Diverse Methyl Sulfone-Containing Benzo[*b*]thiophene Library via Iodocyclization and Palladium-Catalyzed Coupling

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Parallel solution-phase methods for the synthesis of a 72-membered benzo[*b*]thiophene library are reported. Medicinally interesting, drug-like, methyl sulfone-substituted benzo[*b*]thiophenes have been prepared by the palladium-catalyzed substitution of 3-iodobenzo[*b*]thiophenes by Suzuki-Miyaura, Sonogashira, Heck, carboalkoxylation, and aminocarbonylation chemistry. The key intermediates for library generation, methyl sulfone-containing 3-iodobenzo[*b*]thiophenes, are readily prepared by iodocyclization and oxidation methodologies from readily available alkynes.

Introduction

Benzo[*b*]thiophenes are of interest because of their frequent occurrence in nature and their wide range of biological and physiological effects.[1−3] Benzo[*b*]thiophene derivatives currently in pharmaceutical use or development include selective estrogen receptor modulators (SERMs),[4−8] tubulin-binding agents,[7,9,10] modulators of multidrug resistance,[11] and anti-inflammatory[12] agents to name but a few.

Traditional non-steroidal anti-inflammatory drugs (NSAIDs) represent one of the most prescribed medications, although the chronic use of such pharmacological agents is commonly associated with numerous side effects. The use of cyclooxygenase-2 (COX-2) selective or preferential inhibitors has opened up new horizons in the search for safer drugs for the management of inflammation.[13] Cyclooxygenases exist as two isoforms called COX-1 and COX-2.[14,15] In many systems, COX-1 is a constitutively expressed isoform and is responsible for the maintenance of physiological homeostasis, such as renal function and gastrointestinal integrity,[16] whereas COX-2 is induced in response to inflammatory stimuli and is responsible for the progression of inflammation.[17] In addition to its role in inflammatory disorders, COX-2 is also implicated in a variety of other pathologies, such as cancer, cardiac and cerebral ischemia, and Parkinson's[18−22] and Alzheimer's[22−24] diseases. Thus, the search for specific inhibitors of COX-2 by modifications of well-known non-selective agents has been actively pursued, and increasing attention has been devoted to the synthesis of diaryl heterocyclic compounds.[25,26]

Biological evaluation of known compounds has shown that insertion of the coxib-like scaffold gives rise to very potent and selective COX-2 inhibitors. All structures possess 1,2-diaryl substitution on a central hetero- or carbocyclic ring system with a characteristic sulfonyl group on one of the aryl rings that plays a crucial role in COX-2 selectivity. To date highly selective COX-2 inhibitors have been reported to contain the following functional groups: (i) methyl sulfonyl- or sulfonamide-substituted tricyclic compounds, such as DuP-697,[27−30] rofecoxib,[27,31,32] etoricoxib,[27,33] SC-57666,[34] valdecoxib,[27,35] celecoxib,[27,36] SC-558,[36,37] and SC-58125;[27] (ii) acidic methanesulfoanilides, such as nimesulide,[27,38,39] NS-398,[27,29,30,40,41] and (iii) modifications of classical NSAIDs, such as substituted 2-phenylsulfonyl-3-phenylindole analogues **I**,[42−44] and substituted 2-phenylsulfonyl-3-phenylbenzofuran analogues **II**.[45] Interestingly, the drug CH_3SO_2-desmethylarzoxifene (LY2066948,[46] CH_3SO_2-DMA, **III**) was found to bind with high affinity to estrogen receptors α (ERα) and β (ERβ) by a different mode from the other SERMs and is a potent uterine antagonist with minimal effects on the ovaries as determined by serum biomarkers and histological evaluation (Figure 1).[8,46−48] Most importantly, substitution at the *para* position of one of the aromatic systems with a methanesulfonyl or a sulfonamide group is essential for COX inhibition.

The pharmacophore of these diarylheterocyclic inhibitors is characterized by a central carbocyclic or heterocyclic ring system bearing two vicinal aryl moieties with one benzene ring being substituted with a methanesulfonyl or aminosulfonyl group at the *para* position (Figure 1; see **I**, **II**, **III**). For these reasons, 2,3-diarylsubstituted benzo[*b*]thiophenes with a methanesulfonyl group at the *meta* and/or *para* position have been the subject of extensive experimental studies.

In a continuation of our library efforts to adapt heterocyclization chemistry to a high-throughput synthesis format,[49−54] we here report the preparation of a methyl sulfone-containing library of multisubstituted benzo[*b*]thiophenes **6** by electrophilic cyclization chemistry. We demonstrate the significance of this methodology by elaborating the resulting sulfur-containing 3-iodobenzothiophenes **4/5** via various palladium-catalyzed couplings, such as Suzuki-Miyaura, Sonogashira,

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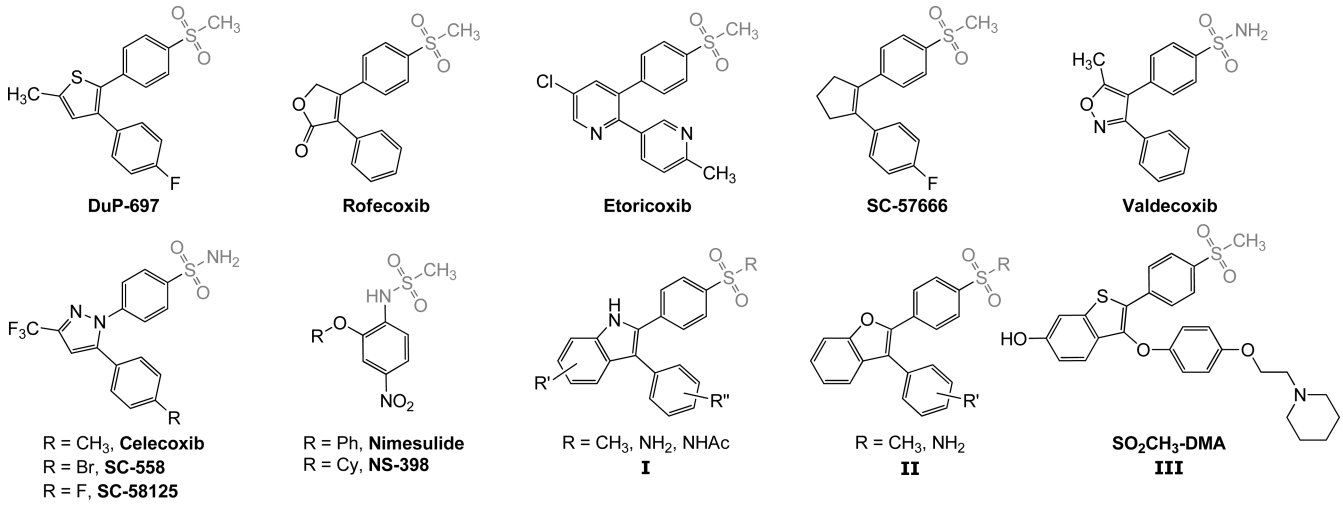
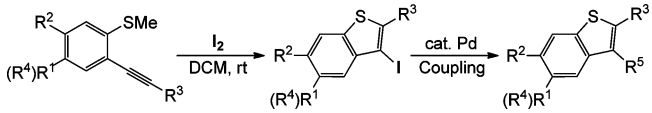


Figure 1. Chemical structures of known selective COX-2 inhibitors and synthetic benzothiophene SERMs, such as CH_3SO_2-DMA (**III**).

Scheme 1. Parallel Synthesis of Multi-Substituted Benzo[*b*]thiophenes



Heck, carboalkoxylation and aminocarbonylation chemistry, to methyl sulfone-containing multisubstituted benzo[*b*]-thiophenes **6**.

Results and Discussion

We have previously developed a general synthesis of 2,3-disubstituted benzo[*b*]thiophenes by the palladium/copper-catalyzed cross-coupling of various *o*-iodothioanisoles and terminal alkynes, followed by electrophilic cyclization under mild conditions.[55] Very recently, a simple and efficient method for the parallel synthesis of multisubstituted benzo-[*b*]thiophenes has also been described via known palladium-catalyzed couplings for generation of a diverse set of building blocks starting from 3-iodobenzo[*b*]thiophenes (Scheme 1).[52]

The strategy for library production is outlined in Scheme 2. For generation of the first methyl sulfone-substituted benzothiophene library, we decided to explore strategies using iodocyclization and oxidation methodologies that would allow us considerable flexibility to introduce a diversity of functionalities for medicinally interesting, drug-like methyl sulfone-substituted benzo[*b*]thiophenes **6** in a high-throughput manner.

A sequence of reactions involving Sonogashira coupling of the bromo-iodoarenes **1**, and subsequent lithiation of compounds **2**{*1*−*7*}, followed by methylthiolation with dimethyl disulfide afforded the corresponding disulfide

Scheme 2. Library Design for a Diverse Methyl Sulfone-Substituted Benzo[*b*]thiophene Library (**6**)

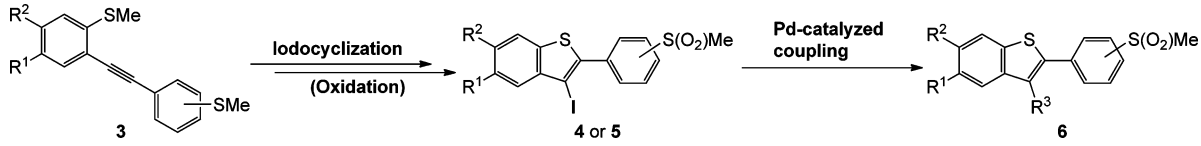
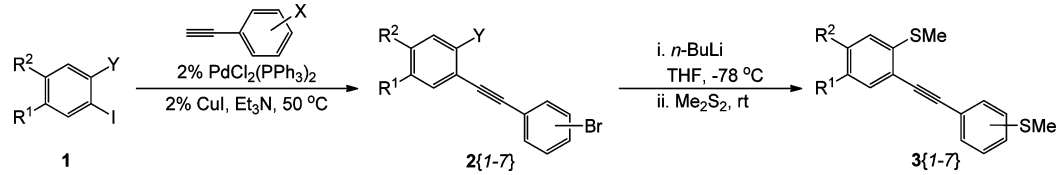


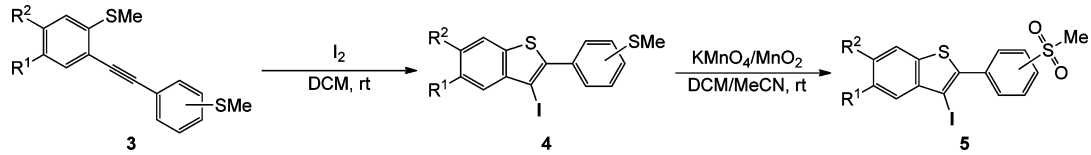
Table 1. Library Data for Compounds **2**{*1*−*7*} and **3**{*1*−*7*}

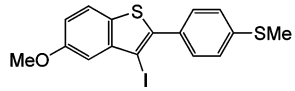
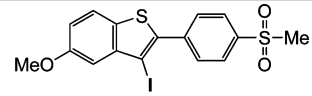
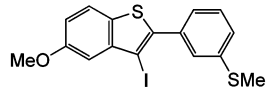
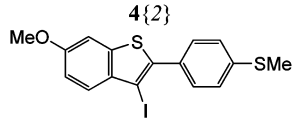
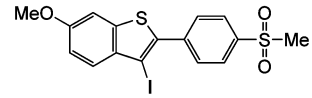
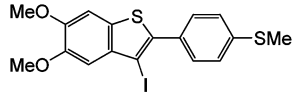
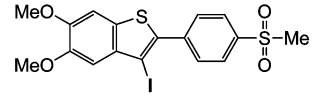
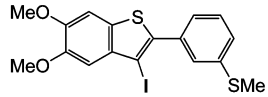
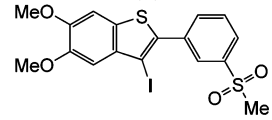
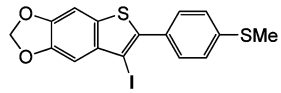
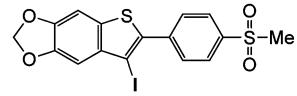
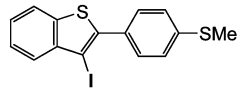
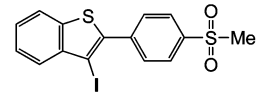


entry	1			X	2	yield (%)[a]	3[b]	yield (%)[a]
	R^1	R^2	Y					
1	MeO	H	Br	4-Br	**2**{*1*}	87	**3**{*1*}	78
2	MeO	H	Br	3-Br	**2**{*2*}	77	**3**{*2*}	70
3	H	MeO	Br	4-Br	**2**{*3*}	72	**3**{*3*}	68
4	MeO	MeO	Br	4-Br	**2**{*4*}	86	**3**{*4*}	73
5	MeO	MeO	Br	3-Br	**2**{*5*}	72	**3**{*5*}	71
6			Br	4-Br	**2**{*6*}	83	**3**{*6*}	58
7	H	H	SMe	4-Br	**2**{*7*}	87	**3**{*7*}	62

[a] Isolated yields after column chromatography. All compounds **2** have been characterized by ^{1}H and ^{13}C NMR spectroscopy. [b] For **3**{*1*−*6*}, *n*-BuLi (3.0 equiv) and Me_2S_2 (2.4 equiv) were used. For **3**{*7*}, *n*-BuLi (1.5 equiv) and Me_2S_2 (1.2 equiv) were used.

Table 2. 3-Iodobenzo[*b*]thiophene Scaffords **4**{*1*−*7*} and **5**{*1*−*6*}



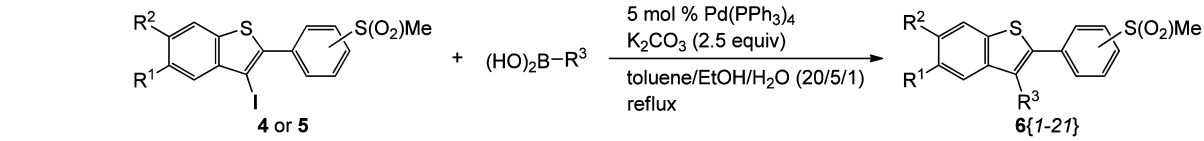
entry	alkyne **3**	3-iodobenzo[*b*]thiophene[a] **4**	yield (%)[c]	3-iodobenzo[*b*]thiophene[b] **5**	yield (%)[c]
1	**3**{*1*}	 **4**{*1*}	92	 **5**{*1*}	90
2	**3**{*2*}	 **4**{*2*}	nr[d]	-	-
3	**3**{*3*}	 **4**{*3*}	92	 **5**{*2*}	91
4	**3**{*4*}	 **4**{*4*}	91	 **5**{*3*}	88
5	**3**{*5*}	 **4**{*5*}	58	 **5**{*4*}	82
6	**3**{*6*}	 **4**{*6*}	93	 **5**{*5*}	86
7	**3**{*7*}	 **4**{*7*}	91	 **5**{*6*}	87

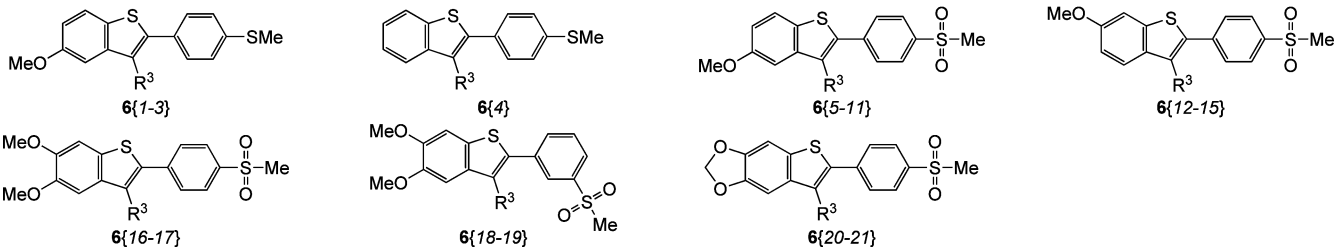
[a] All reactions were carried out using alkynes **3** and 1.5 equiv of I_2 in CH_2Cl_2 at room temperature within 0.5 h, unless otherwise indicated. [b] Reactions of methyl sulfides **4** were carried out at room temperature in CH_3CN/DCM (1:1) using $KMnO_4/MnO_2$. [c] Isolated yields after column chromatography. All compounds **4** and **5** have been characterized by ^1H and ^{13}C NMR spectroscopy. [d] I_2 (1.5 equiv, followed by an additional 1.0 equiv after 12 h) was used for 24 h. The starting material **3**{*2*} was recovered.

products **3**. Initially, the electron-rich substituted dihaloarenes **1** (see Table 1) were chosen as the starting materials because it was envisioned that the oxygen-containing groups would provide desirable polarity in the resulting library members. The starting materials, dihalobenzenes **1**, are easily prepared through regioselective bromination and iodination.[52] In general, the requisite precursors bearing a dibromo-substituted alkyne moiety (**2**) can be easily prepared from bromophenylacetylenes (*para*- and *meta*- positions) by palladium/copper-catalyzed Sonogashira coupling of the corresponding dihaloarenes in good yields (Table 1).[52] *ortho*-Bromophenylacetylene was not chosen as suitable to avoid competing reactions during iodocyclization. The dibromo-substituted alkynes **2**{*1*−*6*} provided the corresponding products **3**{*1*−*6*} in modest yields (Table 1, entries 1−6). In a similar manner, the bromo-containing alkyne **2**{*7*} also afforded the corresponding product **3**{*7*} in modest yields (Table 1, entry 7).

The key cyclization step efficiently generates the methyl sulfide-substituted 3-iodo[*b*]benzothiophenes **4** in 10 min at room temperature by electrophilic cyclization of the corresponding disulfide-containing alkynes **3**{*1*−*6*} and sulfide alkyne **3**{*7*} using I_2 in CH_2Cl_2 at ambient temperature (Table 2). In all cases, good to excellent yields of methyl sulfide-substituted 3-iodo[*b*]benzothiophenes **4** have been obtained, except for **4**{*2*}. The methyl sulfides **4** were immediately converted to the corresponding sulfones **5** by oxidation in good to excellent yields by $KMnO_4$ supported on MnO_2 under heterogeneous conditions at room temperature.[56] Attempts to oxidize species **4** using standard organic solvents, for example, methylene chloride or acetonitrile, individually under the same reaction conditions proved unsuccessful. Both methylene chloride and acetonitrile must be used as co-solvents for this reaction to afford decent yields. All of the reactions were monitored by thin layer chromatography, and the

Table 3. Library Data for Compounds **6**{*1*−*21*}[a]





product **6**	**7**	R^3	yield (%)[c]	purity (%)[e]	ion HRMS	calcd for HRMS	found HRMS
6{*1*}	**7**{*4*}	2,3-dihydrobenzo[1,4]dioxin-6-yl	69	98	M^+	420.0854	ND[f]
6{*2*}	**7**{*5*}	4-hydroxyphenyl[b]	65[d]	>99	M^+	378.0748	378.0753
6{*3*}	**7**{*8*}	2-bromo-5-pyridinyl	58	58	$M+H^+$	441.9935	441.9931
6{*4*}	**7**{*9*}	4-carbamoylphenyl	61	99	$M+H^+$	376.0830	376.0830
6{*5*}	**7**{*1*}	4-methoxyphenyl	72[d]	>99	$M+NH_4^+$	442.1147	442.1169
6{*6*}	**7**{*2*}	4-(methoxymethyl)phenyl	72[d]	>99	$M+NH_4^+$	456.1303	456.1303
6{*7*}	**7**{*4*}	2,3-dihydrobenzo[1,4]dioxin-6-yl	77	98	$M+MeOH^+$	484.1014	485.1102
6{*8*}	**7**{*9*}	4-carbamoylphenyl	57	95	$M+H^+$	438.0834	438.0842
6{*9*}	**7**{*11*}	4-(methylthio)phenyl	71	>99	$M+MeOH^+$	472.0837	473.0939
6{*10*}	**7**{*12*}	2-morpholinopyrimidin-5-yl	65	>99	$M+H^+$	482.1208	482.1201
6{*11*}	**7**{*13*}	4-sulfamoylphenyl	47	>99	$M+MeOH^+$	505.0687	506.0761
6{*12*}	**7**{*6*}	4-acetylphenyl	57	99	$M+H^+$	437.0881	437.0874
6{*13*}	**7**{*11*}	4-(methylthio)phenyl	73[d]	>99	$M+MeOH^+$	472.0837	473.0920
6{*14*}	**7**{*2*}	2-morpholinopyrimidin-5-yl	57[d]	>99	$M+H^+$	482.1208	482.1192
6{*15*}	**7**{*13*}	4-sulfamoylphenyl	38	99	$M+MeOH^+$	505.0687	506.0775
6{*16*}	**7**{*3*}	benzo[1,3]dioxol-5-yl	78[d]	>99	$M+MeOH^+$	500.0963	501.1049
6{*17*}	**7**{*13*}	4-sulfamoylphenyl	18	96	$M+MeOH^+$	535.0793	536.0887
6{*18*}	**7**{*11*}	4-(methylthio)phenyl	69	98	$M+MeOH^+$	502.0942	503.1037
6{*19*}	**7**{*13*}	4-sulfamoylphenyl	34	95	$M+MeOH^+$	535.0793	536.0949
6{*20*}	**7**{*7*}	3-fluoro-4-methoxyphenyl	67[d]	>99	$M+MeOH^+$	488.0764	489.0853
6{*21*}	**7**{*11*}	4-(methylthio)phenyl	53	98	$2M+Na^+$	931.0632	ND[f]

[a] Suzuki-Miyaura reaction: 5 mol % $Pd(PPh_3)_4$, K_2CO_3 (2.5 equiv), $R^3B(OH)_2$ **7** (1.5 equiv), toluene/EtOH/H_2O (20/5/1), reflux. See the Supporting Information for the experimental details. [b] The THP ether-protected boronic acid was deprotected *in situ* using aq. HCl in THF at room temperature. [c] Isolated yield after preparative HPLC. [d] Isolated yield after column chromatography. Isolated desired products **6** were characterized by ^1H and ^{13}C NMR spectroscopy. [e] UV purity determined at 214 nm after preparative HPLC. [f] Not determined by HRMS. Identified by NMR spectroscopy.

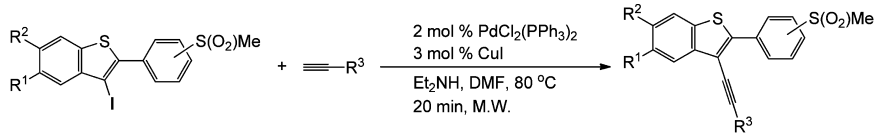
products purified by column chromatography (see the Supporting Information for the experimental details).

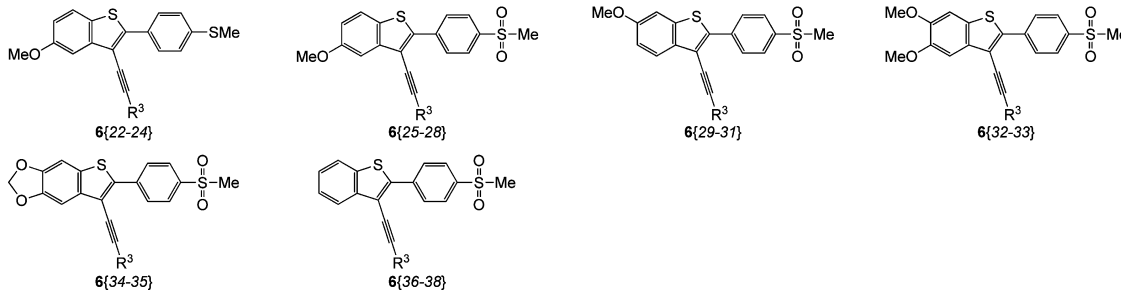
Subsequently, we proceeded to prepare a diverse library of methyl sulfone-substituted benzothiophenes **6** by a variety of palladium-catalyzed processes, such as Suzuki-Miyaura coupling, Sonogashira coupling, Heck coupling, carboalkoxylation, and aminocarbonylation. The Suzuki-Miyaura coupling of the 3-iodobenzo[*b*]thiophenes **4** or **5** with appropriate boronic acids **7** afforded the desired products **6**{*1*−*21*} (Table 3). Sonogashira coupling of the 3-iodobenzo[*b*]-thiophenes **4** or **5** with appropriate terminal alkynes **8** provides the corresponding alkynes **6**{*22*−*38*} under microwave irradiation (Table 4). Moreover, methyl sulfone-substituted, olefin-containing benzothiophenes **6**{*39*−*45*} have been prepared by Heck coupling of the 3-iodobenzo[*b*]-thiophenes **4** or **5** with a small styrene sublibrary **9** (Table 5). Methyl sulfone-substituted, ester-containing benzothiophenes **6**{*46*−*56*} have been prepared by carboalkoxylation of the 3-iodobenzo[*b*]thiophenes **4** or **5** using one atmosphere of carbon monoxide and primary alcohols **10** (Table 6). In addition, aminocarbonylation of the 3-iodobenzo[*b*]thiophenes **4** or **5** using one atmosphere of carbon monoxide in the presence of a palladium catalyst with appropriate primary and secondary amines **11** afforded the desired amide-containing products **6**{*57*−*72*} (Table 7). The sublibraries, for example, boronic acids **7**, terminal alkynes **8**, styrenes **9**, alcohols **10**, and amines **11**, were chosen for their ability to provide the requisite diversity and drug-like properties to the scaffold (Figure 2).

Our goal in synthesizing these relatively low molecular weight heterocycles was to examine their biological properties by high-throughput screening. The overall synthetic process as a whole is quite functional group tolerant and efficient. These reactions have been performed in parallel on approximately a 35−50 mg scale, starting from the 3-iodobenzo[*b*]thiophenes **4** or **5**. All of the crude compounds **6**{*1*-*72*} were isolated by either column chromatography or preparative HPLC. The purity of the reaction mixtures has been analyzed by TLC, LC-MS, and HPLC.

The selected 72 sulfone-substituted benzo[*b*]thiophene template **6** has been evaluated computationally for its drug-like properties on the basis of Lipinski's rule of five.[57] Lipinski calculations have been performed based on the commercial available of boronic acids **7**, terminal alkynes **8**, styrenes **9**, alcohols **10**, and amines **11**. The molecular weight (less than 500), clogP (less than 5), number of hydrogen bond donors (less than 5 H) and acceptors (less than 10 H), and the number of rotatable bonds (less than

Table 4. Library Data for Compounds **6**{*22*−*38*}[a]

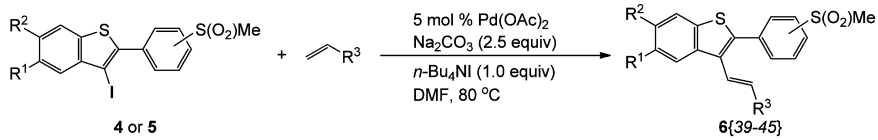


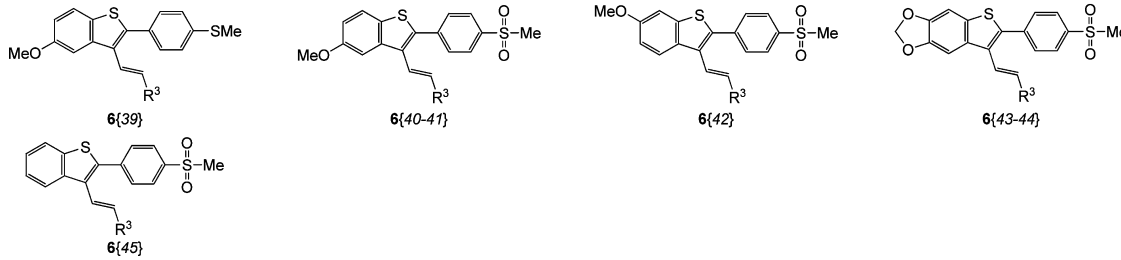


product **6**	**8**	R^3	yield (%)[b]	purity (%)[d]	ion HRMS	calcd for HRMS	found HRMS
6{*22*}	**8**{*1*}	hydroxymethyl	57[c]	98	M^+	378.0748	ND[e]
6{*23*}	**8**{*3*}	(1-hydroxy-1-methyl)ethyl	77	>99	$2M+NH_4^+$	754.2153	754.2177
6{*24*}	**8**{*6*}	2-pyridinyl	19	>99	$M+H^+$	388.0830	388.0836
6{*25*}	**8**{*1*}	hydroxymethyl	37[c]	>99	$M+NH_4^+$	390.0834	390.0843
6{*26*}	**8**{*3*}	(1-hydroxy-1-methyl)ethyl	58	99	$M+NH_4^+$	418.1147	418.1146
6{*27*}	**8**{*4*}	1-hydroxy-1-cyclohexyl	48[c]	98	$2M+NH_4^+$	898.2576	898.2602
6{*28*}	**8**{*5*}	1-methyl-1*H*-imidazol-5-yl	45	>99	$M+H^+$	423.0837	423.0826
6{*29*}	**8**{*2*}	2-hydroxyethyl	57	>99	$M+H^+$	387.0725	387.0701
6{*30*}	**8**{*5*}	1-methyl-1*H*-imidazol-5-yl	43	>99	$M+NH_4^+$	440.1103	440.1188
6{*31*}	**8**{*7*}	3-thiophenyl	55	97	$M+NH_4^+$	442.0605	442.0596
6{*32*}	**8**{*1*}	hydroxymethyl	66	>99	$M+NH_4^+$	420.0939	420.0949
6{*33*}	**8**{*4*}	1-hydroxy-1-cyclohexyl	47[c]	>99	$M+NH_4^+$	488.1565	488.1577
6{*34*}	**8**{*4*}	1-hydroxy-1-cyclohexyl	38	>99	$M+NH_4^+$	472.1252	472.1266
6{*35*}	**8**{*3*}	(1-hydroxy-1-methyl)ethyl	56[c]	>99	$M+NH_4^+$	432.0939	432.0947
6{*36*}	**8**{*2*}	2-hydroxyethyl	65	99	$M+H^+$	357.0619	357.0609
6{*37*}	**8**{*4*}	1-hydroxy-1-cyclohexyl	53	>99	$M+NH_4^+$	428.1354	428.1372
6{*38*}	**8**{*5*}	1-methyl-1*H*-imidazol-5-yl	37[c]	>99	$M+H^+$	393.0731	393.0716

[a] Sonogashira reaction: 3 mol % $PdCl_2(PPh_3)_2$, 3 mol % CuI, Et_2NH, $R^3C{\equiv}CH$ **8** (1.2 equiv), DMF, 80 °C, 20 min, using microwave irradiation. See the Supporting Information for the experimental details. [b] Isolated yield after preparative HPLC. [c] Isolated yield after column chromatography. Isolated desired products **6** were characterized by ^1H and ^{13}C NMR spectroscopy. [d] UV purity determined at 214 nm after preparative HPLC. [e] Not determined by HRMS. Identified by NMR spectroscopy.

Table 5. Library Data for Compounds **6**{*39*−*45*}[a]

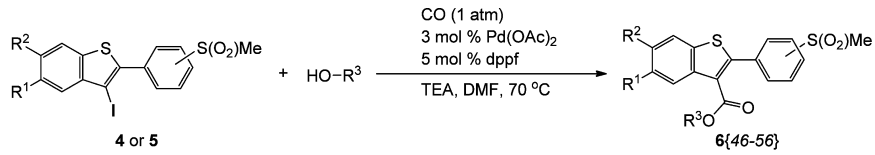


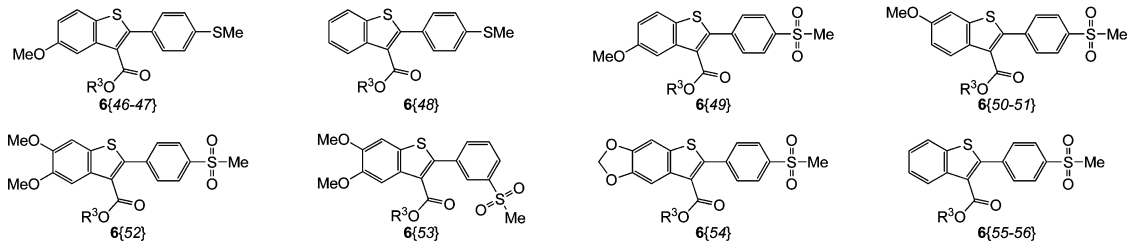


product **6**	**9**	R^3	yield (%)[b]	purity (%)[d]	ion HRMS	calcd for HRMS	found HRMS
6{*39*}	**9**{*2*}	3,4-dimethoxyphenyl	64[c]	95	M^+	448.1167	448.1181
6{*40*}	**9**{*1*}	4-methoxyphenyl	77[c]	84	$M+H^+$	450.0960	451.1040
6{*41*}	**9**{*2*}	3,4-dimethoxyphenyl	68	>99	$M+H^+$	481.1143	ND[e]
6{*42*}	**9**{*1*}	4-methoxyphenyl	57	93	$M+H^+$	451.1038	451.1074
6{*43*}	**9**{*2*}	3,4-dimethoxyphenyl	62	97	$M+H^+$	495.0936	495.0936
6{*44*}	**9**{*3*}	4-pyridinyl	61	97	$M+H^+$	436.0677	436.0691
6{*45*}	**9**{*3*}	4-pyridinyl	66	96	$M+H^+$	392.0779	392.0794

[a] Heck reaction: 5 mol % $Pd(OAc)_2$, *n*-Bu_4NI (1.0 equiv), Na_2CO_3 (2.5 equiv), $R^3CH{=}CH_2$ **9** (1.2 equiv), DMF, 80 °C. See the *Supporting Information* for the experimental details. [b] Isolated yield after preparative HPLC. [c] Isolated yield after column chromatography. Isolated desired products **6** were characterized by ^1H and ^{13}C NMR spectroscopy. [d] UV purity determined at 214 nm after preparative HPLC. [e] Not determined by HRMS. Identified by NMR spectroscopy.

Table 6. Library Data for Compounds **6**{*46*−*56*}[a]

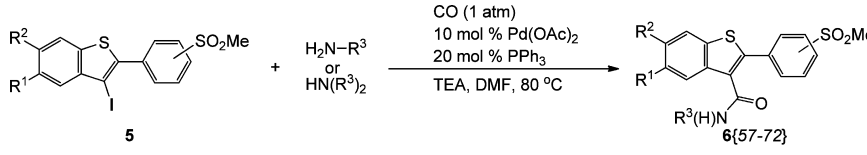


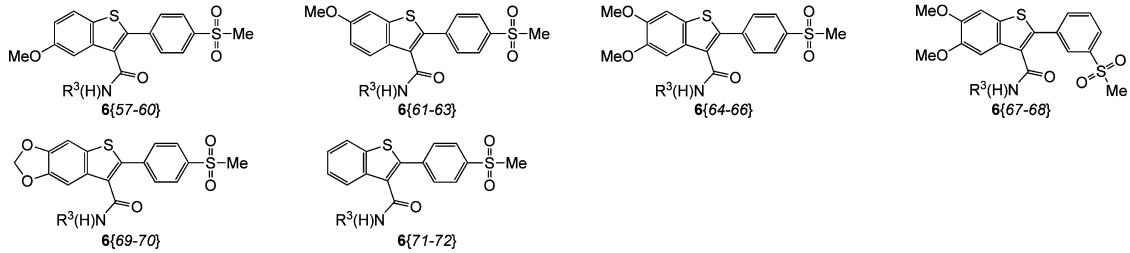


product **6**	**10**	R^3	yield (%)[b]	purity (%)[d]	ion HRMS	calcd for HRMS	found HRMS
6{*46*}	**10**{*1*}	methyl	71[c]	>99	$2M+Na^+$	711.0979	711.0962
6{*47*}	**10**{*3*}	3,4-dimethoxybenzyl	55	98	$M+NH_4^+$	498.1409	498.1409
6{*48*}	**10**{*1*}	methyl	83	>99	$2M+NH_4^+$	646.1214	646.1214
6{*49*}	**10**{*1*}	methyl	81[c]	>99	$M+H^+$	377.0517	377.0511
6{*50*}	**10**{*1*}	methyl	74[c]	>99	$M+H^+$	377.0517	377.0491
6{*51*}	**10**{*2*}	propyl	47	>99	$M+NH_4^+$	422.1096	422.1108
6{*52*}	**10**{*1*}	methyl	41[c]	98	$M+H^+$	407.0623	407.0617
6{*53*}	**10**{*1*}	methyl	62[c]	>99	$M+NH_4^+$	424.0889	424.0886
6{*54*}	**10**{*1*}	methyl	57	>99	$M+H^+$	391.0310	391.0312
6{*55*}	**10**{*1*}	methyl	45	99	$M+H^+$	347.0412	347.0421
6{*56*}	**10**{*3*}	3,4-dimethoxybenzyl	49	>99	$M+H^+$	483.0936	483.0944

[a] Carboalkoxylation: CO (1 atm), 3 mol % $Pd(OAc)_2$, 5 mol % dppf, TEA (2.0 equiv), R^3OH **10** (1.5−5.0 equiv), DMF, 70 °C. See the Supporting Information for the experimental details. [b] Isolated yield after preparative HPLC. [c] Isolated yield after column chromatography. Isolated desired products **6** were characterized by ^1H and ^{13}C NMR spectroscopy. [d] UV purity determined at 214 nm after preparative HPLC.

Table 7. Library Data for Compounds **6**{*57*−*72*}[a]





product **6**	**11**	R^3	yield (%)[b]	purity(%)[d]	ion HRMS	calcd for HRMS	found HRMS
6{*57*}	**11**{*1*}	2-pyridylethylamino	56	62	$M+H^+$	473.1569	473.1548
6{*58*}	**11**{*8*}	4-hydroxybutylamino	27	98	$M+H^+$	434.1096	434.1100
6{*59*}	**11**{*10*}	1-amino-4-methylpiperazino	67[c]	87	$M+H^+$	460.1365	460.1360
6{*60*}	**11**{*12*}	3-(2-oxo-1-pyrrolidinyl)propylamino	48	99	$M+H^+$	487.1361	487.1365
6{*61*}	**11**{*5*}	3,4-(methylenedioxy)benzylamino	65[c]	>99	$M+H^+$	496.0889	496.0889
6{*62*}	**11**{*7*}	1-methyltryptamino	71	>99	$M+H^+$	505.1256	505.1248
6{*63*}	**11**{*8*}	4-hydroxybutylamino	72[c]	>99	$M+H^+$	434.1096	434.1098
6{*64*}	**11**{*3*}	1-methyl-2-pyrrolidineethanamino	48	84	$M+H^+$	503.1674	503.1679
6{*65*}	**11**{*4*}	5-methyl-2-furanmethanamino	61	>99	$M+H^+$	486.1045	486.1057
6{*66*}	**11**{*8*}	4-hydroxybutylamino	58[c]	>99	$M+H^+$	464.1202	464.1190
6{*67*}	**11**{*2*}	1*H*-imidazole-1-ethanamino	17	>99	$M+H^+$	500.1314	500.1323
6{*68*}	**11**{*8*}	4-hydroxybutylamino	51	>99	$M+H^+$	464.1202	ND[e]
6{*69*}	**11**{*6*}	4-morpholinepropanamino	84[c]	>99	$M+H^+$	503.1311	503.1308
6{*70*}	**11**{*9*}	4-morpholinamino	62[c]	>99	$M+H^+$	461.0841	461.0833
6{*71*}	**11**{*6*}	4-morpholinepropanamino	68	>99	$M+H^+$	459.1412	459.1398
6{*72*}	**11**{*11*}	1-(4-fluorophenyl)piperazino	57	99	$M+H^+$	495.1212	495.1205

[a] Aminocarbonylation: CO (1 atm), 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, TEA, R^3NH_2 or $(R^3)_2NH$ **11** (1.5 equiv), DMF, 80 °C. See the *Supporting Information* for the experimental details. [b] Isolated yield after preparative HPLC. [c] Isolated yield after column chromatography. Isolated desired products **6** were characterized by ^1H and ^{13}C NMR spectroscopy. [d] UV purity determined at 214 nm after preparative HPLC. [e] Not determined by HRMS. Identified by NMR spectroscopy.

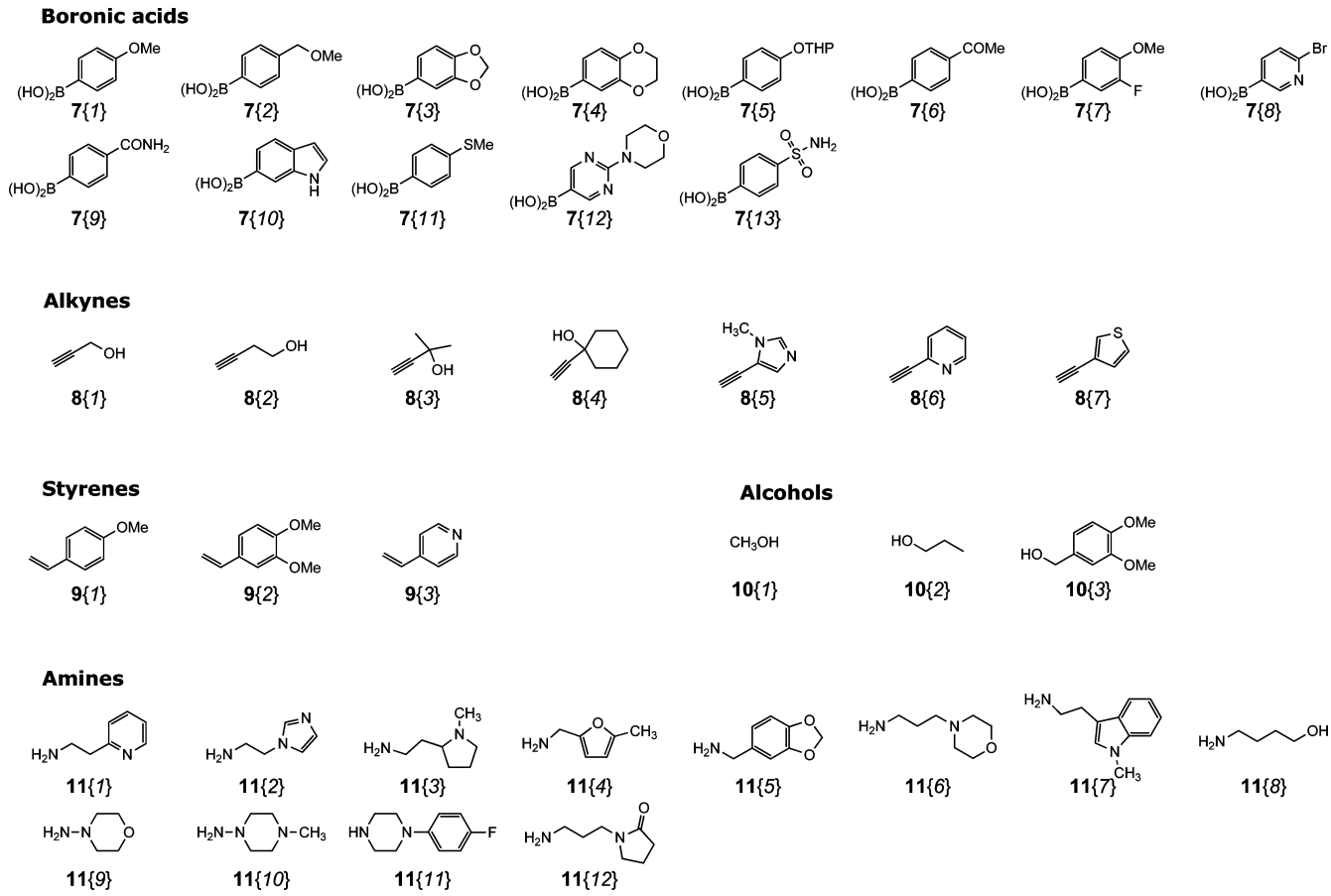


Figure 2. Sublibraries of boronic acids **7**, terminal alkynes **8**, styrenes **9**, alcohols **10**, and amines **11**.

10) were calculated for each of the library members using the SYBYL[58] program. Most of the desired sulfone-substituted benzo[*b*]thiophene library members were highly Lipinski compliant. A small subset of this virtual library, namely, 72 compounds, follows Lipinski's rules with no violations.

Conclusions

We have successfully produced a 72-member library of sulfone-substituted benzo[*b*]thiophenes **6** via palladium-catalyzed couplings, such as Suzuki-Miyaura, Sonogashira, Heck, carboalkoxylation, and aminocarbonylation chemistry, starting from key intermediate sulfur-containing 3-iodobenzo[*b*]thiophenes **5**. The 72 member sulfone-substituted benzo[*b*]thiophene library **6** has been added to the Kansas University NIH Center for Chemical Methodologies and Library Development (KU CMLD) collection and will be submitted to the National Institutes of Health Molecular Library Screening Center Network (MLSCN) for evaluation by a broad range of assays. We expect this basic methodology to find extensive application in the fields of combinatorial chemistry, diversity-oriented synthesis, and drug discovery.

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Supporting Information Available. Synthetic methods, spectral assignments and copies of ^{1}H 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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