol and 90% peanut oil for fulvestrant; 0.5% hydroxypropyl cellulose for tamoxifen; and 10% PEG300, 25% of 20% Solutol, 65% PBS for **10**.

***In Vivo* Pharmacodynamics Marker Assessment in the MCF-7 Breast Cancer Xenograft Model.** At the end of the efficacy study on day 48 postimplantation, MCF-7 tumors were collected and snap frozen 7 h post last dose of **10**, tamoxifen, or fulvestrant.

Quantitative Reverse Transcriptase-PCR. For the analysis of progesterone receptor (PgR) mRNA levels from snap-frozen end of efficacy study MCF-7 tumors, total mRNA was isolated using the RNeasy Mini kit (Qiagen, cat. no. 74104), followed by two-step qRT-PCR using an iScript cDNA synthesis kit (BioRad cat. no. 170-8891) for cDNA synthesis and quantitative PCR by Taqman using Taqman Gene Expression Assays (Applied Biosystems). The C_T values were analyzed to assess relative changes in expression of progesterone receptor (PgR) genes, with B2M as an internal control, using the $2^{-\Delta\Delta C_T}$ method.

Western Blot Analysis. For the analysis of ERα protein levels in the end of efficacy study MCF-7 tumors, snap frozen tumors were transferred to Lysing Matrix Tubes (MP Biomedicals cat. no. 6913-500), mixed with cold lysis buffer (1× cell lysis buffer; Cell Signaling, cat. no. 9803S) containing Complete Mini (1 tablet to 10 mL) and PhosStop (1 tablet to 10 mL and 1 M Urea), and homogenized by a Fast Prep 24 Tissue Lyser (MP Biomedicals). Total protein concentrations of the lysate were measured (Pierce BCA Protein Assay Kit, cat. no. 23225, Thermo Scientific) according to the manufacturer's instructions. Lysates were separated by SDS-PAGE, transferred onto membranes, and then immunoblotted using an anti-ERα antibody (Santa Cruz Biotechnology, HC-20), as well as an anti-β-actin antibody (BioLegend, clone $2F_1$-1 cat. no. 643801) as a loading control. Western blots were scanned into (Bio Rad ChemiDoc Imaging Systems) for quantification of the immunoblotted bands. The percent of ERα remaining was determined by comparing tumors from the treated mice versus those from the vehicle control group.

Statistical Analyses for *in Vivo* Studies. Statistical analyses of data were generated using GraphPad Prism (San Diego, CA, USA). Tests used are listed in the figure legends.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.7b01682.

Crystallographic methods and parameters, as well as pharmacokinetic studies (PDF)

Molecular formula strings as well as IC_{50} and percent ERα remaining data (CSV)

Accession Codes

The PDB code for compound **10** is 6B0F.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

Ac, acetate; Ar, aromatic; AUC, area under the curve; cmpd, compound; Bu, butyl; clogD, calculated logD; C_{max}, maximum concentration; DIBAL-H, diisobutylaluminum hydride; DIEA, *N*,*N*-diisopropylethylamine; DMA, *N*,*N*-dimethylacetamide; DME, 1,2-dimethoxyethane; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; dn, dose normalized; dppf, 1,1′-bis(diphenylphosphino)ferrocene; ERα, estrogen receptor alpha; HATU, *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; iv, intravenous; Me, methyl; Ph, phenyl; po, per os; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator; SD, Sprague−Dawley; $t_{1/2}$, half-life; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TMS, trimethylsilyl; V_{ss}, volume of distribution at steady state

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