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Parallel Synthesis of a Desketoraloxifene Analogue Library via Iodocyclization/Palladium-Catalyzed Coupling

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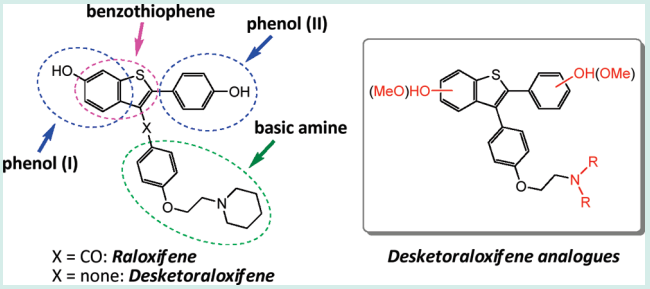
Supporting Information

ABSTRACT: For a future structure−activity relationship (SAR) study, a library of desketoraloxifene analogues has been prepared by parallel synthesis using iodocyclization and subsequent palladium-catalyzed coupling reactions. Points of desketoraloxifene diversification involve the two phenolic hydroxyl groups and the aliphatic amine side chain. This approach affords oxygen-bearing 3-iodobenzo[*b*]thiophenes **4** in excellent yields, which are easily further elaborated using a two-step approach involving Suzuki−Miyaura and Mitsunobu coupling reactions to give multimethoxy-substituted desketoraloxifene analogues **6**. Various hydroxyl-substituted desketoraloxifene analogues **7** were subsequently generated by demethylation with BBr_3.



KEYWORDS: parallel synthesis, desketoraloxifene, iodocyclization, benzo[*b*]thiophene, selective estrogen receptor modulator (SERM), palladium coupling

INTRODUCTION

Early cancer drug discovery efforts focused on the design of small molecule nonsteroidal estrogen receptor (ER) ligands with antagonist properties against breast and other reproductive tissues.[1] The estrogen receptors alpha and beta (ERα and ERβ) are members of a large family of nuclear receptors that regulate gene transcription in response to small molecule binding.[2] Because of the validated therapeutic importance of these receptors in diseases, such as osteoporosis and breast cancer, a number of drugs have been developed that target these estrogen receptors.[3]

Some of the more important estrogen antagonist structures cited in the literature are summarized in Figure 1. Tamoxifen (**I**)[4] is a well-established estrogen antagonist. Traditionally the design of modulators has involved the preparation of triarylethylene analogues of this parent structure. 4-Hydroxytamoxifen (**II**)[5] is an effective antiestrogen for estrogen receptor positive breast tissue. However, hydroxytamoxifen was subsequently discovered to have undesirable estrogenic properties on the endometrium. Several additional selective estrogen receptor modulators (SERMs), including the benzoxepin scaffold (**III**),[6] the 2-phenylspiroindene scaffold (**IV**),[7] ERA-923 (**V**),[6b,8] nafoxidine (**VI**),[9] and trioxifene (**IV**)[6b,10] are presently in late stages of clinical trials. Most approaches to SERMs have involved modifications of the nonsteroidal antagonists tamoxifen (**I**) and raloxifene (**VIII**). Although the current SERMs have clear advantages over conventional hormone replacement therapy (HRT), they retain some of the disadvantages as well. Clearly, an "ideal SERM" has not yet emerged.

Because more potent and safer chemotherapeutic agents are needed, because of the potential side effects of tamoxifen (**I**), considerable attention has been paid to the development of less toxic SERMs.[11] Benzothiophene derivatives, specifically those with oxygen-bearing substituents at the C-2, C-5, and/or C-6 positions are biologically important compounds. Many of these are known to be medicinally and physiologically active substances. Raloxifene (**VIII**) is a SERM, which is currently under clinical evaluation for the prevention and treatment of postmenopausal osteoporosis.[4b,12] Another benzothiophene SERM, arzoxifene (**IX**), is a highly effective agent for the prevention of mammary cancer induced in the rat by the carcinogen nitrosomethylurea and is significantly more potent than raloxifene in this regard.[11,13] Desmethylarzoxifene (DMA) (**X**), with a 4′-OH group, is an active metabolite of arzoxifene (**IX**), which has been observed in highly variable steady-state plasma concentrations.[11,13,14]

Interestingly, removal of the ketone moiety in raloxifene results in a benzothiophene analogue SERM, desketoraloxifene (Figure 1) (**XI**), which is more planar and conformationally more

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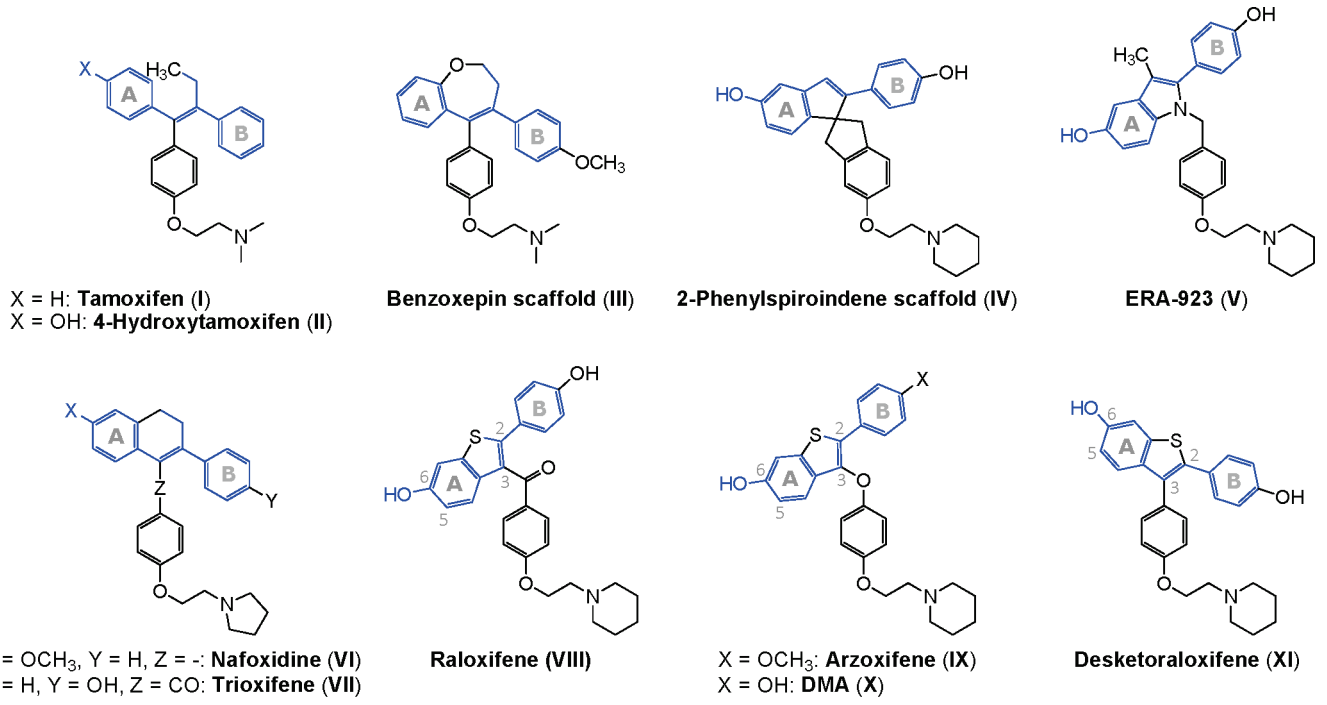


Figure 1. Chemical structures of representative synthetic SERMs with A and B rings corresponding to tamoxifen (**I**) and raloxifene (**VIII**).

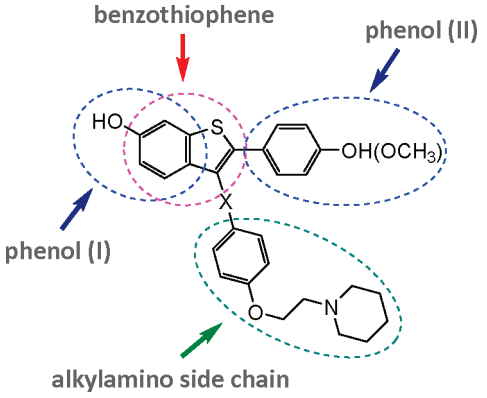


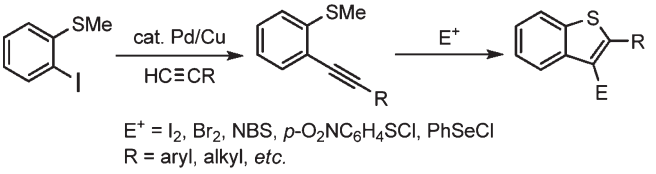
Figure 2. Structure of Benzo[*b*]thiophene SERMs **VIII**−**XI** and the key points of diversification introduced in analogues.

similar to 4-hydroxytamoxifen (**II**). Desketoraloxifene (**XI**) has been found to be a much stronger activator of the Activator Protein-1 (AP-1) site by ERα than ER*β*, and mimics 4-hydroxytamoxifen (**II**) more than raloxifene (**VIII**).[6b,12b,15]

The benzo[*b*]thiophene SERMs **VIII**−**XI** have four important structural features, the benzothiophene aromatic ring, two phenolic hydroxyl groups, and the basic aliphatic amine side chain, which are primarily responsible for their biological activity (Figure 2).[15] Any new methodology suitable for the investigation of structure activity relationships (SAR) of benzothiophene-based SERMs[14,16] must take into account those four key structural features and be aware that many SERMs in clinical use and clinical development are also highly susceptible to oxidative metabolism by electrophilic, redox active quinoids simply because they are based on polyaromatic phenol scaffolds.[17]

In general, benzo[*b*]thiophenes are of interest because of their frequent appearance in nature and wide range of biological and physiological effects.[18] We have recently shown that the electrophilic cyclization of 2-(1-alkynyl)thioanisoles readily prepared by Sonogashira chemistry provides a very mild, high yielding synthesis of benzothiophenes bearing a bromine, iodine, sulfur, or selenium group in the 3 position (Scheme 1).[19]

Scheme 1. Synthesis of 2,3-Disubstituted Benzo[*b*]-thiophenes by Electrophilic Cyclization

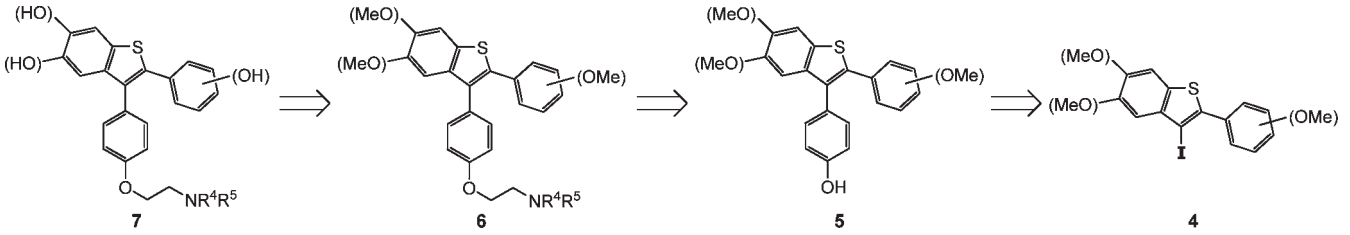


This basic strategy appeared particularly useful for the synthesis of desketoraloxifene analogues **6**. In this series, we proposed to initially change the substituents at the C-2, C-3, C-5, and C-6 positions of the benzothiophene ring system. This decision was based on the structure of desketoraloxifene (**XI**), which has a *para*-substituted phenol at the 2-position, a basic aliphatic amine-containing chain at the 3-position, and an hydroxyl group at the 6-position of the benzothiophene ring system. Herein, we demonstrate the efficient preparation of oxygen-functionalized 3-iodobenzo[*b*]thiophenes **4** by electrophilic cyclization using I_2 and their further elaboration to desketoraloxifene **7** analogues by solution-phase parallel synthesis.

RESULTS AND DISCUSSION

Using our previously developed benzothiophene methodology, we envisioned an efficient strategy that would lead to a library of methoxy- and hydroxy-substituted desketoraloxifene analogues **6**/**7** with multiple points of diversity present in the

Scheme 2. Retrosynthetic Route to Fully Substituted Desketoraloxifene Analogues



benzothiophene SERM desketoraloxifene analogues. Our basic strategy for generating a large number of such analogues is outlined in Scheme 2. Retrosynthetically, we planned to utilize the oxygen-bearing 3-iodobenzo[*b*]thiophene derivatives **4** as key intermediates that can be efficiently prepared using our alkyne iodocyclization chemistry.

The requisite precursors **2**/**3**, bearing appropriate oxygen substituents and an alkyne moiety, can be easily prepared by palladium/copper-catalyzed Sonogashira coupling, according to a reported method (1.0 equiv of **1**, 1.1 equiv of terminal alkyne, 2 mol % of $PdCl_2(PPh_3)_2$, 2 mol % of CuI, and Et_3N as the solvent at 50 °C for 5−8 h).[19b] As can be seen from the results reported in Table 1, using the sequence of reactions shown, involving the Sonogashira coupling of compounds **1**, and subsequent lithiation of compounds **2**{*5*−*15*}, followed by methylthiolation with dimethyl disulfide, afforded the corresponding sulfide products **3**{*1*−*11*} in good to excellent yields.zx

Our first goal was the efficient preparation of a variety of oxygen-bearing 3-iodobenzothiophenes **4**. Those 3-iodobenzo[*b*]thiophenes **4** have been smoothly prepared in excellent yields by electrophilic cyclization of the corresponding methylthio-containing alkynes **2**{*1*−*4*} and **3**{*1*−*11*} using I_2 in CH_2Cl_2 at room temperature for 30 min (Scheme 3 and Figure 3). The chemoselectivity of this reaction is also quite interesting. In examples where MeS and MeO groups are both present *ortho* to the alkyne, only the desired 3-iodobenzo[*b*]thiophenes **4** were produced rapidly in high yields (Scheme 4, Figure 3; **4**{*4,7,10,13,15*}).[20] None of the possible 3-iodobenzofuran products were observed. In fact, most of the crude 3-iodobenzo[*b*]thiophenes **4** were of sufficient purity (>95%) for immediate further use based on their clean ^{1}H NMR spectra. All of the reactions were monitored by thin layer chromatography and the products purified by column chromatography (see the Supporting Information for the experimental details).

The 3-iodobenzo[*b*]thiophenes **4**, having oxygen substituents at the C-5 and/or C-6 benzothiophene positions, are promising desketoraloxifene analogues (**6**/**7**). These 3-iodobenzo[*b*]thiophenes **4** are easily elaborated using a two-step approach involving Suzuki−Miyaura and subsequent Mitsunobu coupling reactions to give desketoraloxifene analogues **6**. Thus, the palladium-catalyzed Suzuki−Miyaura coupling of 3-iodobenzo[*b*]thiophenes **4** with the tetrahydropyranyl (THP) ether-protected boronic acid *p*-$THPOC_6H_4B(OH)_2$, followed by aqueous HCl deprotection, afforded the desired phenolic products **5** in good yields (Scheme 5, see the Supporting Information).[19b] Unfortunately, we could not obtain the desired compound **5** when we used 4-hydroxyphenylboronic acid directly.

For second-generation diversity, various amine-coupled SERM precursors have been produced by reaction of the phenolic benzothiophenes **5** with four different alkylaminoethanol moieties, specifically 1-(2-hydroxyethyl)piperidine, 1-(2-hydroxyethyl)-morpholine, 1-(2-hydroxyethyl)pyrrolidine, and 2-(dimethylamino)-ethanol under Mitsunobu reaction conditions[21] using Ph_3P and diethyl azodicarboxylate (DEAD) for 24−36 h at room temperature to afford multimethoxy-substituted desketoraloxifene analogues **6** in good yields. The desketoraloxifene analogues **6** allow a wide variety of diversity to be incorporated into the final products. The methoxy-substituted desketoraloxifene analogues **6** have been demethylated using BBr_3[16f] to provide the hydroxy-substituted desketoraloxifene analogues **7**. These processes have been performed in parallel on approximately a 40−50 mg scale, starting from the methoxy-substituted desketoraloxifene analogues **6**. Each coupling reaction was worked up by washing with saturated aqueous sodium bicarbonate, water, and brine, and then the crude products were extracted with 5% methanol in chloroform. Concentration of the organic layer delivered each targeted compound in a modest yield and good purity. Overall, only nine compounds (products **7**{*10*}, **7**{*11*}, **7**{*16*}, **7**{*20*}, **7**{*34*}, **7**{*35*}, **7**{*36*}, **7**{*38*} and **7**{*39*}) failed to afford the anticipated desketoraloxifene analogues by preparative HPLC, primarily because of poor solubility. All of the crude products **7** were isolated by either column chromatography or preparative HPLC. The results of the synthesis of the desketoraloxifene analogue library are summarized in Table 2.

Desketoraloxifene (**XI**) itself is an extremely useful compound for biological screening. The dimethoxy-substituted desketoraloxifene analogue **6**{*33*} was readily prepared from phenolic benzothiophene **5**{*9*} using 1-(2-hydroxyethyl)piperidine under Mitsunobu coupling conditions. Compound **6**{*33*} was then readily converted by demethylation using BBr_3 to desketoraloxifene (**XI**) in 78% yield (Scheme 6).

In conclusion, a total synthesis of desketoraloxifene (**XI**) and numerous analogues **6**/**7** has been accomplished from simple alkynes bearing electron-rich aromatic rings by electrophilic cyclization using I_2. An efficient synthesis of the key oxygen-bearing intermediate 3-iodobenzo[*b*]thiophenes **4** has been successfully carried out in good to excellent yields by iodocyclization using I_2. For the synthesis of benzothiophene SERMs, the desketoraloxifene analogues **6**/**7** have been prepared starting from various oxygen-bearing 3-iodobenzo[*b*]thiophenes **4** by a two-step approach involving sequential Suzuki−Miyaura and Mitsunobu couplings. The benzothiophene SERM desketoraloxifene analogue **6**/**7** library is presently being evaluated against various biological screens by the National Institutes of Health Molecular Library Screening Center Network. We believe that this approach to oxygen-bearing 3-iodobenzo[*b*]thiophenes **4** should readily afford many other functionalized desketoraloxifene analogues **6** using known chemistry and parallel synthesis strategies.

Experimental Section. *General Procedure for the Regioselective Sonogashira Reaction to Form Compounds* ***2***. To a solution

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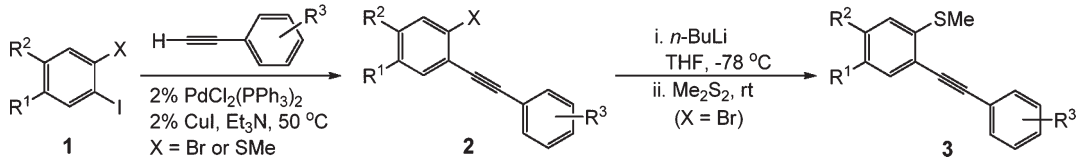
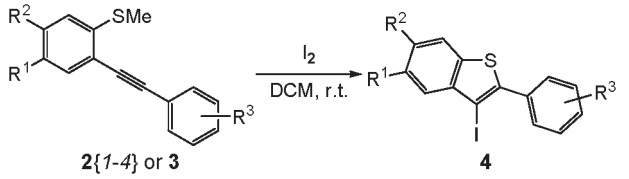
Table 1. Sequential Preparation of Alkynes 2{*1-15*} and 3{*1-11*} from Aryl Halides 1



entry	R^1	R^2	R^3	X	alkyne **2**	yield (%)[a]	alkyne **3**	yield (%)[a]
1	H	H	H	SMe	**2**{*1*}	88		
2	H	H	4-MeO	SMe	**2**{*2*}	88		
3	H	H	3-MeO	SMe	**2**{*3*}	77		
4	H	H	2-MeO	SMe	**2**{*4*}	79		
5	MeO	H	4-MeO	Br	**2**{*5*}	94	**3**{*1*}	86
6	MeO	H	3-MeO	Br	**2**{*6*}	91	**3**{*2*}	93
7	MeO	H	2-MeO	Br	**2**{*7*}	87	**3**{*3*}	89
8	MeO	H	3,5-$(MeO)_2$	Br	**2**{*8*}	83	**3**{*4*}	83
9	H	MeO	4-MeO	Br	**2**{*9*}	73	**3**{*5*}	81
10	H	MeO	2-MeO	Br	**2**{*10*}	77	**3**{*6*}	90
11	MeO	MeO	4-MeO	Br	**2**{*11*}	92	**3**{*7*}	87
12	MeO	MeO	3-MeO	Br	**2**{*12*}	79	**3**{*8*}	63
13	MeO	MeO	2-MeO	Br	**2**{*13*}	71	**3**{*9*}	91
14	OCH_2O		4-MeO	Br	**2**{*14*}	84[b]	**3**{*10*}	73
15	OCH_2O		2-MeO	Br	**2**{*15*}	83[b]	**3**{*11*}	63

[a] Isolated yields after column chromatography.

Scheme 3. Synthesis of Oxygen-Bearing 3-Iodobenzo-[*b*]thiophenes 4 from 2{*1-4*}/3 by Iodocyclization



of dihalobenzene (**1**) (10.0 mmol), 2 mol % $PdCl_2(PPh_3)_2$ and 2 mol % CuI in Et_3N (20 mL), the terminal alkyne (11.0 mmol) was added. The reaction mixture was stirred vigorous at 50 °C for 5−8 h under an Ar atmosphere. The resulting mixture was diluted with EtOAc (2 × 200 mL). The separated organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexanes as the eluent to afford the corresponding products **2**.

*4-Bromo-3-[(4-methoxyphenyl)ethynyl]anisole [**2**{5}].* The product was obtained as a yellow oil (94% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.80 (s, 3H), 6.71 (dd, J = 3.1, 8.9 Hz, 1H), 6.87 (d, J = 8.9 Hz, 2H), 7.05 (d, J = 3.1 Hz, 1H), 7.44 (d, J = 8.9 Hz, 1H), 7.51 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 55.7, 87.1, 94.0, 114.2 (×2), 115.0, 116.2, 116.3, 117.6, 126.3, 133.1, 133.4 (×2), 158.6, 160.1.; HRMS calcd for $C_{16}H_{13}BrO_2$ [M^+], 316.0099, found 316.0094.

*General Procedure for Methylthiolation to Form Compounds **3**.* Bromoalkyne **2** (8.0 mmol) was dissolved in dry tetrahydrofuran (THF, 80 mL) under an Ar atmosphere and cooled to −78 °C for 0.5 h. Then, *n*-BuLi (2.0 M solution in cyclohexane, 12.0 mmol) was added dropwise to the stirred solution. After the addition was complete, the reaction solution was stirred for an additional 1 h at −78 °C. Dimethyl disulfide (9.6 mmol) was then added, and the reaction mixture was stirred further at this temperature before being allowed to warm to room temperature for 2 h under an Ar atmosphere. The resulting mixture was diluted with EtOAc (2 × 160 mL). The separated organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexanes as the eluent to afford the corresponding products **3**.

*4-Methoxy-2-[(4-methoxyphenyl)ethynyl]thioanisole [**3**{1}].* The product was obtained as a colorless oil (86% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 3.76 (s, 3H), 3.76 (s, 3H), 6.83 (dd, J = 2.8, 8.7 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 2.8 Hz, 1H), 7.14 (d, J = 8.7 Hz, 1H), 7.51 (d, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 55.4, 55.5, 86.1, 95.4, 114.1 (×2), 115.2, 115.5, 117.1, 123.9, 127.8, 131.9, 133.2 (×2), 157.3, 159.9; HRMS calcd for $C_{17}H_{16}O_2S$ [M^+], 284.0871, found 284.0873.

*General Procedure for Iodocyclization Using I_2 to Form Compounds **4**.* To a solution of 5.0 mmol of the alkyne **10** and 20 mL of CH_2Cl_2 was added gradually 1.2 equiv of I_2 dissolved in 30 mL of CH_2Cl_2. The reaction mixture was allowed to stir at room temperature for up to 10 min. The reaction was monitored by TLC to establish completion. The remaining I_2 was removed by washing with satd aq $Na_2S_2O_3$. The mixture was then extracted by EtOAc (2 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by flash chromatography using EtOAc/hexanes as the eluent to afford the corresponding products **4**.

*3-Iodo-5-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene [**4**{5}].* The product was obtained as a pale yellow solid (94% yield): mp 114−115 °C (uncorrected); ^{1}H NMR (400 MHz,

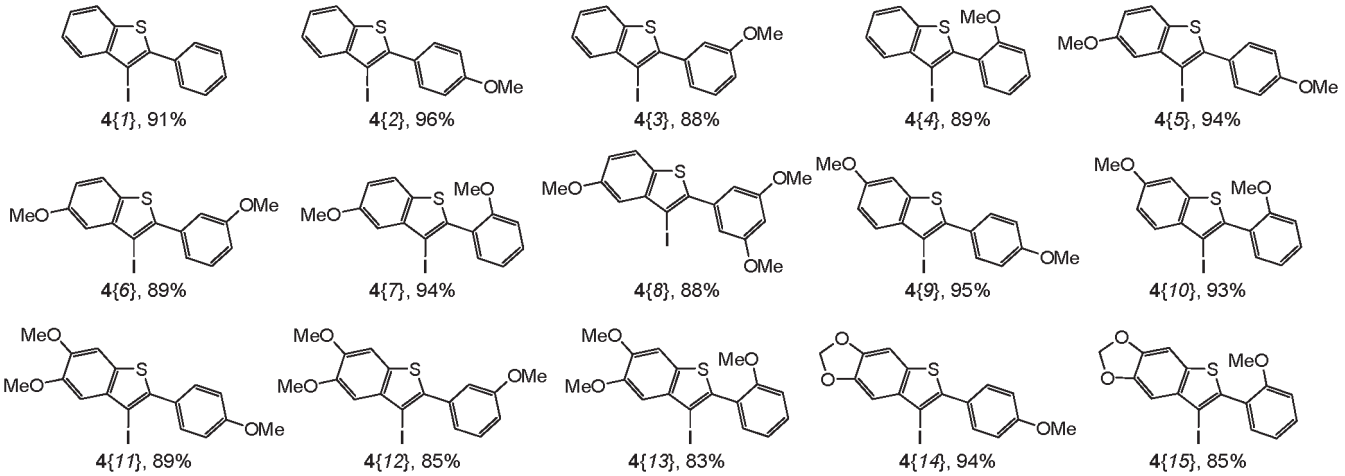
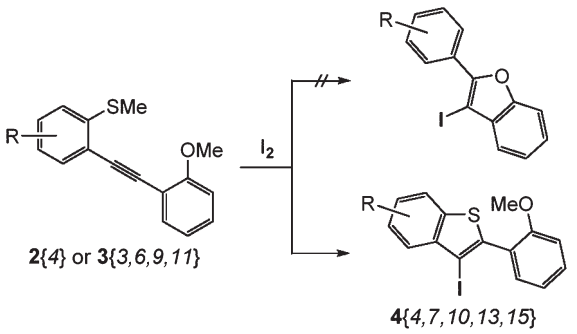
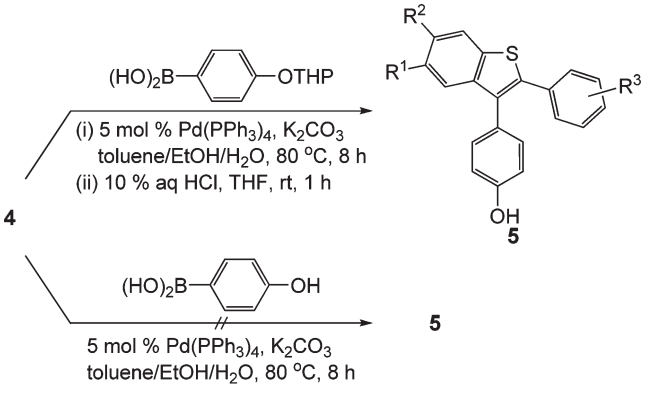


Figure 3. Synthesis of the oxygen-bearing 3-iodobenzo[*b*]thiophenes **4**{*1*−*15*}.

Scheme 4. Competition between MeO- and MeS Group



Scheme 5. Suzuki−Miyaura Coupling to Form Phenolic Benzothiophenes 5



5{*1*}, 88% **5**{*4*}, 89% **5**{*7*}, 91% **5**{*10*}, 83% **5**{*13*}, 84%
5{*2*}, 92% **5**{*5*}, 89% **5**{*8*}, 83% **5**{*11*}, 78% **5**{*14*}, 85%
5{*3*}, 84% **5**{*6*}, 86% **5**{*9*}, 81% **5**{*12*}, 77% **5**{*15*}, 87%

$CDCl_3$) δ 3.83 (s, 3H), 3.90 (s, 3H), 6.95−7.00 (m, 3H), 7.24 (d, J = 2.4 Hz, 1H), 7.58−7.60 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 55.8, 78.8, 108.4, 114.0 (×2), 115.7, 123.0, 127.1, 131.1 (×2), 131.3, 143.2, 143.5, 158.6, 160.2; HRMS calcd for $C_{16}H_{13}IO_2S[M^+]$, 395.9681, found 395.9684.

General Procedure for Suzuki−Miyaura Coupling to Form Compounds ***5***. To a solution of 3-iodobenzo[*b*]thiophene **4** (1.0 mmol) and 5 mol % $Pd(PPh_3)_4$ in toluene (10 mL) was added K_2CO_3 (2.5 mmol) under an Ar atmosphere. To the resulting mixture was added *p*-(THPO)$C_6H_4B(OH)_2$ (1.5 mmol) dissolved in ethanol (2 mL) and water (0.5 mL), and the reaction mixture heated to 80 °C for 6−8 h with vigorous stirring. After concentration of the solvent under reduced pressure, 10% aq HCl was added to the crude product in THF (0.1 M conc.) at room temperature and stirred for 1 h. The mixture was then extracted by EtOAc (2 × 20 mL), and the aqueous phase was also extracted with EtOAc or CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by flash chromatography using EtOAc/hexanes as the eluent to afford the corresponding product **5**.

*3-(4-Hydroxyphenyl)-5-methoxy-2-(4-methoxyphenyl)benzo-[b]thiophene [****5****{5}].* The product was obtained as a pale yellow oil (89% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.78 (s, 3H), 5.12 (br s, 1H), 6.78 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 6.96−7.03 (m, 2H), 7.20 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 55.8, 105.8,114.0 (×2), 114.3, 115.9 (×2), 122.9, 127.1, 128.3, 130.8 (×2), 131.1, 131.85 (×2), 131.89, 140.7, 142.4, 155.0, 157.8, 159.2; HRMS calcd for $C_{22}H_{18}O_3S$ $[M^+]$, 362.0977, found 362.0983.

General Procedure for the Mitsunobu Reaction to Form Compounds ***6***. To a solution of **5** (0.2 mmol), triphenylphosphine (PPh_3) (0.4 mmol), and alkylaminoethanol (0.3 mmol) in anhydrous THF (2 mL) was added diisopropylazodicarboxylate (DIAD) (0.3 mmol) with stirring at 0−5 °C. The resulting solution was stirred at room temperature for 24−32 h (monitored by TLC until completion) and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using methanol/ethyl acetate/hexanes as the eluent to afford the corresponding products **6**.

*5-Methoxy-2-(4-methoxyphenyl)-3-{4-[2-(1-piperidinyl)eth-oxy]phenyl}benzo[b]thiophene [****6****{17}].* The product was obtained as a pale yellow oil (89% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41−1.50 (m, 2H), 1.59−1.66 (m, 4H), 2.50−2.58 (m, 4H), 2.81 (t, J = 6.0 Hz, 2H), 3.779 (s, 3H), 3.780 (s, 3H), 4.15 (t, J = 6.0 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 6.95−7.03 (m, 2H), 7.20−7.27 (m, 4H), 7.70 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 26.2 (×2), 55.3 (×2),

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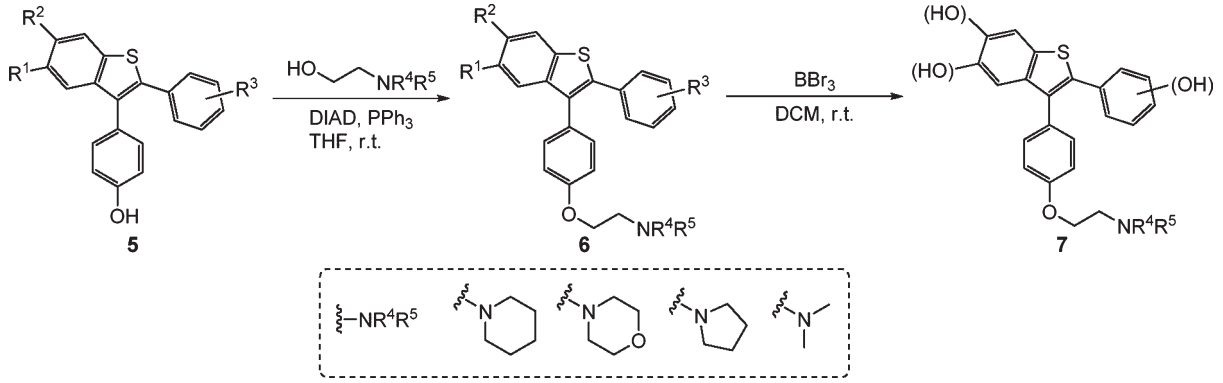
Table 2. Desketoraloxifene Analogue Library[a]



product **6**/**7**	R^1	R^2	R^3	NR^4R^5	ion HRMS	HRMS (calcd)	HRMS (found)	purity (%)[e]	yield (%)[f]
6{*1*}	H	H	H	piperidino	$[M+H]^+$	413.1813	414.1894	98	83
6{*2*}	H	H	H	morpholino	$[M+H]^+$	415.1606	416.1682	>99	78
6{*3*}	H	H	H	pyrrolidino	$[M+H]^+$	399.1657	400.1732	92	81[h]
6{*4*}	H	H	H	NMe_2	$[M+H]^+$	373.1500	374.1576	98	79
6{*5*}	H	H	4-MeO	piperidino	$[M+H]^+$	443.1919	444.1987	98	83
7{*1*}[b]	H	H	4-OH	piperidino	$[M+H]^+$	429.1762	430.1835	98	27[g]
6{*6*}	H	H	4-MeO	morpholino	$[M+H]^+$	445.1712	446.1788	>99	73
7{*2*}[b]	H	H	4-OH	morpholino	$[M+H]^+$	431.1555	432.1636	75	23[g]
6{*7*}	H	H	4-MeO	pyrrolidino	$[M]^+$	429.1762	429.1765		85
7{*3*}[b]	H	H	4-OH	pyrrolidino	$[M+H]^+$	415.1606	416.1681	74	46[g]
6{*8*}	H	H	4-MeO	NMe_2	$[M+H]^+$	403.1606	404.1673	98	81
7{*4*}[b]	H	H	4-OH	NMe_2	$[M+H]^+$	389.1449	390.1528	70	56
6{*9*}	H	H	3-MeO	piperidino	$[M]^+$	443.1919	443.1916		78
7{*5*}[b]	H	H	3-OH	piperidino	$[M+H]^+$	429.1763	430.1843	>99	53[g]
6{*10*}	H	H	3-MeO	morpholino					73
7{*6*}[b]	H	H	3-OH	morpholino	$[M+H]^+$	431.1555	432.1636	>99	47
6{*11*}	H	H	3-MeO	pyrrolidino					76
7{*7*}[b]	H	H	3-OH	pyrrolidino	$[M+H]^+$	415.1606	416.1682	98	35[g]
6{*12*}	H	H	3-MeO	NMe_2					69
7{*8*}[b]	H	H	3-OH	NMe_2	$[M+H]^+$	389.1450	390.1525	>99	51[g]
6{*13*}	H	H	2-MeO	piperidino	$[M]^+$	443.1919	443.1917		76
7{*9*}[b]	H	H	2-OH	piperidino	$[M+H]^+$	429.1763	430.1841	92	17[g]
6{*14*}	H	H	2-MeO	morpholino					78
7{*10*}[b]	H	H	2-OH	morpholino					nd[i]
6{*15*}	H	H	2-MeO	pyrrolidino					67
7{*11*}[b]	H	H	2-OH	pyrrolidino					nd[i]
6{*16*}	H	H	2-MeO	NMe_2					71
7{*12*}[b]	H	H	2-OH	NMe_2	$[M+H]^+$	389.1450	390.1525	>99	12[g]
6{*17*}	MeO	H	4-MeO	piperidino	$[M+H]^+$	473.2025	474.2050	99	87
7{*13*}[c]	OH	H	4-OH	piperidino	$[M+H]^+$	445.1712	446.1787	99	38[g]
6{*18*}	MeO	H	4-MeO	morpholino					74[h]
7{*14*}[c]	OH	H	4-OH	morpholino	$[M+H]^+$	447.1504	448.1579	87	56[g]
6{*19*}	MeO	H	4-MeO	pyrrolidino	$[M]^+$	429.1762	429.1768		81
7{*15*}[c]	OH	H	4-OH	pyrrolidino	$[M+H]^+$	431.1555	432.1638	86	16[g]
6{*20*}	MeO	H	4-MeO	NMe_2					81
7{*16*}[c]	OH	H	4-OH	NMe_2					nd[i]

Table 2. Continued

product **6**/**7**	R^1	R^2	R^3	NR^4R^5	ion HRMS	HRMS (calcd)	HRMS (found)	purity (%)[e]	yield (%)[f]
6{*21*}	MeO	H	3-MeO	piperidino	$[M]^+$	473.2025	473.2031		86
7{*17*}[c]	OH	H	3-OH	piperidino	$[M+H]^+$	445.1712	446.1790	94	48[g]
6{*22*}	MeO	H	3-MeO	morpholino	$[M+H]^+$	475.1817	476.1890	97	83[h]
6{*23*}	MeO	H	3-MeO	pyrrolidino					71
6{*24*}	MeO	H	3-MeO	NMe_2	$[M+H]^+$	433.1712	434.1790	96	82
7{*18*}[c]	OH	H	3-OH	NMe_2	$[M+H]^+$	405.1399	406.1475	89	17[g]
6{*25*}	MeO	H	2-MeO	piperidino	$[M+H]^+$	473.2025	474.2095	99	87
7{*19*}[c]	OH	H	2-OH	piperidino	$[M+H]^+$	445.1712	446.1787	95	52
6{*26*}	MeO	H	2-MeO	morpholino					81[h]
6{*27*}	MeO	H	2-MeO	pyrrolidino	$[M+H]^+$	459.1868	460.1946	98	83
7{*20*}[c]	OH	H	2-OH	pyrrolidino					nd[i]
6{*28*}	MeO	H	2-MeO	NMe_2	$[M]^+$	433.1712	433.1720		83
7{*21*}[c]	OH	H	2-OH	NMe_2	$[M+H]^+$	405.1399	406.1475	93	42[g]
6{*29*}	MeO	H	3,5-$(MeO)_2$	piperidino	$[M]^+$	503.2130	503.2132		77
7{*22*}[d]	OH	H	3,5-$(OH)_2$	piperidino	$[M+H]^+$	461.1661	462.1737	33	7[g]
6{*30*}	MeO	H	3,5-$(MeO)_2$	morpholino					78
6{*31*}	MeO	H	3,5-$(MeO)_2$	pyrrolidino					73
6{*32*}	MeO	H	3,5-$(MeO)_2$	NMe_2					73
7{*23*}[d]	OH	H	3,5-$(OH)_2$	NMe_2	$[M+H]^+$	421.1348	422.1362	82	21[g]
6{*33*}	H	MeO	4-MeO	piperidino	$[M+H]^+$	473.2025	474.2105	98	83
7{*24*}[c]	H	OH	4-OH	piperidino	$[M+H]^+$	445.1712	446.1793	97	78
6{*34*}	H	MeO	4-MeO	morpholino					78
7{*25*}[c]	H	OH	4-OH	morpholino	$[M+H]^+$	447.1504	448.1585	55	43[g]
6{*35*}	H	MeO	4-MeO	pyrrolidino					75
7{*26*}[c]	H	OH	4-OH	pyrrolidino	$[M+H]^+$	431.1555	432.1633	13	38[g]
6{*36*}	H	MeO	4-MeO	NMe_2					76
7{*27*}[c]	H	OH	4-OH	NMe_2	$[M+H]^+$	405.1399	406.1471	30	47
6{*37*}	H	MeO	2-MeO	piperidino	$[M]^+$	473.2025	473.2019		78
7{*28*}[c]	H	OH	2-OH	piperidino	$[M+H]^+$	445.1712	446.1914	97	37[g]
6{*38*}	H	MeO	2-MeO	morpholino					77
7{*29*}	H	OH	2-OH	morpholino	$[M+H]^+$	447.1504	448.1712	97	49[g]
6{*39*}	H	MeO	2-MeO	pyrrolidino					81
7{*30*}[c]	H	OH	2-OH	pyrrolidino	$[M+H]^+$	431.1555	432.1703	92	35[g]
6{*40*}	H	MeO	2-MeO	NMe_2					82
7{*31*}[c]	H	OH	2-OH	NMe_2	$[M+H]^+$	405.1399	406.1538	99	31[g]
6{*41*}	MeO	MeO	4-MeO	piperidino	$[M+H]^+$	503.2130	504.2146	95	76
7{*32*}[d]	OH	OH	4-OH	piperidino	$[M+H]^+$	461.1661	462.1732	>99	12[g]
6{*42*}	MeO	MeO	4-MeO	morpholino					75[h]
7{*33*}[d]	OH	OH	4-OH	morpholino	$[M+H]^+$	463.1453	464.1471	97	53[g]
6{*43*}	MeO	MeO	4-MeO	pyrrolidino	$[M]^+$	489.1974	489.1981		79
7{*34*}[d]	OH	OH	4-OH	pyrrolidino					nd[i]
6{*44*}	MeO	MeO	4-MeO	NMe_2					69
7{*35*}[d]	OH	OH	4-OH	NMe_2					nd[i]
6{*45*}	MeO	MeO	3-MeO	piperidino	$[M]^+$	503.2130	503.2134		79
7{*36*}[d]	OH	OH	3-OH	piperidino					nd[i]
6{*46*}	MeO	MeO	3-MeO	morpholino					81[h]
6{*47*}	MeO	MeO	3-MeO	pyrrolidino	$[M]^+$	489.1974	489.1982		73
6{*48*}	MeO	MeO	3-MeO	NMe_2	$[M]^+$	463.1817	463.1826		72

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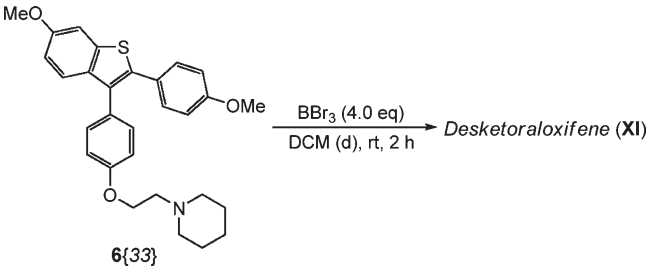
Table 2. Continued

product **6**/**7**	R^1	R^2	R^3	NR^4R^5	ion HRMS	HRMS (calcd)	HRMS (found)	purity (%)[e]	yield (%)[f]
6{*49*}	MeO	MeO	2-MeO	piperidino	$[M+H]^+$	503.2130	504.2209	99	77
6{*50*}	MeO	MeO	2-MeO	morpholino					72
7{*37*}[d]	OH	OH	2-OH	morpholino	$[M+H]^+$	463.1453	464.1527	>99	17[g]
6{*51*}	MeO	MeO	2-MeO	pyrrolidino					68
7{*38*}[d]	OH	OH	2-OH	pyrrolidino					nd[i]
6{*52*}	MeO	MeO	2-MeO	NMe_2					71
7{*39*}[d]	OH	OH	2-OH	NMe_2					nd[i]
6{*53*}	OCH_2O		4-MeO	piperidino	$[M]^+$	487.1817	487.1817		81
6{*54*}	OCH_2O		4-MeO	morpholino	$[M+H]^+$	489.1610	490.1692	>99	77[h]
6{*55*}	OCH_2O		4-MeO	pyrrolidino	$[M+H]^+$	473.1661	474.1754	98	69
6{*56*}	OCH_2O		4-MeO	NMe_2					79
6{*57*}	OCH_2O		2-MeO	piperidino	$[M+H]^+$	487.1817	488.1896	93	76
6{*58*}	OCH_2O		2-MeO	morpholino					63[h]
6{*59*}	OCH_2O		2-MeO	pyrrolidino					69[h]
6{*60*}	OCH_2O		2-MeO	NMe_2	$[M]^+$	447.1504	447.1512		76

[a] Reagents and conditions: (i) *Mitsunobu Coupling*: **5** (0.2 mmol), alkylaminoethanol (1.5 equiv), DIAD (1.5 equiv), PPh_3 (2.0 equiv), THF (2.0 mL), rt, 24−36 h. (ii) *Demethylation*: **6** (0.1 mmol), BBr_3, CH_2Cl_2 (1.0 mL), rt, N_2, 3 h. [b] 2.0 Equiv of BBr_3 used. [c] 4.0 Equiv of BBr_3 used. [d] 6.0 Equiv of BBr_3 used. [e] UV purity determined at 214 nm after preparative HPLC. [f] Isolated yields after column chromatography. All isolated products were characterized by ^1H and ^{13}C NMR spectroscopy (see the Supporting Information). [g] Isolated yield after preparative HPLC. [h] An inseparable mixture was obtained. [i] The final product was not purified, because of poor solubility.

Scheme 6. Demethylation to Form Desketoraloxifene (XI)



55.4, 55.8, 58.3, 66.1, 105.7, 114.0 (×2), 114.4, 115.0 (×2), 122.9, 127.1, 128.2, 130.8 (×2), 131.0, 131.6 (×2), 132.0, 140.6, 142.4, 157.8, 158.2, 159.2; HRMS calcd for $C_{29}H_{32}NO_3S$ $[M+H^+]$, 474.2103, found 474.2050.

General Procedure for Demethylation to Compounds ***7***. To a solution of **6** (0.10 mmol) in anhydrous CH_2Cl_2 (2 mL) cooled in an ice water bath under N_2 was added BBr_3 (1.0 M solution in CH_2Cl_2; 4.0 equiv) while stirring. The solution turned orange in color. This solution was stirred for 3 h after slowly warming to room temperature. The reaction was quenched with satd aq $NaHCO_3$ (2 × 2 mL), and the product was extracted with 5% $CH_3OH/CHCl_3$ (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by column chromatography using 5−10% $CH_3OH/CHCl_3$ as the eluent to provide the desketoraloxifene analogues **7**.

*Desketoraloxifene [****7****{24}, **XI**]*. The product was obtained as a white solid (68% yield): ^1H NMR (400 MHz, DMSO-d_6) δ 1.34−1.43 (m, 2H), 1.48−1.57 (m, 4H), 2.50−2.53 (m, 4H), 2.70−2.76 (m, 2H), 4.10 (t, J = 5.7 Hz, 2H), 6.67 (d, J = 8.7 Hz, 2H), 6.84 (dd, J = 2.2, 8.7 Hz, 1H), 6.99 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.7 Hz, 1H), 7.28 (d, J = 2.2 Hz, 1H), 9.62 (s, 1H), 9.65 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.7, 25.3 (×2), 54.3 (×2), 57.2, 65.3, 107.0, 114.6, 114.7 (×2), 115.3 (×2), 123.2, 124.6, 127.4, 130.1 (×2), 130.7, 131.0 (×2), 133.5, 134.8, 138.8, 155.1, 156.9, 157.6; HRMS calcd for $C_{27}H_{27}NO_3S$ $[M+H^+]$, 446.1790, found 446.1793.

■ ASSOCIATED CONTENT

Supporting Information. Synthetic methods, spectral assignments and copies of ^1H and ^{13}C NMR spectra for all previously unreported starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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