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Late-Stage C–H Bond Arylation of Spirocyclic σ_1 Ligands for Analysis of Complementary σ_1 Receptor Surface

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Direct C–H bond arylation in the α- and β-positions of spirocyclic thiophenes containing various functional groups (amine, ether, acetal, lactone) was accomplished. Selective phenylation in the α-position of the thiophene ring was achieved by using the catalytic system $PdCl_2$/bipy/Ag_2CO_3. The introduction of phenyl moieties to the β-position was performed with the catalytic system $PdCl_2$/P[OCH(CF$_3$)$_2$]$_3$/Ag_2CO_3. Even the five-membered lactone **10** with an electron-withdrawing carbonyl moiety directly attached to the thiophene ring was arylated. Spirocyclic thiophenes substituted with a phenyl moiety in position **A** (top position) or **B** (left position) display low nanomolar σ_1 affinities (e.g., **4a**: K_i = 1.6 nM; **5a**: K_i = 2.4 nM), indicating an additional hydrophobic pocket on the complementary σ_1 receptor protein. A phenyl moiety in position **C** (at the bottom position) is not tolerated by the σ_1 receptor (e.g., **12**: K_i = 483 nM). However, an additional phenyl moiety in position **A** is able to compensate at least partially the unfavorable effects of the phenyl moiety in position **C**.

1. Introduction

The class of σ receptors consists of at least two subtypes termed σ_1 and σ_2 receptors.[1] Whereas the σ_1 receptor has been cloned from various tissues and species including human brain, the σ_2 subtype has not been characterized at the molecular level so far.[2] It has been shown that various ion channels (e.g., K^+ and Ca^{2+} channels) and neurotransmitter systems (e.g., glutamatergic, dopaminergic, and cholinergic neurotransmission) are modulated by σ_1 receptors. Therefore, ligands interacting with σ_1 receptors are of great interest for the treatment of acute and chronic neurological disorders (e.g., schizophrenia, depression, Alzheimer's disease, and neuropathic pain).[3]

As reported recently, the spirocyclic thiophene derivatives **2a**, **2b**,[4] and **3b**[5] possess very high affinity toward σ_1 receptors. According to relevant pharmacophore models[6] the lipophilic region of the thiophene moiety should be enlarged to achieve even higher σ_1 affinity. Moreover, potent conformationally restricted compounds with extended lipophilic regions will provide deeper insights into the elusive complementary surface of the σ_1 receptor protein (Figure 1). In this respect, the influence of the position of an additional phenyl moiety and the sulfur atom on the σ_1 receptor affinity are of particular interest. Therefore, it was planned to attach a lipophilic phenyl moiety at various positions **A** (top position), **B** (left position), and **C** (bottom position) of regioisomeric spirocyclic thiophene derivatives.

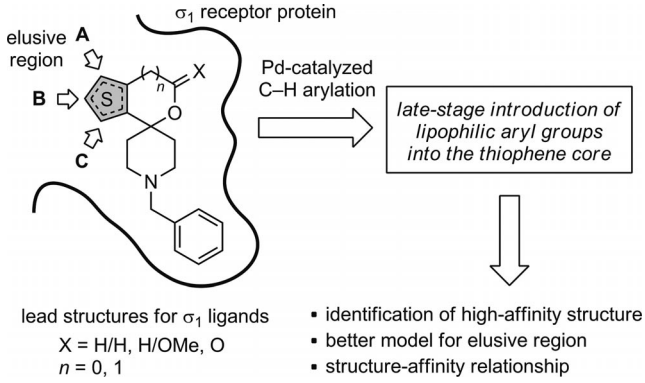

Figure 1. Direct C–H bond arylation of spirocyclic thiophenes.

The phenyl group should be introduced at a very late stage of the synthesis so as to provide access to diverse sets of arylated thiophenes. For this purpose, direct C–H bond functionalization of regioisomeric thiophene cores was envisaged. Enormous efforts have provided useful catalytic systems for reactions that assemble arenes through C–H

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bond functionalization. The first Pd-catalyzed direct C–H bond arylation was reported by Ohta et al. in 1990.[7] Subsequently, various catalysts (Pd,[8] Rh,[9] Ir,[10] Cu[11]) promoting the C–H bond arylation of thiophenes with haloarenes have been developed. Typically these arylation reactions occur regioselectively in the α-position of thiophenes. Nevertheless, some unique catalysts leading to selective β-arylation of thiophene have been established.[12] However, most of the developed catalysts were only applied on simple thiophenes without further functional groups.

Herein, we report the regioselective α-arylation of complex spirocyclic thiophene derivatives with additional functional groups including amine, ether, acetal, and lactone with the catalytic system $PdCl_2$/2,2′-bipyridyl/Ag_2CO_3.[13] Moreover, the same complex thiophenes were subjected to β-arylation by using the catalytic system $PdCl_2$/$P[OCH[CF_3]_2]_3$/Ag_2CO_3.[12a,12b] The effect of the additional phenyl moiety and the position of the sulfur atom on σ_1 receptor binding was studied with radioligand receptor binding studies.

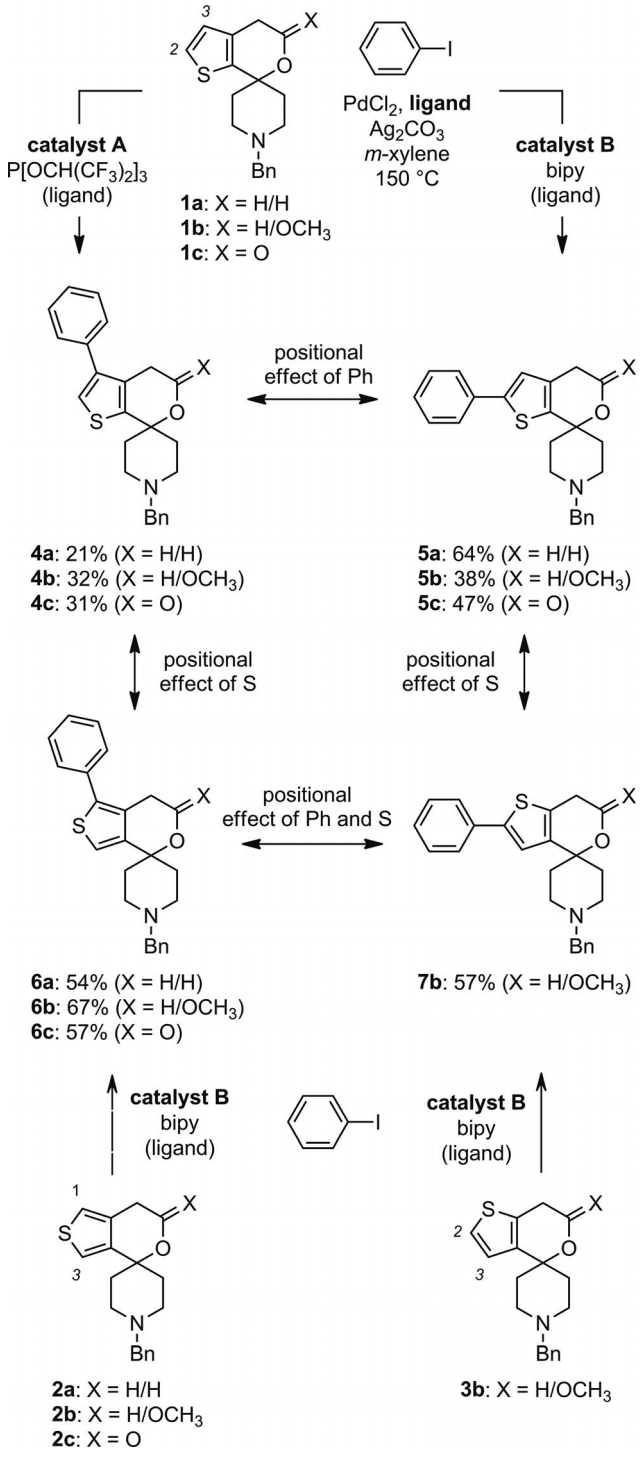
2. Chemistry

spirocyclic thiophenes **1** were first treated with iodobenzene, $PdCl_2$/bipy and Ag_2CO_3 (catalyst **B**)[13] in boiling *m*-xylene (150 °C) to provide the α-phenylated products **5** in 38–64% yields (Scheme 1). Clearly, the functional groups ether, acetal, lactone, and tertiary amine were compatible with the catalyst system and the reaction conditions.

Because the pharmacological properties of the positional isomers **4** were also of great interest, compounds **1** were treated with iodobenzene and $PdCl_2$/$P[OCH[CF_3]_2]_3$/Ag_2CO_3 (catalyst **A**).[12a,12b] These reaction conditions led predominantly to the β-arylated thiophenes **4** and additionally to small amounts of the regioisomeric α-arylated products **5**. Due to similar properties of the regioisomeric thiophenes **4** and **5**, the final purification of **4** for the pharmacological evaluation reduced the yields considerably. However, it should be noted that even the lactones **4c** (31%) and **5c** (47%) were formed in the presence of basic Ag_2CO_3.

To synthesize regioisomers with respect to the sulfur-atom in the spirocyclic system, the regioisomeric spirocyclic thiophenes **2**[4] and **3**[5] were phenylated. The α-phenylation of **2a** and **2b** using catalyst **B** has already been reported to produce **6a** and **6b**.[4] The same reaction conditions were used for the phenylation of lactone **2c** and the regioisomeric thiophene **3b** to provide the phenylated products **6c** and **7b** in 57% yields, respectively, showing the stability of the present functional groups (lactone, acetal) under the given conditions.

Because α-arylation of six-membered lactones **1c** and **2c** took place with high regioselectivity, α-arylation of the corresponding five-membered lactone **10** was envisaged (Scheme 2). Lactone **10** was prepared in a one-pot, three step reaction sequence, which involved two sequential bromine/lithium exchange reactions followed by trapping of the corresponding aryllithium intermediates with 1-benzyl-piperidin-4-one and CO_2, respectively, and a final cyclization with acetic anhydride. A similar synthesis of an *N*-methylated derivative has already been reported in the literature.[14]



Scheme 1. Synthesis of a series of isomers by catalyst-controlled regioselective C–H bond arylation; catalyst **A**: $PdCl_2$/$P[OCH(CF_3)_2]_3$/Ag_2CO_3; catalyst **B**: $PdCl_2$/bipy/Ag_2CO_3; bipy = 2,2′-bipyridyl; yields after gel permeation chromatography.

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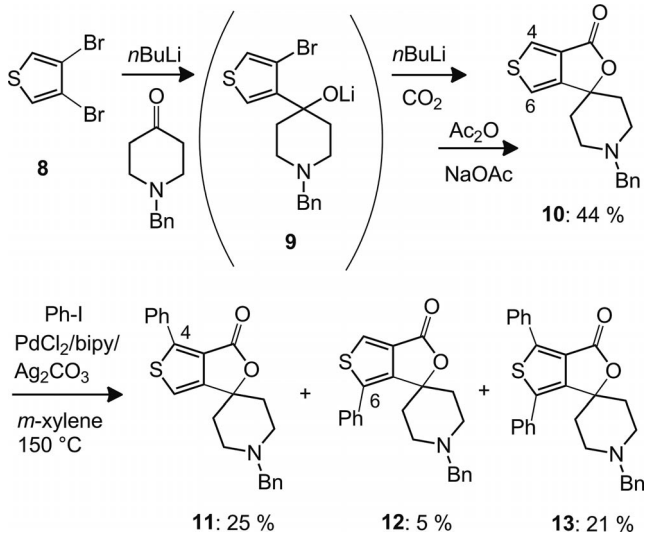

Scheme 2. Synthesis and phenylation of lactone **10**.

Reaction of lactone **10** with iodobenzene and catalyst **B** led to a mixture of three arylated products **11**, **12**, and **13**. Unexpectedly, phenylation of the otherwise unreactive 6-position (compounds **1**–**3**) had taken place. The attack of the 6-position is explained by electronic and steric reasons. In particular, the electron density in the 4-position of the thiophene ring is reduced by the carbonyl moiety directly attached to the thiophene ring. Additionally, the five-membered lactone leads to an expanded angle of the spirocyclic system, which allows the approach of the arylpalladium species to the 6-position. Altogether the arylation of **10** is remarkable because its electron density is considerably lower than those of spirocyclic thiophenes **1**–**3**.

3. Receptor Affinity

The σ_1 receptor affinities of the arylated compounds were determined in receptor binding studies using guinea pig brain preparations and the radioligand [^{3}H]-(+)-pentazocine.[15] In Table 1 the K_i values of the arylated compounds are compared with the K_i values of the parent compounds without a phenyl substituent; reference compounds are also included.

The nonarylated spirocyclic thiophene derivatives **1**–**3** interact in the low nanomolar or even subnanomolar range (e.g., **2a**, **2b**, and **3b**) with σ_1 receptors. In the group of nonphenylated compounds the σ_1 affinity increases in the order **1** (S bottom position) < **2** (S left position) ≈ **3** (S top position).

Although the σ_1 affinity of phenylated compounds is comparable (e.g., **1a**/**5a**) or slightly reduced (e.g., **3b**/**7b**, **2a**/**6a**) compared to the nonphenylated parent compounds, they all bind in the low nanomolar range at σ_1 receptors. Clearly the σ_1 receptor tolerates an additional lipophilic moiety in its binding pocket. As a general trend, a phenyl moiety at the top position (position **A**, compounds **4** and **6**) is better tolerated by the σ_1 receptor than a phenyl moiety at the left position (position **B** compounds **5** and **7**), whereas attachment of the phenyl group at the bottom position (position **C**, compounds **12** and **13**) resulted in considerably reduced σ_1 affinity. With the exception of the pair **4a**/**6a**, the phenylated compounds **6** with the S-atom at the left position (**B**) are more potent than the phenylated compounds **6** with the S-atom at the top position (**A**).

Table 1. The σ_1 affinities of phenylated spirocyclic thiophenes compared with non-phenylated parent compounds and reference compounds.

	X	σ_1 Affinity[a] $K_i \pm$ SEM [nM] (n = 3)
1a	H/H	1.0 ± 0.30
1b	H/OCH_3	1.9 ± 0.44
1c	O	255
2a[4]	H/H	0.35 ± 0.06
2b[4]	H/OCH_3	0.22 ± 0.06
2c	O	40 ± 13
3b[5]	H/OCH_3	0.32 ± 0.10
4a	H/H	1.6 ± 0.70
4b	H/OCH_3	5.4 ± 0.97
4c	O	5.3 ± 0.88
5a	H/H	2.4 ± 0.69
5b	H/OCH_3	16 ± 5.8
5c	O	23 ± 9.9
6a[4]	H/H	4.5 ± 2.9
6b[4]	H/OCH_3	1.0 ± 0.4
6c	O	2.5 ± 0.91
7b	H/OCH_3	5.5 ± 1.5
10	–	16 ± 6.8
11	–	11 ± 3.2
12	–	483
13	–	87 ± 52
(+)-pentazocine		5.7 ± 2.2
Haloperidol		6.3 ± 1.6

[a] K_i values were determined in competition experiments with {^{3}H}-(+)-pentazocine.

Generally, spirocyclic thiophenes with a lactone moiety (**c**-series) show considerably lower σ_1 receptor affinities than their analogues without a substituent (**a**-series) or with an acetalic group (**b**-series). However, the σ_1 affinity of the phenylated lactones **4c**, **5c**, and **6c** is more than tenfold increased compared to the less potent nonphenylated lactones **1c** and **2c**. It is assumed that additional lipophilic interactions of the phenyl moiety are able to compensate for the unfavorable binding properties of the lactone moiety.

Introduction of a phenyl moiety in the top position (**A**) of the five-membered lactone **10** led to a slight increase of σ_1 affinity (**11**). However, the regioisomer **12**, with the phenyl moiety in the bottom position (**C**), is almost inactive at the σ_1 receptor. An additional phenyl moiety in the top position (**13**) is able to compensate a little for the negative effect of the 6-phenyl moiety of **12**.

4. Conclusion

It was shown that the direct regioselective α-arylation of complex spirocyclic thiophenes containing various functional groups (amine, ether, acetal, lactone) is possible by

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C–H bond functionalization with iodobenzene and the catalytic system $PdCl_2$/bipy/Ag_2CO_3. The corresponding β-arylated thiophenes were obtained by using the catalytic system $PdCl_2$/P[OCH(CF$_3$)$_2$]$_3$/Ag_2CO_3. The advantage of these catalytic systems is their compatibility with several functional groups, allowing the introduction of the phenyl moiety as last step of the synthesis. Spirocyclic thiophenes with various functional groups containing the S-atom and the phenyl moiety at different ring positions are available through this novel synthetic strategy. Thus, the pharmacological properties of a diverse set of spirocyclic thiophenes could be investigated. To achieve high σ_1 receptor affinity the spirocyclic thiophenes should contain the S-atom in the left or top position, the phenyl moiety at the top position, and either a proton or a methoxy group adjacent to the ring O-atom. The promising σ_1 affinity of the phenylated compounds indicate a hydrophobic pocket of the σ_1 receptor protein in this region.

Experimental Section

General: Unless otherwise noted, moisture- and oxygen-sensitive reactions were conducted in dry glassware (Schlenk flask sealed with a rubber septum) under N_2 [dried with phosphorus pentoxide (Granusic® A, Baker)]. THF and Et_2O were dried with sodium/benzophenone and were freshly distilled before use. Thin-layer chromatography (tlc): Silica gel 60 F254 plates (Merck). Flash chromatography (fc): Silica gel 60, 40–64 μm (Merck); parentheses include: diameter of the column [cm], length of the stationary phase [cm], eluent, fraction size [mL] and retention factor R_f. Gel permeation chromatography (gpc): LC-9204 instrument (JAI) with JAIGEL-1H/JAIGEL-2H columns, eluent $CHCl_3$; preparative thin-layer chromatography (prep. tlc): Wako-gel® B5-F silica coated plates (0.75 mm) prepared in the Itami laboratory. IR were obtained with a 480Plus FT-ATR-IR (Jasco) spectrophotometer. ^{1}H NMR (400 MHz, 300 MHz, 600 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a Unity Mercury Plus 400 (400 MHz) NMR spectrometer (Varian), JNM-ECA-400 (400 MHz) spectrometer (JEOL), Bruker AV 300 (300 MHz), or Varian Unity Plus 600 (600 MHz) operating at 23 °C. Chemical shifts δ are reported in parts per million (ppm) against the reference compound tetramethylsilane and calculated using the chemical shift of the signal of the residual nondeuterated solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quatet, m = multiplet), coupling constant [Hz] and integration. HRMS (ESI): Finnigan MAT 4200s, Bruker Daltonics Micro Tof and Waters Micromass Quatro LCZ, peaks are given in *m*/*z* (% of basis peak). EI, electron impact, MAT GCQ (Thermo-Finnigan). HRMS: JMS-T100TD instrument (DART); HPLC: Agilent Technologies® equipment: UV detector: Agilent 1200 variable wavelength detector G13143/G1314C (SL); autosampler: Agilent 1200; pump: quaternary pump for gradient analysis; degasser: Agilent 1200 micro vacuum degasser; column: ZORBAX Eclipse Plus X18 2.1 × 150 mm, 3.5 μm; temperature: 23 °C; flow rate: 0.40 mL/min; injection volume: 1.0 μL; detection at λ = 254 nm; solvents: A: water with 5 mM NH_4HCO_2; B: acetonitrile; gradient elution: (A%): 0–5 min: gradient from 80 to 0%, 5–13 min: 0%, 13–18 min: 0 to 80%. The purity of all test compounds was greater than 95%.

General Procedures

General Procedure A for the α-Arylation of Spirocyclic Thiophenes with Iodoarenes: A 20 mL glass vessel was equipped with a magnetic stirring bar and closed by a J. Young O-ring tap. The flask was flame-dried under vacuo and filled with Ar after cooling to room temp. Under a permanent stream of Ar, the catalyst $PdCl_2$/bipy (10 mol-%) and Ag_2CO_3 (1 equiv.) were added into the vessel and suspended in anhydrous *m*-xylene (0.4 mL). The mixture was stirred at 60 °C for 30 min. Finally, a solution of iodobenzene (1.1 equiv.) and a solution of the spirocyclic starting material (1 equiv.) in anhydrous *m*-xylene (0.6 mL in total) were added dropwise. The vessel was sealed with the O-ring tap and heated at 150 °C for 12 h in an eight-well reaction block. After cooling the vessel to room temp., the mixture was filtered through a short silica pad (EtOAc). The filtrate was concentrated in vacuo and the crude product was purified by gel permeation chromatography ($CHCl_3$) followed by preparative thin-layer chromatography or flash chromatography (short column) to yield the corresponding arylthiophene in high purity.

General Procedure B for the β-Arylation of Spirocyclic Thiophenes with Iodoarenes: A 20 mL glass vessel was equipped with a magnetic stirring bar and closed by a J. Young O-ring tap. The flask was flame-dried under vacuo and filled with Ar after cooling to room temp. Under a permanent stream of Ar, $PdCl_2$ (10 mol-%) and Ag_2CO_3 (1 equiv.) were added to the vessel. The phosphite ligand P[OCH(CF$_3$)$_2$]$_3$ (20 mol-%) and subsequently anhydrous *m*-xylene (0.5 mL) were added and the mixture was stirred at 60 °C for 30 min to form the active catalyst. Finally, a solution of the iodoarene (1.1 equiv.) and a solution of the spirocyclic starting material (1 equiv.) in anhydrous *m*-xylene (0.5 mL in total) were added. The vessel was sealed with the O-ring tap and heated at 150 °C for 12 h in an eight-well reaction block. After cooling the vessel to room temp., the mixture was filtered through a short silica pad (EtOAc). The filtrate was concentrated in vacuo and the crude product was purified by gel permeation chromatography ($CHCl_3$) followed by preparative thin-layer chromatography or flash chromatography (short column) to yield the corresponding arylthiophene in high purity.

Procedures for the Preparation of Compounds

1-Benzyl-3′-phenyl-4′,5′-dihydrospiro(piperidine-4,7′-thieno[2,3-*c*]-pyran) (4a): According to General Procedure B, spirocyclic thiophene **1a** (31.3 mg, 0.105 mmol) was treated with iodobenzene (12.8 μL, 0.11 mmol), Ag_2CO_3 (28.1 mg, 0.10 mmol), $PdCl_2$ (2.0 mg, 0.01 mmol), and P[OCH(CF$_3$)$_2$]$_3$ (7.1 μL, 0.02 mmol) in *m*-xylene (1.2 mL). The crude product was purified by $CHCl_3$-gpc and prep. tlc (*h* = 15 cm; hexane/EtOAc = 10:1; R_f = 0.06; 4 runs). Pale-yellow resin; yield 8.2 mg [21% after gpc, mixture of regioisomers; HPLC: t_R = 8.11 (**4a**; 89.5%), 8.46 (regioisomer **5a**; 9.4%) min]; colorless resin, yield 2.5 mg (6% after prep. tlc). ^{1}H NMR (400 MH, $CDCl_3$): δ = 1.96–2.08 [m, 4 H, N(CH$_2$C*H*$_2$)$_2$], 2.44 [td, *J* = 11.4, 4.0 Hz, 2 H, N(CH$_2$C*H*$_2$)$_2$], 2.69 (t, *J* = 5.4 Hz, 2 H, thiophC*H*$_2$CH$_2$), 2.75 [d, *J* = 11.5 Hz, 2 H, N(C*H*$_2$CH$_2$)$_2$], 3.57 (s, 2 H, NC*H*$_2$Ph), 3.90 (t, *J* = 5.4 Hz, 2 H, thiophCH$_2$C*H*$_2$), 7.13 (s, 1 H, 2′-*H*-thioph), 7.27–7.42 (m, 10 H, Ph-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.2 (1C, thiophC*H*$_2$CH$_2$), 38.7 [2C, N(CH$_2$*C*H$_2$)$_2$], 49.4 [2C, N(*C*H$_2$CH$_2$)$_2$], 59.5 (1C, thiophCH$_2$*C*H$_2$), 63.5 (1C, N*C*H$_2$Ph), 73.3 (1C, thioph*C*$_{spiro}$), 119.7 (1C, *C*H-2′-thioph), 127.2 (Ph-*C*H), 127.3 (Ph-*C*H), 128.4 (Ph-*C*H), 128.4 (Ph-*C*H), 128.7 (Ph-*C*H), 129.5 (Ph-*C*H), 131.8 (1C, *C*$_{quat}$), 136.5 (1C, *C*$_{quat}$), 138.8 (1C, *C*$_{quat}$), 141.7 (1C, *C*$_{quat}$), 144.0 (1C, *C*$_{quat}$) ppm. HRMS (APCI): calcd. for $C_{24}H_{26}NOS$ [MH$^+$] 376.1730; found 376.1684.

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1-Benzyl-5′-methoxy-3′-phenyl-4′,5′-dihydrospiro(piperidine-4,7′-thieno[2,3-*c*]pyran) (4b): According to General Procedure B, spirocyclic thiophene **1b** (48 mg, 0.15 mmol) was treated with iodobenzene (17.9 μL, 0.16 mmol), Ag_2CO_3 (46.6 mg, 0.17 mmol), $PdCl_2$ (2.9 mg, 0.016 mmol), and $P[OCH(CF_3)_2]_3$ (10.3 μL, 0.032 mmol) in *m*-xylene (1.5 mL). The crude product was purified by $CHCl_3$-gpc and prep. tlc (*h* = 15 cm; hexane/EtOAc = 14:1, NEt_3 2%; R_f = 0.10; 7 runs). Colorless solid, yield 18.9 mg (32% after gpc, mixture of regioisomers); colorless solid, yield 7.5 mg (13% after prep. tlc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.97 [td, *J* = 12.8, 3.3 Hz, 1 H, N(CH_2CH_2)$_2$], 2.02–2.16 [m, 3 H, N(CH_2-CH_2)$_2$], 2.49 [td, *J* = 12.1, 2.4 Hz, 1 H, N(CH_2CH_2)$_2$], 2.59 [td, *J* = 11.6, 2.9 Hz, 1 H, N(CH_2CH_2)$_2$], 2.74–2.86 [m, 4 H, N(CH_2-CH_2)$_2$, thiophCH_2CH], 3.54 (s, 3 H, OCH_3), 3.58 (d, *J* = 13.7 Hz, 1 H, NCH_2Ph), 3.61 (d, *J* = 13.4 Hz, 1 H, NCH_2Ph), 4.85 (dd, *J* = 6.8, 3.7 Hz, 1 H, thiophCH$_2$C*H*), 7.16 (s, 1 H, 2′-*H*-thioph), 7.27–7.41 (m, 10 H, Ph-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.8 (1C, thiophCH_2CH), 37.9 [1C, N(CH_2CH_2)$_2$], 40.9 [1C, N(CH_2CH_2)$_2$], 49.4 [2C, N(CH_2CH_2)$_2$], 56.7 (1C, OCH_3), 63.4 (1C, NCH_2Ph), 74.2 (1C, thiophC_{spiro}), 97.5 (1C, thiophCH$_2$*C*H), 120.6 (1C, *C*H-2′-thioph), 127.4 (Ph-*C*H), 127.4 (Ph-*C*H), 128.4 (Ph-*C*H), 128.5 (Ph-*C*H), 128.7 (Ph-*C*H), 129.6 (1C, C_{quat}), 129.7 (1C, C_{quat}), 136.2 (1C, C_{quat}), 141.6 (1C, C_{quat}), 143.0 (1C, C_{quat}) ppm. HRMS (ESI): calcd. for $C_{25}H_{27}NO_2S$ [M^+] 405.1762; found 405.1780.

1-Benzyl-3′-phenylspiro(piperidine-4,7′-thieno[2,3-*c*]pyran)-5′-(4′*H*)-one (4c): According to General Procedure B, spirocyclic thiophene **1c** (30.6 mg, 0.098 mmol) was treated with iodobenzene (12 μL, 0.11 mmol), Ag_2CO_3 (29.2 mg, 0.11 mmol), $PdCl_2$ (1.7 mg, 0.01 mmol), and $P[OCH(CF_3)_2]_3$ (6.3 μL, 0.02 mmol) in *m*-xylene (1.2 mL). The crude product was purified by $CHCl_3$-gpc and prep. tlc (*h* = 15 cm; hexane/EtOAc = 7:3; R_f = 0.06; 4 runs). Colorless solid; m.p. 115 °C; yield 11.8 mg [31%, mixture of regioisomers, HPLC: t_R = 7.25 (**4c**; 96.3%) min]; colorless solid, yield 3.7 mg (9.7% after prep. tlc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 [d, *J* = 12.8 Hz, 2 H, N(CH_2CH_2)$_2$], 2.19 [td, *J* = 14.4, 3.8 Hz, 2 H, N(CH_2CH_2)$_2$], 2.63 [td, *J* = 11.6, 2.7 Hz, 2 H, N(CH_2CH_2)$_2$], 2.82 [d, *J* = 11.6 Hz, 2 H, N(CH_2CH_2)$_2$], 3.61 (s, 2 H, NCH_2Ph), 3.70 (s, 2 H, thiophCH_2), 7.23 (s, 1 H, 2′-*H*-thioph), 7.27–7.48 (m, 10 H, Ph-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.0 (1C, thiophCH_2C=O), 38.8 [2C, N(CH_2CH_2)$_2$], 48.7 [2C, N(CH_2CH_2)$_2$], 63.2 (1C, NCH_2Ph), 81.4 (1C, thiophC_{spiro}), 121.9 (*C*H-2′-thioph), 127.4 (Ph-*C*H), 128.0 (Ph-*C*H), 128.3 (Ph-*C*H), 128.5 (Ph-*C*H), 129.0 (Ph-*C*H), 129.2 (1C, C_{quat}), 129.4 (Ph-*C*H), 135.2 (1C, C_{quat}), 138.5 (1C, C_{quat}), 139.5 (1C, C_{quat}), 141.1 (1C, C_{quat}), 169.3 (1C, *C*=O) ppm. HRMS (APCI): calcd. for $C_{24}H_{24}NO_2S$ [MH^+] 390.1522; found 390.1545.

1-Benzyl-2′-phenyl-4′,5′-dihydrospiro(piperidine-4,7′-thieno[2,3-*c*]pyran) (5a): According to General Procedure A, spirocyclic thiophene **1a** (29.4 mg, 0.098 mmol) was treated with iodobenzene (12.1 μL, 0.11 mmol), Ag_2CO_3 (29.2 mg, 0.11 mmol), and $PdCl_2$/bipy (3.4 mg, 0.01 mmol) in *m*-xylene (1.2 mL). The crude product was purified by $CHCl_3$-gpc and fc (Ø = 1.5 cm, *h* = 5 cm; hexane/EtOAc = 3:2, 3 mL; R_f = 0.52). Colorless resin, yield 23.6 mg (64% after gpc); colorless resin, yield 14.5 mg (40% after fc). HPLC: t_R = 8.57 (90%), 8.24 (8.0% regioisomer **4a**) min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94–2.09 [m, 4 H, N(CH_2CH_2)$_2$], 2.43 [td, *J* = 11.3, 4.1 Hz, 2 H, N(CH_2CH_2)$_2$], 2.69 (t, *J* = 5.5 Hz, 2 H, thiophCH_2CH$_2$), 2.74 [d, *J* = 11.6 Hz, 2 H, N(CH_2CH_2)$_2$], 3.57 (s, 2 H, NCH_2Ph), 3.94 (t, *J* = 5.5 Hz, 2 H, thiophCH$_2$CH_2), 6.96 (s, 1 H, 3′-*H*-thioph), 7.22–7.25 (m, 1 H, Ph-*H*), 7.27–7.29 (m, 1 H, Ph-*H*), 7.29–7.41 (m, 6 H, Ph-*H*), 7.51–7.56 (m, 2 H, Ph-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.6 (1C, thiophCH_2CH$_2$), 38.4 [2C, N(CH_2CH_2)$_2$], 49.3 [2C, N(CH_2CH_2)$_2$], 59.2 (1C, thiophCH$_2$CH_2), 63.5 (1C, NCH_2Ph), 73.0 (1C, thiophC_{spiro}), 123.1 (1C, *C*H-3′-thioph), 125.8 (Ph-*C*H), 127.2 (Ph-*C*H), 127.5 (Ph-*C*H), 128.4 (Ph-*C*H), 129.0 (Ph-*C*H), 129.4 (Ph-*C*H), 134.2 (1C, C_{quat}), 134.6 (1C, C_{quat}), 138.9 (1C, C_{quat}), 141.6 (1C, C_{quat}), 142.4 (1C, C_{quat}) ppm. HRMS (APCI): calcd. for $C_{24}H_{26}NOS$ [MH^+] 376.1730; found 376.1679.

1-Benzyl-5′-methoxy-2′-phenyl-4′,5′-dihydrospiro(piperidine-4,7′-thieno[2,3-*c*]pyran) (5b): According to General Procedure A, spirocyclic thiophene **1b** (19.5 mg, 0.060 mmol) was treated with iodobenzene (7.5 μL, 0.07 mmol), Ag_2CO_3 (17.3 mg, 0.06 mmol), and $PdCl_2$/bipy (2.1 mg, 0.006 mmol) in *m*-xylene (1.0 mL). The crude product was purified by $CHCl_3$-gpc and prep. tlc (*h* = 15 cm; hexane/EtOAc = 3:2; R_f = 0.5). Colorless solid, yield 9.2 mg (38% after $CHCl_3$-gpc); colorless solid, yield 4.5 mg (19% after prep. tlc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91–2.07 [m, 2 H, N(CH_2CH_2)$_2$], 2.08–2.17 [m, 2 H, N(CH_2CH_2)$_2$], 2.47 [td, *J* = 11.5, 2.8 Hz, 1 H, N(CH_2CH_2)$_2$], 2.57 [td, *J* = 11.8, 2.9 Hz, 1 H, N(CH_2CH_2)$_2$], 2.72 (dd, *J* = 15.5, 7.4 Hz, 1 H, thiophCH_2CH), 2.77–2.84 [m, 2 H, N(CH_2CH_2)$_2$], 2.87 (dd, *J* = 15.5, 3.3 Hz, 1 H, thiophCH_2CH), 3.57 (s, 3 H, OCH_3), 3.57 (d, *J* = 13.2 Hz, 1 H, NCH_2Ph), 3.61 (d, *J* = 13.2 Hz, 1 H, NCH_2Ph), 4.92 (dd, *J* = 7.3, 3.3 Hz, 1 H, thiophCH$_2$C*H*), 6.94 (s, 1 H, 3′-*H*-thioph), 7.27–7.39 (m, 8 H, Ph-*H*), 7.49–7.54 (m, 2 H, Ph-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.4 (1C, thiophCH_2CH), 37.6 [1C, N(CH_2CH_2)$_2$], 40.8 [1C, N(CH_2CH_2)$_2$], 49.4 [2C, N(CH_2CH_2)$_2$], 56.7 (1C, OCH_3), 63.4 (1C, NCH_2Ph), 74.1 (1C, thiophC_{spiro}), 97.2 (1C, thiophCH$_2$*C*H), 122.9 (1C, *C*H-3′-thioph), 125.7 (Ph-*C*H), 127.3 (Ph-*C*H), 127.6 (Ph-*C*H), 128.4 (Ph-*C*H), 129.0 (Ph-*C*H), 129.5 (Ph-*C*H), 132.0 (1C, C_{quat}), 134.4 (1C, C_{quat}), 138.4 (1C, C_{quat}), 141.0 (1C, C_{quat}), 142.6 (1C, C_{quat}) ppm. HRMS (ESI): calcd. for $C_{25}H_{27}NO_2S$ [M^+] 405.1762; found 405.1781.

1-Benzyl-2′-phenylspiro(piperidine-4,7′-thieno[2,3-*c*]pyran)-5′-(4′*H*)-one (5c): According to General Procedure A, spirocyclic thiophene **1c** (30.8 mg, 0.098 mmol) was treated with iodobenzene (12.1 μL, 0.11 mmol), Ag_2CO_3 (30.2 mg, 0.11 mmol), and $PdCl_2$/bipy (3.4 mg, 0.01 mmol) in *m*-xylene (1.2 mL). The crude product was purified by $CHCl_3$-gpc and fc (Ø = 1.5 cm, *h* = 5 cm; hexane/EtOAc = 4:1, 3 mL; R_f = 0.20). Colorless solid; m.p. 140 °C; yield 17.8 mg (47% after gpc); colorless solid, yield 12.5 mg (33% after fc). HPLC: t_R = 7.42 (97.3%) min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.08 [dd, *J* = 14.5, 2.3 Hz, 2 H, N(CH_2CH_2)$_2$], 2.17 [td, *J* = 14.2, 4.4 Hz, 2 H, N(CH_2CH_2)$_2$], 2.62 [td, *J* = 11.7, 2.8 Hz, 2 H, N(CH_2CH_2)$_2$], 2.81 [d, *J* = 11.5 Hz, 2 H, N(CH_2CH_2)$_2$], 3.60 (s, 2 H, NCH_2Ph), 3.70 (s, 2 H, thiophCH_2), 7.00 (s, 1 H, 3′-*H*-thioph), 7.27–7.43 (m, 8 H, Ph-*H*), 7.49–7.58 (m, 2 H, Ph-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.7 (1C, thiophCH_2C=O), 39.0 [2C, N(CH_2CH_2)$_2$], 48.7 [2C, N(CH_2CH_2)$_2$], 63.2 (1C, NCH_2Ph), 81.8 (1C, thiophC_{spiro}), 121.7 (1C, *C*H-3′-thioph), 126.0 (Ph-*C*H), 127.4 (Ph-*C*H), 128.3 (Ph-*C*H), 128.6 (Ph-*C*H), 129.3 (Ph-*C*H), 129.4 (Ph-*C*H), 130.5 (1C, C_{quat}), 133.8 (1C, C_{quat}), 137.5 (1C, C_{quat}), 138.6 (1C, C_{quat}), 144.7 (1C, C_{quat}), 169.1 (1C, *C*=O). HRMS (APCI): calcd. for $C_{24}H_{24}NO_2S$ [MH^+] 390.1522; found 390.1531.

1-Benzyl-1′-phenyl-6′,7′-dihydrospiro(piperidine-4,4′-thieno[3,4-*c*]-pyran) (6a):[4] According to General Procedure A, spirocyclic thiophene **2a** (27.7 mg, 0.093 mmol) was treated with iodobenzene (11.3 μL, 0.10 mmol), Ag_2CO_3 (28 mg, 0.10 mmol), and $PdCl_2$/bipy (3.6 mg, 0.01 mmol) in *m*-xylene (1.2 mL). The crude product was purified by $CHCl_3$-gpc and prep. tlc (*h* = 15 cm, hexane/EtOAc = 9:1; R_f = 0.42). Colorless solid, yield 18.8 mg (54% after gpc); colorless solid, yield 12.0 mg (35% after prep. tlc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95–2.06 [m, 4 H, N(CH_2CH_2)$_2$], 2.42 [td,

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J = 10.8, 4.9 Hz, 2 H, N(CH_2CH$_2$)$_2$], 2.74 [d, J = 11.5 Hz, 2 H, N(CH_2CH$_2$)$_2$], 2.86 (t, J = 5.5 Hz, 2 H, thiophCH_2CH$_2$), 3.58 (s, 2 H, NCH_2Ph), 3.82 (t, J = 5.5 Hz, 2 H, thiophCH$_2$CH_2), 6.97 (s, 1 H, 3′-*H*-thioph), 7.27–7.50 (m, 10 H, Ph-*H*) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 27.8 (1C, thiophCH_2CH$_2$), 37.9 [2C, N(CH$_2$CH_2)$_2$], 49.3 [2C, N(CH_2CH$_2$)$_2$], 59.3 (1C, thiophCH$_2$CH_2), 63.6 (1C, NCH$_2$Ph), 73.9 (1C, thiophC_{spiro}), 118.0 (1C, *C*H-3′-thioph), 127.3 (Ph-*C*H), 127.5 (Ph-*C*H), 128.5 (Ph-*C*H), 128.6 (Ph-*C*H), 128.9 (Ph-*C*H), 129.6 (Ph-*C*H), 131.1 (1C, C_{quat}), 134.6 (1C, C_{quat}), 137.5 (1C, C_{quat}), 138.6 (1C, C_{quat}), 145.5 (1C, C_{quat}). HRMS (ESI): calcd. for $C_{24}H_{25}NOS$ [M$^+$] 375.1657; found 375.1643.

1-Benzyl-6′-methoxy-1′-phenyl-6′,7′-dihydrospiro(piperidine-4,4′-thieno[3,4-*c*]pyran) (6b):[4] According to General Procedure A, spirocyclic thiophene **2b** (87.8 mg, 0.27 mmol) was treated with iodobenzene (35.2 mg, 0.17 mmol), Ag_2CO_3 (49.3 mg, 0.18 mmol), and $PdCl_2$/bipy (5.5 mg, 0.016 mmol) in *m*-xylene (1.5 mL). The crude product was purified by $CHCl_3$-gpc and prep. tlc (h = 15 cm, hexane/EtOAc = 3:2; R_f = 0.4). Pale-yellow resin, yield 46.3 mg (67% after gpc); colorless resin, yield 33.2 mg (48% after prep. tlc). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.91 [td, J = 13.6, 4.6 Hz, 1 H, N(CH$_2$CH_2)$_2$], 2.01 [dd, 13.9, 3.2 Hz, 1 H, N(CH$_2$CH_2)$_2$], 2.06–2.19 [m, 2 H, N(CH$_2$CH_2)$_2$], 2.47 [td, J = 11.8, 2.3 Hz, 1 H, N(CH_2CH$_2$)$_2$], 2.58 [td, J = 11.9, 2.7 Hz, 1 H, N(CH_2CH$_2$)$_2$], 2.74–2.84 [m, 2 H, N(CH_2CH$_2$)$_2$], 2.88 (dd, J = 15.5, 7.4 Hz, 1 H, thiophCH_2CH), 3.02 (dd, J = 15.5, 3.0 Hz, 1 H, thiophCH_2CH), 3.52 (s, 3 H, OCH_3), 3.58 (d, J = 13.0 Hz, 1 H, NCH_2Ph), 3.62 (d, J = 13.0 Hz, 1 H, NCH_2Ph), 4.80 (dd, J = 7.4, 3.1 Hz, 1 H, thiophCH$_2$C*H*), 6.96 (s, 1 H, 3′-*H*-thioph), 7.27–7.46 (m, 10 H, Ph-*H*) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 33.3 (1C, thiophCH_2CH), 37.5 [1C, N(CH$_2$CH_2)$_2$], 39.9 [1C, N(CH$_2$CH_2)$_2$], 49.4 [2C, N(CH_2CH$_2$)$_2$], 56.7 (1C, OCH_3), 63.4 (1C, NCH_2Ph), 74.0 (1C, thiophC_{spiro}), 97.5 (1C, thiophCH$_2$C*H*), 117.5 (1C, *C*H-3′-thioph), 127.5 (Ph-*C*H), 128.1 (Ph-*C*H), 128.2 (Ph-*C*H), 128.5 (Ph-*C*H), 128.5 (Ph-*C*H), 128.8 (Ph-*C*H), 129.1 (Ph-C_{quat}), 129.6 (Ph-*C*H), 131.6 (Ph-*C*H), 134.0 (1C, C_{quat}), 138.1 (1C, C_{quat}, Ph-C), 138.4 (1C, C_{quat}, Ph-C), 144.2 (1C, C_{quat}). HRMS (ESI): calcd. for $C_{25}H_{27}NO_2S$ [M$^+$] 405.1762; found 405.1782.

1-Benzyl-1′-phenylspiro(piperidine-4,4′-thieno[3,4-*c*]pyran)-6′-(7′*H*)-one (6c): According to General Procedure A, spirocyclic thiophene **2c** (32.2 mg, 0.103 mmol) was treated with iodobenzene (12.6 µL, 0.11 mmol), Ag_2CO_3 (29.7 mg, 0.11 mmol), and $PdCl_2$/bipy (3.4 mg, 0.01 mmol) in *m*-xylene (1.2 mL). The crude product was purified by $CHCl_3$-gpc and fc (Ø = 1.5 cm, h = 5 cm; hexane/EtOAc = 4:1, 3 mL; R_f = 0.20). Colorless solid; m.p. 125 °C; yield 22.6 mg (57% after gpc); colorless solid, yield 13.4 mg (34% after fc). HPLC: t_R = 7.09 (98.4%) min. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.09 [dd, J = 14.8, 2.2 Hz, 2 H, N(CH$_2$CH_2)$_2$], 2.19 [td, J = 13.7, 4.6 Hz, 2 H, N(CH$_2$CH_2)$_2$], 2.61 [td, J = 11.9, 2.6 Hz, 2 H, N(CH_2CH$_2$)$_2$], 2.82 [dd, J = 9.0, 2.4 Hz, 2 H, N(CH_2CH$_2$)$_2$], 3.60 (s, 2 H, NCH_2Ph), 3.83 (s, 2 H, thiophCH_2), 7.10 (s, 1 H, 3′-*H*-thioph), 7.30–7.47 (m, 10 H, Ph-*H*) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 32.7 (1C, thiophCH_2C=O), 37.1 [2C, N(CH$_2$CH_2)$_2$], 48.7 [2C, N(CH_2CH$_2$)$_2$], 63.2 (1C, NCH_2Ph), 81.2 (1C, thiophC_{spiro}), 117.7 (1C, *C*H-3′-thioph), 126.4 (1C, C_{quat}), 127.4 (Ph-*C*H), 128.4 (Ph-*C*H), 128.6 (Ph-*C*H), 128.8 (Ph-*C*H), 129.2 (Ph-*C*H), 129.5 (Ph-*C*H), 133.1 (1C, C_{quat}), 138.1 (1C, C_{quat}), 141.3 (1C, C_{quat}), 169.5 (1C, *C*=O) ppm. One signal for a quaternary carbon atom was not visible. HRMS (APCI): calcd. for $C_{24}H_{24}NO_2S$ [MH$^+$] 390.1522; found 390.1528.

1-Benzyl-6′-methoxy-2′-phenyl-6′,7′-dihydrospiro(piperidine-4,4′-thieno[3,2-*c*]pyran) (7b): According to General Procedure A, spirocyclic thiophene **3b** (33.2 mg, 0.101 mmol) was treated with iodobenzene (12.4 µL, 0.11 mmol), Ag_2CO_3 (27.5 mg, 0.01 mmol), and $PdCl_2$/bipy (3.2 mg, 0.01 mmol) in *m*-xylene (1.2 mL). The crude product was purified by $CHCl_3$-gpc and fc (Ø = 1.5 cm, h = 5 cm; hexane/EtOAc = 4:1, 3 mL; R_f = 0.10). Colorless solid; m.p. 137 °C; yield 23.4 mg (57% after gpc); colorless solid, yield 18.9 mg (46% after fc). HPLC: t_R = 7.83 (96%) min. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.84–2.01 [m, 3 H, N(CH$_2$CH_2)$_2$], 2.15 [td, J = 13.2, 4.4 Hz, 1 H, N(CH$_2$CH_2)$_2$], 2.45 [td, J = 11.6, 3.3 Hz, 1 H, N(CH_2CH$_2$)$_2$], 2.54 [td, J = 12.4, 2.5 Hz, 1 H, N(CH_2CH$_2$)$_2$], 2.74–2.81 [m, 2 H, N(CH_2CH$_2$)$_2$], 2.86 (dd, J = 15.8, 7.2 Hz, 1 H, thiophCH_2CH), 2.99 (dd, J = 15.8, 3.3 Hz, 1 H, thiophCH_2CH), 3.57 (s, 3 H, OCH_3), 3.57 (d, J = 13.0 Hz, 1 H, NCH_2Ph), 3.61 (d, J = 13.1 Hz, 1 H, NCH_2Ph), 4.91 (dd, J = 7.2, 3.3 Hz, 1 H, thiophCH$_2$C*H*), 7.02 (s, 1 H, 3′-*H*-thioph), 7.27–7.41 (m, 8 H, Ph-*H*), 7.49–7.54 (m, 2 H, Ph-*H*) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 31.6 (1C, thiophCH_2CH), 35.6 [1C, N(CH$_2$CH_2)$_2$], 38.6 [1C, N(CH$_2$CH_2)$_2$], 49.3 [1C, N(CH_2CH$_2$)$_2$], 49.4 [1C, N(CH_2CH$_2$)$_2$], 56.7 (1C, OCH_3), 63.6 (1C, NCH_2Ph), 74.5 (1C, thiophC_{spiro}), 96.8 (1C, thiophCH$_2$C*H*), 120.0 (1C, *C*H-3′-thioph), 125.8 (Ph-*C*H), 127.3 (Ph-*C*H), 127.7 (Ph-*C*H), 128.5 (Ph-*C*H), 129.1 (Ph-*C*H), 129.5 (Ph-*C*H), 130.3 (1C, C_{quat}), 134.5 (1C, C_{quat}), 138.8 (1C, C_{quat}), 141.9 (1C, C_{quat}), 142.4 (1C, C_{quat}) ppm. HRMS (APCI): calcd. for $C_{25}H_{28}NO_2S$ [MH$^+$] 406.1835; found 406.1846.

1-Benzylspiro(piperidine-4,1′-thieno[3,4-*c*]furan)-3′-one (10): In a three-necked flask, 3,4-dibromothiophene (**8**; 654 mg, 2.7 mmol) was dissolved in freshly distilled Et$_2$O (8 mL) and cooled under N$_2$ to –78 °C. After 15 min stirring at –78 °C, *n*-butyllithium (1.35 M in *n*-hexane, 2 mL, 2.7 mmol) was added and the mixture was stirred for 10 min. 1-Benzylpiperidin-4-one (511 mg, 2.7 mmol), dissolved in Et$_2$O (3 mL), was added dropwise and the solution was stirred for 30 min. The reaction mixture was diluted with Et$_2$O (15 mL). For the second halogen–metal exchange reaction, a second equivalent of *n*-butyllithium (1.35 M in *n*-hexane, 2 mL, 2.7 mmol) was added slowly and the mixture was stirred for 10 min at –78 °C. Finally, CO_2 (generated from dry ice and dried with H_2SO_4) was bubbled through the mixture for 1 h while the temperature was kept below –70 °C. The flask was then warmed to room temp. and the solvent was removed in vacuo almost completely. The remaining crude product was poured into water (20 mL), basified with 2 M NaOH, and extracted twice with Et$_2$O. The aqueous layer was acidified with 2 M HCl and washed several times with Et$_2$O. The aqueous layer was concentrated in vacuo and the intermediate salt was directly used for cyclization without purification. The crude product was dissolved in a mixture of Ac$_2$O (3 mL) and NaOAc (532 mg, 6.5 mmol) in toluene (20 mL) and the mixture was heated to reflux overnight (125 °C). The reaction mixture was cooled to room temp., poured into saturated K_2CO_3, and the mixture was stirred for 1 h. When gas formation was finished, the toluene layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. Finally, the combined organic layers were dried (K_2CO_3), filtered, and the solvent was removed in vacuo. The remaining solid was purified by fc [Ø = 4.5 cm, h = 15 cm; cyclohexane/EtOAc = 7:3 (NHEt$_2$ 2%), 30 mL]. In addition to the desired lactone **10**, traces of a brominated side product [R_f = 0.60 (cyclohexane/EtOAc = 3:7)] were separated. Compound **10**: R_f = 0.42 (cyclohexane/EtOAc = 3:7); colorless solid; m.p. 95 °C; yield 353 mg (44%, relative to 3,4-dibromothiophene **8**); HPLC: t_R = 13.7 (98.7%) min. IR (neat): $\tilde{\nu}$ = 3102 (C–H$_{Ar}$), 2922 (C–H), 2811 (C–H), 1758 (C=O), 698 (C–H) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.96 [d, J = 13.5 Hz, 2 H, N(CH$_2$CH_2)$_2$], 2.08 [td, J = 10.0, 3.9 Hz, 2 H, N(CH$_2$CH_2)$_2$], 2.61 [t, J = 9.8 Hz, 2 H, N(CH_2CH$_2$)$_2$], 2.75 [d, J = 11.7 Hz, 2 H, N(CH_2CH$_2$)$_2$], 3.61 (s, 2

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H, NCH_2Ph), 7.07 (d, J = 2.3 Hz, 1 H, 6′-*H*-thioph), 7.27–7.39 (m, 5 H, Ph-*H*). 7.88 (d, J = 2.4 Hz, 1 H, 4′-*H*-thioph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.8 [2C, N(CH_2CH_2)$_2$], 49.7 [2C, N(CH_2CH_2)$_2$], 63.1 (1C, NCH_2Ph), 83.7 (1C, C_{spiro}), 115.5 (1C, *C*-6′-thioph), 126.6 (1C, *C*-4′-thioph), 127.4 (1C, Ph-*C*), 128.5 (2C, Ph-*C*), 129.4 (2C, Ph-*C*), 133.3 (1C, C_{quat}), 138.0 (1C, C_{quat}, Ph-C), 154.7 (1C, C_{quat}), 162.8 (1C, *C*=O) ppm. HRMS (APCI): calcd. for $C_{17}H_{17}NO_2S$ [MH^+] 300.1053; found 300.1081.

1-Benzyl-4′-phenylspiro(piperidine-4,1′-thieno[3,4-*c*]furan)-3′-one (11) and 1-Benzyl-6′-phenylspiro(piperidine-4,1′-thieno[3,4-*c*]furan)-3′-one (12) and 1-Benzyl-4′,6′-diphenylspiro(piperidine-4,1′-thieno[3,4-*c*]furan)-3′-one (13): According to General Procedure A, spirocyclic thiophene **10** (31.9 mg, 0.107 mmol) was treated with iodobenzene (13.1 μL, 0.12 mmol), Ag_2CO_3 (32.5 mg, 0.12 mmol), and $PdCl_2$/bipy (4.0 mg, 0.01 mmmol) in *m*-xylene (1.2 mL). The residue was purified by $CHCl_3$-gpc to yield the double arylated product in the first fraction and two monoarylated products in the second fraction of the gpc. The double arylated product **13** was purified by fc (Ø = 1.5 cm, h = 5 cm; hexane/EtOAc = 9:1; 3 mL; R_f = 0.12). The monoarylated products **11** and **12** were separated by preparative thin layer chromatography [h = 15 cm; hexane/EtOAc = 7:3; R_f = 0.22 (**11**), 0.48 (**12**) min].

Compound 11: Colorless solid; m.p. 137 °C; yield 19.9 mg (50% after gpc), mixture of regioisomers; yield 10.1 mg (25% after prep. tlc). HPLC: t_R = 7.37 (97%) min. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.99 [d, J = 13.4 Hz, 2 H, N(CH_2CH_2)$_2$], 2.12 [td, J = 12.0, 3.8 Hz, 2 H, N(CH_2CH_2)$_2$], 2.64 [td, J = 12.7, 2.6 Hz, 2 H, N(CH_2CH_2)$_2$], 2.80 [d, J = 11.8 Hz, 2 H, N(CH_2CH_2)$_2$], 3.63 (s, 2 H, NCH_2Ph), 6.93 (s, 1 H, 6′-*H*-thioph), 7.27–7.49 (m, 8 H, Ph-*H*), 8.02–8.08 (m, 2 H, Ph-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.9 [2C, N(CH_2CH_2)$_2$], 49.6 [2C, N(CH_2CH_2)$_2$], 63.1 (1C, NCH_2Ph), 82.1 (1C, thiophC_{spiro}), 112.4 (1C, *C*H-6′-thioph), 126.5 (1C, C_{quat}), 127.5 (Ph-*C*H), 128.2 (Ph-*C*H), 128.6 (Ph-*C*H), 129.2 (Ph-*C*H), 129.5 (Ph-*C*H), 129.8 (Ph-*C*H), 131.4 (1C, C_{quat}), 138.1 (1C, C_{quat}), 148.4 (1C, C_{quat}), 156.7 (1C, C_{quat}), 163.1 (1C, *C*=O) ppm. HRMS (APCI): calcd. for $C_{23}H_{22}NO_2S$ [MH^+] 376.1366; found 376.1352.

Compound 12: Colorless solid; m.p. 122 °C; yield 19.9 mg (50% after gpc), mixture of regioisomers; yield 2.2 mg (5% after prep. tlc). HPLC: t_R = 7.20 (95.2%) min. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.84 [d, J = 12.9 Hz, 2 H, N(CH_2CH_2)$_2$], 2.17 [t, J = 14.2 Hz, 2 H, N(CH_2CH_2)$_2$], 2.49 [t, J = 9.2 Hz, 2 H, N(CH_2CH_2)$_2$], 2.78 [d, J = 9.0 Hz, 2 H, N(CH_2CH_2)$_2$], 3.53 (s, 2 H, NCH_2Ph), 7.27–7.34 (m, 4 H, Ph-*H*), 7.39–7.56 (m, 6 H, Ph-*H*), 7.84 (s, 1 H, 4′-*H*-thioph). **12** was obtained only in traces and the measurement of a ^{13}C NMR spectrum was not possible. HRMS (APCI): calcd. for $C_{23}H_{22}NO_2S$ [MH^+] 376.1366; found 376.1393.

Compound 13: Colorless solid; m.p. 183 °C; yield 13.2 mg (27% after gpc); yield 10.2 mg (21% after fc). HPLC: t_R = 8.62 (96.6%) min. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.87 [d, J = 12.0 Hz, 2 H, N(CH_2CH_2)$_2$], 2.17 [td, J = 13.3, 4.7 Hz, 2 H, N(CH_2CH_2)$_2$], 2.52 [td, J = 12.3, 2.2 Hz, 2 H, N(CH_2CH_2)$_2$], 2.78 [dd, J = 11.1, 4.2 Hz, 2 H, N(CH_2CH_2)$_2$], 3.54 (s, 2 H, NCH_2Ph), 7.27–7.56 (m, 13 H, Ph-*H*), 8.03–8.08 (m, 2 H, Ph-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.4 [2C, N(CH_2CH_2)$_2$], 49.3 [2C, N(CH_2CH_2)$_2$], 63.0 (1C, NCH_2Ph), 83.0 (1C, thiophC_{spiro}), 127.3 (Ph-*C*H), 127.3 (1C, C_{quat}), 128.4 (Ph-*C*H), 128.5 (Ph-*C*H), 129.1 (Ph-*C*H), 129.2 (Ph-*C*H), 129.2 (Ph-*C*H), 129.3 (Ph-*C*H), 129.7 (Ph-*C*H), 129.9 (Ph-*C*H), 131.3 (1C, C_{quat}), 131.6 (1C, C_{quat}), 132.7 (1C, C_{quat}), 138.6 (1C, C_{quat}), 146.9 (1C, C_{quat}), 151.0 (1C, C_{quat}), 163.0 (1C, *C*=O) ppm. HRMS (APCI): calcd. for $C_{29}H_{26}NO_2S$ [MH^+] 452.1679; found 452.1687.

Receptor Binding Studies

σ_1 Assay:[15] In the σ_1 assay, membrane preparations from guinea pig brains were used as receptor material and [^{3}H]-(+)-pentazocine was employed as radioligand.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all synthesized compounds.

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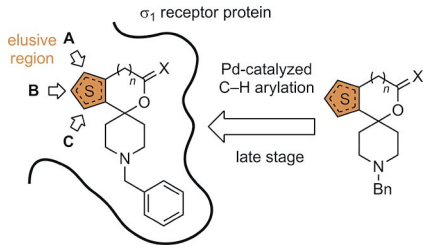
Spirocyclic Thiophenes

Diverse spirocyclic thiophenes were synthesized regioselectively by direct C–H bond arylation using the catalytic systems $PdCl_2$/bipy/Ag_2CO_3 and $PdCl_2$/P[$OCH(CF_3)_2$]$_3$/Ag_2CO_3. Compounds bearing the phenyl moiety at the top position and the sulfur atom in left position show the highest σ_1 affinity.



Keywords: C–C coupling / Arylation / Sulfur heterocycles / Ligand design / Spiro compounds / Protein structures

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