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Efficient Synthesis of 3-Benzoyl Benzo[*b*]thiophenes and Raloxifene *via* Mercury(II)-Catalyzed Cyclization of 2-Alkynylphenyl Alkyl Sulfoxides

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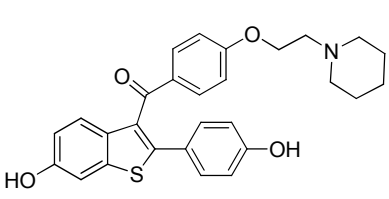
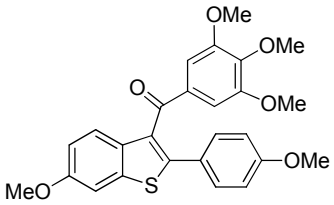
Abstract

The unique selective estrogen receptor modulator, Raloxifene (**1**), and antitubulin agent **2** were synthesized through the key intermediate, 4-methoxybenzyl 2-bromo-4-methoxyphenyl sulfoxide (**6**), respectively. It was found that compared with the o-sulfanyl aryl bromides, the sulfinyl group at *ortho* position accelerated the Sonogashira coupling reaction of aryl bromides. Thus, compound **6** was coupled with 3,4,5-trimethoxyphenyl acetylene, followed by mercury-catalyzed cyclization reaction afford compound **2** in 79% overall yield. Raloxifene (**1**) was prepared from compound **6** in four steps and 33% overall yield *via* coupling reaction with 1-trimethylsily-2-(4-*tert*-butyldimethylsiloxy)phenylethyne, mercury-catalyzed cyclization reaction, alkylation and demethylation.

Raloxifene (**1**) is a unique selective estrogen receptor modulator and is used to prevent osteoporosis and reduce the risk of invasive breast cancer in postmenopausal women.[1] Compound **2** was found to be a potent antitubulin drug.[2]Both of these compounds exhibit 3-benzoyl benzo[*b*]thiophene core structure. Therefore, the construction of 3-benzoyl benzo[*b*]thiophenes has become an important issue for new drug development. Most of the common method to construct this ring system is by way of Friedel-Crafts acylation reaction between 2-substituted benzo[*b*]thiophenes and the corresponding benzoyl chlorides.[3] Recently, we reported the cyclization reaction of 2-alkynylphenyl alkyl sulfoxides catalyzed by mercury chloride that provides a new synthetic way to construct 3-benzoyl benzo[*b*]thiophenes.[4] Herein, we wish to report our application of this methodology to synthesize raloxifene (**1**) and compound **2**. We also report the development of Sonogashira coupling reaction of various terminal alkynes with o-sulfinyl aryl bromides.



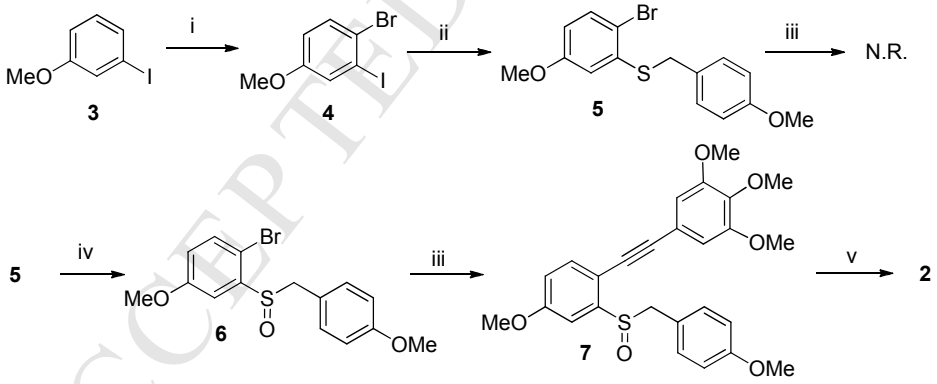
Raloxifene (1)



2

For the synthesis of compound **2**, 3-iodoanisole (**3**) was chosen as the starting material. Bromination of **3** with NBS gave compound **4** in 95% yield. Selective C-S bond formation of **4** with 4-methoxylbenzylmercaptan using copper iodide as the catalyst gave sulphide **5** in 60% yield. Attempt to do the bromo-Sonogashira coupling reaction of **5** with 3,4,5-trimethoxyphenyl acetylene under the literature's procedure[5a] failed to produce the coupling product. According to the descriptions of that paper and literature's report,[5b] the electron-rich aryl halides always undergo the coupling reaction slowly. We therefore switch our synthetic procedures, thus, sulphide **5** was oxidized first to sulfoxide **6** using *m*CPBA. The resulting sulfoxide **6** was coupled with 3,4,5-trimethoxyphenyl acetylene under the reported reaction conditions to give the desired compound **7** in 70% yield. Finally, cyclization reaction of compound **7** was carried out under our reported mercury(II)-catalyzed conditions to give compound **2** in 97% yield. (Scheme 1)

Scheme 1. Synthesis Strategy to Compound **2** [a]

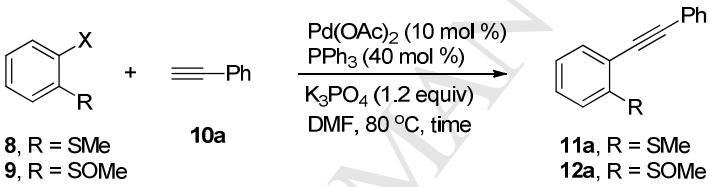


[a] (i) NBS, DMF, 80 °C, 6 h, 95%. (ii) *p*-methoxybenzyl mercaptan, CuI (15 mol %), pipecolic acid, $CsCO_3$, DMF/dioxane (1:9), 110 °C, 24 h, 60%. (iii) 3,4,5-trimethoxyphenyl acetylene, $Pd(OAc)_2$, PPh_3, K_3PO_4, DMF, 80 °C, 6 h. 70% from **6** to **7** (iv) *m*CPBA, $NaHCO_3$, CH_2Cl_2, ice bath, 2 h, 81%. (v) $HgCl_2$ (10 mol %), DDQ (1 equiv), benzene, reflux, 24 h, 97%.

Since the sulfide and sulfonyl groups have strong influences on the Sonogashira coupling reaction of aryl bromides, the substituent effects on the reactivity with different aryl halides were explored. The results were summarized in Table 1. For the aryl iodides **8a** and **9a**, both of them undergo the coupling reaction very smoothly to give the coupling products in good yields. (Table 1, entries 1 and 4)

But the sulfoxide **9a** reacts much faster than **8a** to give the product in higher yield. For the bromo cases, (Table 1, entries 2 and 5) compound **8b** undergoes the coupling reaction much slower than **9b** and the yield is also poor. Compound **9b** proceeds in reasonable rate to give the product **11** in acceptable yield. Finally, both chlorides, **8c** and **9c**, do not undergo the coupling reactions even after stirring the reaction mixtures for 24 hours under the described reaction conditions. (Table 1, entries 3 and 6) We also carried out the coupling reaction of *o*-bromoanisole and *o*-bromoacetophenone with phenylacetylene under the described reaction conditions, respectively. The reaction of *o*-bromoanisole with phenylacetylene for 24 h gave trace amount of the coupling product detected by GC-MS and recovered most the starting *o*-bromoanisole. For the reaction of *o*-bromoacetophenone with phenylacetylene, the starting materials consumed within two hours and gave a complicated product mixture and no desired coupling product was detected.

Table 1. Substituent Effects on Sonogashira Coupling Reaction.



8, R = SMe
9, R = SOMe

10a

11a, R = SMe
12a, R = SOMe

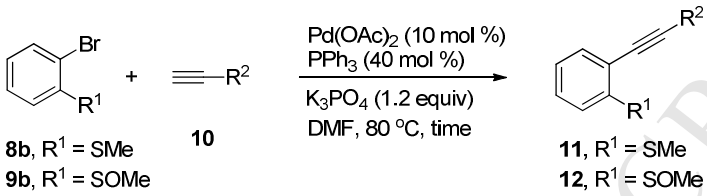
Entry	Compounds	Time (h)	Products/Yields (%)
1	**8a**, X = I	12	**11a**/87
2	**8b**, X = Br	24	**11a**/28
3	**8c**, X = Cl	24	**11a**/0 [a]
4	**9a**, X = I	2	**12a**/95
5	**9b**, X = Br	6	**12a**/74
6	**9c**, X = Cl	24	**12a**/0 [a]

[a]Starting materials **8c** and **9c** were recovered respectively.

Further exploration on the relative reactivity of the coupling reaction of aryl bromides **8b** and **9b** with various terminal alkynes were also carried out. The results were summarized in Table 2. The coupling reactions of sulfide **8b** take place very slowly to give the coupling products in low yields except when **8b** was coupled with alkyne **10d**. (Table 2, entries 1-3) The electron-poor alkynes **10e** and **10f** do not undergo coupling reaction under the described reaction conditions. (Table 2, entries

4-5) However for sulfoxide **9b**, the coupling reaction took place very smoothly with electron-rich alkynes to give the products in good yields. (Table 2, entries 6-8) Although the electron-poor *p*-nitrophenyl acetylene **10e** does not undergo coupling reaction with **9b**, the other electron-poor *p*-trifluoromethylphenyl acetylene **10f** does react with **9b** to give the coupling product **12f** albeit in low yield.

Table 2. Relative reactivity of **8b** and **9b** on Sonogashira coupling reaction.



8b, R^1 = SMe
9b, R^1 = SOMe

10

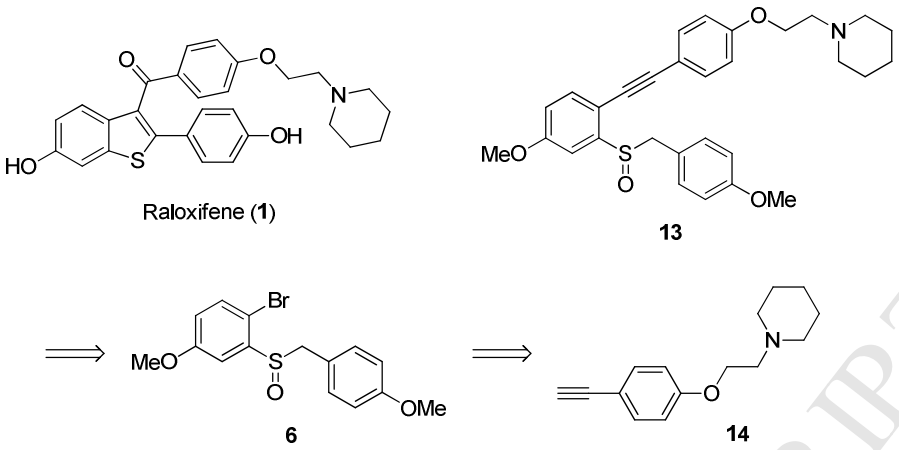
11, R^1 = SMe
12, R^1 = SOMe

Entry	Compounds	Alkynes	Time (h)	Products/Yields (%)
1	**8b**	**10b**, R^2 = 4-$MeOC_6H_4$	24	**11b**/trace
2	**8b**	**10c**, R^2 = *n*-Bu	24	**11c**/36
3	**8b**	**10d**, R^2 = *t*-Bu	24	**11d**/82
4	**8b**	**10e**, R^2 = 4-$NO_2C_6H_4$	24	**11e**/0 [a]
5	**8b**	**10f**, R^2 = 4-$CF_3C_6H_4$	24	**11f**/0 [a]
6	**9b**	**10b**, R^2 = 4-$MeOC_6H_4$	6	**12b**/78
7	**9b**	**10c**, R^2 = *n*-Bu	6	**12c**/60
8	**9b**	**10d**, R^2 = *t*-Bu	6	**12d**/83
9	**9b**	**10e**, R^2 = 4-$NO_2C_6H_4$	6	**12e**/0 [a]
10	**9b**	**10f**, R^2 = 4-$CF_3C_6H_4$	6	**12f**/37

[a]Starting materials **8b** and **9b** were recovered respectively.

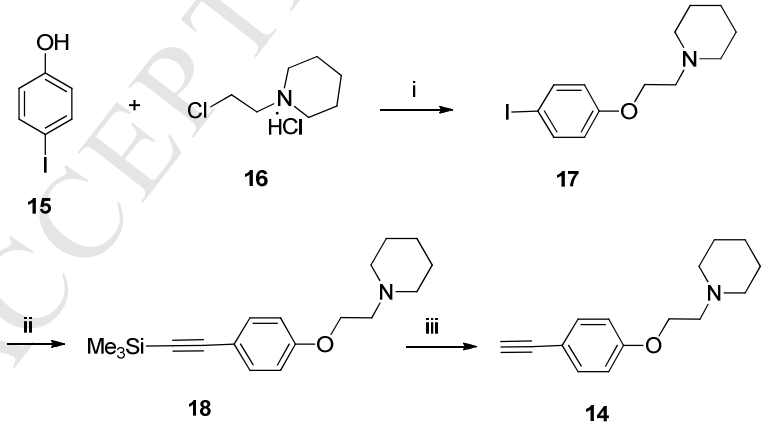
To synthesize raloxifene (**1**), we anticipated that using our reported mercury(II)-catalyzed cyclization reaction of compound **13** followed by demethylation would allow us to complete the synthesis of raloxifene (**1**). Compound **13** should be easily prepared by Sonogashira coupling reaction of the sulfoxide substituted aryl bromide **6** with acetylene **14**. (Scheme 2)

Scheme 2. Retrosynthetic analysis of raloxifene (**1**)

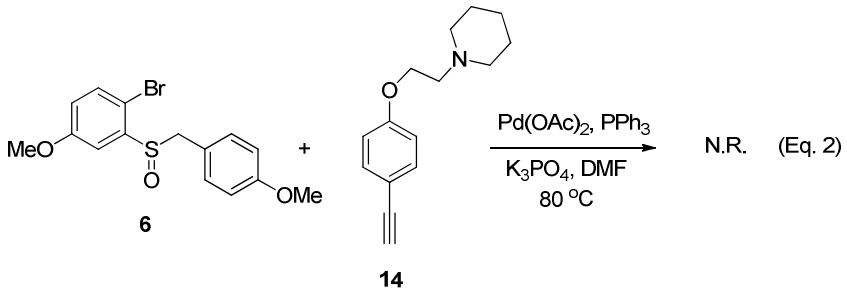


Thus, compound **9** was synthesized and the procedure is summarized in scheme 3. Alkylation of 4-iodophenol (**15**) with **16** gave phenyl ether **17** in 77% yield. Sonogashira coupling reaction[6] of **17** with trimethylsilyl acetylene afforded **18** in 60% yield. Finally, desilylation of **18** using TBAF in THF gave acetylene **14** in 92% yield. With acetylene **14** in hand, we then attempt the coupling reaction of **6** with **14** under the described reaction conditions. Surprisingly no desired product was formed and recovered most of the starting materials. (Eq. 2) The failure to produce the coupling product probably due to the coordination of amino ether functionality on the alkyne **14** with the central metal of the catalyst or reduction of palladium(II) with tertiary amine[7] to reduce the reactivity.

Scheme 3. The Synthetic strategy of acetylene**14**[a]

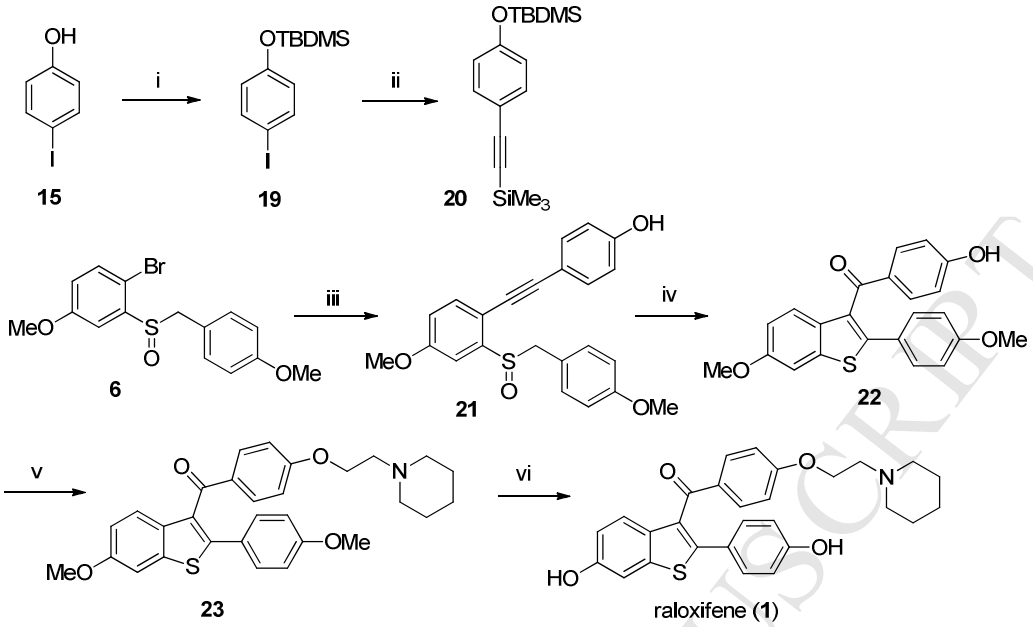


[a] (i) K_2CO_3, DMF, 110 °C, 6 h, 77%. (ii) trimethylsilyl acetylene, $Pd(PPh_3)_4$, CuI, *n*-$BuNH_2$, Et_2O, r.t., 6 h, 60%. (iii) TBAF, THF, r.t., 1 h, 92%.



In the revised synthetic pathway, we decided to do the coupling and cyclization reactions before introducing the amino ether side chain. (Scheme 4) Thus, 4-iodophenol (**15**) was converted to *tert*-butyldimetylsilyl ether **19** first. Compound **19** was then coupled with trimethylsilyl acetylene to give **20**. It was found that the acetylene **20** can be used directly without removing the trimethylsilyl group to couple with aryl bromide **6** under the described reaction conditions to give the product **21** in 70% yield. Under this reaction conditions, both silyl groups were removed spontaneous after the reaction. Cyclization of **21** was carried out using 10 mol % of mercury chloride in the presence of one equivalent of DDQ in refluxing benzene for six hours to give the product **22** in 87% yield. The amino ether side chain was then introduced at this stage.[8] Treatment of **22** with *N*-(2-chloroethyl)pipperidine hydrogen chloride salt using K_2CO_3 as the base in DMF gave the ether **23** in 90% yield. Finally, demethylation[9] was carried out using BBr_3 in CH_2Cl_2 to give the final product, raloxifene (**1**), in 60% yield. The residues of mercury in this final product is 22 ng/g detected by ICP-MS spectrometry.

Scheme 4. Total Synthesis to Raloxifene (**1**) [a]



[a] (i) TBDMSCl, imidazole, CH_2Cl_2, ice bath, 24 h, 98%. (ii) Trimethyl silyl acetylene, $Pd(PPh_3)_4$, CuI, *n*-$BuNH_2$, Et_2O, 6 h, 92%. (iii) **20**, $Pd(OAc)_2$, PPh_3, K_3PO_4, DMF, 100 ^oC, 6 h, 70%. (iv) $HgCl_2$, DDQ, benzene, reflux, 24 h, 87%. (v) *N*-(2-chloroethyl)pipperidine, K_2CO_3, DMF, 110 ^oC, 6 h, 90%. (vi) BBr_3, CH_2Cl_2, 0 ^oC, 24 h, 60%.

In conclusion, the mercury-catalyzed cyclization reaction of 2-alkynylphenyl alkyl sulfoxides became a powerful tool to construct 3-benzoyl benzo[*b*]thiophenes. Herein, we have successfully applied this methodology to synthesize the selective estrogen receptor modulator raloxifene (**1**) and antitubulin agent **2**. During this study, we also found the sulfoxide could assist the Sonogashira coupling reaction of aryl bromides. We believe that these findings will have a strong impact to synthetic organic chemistry and pharmaceutical industry.

Experimental Section

4-Bromo-3-iodoanisole (4)

To a round bottomed flask (100 mL) containing a magnetic stirrer and 3-iodoanisole (**3**) (2.0 g, 8.5 mmol) in DMF (20 mL) was added *N*-bromosuccinimide (1.54 g, 8.67 mmol). The reaction mixture was heated to 80 ^oC and stirred at this temperature for 6 hours. After cooling to room temperature, the mixture was quenched with the saturated aqueous NaCl solution (100 mL), 6N aqueous solution of HCl (10 mL), and extracted with EtOAc (50 mL × 3).The combined organic extracts were dried over anhydrous $MgSO_{4(S)}$. After filtration and removal of solvent, the residue was purified by column chromatography on silica using 20/1 (Hexane/EtOAc)

as elution to give product **4** (2.40 g, 90%) as a yellow oil. R*f* = 0.65 (20:1 Hex/EtOAc); ^{1}H NMR (500 MHz,$CDCl_3$) δ 3.75 (s, 3H), 6.74 (dd, *J* = 9.0, 3.0 Hz, 1 H), 7.36 (d, *J* = 3.0 Hz, 1H), 7.44 (d, *J* = 9.0 Hz, 1H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 55.6, 101.0, 115.9, 120.1, 125.3, 132.5, 158.6; MS (EI, *m/z*) 314 (M^++2, 100), 312 (M^+, 100), 297 (14), 269 (12), 185 (12), 170 (21), 78 (16), 63 (33); HRMS (EI-magnetic sector) *m/z*: calcd for C_7H_6BrIO 311.8647, found 311.8646.

4-Bromo-3-(4-methoxybenzylmercapto)anisole (5)

To a flame-dried two-necked flask (100 mL) containing a magnetic stirrer, CuI (0.183 g, 0.96 mmol), DL-pipecolic acid (0.124 g, 0.96 mmol) and Cs_2CO_3 (4.18 g , 12.80 mmol) in 50 mLof DMF/1,4-dioxane (1/9) was added 4-methoxylbenzyl mercaptan (1.07 mL, 7.69 mmol) and the reaction mixture was stirred at room temperature for 3 minutes. 4-Bromo-3-iodoanisole (**4**)(2.0 g, 6.41 mmol) was then added into the mixture and the resulting solution was heated to 100 ^{o}C and stirred at this temperature for 24 hours. After cooling to room temperature, the mixture was filtrated through celite and washed with EtOAc (20 mL), the organic layer was added saturated aqueous NaCl solution (100 mL) and was extracted with EtOAc (50 mL × 3). The combined organic extracts were dried over anhydrous $MgSO_{4(S)}$. After filtration and removal of solvent, the residue was purified by column chromatography on silica gel using 10/1 (Hexane/EtOAc) as elution to give compound **5** (1.60 g, 75%) as a red oil. R*f* = 0.30 (20:1 Hex/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.79 (s, 3H), 4.10 (s, 2H), 6.58 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.78 (d, *J* = 3.0 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 9.0 Hz, 2H), 7.41 (d, *J* = 9.0 Hz, 1H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 37.3, 55.2, 55.4, 112.3, 113.6, 113.9, 114.4, 127.8, 130.0, 133.2, 138.9, 158.9, 159.0; MS (EI, *m/z*) 340 (M^+, 7), 338 (6), 138 (7), 121 (100), 71 (8), 57 (8); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{15}H_{15}BrO_2S$ 339.9956, found 339.9979.

2-Bromo-5-methoxyphenyl 4-methoxybenzyl sulfoxide (6)

To a round bottomed flask (100 mL) containing a magnetic stirrer and compound **5** (1.60 g, 4.7 mmol) in dichloromethane (40 mL) was added *m*CPBA (0.817 g, 4.7 mmol) and sodium bicarbonate (0.395 g, 4.7 mmol). The reaction mixture was stirred at room temperature for 2 hours and quenched with saturated aqueous $Na_2S_2O_3$ solution (100 mL) and extracted with dichloromethane (30 mL × 3). The combined organic extracts were dried over anhydrous $MgSO_{4(S)}$. After filtration and removal of solvent, the residue was purified by column chromatography on silica gel using 1/1 (Hexane/EtOAc) as elution to give product **6** (1.35 g, 81%) as a colorless oil. R*f* = 0.65 (1:1 Hex/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.77 (s, 3H), 3.95 (d, *J* = 13.5 Hz, 1H), 4.24 (d, *J* = 13.5 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.84 (dd, *J* =

8.5, 3.0 Hz, 1H), 6.90 (d, *J* = 3.0 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 1H); $^{13}C\{H\}$ NMR (125 MHz, $CDCl_3$) δ 55.2, 55.6, 58.9, 108.5, 110.8, 113.6, 119.8, 121.1, 131.6, 133.3, 143.1, 159.6, 159.7; MS (EI, *m/z*) 235 (7), 233 (7), 121 (100), 106 (4), 91 (11), 78 (19), 77 (15); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{15}H_{15}BrO_3S$ 355.9905, found 355.9927.

1,2,3-Trimethoxy-5-((4-methoxy-2-((4-methoxybenzyl)sulfinyl)phenyl)ethynyl)benzene (7)

To a flame-dried two-necked flask (100 mL) containing a magnetic stirrer and compound **6** (1.0 g, 2.8 mmol) in DMF (20 mL) was added $Pd(OAc)_2$ (75 mg, 0.285 mmol), PPh_3 (349 mg, 1.13 mmol) and K_3PO_4 (2.0 g, 5.6 mmol) subsequently. Then, the flask was evacuated and backfilled with nitrogen and the mixture was stirred at room temperature for 3 minutes. 3,4,5-trimethoxyphenylacetylene (0.8 g, 4.2 mmol) was then added into the reaction mixture. The reaction mixture was heated to 100 ^oC and stirred at this temperature for 6 hours. After cooling to room temperature, the mixture was quenched with the saturated aqueous NaCl solution (50 ml), 6N aqueous solution of HCl (10 mL) and extracted with EtOAc (40 mL × 3).The combined organic extracts were dried over anhydrous $MgSO_{4(S)}$. After filtration and removal of solvent, the residue was purified by column chromatography on silica gel using 1/1 (Hexane/EtOAc) as elution to give product **7** (0.92 g, 70%) as a yellow solid.
mp 114-116 ^oC; R*f* = 0.40 (1:1 Hex/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 3.76 (d, *J* = 4.5 Hz, 6H), 3.89 (d, *J* = 5.5 Hz, 9H), 3.96 (d, *J* = 13.0 Hz, 1H), 4.32 (d, *J* = 13.0 Hz, 1H), 6.76 (s, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 6.95 (dd, *J* = 8.0, 2.5 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 2.5 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 1H); $^{13}C\{H\}$ NMR (125 MHz, $CDCl_3$) δ 55.3, 55.7, 56.2, 60.5, 61.0, 83.6, 96.6, 108.4, 108.6, 111.3, 113.8, 117.5, 117.9, 121.9, 131.6, 133.4, 139.3, 146.5, 153.2, 159.7, 160.5; MS (EI, *m/z*) 466 (M^+, 4), 345 (6), 257 (25), 141 (19), 121 (72), 97 (59), 85 (94), 71 (100), 57 (87); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{26}H_{26}O_6S$ 466.1450, found 466.1451.

(6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)(3,4,5-trimethoxyphenyl)methanone (2)

To a round bottomed flask (100 mL) containing a magnetic stirrer and compound **7** 0.9 g (1.93 mmol) in benzene (20 mL) was added $HgCl_2$ (52.4 mg, 0.193 mmol) and 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0. 44 g, 1.93 mmol). The reaction mixture was heated to refluxing temperature and stirred for 24 hours. After cooling to room temperature, the reaction mixture was filtrated through celite and washed with EtOAc (20 mL). The organic solvent was the removed *in vacuum* and the residue was purified by column chromatography on silica gel using 1/1

(Hexane/EtOAc) as elution to give compound **2** (0.65 g, 97%) as a yellow solid. mp 109-111 ^{o}C; R*f* = 0.75 (1:1 Hex/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (s, 6H), 3.75 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 6.75 (d, *J* = 8.5 Hz, 2H), 7.00 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.07 (s, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 2.0 Hz, 1H), 7.65 (d, *J* = 9.0 Hz, 1H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 55.3, 55.7, 56.1, 60.9, 104.5, 107.5, 114.1, 114.9, 124.3, 126.1, 129.9, 130.4, 132.3, 133.9, 140.1, 142.6, 143.8, 152.7, 157.8, 159.9, 193.0; MS (EI, *m/z*) 464 (M^+, 13), 169 (14), 141 (20), 127 (24), 99 (40), 85 (95), 71 (100), 57 (94); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{26}H_{24}O_6S$ 464.1294, found 464.1292.

1-iodo-2-(methylsulfinyl)benzene (9a)

To a flask was added 2-iodothioanisole (1.0 g, 4.0 mmol), *m*CPBA (0.99 g, 4.0 mmol) and $NaHCO_3$(0.34 g, 4.0 mmol) at 0 ^{o}C in CH_2Cl_2 (40 mL) for 2 hr. Then, 100 mL of $Na_2S_2O_{3(aq)}$ was poured into the flask and extract ed by CH_2Cl_2 (30 mL x 3). The combined organic layer was dried by $MgSO_4$ and was purified by chromatography in silica gel (*n*-hexane/EtOAc = 2/1 as eluent) to give compound **9a** (1.0 g, 95%). The status of compound **9a**: Colorless oil, R*f* = 0.33 (2:1 Hex/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.79 (s, 3H), 7.22 (td, *J* = 7.5, 1.5 Hz, 1H), 7.61 (td, *J* = 7.5, 1.0 Hz, 1H), 7.81 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.5 Hz, 1H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 42.1, 91.3, 125.7, 129.5, 132.5, 139.3, 148.2; MS (ESI, *m/z*) 289 (M^++23, 100), 267 (31); HRMS (EI-magnetic sector) *m/z*: calcd for C_7H_7INaOS 288.9155, found 288.9153.

1-bromo-2-(methylsulfinyl)benzene (9b)

To a flask was added 2-bromothioanisole (1.0 g, 5.0 mmol), *m*CPBA (1.22 g, 5.0 mmol) and $NaHCO_3$(0.42 g, 5.0 mmol) at 0 ^{o}C in CH_2Cl_2 (40 mL) for 2 hr. Then, 100 mL of $Na_2S_2O_{3(aq)}$ was poured into the flask and extract ed by CH_2Cl_2 (30 mL x 3). The combined organic layer was dried by $MgSO_4$ and was purified by chromatography in silica gel (*n*-hexane/EtOAc = 2/1 as eluent) to give compound **9b** (1.06 g, 98%). The status of compound **9b**: Colorless oil, R*f* = 0.33 (2:1 Hex/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.81 (s, 3H), 7.36 (td, *J* = 7.5, 1.5 Hz, 1H), 7.54-7.59 (m, 2H), 7.93 (dd, *J* = 8.0, 1.5 Hz, 1H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 41.8, 118.3, 125.6, 128.7, 132.2, 132.9, 145.2; MS (ESI, *m/z*) 219 (M^++1, 100), 221 (100); HRMS (EI-magnetic sector) *m/z*: calcd for C_7H_7BrOS 218.9474, found 218.9472.

1-chloro-2-(methylsulfinyl)benzene (9c)

To a flask was added 2-chlorothioanisole (1.0 g, 6.33 mmol), *m*CPBA (1.56 g, 6.33 mmol) and $NaHCO_3$(0.53 g, 6.33 mmol) at 0 ^{o}C in CH_2Cl_2 (40 mL) for 2 hr. Then, 100 mL of $Na_2S_2O_{3(aq)}$ was poured into the flask and extract ed by CH_2Cl_2 (30 mL x 3).

The combined organic layer was dried by $MgSO_4$ and was purified by chromatography in silica gel (*n*-hexane/EtOAc = 2/1 as eluent) to give compound **9c** (1.06 g, 96%). The status of compound **9c**: Colorless oil, R*f* = 0.33 (2:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 (s, 3H), 7.39-7.48 (m, 2H), 7.54 (td, *J* = 7.6, 1.2 Hz, 1H), 7.96 (td, *J* = 8.0, 1.6 Hz, 1H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 41.6, 125.2, 128.1, 129.7, 131.9, 143.5; MS (ESI, *m/z*) 199 (M^++25, 38), 197 (M^++23, 100), 177 (7), 175 (21); HRMS (EI-magnetic sector) *m/z*: calcd for C_7H_7ClOS 196.9798, found 196.9796.

General Procedure for the Testing of Bromo-Sonogashira Coupling Reaction:

To a flame-dried two-necked flask (25 mL) containing a magnetic stirrer and aryl bromide(0.5 mmol) in DMF (5 mL) was added $Pd(OAc)_2$ (11 mg, 0.05 mmol), PPh_3 (52 mg, 0.2 mmol) and K_3PO_4 (0.13 g, 0.6 mmol) subsequently. Then, the flask was evacuated and backfilled with nitrogen and the mixture was stirred at room temperature for 3 minutes. Acetylene (0.74 mmol) was then added into the reaction mixture. The reaction mixture was heated to 80 ^{o}C and stirred at this temperature for 6 hours. After cooling to room temperature, the mixture was quenched with the saturated aqueous NaCl solution (10 mL), 6N aqueous solution of HCl (5 mL) and extracted with EtOAc (10 mL × 3).The combined organic extracts were dried over anhydrous $MgSO_{4(S)}$. After filtration and removal of solvent, the residue was purified by column chromatography on silica gel using 1/1 (Hexane/EtOAc) as elution to give the product.

2-(2-phenylethynyl)thioanisole (11a)

Compound **11a** was obtained in 28% yield (31 mg) as yellow oil by the reaction of phenylacetylene (76 mg, 0.74 mmol) and 2-bromoanisole (0.1 g, 0.5 mmol). R*f* = 0.44 (Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.53 (s, 3H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.30-7.37 (m, 4H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.60 (dd, *J* = 7.5, 1.5 Hz, 2H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 15.1, 86.8, 95.8, 121.3, 123.1, 124.1, 124.2, 128.3, 128.4, 128.7, 131.6, 132.2, 141.7; MS (EI, *m/z*) 224 (M^+, 14), 58 (55), 57 (100); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{15}H_{12}S$ 224.0660, found 224.0658.

2-(Hexyn-1-yl)thioanisole (11c)

Compound **11c** was obtained in 36% yield (37 mg) as yellow oil by the reaction of 2-bromothioanisole (0.1 g, 0.50 mmol) and 1-hexyne (61 mg, 0.74 mmol). R*f* = 0.48 (Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.5 Hz, 3H), 1.51-1.57 (m, 2H), 1.61-1.67 (m, 2H), 2.48 (s, 3H), 2.50 (t, *J* = 7.0 Hz, 2H), 7.05 (td, *J* = 7.5, 1.0 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.25 (td, *J* = 8.0, 1.0 Hz, 1H), 7.35 (dd, *J* = 7.5, 1.0 Hz, 1H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 13.6, 14.9, 19.3, 22.0, 30.8, 78.0, 97.4, 122.1, 123.8,

124.1, 128.0, 132.2, 141.1; MS (EI, *m/z*) 189 (M^+-15, 38), 162 (21), 147 (100); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{13}H_{16}S$ 205.1051, found 205.1044.

2-(3,3-Dimethylbutyn-1-yl)thioanisole (11d)

Compound **11d** was obtained in 82% yield (84 mg) as yellow oil by the reaction of 2-bromothioanisole (0.1 g, 0.50 mmol) and 3,3-dimethylbut-1-yne (61 mg, 0.74 mmol). R*f* = 0.44 (Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 9H), 2.46 (s, 3H), 7.04 (td, *J* = 7.5, 1.0 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.23 (td, *J* = 7.8, 1.3 Hz, 1H), 7.33 (dd, *J* = 7.5, 1.0 Hz, 1H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 14.9, 28.3, 31.0, 76.6, 105.5, 121.9, 123.6, 124.0, 127.9, 132.0, 141.3; MS (EI, *m/z*) 204 (M^+, 100), 189 (50), 174 (31), 147 (36); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{13}H_{16}S$ 204.0971, found 204.097

2-(2-phenylethynyl)phenyl methyl sulfoxide (12a)

Compound **12a** was obtained in 74% yield (82 mg) as yellow oil by the reaction of 2-bromophenyl methyl sulfoxide (100.0 mg, 0.46 mmol) and phenylacetylene (70 mg, 0.69 mmol). R*f* = 0.33 (2:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (s, 3H), 7.38-7.42 (m, 3H), 7.46-7.62 (m, 5H), 8.00 (dd, *J* = 8.0, 1.2 Hz, 1H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 29.7, 42.1, 84.2, 98.0, 119.3, 122.0, 123.3, 128.6, 129.2, 129.5, 130.4, 131.5, 132.4, 147.2; MS (ESI, *m/z*) 241 (M^++1, 100), 194 (7); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{15}H_{13}OS$ 241.0682, found 241.0680.

2-(2-(4-(Methoxyphenyl)ethynyl)phenyl methyl sulfoxide (12b)

Compound **12b** was obtained in 78% yield (97 mg) as yellow oil by the reaction of 2-bromophenyl methyl sulfoxide (100 mg, 0.46 mmol) and 4-methoxyphenylacetylene (91 mg, 0.69 mmol). R*f* = 0.29 (1:1 Hex/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.88 (s, 3H), 3.85 (s, 3H), 6.91 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 9.0 Hz, 3H), 7.56 (q, *J* = 7.5 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 1H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 42.0, 55.4, 83.1, 98.3, 114.0, 114.2, 119.7, 123.3, 129.2, 130.3, 132.2, 133.0, 146.9, 160.4; MS (EI, *m/z*) 255 (M^+-15, 100), 227 (84), 184 (53), 152 (23); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{16}H_{14}O_2S$ 270.0715, found 270.0714.

2-(Hexyn-1-yl)phenyl methyl sulfoxide (12c)

Compound **12c** was obtained in 60% yield (61 mg) as yellow oil by the reaction of 2-bromophenyl methyl sulfoxide (100 mg, 0.46 mmol) and 1-hexyne (57 mg, 0.69 mmol). R*f* = 0.49 (2:1 Hex/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.0 Hz, 3H), 1.45-1.53 (m, 2H), 1.58-1.64 (m, 2H), 2.47 (t, *J* = 7.0 Hz, 2H), 2.82 (s, 3H), 7.36-7.43 (m, 2H), 7.52 (td, *J* = 8.0, 2.0 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 1H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 13.5, 19.2, 22.0, 30.4, 41.9, 75.9, 99.9, 120.1, 123.1, 128.8, 130.2, 132.5,

146.9; MS (ESI, *m/z*) 243 (M^++23, 100), 221 (M^++1, 36); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{13}H_{16}NaOS$ 243.0814, found 243.0812.

2-(3,3-Dimethylbutyn-1-yl)phenyl methyl sulfoxide (12d)

Compound **12d** was obtained in 83% yield (84 mg) as yellow oil by the reaction of 2-bromophenyl methyl sulfoxide (100 mg, 0.46 mmol) and 3,3-dimethylbut-1-yne (57 mg, 0.69 mmol). R*f* = 0.58 (1:1 Hex/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 9H), 2.82 (s, 3H), 7.38-7.41 (m, 2H), 7.48-7.54 (m, 1H), 7.90 (d, *J* = 8.0 Hz, 1H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 28.3, 30.6, 41.7, 74.6, 107.8, 120.0, 123.0, 128.7, 130.1, 132.1, 146.9; MS (EI, *m/z*) 220 (M^+, 26), 205 (28), 164 (91), 135 (100); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{13}H_{16}OS$ 220.0922, found 220.0922.

2-(2-(4-(Trifluoromethylphenyl)ethynyl)phenyl methyl sulfoxide (12f)

Compound **12f** was obtained in 37% yield (52 mg) as yellow oil by the reaction of 2-bromophenyl methyl sulfoxide (100.0 mg, 0.46 mmol) and 4-(trifluoromethyl)phenylacetylene (0.12 g, 0.69 mmol). R*f* = 0.33 (2:1 Hex/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.88 (s, 3H), 7.51 (td, *J* = 7.5, 1.0 Hz, 1H), 7.59-7.67 (m, 6H), 8.02 (dd, *J* = 8.0, 0.5 Hz, 1H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 29.7, 42.2, 86.3, 96.1, 118.6, 123.5, 125.4, 125.5, 125.5, 125.6, 130.2, 130.5, 131.8, 132.6; MS (ESI, *m/z*) 331 (M^++23, 100), 309 (M^++1, 68); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{16}H_{11}F_3NaOS$ 331.0375, found 331.0373.

1-(2-(4-Iodophenoxy)ethyl)piperidine (17)

To a round bottomed flask (250 mL) containing a magnetic stirrer and 4-iodophenol (2.0 g, 9.1 mmol) in DMF (100 mL) was added 1-(2-chloroethyl)piperidine hydrochloride (2.01 g, 10.9 mmol) and potassium carbonate (3.01 g, 21.8 mmol). The reaction mixture was heated to 110 ^{o}C and stirred at this temperature for 6 hours. After cooling to room temperature, the mixture was quenched with the saturated aqueous NH_4Cl solution (100 mL) and extracted with EtOAc (100 mL × 3). The combined organic extracts were dried over anhydrous $MgSO_{4(S)}$. After filtration and removal of solvent, the residue was purified by column chromatography on silica gel using 10/1 (dichloromethane/methanol) as elution to give compound **17** (2.32 g, 77%) as a yellow oil. R*f* = 0.50 (10:1 Dichloromethane/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 2H), 1.53-1.57 (m, 4H), 2.44 (s, 4H), 2.69 (t, *J* = 6.0 Hz, 2H), 4.00 (t, *J* = 6.0 Hz, 2H), 6.62 (d, *J* = 9.0 Hz, 2H), 7.48 (d, *J* = 9.0 Hz, 2H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 24.1, 25.8, 55.0, 57.7, 66.0, 82.7, 116.9, 138.1, 158.6; MS (EI, *m/z*) 331 (M^+, 4), 203 (10), 99 (71), 98 (100), 76 (15), 55 (13); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{13}H_{18}INO$ 331.0433, found

331.0433.

1-(2-(4-(2-Trimethylsilylethynyl)phenoxy)ethyl)piperidine (18)

To a flame-dried two-necked flask (100 mL) containing a magnetic stirrer and compound **17** (1.0 g, 3.02 mmol) in ethyl ether (30 mL) was added $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol). After stirring for 3 minutes, CuI (0.03 g, 0.15 mmol), trimethylsilylacetylene (0.44 g, 4.53 mmol) and *n*-butylamine (0.89 ml, 9.06 mmol) were added into the flask. The reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (50 mL) and extracted with EtOAc (30 mL × 3).The combined organic extracts were dried over anhydrous $MgSO_{4(S)}$. After filtration and removal of solvent, the residue was purified by column chromatography on silica using 10/1 (Hexane/EtOAc) as eluent to give compound **18** (0.55 g, 60%) as a yellow oil. R*f* = 0.45 (10:1 Dichloromethane/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.23 (s, 9H), 1.49 (s, 2H), 1.71 (t, *J* = 5.5 Hz, 4H), 2.67 (s, 4H), 2.91 (t, *J* = 5.5 Hz, 2H), 4.20 (t, *J* = 5.5 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 7.39 (d, *J* = 9.0 Hz, 2H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 0.03, 14.1, 22.7, 23.6, 25.1, 29.3, 29.6, 31.9, 54.7, 57.4, 65.2, 92.6, 105.0, 114.4, 115.6, 133.5, 158.5; MS (ESI, *m/z*) 302 (M^++1, 100); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{18}H_{27}NOSi$ 302.1935, found 302.1935.

1-(2-(4-Ethynylphenoxy)ethyl)piperidine (14)

To a round-button flask containing **18** (0.30 g, 0.99 mmol) in THF (10 mL) was added TBAF (0.39 g, 1.49 mmol) slowly at 0 ^{o}C. The reaction mixture was allowed to warm to room temperature and stirred for another one hour. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic extracts were dried over anhydrous $MgSO_4$. After filtration and removal of solvent, the residue was purified by column chromatography on silica gel using hexanes as eluent to give **14** (0.21 g, 92%) as yellow oil. R*f* = 0.43 (10:1 Dichloromethane/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 2H), 1.64 (t, *J* = 5.5 Hz, 4H), 2.55 (s, 4H), 2.81 (t, *J* = 6.0 Hz, 2H), 2.99 (s, 1H), 4.14 (t, *J* = 6.0 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 7.41 (d, *J* = 9.0 Hz, 2H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 23.9, 25.7, 29.7, 54.9, 57.7, 65.8, 75.8, 83.6, 114.2, 114.5, 133.6, 159.1; MS (ESI, *m/z*) 230 (M^++1, 100); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{15}H_{19}NO$ 230.1539, found 230.1539.

4-Iodophenyl *tert*-butyldimethylsilyl ether (19)

To a flame-dried two-necked flask (100 mL) containing a magnetic stirrer and compound **15** (2.0 g, 9.0 mmol) in dichloromethane (50 mL) was cooled to 0 ^{o}C and

added *tert*-butyldimethylsilyl chloride (60 g, 10.0 mmol) followed by imidazole (0.68 g, 10.0 mmol). The reaction mixture was stirred for 30 minutes at this temperature then warmed to room temperature and stirred for another 24 hours. During which time a white solid precipitated and that was removed by filtration. The filtrate was concentrated under vacuum and the residue was purified by column chromatography on silica using Hexane as eluent to give compound **19** (2.90 g, 98%) as a colorless oil. R*f* = 0.65 (Hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.21 (s, 6H), 0.99 (s, 9H), 6.63 (d, *J* = 9.0 Hz, 2H), 7.52 (d, *J* = 9.0 Hz, 2H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ -4.5, 18.2, 25.6, 83.7, 122.5, 138.3, 155.6; MS (EI, *m/z*) 334 (M^+, 34), 277 (100), 150 (68), 279 (6), 135 (27); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{12}H_{19}IOSi$ 334.0250, found 334.0252.

4-*tert*-Butyldimethylsiloxyphenyl trimethylsily acetylene (20)

To a flame-dried two-necked flask (100 mL) containing a magnetic stirrer and compound **19** (2.0 g, 6.0 mmol) in ethyl ether (50 mL) was added $Pd(PPh_3)_4$ (0.35 g, 0.3 mmol). After stirring for 3 minutes, CuI (0.11 g, 0.6 mmol), trimethylsilylacetylene (1.28 mL, 9.0 mmol) and *n*-butylamine (2.0 mL, 18.0 mmol) were added into the flask. The reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (100 mL) and extracted with EtOAc (50 mL × 3).The combined organic extracts were dried over anhydrous $MgSO_{4(S)}$. After filtration and removal of solvent, the residue was purified by column chromatography on silica using 10/1 (Hexane/EtOAc) as eluent to give compound **20** (1.67 g, 92%) as a yellow oil. R*f* = 0.50 (Hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.19 (s, 6H), 0.25 (s, 9H), 0.98 (s, 9H), 6.76 (d, *J* = 9.0 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 2H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ -4.5, 0.1, 18.2, 25.6, 92.6, 105.2, 115.9, 120.1, 133.4, 156.1; MS (EI, *m/z*) 304 (M^+, 27), 247 (100), 116 (13), 73 (34); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{17}H_{28}OSi_2$ 304.1679, found 304.1679.

2-(2-(4-Hydroxyphenyl)ethynyl)-5-methoxyphenyl 4-methoxybenzyl sulfoxide (21)

To a flame-dried two-necked flask (100 mL) containing a magnetic stirrer and compound **6** (1.0 g, 2.8 mmol) in DMF (20 mL) was added $Pd(OAc)_2$ (75 mg, 0.285 mmol), PPh_3 (349 mg, 1.13 mmol) and K_3PO_4 (2.0 g, 5.6 mmol) subsequently. Then, the flask was evacuated and backfilled with nitrogen and the mixture was stirred at room temperature for 3 minutes. Compound **20** (1.5 g, 4.2 mmol) was then added into the reaction mixture. The reaction mixture was heated to 100 ^{o}C and stirred at this temperature for 6 hours. After cooling to room temperature, the mixture was quenched with the saturated aqueous NaCl solution (50 mL), 6N aqueous solution of HCl (10 mL) and extracted with EtOAc (40 mL × 3). The combined organic extracts

were dried over anhydrous $MgSO_{4(S)}$. After filtration and removal of solvent, the residue was purified by column chromatography on silica gel using 1/1 (Hexane/EtOAc) as eluent to give product 21**7** (0.78 g, 70%) as a yellow solid. mp 159-161 ^{o}C; R*f* = 0.40 (1:1 Hex/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (d, *J* = 4.0 Hz, 6H), 4.00 (d, *J* = 13.0 Hz, 1H), 4.33 (d, *J* = 13.0 Hz, 1H), 6.10 (s, 1H), 6.75 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.94 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 2.5 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 1H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 55.3, 55.7, 60.0, 83.0, 96.8, 108.5, 111.9, 113.8, 114.3, 115.8, 117.9, 121.6, 131.7, 133.1, 133.3, 145.6, 156.7, 159.7, 160.2; MS (EI, *m/z*) 394 (M^{+}+2, 1), 257 (11), 111(21), 97 (38), 85 (64), 57 (100); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{23}H_{20}O_4S$ 392.1082, found 392.1082.

2-(4-Methoxyphenyl)-3-(4-hydroxybenzoyl)-6-methoxythiophene (22)

To a round bottomed flask (100 mL) containing a magnetic stirrer and compound **21** (0.78 g, 2.0 mmol) in benzene (20 mL) was added $HgCl_2$ (54 mg, 0.198 mmol) and 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.45 g, 2.0 mmol). The reaction mixture was heated to refluxing temperature and stirrer for 24 hours. After cooling to room temperature, the reaction mixture was filtrated through celite and washed with EtOAc (30 mL). The organic solvent was the removed *in vacuum* and the residue was purified by column chromatography on silica gel using 1/1 (Hexane/EtOAc) as eluent to give product **22** (0.65 g, 84%) as a yellow oil. R*f* = 0.55 (1:1 Hex/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.88 (s, 3H), 6.41 (brs, OH), 6.67 (d, *J* = 9.0, 2.0 Hz, 1H), 7.32 (s, 1H), 7.33 (d, *J* = 8.5 Hz, 2 H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 2H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 55.2, 55.6, 104.5, 114.1, 114.8, 115.3, 124.0, 125.9, 130.2, 130.3, 130.4, 132.7, 133.9, 140.0, 142.9, 157.6, 159.7, 160.7, 193.6; MS (EI, *m/z*) 390 (M^{+}, 12), 85 (69), 71 (98), 57 (100); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{23}H_{18}O_4S$ 390.0926, found 390.0925.

2-(4-Methoxyphenyl)-3-(4-(2-pipperidinylethoxy)benzoyl)-6-methoxythiophene (23)

To a round bottomed flask (100 mL) containing a magnetic stirrer and compound **22** (0.65 g, 1.7 mmol) in DMF (20 mL) was added 1-(2-chloroethyl)piperidine hydrogen chloride salt (0.37 g , 2.0 mmol) and potassium carbonate (0.55 g, 4.0 mmol). The reaction mixture was heated to 110 ^{o}C and stirred at this temperature for 6 hours. After cooling to room temperature, the mixture was quenched with the saturated aqueous NH_4Cl solution (100 mL) and extracted with EtOAc (30 mL × 3). The combined organic extracts were dried over anhydrous $MgSO_{4(S)}$. After filtration and removal of solvent, the residue was purified by column

chromatography on silica gel using 10/1 (dichloromethane/methanol) as eluent to give compound **23** (0.69 g, 83%) as a yellow oil. R*f* = 0.45 (10:1 Dichloromethane/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (d, *J* = 5.5 Hz, 2H), 1.57-1.62 (m, 4H), 2.48 (s, 4H), 2.74 (t, *J* = 6.0 Hz, 2H), 3.75 (s, 3H), 3.88 (s, 3H), 4.09 (t, *J* = 6.0 Hz, 2H), 6.76 (dd, *J* = 9.0, 3.0 Hz, 4H), 6.95 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 7.34 (d, *J* = 9.0 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 9.0 Hz, 2H); ^{13}C{H} NMR (125 MHz, $CDCl_3$) δ 24.1, 25.8, 55.0, 55.2, 55.6, 57.6, 66.1, 104.5, 114.0, 114.2, 114.7, 124.0, 125.9, 130.2, 130.4, 130.5, 132.3, 133.9, 140.0, 142.4, 157.6, 159.7, 162.9, 193.2; MS (EI, *m/z*) 501 (M^+, 5), 98 (100), 71 (89), 57 (86); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{30}H_{31}NO_4S$ 501.1974, found 501.1976.

Raloxifene (1)

To a flame-dried two-necked flask (100 mL) containing a magnetic stirrer and compound **23** (0.69 g, 1.4 mmol) in dried dichloromethane (40 mL) was added BBr_3 (12 mL, 12 mmol, 1 M solution in dichloromethane) slowly at 0 ^{o}C. After stirring at 0 ^{0}C for 30 minutes, the reaction mixture was allowed to warm to room temperature and stirred for another 24 hours. The saturated aqueous $NaHCO_3$solution was added slowly into the reaction mixture and the pH value of the solution was controlled at 7.0. After stirring for 30 minutes, the reaction mixture was added saturated aqueous NaCl solution (100 mL) and extracted with EtOAc (40 mL × 3). The combined organic extracts were dried over anhydrous $MgSO_{4(S)}$. After filtration and removal of solvent, the residue was purified by column chromatography on silica gel using 10/1 (dichloromethane/methanol) as eluent to give raloxifene **1** (0.39 g, 60 %) as a yellow solid. mp 120-125 ^{o}C; R*f* = 0.23 (10:1 Dichloromethane/MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.33 (d, *J* = 5.0 Hz, 2H), 1.45 (t, *J* = 6.0 Hz, 4H), 2.40 (s, 4 H), 2.62 (t, *J* = 5.5 Hz, 2H), 4.06 (t, *J* = 5.5 Hz, 2H), 6.68 (d, *J* = 8.5 Hz, 2H), 6.86 (dd, *J* = 9.0, 2.0 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 2H), 7.18 (d, *J* = 9.0 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 1H), 7.35 (d, *J* = 2.0 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 9.82 (br, 2OH); ^{13}C{H} NMR (125 MHz, DMSO-d_6) δ 23.8, 25.4, 54.3, 57.0, 65.8, 107.2, 114.5, 115.2, 115.7, 123.4, 123.8, 129.73, 129.75, 131.8, 132.3, 139.3, 140.4, 155.5, 157.9, 162.8, 192.6; MS (EI, *m/z*) 475 (M^++2, 31), 474 (M^++1, 100); HRMS (EI-magnetic sector) *m/z*: calcd for $C_{28}H_{27}NO_4S$ 474.1734, found 474.1731.

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References:

(1) (a) Maximov, P. Y.; Lee, T. M.; Jordan, V. C. *Curr. Clin. Pharmacol.* **2013**, *8*, 135. (b) Muchmore, D. B. *The Oncologist* **2000**, *5*, 388.

(2) (a) Pinney, K. G.; Bounds, A. D.; Dingeman, K. M.; Mocharla, V. P.; Pettit, G. R.; Bai, R.; Hamel, E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1081. (b) Palkowitz, A. D.;Glasebrook, A. L.; Thrascher, K. J.; Hauser, K. L.;S hort, L. L.; Phillip, D. L.; Muehl, B. S.; Sato, M.; Shetler, P. K.; Cullinan, G. J.; Pell, T. R.; Bryant, H. U. *J. Med. Chem.* **1997**, *40*, 1407.

(3) (a) Jones, C. D.; Jevnikar, M. G.; Pike, A. J.; Peters, M. K.; Black, L. J.; Thompson, A. R.; Falcone, J. F.; Clemens, J. A. *J. Med. Chem.*, **1984**, *27*, 1057. (b) Grese, T. A.; Cho, S.; Finley, D. R.; Godfrey, A. G.; Jones, C. D.; Lugar III, C. W.; Martin, M. J.; Matsumoto, K.; Pennington, L. D.; Winter, M. A.; Adrian, M. D.; Cole, H. W.; Magee, D. E.; Phillips, D. L.; Rowley, E. R.; Short, L. L.; Glasebrook, A. L.; Bryant, H. U. *J. Med. Chem.*, **1997**, *40*, 146. (c) Flynn, B. L.; Pascal, V. P.; Hamel, E. *Org. Lett.*, **2001**, *3*, 651.

(4) Lin, C. H.; Chen, C. C.; Wu, M. J. *Chem. Eur. J.*, **2013**, *19*, 2578.

(5) (a) Shirakawa, E.; Kitabata, T.; Otsuka, H.; Tsuchimoto, T. *Tetrahedron*, **2005**, *61*, 9878. (b) Schilz, M.; Plenio, H. *J. Org. Chem*. **2012**, *77*, 2798.

(6) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.*, **1975**, *16*, 4467.

(7) Murahashi, S.-I.; Hirano, T.; Yano, T. *J. Am. Chem. Soc.*, **1978**, *100*, 348.

(8) Wang, H; Wei, L.; Yan, H.; Gao, X.; Xu,B.; Tang, N. *Chem. Pharm. Bull.* **2013**, *61*, 599.

(9) Dadiboyena, S. *Eur. J. Med. Chem.* **2012**, *51*, 17