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Improvement of σ_1 receptor affinity by late-stage C–H-bond arylation of spirocyclic lactones

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ABSTRACT

The direct C–H-bond arylation of the complex spirocyclic lactones **13**, **14**, and **18** allows the introduction of diverse aryl moieties in the last step of the synthesis. A selective α-arylation of the thiophene moiety was performed with the catalytic system $PdCl_2$/2,2′-bipyridyl/Ag_2CO_3, whereas the β-position of the thiophene ring was addressed by using the alternative catalytic system $PdCl_2$/P[OCH(CF_3)$_2$]$_3$/Ag_2CO_3. Due to electronic and steric reasons the arylation of the five-membered lactone **18** occurred in both α-positions providing 4′-mono-, 6′-mono- and 4′,6′-diarylated thiophenes **22**–**26a**–**c**. Compounds with an additional aryl moiety at the 'upper left (top)' position (1′-position of **13**, 3′-position of **14**, 4′-position of **18**) showed increased σ_1 affinity compared to the non-arylated parent compounds. A phenyl moiety at the 'left' position (2′-position in **20a**) also increased the σ_1 affinity but to a lower extent. A considerable reduction of σ_1 affinity was observed after introducing an aryl moiety in 6′-position of **18**, which might result from shielding the tertiary amine, which is crucial for interaction with the σ_1 receptor. The discussion of the experimental results is supported by high-level quantum chemical DFT-calculations of the NBO-charges of **13** and **18** and the relative energies of the related arylated products.

1. Introduction

The group of σ receptors has been divided into at least two subtypes, which are termed σ_1 and σ_2 receptors. The gene of the human σ_1 receptor encodes for a protein of 223 amino acids with a molecular weight of 25.3 kDa. On the level of amino acid sequence the σ_1 receptor is well characterized. The amino and carboxy termini of the membrane bound σ_1 receptor protein are linked by two transmembrane domains and both are located on the intracellular side of the membrane.[1–4] Although the σ_2 receptor is less characterized than the σ_1 receptor, the identity of the σ_2 receptor and the progesterone receptor membrane component 1 (pgrmc1) was postulated recently. In 1996 the pgrmc1 was cloned and the resulting protein consists of 194 amino acids with a molecular weight of 21.7 kDa.[5,6]

Ligands which are able to modulate the σ_1 receptor activity possess a high potential for the treatment of acute and chronic neurological disorders (e.g., depression, schizophrenia, (neuropathic) pain, Alzheimer's disease). Unpleasant and dangerous effects after withdrawal of alcohol, cocaine, or methamphetamine from addicted animals can be reduced by σ_1 antagonists.[7–10] Furthermore, σ_1 antagonists are valuable tools in cancer research due to the fact that several human tumor cells produce numerous copies of σ_1 (and σ_2) receptors.[11,12]

Our interest has been focused on the development of novel compounds with high affinity towards σ_1 receptors within the central nervous system. We found that spirocyclic piperidines with the privileged 2-benzofuran (**1**) or 2-benzopyran (**3**) substructure are potent σ_1 receptor antagonists binding in the low nanomolar range (Fig. 1). The methoxy moiety replaced with a carbonyl group led to the lactones **2** and **4** with 20-fold reduced σ_1 receptor affinity.[13] Very recently it was shown that an additional aryl moiety at the 'upper left (top)' position of the spirocyclic compounds is well tolerated by the σ_1 receptor protein or even increases the σ_1 affinity. It was postulated that the additional aryl moiety of the ligands might occupy an additional hydrophobic pocket of the σ_1 receptor protein.[14,15]

Replacement of the benzene substructure of the spirocyclic σ_1 ligands **1** and **3** with a bioisosteric thiophene moiety (**5**) led to very potent σ_1 ligands, which even exceed the σ_1 affinity of the parent benzene derivatives **1** and **3**. The σ_1 affinity of the spirocyclic thiophenes **5** is in the subnanomolar range.[15–17] In this project the effect of an oxo group (**6**) instead of an acetalic methoxy moiety (**5**)

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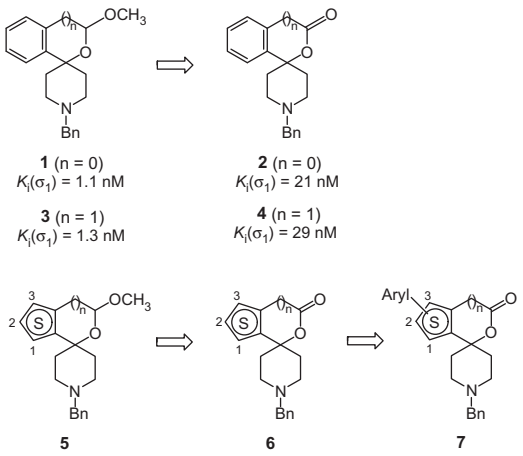


Figure 1. Potent σ_1 ligands with benzofuran and benzopyran structure and design of novel thiophene annulated lactones with additional aryl substituents.

on the σ_1 receptor affinity is investigated. Subsequently, a broad selection of aryl moieties with different substituents is introduced in α- or β-position of the thiophene ring by direct C–H-bond arylation. This arylation should be performed at the end of the synthesis to allow the preparation of a large collection of diversely arylated compounds. A direct C–H-bond arylation of complex spirocyclic thiophenes with a lactone substructure has not been performed so far. In particular the compatibility of the lactone moiety with the basic reaction conditions (Ag_2CO_3) and the high temperature (150 °C) should be investigated. The arylation of a constrained five-membered lactone directly connected to the thiophene ring (**18**) is a particular challenge, since the electron density of the thiophene ring is reduced by the carbonyl group. It was found that in the series of thiophene bioisosteric lactones **6** the σ_1 affinity was reduced compared to the σ_1 affinities of the corresponding methoxy derivatives **5**. Therefore it was of particular interest, whether the introduction of an additional aryl moiety into the lactones **6** is able to compensate the reduced σ_1 receptor affinities of the non-arylated lactones **6**.

2. Chemistry

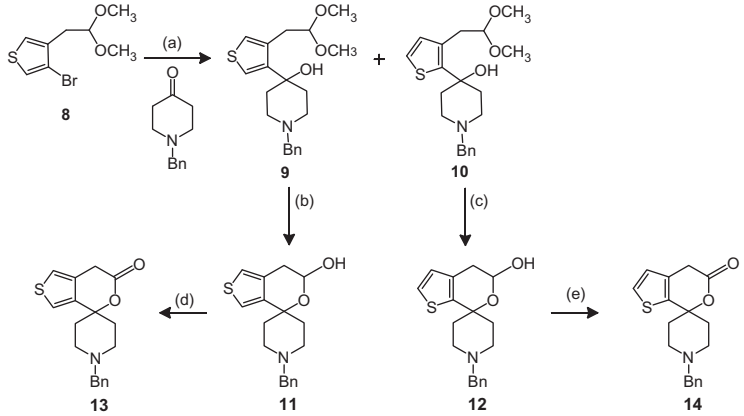
The synthesis started with the (thiophen-3-yl)acetaldehyde acetal **8**.[15] Bromine lithium exchange with *n*-butyllithium at −78 °C and subsequent trapping of the resulting thienyllithium intermediate with 1-benzylpiperidin-4-one led to the regioisomeric hydroxyacetals **9** and **10** in 53% and 12% yields, respectively.[15] The formation of the regioisomer **10** is explained by migration of the lithium atom from the original 4-position to the thermodynamically more stable 2-position. Addition of this thiophen-2-yllithium intermediate to 1-benzylpiperidin-4-one provided the hydroxyacetal **10** (Scheme 1).

The hydroxyacetals **9** and **10** were treated with diluted HCl to afford the cyclic hemiacetals (lactols) **11** and **12**. Since the oxidation of the lactols **11** and **12** with tetrapropylammonium perruthenate (TPAP) in presence of an excess of *N*-methylmorpholine-*N*-oxide (NMMO),[18] with oxalyl chloride/DMSO (Swern oxidation),[19] or with Dess–Martin-Periodinane[20] failed to provide the lactones **13** and **14**, Cr(VI)-salts[21–23] were considered as oxidants. After optimization, the oxidation of lactols **11** and **12** with pyridinium chlorochromate (PCC) provided lactones **13** and **14** in 71% yield, respectively.

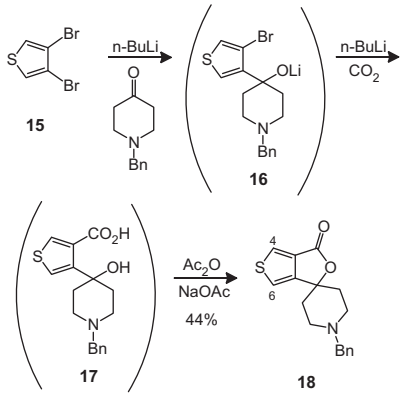
In addition to the six-membered lactones **13** and **14** the corresponding smaller homologue **18** was envisaged. Both the carbonyl moiety directly attached to the thiophene ring and the reduced size of the lactone ring might influence the direct C–H-bond arylation process as well as the σ affinity of the resulting compounds.

A one-pot three step procedure for the synthesis of similar lactones was reported in literature,[24] which was followed herein. At first dibromothiophene **15** was reacted with one equivalent of *n*-butyllithium followed by addition of 1-benzylpiperidin-4-one. The resulting lithium alcoholate **16** was treated with an additional equivalent of *n*-butyllithium and the new aryllithium intermediate was trapped with CO_2. Finally, the formed γ-hydroxyacid **17** was heated with acetic anhydride to provide the γ-lactone **18** in 44% yield. During the flash chromatographic purification process small amounts (3%) of 1-benzyl-3′-bromospiro[piperidine-4,4′-thieno[2,3-*c*]furan]-6′-one were also isolated (Scheme 2).

Pd-catalyzed cross-coupling reactions of metalated arene/heteroarene and halogenated arene/heteroarene species are among the most reliable methods for preparing biaryls and heterobiaryls, as exemplified by the Suzuki–Miyaura coupling reaction.[25] However, the direct C–H-bond arylation will avoid the lengthy activation of one arene moiety. After the first pioneering report of Ohta in 1990,[26] a number of catalysts including Pd,[27] Rh,[28,29] Ir,[30] and Cu[31] catalysts were developed promoting the direct α-arylation of thiophene derivatives with haloarenes. After our successful Pd-catalyzed direct α-arylation of related spirocyclic thiophenes containing an ether or acetal group,[15,32,33] we envisaged the catalytic system $PdCl_2$/2,2′-bipyridyl/Ag_2CO_3,[34,35] for the α-arylation of the lactones **13**, **14** and **18**. In particular it was of great interest to determine whether the basic reaction conditions were tolerated



Scheme 1. Synthesis of the spirocyclic thiophene annulated lactones **13** and **14**. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, 15 min, then 1-benzylpiperidin-4-one, −78 °C, 3 h, **9** (53%) and **10** (12%); (b) THF, 1 M HCl, rt, 16 h, 76%; (c) THF, 1 M HCl, rt, 16 h, 30%; (d) PCC, CH_2Cl_2, rt, 16 h, 71%; (e) PCC, CH_2Cl_2, rt, 16 h, 71%.



Scheme 2. Synthesis of spirocyclic thiophene annulated lactone **18**. Reagents and conditions: *n*-BuLi, Et_2O, −78 °C, 10 min, 1-benzylpiperidin-4-one, −78 °C, 30 min; then *n*-BuLi, −78 °C, 10 min, CO_2, <−70 °C, 1 h: then Ac_2O, NaOAc, toluene, 110 °C, 16 h, 44%.

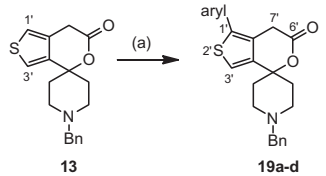
by the lactone moieties. The direct C–H-bond arylation of the lactones **13**, **14** and **18** will allow the step-economical introduction of diverse aryl substituents as last step of the synthesis.

At first the thieno[3,4-*c*]pyranone **13** was reacted with iodobenzene, $PdCl_2$, 2,2′-bipyridyl and Ag_2CO_3 in boiling *m*-xylene (150 °C) to afford the biaryl **19a** in 57% yield (Table 1). The regioisomeric arylation product with the phenyl moiety in 3′-position was not observed. Despite the presence of basic Ag_2CO_3 the lactone moiety of **13** was stable during this transformation. Therefore substituted iodoarenes were also applied for the direct C–H-bond arylation of lactone **13**. Table 1 shows that electron rich (**19b**), electron deficient (**19c**) and sterically demanding (**19d**) aryl moieties could be successfully introduced into the α-position of **13** although the yields were somewhat reduced.

The same reaction conditions were applied for the direct C–H-bond arylation of the regioisomeric lactone **14** with a thieno[2,3-*c*]pyran scaffold. Although the arylation of **14** with iodobenzene yielded the phenylated lactone **20**, a second purification step (preparative thin layer chromatography) had to be performed to achieve the required purity for pharmacological tests. This additional purification step slightly reduced the final yield to 33% (Table 2).

Typically, the catalytic system $PdCl_2$/2,2′-bipyridyl/Ag_2CO_3 leads to a regioselective α-arylation of the thiophene ring. Additionally,

Table 1
Yields after α-arylation of the spirocyclic lactone **13** with various iodoarenes

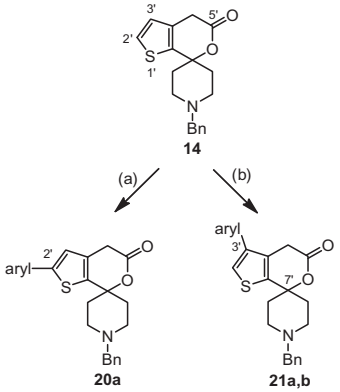


(a) $PdCl_2$/2,2′-bipyridyl, Ag_2CO_3, Aryl-I, *m*-xylene, 150 °C, 12 h.

Compd	Aryl	Yield[a] (%)
19a	C_6H_5	57
19b	*p*-$MeOC_6H_4$	20
19c	*p*-$NC\text{-}C_6H_4$	18
19d	*p*-$C_6H_5\text{-}C_6H_4$	25

[a] Yields after gel permeation chromatography.

Table 2
Yields after α- and β-arylation of spirocyclic lactone **14** with various iodoarenes



(a) $PdCl_2$/2,2′-bipyridyl, Ag_2CO_3, Aryl-I, *m*-xylene, 150 °C, 12 h.

(b) $PdCl_2$, $P[OCH(CF_3)_2]_3$, Ag_2CO_3, Aryl-I, *m*-xylene, 150 °C, 12 h.

Compd	Aryl	Catalyst	Yield[a] (%)	Yield[b] (%)
20a	C_6H_5	$PdCl_2$/bipy	47	33
21a	C_6H_5	$PdCl_2/P[OCH(CF_3)_2]_3$	31	10[c]
21b	*p*-$MeOC_6H_4$	$PdCl_2/P[OCH(CF_3)_2]_3$	54	8[c]

[a] Yields after gel permeation chromatography.
[b] Yields after preparative thin layer chromatography.
[c] Yields after flash chromatography.

some unique catalysts have been reported to induce a selective arylation in β-position of the thiophene ring.[35–37] However, most of these catalysts were used exclusively for the arylation of simple thiophenes without additional functional groups. Herein the catalytic system $PdCl_2/P[OCH(CF_3)_2]_3/Ag_2CO_3$[36,37] was investigated for the β-arylation of the key spirocyclic thieno[2,3-*c*]pyranone **14**.

Thus the reaction of lactone **14** with iodobenzene in the presence of $PdCl_2/P[OCH(CF_3)_2]_3/Ag_2CO_3$ in boiling *m*-xylene occurred regioselectively in 3′-position to produce the 3′-phenylated thienopyranone **21a**. In contrast to the reaction of the lactone **14** with the donor substituted 1-iodo-4-methoxybenzene providing a moderate yield of the arylation product **21b**, the corresponding electron deficient 4-iodobenzonitrile and the sterically demanding 1-iodo-4-phenylbenzene did not yield the corresponding arylation products. A second purification procedure (flash chromatography) was performed to obtain the β-arylated products **21a** and **21b** in the requested purity for biological experiments. This purification step reduced the yields of both arylation products **21** considerably.

After the successful α- and β-arylation of the spirocyclic thienopyranones **13** and **14**, the arylation of the corresponding thienofuranone **18** was envisaged. It should be investigated whether the smaller, more constrained five-membered lactone is also stable under the arylation conditions. Moreover, the influence of the carbonyl moiety directly attached to the thiophene ring (see Fig. 2) was evaluated.

At first the thienofuranone **18** was reacted with iodobenzene and the catalytic system $PdCl_2$/2,2′-bipyridyl/Ag_2CO_3 in boiling *m*-xylene as described for the six-membered lactones **13** and **14**. This transformation led to three arylation products, which were separated by chromatography (Table 3). Unexpectedly, both α-positions of the thiophene moiety were attacked by the catalyst to produce the 4′- and 6′-monophenylated products **22a** and **22b** as well as the diphenylated product **22c**.

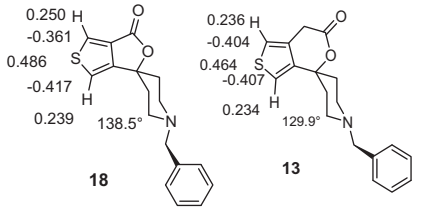
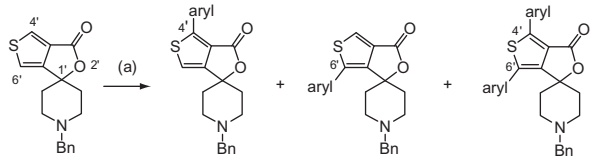


Figure 2. NBO-charges (B97-D/def2-TZVP) at C-, H-, and S-atoms of the thiophene subunit and the thiophene-piperidine angle in thienopyranone **13** and thienofuranone **18**.

Table 3
Products and yields after α-arylation of spirocyclic lactone **18** with various iodoarenes



(a) $PdCl_2$/2,2'-bipyridyl, Ag_2CO_3, Aryl-I, *m*-xylene, 150 °C, 12h.

Compd	Aryl	Position	Yield[a] (%)	Yield (%)
22a	C_6H_5	C-4′	50 (m. r.)	25[b]
22b	C_6H_5	C-6′		5[b]
22c	C_6H_5	C-4′/C-6′	27	21[c]
23a	*p*-$MeOC_6H_4$	C-4′	25 (m. r.)	16[b]
23b	*p*-$MeOC_6H_4$	C-6′		8[b]
23c	*p*-$MeOC_6H_4$	C-4′/C-6′	14	9[c]
24a	*p*-NCC_6H_4	C-4′	35 (m. r.)	23[b]
24b	*p*-NCC_6H_4	C-6′		6[b]
24c	*p*-NCC_6H_4	C-4′/C-6′	25	17[c]
25a	1-Naphthyl	C-4′	61 (m. r.)	31[b]
25b	1-Naphthyl	C-6′		4[b]
25c	1-Naphthyl	C-4′/C-6′	38	11[c]
26a	*p*-C_6H_5-C_6H_4	C-4′	40 (m. r.)	16[b]
26b	*p*-C_6H_5-C_6H_4	C-6′		9[b]
26c	*p*-C_6H_5-C_6H_4	C-4′/C-6′	28	20[c]

(m. r.) Mixture of regioisomers.
[a] Yields after gel permeation chromatography.
[b] Yields after preparative thin layer chromatography.
[c] Yields after flash chromatography.

The scope of this transformation was investigated by employing electron rich (1-iodo-4-methoxybenzene), electron deficient (4-iodobenzonitrile) and sterically demanding (1-iodo-4-phenylbenzene, 1-iodonaphthalene) aryl iodides. Table 3 shows that the arylation conditions were well tolerated by the five-membered lactone **18**. The arylation of **18** with iodobenzene derivatives always led to both monoarylated **22a**,**b**–**26a**,**b** and the diarylated products **22c**–**26c**. Even sterically demanding aryl iodides like 1-iodo-4-phenylbenzene and 1-iodonaphthalene led to the 6′-arylated products.

Generally the yields of the arylated products were rather high. However, due to the formation of product mixtures, careful separations had to be performed to obtain pure products for the biological assays. Generally all compounds were purified by gel permeation chromatography (gpc) to separate the diarylated compounds **22c**–**26c**. The remaining mixtures of regioisomeric monoarylated products were purified either by preparative thin layer chromatography or flash chromatography.

3. DFT calculations and mechanistic considerations

In order to determine the structural and electronic properties of compounds **13** and **18** and their arylated derivatives **19** and **22**–**26**, quantum chemical DFT-calculations at various levels of theory were performed. The input files were generated using PCModel.[38] Structures **13** and **18** were completely optimized at the B3LYP/6-31G(d) and B3LYP/6-311+G(d,p)[39,40] levels of theory employing the GAUSSIAN09 series of programs.[41] Then, SCS-MP2-single point energies were evaluated.[42] Since electronic interaction between the adjacent aromatic moieties seemed to be important, additionally B97-D/def2-TZVP[43,44] optimizations were carried out. The 'natural' charges as calculated from a Natural Bond Orbital analysis[45] ('NBO-charges') obtained for **13** and **18** at the B97-D level are given in Figure 2.

At first, the precursor molecules **13** and **18** were inspected with respect to their NBO-charges. For both *exo*- and *endo*-carbon atoms of thienopyranone **13** (positions 1′ and 3′) NBO-calculations provided very similar negative charges, both equally suitable for an attack of an electrophilic arylation reagent like the $PdCl_2$/bipy/Ag_2CO_3/Aryl-I system employed in the experiments. In contrast in thienofuranone **18**, due to the adjacent carbonyl moiety, the NBO-charge at the *exo*-carbon atom 4′ (−0.36 e) is substantially smaller compared to that at the *endo*-position 6′ (−0.42 e) indicating significantly reduced nucleophilicity at 4′-center.

The calculated structural properties for **13** indicate that the accessibility at the *endo*-carbon atom 3′ is limited as seen from the angle between the thiophene and the spirocyclic connected piperidine ring (129.9°). For **18**, the corresponding angle amounts to 138.5°, thus allowing a less hindered approach of spacious reagents in this position (Figure 2).

In order to evaluate the energetically preferred site for arylation at the thiophene moieties of **13** and **18** the four possible aryl-substituted species **19a**, **22a**, **22b** and the experimentally not observed 3′-phenyl-substituted lactone **19x** were calculated at the same levels of theory; additionally B2PLYP-D/def2-TZVP-single point energies[46–48] were evaluated (Table 4). As Table 4 indicates, the *exo*-aryl-coupling products are generally energetically favored, although the preference is quite dependent on the computational method used. This is well in line with the reduced sterical strain in the *exo*-position. As the dispersion corrected methods B97-D and B2PLYP-D are expected to give the more reliable results, a slightly higher thermodynamic preference for the *exo*-position is anticipated from these calculations for the five-membered ring systems **22**–**26** compared to the six-membered ring systems **19a**–**d**.

Thus, the isolation of compounds **19a**–**d**, which result exclusively from attack at the *exo*-(1′)-position of thienopyranone **13**, is well in line with the calculated energetic preference and the restricted accessibility of position 3′. However, the formation of the experimentally obtained mixtures **22a**–**c**, **23a**–**c**, **24a**–**c**, **25a**–**c**, and **26a**–**c** from thienofuranone **18** indicates that now arylation at 6′-position becomes kinetically competitive due to less steric hindrance and to the more favorable electronic situation at 6′-position, overcoming the thermodynamic disadvantages.

Very recently, an experimental and theoretical study of the Pd-catalyzed direct C–H-bond arylation of 2-substituted thiophenes was published indicating kinetic reasons for the observed C-4/C-5-selectivity in this carbopalladation pathway.[49]

4. Receptor affinity

The σ_1 and σ_2 receptor affinities of the five- and six-membered lactones were recorded in competition experiments with radioligands. In the σ_1 assay membrane preparations of guinea pig brains

Table 4
Relative energies [kcal/mol] for compounds **19a**/**19x** (compound **13** with additional phenyl moiety in 3′-position) and **22a**/**22b** obtained by quantum chemical calculations at various levels of theory (stated in the table)

Compd	B3LYP/6-31G(d)(ZPE)	B3LYP/6-311 + G(d,p)(ZPE)	SCS-MP2/6-311 + G(d,p)//B3LYP/6-311 + G(d,p)(ZPE)	B97-D/def-TZVP (ZPE)	B2PLYP-D/def2-TZVP//B97-D/def2-TZVP
19a Pyranone, 1′-phenyl (*exo*)	0.00	0.00	0.00	0.00	0.00
19x Pyranone, 3′-phenyl (*endo*)	6.58	5.85	1.70	2.92	3.46
22a Furanone 4′-phenyl (*exo*)	0.00	0.00	0.00	0.00	0.00
22b Furanone 6′-phenyl (*endo*)	5.93	5.61	0.47	3.74	4.32

containing σ_1 receptors were incubated with the radioligand [^{3}H]-(+)-pentazocine and increasing concentrations of the test compound. A large excess of non-tritiated (+)-pentazocine was used to determine the non-specific binding of the radioligand.[50–53] Since σ_1 receptors of different species (human, guinea pig, rat) are more than 92% identical and more than 95% similar at the level of amino acid sequence,[54] the resulting K_i-values can be considered as representative for many species. The source for σ_2 receptors in the σ_2 assay were rat liver homogenates and [^{3}H]-di-*o*-tolylguanidine was employed as radioligand. Due to the interaction of di-*o*-tolylguanidine with both σ_1 and σ_2 receptors a large amount of non-radiolabeled (+)-pentazocine was added to selectively mask σ_1 receptors. A large excess of non-tritiated di-*o*-tolylguanidine was used to determine the non-specific binding.[50–53]

In Table 5 the σ_1 and σ_2 receptor affinities of the spirocyclic lactones are summarized. Furthermore, the affinities of the lead compounds **1**–**4** and important reference compounds (haloperidol, di-*o*-tolylguanidine, (+)-pentazocine, progesterone) are given for comparison. The σ_1 affinities of the thienopyranone **13** and the thienofuranone **18** are in the same range as the σ_1 affinities of the benzofuranone **2** and benzopyranone **4**. However the regioisomeric thienopyranone **14** is about 10-fold less active than the other lactones. Obviously the position of the S-atom in the thiophene system has a strong impact on the σ_1 receptor affinity.

Table 5
σ_1 and σ_2 Receptor affinities of the synthesized spirocyclic thiophenes and reference compounds

Compd	Aryl	K_i ± SEM (nM) (n = 3)		Selectivity
		σ_1	σ_2	σ_1/σ_2
1[a]	—	1.1 ± 0.22	1280 ± 137	>1000
2[a]	—	21 ± 3.5	1460 ± 108	70
3[a]	—	1.3 ± 0.18	3500 ± 352	>1000
4[a]	—	29 ± 0.9.0	1157 ± 148	40
13	H	40 ± 13	732	18
14	H	255	>1000	>4
18	H	16 ± 6.8	>1000	>60
19a	C_6H_5	2.5 ± 0.91	720	288
19b	*p*-$MeOC_6H_4$	11 ± 3.0	872	79
19c	*p*-CNC_6H_4	11 ± 3.4	>1000	>91
19d	*p*-Biphenyl	108 ± 46	>1000	>9
20a	C_6H_5	23 ± 9.9	>1000	>43
21a	C_6H_5	5.3 ± 0.88	300	57
21b	*p*-$MeOC_6H_4$	43 ± 13	>1000	>23
22a	C_6H_5	11 ± 3.2	236	21
22b	C_6H_5	483	>1000	>2
22c	C_6H_5	87 ± 52	935	11
23a	*p*-$MeOC_6H_4$	9.0 ± 3.2	584	65
23b	*p*-$MeOC_6H_4$	–/–	–/–	–/–
23c	*p*-$MeOC_6H_4$	158	>1000	6
24a	*p*-CNC_6H_4	6.3 ± 2.1	295	47
24b	*p*-CNC_6H_4	190	305	2
24c	*p*-CNC_6H_4	>1000	>1000	—
25a	1-Naphthyl	5.3 ± 2.3	546	103
25b	1-Naphthyl	639	>1000	>2
25c	1-Naphthyl	784	>1000	>1
26a	*p*-Biphenyl	777	>1000	>1
26b	*p*-Biphenyl	402	>1000	>2
26c	*p*-Biphenyl	>1000	>1000	—
Haloperidol		6.3 ± 1.6	78 ± 2.3	12
Di-*o*-tolylguanidine		89 ± 29	58 ± 18	0.7
(+)-Pentazocine		5.7 ± 2.2	—	—
Progesterone		661 ± 115	—	

[a] K_i Values are reported in Ref. 13.

Introduction of a phenyl moiety in 1′-position of the lactone **13** led to the very potent σ_1 ligand **19a** with a K_i-value of 2.5 nM. Ligands with a *p*-methoxy (**19b**) and *p*-cyano (**19c**) moiety at the new phenyl group show σ_1 affinities between the unsubstituted lactone **13** and the phenylated lactone **19a**. The substituted aryl moieties in 1′-position of **19b** and **19c** still favor the interaction with the σ_1 receptor protein although to a lower extend than the non-substituted phenyl moiety of **19a**. The size of the biphenylyl substituent in 1′-position of **19d** (K_i = 108 nM) leads to a decreased σ_1 receptor affinity.

A phenyl moiety in 2′-position of the regioisomeric thienopyranone **14** led to a 10-fold increased σ_1 affinity (**20a**: K_i = 23 nM) compared to the σ_1 affinity of the parent compound **14** (K_i = 255 nM). However, introduction of the phenyl moiety in β-position of the thiophene ring produced the even more potent lactone **21a** (K_i = 5.3 nM). The regioisomeric lactones **19a** and **21a** bearing the phenyl moiety in comparable positions show very similar σ_1 receptor affinities. Obviously a phenyl moiety in the 'upper left' position (1′-position in **19a**, 3′-position in **21a**) favors the interaction of ligands with the σ_1 receptor binding site. As shown for the series **19** a methoxy group within the additional phenyl moiety reduces the σ_1 affinity (compare **19b** and **21b**).

The five-membered lactone **18** has the highest σ_1 affinity (K_i = 16 nM) of the non-arylated lactones. Nevertheless the σ_1 receptor affinity was further increased by introduction of an aryl moiety in the 'upper left (top)' position (4′-position). The phenyl (**22a**, K_i = 11 nM), the donor substituted *p*-methoxyphenyl (**23a**, K_i = 9.0 nM), the acceptor substituted *p*-cyanophenyl (**24a**, K_i = 6.3 nM)) and the sterically demanding 1-naphthyl (**25a**, K_i = 5.3 nM) substituted derivatives show very similar σ_1 receptor affinities in the low nanomolar range. As already observed within the other series, the *p*-biphenylyl substituted derivative **26a** (K_i = 777 nM) exhibits a very low σ_1 affinity indicating that the biphenylyl substituent is too large to fit into the binding pocket of the σ_1 receptor protein.

Introduction of the phenyl moiety in the second α-position (6′-position) of the thiophene ring led to **22b** (K_i = 483 nM) with almost negligible σ_1 receptor affinity. A similar reduction of σ_1 receptor affinity was also observed for the spirocyclic lactones **23b**–**26b** with substituted or sterically demanding aryl moieties in 6′-position. It is assumed that the phenyl moiety in 6′-position shields the basic N-atom and thus inhibits the formation of an ionic interaction with the σ_1 receptor protein, which is crucial for high receptor affinity.

The lactones **24c**–**26c** with two aryl moieties in both α-positions (4′- and 6′-position) are even less potent than the 6′-arylated compounds **24b**–**26b**. The slightly increased σ_1 affinity of **22c** leads to the assumption that the additional phenyl group in 4′-position is able to partially compensate the detrimental effects of the 6′-phenyl moiety.

The σ_2 receptor affinities of the arylated lactones are considerably lower than their σ_1 receptor affinities, that is all compounds show high selectivity for the σ_1 receptor over the σ_2 subtype. In particular the very potent σ_1 ligands **19a**, **19b**, **19c**, **21a**, **23a**, **24a**, and **25a** display excellent σ_1 receptor selectivities (σ_1/σ_2 >47).

5. Conclusion

The six-membered lactones **13** and **14** were selectively arylated in α- and β-position using the catalytic systems $PdCl_2$/2,2′-bipyridyl/Ag_2CO_3 and $PdCl_2$/P[OCH(CF$_3$)$_2$]$_3$/Ag_2CO_3, respectively. Unexpectedly, the direct C–H-bond arylation of the five-membered lactone **18** afforded both α-arylated products, thereby giving access to the 6′-arylated thiophenes **22b**,**c**–**26b**,**c** for the first time. A considerably increased σ_1 receptor affinity was found for compounds bearing the aryl moiety in the 'upper left' position of the thiophene system (e.g., compounds **19a**, **21a**, **24a**, **25a**). Whereas a phenyl moiety in 2′-position ('left' position, compound **20a**) leads to moderate σ_1 affinity, the σ_1 receptor does not tolerate an aryl moiety at 6′-position (e.g., compounds **22b**, **25b**). The double arylated compounds **24c**–**26c** show even lower σ_1 affinities than the 6′-arylated compounds **24b**–**26b**.

6. Experimental

6.1. Chemistry

6.1.1. 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 using phosphorous pentoxide (Granusic® A, Baker)). THF and Et_2O were dried using 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). IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400, 300, 600 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Unity Mercury Plus 400 (400 MHz) NMR spectrometer (Varian), JNM-ECA-400 (400 MHz) spectrometer (JEOL), Brucker AV 300 (300 MHz), and 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 non-deuterated solvent. HRMS (ESI): Finnigan MAT 4200s, Brucker 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 method A: Merck Hitachi Equipment; UV detector: L-7400; autosampler:L-7200; pump: L-7100; degasser: L-7614; column: LiChrospher® 60 RP-select B (5 μm); LiChroCART® 250–4 mm cartridge; flow rate: 1.000 mL/min; injection volume: 5.0 μL; detection at λ = 210 nm; solvents: A: water with 0.05% (v/v) trifluoroacetic acid; B: acetonitrile with 0.05% (v/v) trifluoroacetic acid: gradient elution: (A%): 0–4 min: 90% 4–29 min: gradient from 90%,to 0%, 29–31 min: 0%, 31–31.5 min: 0% to 90%, 31.5–40 min: 90%. HPLC method B: Agilent Technologies®; UV and mass detection: Agilent 1200 Series Variable Wavelength Detector G13143/G1314C (SL) and Agilent G1978AQ/B Multimode source (mass detector); autosampler: Agilent 1200 Series High Performance autosampler and Micro Well Plate autosampler; quaternary pump for gradient analysis, degasser: Agilent 1200 Series Micro Vacuum Degasser; column: ZOBRAX Eclipse Plus C18 150–2 mm, 3.5 μm; flow rate: 0.40 mL/min; injection volume: 1 μL; detection: λ = 254 nm, cut off time: 13 min; solvents: A: H_2O dest. + 5 mM NH_4HCO_2; B: acetonitrile; gradient elution: (A%): 0 min: 80%, 0–5 min: gradient form 80% to 0%, 5–13 min: 0%, 13–18 min: gradient from 0% to 80%. The purity of all test compounds was greater than 95%, which was determined by HPLC method A or B.

6.1.2. 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 rt. Under a permanent stream of Ar the catalyst $PdCl_2$/bipy (10 mol %) and Ag_2CO_3 (1 equiv) were filled into the vessel and suspended in dry *m*-xylene (0.4 mL). This mixture was stirred at 60 °C for 30 min. Finally, a solution of iodoarene (1.1 equiv) and a solution of the spirocyclic lactone (1 equiv) in dry *m*-xylene (0.6 mL in total) were added dropwise. The vessel was sealed with the O-ring tap and heated up at 150 °C for 12 h in an 8-well reaction block. After cooling the vessel to rtk the mixture was filtered through a short silica pad using EtOAc as the eluent. 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 fc (short column) to yield the corresponding arylthiophene in high purity.

6.1.3. 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 rt. Under a permanent stream of Ar $PdCl_2$ (10 mol %) and Ag_2CO_3 (1 equiv) were filled into the vessel. The phosphite ligand P[OCH(CF$_3$)$_2$]$_3$ (20 mol %) and subsequently dry *m*-xylene (0.5 mL) were added and this 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 lactone (1 equiv) in dry *m*-xylene (0.5 mL in total) were added. The vessel was sealed with the O-ring tap and heated up at 150 °C for 12 h in an 8-well reaction block. After cooling the vessel to rt, 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 fc (short column) to yield the corresponding arylthiophene in high purity.

6.1.4. 1-Benzyl-4-[4-(2,2-dimethoxyethyl)thiophen-3-yl]piperidin-4-ol (9) and 1-benzyl-4-[3-(2,2-dimethoxyethyl)thiophen-2-yl]piperidin-4-ol (10)[15]

Under N_2 and at −78 °C *n*-butyllithium in *n*-hexane (1.26 M, 2.74 mL, 3.44 mmol) was added slowly to a stirred solution of the bromothiophene **8** (0.67 g, 2.65 mmol) in dry THF (15 mL). The mixture was stirred for 15 min. Then 1-benzylpiperidin-4-one (0.57 mL, 3.2 mmol) was added slowly into the solution. After 3 h stirring at −78 °C, the flask was warmed up to rt and water was added. The aqueous layer was separated and extracted twice with CH_2Cl_2. The combined organic layers were dried using K_2CO_3, filtered and the solvent was removed in vacuo. The regioisomeric

alcohols **9** and **10** were separated by fc (5 cm, h = 15 cm, cyclohexane/EtOAc = 4:1, 20 mL).

Compound **10** (R_f = 0.35, cyclohexane/EtOAc = 3:7): Pale yellow oil, yield 0.11 g (12%). $C_{20}H_{27}NO_3S$ (361.5 g/mol). MS (EI): m/z = 361 [M^+], 328 [M^+ –OCH_3,–2H], 298 [M^+ –$(OCH_3)_2$, –H], 91 [$^+CH_2Ph$]. IR (neat): ν (cm^{-1}) = 3430 (O–H), 3026 (C–H_{aryl}), 2934, 2812 (C–H), 1118 (C–O), 697 (C–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.90–1.97 (m, 2H, N(CH_2CH_2)$_2$), 2.07–2.16 (m, 2H, N(CH_2CH_2)$_2$), 2.49–2.56 (m, 2H, N(CH_2CH_2)$_2$), 2.71–2.80 (m, 2H, N(CH_2CH_2)$_2$), 3.22 (d, J = 5.5 Hz, 2H, thiophCH_2CH), 3.35 (s, 6H, CH(OCH_3)$_2$), 3.57 (s, 2H, NCH_2Ph), 3.62 (s, 1H, OH), 4.48 (t, J = 5.5 Hz, 1H, thiophCH$_2$CH), 6.81 (d, J = 5.1 Hz, 1H, 4-H-thioph), 7.09 (d, J = 5.1 Hz, 1H, 5-H-thioph), 7.29–7.37 (m, 5H, Ph-H).

Compound **9** (R_f = 0.22, cyclohexane/EtOAc = 3:7): Pale yellow oil, yield 0.50 g (53%). $C_{20}H_{27}NO_3S$ (361.5 g/mol). MS (EI): m/z = 361 [M^+], 330 [M^+ –OCH_3], 298 [M^+ –$(OCH_3)_2$, –H], 91 [$^+CH_2Ph$]. IR (neat): ν (cm^{-1}) = 3442 (O–H), 3027 (C–H_{aryl}), 2926, 2814 (C–H), 1119 (C–O), 698 (C–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.88–1.95 (m, 2H, N(CH_2CH_2)$_2$), 2.06 (td, J = 12.9/4.3 Hz, 2H, N(CH_2CH_2)$_2$), 2.51 (td, J = 11.9/2.5 Hz, 2H, N(CH_2CH_2)$_2$), 2.70–2.78 (m, 2H, N(CH_2CH_2)$_2$), 3.24 (d, J = 5.6 Hz, 2H, thiophCH_2CH), 3.35 (s, 6H, CH(OCH_3)$_2$), 3.51 (s, 1H, OH), 3.57 (s, 2H, NCH_2Ph), 4.52 (t, J = 5.6 Hz, 1H, thiophCH$_2$CH), 7.06 (d, J = 3.2 Hz, 1H, 5-H-thioph), 7.08 (d, J = 3.2 Hz, 1H, 2-H-thioph), 7.26–7.37 (m, 5H, Ph-H).

6.1.5. 1-Benzyl-6′,7′-dihydrospiro[piperidine-4,4′-thieno[3,4-*c*]pyran]-6′-ol (11)

The hydroxyacetal **9** (1.06 g, 2.94 mmol) was dissolved in THF (5 mL) and HCl (1 M, 30 mL, 30 mmol) was added. The mixture was stirred at rt for 16 h. Subsequently 2 M NaOH was added dropwise until pH 8, the aqueous layer was separated and extracted twice with CH_2Cl_2. The combined organic layers were dried using K_2CO_3, filtered and the solvent was removed in vacuo. The remaining paste was purified by fc (6 cm, h = 15 cm, cyclohexane/EtOAc = 3:2, 20 mL, R_f = 0.18). Colorless solid, mp 146 °C, yield 703.1 mg (76%). $C_{18}H_{21}NO_2S$ (315.4 g/mol). Purity (HPLC, method A): 97.3%, t_R = 14.0 min MS (EI): m/z = 315 [M^+], 224 [M^+ –CH_2Ph], 91 [$^+CH_2Ph$]. IR (neat): ν (cm^{-1}) = 3079 (O–H), 2937 (C–H), 2836 (C–H), 1051 (C–O), 698 (C–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.91–2.20 (m, 4H, N(CH_2CH_2)$_2$), 2.44–2.61 (m, 2H, N(CH_2CH_2)$_2$), 2.68–2.85 (m, 3H, thiophCH_2CH, N(CH_2CH_2)$_2$), 3.05 (dd, J = 15.3/3.0 Hz, 1H, thiophCH_2CH), 3.59 (s_{broad}, 2H, NCH_2Ph), 5.30 (dd, J = 7.4/3.0 Hz, 1H, thiophCH$_2$CH), 6.94 (d, J = 3.0 Hz, 3′-H-thioph), 6.99 (d, J = 2.9 Hz, 1H, 1′-H-Thioph), 7.28–7.41 (m, 5H, Ph-H). A signal for the OH-proton is not visible. ^{13}C NMR ($CDCl_3$): δ (ppm) = 34.3 (1C, thiophCH_2CH), 37.3 (1C, N(CH_2CH_2)$_2$), 39.9 (1C, N(CH_2CH_2)$_2$), 49.3 (1C, N(CH_2CH_2)$_2$), 49.5 (1C, N(CH_2CH_2)$_2$), 63.4 (1C, NCH_2Ph), 74.6 (1C, thiophC_{spiro}), 90.5 (1C, thiophCH$_2$CH), 118.7 (1C, C-1′-thioph), 120.3 (1C, C-3′-thioph), 127.4 (Ph-CH), 128.5 (Ph-CH), 129.6 (Ph-CH), 133.2 (1C, C_{quart}), 142.9 (1C, C_{quart}). One signal for a quaternary carbon atom is not visible.

6.1.6. 1-Benzyl-4′,5′-dihydrospiro[piperidine-4,7′-thieno[2,3-*c*]pyran]-5′-ol (12)

The alcohol **10** (1.99 g, 5.5 mmol) was dissolved in THF (10 mL) and HCl (1 M, 55 mL, 55 mmol) was added. The mixture was stirred at rt for 16 h. Subsequently, 2 M NaOH was added dropwise until pH 8, the aqueous layer was separated and extracted twice with CH_2Cl_2. The combined organic layers were dried using K_2CO_3, filtered and the solvent was removed in vacuo. The remaining solid was purified by flash chromatography (Ø = 5.5 cm, h = 15 cm, cyclohexane/EtOAc = 4:1 (NEt_3 2%), 30 mL, R_f = 0.26) followed by recrystallization. Colorless solid, mp 168 °C, yield 515 mg (30%). $C_{18}H_{21}NO_2S$ (315.4 g/mol). Purity (HPLC, method A): 99.2%, t_R = 14.3 min MS (EI): m/z = 315 [M^+], 224 [M^+ –CH_2Ph], 91 [$^+CH_2Ph$]. IR (neat): ν (cm^{-1}) = 3104 (O–H), 2936 (C–H), 2840 (C–H), 1055 (C–O), 695 (C–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.89–2.15 (m, 4H, N(CH_2CH_2)$_2$), 2.42–2.63 (m, 2H, N(CH_2CH_2)$_2$), 2.68 (dd, 15.5/7.4 Hz, 1H, thiophCH_2CH), 2.72–2.82 (m, 2H, N(CH_2CH_2)$_2$), 2.96 (dd, J = 15.5/3.2 Hz, 1H, thiophCH_2CH), 3.59 (s_{broad}, 2H, NCH_2Ph), 5.33 (dd, J = 7.4/3.2 Hz, 1H, thiophCH$_2$CH), 6.75 (d, J = 5.0 Hz, 1H, 3′-H-thioph), 7.17 (d, J = 5 Hz, 1H, 2′-H-Thioph), 7.27–7.40 (m, 5H, Ph-H). A signal for the OH-proton is not visible. ^{13}C NMR ($CDCl_3$): δ (ppm) = 34.0 (1C, thiophCH_2CH), 37.7 (1C, N(CH_2CH_2)$_2$), 40.9 (1C, N(CH_2CH_2)$_2$), 49.2 (1C, N(CH_2CH_2)$_2$), 49.3 (1C, N(CH_2CH_2)$_2$), 63.3 (1C, NCH_2Ph), 74.6 (1C, thiophC_{spiro}), 90.4 (1C, thiophCH$_2$CH), 123.8 (1C, C-2′-thioph), 126.8 (1C, C-3′-thioph), 127.3 (1C, Ph-CH), 128.4 (2C, Ph-CH), 129.5 (2C, Ph-CH), 131.0 (1C, C_{quart}), 141.4 (1C, C_{quart}). One signal for a quaternary carbon atom is not visible.

6.1.7. 1-Benzylspiro[piperidine-4,4′-thieno[3,4-*c*]pyran]-6′(7′*H*)-one (13)

Under N_2 PCC (274 mg, 1.27 mmol) was suspended in dry CH_2Cl_2 (5 mL) and stirred for 2 min. Then lactol **11** (309 mg, 0.98 mmol) was suspended in CH_2Cl_2 (10 mL) and added to the PCC suspension rapidly. This mixture was stirred at rt for 16 h. Then saturated $NaHCO_3$ solution (30 mL) was added and the aqueous layer was extracted twice with Et_2O. The combined organic layers were filtered, dried using K_2CO_3 and filtered again. The solvent was removed in vacuo and the residue was purified by fc (3 cm, h = 15 cm, cyclohexane/EtOAc = 7.5:2.5, NEt_3 2%, 20 mL, R_f = 0.24 cm). Pale yellow oil, yield 216 mg (71%). $C_{18}H_{19}NO_2S$ (313.4 g/mol). Purity (HPLC, method A): 99.3%, t_R = 14.4 min MS (ESI): m/z = 314 [MH^+]. IR (neat): ν (cm^{-1}) = 3100 (C–H_{aryl}), 2924, 2816 (C–H), 1735 (C=O), 698 (C–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.03 (dd, J = 14.7/2.3 Hz, 2H, N(CH_2CH_2)$_2$), 2.15 (td, J = 12.4/4.4 Hz, 2H, N(CH_2CH_2)$_2$), 2.59 (td, J = 12.0/2.4 Hz, 2H, N(CH_2CH_2)$_2$), 2.80 (d, J = 11.6 Hz, 2H, N(CH_2CH_2)$_2$), 3.59 (s, 2H, NCH_2Ph), 3.76 (s, 2H, thiophCH_2), 7.04 (d, J = 2.8 Hz, 1H, 3′-H-thioph), 7.12 (d, J = 2.9 Hz, 1H, 1′-H-thioph), 7.27–7.37 (m, 5H, Ph-H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 32.8 (1C, thiophCH_2C=O), 37.2 (2C, N(CH_2CH_2)$_2$), 48.7 (2C, N(CH_2CH_2)$_2$), 63.1 (1C, NCH_2Ph), 81.4 (1C, thiophC_{spiro}), 119.2 (1C, C-1′-thioph), 120.8 (1C, C-3′-thioph), 127.5 (1C, Ph-C), 128.5 (2C, Ph-C), 129.5 (2C, Ph-C), 130.7 (1C, C_{quart}), 146.0 (1C, C_{quart}), 169.3 (1C, C=O). One signal for a quaternary carbon atom is not visible.

6.1.8. 1-Benzylspiro[piperidine-4,7′-thieno[2,3-*c*]pyran]-5′(4′*H*)-one (14)

Under N_2 PCC (152 mg, 0.7 mmol) was suspended in dry CH_2Cl_2 (5 mL) and stirred for 2 min. Then lactol **12** (170 mg, 0.54 mmol) was suspended in CH_2Cl_2 (5 mL) and added to the PCC suspension rapidly. This mixture was stirred at rt for 16 h. Then saturated $NaHCO_3$ solution (20 mL) was added and the aqueous layer was extracted twice with Et_2O. The combined organic layers were filtered, dried using K_2CO_3 and filtered again. The solvent was removed in vacuo and the residue was purified by fc (3 cm, h = 15 cm, cyclohexane/EtOAc = 4:1, NEt_3 2%, 15 mL, R_f = 0.27 cm). Pale yellow oil, yield 120 mg (71%). $C_{18}H_{19}NO_2S$ (313.4 g/mol). Purity (HPLC, method A): 98.2%, t_R = 14.4 min. Exact mass (APCI): m/z = calcd for $C_{18}H_{19}NO_2S$ [MH^+] 314.1209, found 314.1217. IR (neat): ν (cm^{-1}) = 3099 (C–H_{aryl}), 2918, 2815 (C–H), 1737 (C=O), 697 (C–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.05 (dd, J = 14.6/2.3 Hz, 2H, N(CH_2CH_2)$_2$), 2.14 (td, J = 12.0/4.4 Hz, 2H, N(CH_2CH_2)$_2$), 2.61 (td, J = 11.8/2.6 Hz, 2H, N(CH_2CH_2)$_2$), 2.79 (d, J = 11.6 Hz, 2H, N(CH_2CH_2)$_2$), 3.59 (s, 2H, NCH_2Ph), 3.70 (s, 2H, thiophCH_2), 6.81 (d, J = 5.0 Hz, 1H, 3′-H-thioph), 7.27–7.38 (m, 6H, 2′-H-thioph, Ph-H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 31.9 (1C, thiophCH_2C=O), 39.2 (2C, N(CH_2CH_2)$_2$), 48.7 (2C, N(CH_2CH_2)$_2$), 63.2 (1C, NCH_2Ph), 81.8 (1C, thiophC_{spiro}), 125.3 (1C, CH-2′-thioph), 125.9 (1C, C-3′-thioph), 127.3 (Ph-CH), 128.5 (Ph-CH), 129.3 (Ph-CH), 129.7 (1C, C_{quart}), 138.2 (1C, C_{quart}), 138.4 (1C, C_{quart}), 169.1 (1C, C=O).

6.1.9. 1-Benzylspiro[piperidine-4,1′-thieno[3,4-*c*]furan]-3′-one (18) and 1-benzyl-3′-bromospiro[piperidine-4,4′-thieno[2,3-*c*]furan]-6′-one

In a three-necked flask 3,4-dibromothiophene (**15**, 654 mg, 2.7 mmol) was dissolved in freshly distilled Et_2O (8 mL) and cooled down under N_2 to −78 °C. After 15 min stirring at −78 °C, *n*-butyllithium in *n*-hexane (1.35 M, 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_2O (3 mL), was added dropwise into the solution and the solution was stirred for 30 min (→**16**). Next the reaction mixture was diluted with Et_2O (15 mL). For the second halogen-metal-exchange-reaction a second equivalent of *n*-butyllithium in *n*-hexane (1.35 M, 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 by H_2SO_4) was bubbled through the mixture for 1 h while the temperature was kept below −70 °C. For the workup the flask was warmed up to rt 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_2O. Next the aqueous layer was acidified with 2 M HCl and washed several times with Et_2O. The aqueous layer was concentrated in vacuo and the intermediate **17** was directly used for cyclization without purification. The crude product was dissolved in a mixture of Ac_2O (3 mL) and NaOAc (532 mg, 6.5 mmol) in toluene (20 mL) and the mixture was heated to reflux for 16 h. For the workup the reaction mixture was cooled down to rt, poured into saturated K_2CO_3 solution and the mixture was stirred for 1 h. When the 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 using K_2CO_3, filtered and the solvent was removed in vacuo. The remaining solid was purified by fc (4.5 cm, h = 15 cm, cyclohexane/EtOAc = 7:3 ($NHEt_2$ 2%), 30 mL). In addition to the desired lactone **18**, traces of the side product 1-benzyl-3′-bromospiro[piperidine-4,4′-thieno[2,3-*c*]furan]-6′-one (R_f = 0.60, cyclohexane/EtOAc = 3:7) were separated.

Compound **18** (R_f = 0.42, cyclohexane/EtOAc = 3:7), colorless solid, mp 95 °C, yield 353 mg (44%, calculated from **15**). $C_{17}H_{17}NO_2S$ (299.1 g/mol). Purity (HPLC, method A): 98.7%, t_R = 13.7 min. Exact MS (APCI): m/z = calcd for $C_{17}H_{17}NO_2S$ [MH^+] 300.1053, found 300.1081. IR (neat): ν (cm^{-1}) = 3102 (C–H_{aryl}), 2922 (C–H), 2811 (C–H), 1758 (C=O), 698 (C–H). ^1H NMR ($CDCl_3$): δ (ppm) = 1.96 (d, J = 13.5 Hz, 2H, N(CH_2CH_2)$_2$), 2.08 (td, J = 10.0/3.9 Hz, 2H, N(CH_2CH_2)$_2$), 2.61 (t, J = 9.8 Hz, 2H, N(CH_2CH_2)$_2$), 2.75 (d, J = 11.7 Hz, 2H, N(CH_2CH_2)$_2$), 3.61 (s, 2H, NCH_2Ph), 7.07 (d, J = 2.3 Hz, 1H, 6′-*H*-thioph), 7.27–7.39 (m, 5H, Ph-*H*). 7.88 (d, J = 2.4 Hz, 1H, 4′-*H*-thioph). ^{13}C NMR ($CDCl_3$): δ (ppm) = 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_{quart}), 138.0 (1C, C_{quart})(Ph-C), 154.7 (1C, C_{quart}), 162.8 (1C, *C*=O).

1-Benzyl-3′-bromospiro[piperidine-4,4′-thieno[2,3-*c*]furan]-6′-one (R_f = 0.60, cyclohexane/EtOAc = 3:7): Colorless solid, mp 105 °C, yield 28.4 mg (3%, referring to **15**). $C_{17}H_{16}BrNO_2S$ (378.2 g/mol). Purity (HPLC, method A): 97.5%, t_R = 15.7 min. Exact MS (APCI): m/z = calcd for $C_{17}H_{16}BrNO_2S$ [MH^+] 378.0158, found 378.0163. IR (neat): ν (cm^{-1}) = 3112 (C–H_{aryl}), 1763 (C=O), 1051 (C-Br), 697 (C–H). ^1H NMR ($CDCl_3$): δ (ppm) = 1.68 (d, J = 10.6 Hz, 2H, N(CH_2CH_2)$_2$), 2.44–2.58 (m, 4H, N(CH_2CH_2)$_2$), 2.91 (d, J = 7.3 Hz, 2H, N(CH_2CH_2)$_2$), 3.61 (s, 2H, NCH_2Ph), 7.27–7.40 (m, 5H, Ph-*H*), 7.69 (s, 1H, 2′-*H*-thioph). ^{13}C NMR ($CDCl_3$): δ (ppm) = 33.8 (2C, N(CH_2CH_2)$_2$), 49.3 (2C, N(CH_2CH_2)$_2$), 63.1 (1C, NCH_2Ph), 85.1 (1C, C_{spiro}), 103.6 (1C, Br-C_{quart}), 127.3 (Ph-CH), 128.4 (Ph-CH), 129.2 (Ph-CH), 131.2 (1C, C_{quart}), 136.9 (1C, CH-2′-thioph), 138.3 (1C, C_{quart}), 140.4 (1C, C_{quart}), 163.7 (1C, *C*=O).

6.1.10. 1-Benzyl-1′-phenylspiro[piperidine-4,4′-thieno[3,4-*c*]pyran]-6′(7′*H*)-one (19a)

According to General Procedure A the spirocyclic thiophene **13** (32.2 mg, 0.103 mmol) was reacted 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 (yield 22.6 mg, 57%) and fc (1.5 cm, h = 5 cm, hexane/EtOAc = 4:1, R_f = 0.20). Colorless solid, mp 124–125 °C, yield 13.4 mg (34%). $C_{24}H_{23}NO_2S$ (389.5 g/mol). Purity (HPLC, method B): 98.4%, t_R = 7.09 min. Exact MS (APCI): m/z = calcd for $C_{24}H_{24}NO_2S$ [MH^+] 390.1522, found 390.1528. ^1H NMR ($CDCl_3$): δ (ppm) = 2.09 (dd, J = 14.8/2.2 Hz, 2H, N(CH_2CH_2)$_2$), 2.19 (td, J = 13.7/4.6 Hz, 2H, N(CH_2CH_2)$_2$), 2.61 (td, J = 11.9/2.6 Hz, 2H, N(CH_2CH_2)$_2$), 2.82 (dd, J = 9.0/2.4 Hz, 2H, N(CH_2CH_2)$_2$), 3.60 (s, 2H, NCH_2Ph), 3.83 (s, 2H, thiophCH_2), 7.10 (s, 1H, 3′-*H*-thioph), 7.30–7.47 (m, 10H, Ph-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 32.7 (1C, thiophCH_2C=O), 37.1 (2C, N(CH_2CH_2)$_2$), 48.7 (2C, N(CH_2CH_2)$_2$), 63.2 (1C, NCH_2Ph), 81.2 (1C, thiophC$_{spiro}$), 117.7 (1C, CH-3′-thioph), 126.4 (1C, C_{quart}), 127.4 (Ph-CH), 128.4 (Ph-CH), 128.6 (Ph-CH), 128.8 (Ph-CH), 129.2 (Ph-CH), 129.5 (Ph-CH), 133.1 (1C, C_{quart}), 138.1 (1C, C_{quart}), 141.3 (1C, C_{quart}), 169.5 (1C, C=O). One signal for a quaternary carbon atom is not visible.

6.1.11. 1-Benzyl-1′-(4-methoxyphenyl)spiro-[piperidine-4,4′-thieno[3,4-*c*]pyran]-6′(7′*H*)-one (19b)

According to General Procedure A the spirocyclic thiophene **13** (33.2 mg, 0.106 mmol) was reacted with *p*-iodoanisole (30.9 mg, 0.13 mmol), Ag_2CO_3 (34.2 mg, 0.12 mmol) and $PdCl_2$/bipy (3.3 mg, 0.01 mmol) in *m*-xylene (1.2 mL). The crude product was purified by $CHCl_3$-gpc (yield 8.8 mg, 20%) and fc (1.5 cm, h = 5 cm, hexane/EtOAc = 1:1, 3 mL, R_f = 0.48). Colorless solid, mp 159–160 °C, yield 4.6 mg (10%). $C_{25}H_{25}NO_3S$ (419.5 g/mol). Purity (HPLC, method B): 97%, t_R = 7.07 min. Exact MS (APCI): m/z = calcd for $C_{25}H_{26}NO_3S$ [MH^+] 420.1628, found 420.1665. ^1H NMR ($CDCl_3$): δ (ppm) = 2.08 (dd, J = 14.4/2.2 Hz, 2H, N(CH_2CH_2)$_2$), 2.18 (td, J = 12.5/4.2 Hz, 2H, N(CH_2CH_2)$_2$), 2.60 (td, J = 11.9/2.5 Hz, 2H, N(CH_2CH_2)$_2$), 2.82 (d, J = 11.4 Hz, 2H, N(CH_2CH_2)$_2$), 3.60 (s, 2H, NCH_2Ph), 3.79 (s, 2H, thiophCH_2), 3.85 (s, 3H, OCH_3), 6.94–6.97 (m, 2H, o-OCH$_3$-Ph-*H*), 7.04 (s, 1H, 3′-*H*-thioph), 7.28–7.38 (m, 7H, Ph-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 32.7 (1C, thiophCH_2CO), 37.1 (2C, N(CH_2CH_2)$_2$), 48.7 (2C, N(CH_2CH_2)$_2$), 55.5 (1C, OCH_3), 63.2 (1C, NCH_2Ph), 81.2 (1C, C_{spiro}), 114.6 (Ph-CH), 116.9 (1C, CH-3′-thioph), 125.5 (1C, C_{quart}), 125.6 (1C, C_{quart}), 127.4 (Ph-CH), 128.6 (Ph-CH), 129.5 (Ph-CH), 130.0 (Ph-CH), 138.6 (1C, C_{quart}), 139.2 (1C, C_{quart}), 141.2 (1C, C_{quart}), 159.9 (1C, Ph-C_{quart}-OCH$_3$), 169.7 (1C, C=O).

6.1.12. 4-(1-Benzyl-6′-oxo-6′,7′-dihydrospiro-[piperidine-4,4′-thieno[3,4-*c*]pyran]-1′-yl) benzonitrile (19c)

According to General Procedure A the spirocyclic thiophene **13** (33.2 mg, 0.106 mmol) was reacted with *p*-iodobenzonitrile (30.5 mg, 0.13 mmol), Ag_2CO_3 (33.1 mg, 0.12 mmol) and $PdCl_2$/bipy (3.5 mg, 0.01 mmol) in *m*-xylene (1.2 mL). The crude product was purified by $CHCl_3$-gpc (yield 7.8 mg, 18%) and fc (1.5 cm, h = 10 cm, hexane/EtOAc = 7:3, 3 mL, R_f = 0.08). Colorless solid, mp 183–184 °C, yield 5.1 mg (12%). $C_{25}H_{22}N_2O_2S$ (414.5 g/mol). Purity (HPLC, method B): 96.2%, t_R = 6.66 min. Exact MS (APCI): m/z = calcd for $C_{25}H_{23}N_2O_2S$ [MH^+] 415.1475, found 415.1469. ^1H NMR ($CDCl_3$): δ (ppm) = 2.08 (d, J = 12.3 Hz, 2H, N(CH_2CH_2)$_2$), 2.18 (td, J = 12.5/4.5 Hz, 2H, N(CH_2CH_2)$_2$), 2.61 (td, J = 11.9/2.3 Hz, 2H, N(CH_2CH_2)$_2$), 2.83 (d, J = 11.3 Hz, 2H, N(CH_2CH_2)$_2$), 3.60 (s, 2H, NCH_2Ph), 3.82 (s, 2H, thiophCH_2), 7.21 (s, 1H, 3′-*H*-thioph), 7.27–7.38 (m, 5H, Ph-*H*), 7.50 (d, J = 8.2 Hz, 2H, m-NC-Ph-*H*), 7.73 (d, J = 8.2 Hz, 2H, o-NC-Ph-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 32.8 (1C, thiophCH_2), 37.1 (2C, N(CH_2CH_2)$_2$), 48.6 (2C, N(CH_2CH_2)$_2$), 63.2 (1C, NCH_2Ph), 81.1 (1C, thiophC$_{spiro}$), 111.9 (1C, Ph-C_{quart}-

C≡N), 118.6 (1C, *C*≡N), 119.6 (1C, *C*H-3′-thioph), 127.4 (Ph-*C*H), 128.1 (1C, C_{quart}), 128.6 (Ph-*C*H), 129.1 (Ph-*C*H), 129.4 (Ph-*C*H), 133.0 (Ph-*C*H), 137.1 (1C, C_{quart}), 137.6 (1C, C_{quart}), 138.4 (1C, C_{quart}), 141.9 (1C, C_{quart}), 168.9 (1C, *C*=O).

6.1.13. 1-Benzyl-1′-(1,1′-biphenyl-4-yl)-spiro-[piperidine-4,4′-thieno[3,4-*c*]pyran]-6′ (7′*H*)-one (19d)

According to General Procedure A the spirocyclic thiophene **13** (30.5 mg, 0.097 mmol) was reacted with 4-iodo-1,1′-biphenyl (33.9 mg, 0.12 mmol), Ag_2CO_3 (32.3 mg, 0.12 mmol) and $PdCl_2$/bipy (3.3 mg, 0.01 mmol) in *m*-xylene (1.2 mL). The crude product was purified by $CHCl_3$-gpc (yield 11.3 mg, 25%) and prep. tlc (h = 15 cm, hexane/EtOAc = 1:1, R_f = 0.20). Colorless solid, mp 200–201 °C, yield 5.6 mg (12%). $C_{30}H_{27}NO_2S$ (465.6 g/mol). Purity (HPLC, method B): 95.5%, t_R = 8.15 min. Exact MS (APCI): m/z = calcd for $C_{30}H_{28}NO_2S$ [MH^+] 466.1835, found 466.1792. ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.10 (dd, J = 14.3/1.8 Hz, 2H, N(CH_2CH_2)$_2$), 2.20 (td, J = 14.4/4.6 Hz, 2H, N(CH_2CH_2)$_2$), 2.62 (td, J = 11.7/2.3 Hz, 2H, N(CH_2CH_2)$_2$), 2.83 (d, J = 11.3 Hz, 2H, N(CH_2CH_2)$_2$), 3.61 (s, 2H, NCH_2Ph), 3.88 (s, 2H, thiophCH_2), 7.12 (s, 1H, 3′-*H*-thioph), 7.28–7.41 (m, 6H, Ph-*H*), 7.44–7.50 (m, 4H, Ph-*H*), 7.60–7.70 (m, 4H, Ph-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 32.8 (1C, thiophCH_2CO), 37.1 (2C, N(CH_2CH_2)$_2$), 48.7 (2C, N(CH_2CH_2)$_2$), 63.2 (1C, NCH_2Ph), 81.2 (1C, thiophC_{spiro}), 117.8 (1C, *C*H-3′-thioph), 126.2 (1C, C_{quart}), 126.4 (1C, C_{quart}), 127.3 (Ph-*C*H), 127.4 (Ph-*C*H), 127.9 (Ph-*C*H), 127.9 (Ph-*C*H), 128.6 (Ph-*C*H), 129.1 (Ph-*C*H), 129.2 (Ph-*C*H), 129.5 (Ph-*C*H), 138.6 (1C, C_{quart}), 140.5 (1C, C_{quart}), 141.3 (1C, C_{quart}), 141.4 (1C, C_{quart}), 169.5 (1C, *C*=O). One signal for a quaternary carbon atom is not visible.

6.1.14. 1-Benzyl-2′-phenylspiro[piperidine-4,7′-thieno[2,3-*c*]pyran]-5′ (4′*H*)-one (20a)

According to General Procedure A the spirocyclic thiophene **14** (30.8 mg, 0.098 mmol) was reacted 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 (yield 17.8 mg, 47%) and fc (1.5 cm, h = 5 cm, hexane/EtOAc = 4:1, 3 mL, R_f = 0.20). Colorless solid, mp 140–141 °C, yield 12.5 mg (33%). $C_{24}H_{23}NO_2S$ (389.5 g/mol). Purity (HPLC, method B): 97.3%, t_R = 7.42 min. Exact MS (APCI): m/z = calcd for $C_{24}H_{24}NO_2S$ [MH^+] 390.1522, found 390.1531. ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.08 (dd, J = 14.5/2.3 Hz, 2H, N(CH_2CH_2)$_2$), 2.17 (td, J = 14.2/4.4 Hz, 2H, N(CH_2CH_2)$_2$), 2.62 (td, J = 11.7/2.8 Hz, 2H, N(CH_2CH_2)$_2$), 2.81 (d, J = 11.5 Hz, 2H, N(CH_2CH_2)$_2$), 3.60 (s, 2H, NCH_2Ph), 3.70 (s, 2H, thiophCH_2), 7.00 (s, 1H, 3′-*H*-thioph), 7.27–7.43 (m, 8H, Ph-*H*), 7.49–7.58 (m, 2H, Ph-*H*). ^{13}C NMR^{13}C NMR ($CDCl_3$): δ (ppm) = 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_{quart}), 133.8 (1C, C_{quart}), 137.5 (1C, C_{quart}), 138.6 (1C, C_{quart}), 144.7 (1C, C_{quart}), 169.1 (1C, *C*=O).

6.1.15. 1-Benzyl-3′-phenylspiro[piperidine-4,7′-thieno[2,3-*c*]pyran]-5′ (4′*H*)-one (21a)

According to General Procedure B the spirocyclic thiophene **14** (30.6 mg, 0.098 mmol) was reacted 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 (yield 11.8 mg, 31%) and prep. tlc (h = 15 cm, hexane/EtOAc = 7:3, R_f = 0.06, 4 runs). Colorless solid, mp 114–115 °C, yield 3.7 mg (9.7%). $C_{24}H_{23}NO_2S$ (389.5 g/mol). Purity (HPLC, method B): 96.3%, t_R = 7.25 min. Exact MS (APCI): m/z = calcd for $C_{24}H_{24}NO_2S$ [MH^+] 390.1522, found 390.1545. ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.11 (d, J = 12.8 Hz, 2H, N(CH_2CH_2)$_2$), 2.19 (td, J = 14.4/3.8 Hz, 2H, N(CH_2CH_2)$_2$), 2.63 (td, J = 11.6/2.7 Hz, 2H, N(CH_2CH_2)$_2$), 2.82 (d, J = 11.6 Hz, 2H, N(CH_2CH_2)$_2$), 3.61 (s, 2H, NCH_2Ph), 3.70 (s, 2H, thiophCH_2), 7.23 (s, 1H, 2′-*H*-thioph), 7.27–7.48 (m, 10H, Ph-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 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_{quart}), 129.4 (Ph-*C*H), 135.2 (1C, C_{quart}), 138.5 (1C, C_{quart}), 139.5 (1C, C_{quart}), 141.1 (1C, C_{quart}), 169.3 (1C, *C*=O).

6.1.16. 1-Benzyl-3′-(4-methoxyphenyl)spiro[piperidine-4,7′-thieno-[2,3-*c*]pyran]-5′ (4′*H*)-one (21b)

According to General Procedure B the spirocyclic thiophene **14** (29.1 mg, 0.093 mmol) was reacted with *p*-iodoanisole (30.8 mg, 0.13 mmol), Ag_2CO_3 (31.1 mg, 0.11 mmol), $PdCl_2$ (1.8 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 (yield 21.2 mg, 54%) and fc (1.5 cm, h = 5 cm, hexane/EtOAc = 7:3, 3 mL, R_f = 0.13). Colorless solid, mp 155–156 °C, yield 3.1 mg (8%). $C_{25}H_{25}NO_3S$ (419.5 g/mol). Purity (HPLC, method B): 99.5%, t_R = 7.18 min. Exact MS (APCI): m/z = calcd for $C_{25}H_{26}NO_3S$ [MH^+] 420.1628, found 420.1671. ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.10 (d, J = 12.4 Hz, 2H, N(CH_2CH_2)$_2$), 2.18 (td, J = 12.4/4.0 Hz, 2H, N(CH_2CH_2)$_2$), 2.63 (td, J = 11.5/2.9 Hz, 2H, N(CH_2CH_2)$_2$), 2.82 (d, J = 11.7 Hz, 2H, N(CH_2CH_2)$_2$), 3.60 (s, 2H, NCH_2Ph), 3.68 (s, 2H, thiophCH_2), 3.84 (s, 3H, OCH_3), 6.95 (d, J = 8.8 Hz, 2H, m-H_3CO-Ph-*H*), 7.15 (s, 1H, 2′-*H*-thioph), 7.22–7.25 (m, 2H, o-H_3CO-Ph-*H*), 7.29–7.39 (m, 5H, Ph-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 32.0 (1C, thiophCH_2C=O), 38.8 (2C, N(CH_2CH_2)$_2$), 48.7 (2C, N(CH_2CH_2)$_2$), 55.5 (1C, OCH_3), 63.2 (1C, NCH_2Ph), 81.5 (1C, thiophC_{spiro}), 114.4 (Ph-*C*H), 121.1 (*C*H-2′-thioph), 127.4 (Ph-*C*H), 127.7 (1C, C_{quart}), 128.4 (1C, C_{quart}), 128.5 (Ph-*C*H), 129.4 (Ph-*C*H), 129.5 (Ph-*C*H), 138.5 (1C, C_{quart}), 139.3 (1C, C_{quart}), 140.8 (1C, C_{quart}), 159.5 (1C, C_{quart}), 169.4 (1C, *C*=O).

6.1.17. 1-Benzyl-4′-phenylspiro[piperidine-4,1′-thieno[3,4-*c*]furan]-3′-one (22a) and 1-benzyl-6′-phenylspiro[piperidine-4,1′-thieno[3,4-*c*]furan]-3′-one (22b) and 1-benzyl-4′,6′-diphenylspiro[piperidine-4,1′-thieno[3,4-*c*]furan]-3′-one (22c)

According to General Procedure A the spirocyclic thiophene **18** (31.9 mg, 0.107 mmol) was reacted 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 **22c** in the first fraction (yield 13.2 mg, 27%) and **22a** and **22b** in the second fraction of the gpc (yield 19.9 mg, 50%, mixture of regioisomers). **22a** and **22b** were separated by prep. tlc (h = 15 cm, hexane/EtOAc = 7:3, R_f (**22a**) = 0.22, R_f (**22b**) = 0.48).

Compound **22a** colorless solid, mp 136–137 °C, yield 10.1 mg (25%). $C_{23}H_{21}NO_2S$ (375.5 g/mol). Purity (HPLC, method B): 97%, t_R = 7.37 min. Exact MS (APCI): m/z = calcd for $C_{23}H_{22}NO_2S$ [MH^+] 376.1366, found 376.1352. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.99 (d, J = 13.4 Hz, 2H, N(CH_2CH_2)$_2$), 2.12 (td, J = 12.0/3.8 Hz, 2H, N(CH_2CH_2)$_2$), 2.64 (td, J = 12.7/2.6 Hz, 2H, N(CH_2CH_2)$_2$), 2.80 (d, J = 11.8 Hz, 2H, N(CH_2CH_2)$_2$), 3.63 (s, 2H, NCH_2Ph), 6.93 (s, 1H, 6′-*H*-thioph), 7.27–7.49 (m, 8H, Ph-*H*), 8.02–8.08 (m, 2H, Ph-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 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_{quart}), 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_{quart}), 138.1 (1C, C_{quart}), 148.4 (1C, C_{quart}), 156.7 (1C, C_{quart}), 163.1 (1C, *C*=O).

Compound **22b** colorless solid, mp 122–123 °C, yield 2.2 mg (5%). $C_{23}H_{21}NO_2S$ (375.5 g/mol). Purity (HPLC, method B): 95.2%, t_R = 7.20 min. Exact MS (APCI): m/z = calcd for $C_{23}H_{22}NO_2S$ [MH^+] 376.1366, found 376.1393. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.84 (d,

J = 12.9 Hz, 2H, N(CH_2CH_2)$_2$), 2.17 (t, J = 14.2 Hz, 2H, N(CH_2CH_2)$_2$), 2.49 (t, J = 9.2 Hz, 2H, N(CH_2CH_2)$_2$), 2.78 (d, J = 9.0 Hz, 2H, N(CH_2CH_2)$_2$), 3.53 (s, 2H, NCH_2Ph), 7.27–7.34 (m, 4H, Ph-*H*), 7.39–7.56 (m, 6H, Ph-*H*), 7.84 (s, 1H, 4′-*H*-thioph). Due to the low amount of **22b** recording of a ^{13}C NMR-spectrum was not possible.

Compound **22c** was purified by fc (1.5 cm, h = 5 cm, hexane/EtOAc = 9:1, 3 mL, R_f = 0.12). Colorless solid, mp 182–183 °C, yield 10.2 mg (21%). $C_{29}H_{25}NO_2S$ (451.6 g/mol). Purity (HPLC, method B): 96.6%, t_R = 8.62 min. Exact MS (APCI): m/z = calcd for $C_{29}H_{26}NO_2S$ [MH$^+$] 452.1679, found 452.1687. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.87 (d, J = 12.0 Hz, 2H, N(CH_2CH_2)$_2$), 2.17 (td, J = 13.3/4.7 Hz, 2H, N(CH_2CH_2)$_2$), 2.52 (td, J = 12.3/2.2 Hz, 2H, N(CH_2CH_2)$_2$), 2.78 (dd, J = 11.1/4.2 Hz, 2H, N(CH_2CH_2)$_2$), 3.54 (s, 2H, NCH_2Ph), 7.27–7.56 (m, 13H, Ph-*H*), 8.03–8.08 (m, 2H, Ph-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 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-*CH*), 127.3 (1C, C_{quart}), 128.4 (Ph-*CH*), 128.5 (Ph-*CH*), 129.1 (Ph-*CH*), 129.2 (Ph-*CH*), 129.2 (Ph-*CH*), 129.3 (Ph-*CH*), 129.7 (Ph-*CH*), 129.9 (Ph-*CH*), 131.3 (1C, C_{quart}), 131.6 (1C, C_{quart}), 132.7 (1C, C_{quart}), 138.6 (1C, C_{quart}), 146.9 (1C, C_{quart}), 151.0 (1C, C_{quart}), 163.0 (1C, *C*=O).

6.1.18. 1-Benzyl-4′-(4-methoxyphenyl)spiro[piperidine-4,1′-thieno[3,4-*c*]furan]-3′-one (23a) and 1-benzyl-6′-(4-methoxyphenyl)spiro[piperidine-4,1′-thieno[3,4-*c*]furan]-3′-one (23b) and 1-benzyl-4′,6′-bis(4-methoxyphenyl)spiro[piperidine-4,1′-thieno[3,4-*c*]furan]-3′-one (23c)

According to General Procedure A the spirocyclic thiophene **18** (30.7 mg, 0.103 mmol) was reacted with *p*-iodoanisole (26.5 mg, 0.11 mmol), Ag_2CO_3 (30.5 mg, 0.11 mmol) and $PdCl_2$/bipy (4.7 mg, 0.01 mmol) in *m*-xylene (1.2 mL). The residue was purified by $CHCl_3$-gpc to yield **23c** in the first fraction (yield 7.4 mg, 14%) and **23a** and **23b** in the second fraction of the gpc (yield 10.5 mg, 25%, mixture of regioisomers). **23a** and **23b** were separated by prep. tlc (h = 15 cm, hexane/EtOAc = 7:3, R_f (**23a**) = 0.18, R_f (**23b**) = 0.34, 3 runs).

Compound **23a** colorless solid, mp 158–159 °C, yield 6.7 mg (16%). $C_{24}H_{23}NO_3S$ (405.5 g/mol). Purity (HPLC, method B): 99.1%, t_R = 7.38 min. Exact MS (APCI): m/z = calcd for $C_{24}H_{24}NO_3S$ [MH$^+$] 406.1471, found 406.1592. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.98 (d, J = 13.5 Hz, 2H, N(CH_2CH_2)$_2$), 2.08 (td, J = 10.8/4.1 Hz, 2H, N(CH_2CH_2)$_2$), 2.62 (m, 2H, N(CH_2CH_2)$_2$), 2.78 (d, J = 11.7 Hz, 2H, N(CH_2CH_2)$_2$), 3.61 (s, 2H, NCH_2Ph), 3.85 (s, 3H, OCH_3), 6.83 (s, 1H, 6′-*H*-thioph), 6.95 (d, J = 8.9 Hz, 2H, m-OCH$_3$-Ph-*H*), 7.27–7.38 (m, 5H, Ph-*H*), 8.03 (d, J = 8.9 Hz, 2H, o-OCH$_3$-Ph-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 36.9 (2C, N(CH_2CH_2)$_2$), 49.6 (2C, N(CH_2CH_2)$_2$), 55.5 (1C, OCH_3), 63.2 (1C, NCH_2Ph), 82.1 (1C, thiophC$_{spiro}$), 111.0 (1C, *C*H-6′-thioph), 114.5 (Ph-*CH*), 124.3 (1C, C_{quart}), 125.3 (1C, C_{quart}), 127.4 (Ph-*CH*), 128.5 (Ph-*CH*), 129.4 (Ph-*CH*), 129.7 (Ph-*CH*), 138.3 (1C, C_{quart}), 148.7 (1C, C_{quart}), 156.5 (1C, C_{quart}), 160.9 (1C, C_{quart}), 163.4 (1C, *C*=O).

Compound **23b** colorless solid, yield 3.5 mg (8%). $C_{24}H_{23}NO_3S$ (405.5 g/mol). Purity (HPLC, method B): 87.6%, t_R = 7.16 min. Exact MS (APCI): m/z = calcd for $C_{24}H_{24}NO_3S$ [MH$^+$] 406.1471, found 406.1503. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.82 (dd, J = 14.0/1.6 Hz, 2H, N(CH_2CH_2)$_2$), 2.15 (td, J = 13.2/4.5 Hz, 2H, N(CH_2CH_2)$_2$), 2.48 (td, J = 12.3/2.4 Hz, 2H, N(CH_2CH_2)$_2$), 2.77 (d, J = 10.5 Hz, 2H, N(CH_2CH_2)$_2$), 3.54 (s, 2H, NCH_2Ph), 3.88 (s, 3H, OCH_3), 6.98 (d, J = 8.6 Hz, 2H, m-H$_3$CO-Ph-*H*), 7.27–7.33 (m, 5H, Ph-*H*), 7.39 (d, J = 8.6 Hz, 2H, o-H$_3$CO-Ph-*H*), 7.79 (s, 1H, 4′-*H*-thioph). Due to the low amount of **23b** recording of a ^{13}C NMR -spectrum was not possible.

Compound **23c** was purified by fc (1.5 cm, h = 5 cm, hexane/EtOAc = 3:2, 3 mL, R_f = 0.58). Pale yellow solid, mp 213–214 °C, yield 4.5 mg (9%). $C_{31}H_{29}NO_4S$ (511.6 g/mol). Purity (HPLC, method B): 98.9%, t_R = 8.44 min. Exact MS (APCI): m/z = calcd for $C_{31}H_{30}NO_4S$ [MH$^+$] 512.1890, found 512.1935. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.85 (d, J = 12.4 Hz, 2H, N(CH_2CH_2)$_2$), 2.14 (td, J = 13.3/4.3 Hz, 2H, N(CH_2CH_2)$_2$), 2.50 (td, J = 12.3/1.9 Hz, 2H, N(CH_2CH_2)$_2$), 2.77 (d, J = 10.6 Hz, 2H, N(CH_2CH_2)$_2$), 3.54 (s, 2H, NCH_2Ph), 3.85 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.97 (m, 4H, m- H$_3$CO-Ph-*H*), 7.27–7.34 (m, 5H, Ph-*H*), 7.41(d, J = 8.7 Hz, 2H, o-H$_3$CO-Ph-*H*), 8.01 (d, J = 8.8 Hz, 2H, o-H$_3$CO-Ph-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 36.4 (2C, N(CH_2CH_2)$_2$), 49.4 (2C, N(CH_2CH_2)$_2$), 55.5 (1C, OCH_3), 55.5 (1C, OCH_3), 63.1 (1C, NCH_2Ph), 82.8 (1C, thiophC$_{spiro}$), 114.5 (Ph-*CH*), 123.8 (1C, C_{quart}), 124.3 (1C, C_{quart}), 127.3 (Ph-*CH*), 128.5 (Ph-*CH*), 129.4 (Ph-*CH*), 129.9 (Ph-*CH*), 131.2 (Ph-*CH*), 138.6 (1C, C_{quart}), 140.3 (1C, C_{quart}), 150.5 (1C, C_{quart}), 160.4 (1C, C_{quart}), 160.9 (1C, C_{quart}), 163.4 (1C, C=O). Two signals for quaternary carbon atoms are not visible.

6.1.19. 4-(1-Benzyl-3′-oxospiro[piperidine-4,1′-thieno[3,4-*c*]furan]-4′-yl)-benzonitrile (24a) and 4-(1-benzyl-3′-oxospiro[piperidine-4,1′-thieno[3,4-*c*] furan]-6′-yl)benzonitrile (24b) and 4,4′-(1-benzyl-3′-oxospiro[piperidine-4,1′-thieno[3,4-*c*]furan]-4′,6′diyl)dibenzonitrile (24c)

According to General Procedure A the spirocyclic thiophene **18** (27.8 mg, 0.093 mmol) was reacted with *p*-iodobenzonitrile (30.1 mg, 0.13 mmol), Ag_2CO_3 (29.9 mg, 0.11 mmol) and $PdCl_2$/bipy (4.2 mg, 0.01 mmol) in *m*-xylene (1.2 mL). The residue was purified by $CHCl_3$-gpc to yield **24c** in the first fraction (11.8 mg, 25%) and **24a** and **24b** in the second fraction of the gpc (yield 13.0 mg, 35%, mixture of regioisomers). **24a** and **24b** were separated by prep. tlc (h = 15 cm, hexane/EtOAc = 7:3, NHEt$_2$ 2%, R_f (**24a**) = 0.18, R_f (**24b**) = 0.08, 3 runs).

Compound **24a** colorless solid, mp 1659–160 °C, yield 8.4 mg (23%). $C_{24}H_{20}N_2O_2S$ (400.5 g/mol). Purity (HPLC, method B): 96.2%, t_R = 7.02 min. Exact MS (APCI): m/z = calcd for $C_{24}H_{21}N_2O_2S$ [MH$^+$] 401.1318, found 401.1358. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.98 (d, J = 13.6 Hz, 2H, N(CH_2CH_2)$_2$), 2.10 (td, J = 11.4/3.6 Hz, 2H, N(CH_2CH_2)$_2$), 2.61 (td, J = 11.5/2.3 Hz, 2H, N(CH_2CH_2)$_2$), 2.79 (d, J = 11.9 Hz, 2H, N(CH_2CH_2)$_2$), 3.61 (s, 2H, NCH_2Ph), 7.07 (s, 1H, 6′-*H*-thioph), 7.27–7.39 (m, 5H, Ph-*H*), 7.72 (d, J = 8.3 Hz, 2H, m-CN-Ph-*H*), 8.21 (d, J = 8.3 Hz, 2H, o-CN-Ph-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 36.9 (2C, N(CH_2CH_2)$_2$), 49.6 (2C, N(CH_2CH_2)$_2$), 63.2 (1C, NCH_2Ph), 82.8 (1C, thiophC$_{spiro}$), 112.8 (1C, Ph-C_{quart}-C≡N), 114.4 (1C, *C*H-6′-thioph), 118.7 (1C, *C*≡N), 127.5 (Ph-*CH*), 128.5 (Ph-*CH*), 128.6 (Ph-*CH*), 129.4 (Ph-*CH*), 132.9 (Ph-*CH*), 135.5 (1C, C_{quart}), 138.3 (1C, C_{quart}), 145.0 (1C, C_{quart}), 157.4 (1C, C_{quart}), 162.8 (1C, *C*=O). One signal for a quaternary carbon atom is not visible.

Compound **24b** colorless solid, mp 163–164 °C, yield 2.3 mg (6%). $C_{24}H_{20}N_2O_2S$ (400.5 g/mol). Purity (HPLC, method B): 96.2%, t_R = 6.67 min. Exact MS (APCI): m/z = calcd for $C_{24}H_{21}N_2O_2S$ [MH$^+$] 401.1318, found 401.1350. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.86 (d, J = 12.8 Hz, 2H, N(CH_2CH_2)$_2$), 2.12 (td, J = 13.3/4.6 Hz, 2H, N(CH_2CH_2)$_2$), 2.49 (td, J = 12.4/1.8 Hz, 2H, N(CH_2CH_2)$_2$), 2.79 (d, J = 9.2 Hz, 2H, N(CH_2CH_2)$_2$), 3.54 (s, 2H, NCH_2Ph), 7.27–7.35 (m, 5H, Ph-*H*), 7.62 (d, J = 8.3 Hz, 2H, m-CN-Ph-*H*), 7.77 (d, J = 8.3 Hz, 2H, o-CN-Ph-*H*), 7.93 (s, 1H, 4′-*H*-thioph). ^{13}C NMR ($CDCl_3$): δ (ppm) = 36.6 (2C, N(CH_2CH_2)$_2$), 49.3 (2C, N(CH_2CH_2)$_2$), 63.1 (1C, NCH_2Ph), 84.4 (1C, thiophC$_{spiro}$), 113.0 (1C, Ph-C_{quart}-C≡N), 118.3 (1C, *C*≡N), 126.9 (1C, *C*H-4′-thioph), 127.4 (Ph-*CH*), 128.5 (Ph-*CH*), 129.3 (Ph-*CH*), 130.1 (Ph-*CH*), 133.0 (Ph-*CH*), 133.6 (1C, C_{quart}), 134.9 (1C, C_{quart}), 136.4 (1C, C_{quart}), 138.3 (1C, C_{quart}), 150.5 (1C, C_{quart}), 162.3 (1C, *C*=O).

Compound **24c** was purified by fc (1.5 cm, h = 5 cm, hexane/EtOAc = 3:2, 3 mL, R_f = 0.49). Colorless solid, mp 222–123 °C, 7.9 mg (17%). $C_{31}H_{23}N_3O_2S$ (501.6 g/mol). Purity (HPLC, method B): 98.9%, t_R = 7.47 min. Exact MS (APCI): m/z = calcd for $C_{31}H_{24}N_3O_2S$ [MH$^+$] 502.1584, found 502.1638. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.89 (d, J = 12.5 Hz, 2H, N(CH_2CH_2)$_2$), 2.11 (td, J = 13.3/4.6 Hz, 2H, N(CH_2CH_2)$_2$), 2.50 (td, J = 11.8/2.3 Hz, 2H, N(CH_2CH_2)$_2$), 2.80 (dd, J = 10.7/3.3 Hz, 2H, N(CH_2CH_2)$_2$), 3.55 (s, 2H, NCH_2Ph),

7.27–7.35 (m, 5H, Ph-*H*), 7.65 (d, *J* = 8.4 Hz, 2H, m-CN-Ph-*H*), 7.75 (d, *J* = 8.5 Hz, 2H, m-CN-Ph-*H*), 7.81 (d, *J* = 8.3 Hz, 2H, o-NC-Ph-*H*), 8.20 (d, *J* = 8.5 Hz, 2H, o-NC-Ph-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 36.6 (2C, N(CH_2CH_2)$_2$), 49.2 (2C, N(CH_2CH_2)$_2$), 63.1 (1C, NCH_2Ph), 83.4 (1C, thiophC$_{spiro}$), 113.3 (1C, Ph-C_{quart}-C≡N), 113.5 (1C, Ph-C_{quart}-C≡N), 118.2 (1C, *C*≡N), 118.5 (1C, *C*≡N), 127.4 (Ph-*CH*), 128.5 (Ph-*CH*), 128.8 (Ph-*CH*), 129.3 (Ph-*CH*), 129.7 (1C, C_{quart}), 130.3 (Ph-*CH*), 132.1 (1C, C_{quart}), 133.0 (Ph-*CH*), 133.0 (Ph-*CH*), 134.8 (1C, C_{quart}), 135.7 (1C, C_{quart}), 138.2 (1C, C_{quart}), 144.9 (1C, C_{quart}), 152.9 (1C, C_{quart}), 162.1 (1C, *C*=O).

6.1.20. 1-Benzyl-4′-(naphthalen-1-yl)-spiro[piperidine-4,1′-thieno[3,4-*c*]furan]-3′-one (25a) and 1-benzyl-6′-(naphthalen-1-yl)-3′*H*-spiro[piperidine-4,1′-thieno[3,4-*c*]furan]-3′-one (25b) and 1-benzyl-4′,6′-di(naphthalen-1-yl)-spiro[piperidine-4,1′-thieno-[3,4-*c*]furan]-3′-one (25c)

According to General Procedure A the spirocyclic thiophene **18** (32.9 mg, 0.11 mmol) was reacted with 1-iodonaphthalene (17.6 μL, 0.12 mmol), Ag_2CO_3 (33.7 mg, 0.12 mmol) and $PdCl_2$/bipy (4.6 mg, 0.01 mmol) in *m*-xylene (1.2 mL). The residue was purified by $CHCl_3$-gpc to yield **25c** in the first fraction (yield 23.1 mg, 38%) and **25a** and **25b** in the second fraction of the gpc (yield 28.4 mg, 61%, mixture of regioisomers). Compound **25a** and **25b** were separated by prep. tlc (*h* = 15 cm, hexane/EtOAc = 7:3, R_f (**25a**) = 0.16, R_f (**25b**) = 0.40, 3 runs).

Compound **25a** colorless solid, mp 165–166 °C, yield 14.7 mg (31%). $C_{27}H_{23}NO_2S$ (425.5 g/mol). Purity (HPLC, method B): 96.6%, t_R = 7.56 min. Exact MS (APCI): *m*/*z* = calcd for $C_{27}H_{24}NO_2S$ [MH^+] 426.1522, found 426.1555. ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.07 (m, 2H, N(CH_2CH_2)$_2$), 2.16 (td, *J* = 10.6/4.5 Hz, 2H, N(CH_2CH_2)$_2$), 2.67 (m, 2H, N(CH_2CH_2)$_2$), 2.81 (d, *J* = 11.9 Hz, 2H, N(CH_2CH_2)$_2$), 3.63 (s, 2H, NCH_2Ph), 7.13 (s, 1H, 6′-*H*-thioph), 7.27–7.41 (m, 5H, Ar-*H*), 7.49–7.57 (m, 3H, Ar-*H*), 7.65 (dd, *J* = 7.1/1.2 Hz, 1H, Ar-*H*), 7.89–7.98 (m, 2H, Ar-*H*), 8.00–8.06 (m, 1H, Ar-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 37.0 (2C, N(CH_2CH_2)$_2$), 49.7 (2C, N(CH_2CH_2)$_2$), 63.2 (1C, NCH_2Ph), 82.5 (1C, thiophC$_{spiro}$), 114.5 (1C, *C*H-6′-thioph), 125.3 (Ar-*CH*), 125.6 (Ar-*CH*), 126.6 (Ar-*CH*), 127.1 (Ar-*CH*), 127.5 (Ar-*CH*), 127.9 (1C, C_{quart}), 128.6 (Ar-*CH*), 128.7 (Ar-*CH*), 129.5 (Ar-*CH*), 129.6 (Ar-*CH*), 130.5 (Ar-*CH*), 131.5 (1C, C_{quart}), 134.0 (1C, C_{quart}), 138.4 (1C, C_{quart}), 145.2 (1C, C_{quart}), 155.5 (1C, C_{quart}), 162.4 (1C, C=O). One signal for a quaternary carbon atom is not visible.

Compound **25b** colorless solid, mp 145–146 °C, yield 1.9 mg (4%). $C_{27}H_{23}NO_2S$ (425.5 g/mol). Purity (HPLC, method B): 95.8%, t_R = 7.75 min. Exact MS (APCI): *m*/*z* = calcd for $C_{27}H_{24}NO_2S$ [MH^+] 426.1522, found 426.1580. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.78 (m, 4H, N(CH_2CH_2)$_2$), 2.41 (m, 2H, N(CH_2CH_2)$_2$), 2.62 (d, *J* = 11.3 Hz, 2H, N(CH_2CH_2)$_2$), 3.41 (s, 2H, NCH_2Ph), 7.11–7.24 (m, 5H, Ar-*H*), 7.43–7.64 (m, 5H, Ar-*H*), 7.88–8.04 (m, 2H, Ar-*H*), 7.98 (s, 1H, 4′-*H*-thioph). ^{13}C NMR ($CDCl_3$): δ (ppm) = 35.9 (2C, N(CH_2CH_2)$_2$), 49.1 (2C, N(CH_2CH_2)$_2$), 63.1 (1C, NCH_2Ph), 84.3 (1C, thiophC$_{spiro}$), 125.2 (Ar-*CH*), 125.7 (Ar-*CH*), 126.5 (Ar-*CH*), 126.7 (Ar-*CH*), 127.2 (Ar-*CH*), 127.2 (Ar-*CH*), 128.1 (1C, C_{quart}), 128.4 (Ar-*CH*), 128.6 (Ar-*CH*), 129.4 (Ar-*CH*), 129.9 (Ar-*CH*), 130.4 (Ar-*CH*), 133.0 (1C, C_{quart}), 133.3 (1C, C_{quart}), 133.5 (1C, C_{quart}), 133.8 (1C, C_{quart}), 138.0 (1C, C_{quart}), 151.6 (1C, C_{quart}), 162.9 (1C, C=O).

Compound **25c** was purified by fc (1.5 cm, *h* = 5 cm, hexane/EtOAc = 3:2, $NHEt_2$ 2%, 3 mL, R_f = 0.40). Colorless solid, mp 230 °C, yield 6.5 mg (11%). $C_{37}H_{29}NO_2S$ (551.7 g/mol). Purity (HPLC, method C): 96%, t_R = 9.20 min. Exact MS (APCI): *m*/*z* = calcd for $C_{37}H_{30}NO_2S$ [MH^+] 552.1992, found 552.2050. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.82–1.94 (m, 4H, N(CH_2CH_2)$_2$), 2.45 (td, *J* = 11.0/3.7 Hz, 2H, N(CH_2CH_2)$_2$), 2.65 (d, *J* = 11.5 Hz, 2H, N(CH_2CH_2)$_2$), 3.43 (s, 2H, NCH_2Ph), 7.13–7.25 (m, 5H, Ar-*H*), 7.50–7.66 (m, 7H, Ar-*H*), 7.76–7.84 (m, 2H, Ar-*H*), 7.91–8.24 (m, 5H, Ar-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 36.1 (2C, N(CH_2CH_2)$_2$), 49.1 (2C, N(CH_2CH_2)$_2$), 63.1 (1C, NCH_2Ph), 83.0 (1C, thiophC$_{spiro}$), 125.3 (Ar-*CH*), 125.3 (Ar-*CH*), 125.7 (Ar-*CH*), 125.9 (Ar-*CH*), 126.6 (Ar-*CH*), 126.9 (Ar-*CH*), 127.1 (Ar-*CH*), 127.2 (Ar-*CH*), 127.2 (Ar-*CH*), 127.8 (1C, C_{quart}), 128.1 (1C, C_{quart}), 128.4 (Ar-*CH*), 128.7 (Ar-*CH*), 128.8 (Ar-*CH*), 129.1 (1C, C_{quart}), 129.4 (Ar-*CH*), 129.7 (Ar-*CH*), 130.0 (Ar-*CH*), 130.4 (Ar-*CH*), 130.5 (Ar-*CH*), 131.4 (1C, C_{quart}), 131.7 (1C, C_{quart}), 133.6 (1C, C_{quart}), 133.9 (1C, C_{quart}), 134.0 (1C, C_{quart}), 138.1 (1C, C_{quart}), 144.8 (1C, C_{quart}), 152.1 (1C, C_{quart}), 162.3 (C=O).

6.1.21. 1-Benzyl-4′-(1,1′-biphenyl-4-yl)spiro[piperidine-4,1′-thieno-[3,4-*c*]furan]-3′-one (26a) and 1-benzyl-6′-(1,1′-biphenyl-4-yl)spiro[piperidine-4,1′-thieno[3,4-*c*] furan]-3′-one (26b) and 1-benzyl-4′,6′-di(1,1′-biphenyl-4-yl)spiro[piperidine-4,1′-thieno[3,4-*c*]furan]-3′-one (26c)

According to General Procedure A the spirocyclic thiophene **18** (33.7 mg, 0.11 mmol) was reacted with 4-iodo-1,1′-biphenyl (33.0 mg, 0.12 mmol), Ag_2CO_3 (33.0 mg, 0.12 mmol) and $PdCl_2$/bipy (3.5 mg, 0.01 mmmol) in *m*-xylene (1.2 mL). The residue was injected into the $CHCl_3$-gpc to yield **26c** in the first fraction (yield 19.2 mg, 28%) and **26a** and **26b** in the second fraction of the gpc (yield 20.5 mg, 40%, mixture of regioisomers). Compound **26a** and **26b** were separated by prep. tlc (*h* = 15 cm, hexane/EtOAc = 4:1, R_f (**26a**) = 0.10, R_f (**26b**) = 0.46).

Compound **26a** colorless solid, mp 187–188 °C, yield 8 mg (16%). $C_{29}H_{25}NO_2S$ (451.6 g/mol). Purity (HPLC, method B): 97.2%, t_R = 8.38 min. Exact MS (APCI): *m*/*z* = calcd for $C_{29}H_{26}NO_2S$ [MH^+] 452.1679, found 452.1736. ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.00 (d, *J* = 13.5 Hz, 2H, N(CH_2CH_2)$_2$), 2.09 (td, *J* = 10.4/3.9 Hz, 2H, N(CH_2CH_2)$_2$), 2.63 (td, *J* = 12.3/2.9 Hz, 2H, N(CH_2CH_2)$_2$), 2.79 (d, *J* = 11.8 Hz, 2H, N(CH_2CH_2)$_2$), 3.62 (s, 2H, NCH_2Ph), 6.93 (s, 1H, 6′-*H*-thioph), 7.27–7.40 (m, 6H, Ph-*H*), 7.46 (t, *J* = 7.5 Hz, 2H, Ph-*H*), 7.60–7.70 (m, 4H, Ph-*H*), 8.12–8.17 (m, 2H, Ph-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 37.0 (2C, N(CH_2CH_2)$_2$), 49.7 (2C, N(CH_2CH_2)$_2$), 63.2 (1C, NCH_2Ph), 82.3 (1C, thiophC$_{spiro}$), 112.2 (1C, *C*H-6′-thioph), 126.6 (1C, C_{quart}), 127.2 (Ph-*CH*), 127.4 (Ph-*CH*), 127.8 (Ph-*CH*), 128.0 (Ph-*CH*), 128.5 (Ph-*CH*), 128.6 (Ph-*CH*), 129.1 (Ph-*CH*), 129.4 (Ph-*CH*), 130.4 (1C, C_{quart}), 138.4 (1C, C_{quart}), 140.4 (1C, C_{quart}), 142.4 (1C, C_{quart}), 148.0 (1C, C_{quart}), 156.8 (1C, C_{quart}), 163.2 (1C, *C*=O).

Compound **26b** pale yellow solid, mp 172–173 °C, yield 4.4 mg (9%). $C_{29}H_{25}NO_2S$ (451.6 g/mol). Purity (HPLC, method B): 97%, t_R = 8.09 min. Exact MS (APCI): *m*/*z* = calcd for $C_{29}H_{26}NO_2S$ [MH^+] 452.1679, found 452.1736. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.87 (d, *J* = 12.5 Hz, 2H, N(CH_2CH_2)$_2$), 2.24 (td, *J* = 13.3/4.6 Hz, 2H, N(CH_2CH_2)$_2$), 2.51 (td, *J* = 12.4/1.9 Hz, 2H, N(CH_2CH_2)$_2$), 2.80 (dd, *J* = 10.9/3.8 Hz, 2H, N(CH_2CH_2)$_2$), 3.55 (s, 2H, NCH_2Ph), 7.27–7.73 (m, 14H, Ph-*H*), 7.86 (s, 1H, 4′-*H*-thioph). ^{13}C NMR ($CDCl_3$): δ (ppm) = 36.4 (2C, N(CH_2CH_2)$_2$), 49.4 (2C, N(CH_2CH_2)$_2$), 63.1 (1C, NCH_2Ph), 84.6 (1C, thiophC$_{spiro}$), 125.5 (1C, *C*H-4′-thioph), 127.3 (Ph-*CH*), 127.3 (Ph-*CH*), 127.8 (Ph-*CH*), 128.1 (Ph-*CH*), 128.5 (Ph-*CH*), 129.2 (Ph-*CH*), 129.4 (Ph-*CH*), 130.1 (Ph-*CH*), 130.6 (1C, C_{quart}), 134.4 (1C, C_{quart}), 136.0 (1C, C_{quart}), 138.4 (1C, C_{quart}), 142.0 (1C, C_{quart}), 149.2 (1C, C_{quart}), 157.5 (1C, C_{quart}), 162.5 (1C, *C*=O).

Compound **26c** was purified by fc (1.5 cm, *h* = 5 m, hexane/EtOAc = 7:3, 3 mL, R_f = 0.54). Pale yellow solid, mp 117–118 °C, 13.3 mg (20%). $C_{41}H_{33}NO_2S$ (603.8 g/mol). Purity (HPLC, method B): 97.7%, t_R = 10.82 min. Exact MS (APCI): *m*/*z* = calcd for $C_{41}H_{34}NO_2S$ [MH^+] 604.2305, found 604.2340. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.92 (d, *J* = 12.8 Hz, 2H, N(CH_2CH_2)$_2$), 2.26 (td, *J* = 13.3/4.6 Hz, 2H, N(CH_2CH_2)$_2$), 2.55 (td, *J* = 12.4/1.8 Hz, 2H, N(CH_2CH_2)$_2$), 2.81 (d, *J* = 8.8 Hz, 2H, N(CH_2CH_2)$_2$), 3.56 (s, 2H, NCH_2Ph), 7.27–7.54 (m, 11H, Ph-*H*), 7.56–7.74 (m, 10H, Ph-*H*), 8.16 (m, 2H, Ph-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 36.4 (2C, N(CH_2CH_2)$_2$), 49.4 (2C, N(CH_2CH_2)$_2$), 63.1 (1C, NCH_2Ph), 83.1 (1C, thiophC$_{spiro}$), 127.3 (Ph-*CH*), 127.3 (Ph-*CH*), 127.3 (Ph-*CH*), 127.5 (1C, C_{quart}), 127.8 (Ph-*CH*), 127.8 (Ph-*CH*), 128.0 (Ph-*CH*), 128.1 (Ph-*CH*), 128.5 (Ph-

CH), 128.8 (Ph-CH), 129.1 (Ph-CH), 129.2 (Ph-CH), 129.4 (Ph-CH), 130.2 (Ph-CH), 130.3 (1C, C_{quart}), 130.5 (1C, C_{quart}), 132.4 (1C, C_{quart}), 138.5 (1C, C_{quart}), 140.3 (1C, C_{quart}), 140.5 (1C, C_{quart}), 142.0 (1C, C_{quart}), 142.4 (1C, C_{quart}), 146.6 (1C, C_{quart}), 151.1 (1C, C_{quart}), 163.1 (1C, C=O).

6.2. Receptor binding studies[50–53]

6.2.1. Materials

The guinea pig brains and rat liver for the σ_1 and σ_2 receptor binding assays were commercially available (Harlan-Winkelmann, Borchen, Germany). Homogenizer: Elvehjem Potter (B. Braun Biotech International, Melsungen, Germany). Cooling centrifuge model Rotina 35R (Hettich, Tuttlingen, Germany) and High-speed cooling centrifuge model Sorvall RC-5C plus (Thermo Fisher Scientific, Langenselbold, Germany). Multiplates: standard 96-well multiplates (Diagonal, Muenster, Germany). Shaker: self-made device with adjustable temperature and tumbling speed (scientific workshop of the institute). Vortexer: Vortex Genie 2 (Thermo Fisher Scientific, Langenselbold, Germany). Harvester: MicroBeta FilterMate-96 Harvester. Filter: Printed Filtermat Typ A and B. Scintillator: Meltilex (Typ A or B) solid state scintillator. Scintillation analyzer: MicroBeta Trilux (all Perkin Elmer LAS, Rodgau-Jügesheim, Germany). Chemicals and reagents were purchased from different commercial sources and of analytical grade.

6.2.2. Preparation of membrane homogenates from guinea pig brain

Five guinea pig brains were homogenized with the potter (500–800 rpm, 10 up-and-down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1200×*g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 23,500×*g* for 20 min at 4 °C. The pellet was resuspended in 5-6 volumes of buffer (50 mM TRIS, pH 7.4) and centrifuged again at 23,500×*g* (20 min, 4 °C). This procedure was repeated twice. The final pellet was resuspended in 5-6 volumes of buffer and frozen (−80 °C) in 1.5 mL portions containing about 1.5 mg protein/mL.

6.2.3. Preparation of membrane homogenates from rat liver

Two rat livers were cut into small pieces and homogenized with the potter (500–800 rpm, 10 up-and-down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1200×*g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 31,000×*g* for 20 min at 4 °C. The pellet was resuspended in 5–6 volumes of buffer (50 mM TRIS, pH 8.0) and incubated at room temperature for 30 min. After the incubation, the suspension was centrifuged again at 31,000×*g* for 20 min at 4 °C. The final pellet was resuspended in 5–6 volumes of buffer and stored at −80 °C in 1.5 mL portions containing about 2 mg protein/mL.

6.2.4. Protein determination

The protein concentration was determined by the method of Bradford,[55] modified by Stoscheck.[56] The Bradford solution was prepared by dissolving 5 mg of Coomassie Brilliant Blue G 250 in 2.5 mL of EtOH (95%, v/v). 10 mL deionized H_2O and 5 mL phosphoric acid (85%, m/v) were added to this solution, the mixture was stirred and filled to a total volume of 50.0 mL with deionized water. The calibration was carried out using bovine serum albumin as a standard in 9 concentrations (0.1, 0.2, 0.4, 0.6, 0.8, 1.0, 1.5, 2.0 and 4.0 mg/mL). In a 96-well standard multiplate, 10 μL of the calibration solution or 10 μL of the membrane receptor preparation were mixed with 190 μL of the Bradford solution, respectively. After 5 min, the UV absorption of the protein-dye complex at λ = 595 nm was measured with a platereader (Tecan Genios, Tecan, Crailsheim, Germany).

6.2.5. General protocol for the binding assays

The test compound solutions were prepared by dissolving approximately 10 μmol (usually 2–4 mg) of test compound in DMSO so that a 10 mM stock solution was obtained. To obtain the required test solutions for the assay, the DMSO stock solution was diluted with the respective assay buffer. The filtermats were presoaked in 0.5% aqueous polyethylenimine solution for 2 h at room temperature before use. All binding experiments were carried out in duplicates in 96-well multiplates. The concentrations given are the final concentrations in the assay. Generally, the assays were performed by addition of 50 μL of the respective assay buffer, 50 μL test compound solution in various concentrations (10^{-5}, 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9} and 10^{-10} mol/L), 50 μL of corresponding radioligand solution and 50 μL of the respective receptor preparation into each well of the multiplate (total volume 200 μL). The receptor preparation was always added last. During the incubation, the multiplates were shaken at a speed of 500–600 rpm at the specified temperature. Unless otherwise noted, the assays were terminated after 120 min by rapid filtration using the harvester. During the filtration each well was washed five times with 300 μL of water. Subsequently, the filtermats were dried at 95 °C. The solid scintillator was melted on the dried filtermats at a temperature of 95 °C for 5 min. After solidifying of the scintillator at room temperature, the trapped radioactivity in the filtermats was measured with the scintillation analyzer. Each position on the filtermat corresponding to one well of the multiplate was measured for 5 min with the [^{3}H]-counting protocol. The overall counting efficiency was 20%. The IC_{50}-values were calculated with the program GraphPad Prism® 3.0 (GraphPad Software, San Diego, CA, USA) by non-linear regression analysis. Subsequently, the IC_{50} values were transformed into K_i-values using the equation of Cheng and Prusoff.[57] The K_i-values are given as mean value ± SEM from three independent experiments.

6.2.6. Protocol of the σ_1 receptor binding assay

The assay was performed with the radioligand [^{3}H]-(+)-Pentazocine (22.0 Ci/mmol; Perkin Elmer). The thawed membrane preparation of guinea pig brain cortex (about 100 μg of protein) was incubated with various concentrations of test compounds, 2 nM [^{3}H]-(+)-Pentazocine, and TRIS buffer (50 mM, pH 7.4) at 37 °C. The non-specific binding was determined with 10 μM unlabeled (+)-Pentazocine. The K_d-value of (+)-Pentazocine is 2.9 nM.[58]

6.2.7. Protocol of the σ_2 receptor binding assay

The assays were performed with the radioligand [^{3}H]DTG (specific activity 50 Ci/mmol; ARC, St. Louis, MO, USA). The thawed membrane preparation of rat liver (about 100 μg of protein) was incubated with various concentrations of the test compound, 3 nM [^{3}H]DTG and buffer containing (+)-pentazocine (500 nM (+)-pentazocine in 50 mM TRIS, pH 8.0) at room temperature. The non-specific binding was determined with 10 μM non-labeled DTG. The K_d value of [^{3}H]DTG is 17.9 nM.[59]

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