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Synthesis and Binding Affinities of Fluoroalkylated Raloxifenes

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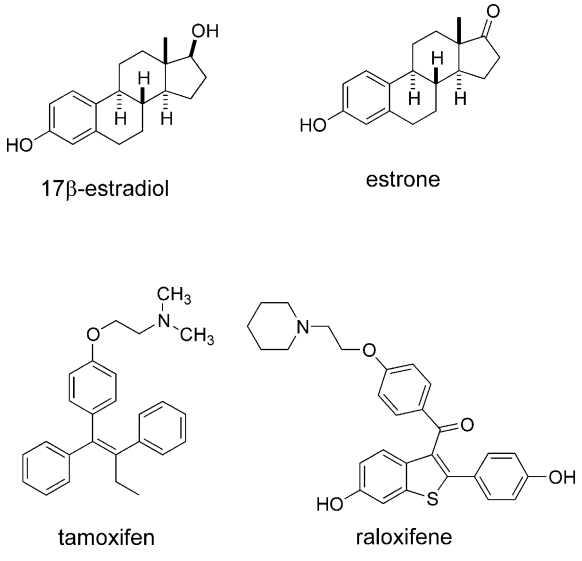
Abstract—Three fluoroalkylated derivatives (**1**–**3**) of the selective estrogen receptor modulator (SERM), raloxifene, have been synthesized. The key step in the synthesis is the C–C bond formation of benzo[*b*]thiophene and a substituted phenyl group (ring C) using a Stille reaction. The in vitro binding affinities of the substituted raloxifenes **1**–**3** are 45, 60, 89%, respectively, relative to the affinity of estradiol, which is higher than the affinity of raloxifene itself (25%). When labeled with the positron-emitting radionuclide, these compounds might be useful as PET imaging agents for estrogen receptor-positive breast tumors.

Introduction

The roles played by endogeneous estrogens, such as 17β-estradiol and estrone, as important regulators of the development and maintenance of the female reproductive organs and other sexual characteristics have long been appreciated.[1] More recently, their involvement in maintaining the healthy function of a number of other systems in humans, such as bone, the cardiovascular system, and the central nervous system, has been recognized, as well.[2] The decreased production of ovarian steroids which occurs after menopause has been linked to a number of pathologies, particularly osteoporosis and coronary artery disease, as well as with changes in cognitive function.

Tamoxifen, an antiestrogen widely used for the treatment of breast cancer, possesses mixed agonist–antagonist activities, thus limiting its efficiency as a blocker of estrogen action.[3] Recently, some groups have developed molecules termed Selective estrogen receptor modulators (SERMs) that fully antagonize the effects of estrogen on uterine and mammary tissue, while retaining the effects of estrogen on bone and blood lipid profile.[4,5] Raloxifene, 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidin-1-yl)ethoxybenzoyl]benzo[*b*]thiophene, is a SERM that displays potent estrogen antagonist properties in the breast and uterus, yet possesses estrogen agonist-like actions on bone and blood lipid profiles.[6]

Raloxifene binds with high affinity to the estrogen receptor (ER).[5a] Thus, radiolabeled raloxifene derivatives might be useful for imaging ER-positive breast tumors in vivo, as has been done using several radiolabeled steroidal estrogen agonists, including ones labelled with fluorine-18.[7] By contrast, receptor imaging studies with estrogen antagonists have been limited, and there have been only a few reports of imaging and tissue



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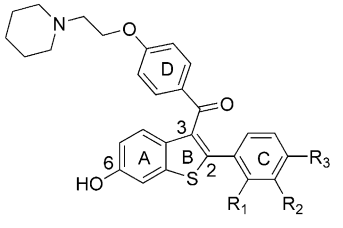
distribution studies with radio-emitting tamoxifen derivatives, many of which have low binding affinity for the ER.[8] In vivo tissue distribution studies of radiolabeled raloxifene have not been reported.

Radiopharmaceuticals labeled with fluorine-18 are being increasingly used in clinical diagnosis.[9] Although fluorine-18 is the most attractive radionuclide for the preparation of imaging agents for positron emission tomography (PET), labeling of organic compounds with fluorine-18 is often difficult, particularly at aromatic positions. Because fluorine-18 at the high specific activity level required for imaging receptors is only practically available in nucleophilic form (i.e., as fluoride ion), direct arene labeling with fluorine requires nucleophilic aromatic substitution, which further limits the scope of systems that can be labeled easily.[10]

An alternative way to label aromatic systems with fluorine-18 involves introduction of a fluoroalkyl group on an aromatic position, rather than labeling with a fluorine atom directly.[11] According to various in vivo stability studies of [^{18}F]fluoroalkyl aromatic compounds, as well as metabolism studies in vitro, the [^{18}F]fluoroethyl group appears to be the most stable, with the in vivo stability of fluoroalkyl groups following the order: fluoroethyl > fluoropropyl > fluoromethyl.[12]

If a fluoroalkyl group could be introduced into raloxifene without compromising its high affinity binding to the ER, this might provide a convenient strategy for developing an easily radiolabeled raloxifene-based agent for imaging estrogen receptor in vivo. In this report, we describe our investigations of methods for preparing raloxifene analogues containing fluoroalkyl groups that might be readily labeled with fluorine-18. Our selection of sites for fluoroalkyl substitution on raloxifene was based on the known relative binding affinity (RBA) and IC_{50} values of various substituted and modified raloxifene analogues, through which it is known that the C-ring is particularly tolerant of substitution (e.g., Fig. 1).[5a] Therefore, we elected to introduce fluoroethyl and fluoropropyl groups at the R_1 and R_2 positions. Herein, we wish to report the synthesis and in vitro binding affinities of these analogues. Further studies of their labeling with fluorine-18 and in vivo studies will be described elsewhere.



raloxifene RBA = 34%, IC_{50} = 0.2 nM

R_1 = Me,	R_2 = H,	R_3 = OH	RBA = 40%, IC_{50} = 0.7 nM
R_1 = H,	R_2 = Me,	R_3 = OH	RBA = 13%, IC_{50} = 1 nM
R_1 = H,	R_2 = F,	R_3 = OH	RBA = 20%, IC_{50} = 0.3 nM
R_1 = H,	R_2 = F,	R_3 = H	RBA = 29%, IC_{50} = 0.29 nM

RBA = relative binding affinity by competition with [^{3}H]-17β-estradiol

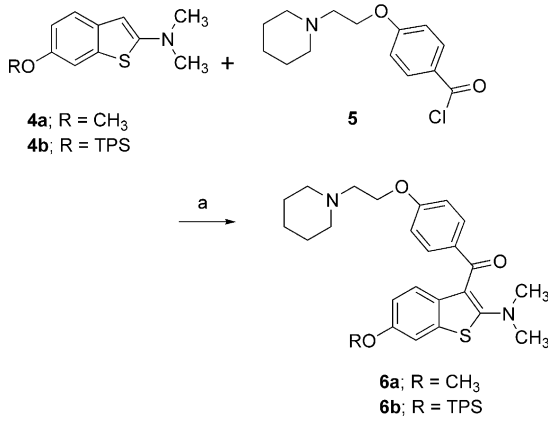
Figure 1. Estrogen receptor binding affinity of raloxifene derivatives modified on the C ring (from ref 5a).

Results and Discussion

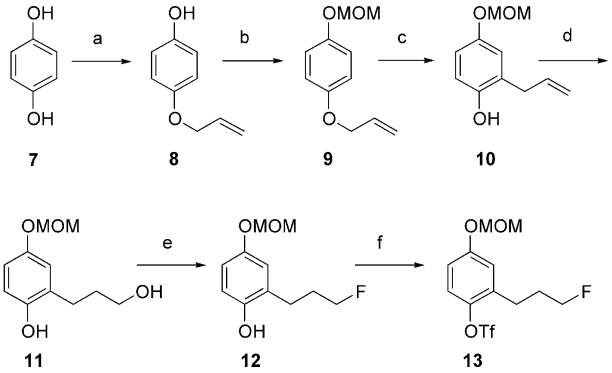
2-Arylbenzothiophene **4a**[5a] and 4-(2-piperidin-1-yl) ethoxybenzoyl chloride (**5**)[5a] were prepared according to literature procedures. The Friedel–Crafts acylation of a **4a** with **5** in chlorobenzene at 100 °C provided 2-dimethylamino-6-methoxy-3-[4-(2-piperidin-1-yl)ethoxy-benzoyl]benzo[*b*]thiophene (**6a**) in 64% isolated yield (Scheme 1). 6-*tert*-Butyldiphenylsilyl (TPS) protected derivatives **4b** and **6b** were also prepared by a similar route.

Synthesis of fluoroalkylated aryl compounds for ring C. Three fluoroalkylated aryl compounds **13**, **20,** and **25**, which are the precursors of the ring C part required for the coupling reaction of rings B and C, were prepared by different synthetic routes, as shown in Schemes 2–4.

Synthesis of 2-(3-fluoropropyl)-4- (methoxymethoxy)-1-trifluoromethanesulfonyloxy-benzene (13). Treatment of hydroquinone with allyl bromide in anhydrous acetonitrile at reflux for 12 h provided monoallyl ether **8** in



Scheme 1. (a) Chlorobenzene, 100 °C, 9 h, **6a**: 64%; **6b**; 68%.

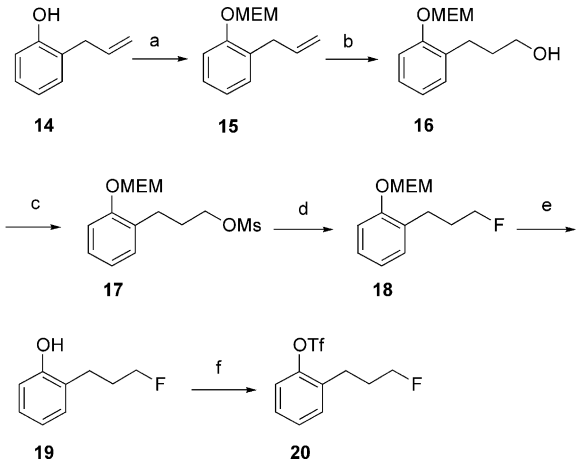


Scheme 2. (a) Allyl bromide, K_2CO_3, CH_3CN, reflux, 12 h, 92%; (b) MOMCl, NaH, THF, 0 °C to reflux, 1 h, 92%; (c) *N*,*N*-dimethylaniline, reflux, 2 h, 80%; (d) borane–THF complex, H_2O_2, 4 N NaOH, THF, 0 °C, 1 h, 78%; (e) DAST, CH_2Cl_2, −78 °C to rt, 30 min, 15%; (f) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, N_2, 30 min, 92%.

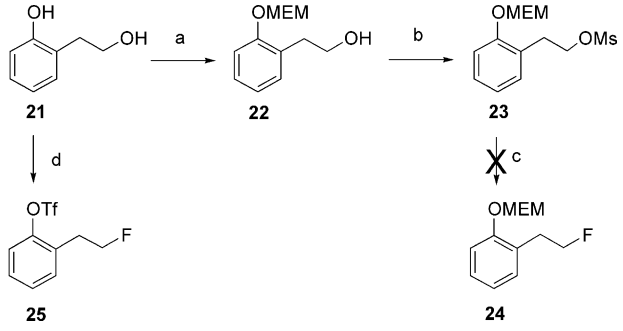
92% yield. After protection of the free phenol group with methoxymethyl chloride (MOMCl), Claisen rearrangement reaction gave allylbenzene **10** in 80% yield. Hydroboration of alkene **10** using borane–THF complex and subsequent oxidation with alkaline peroxide gave the aliphatic alcohol **11**; fluorination using diethylaminosulfur trifluoride (DAST) gave the fluoropropyl compound **12**, followed by trifluoromethanesulfonylation (triflation afforded triflate **13** as shown in Scheme 2).

The conventional method for fluorination is a nucleophilic displacement of a methanesulfonate (mesylate) using fluoride ion. However, our attempts at mesylation of primary alcohol **11** failed because the phenol group attacked the α-carbon of the mesylate, giving a cyclic ether. Thus, the fluoropropyl compound **12** was prepared using DAST. Before the triflate **13** was prepared, the MOM protecting group was replaced by the methyl ether derivative. As discussed later in detail, we were unable to use the methylated derivative, because defluorination occurred during the demethylation step.

Synthesis of 2-(3-fluoropropyl)-1-trifluoromethanesulfonyloxybenzene (20). From 2-allylphenol (**14**), protection of the phenol using methoxyethoxymethyl chloride (MEMCl), hydroboration–oxidation, mesylation of the terminal alcohol, fluorination, deprotection of the MEM group and triflation gave **20**, one of the C-ring precursors. Yields and details for each step are shown in Scheme 3.



Scheme 3. (a) MEMCl, NaH, THF, 0 °C to reflux, 1 h, 82%; (b) borane–THF complex, H_2O_2, 4 N NaOH, THF, 0 °C, 1 h, 48%; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C, 20 min, 56%; (d) *n*-$Bu_4NF{\cdot}xH_2O$, CH_3CN, 110 °C, 30 min, 74%; (e) concd HCl, MeOH, 60 °C, 1 h, 90%; (f) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, N_2, 30 min, 82%.

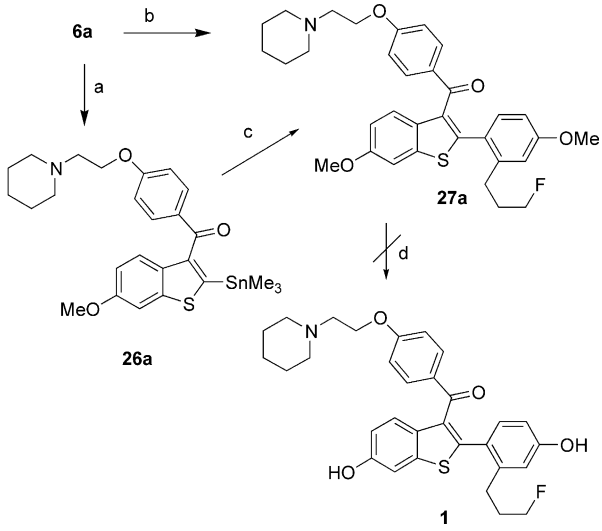


Scheme 4. (a) MEMCl, NaH, THF, 0 °C to reflux, 1 h, 70%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 20 min, 82%; (c) *n*-$Bu_4NF{\cdot}xH_2O$, CH_3CN, 110 °C, 30 min, obtained vinyl compound; (d) (i) DAST, CH_2Cl_2, −78 °C to rt, 30 min; (ii) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, N_2, 30 min, 26%.

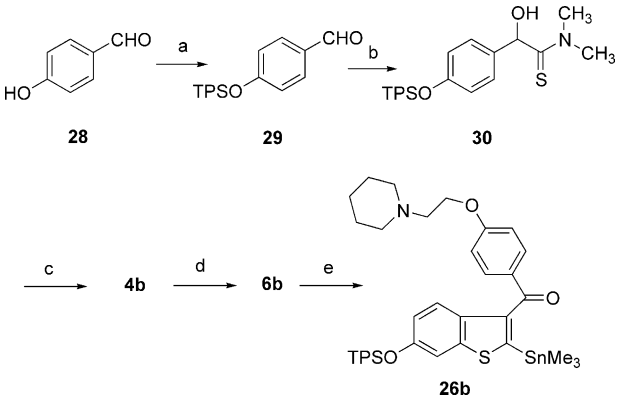
Synthesis of 2-(2-fluoroethyl)-1-trifluoromethanesulfonyloxybenzene (25). After selective protection of phenol **21**, using MEMCl, mesylated compound **23** was obtained. However, fluorination of the phenethyl mesylate failed because of competitive elimination. Thus, the phenethyl alcohol was fluorinated using DAST, and triflation afforded triflate **25**, as shown in Scheme 4.

Ring B and ring C coupling reactions

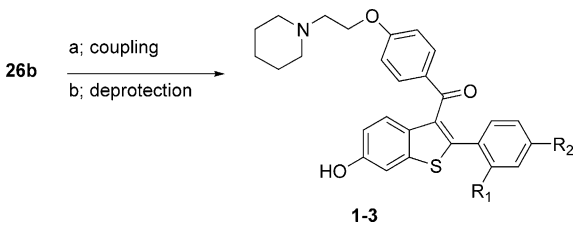
Synthesis of 2-(4-methoxy-2-fluoropropylphenyl)-3-[4-(2-piperidin - 1 - yl)ethoxybenzoyl] - 6 - methoxybenzo[*b*]thiephene (27a). Two different methods were used to couple rings B and C: a Stille coupling reaction and a Grignard



Scheme 5. (a) $LiMe_3Sn$, THF, −78 °C to rt, 5 h, 99%; (b) 2-(3-fluoropropyl)-4-methoxyphenylmagnesium bromide, THF, −78 °C to rt, 2 h, 60%; (c) compound **13**, $Pd(PPh_3)_4$, DMF, 120 °C, 9 h, 57%; (d) BBr_3, CH_2Cl_2, rt, 1 h or $AlCl_3$, CH_3CH_2SH, CH_2Cl_2, rt, 1 h or $SiCl_4$, NaI, CH_2Cl_2, rt, 1 h or CH_3SiI, $CHCl_3$, rt, 1 h.



Scheme 6. (a) TPSCl, imidazole, DMF, rt, 3 h, 99%; (b) *N*,*N*-dimethylthioformamide, LDA, THF/hexane (5:1), −100 to −78 °C, 1 h, 57%; (c) methanesulfonic acid, CH_2Cl_2, −10 °C, 10 min, 49%; (d) compound **5**, chlorobenzene, 100 °C, 9 h, 68%; (e) $LiMe_3Sn$, THF, −78 °C to rt, 5 h, 71%.



Scheme 7. (a) Compound **13**, **20** or **25**, $Pd(PPh_3)_4$, DMF, 100 °C, 12 h, (b) *n*-$Bu_4NF{\cdot}xH_2O$, THF, rt, 1 min, 47% (compound **1**; including MOM deprotection, concd HCl in isopropanol, 60 °C, 30 min), 68% (compound **2**) or 80% (compound **3**).

reaction. Reaction of **6a** with Me_3SnLi, generated from lithium metal and trimethylstannyl chloride in THF, provided the aryl stannane **26a** in quantitative yield. The coupling reaction between stannane **26a** and triflate **13** using $Pd(PPh_3)_4$ gave the protected raloxifene analogue **27a** in 57% yield. A Grignard reaction between **26a** and 2-(3-fluoropropyl)-4-methoxyphenylmagnesium bromide also afforded **27a** in 78% yield. We encountered unexpected problems in the deprotection of the two methyl groups in compound **27a**. All well-known deprotection reagents that we tried, such as BBr_3, $AlCl_3$ with ethane thiol and tetramethylsilyl iodide, gave deprotected as well as defluorinated compound. Thus, we were unable to obtain the demethylated compound without losing the fluorine (Scheme 5).

At this point, an alternate function to protect the 6-hydroxy group of the benzothiophene group was required. In place of the methyl group, we considered other groups, such as methoxymethyl (MOM) and *tert*-butyldiphenylsilyl (TPS). When 4-hydroxybenzaldehyde was treated with MOMCl, a quinone derivative was obtained. Thus, we prepared **6b** and **26b** protected with TPS, as shown in Scheme 6.

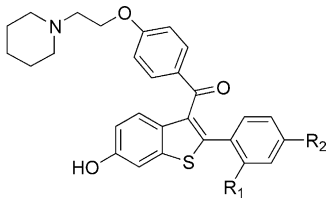
Synthesis of fluoroalkyl raloxifene derivatives 1, **2**, and **3**. Coupling reactions between **26b** and **13**, **20** or **25** were carried out using $Pd(PPh_3)_4$ in DMF at 100 °C for 12 h (Scheme 7). While the fluorine group is lost under conditions used to remove the methyl group, deprotection of the TPS groups by treatment with *n*-$Bu_4NF{\cdot}xH_2O$ was successful and provided compound **1**, **2**, or **3** in 47, 68, and 80% yields, respectively. To produce compound **1**, the TPS group on the C6 position as well as the MOM group on *para* position of the C ring had to be removed. All modifications for the synthesis of stannyl compound **26b** protected with a TPS group on the C6 position from *p*-hydroxybenzaldehyde **28** were done according the same route as that for the methyl protected stannyl compound **26a**, and the yields of each step are shown in Scheme 6.

Estrogen binding affinities of raloxifene derivatives 1–3. The in vitro binding affinity of raloxifene and the three fluoroalkylated raloxifene derivatives **1–3** (Fig. 2) to the ER was determined by a competitive radiometric binding assay, using established methods described previously.[13] Affinity is expressed as relative binding affinity (RBA) values, where the RBA of estradiol is 100%. Binding affinities to the purified human ERα and ERβ, as well as to the estrogen receptor from lamb uterus (predominantly ERα),[14] are shown in Table 1.

From literature precedent, it is known that introduction of a methyl group on the C2 position of ring C results in a slight increase in RBA value over that for raloxifene itself, when affinities are measured in uterine cytosol, whereas introducing a methyl group on the C3 position of ring C decreases the RBA value (cf. Fig. 1).[5a] It was on this basis that we designed the fluoroalkyl raloxifene analogues **1–3**.

Gratifyingly, all three compounds that we have prepared show much better ER binding affinities than does raloxifene (Table 1). The uterine cytosol RBA value of compound **1** having both hydroxy and fluoropropyl groups on ring C is somewhat elevated, but the derivatives **2** and **3,** with no hydroxy group on ring C, have RBA values that are considerably higher than raloxifene. Thus, considering binding values to this receptor preparation, compound **3**, the fluoroethyl derivative, appears to be the most promising compound for further study. The structure–binding affinity relationships with pure human ERα and ERβ are somewhat different, with raloxifene and the three compounds having more comparable affinities on the α subtype, but the compounds **1–3** binding much better than raloxifene on the β subtype. Overall, we consider compound **3** to be the most promising to investigate further for fluorine-18 labeling, although there is not a great difference among the three fluoroalkyl raloxifene derivatives.

In conclusion, based on known structure affinity relationship data for raloxifene derivatives, we have



1; $R_1 = CH_2CH_2CH_2F$, $R_2 = OH$
2; $R_1 = CH_2CH_2CH_2F$, $R_2 = H$
3; $R_1 = CH_2CH_2F$, $R_2 = H$

Figure 2. Structures of fluoroalkylated raloxifenes **1–3**.

Table 1. Relative binding affinities (RBA) of fluoroalkylated raloxifene derivatives **1–3**[a]

Compd	Lamb uterine ER RBA	Human ER α RBA	Human ER β RBA
Raloxifene	25±0	48±8	3.5±1.7
1	45	71	24
2	60	35	30
3	89	63	27

[a]Relative binding affinity (RBA) values in this study were determined in a competitive radiometric binding assay. Values are expressed as percentages relative to the affinity of the indicated tritium-labeled tracer. For procedural details, see Methods.

designed three target compounds **1**–**3** bearing a fluoroalkyl substituent. Compound **1** has a hydroxyl group on ring C, as is found in raloxifene, but the other two compounds (**2** and **3**) lack this hydroxy group. As is apparent from the binding affinity of our compounds, as well as that for other raloxifene analogues,[5a] the hydroxy group on ring C is not crucial, and introduction of the fluoroalkyl groups, especially the fluoroethyl group, on ring C actually increases binding affinity to the estrogen receptor. We anticipate that these substitutions will not have a major effect on the pharmacology or pharmacokinetics of these high affinity raloxifene derivatives. Therefore, when labeled with fluorine-18, these compounds may hold promise as a PET imaging estrogen antagonist agent for ER-positive tumors, particularly those rich in the ERα subtype.[15]

Experimental

2-Dimethylamino-6-methoxybenzo[*b*]thiophene (4a). α-Hydroxythioacetamide (0.316 mmol) was dissolved in dichloromethane (10 mL) and cooled to −10 °C. Methansulfonic acid (0.10 mL, 1.54 mmol) was added, resulting in a green-brown solution that turned colorless within 10 min, when TLC analysis indicated the absence of starting material. The solution was washed with saturated sodium bicarbonate solution (10 mL), water (10 mL), dried ($MgSO_4$), filtered, and solvent removed to yield the arene, which was recrystallized from 95% ethanol or flash chromatography (5% EtOAc/hexane) to give a pale yellow crystalline solid (52.4 mg, 80%); mp 69–70 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.95 (s, 6H), 3.80 (s, 3H), 5.95 (s, 1H), 6.85 (dd, J = 8.6, 2.3 Hz, 1H), 7.10 (d, J = 2.3 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.3, 53.3, 94.4, 103.2, 110.9, 118.5, 131.4, 132.7, 152.4, 153.6. The spectroscopic data is in agreement with that in the literature.[5a]

4-(2-Piperidin-1-yl-ethoxy)benzoic acid monohydrochloride. The crude methyl 4-(2-piperidin-1-yl-ethoxy)benzoate was hydrolyzed by dissolving the oil in MeOH, adding 5 N NaOH, and allowing the reaction mixture to stirring under N_2 atmosphere for 48 h. The mixture was then evaporated to remove most of the MeOH, and the residue was diluted with water to make a total volume of 200 mL. The resulting solution was cooled to 5 °C and acidified by the gradual addition of 6 N HCl, while the temperature was maintained below −10 °C. The white crystals that precipitated were collected and washed with cold MeOH. The product was then recrystallized from MeOH to provide a white crystalline solid (11.54 g, 67%): ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.36 (br s, 1H), 1.62–1.76 (m, 5H), 2.97 (br s, 2H), 3.41 (br s, 4H), 4.48–4.51 (m, 2H), 7.04 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.6 Hz, 2H), 11.28 (brs, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 20.19, 21.20, 51.49, 53.41, 61.58, 113.49, 122.73, 130.33, 160.03, 165.80. The spectroscopic data is agreement with that in the literature.[5a]

2-Dimethylamino-6-methoxy-3-[4-(2-piperidin-1-yl)ethoxybenzoyl]benzo[*b*]thiophene (6a). A portion of 4-(2-piperidin-1-yl-ethoxy)benzoic acid monohydrochloride (1.35 g, 4.74 mmol) was converted to its acid chloride by dissolving it in 1,2-dichloroethane and adding one drop of DMF and $SOCl_2$. The mixture was stirred at reflux under a N_2 atmosphere for 2 h and was then evaporated in vacuo to obtain the tannic white crystalline acid chloride. The acid chloride was dissolved in chlorobenzene was treated with **4a** (653 mg, 3.16 mmol) and warmed to 100–105 °C for 9 h. The mixture was then allowed to cool to rt resulting in complete solidification. The solid was broken up and treated with saturated Na_2CO_3 (4 mL), water (2 mL), CH_2Cl_2 (2 mL) and 50% aqueous NaOH (1 mL). After stirring for a short period, the mixture was diluted with CH_2Cl_2 and water. The layers were separated and the organic layer was washed with 50% saturated Na_2CO_3. The organic layer was dried (Na_2SO_4), decanted and concentrated under reduced pressure. Purification via flash chromatography (0–5% MeOH/CH_2Cl_2) provided **6a** (1.33 g, 64%) as a thick dark oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30–1.40 (m, 2H), 1.50–1.60 (m, 4H), 2.50–2.52 (m, 4H), 2.70 (t, J = 5.9 Hz, 2H), 2.76 (s, 6H), 3.70 (s, 3H), 4.07 (t, J = 5.9 Hz, 2H), 6.73 (dd, J = 8.9, 2.4 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 8.9 Hz, 1H), 7.76 (d, J = 8.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.8, 25.5, 44.6, 54.7, 55.2, 57.4, 65.8, 104.9, 111.2, 113.9, 121.8, 131.4, 131.5, 132.0, 133.2, 155.3, 160.8, 162.1, 190.8. The experiment data is in agreement with in the literature.[5a]

3-[4-(2-piperidin-1-yl)ethoxybenzoyl]-6-methoxy-2-tributylstannylbenzo[*b*]thiophene (26a). Lithium metal (7.1 g, 1.02 mol) was suspended in THF (100 mL) and treated with trimethylstannyl chloride (1.0 M in THF, 103 mL, 103 mmol) dropwise at 0 °C. After warming to rt, the mixture was allowed to stir overnight. An aliquot of the resulting Me_3SnLi solution (0.507 M in THF, 19.4 mL, 9.85 mmol) was added dropwise to a solution of **6a** (2.4 g, 5.47 mmol) in THF (48 mL) at −78 °C. The mixture was allowed to slowly warm to rt over 5 h. The reaction quenched rapidly by pouring into a mixture of ice-cold saturated, and the quenched product was extracted with CH_2Cl_2 and water. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to provide compound **26a** (3.2 g, 99%) as a brown oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.34 (s, 9H), 1.40–1.60 (m, 2H), 1.60–1.80 (m, 4H), 2.60–2.80 (m, 4H), 2.83 (t, J = 5.9 Hz, 2H), 3.86 (s, 3H), 4.20 (t, J = 5.9 Hz, 2H), 6.84 (dd, J = 8.9, 2.3 Hz, 1H), 6.92 (d, J = 8.7 Hz, 2H), 7.24–7.28 (m, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.77 (d, J = 8.6 Hz, 2H). The spectroscopic data is in agreement with that in the literature.[5a]

2-(4-Methoxy-2-fluoropropylphenyl)-3-[4-(2-piperidin-1-yl)ethoxybenzoyl]-6-methoxybenzo[*b*]thiophene (27a)

Method A (Stille reaction). A solution of **23** (2.5 g, 5.47 mmol), 4-bromo-2-fluoropropylanisole (3.75 g, 16.41 mmol) and $Pd(PPh_3)_4$ (0.41 g, 0.4 mmol) in anhydrous DMF (20 mL) was heated at 100 °C for 12 h. After cooling to rt, the mixture was concentrated, and the residue was purified via flash chromatography (50% EAOAc/hexane, 0–1% MeOH) to provide the title compound (1.7 g, 57%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42–1.45 (m, 2H), 1.57–1.65 (m, 4H), 1.72–1.92 (m,

2H), 2.46–2.63 (m, 6H), 2.74 (t, $J=6.0$ Hz, 2H), 3.75 (s, 3H), 3.87 (s, 3H), 4.08 (t, $J=5.9$ Hz, 2H), 4.30 (dt, $J=47.4$, 6.1 Hz, 2H), 6.67–6.77 (m, 3H), 6.95 (dd, $J=9.2$, 2.4 Hz, 1H), 7.14 (d, $J=2.4$ Hz, 1H), 7.23–7.31 (m, 2H), 7.56 (d, $J=9.2$ Hz, 1H), 7.75 (d, $J=7.0$ Hz, 2H).

Method B (Grignard reaction). A solution of **6a** (1.5 g, 3.4 mmol) in THF (20 mL) at 0 °C was treated portionwise with a 1 M THF solution of 4-methoxy-2-(3-fluoropropyl)phenylmagnesium bromide (10 mL, 10 mmol), which was prepared from magnesium turnings and 4-bromo-3-(3-fluoropropyl)anisole (Due to the defluorination during the deprotection of methyl group, the preparation of this compound is not described in this report.). After warming to rt, the reaction mixture was stirred for 90 min and then recooled and quenched with ice water. The mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried (Na_2SO_4), concentrated and purified by flash chromatography (0–10% MeOH/CH_2Cl_2) to give the title compound (1.11 g, 60%).

4-(*tert*-Butyldiphenylsilyloxy)benzaldehyde (29). To a stirred solution of the 4-hydroxybenzaldehyde (**28**, 5.0 g, 41 mmol) in DMF were added imidazole (4.2 g, 61.35 mmol) and *tert*-butyldiphenylsilyl chloride (12.8 mL, 49.1 mmol) at rt. The reaction mixture was stirred at the same temperature for 3 h. After dilution with brine, the aqueous layer was extracted with ether. The combined organic extracts were washed water, dried (Na_2SO_4) and concentrated to afforded an oily residue, which was purified by silica gel column chromatography (5% EtOAc/hexane) to give the silyl ether **28** (22.12 g, 99%) as white crystals: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.11 (s, 9H), 6.86 (d, $J=8.8$ Hz, 2H), 7.31–7.47 (m, 6H), 7.60–7.76 (m, 6H), 9.81 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.04, 23.96, 117.86, 125.55, 127.82, 129.26, 129.51, 132.95, 158.76, 188.39; MS (FAB) m/z 361 (MH^+). HRMS calcd for $C_{23}H_{25}O_2Si$ 361.1624, found 361.1611.

2-[4-(*tert*-Butyldiphenylsilyloxy)phenyl]-2-hydroxy-*N*,*N*-dimethylthioacetamide (30). To a stirred solution of LDA (2 M solution in THF, 10 mL) in THF/hexane was added a solution of *N*,*N*-dimethylthioformamide (1.65 mL, 20 mmol) over a 1-min period at −100 °C. After 3 min, the yellow reaction solution is treated with a solution of **29** (1.65 mL, 20 mmol), and the bath temperature is allowed to rise to −78 °C over a period of 1 h. The reaction mixture was then neutralized with glacial acetic acid (3 mL) and then extracted with CH_2Cl_2, and the combined extracts were dried over sodium sulfate, and evaporated under reduced pressure. The desired product **30** was purified flash chromatography (15% EtOAc/hexane) to produce pale yellow crystals (5.13 g, 57%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10 (s, 9H), 3.01 (s, 3H), 3.46 (s, 3H), 5.24 (q, 2H), 6.74 (d, $J=8.8$ Hz, 2H), 7.11 (d, $J=8.8$ Hz, 2H), 7.31–7.52 (m, 6H), 7.58–7.74 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.30, 26.38, 40.90, 45.38, 73.22, 119.50, 127.65, 128.34, 129.83, 132.28, 132.52, 135.34, 155.56, 203.65; MS (FAB) m/z 450 (MH^+). HRMS calcd for $C_{26}H_{32}NO_2SSi$ 450.1923, found 450.1919.

6-(*tert*-Butyldiphenylsilyloxy)-2-dimethylaminobenzo[*b*]-thiophene (4b). α-Hydroxythioacetamide **30** (3.0 g, 6.65 mmol) was dissolved in dichloromethane and cooled to −10 °C. Methansulfonic acid (2.15 mL, 33.25 mmol) was added. After warming to rt, the reaction mixture was stirred for 4 h and then recooled, and the reaction quenched with saturated $NaHCO_3$. The solution was washed with saturated sodium bicabonate solution, water, dried (Na_2SO_4), filtered, and solvent removed to give the title compound. The desired product **4b** was purified flash chromatography (1–5% EtOAc/hexane) producing a yellow oil (1.41 g, 49%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10 (s, 9H), 2.86 (s, 6H), 5.83 (s, 1H), 6.70 (dd, $J=8.8$, 2.0 Hz, 1H), 7.02 (d, $J=8.8$ Hz, 1H), 7.12 (d, $J=8.8$ Hz, 1H), 7.28–7.49 (m, 6H), 7.62–7.74 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.46, 26.55, 42.63, 96.67, 111.92, 117.58, 120.41, 127.68, 129.75, 133.16, 133.32, 135.22, 135.50, 150.18, 156.08; MS (FAB) m/z 431 (MH^+). HRMS calcd for $C_{26}H_{29}NOSSi$ 431.1739, found 431.1738.

6-(*tert*-Butyldiphenylsilyloxy)-2-dimethylamino-3-[4-(2-piperidin-1-yl)ethoxybenzoyl]benzo[*b*]thiophene (6b). A portion of 4-(2-piperidin-1-yl-ethoxy)benzoic acid monohydrochloride (2.0 g, 7.0 mmol) was converted to its acid chloride by dissolving it in 1,2-dichloroethane and adding one drop of DMF and $SOCl_2$. The mixture was stirred at reflux under a N_2 atmosphere for 2 h and was then evaporated in vacuo to obtain the off-white crystalline acid chloride **5**. The acid chloride was dissolved in chlorobenzene, treated with **4b** (1.6 g, 3.5 mmol), and then warmed to 100–105 °C for 9 h. The mixture was then allowed to cool to rt, resulting in complete solidification. The solid was broken up and treated with saturated Na_2CO_3, water, CH_2Cl_2 and 50% aqueous NaOH. After stirring for a short period, the mixture was diluted with CH_2Cl_2 and water. The layers were separated and the organic layer was washed with 50% saturated Na_2CO_3. The organic layer was dried over Na_2SO_4, decanted and concentrated under reduced pressure to thick dark oil. Purification via flash chromatography (2% MeOH/CH_2Cl_2) provided **6b** (1.58 g, 68%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.41–1.54 (m, 2H), 1.51–1.66 (m, 4H), 2.41–2.54 (m, 4H), 2.58–2.92 (m, 8H), 4.15 (t, $J=6.0$ Hz, 2H), 6.67 (dd, $J=8.8$, 2.0 Hz, 1H), 6.89 (dd, $J=7.0$, 1.8 Hz, 2H), 6.98 (d, $J=2.2$ Hz, 1H), 7.16 (d, $J=8.8$ Hz, 1H), 7.31–7.47 (m, 6H), 7.68–7.86 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.42, 24.03, 25.78, 26.52, 44.85, 55.01, 57.69, 66.09, 111.51, 114.13, 118.01, 121.76, 127.69, 129.79, 131.38, 131.73, 132.26, 132.95, 133.71, 135.46, 151.15, 161.21, 162.34, 191.25; MS (FAB) m/z 662 (MH^+). HRMS calcd for $C_{40}H_{46}N_2O_3SSi$ 662.2999, found 662.2993.

6-(*tert*-Butyldiphenylsilyloxy)-3-[4-(2-piperidin-1-yl)ethoxybenzoyl]-2-tributylstannylbenzo[*b*]thiophene (26b). Lithium metal (710 mg, 0.10 mol) was suspended in THF (10 mL) and treated with trimethylstannyl chloride (1.0 M in THF, 10 mL, 10 mmol) dropwise at 0 °C.

After warming to rt, the mixture was allowed to stir overnight. An aliquot of the Me_3SnLi solution prepared above (0.507 M in THF, 2.0 mL, 1.04 mmol) was added dropwise to a solution of **6b** (360 mg, 0.52 mmol) in THF (15 mL) at −78 °C. The mixture was allowed to slowly warm to rt over 5 h. The reaction quenched rapidly by pouring into a mixture of ice-cold saturated $NaHCO_3$ (100 mL), dried (Na_2SO_4). Purification by flash chromatography (100% EtOAc) provided **26b** (290 mg, 71%) as a brown oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.30 (s, 9H), 1.11 (s, 9H), 1.45–1.47 (m, 2H), 1.56–1.69 (m, 4H), 2.60–2.80 (m, 4H), 2.52 (t, J = 5.2 Hz, 4H), 2.79 (t, J = 6.1 Hz, 2H), 4.16 (t, J = 6.1 Hz, 2H), 6.73 (dd, J = 8.8, 2.2 Hz, 1H), 6.90 (d, J = 9.0 Hz, 2H), 7.12 (d, t, J = 8.8 Hz, 1H), 7.20 (d, J = 2.2 Hz, 1H), 7.31–7.43 (m, 6H), 7.69–7.76 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 7.36, 14.09, 19.35, 24.07, 25.86, 26.45, 54.96, 57.64, 66.26, 111.40, 114.08, 118.09, 123.64, 127.69, 129.85, 131.59, 132.01, 132.58, 133.55, 135.36, 143.04, 145.91, 152.56, 162.62, 192.24; MS (FAB) m/z 784 (MH^+). HRMS calcd for $C_{41}H_{50}NO_3S$ SiSn 784.2302, found 784.2322.

4-Allyloxyphenol (8). A mixture of hydroquinone (**7**, 10.0 g, 90.82 mmol) of allyl bromide (5.50 mL, 22.70 mmol), anhydrous potassium carbonate (3.13 g, 22.70 mmol), and dried acetonitrile (20 mL) was refluxed for 12 h and cooled. Flash column chromatography (20% EtOAc/hexane) provided allyl substituted **8** (3.14 g, 92%) as a brown oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.48 (d, 2H, J = 6.6 Hz), 4.56 (bs, 1H), 5.34 (dd, 2H, J = 28.2, 21.2 Hz), 5.95–6.11 (m, 1H), 6.72–6.84 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 67.30, 113.64, 115.00, 131.17, 134.11, 147.31, 150.35; MS (EI) m/z 150 (M^+). HRMS calcd for $C_9H_{10}O_2$ 150.0681, found 150.0687.

1-Allyloxy-4-(methoxymethoxy)benzene (9). A solution of 4-allyloxyphenol (**8**, 3.34 g, 22.24 mmol) in 10 mL of dried THF at 0 °C was treated with NaH (1.43 g, 37.14 mmol) in several portions over 5 min. After 10 min, chloromethylmethyl ether (2.53 mL, 33.36 mmol) was added. The reaction mixture was refluxed for 1 h and cooled. The reaction mixture was quenched by the slow addition of 10 mL of H_2O. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with 10% aqueous $NaHCO_3$ and H_2O, dried over Na_2SO_4, and evaporated. Flash column chromatography (5% EtOAc/hexane) provided MOM protected **9** (3.98 g, 92%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.47 (s, 3H), 4.49 (d, 2H, J = 3.6 Hz), 5.10 (s, 2H), 5.34 (dd, 2H, J = 29.0, 19.2 Hz), 5.95–6.14 (m, 1H), 6.82–6.99 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.82, 69.36, 95.24, 115.59, 117.50, 133.50, 151.41, 153.71; MS (EI) m/z 194 (M^+). HRMS calcd for $C_{11}H_{14}O_3$ 194.0942, found 194.0948.

2-Allyl-4-(methoxymethoxy)phenol (10). A mixture of allyl ether (3.10 g, 15.98 mmol) and *N*,*N*-dimethylaniline (5 mL) was cautiously brought to boiling in a round-bottom flask, refluxed for 2 h, and cooled. Flash column chromatography (20% EtOAc/hexane) provided 2-allylphenol **10** (2.47 g, 80%) as a dark yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.36 (d, 2H, J = 6.2 Hz), 3.48 (s, 3H), 5.10 (s, 2H), 5.16–5.18 (m, 2H), 5.27 (bs, 1H), 5.89–6.10 (m, 1H), 6.71–6.83 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 35.02, 55.80, 95.43, 115.72, 116.36, 118.76, 126.71, 136.16, 149.11, 151.27; MS (EI) m/z 194 (M^+). HRMS calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0942.

2-(3-Hydroxypropyl)-4-(methoxymethoxy)phenol (11). To 2-allylphenol **10** (545 mg, 2.81 mmol) was added borane–THF complex (3.37 mL, 3.37 mmol) in dried THF at 0 °C over 5 min. After 1 h, water was added cautiously to decompose excess hydride. Oxidation was carried out by adding 3.37 mL of 4 N NaOH, followed by dropwise addition of 3.37 mL of 30% hydrogen peroxide. Flash column chromatography (40% EtOAc/hexane) provided alcohol **11** (341 mg, 57%) as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.85 (q, 2H, J = 6.3 Hz), 2.73 (t, 2H, J = 7.0 Hz), 3.48 (s, 3H), 3.62 (t, 2H, J = 5.9 Hz), 5.09 (s, 2H), 6.78–6.84 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.50, 32.20, 55.83, 60.85, 95.44, 115.60, 116.71, 118.69, 128.41, 149.58, 151.26; MS (EI) m/z 212 (M^+). HRMS calcd for $C_{11}H_{16}O_4$ 212.1049, Found 212.1043.

2-(3-Fluoropropyl)-1-hydroxy-4-(methoxymethoxy)benzene (12). A solution of DAST (226 μL, 1.71 mmol) in dichloromethane (2 mL) was added dropwise to a solution of **11** (362 mg, 1.71 mmol) in dichloromethane (3 mL) and stirred at −78 °C for several minutes. The reaction mixture was stirred at rt for 30 min. and 10 mL of water added. The organic layer was separated and the organic layer was dried (Na_2SO_4) and evaporated; flash column chromatography (10% EtOAc/hexane) provided fluoride **12** (55 mg, 15%) as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.00 (dq, 2H, J = 25.6, 5.9 Hz), 2.71 (t, 2H, J = 7.5 Hz), 3.48 (s, 3H), 4.48 (dt, 2H, J = 47.2, 5.9 Hz), 4.80 (bs, 1H), 5.10 (s, 2H), 6.67 (d, 1H, J = 8.4 Hz), 6.76–6.84 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.78 (J = 5.7 Hz), 30.37 (J = 19.8 Hz), 55.85, 83.39 (J = 163.1 Hz), 95.43, 97.93, 115.41, 116.05, 118.85, 128.24, 148.71, 151.34; MS (CI) m/z 214 (MH^+). HRMS calcd for $C_{11}H_{15}FO_3$ 214.1005, found 215.1083.

2-(3-Fluoropropyl)-4-(methoxymethoxy)-1-(trifluoromethanesulfonyloxy)benzene (13). Trifluoromethanesulfonic anhydride (48 μL, 0.28 mmol) was added dropwise to a solution of **12** (55 mg, 0.26 mmol) in dichloromethane (3 mL) and 2,6-lutidine (75 μL, 0.64 mmol) and stirred at 0°C to rt for 30 min. The reaction mixture quenched with a small amount of water. The organic layer was separated and the organic layer was dried (Na_2SO_4) and evaporated. Flash column chromatography (5% EtOAc/hexane) provided triflate **13** (84 mg, 92%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.02 (dq, 2H, J = 25.8, 5.7 Hz), 2.81 (t, 2H, J = 7.9 Hz), 3.48 (s, 3H), 4.48 (dt, 2H, J = 46.8, 5.7 Hz), 5.16 (s, 2H), 6.91–6.99 (m, 2H), 7.17 (d, 1H, J = 8.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.12 (J = 5.7 Hz), 30.46 (J = 19.8 Hz), 56.12, 82.78 (J = 165.0 Hz), 94.64, 115.31, 118.50, 121.78, 122.42, 135.28, 142.23, 156.76; MS (CI) m/z 346 (MH^+). HRMS calcd for $C_{12}H_{14}F_4O_5S$ 346.0498, found 346.0498.

1-Allyl-2-[(2-methoxyethoxy)methoxy]benzene (15). A solution of 2-allylphenol (**14**, 1.00 g, 7.45 mmol) in 5 mL of dried THF at 0 °C was treated with NaH (418 mg, 12.45 mmol) in several potions over 5 min. After 10 min, 2-methoxyethoxymethyl chloride (1276 μL, 11.18 mmol) was added. The reaction mixture was refluxed for 1 h and cooled. Flash column chromatography (10% EtOAc/hexane) provided MEM protected **15** (1.35 g, 82%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.38 (s, 3H), 3.41 (s, 2H), 3.56 (t, 2H, J = 4.8 Hz), 3.83 (t, 2H, J = 4.7 Hz), 5.00–5.08 (m, 2H), 5.29 (s, 2H), 5.89–6.09 (m, 1H), 6.88–6.99 (m, 1H), 7.10–7.18 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.34, 58.93, 67.70, 71.67, 93.61, 114.23, 115.28, 121.77, 127.34, 129.25, 129.95, 136.98, 155.02; MS (EI) m/z 222 (M^+). HRMS calcd for $C_{13}H_{18}O_3$ 222.1250, found 222.1253.

2-(3-Hydroxypropyl)-1-[(2-methoxyethoxy)methoxy]benzene (16). According to the procedure for the preparation of compound **11** described above, to 8.83 g (39.79 mmol) of olefin **15** was added to 47.75 mL (47.75 mmol) of borane–THF complex in dried THF at 0 °C over 5 min. After 1 h, water was added cautiously to decompose excess hydride. Oxidation was carried out by adding 47.75 mL of 4N NaOH, followed by dropwise addition of 47.75 mL of 30% hydrogen peroxide. Flash column chromatography (30% EtOAc/hexane) provided alcohol **16** (4.59 g, 48%) as a white oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.84 (q, 2H, J = 7.0 Hz), 2.28 (bs, 1H), 2.72 (t, 2H, J = 7.5 Hz), 3.37 (s, 3H), 3.55–3.64 (m, 4H), 3.83 (t, 2H, J = 4.7 Hz), 5.29 (s, 2H), 6.89–6.97 (m, 1H), 7.11–7.16 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.17, 32.93, 58.79, 61.90, 67.68, 71.54, 93.62, 114.07, 121.73, 127.73, 129.97, 130.70, 155.12; MS (EI) m/z 240 (M^+). HRMS calcd for $C_{13}H_{20}O_4$ 240.1361, found 240.1353.

1-(3-Methanesulfonyloxypropyl)-2-[(2-methoxyethoxy)-methoxy]benzene (17). To alcohol **16** (1.21 g, 5.05 mmol) in dichloromethane (10 mL) was added triethylamine (1056 μL, 7.58 mmol) and methanesulfonyl chloride (430 μL, 5.56 mmol) at 0 °C for 20 min. Flash column chromatography (30% EtOAc/hexane) provided mesylate **17** (906 mg, 56%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.06 (q, 2H, J = 7.0 Hz), 2.76 (t, 2H, J = 7.4 Hz), 2.99 (s, 3H), 3.38 (s, 3H), 3.56 (t, 2H, J = 4.6 Hz), 3.83 (t, 2H, J = 4.6 Hz), 4.24 (t, 2H, J = 6.4 Hz), 5.30 (s, 2H), 6.90-6.98 (m, 1H), 7.10–7.18 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.46, 29.34, 37.36, 58.92, 67.80, 69.62, 71.62, 93.53, 114.10, 121.68, 127.57, 129.26, 130.05, 155.16; MS (CI) m/z 318 (MH^+). HRMS calcd for $C_{14}H_{22}O_6S$ 318.1137, found 318.1140.

1-(3-Fluoropropyl)-2-[(2-methoxyethoxy)methoxy]benzene (18). To mesylate **17** (906 mg, 2.85 mmol) in acetonitrile (3 mL) was added tetra-*n*-butylammonium fluoride hydrate (897 mg, 2.85 mmol) and heated at 110 °C for 30 min in a pressure bottle. Flash column chromatography (10% EtOAc/hexane) provided fluoride **18** (512 mg, 74%) as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.98 (dq, 2H, J = 25.6, 6.2 Hz), 2.75 (t, 2H, J = 7.5 Hz), 3.38 (s, 3H), 3.56 (t, 2H, J = 4.7 Hz), 3.83 (t, 2H, J = 4.7 Hz), 4.46 (dt, 2H, J = 47.2, 6.0 Hz), 5.30 (s, 2H), 6.90–6.98 (m, 1H), 7.10–7.17 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.07 (J = 6.1 Hz), 30.68 (J = 19.4 Hz), 58.95, 67.76, 71.68, 83.49 (J = 163.9 Hz), 93.61, 114.15, 121.71, 127.38, 130.12, 155.32; MS (CI) m/z 242 (MH^+). HRMS calcd for $C_{13}H_{19}FO_3$ 242.1318, found 242.1320.

2-(3-Fluoropropyl)phenol (19). To MEM protected **18** (534 mg, 2.21 mmol) in methanol (5 mL) was added 6N HCl (3 mL) and heated at 60 °C for 1 h. Methanol was removed under vacuum, and and the reaction mixture was extracted with ethyl acetate and washed (H_2O, brine) and the organic layer was dried (Na_2SO_4) and evaporated. Flash column chromatography (10% EtOAc/hexane) provided the deprotected phenol **19** (512 mg, 74%) as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.01 (dq, 2H, J = 26.0, 6.5 Hz), 2.74 (t, 2H, J = 7.4 Hz), 4.47 (dt, 2H, J = 47.2, 5.7 Hz), 5.35 (bs, 1H), 6.76–6.90 (m, 2H), 7.10 (t, 2H, J = 8.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.15 (J = 5.7 Hz), 27.98 (J = 19.4 Hz), 81.16 (J = 162.7 Hz), 113.00, 118.40, 124.68, 125.05, 128.05, 151.28; MS (EI) m/z 154 (M^+). HRMS calcd for $C_9H_{11}FO$ 154.0794, found 154.0797.

1-(3-Fluoropropyl)-2-(trifluoromethanesulfonyloxy)benzene (20). Trifluoromethanesulfonic anhydride (367 μL, 2.18 mmol) was added dropwise to a solution of **49** (305 mg, 1.98 mmol) in dichloromethane (3 mL) and 2,6-lutidine (277 μL, 2.38 mmol) stirred at 0 °C to rt for 30 min. Flash column chromatography (5% EtOAc/hexane) provided triflate **20** (462 mg, 82%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.03 (dq, 2H, J = 28.2, 5.7 Hz), 2.87 (t, 2H, J = 7.7 Hz), 4.50 (dt, 2H, J = 47.2, 5.7 Hz), 7.29–7.34 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.90 (J = 5.7 Hz), 30.53 (J = 20.1 Hz), 82.77 (J = 165.4 Hz), 115.45, 121.49, 121.81, 128.17, 128.46, 131.40, 133.90, 148.07; MS (CI) m/z 286 (MH^+). HRMS calcd for $C_{10}H_{10}F_4O_3S$ 286.2442, found 287.0358.

1-(2-Hydroxyethyl)-2-[(2-methoxyethoxy)methoxy]benzene (22). A solution of 2-(2-hydroxyethyl)phenol (**21**, 3.93 g, 28.46 mmol) in 15 mL of dried THF at 0 °C was treated with NaH (1.15 g, 34.16 mmol) in several potions over 5 min. After 10 min, 2-methoxyethoxymethyl chloride (3.25 mL, 28.46 mmol) was added. The reaction mixture was refluxed for 1 h and cooled. Flash column chromatography (40% EtOAc/hexane) provided MEM protected **22** (4.51 g, 70%) as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.05 (bs, 1H), 2.91 (t, 2H, J = 6.6 Hz), 3.36 (s, 3H), 3.55 (t, 2H, J = 4.2 Hz), 3.80–3.84 (m, 4H), 5.29 (s, 2H), 6.95 (t, 1H, J = 7.1 Hz), 7.10–7.19 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.03, 58.89, 62.72, 67.81, 71.61, 93.63, 114.26, 121.81, 127.72, 130.82; MS (EI) m/z 226 (M^+). HRMS calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1202.

1-(2-Methanesulfonyloxyethyl)-2-[(2-methoxyethoxy)methoxy]benzene (23). According to the procedure of **17** described above, to alcohol **21** (2.76 g, 12.22 mmol) in dichloromethane (10 mL) was added triethylamine (2.56

mL, 18.33 mmol) and methanesulfonyl chloride (1.04 mL, 13.44 mmol) at 0 °C for 20 min. Flash column chromatography (50% EtOAc/hexane) provided mesylate **23** (3.05 g, 82%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.83 (s, 3H), 3.09 (t, 2H, J = 6.9 Hz), 3.38 (s, 3H), 3.56 (t, 2H, J = 4.5 Hz), 3.84 (t, 2H, J = 4.6 Hz), 4.43 (t, 2H, J = 7.0 Hz), 5.32 (s, 2H), 6.91–6.99 (m, 1H), 7.12–7.27 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.80, 37.24, 58.93, 67.93, 69.26, 71.61, 93.52, 114.08, 121.79, 128.52, 131.03, 155.40; MS (CI) m/z 304 (MH^+). HRMS calcd for $C_{13}H_{20}O_6S$ 304.0980, found 304.0986.

1-(2-Fluoroethyl)-2-(trifluoromethanesulfonyloxy)benzene (25). A solution of DAST (963 μL, 7.29 mmol) in dichloromethane (5 mL) was added dropwise to a solution of **21** (1.0 g, 7.29 mmol) in dichloromethane (10 mL) and stirred at −78 °C for several minutes. The reaction mixture was stirred at rt for 30 min and 10 mL of water added. The organic layer was separated and the organic layer was dried (Na_2SO_4) and evaporated. Trifluoromethanesulfonic anhydride (500 μL, 2.97 mmol) was added dropwise to a solution of crude fluoride in dichloromethane (10 mL) and 2,6-lutidine (472 μL, 4.05 mmol) and stirred at 0 °C to rt for 30 min. Flash column chromatography (5% EtOAc/hexane) provided triflate **25** (516 mg, 26%) as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.12 (dt, 2H, J = 24.6, 6.0 Hz), 4.67 (dt, 2H, J = 46.8, 6.2 Hz), 7.27–7.45 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.98 (J = 21.2 Hz), 82.22 (J = 168.8 Hz), 109.32, 115.42, 120.29, 121.49, 121.77, 124.89, 127.89, 128.49, 128.77, 130.22 (J = 4.6 Hz), 131.92, 148.04; MS (CI) m/z 273 (MH^+). HRMS calcd for $C_9H_8F_4O_3S$ 272.0130, found 272.0130.

2-[2-(3-Fluoroethyl)-4-hydroxyphenyl]-3-[4-(2-piperidin-1-yl)ethoxybenzoyl]-6-hydroxybenzo[*b*]thiophene (1). A solution of **13** (94 mg, 0.27 mmol), **26b** (75 mg, 0.096 mmol), and $Pd(PPh_3)_4$ (2 mg, 0.002 mmol) in anhydrous DMF (10 mL) was heated at 100 °C for 12 h. The protected crude coupled product, separated by silica gel column chromatography (5% MeOH/CH_2Cl_2), was treated tetra-*n*-butylammonium fluoride hydrate (2 equiv) in THF at rt for 1 min. The crude mixture isolated by silica gel flash column chromatography (10% MeOH/CH_2Cl_2) was treated with three drops of concd HCl in isopropanol (10 mL) at 60 °C for 30 min. The reaction mixture was extracted with EtOAc (10 mL) and water (20 mL) and dried over Na_2SO_4. Flash column chromatography (12% MeOH/CH_2Cl_2) gave **1** (24 mg, 47%) as a pale yellow oil: ^{1}H NMR (200 MHz, CD_3OD) δ 7.62 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.8 Hz, 1H), 7.25 (d, J = 2.2 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 2.2 Hz, 1H), 6.82 (d, J = 8.6 Hz, 2H), 6.54–6.46 (m, 2H), 4.42 (t, J = 6.1 Hz, 1H), 4.21–4.12 (m, 3H), 2.83 (t, J = 5.3 Hz, 2H), 2.65–2.57 (m, 6H), 1.89–1.48 (m, 7H); ^{13}C NMR (50 MHz, CD_3OD) δ 194.6, 164.0, 159.1, 156.7, 143.9, 143.1, 142.0, 134.2, 133.9, 133.2, 132.2, 125.1, 124.6, 116.7, 116.0, 115.1, 113.9, 107.6, 84.1 (d, J = 163 Hz, 1C), 66.2, 58.4, 55.7, 32.7 (d, J = 20. Hz, 1C), 30.7, 30.1 (d, J = 6 Hz), 26.1, 24.7; MS (FAB) m/z 534 (M^+ + H), 386, 371, 231, 154, 117 (100), 91. HRMS (FAB) calcd for $C_{31}H_{32}FNO_4S$ 534.2036, found 534.2065.

2-[2-(3-Fluoropropyl)phenyl]-3-[4-(2-piperidin-1-yl)ethoxybenzoyl]-6-hydroxybenzo[*b*]thiohene (2). According to the procedure of **24** described above, a solution of **32** (200 mg, 0.26 mmol), **50** (206 mg, 0.77 mmol) and $Pd(PPh_3)_4$ (6 mg, 0.005 mmol) in anhydrous DMF (10 mL) was heated at 100 °C for 12 h. Protected crude fluoropropyl compounds, separated by silica gel column chromatography (5% MeOH/CH_2Cl_2), was treated tetra-*n*-butylammonium fluoride hydrate (2 equiv) in THF at rt for 1 min. The reaction mixture was quenched by water, and extacted with EtOAc. The organic layer was dried with sodium sulfate, and evaporated. Flash column chromatography (10% MeOH/CH_2Cl_2) provided **3** (88 mg, 68%) as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47–1.49 (m, 2H), 1.67 (bs, 4H), 1.93 (dq, 2H, J = 24.8, 6.0 Hz), 2.61 (bs, 4H), 2.74 (t, 2H, J = 7.9 Hz), 2.84 (t, 2H, J = 5.3 Hz), 4.13 (t, 2H, J = 5.5 Hz), 4.32 (dt, 2H, J = 47.2, 6.0 Hz), 6.37 (bs, 1H), 6.64 (d, 2H, J = 8.8 Hz), 6.83 (dd, 1H, J = 8.8, 2.2 Hz), 7.06–7.26 (m, 5H), 7.39 (d, 1H, J = 8.8 Hz), 7.64 (d, 2H, J = 8.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.85, 25.26, 28.85, 31.43 (J = 19.8 Hz), 54.96, 57.62, 65.36, 83.31 (J = 163.9 Hz), 107.27, 113.97, 115.33, 124.57, 125.75, 128.96, 129.12, 130.92, 131.57, 132.11, 132.44, 133.58, 140.39, 140.82, 142.10, 154.68, 162.60, 192.18; MS (FAB) m/z 518 (MH^+). HRMS calcd for $C_{31}H_{32}FNO_3S$ 517.2087, found 518.2161.

2-[2-(3-Fluoroethyl)phenyl]-3-[4-(2-piperidin-1-yl)ethoxybenzoyl]-6-hydroxybenzo[*b*]thiephene (3). According to the procedure of **24** described above, a solution of **32** (120 mg, 0.15 mmol), **55** (117 mg, 0.46 mmol) and $Pd(PPh_3)_4$ (4 mg, 0.003 mmol) in anhydrous DMF (8 mL) was heated at 100 °C for 12 h. Flash chromatography (10% MeOH/CH_2Cl_2) provided **4** (62 mg, 80%) as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47–1.49 (m, 2H), 1.67 (bs, 4H), 2.60 (bs, 4H), 2.74 (t, 2H, J = 7.9 Hz), 2.83 (t, 2H, J = 5.4 Hz), 3.07 (dt, 2H, J = 22.8, 6.6 Hz), 4.12 (t, 2H, J = 5.5 Hz), 4.56 (dt, 2H, J = 47.2, 6.6 Hz), 6.64 (d, 2H, J = 8.8 Hz), 6.82 (dd, 1H, J = 8.8, 1.8 Hz), 7.07–7.27 (m, 5H), 7.37 (d, 1H, J = 8.8 Hz), 7.63 (d, 2H, J = 8.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.85, 25.21, 34.17 (J = 20.5 Hz), 54.93, 57.60, 65.26, 83.51 (J = 168.0 Hz), 107.28, 114.01, 115.45, 124.56, 126.30, 128.99, 129.69, 130.80, 131.51, 132.09, 132.83, 133.79, 136.55 (J = 6.1 Hz), 140.87, 141.44, 154.85, 162.65, 192.16; MS (FAB) m/z 504 (MH^+). HRMS calcd for $C_{30}H_{30}FNO_3S$ 503.1930, found 504.1988.

Estrogen receptor binding affinity assays

Relative binding affinities were determined by a competitive radiometric binding assay as previously described,[13] using 10 nM [^{3}H]estradiol as tracer ([6,7-^{3}H]estra-1,3,5,(10)-triene-3,17-β-diol, 51-53 Ci/mmol, Amersham BioSciences, Piscataway, NJ, USA) and either lamb uterine cytosol (containing mostly ERα) or purified full length human ERα and ERβ receptor purchased from Pan Vera (Madison, WI, USA). Incubations were for 18–24 h at 0 °C. With the uterine cytosol, charcoal–dextran was used to adsorb free ligand and was pelleted by centrifugation,[13a] and with the purified ER hydroxyapatite

(BioRad, Hercules, CA, USA) was used to absorb the receptor–ligand complexes, and free ligand was washed away.[13b] The binding affinities are expressed as relative binding affinity (RBA) values with the RBA of estradiol set to 100%. The values given for raloxifene are the average ± range or SD of 2–3 independent determinations. The other values are for single determinations. It should be noted that in this series of compounds, binding affinity determinations are highly reproducible, with coefficient of variations being typically 0.15. This is exemplified by the small SD values for the multiple determinations for raloxifene on all three receptor systems. Estradiol binds to ERα with a K_d of 0.2 nM and to ERβ with a K_d of 0.5 nM, and to the estrogen receptor in lamb uterine cytosol with a K_d of 0.17 nM.

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