# Preparation of 3-Aminoalkylbenzo[*b*]thiophenes

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We report an efficient entry into substituted 3-(ω-aminoalkyl)-benzo[*b*]thiophenes that allows rapid generation of structural diversity. Alkylation of α,ω-dihaloketones with thiophenols followed by acid-catalysed cyclisation led to an efficient synthesis of 3-(ω-aminoalkyl)benzo[*b*]thiophenes. 2-Carboethoxy derivatives were prepared using a directed *ortho*-metallation approach. These derivatives were readily converted into the corresponding amines.

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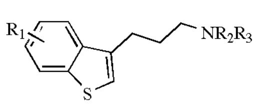
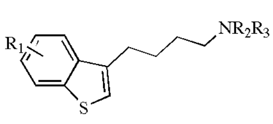
In the course of investigating compounds as potential anti-depressants we wanted access to a diverse set of substituted benzo[*b*]thiophenes. In particular, we required benzo[*b*]thiophenes functionalised at the 3-position with a variety of amino groups linked *via* an *n*-propyl (**1**) or *n*-butyl chain (**2**).

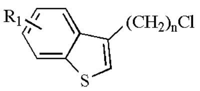


(1)



(2)

We set out to prepare late stage intermediates which could be modified to enable introduction of the amino and benzo[*b*]thiophene substituents independently. To provide such flexibility we initially targeted 3-(ω-chloroalkyl)-benzo[*b*]thiophenes (**3**) substituted on the aromatic core with a variety of groups including those suitable for subsequent modification *via* palladium cross-coupling reactions either directly, such as halogen substituents, or following modification, such as alkoxy substituents.



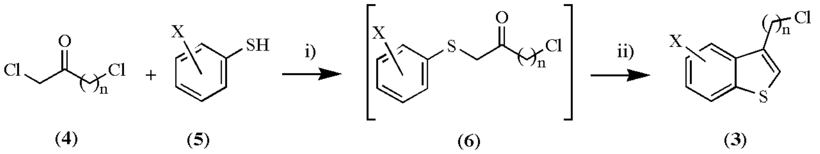
(3)

n=3,4
$R_1$=Br, MeO

After surveying known methodologies [1] we envisaged an extension of the reported preparation of 3-methylbenzo[*b*]thiophene from thiophenol and chloroacetone [2]. Thus, *S*-alkylation of thiophenol was followed by intramolecular condensation under strongly acidic conditions at elevated temperature. We were intrigued by the possibility that α,ω-dihaloketones might be used in place of chloroacetone to afford the required 3-(ω-haloalkyl)-benzo[*b*]thiophenes directly (Scheme 1) [3]. Our sequence was consequently dependent both on a selective nucleophilic mono-displacement of the α,ω-dihaloketone (**4**) with a substituted thiophenol (**5**) and on the stability of the ω-chloroalkyl derivatives (**6**) and (**3**) towards the cyclisation conditions. The approach was attractive, since it would take advantage of commercially available substituted thiophenols and non-commercial thiophenols could be effectively accessed *via* the corresponding phenols (Newman-Kwart rearrangement) [4]. It was also anticipated that the required α-haloketones (**4**) would be accessible by Clibbens-Nierenstein [5] reaction of the appropriate acid chloride.

1,5-Dichloro-2-pentanone (**4a**) was prepared from 4-chlorobutanoyl chloride by treatment with diazomethane according to the literature [6]. Alternatively, the use of commercial (trimethylsilyl)diazomethane circumvented the use of diazomethane as a potential hazard and led to similar results. The yields and purities of the crude product obtained were >95 % as judged by $^1$H-nmr spectroscopy on a laboratory scale of up to 0.4 mol, and the product could be reacted in the next step without further purifica-

Scheme 1

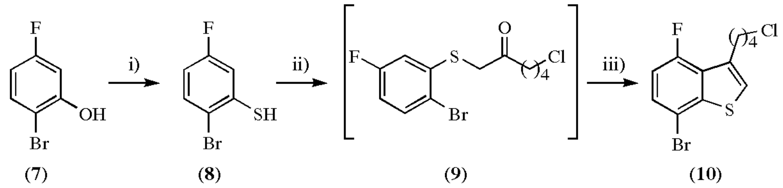


**a**, n=3
**b**, n=4

Reagents: i) $K_2CO_3$, *N,N*-dimethylformamide; ii) polyphosphoric acid, chlorobenzene tion. As a possible alternative, the α-bromination of 5-chloro-2-pentanone according to Dumas [7] was also investigated but led to inseparable mixtures of the 1- and 3-bromoisomers which decomposed on storage at -18° within a few days. 1,5-Dichloro-2-pentanone, however, proved stable on storage at 3° for several weeks.

With the required (**4a**) in hand, we were delighted to find that a range of substituted thiophenols reacted selectively at the α-position by stirring with the appropriate thiophenol in *N*,*N*-dimethylformamide at room temperature for 2 hours, using potassium carbonate as base. The ω-chloro substituent proved inert under the reaction conditions employed. After aqueous work-up, the crude α-arylthio ketones (**6**) were dissolved in chlorobenzene and heated at 150° in the presence of polyphosphoric acid for 2 - 36 hours, depending on the electronic nature of the substituent on the aromatic ring, to yield the required substituted 3-ω-(chloroalkyl)benzo[*b*]thiophenes (**3**) in moderate to good overall yields.

Scheme 2



Reagents: i) a) *N*,*N*-Dimethylcarbamoyl choride, 1,4-diazabicyclo[2.2.2]octane, *N*,*N*-dimethylformamide; b) Δ; c) 1N NaOH, EtOH; ii) 1,6-dichlorohexan-2-one, $K_2CO_3$, *N*,*N*-dimethylformamide; iii) polyphosphoric acid, chlorobenzene

In the cyclisation step, methoxy substituted thiophenols readily cyclised within 2 hours whereas the halo-derivatives required prolonged heating (in general 24 to 36 hours). α-Sulfenylated ketones (**6**) having electron withdrawing groups on the aromatic ring such as nitro or trifluoromethyl were found to be inert under the reaction conditions (Table 1). *m*-Substituted thiophenols furnished mixtures of 3,4- and 3,6-disubstituted benzo[*b*]thiophenes in ratios of 1:1 (3-bromothiophenol) up to 1:3 (3-methoxy- and 3-fluorothiophenol). These were separable by column chromatography.

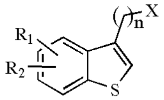
In order to prepare 3,4-disubstituted benzo[*b*]thiophenes (**3**) regioselectively, the following blocking group strategy was devised. It was envisaged that 2,5-disubstituted thiophenols would cyclise in a regiospecific manner. Subsequent removal of the substituent at the 7-position of the resultant benzo[*b*]thiophene would afford the requisite 3,4-disubstitution pattern. Bromine was selected as the blocking group, because of its robust nature and the possibility of reductive removal. Furthermore, the bromine also offers further structural modification of the 3,4,7-trisubstituted benzo[*b*]thiophene core *via* transition metal mediated couplings [11].

As depicted in Scheme 2, 2-bromo-5-fluorophenol (**7**) was converted into the corresponding thiophenol (**8**) [8] following the precedent of Newman and Kwart [4]. In accordance with similar reports in the literature [9], we found that heating the intermediate thiocarbamate neat under a blanket of nitrogen for 3 hours at 230° resulted in a clean rearrangement. The resulting *S*-thiocarbamoyl derivative could be saponified using 1 *N* sodium hydroxide in ethanol at reflux to furnish the desired thiophenol in 60 % yield after distillation. Alkylation of (**8**) using 1,6-dichlorohexan-2-one (**4b**) [10] proceeded *via* displacement of the chlorine adjacent to the carbonyl group to give (**9**). Cyclisation afforded the 7-bromo-4-fluorobenzo[*b*]thiophene (**10**) within 36 hours in 59 % yield after column chromatography.

In exploring the influence of chain length on cyclisation, it was found that the desired products could be obtained for n > 2. Using 1,3-dichloroacetone (n = 1) and 1,4-dichloro-

Table 1

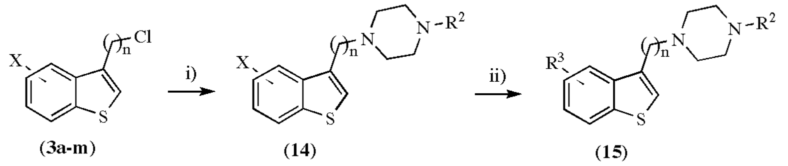
Results of Cyclisation Studies



| Compound | $R_1$ | $R_2$ | n | X | Reaction Time (hours) | Yield [a] (%) |
|---|---|---|---|---|---|---|
| **3a** | 7-Br | H | 3 | Cl | 60 | 96 |
| **3b** | 7-OMe | H | 3 | Cl | 3 | 51 |
| **3c** | 5-Br | H | 3 | Cl | 60 | 85 |
| **3d** | 5-OMe | H | 3 | Cl | 3 | 55 |
| **3e** | 5-Br | H | 1 | Cl | 60 | _ [b] |
| **3f** | 5-Br | H | 2 | Cl | 60 | _ [b] |
| **3g**:**3h** | 4-Br:6-Br | H | 3 | Cl | 20 | 23 : 24 |
| **3i**:**3k** | 4-OMe:6-OMe | H | 3 | Cl | 3 | 19 : 61 |
| **3l**:**3m** | 4-F:6-F | H | 3 | Cl | 20 | 13 : 46 |
| **3n**:**3o** | 4-$CF_3$:6-$CF_3$ | H | 3 | Cl | 60 | _ [c] |
| **10** | 4-F | 7-Br | 4 | Cl | 60 | 59 |
| **11**:**12** | 4-F:6-F | H | 2 | $CO_2Me$ | 60 | 3:14 |
| **13** | 4-F | 7-Br | 2 | $CO_2Me$ | 60 | 8 |

[a] Isolated yield; [b] Complex mixture obtained; [c] No product could be detected.

Scheme 3



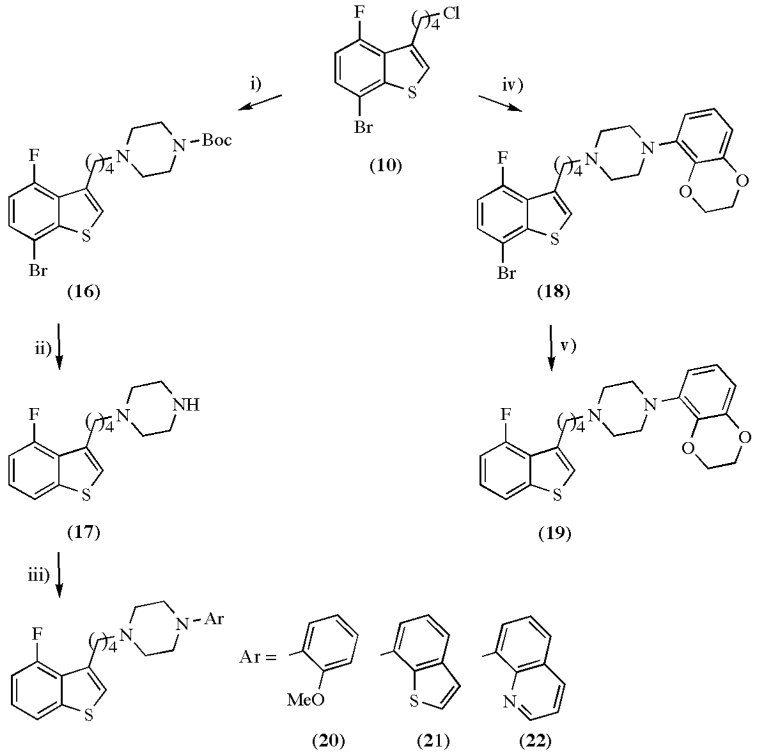
Reagents: i) NH-piperazine, NaI, $K_2CO_3$, $CH_3CN$; ii) $R^3B(OH)_2$, $Pd(PPh_3)_4$, toluene, 2M $Na_2CO_3$ or $R'_2NH$, $Cs_2CO_3$, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, $Pd(OAc)_2$, toluene

2-butanone (n = 2), in an effort to prepare (**3e**) and (**3f**) respectively, resulted in complex mixtures which were not purified any further. In addition, substituting the ω−chloro-functionality for a methyl ester resulted in poor isolated yields of the corresponding benzo[*b*]thiophenes (**11**, **12** and **13**), presumably due to the harsh reaction conditions. A selection of benzo[*b*]thiophenes synthesised following this approach is shown in Table 1.

The substituted 3-(chloroalkyl)benzo[*b*]thiophenes (**3a-n**) provide various opportunities for 2-dimensional structural modification. In our search for antidepressant compounds we chose first to react the chloro functionality with substituted piperazines to yield (**14**). Palladium mediated couplings [11] of the aromatic halogen were then carried out, leading to the desired targets (**15**) (Scheme 3).

An alternative strategy designed to enable derivatisation of the piperazine at the final stage is outlined in Scheme 4. Thus, chlorobutyl derivative (**10**) was reacted with 1-(2,3-dihydro-1,4-benzodioxine-5-yl)piperazine to give (**18**) in analogy to Scheme 3. Due to our specific interest in 4-fluoro-substituted benzo[*b*]thiophene cores, the 7-bromo substituent was removed *via* lithium aluminium hydride reduction to give (**19**) rather than being utilised in transition metal mediated couplings. To further vary the 1,4-benzodioxin motif on the piperazine, (**10**) was initially reacted with *N*-Boc piperazine followed by reduction of

Scheme 4



Reagents: i) *N*-Boc-piperazine, NaI, $K_2CO_3$, $CH_3CN$; ii) a) TFA, dichloromethane; b) lithium aluminium hydride, tetrahydrofurane; iii) Ar-Br, $Cs_2CO_3$, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, $Pd(OAc)_2$, toluene; iv) 1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-piperazine, NaI, $K_2CO_3$, $CH_3CN$; v) lithium aluminiumhydride, tetrahydrofurane the bromine and removal of the Boc-group to give the 4-fluorobenzothiophene derivative (**17**). This compound readily underwent palladium mediated amination according to Buchwald *et al.* [11b] as exemplified by the formation of (**20**, **21** and **22**). Table 2 shows selected results of our efforts following both strategies.

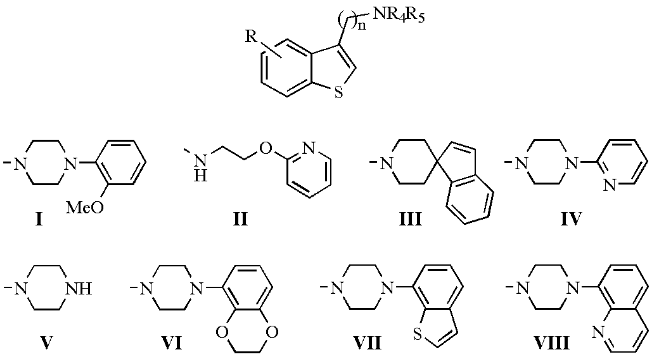
An alternative sequence was established to access benzo[*b*]thiophene-2-carboxylates (**26**). Bridges *et al.* reported a directed *ortho*-metallation-acylation approach using fluorine as the directing group followed by displacement of the activated fluorine [12]. In an extension of this approach (Scheme 5), 3-fluoro-benzotrifluoride (**23**) was metallated with lithium diisopropylamide in tetrahydrofurane at –78° and equilibrated for 1 hour at the same temperature. *Trans*-metallation to the corresponding zinc derivative followed by palladium mediated acylation with 3-chloropropionyl chloride and substitution with methyl thioglycolate in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene yielded the 6-trifluoromethylbenzo[*b*]thiophene-2-carboxylate (**25**) as the only detectable regioisomer ($^1$H-nmr spectroscopy) in 40% overall yield. Treatment with 1-(2-methoxyphenyl)piperazine afforded the required target derivative (**26**).

Interestingly, reaction of (**25**) with phenethylamine followed by trimethylaluminium-mediated cyclisation and reduction of the resulting lactam with lithium aluminium hydride afforded the tricyclic thiophene (**27**) in 40 % yield (Scheme 6).

In conclusion, we have demonstrated two efficient approaches from commercially available starting materials to prepare substituted 3-(chloroalkyl)-benzo[*b*]thiophenes. These sequences allow a minimum number of purification steps involving column chromatography. It has also been demonstrated that the advanced intermediate (**10**) provides a specific entry into 4-fluorobenzo[*b*]thiophenes and may be further modified orthogonally, resulting in a quick generation of structural diversity.

Table 2

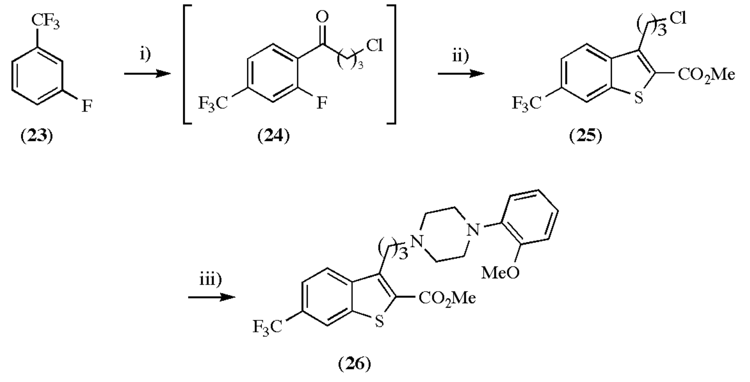
3-(Aminoalkyl)benzo[*b*]thiophenes Prepared



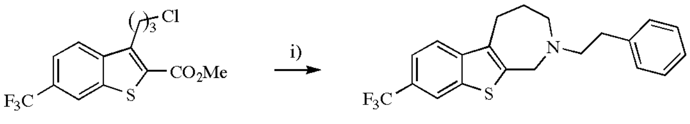
| Compound | Starting Material | R | n | $NR_4R_5$ | Yield [a] (%) |
|---|---|---|---|---|---|
| **14a** | **3I** | 4-OMe | 3 | I | 62 |
| **14b** | **3d** | 5-OMe | 3 | I | 81 |
| **14c** | **3k** | 6-OMe | 3 | I | 53 |
| **14d** | **3b** | 7-OMe | 3 | I | 71 |
| **14e** | **3g** | 4-Br | 3 | I | 65 |
| **14f** | **3e** | 5-Br | 3 | I | 78 |
| **14g** | **3h** | 6-Br | 3 | I | 47 |
| **14i** | **3l** | 4-F | 3 | II | 55 |
| **14k** | **3b** | 7-OMe | 3 | III | 90 |
| **14l** | **3l** | 4-F | 3 | IV | 57 |
| **15a** | **14e** | 4-Ph | 3 | I | 89 |
| **15b** | **14e** | 4-(4-Morpholinyl) | 3 | I | 71 |
| **15c** | **14g** | 6-Ph | 3 | I | 80 |
| **15d** | **14g** | 6-(4-Morpholinyl) | 3 | I | 80 |
| **15e** | **14h** | 7-(4-Anisyl) | 3 | I | 85 |
| **17** | **10** | 4-F | 4 | V | 81 |
| **18** | **10** | 4-F, 7-Br | 4 | VI | 86 |
| **19** | **18** | 4-F | 4 | VI | 67 |
| **20** | **17** | 4-F | 4 | I | 27 |
| **21** | **17** | 4-F | 4 | VII | 39 |
| **22** | **17** | 4-F | 4 | VIII | 74 |

[a] Isolated yield.

Scheme 5



Reagents: i) a) t-BuLi, tetrahydrofurane; b) $ZnCl_2$; c) 4-chlorobutanoyl chloride, $Pd(PPh_3)_4$; ii) methyl thioglycolate, 1,8-diazabicyclo[5.4.0]undec-7-ene, toluene; iii) 1-(2-methoxyphenyl)-piperazine, NaI, $K_2CO_3$, $CH_3CN$



Scheme 6

**(25)** **(27)**

Reagents: i) a) 2-phenethylamine, NaI, $K_2CO_3$, $CH_3CN$; b) trimethylaluminium, 1,2-dichloroethane; c) lithium aluminium hydride, tetrahydrofurane

## EXPERIMENTAL

All reactions involving air- and/or water-sensitive reagents were carried out under an atmosphere of nitrogen. Unless otherwise noted, starting materials were obtained from commercial sources and used without further purification. Solvents for reactions and chromatography were also of commercial origin. Solutions in organic solvents were dried over anhydrous sodium sulfate. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The $^1$H nmr spectra were recorded on a Varian Unity Plus-300 (300 MHz) spectrometer using deuteriochloroform or deuteriodimethyl sulfoxide as solvent and tetramethylsilane as internal standard. Mass spectra were obtained using a VG-quattro spectrometer. Gas-chromatography coupled mass spectroscopy was carried out using an HP5890 gas chromatograph with an HP5971 EI mass spectrometer connected to chemstation software (v 3.0). The column used was an RTX1 (15m by 0.25 mm inner diameter) with a flow rate of 1 mL/minute and a temperature gradient as follows: 0 to 1 minute: 50°, heat up to 340° at 15°/minute, hold at 340° for 1 minute. Column chromatography was performed using silica gel 60, 70-230 mesh ASTM (Merck).

2-(2-Aminoethyl)pyridine [13], spiro(1*H*-indene-1,4'-piperidine) [14] and 1-(2,3-dihydro[1,4]benzodioxin-5-yl)piperazine [15] were prepared according to the literature.

### General Procedure for the Preparation of α-Chloroketones (**4a**) [6], (**4b**) [10] and (**4c**)[16].

According to the literature preparation, the corresponding acid chlorides were converted with diazomethane into the corresponding α-diazomethyl ketones followed by treatment with hydrogen chloride in diethyl ether (Clibbens-Nieren-stein reaction) [5].

### 1,5-Dichloropentan-2-one (**4a**) [6].

This compound was obtained in 97% yield,15 g colourless liquid; bp: 60 - 66° / 0.01 torr (lit.[6]: 82%; 43 - 45° / 0.001 torr); $^1$H nmr (deuteriochloroform): δ 2,10 (m, 2H, $CH_2$), 2.81 (t, J = 5.4 Hz, 2H, $CH_2$), 3.60 (t, J = 4.8 Hz, 2H, $CH_2$), 4.12 (s, 2H, $CH_2$).

### 1,6-Dichlorohexan-2-one (**4b**) [10].

This compound was obtained in quantitative yield, 34.9 g colourless liquid; bp: 74 - 80° / 0.01 torr (lit.[10]: 120 - 125° / 14 torr); $^1$H nmr (deuteriochloroform): δ 1.81 (m, 4H, $CH_2$), 2.65 (m, 2H, $CH_2$), 3.55 (m, 2H, $CH_2$), 4.08 (s, 2H, $CH_2$).

### Methyl 5-Chloro-4-oxopentanoate (**4c**) [16].

This compound was obtained in quantitative yield, 31.8 g colourless liquid (lit.[16]: 74 %); $^1$H nmr (deuteriochloroform): δ 2.66 (m, 4H, $CH_2$), 2.90 (m, 2H, $CH_2$), 3.69 (s, 3H, $CH_3$), 4.16 (s, 2H, $CH_2$); Lit.: δ 2.67 (t, J = 7 Hz, 2H, $CH_2$), 2.90 (t, J = 7 Hz, 2H, $CH_2$), 3.68 (s, 3H, $CH_3$), 4.18 (s, 2H, $CH_2$).

### 2-Bromo-5-fluorothiophenol (**8**).

This compound was obtained in 51% yield, 35 g colourless liquid; bp: 82 - 92° / 10 torr (lit. [9]: bp: 112 - 116° / 35 torr). $^1$H nmr (deuteriochloroform): δ 6.73 (td, J (F,H) = 6.8 Hz, J = 6.8 Hz, J = 2.2 Hz, 1H, CH), 7.08 (dd, J (F,H) = 6.8 Hz, J = 2.2 Hz, 1H, CH), 7.46 (dd, J (F,H) = 4.2 Hz, J = 6.8 Hz, 1H, CH).

### General Procedure for the Preparation of 3-(ω-Chloroalkyl)-benzo[*b*]thiophenes (**3**).

At room temperature anhydrous potassium carbonate (1.1 equivalents) was added in one portion to a 1 molar solution of the corresponding thiophenol in dry *N,N*-dimethyl formamide followed by the dropwise addition of the corresponding α-chloro ketone (**4a**, **4b** or **4c**; 1.1 equivalents). The mixture was stirred at room temperature under nitrogen for one hour and poured onto ice-water and the product was extraced into diethyl ether. The organic extract was washed with water and brine, then dried over anhydrous sodium sulfate and finally filtered and concentrated to yield the crude α-sulfenylated ketones, which were used without further purification.

A 1 molar solution of the α-sulfenylated ketone (**6**) in chlorobenzene was heated up to 150° while stirring under nitrogen. Polyphosphoric acid (1mL / 5 mmoles substrate) was heated in a round bottomed flask to yield a mobile clear liquid and then added to the chlorobenzene solution. Stirring was continued for the time indicated in Table 1 and the upper phase of the resulting dark two-phase system was decanted off the polyphosphoric acid. After adding the same amount of chlorobenzene, the mixture was heated for another 30 minutes at 150° while stirring to extract the remaining product. The decanted chlorobenzene phases were combined and concentrated under reduced pressure using a rotary evaporator and the dark residue was dissolved in diethyl ether and adsorbed onto silica gel. Purification by column chromatography yielded the title compounds as viscous oils.

### 7-Bromo-3-(3-chloropropyl)benzo[*b*]thiophene (**3a**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 20:1) to yield 0.91 g (96 %) of a yellow oil; $^1$H nmr (deuteriochloroform): δ 2,19 (m, 2H, $CH_2$), 3.00 (t, J = 5.7 Hz, 2H, $CH_2$), 3.57 (t, J = 4.8 Hz, 2H, $CH_2$), 7.21 (s, 1H, CH), 7.27 (t, J = 6.0 Hz, 1H, CH), 7.50 (d, J = 6.0 Hz, 1H, CH), 7.71 (d, J = 6.0 Hz, 1H, CH).

*Anal.* Calcd. for $C_{11}H_{10}BrClS{\bullet}0.1\ C_6H_{14}$ (289.62): C, 46.72; H, 3.85. Found: C, 46.59; H, 3.50.

### 3-(3-Chloropropyl)-7-methoxybenzo[*b*]thiophene (**3b**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 20:1) to yield 3.56 g (51 %) of a yellow oil; $^1$H nmr (deuteriochloroform): δ 2,19 (m, 2H, $CH_2$), 3.17 (m, 2H, $CH_2$), 3.39 (m, 2H, $CH_2$), 3.86 (s, 3H, $CH_3$), 6.78 (d, J = 6.3 Hz, 1H, CH), 7.12 (s, 1H, CH), 7.33 (dd, J = 6.0 Hz, J = 5.7 Hz, 1H, CH), 7.39 (d, J = 5.7 Hz, 1H, CH).

*Anal.* Calcd. for $C_{12}H_{13}ClOS$ (240.75): C, 59.87; H, 5.44. Found: C, 60.01; H, 5.38.

5-Bromo-3-(3-chloropropyl)benzo[*b*]thiophene (**3c**).

The product was purified by column chromatography (*iso*-hexane) to yield 1.31 g (85 %) of a yellow oil; $^1$H nmr (deuteriochloroform): δ 2,20 (m, 2H, $CH_2$), 3.21 (m, 2H, $CH_2$), 3.38 (m, 2H, $CH_2$), 7.12 (t, J = 5.7 Hz, 1H, CH), 7.21 (s, 1H, CH), 7.57 (d, J = 5.7 Hz, 1H, CH), 7.80 (d, J = 5.7 Hz, 1H, CH).

*Anal.* Calcd. for $C_{11}H_{10}BrClS$ (289.62): C, 45.62; H, 3.48. Found: C, 45.85; H, 3.67.

3-(3-Chloropropyl)-5-methoxybenzo[*b*]thiophene (**3d**).

The product was purified by column chromatography (*iso*-hexane/ ethyl acetate = 20:1) to yield 1.11 g (55 %) of a yellow oil; $^1$H nmr (deuteriochloroform): δ 1.81 (m, 2H, $CH_2$), 3.13 (m, 2H, $CH_2$), 3.37 (m, 2H, $CH_2$), 3.91 (s, 3H, $CH_3$), 6.95 (dd, J = 6.5 Hz, J = 1.7 Hz, 1H, CH), 7.11 (s, 1H, CH), 7.22 (d, J = 1.7 Hz, 1H, CH), 7.69 (d, J = 6.5 Hz, 1H, CH).

*Anal.* Calcd. for $C_{12}H_{13}ClOS$ (240.75): C, 59.87; H, 5.44. Found: C, 60.05; H, 5.70.

4-Bromo-3-(3-chloropropyl)benzo[*b*]thiophene (**3g**).

The product was purified by column chromatography (*iso*-hexane/ ethyl acetate = 20:1) to yield 1.85 g (23 %) of a yellow oil; $^1$H nmr (deuteriochloroform): δ 2,20 (m, 2H, $CH_2$), 3.23 (m, 2H, $CH_2$), 3.48 (m, 2H, $CH_2$), 7.13 (t, J = 6.0 Hz, 1H, CH), 7.22 (s, 1H, CH), 7.57 (d, J = 6.0 Hz, 1H, CH), 7.79 (d, J = 6.0 Hz, 1H, CH).

*Anal.* Calcd. for $C_{11}H_{10}BrClS{\bullet}0.33C_4H_8O_2$ (289.62): C, 46.44; H, 4.00. Found: C, 46.68; H, 3.56.

6-Bromo-3-(3-chloropropyl)benzo[*b*]thiophene (**3h**).

The product was purified by column chromatography (*iso*-hexane) to yield 1.93 g (24 %) of a yellow oil; $^1$H nmr (deuteriochloroform): δ 2,14 (m, 2H, $CH_2$), 2.96 (m, 2H, $CH_2$), 3.59 (m, 2H, $CH_2$), 7.09 (s, 1H, CH), 7.48 (dd, J = 6.7 Hz, J = 1.4 Hz, 1H, CH), 7.62 (d, J = 6.7 Hz, 1H, CH), 7.98 (d, J = 1.4 Hz, 1H, CH).

*Anal.* Calcd. for $C_{11}H_{10}BrClS{\bullet}0.1C_6H_{14}$ (289.62): C, 46.72; H, 3.85. Found: C, 46.61; H, 3.50.

3-(3-Chloropropyl)-4-methoxybenzo[*b*]thiophene (**3i**).

The product was purified by column chromatography (gradient: *iso*-hexane to *iso*-hexane/ethyl acetate = 20 :1) to yield 0.45 g (19 %) of a yellow oil; $^1$H nmr (deuteriochloroform): δ 2.15 (m, 2H, $CH_2$), 3.17 (t, J = 5.5 Hz, 2H, $CH_2$), 3.57 (t, J = 5.0 Hz, 2H, $CH_2$), 3.92 (s, 3H, $CH_3$), 6.73 (d, J = 6.0 Hz, 1H, CH), 6.96 (s, 1H, CH), 7.23 (t, J = 6.0 Hz, 1H, CH), 7.41 (d, J = 6.0 Hz, 1H, CH).

*Anal.* Calcd. for $C_{12}H_{13}ClOS$ (240.75): C, 59.87; H, 5.44. Found: C, 60.19; H, 5.51.

3-(3-Chloropropyl)-6-methoxybenzo[*b*]thiophene (**3k**).

The product was purified by column chromatography (gradient: *iso*-hexane to *iso*-hexane/ethyl acetate = 20 :1) to yield 1.46 g (61 %) of a yellow oil; $^1$H nmr (deuteriochloroform): δ 2.18 (m, 2H, $CH_2$), 2.97 (t, J = 5.5 Hz, 2H, $CH_2$), 3.58 (t, J = 4.9 Hz, 2H, $CH_2$), 3.87 (s, 3H, $CH_3$), 6.94 (s, 1H, CH), 7.0 (dd, J = 6.8 Hz, J = 1.8 Hz, 1H, CH), 7.32 (d, J = 1.8 Hz, 1H, CH), 7.61 (d, J = 6.8 Hz, 1H, CH).

*Anal.* Calcd. for $C_{12}H_{13}ClOS$ (240.75): C, 59.87; H, 5.44. Found: C, 59.66; H, 5.41.

3-(3-Chloropropyl)-4-fluorobenzo[*b*]thiophene (**3l**).

The product was purified by column chromatography (*iso*-hexane) to yield 1.61 g (13 %) of a yellow oil; $^1$H nmr (deuteriochloroform): δ 2,19 (m, 2H, $CH_2$), 3.13 (t, J = 5.7 Hz, 2H, $CH_2$), 3.58 (t, J = 4.9 Hz, 2H, $CH_2$), 6.99 (dd, J(F,H) = 9.1 Hz, J = 8.9 Hz, 1H, CH), 7.08 (s, 1H, CH), 7.24 (m, 1H, CH), 7.24 (m, 1H, CH), 7.59 (d, J = 6.1 Hz, 1H, CH).

*Anal.* Calcd. for $C_{11}H_{10}ClFS$ (228.71): C, 57.77; H, 4.41. Found: C, 57.43; H, 4.51.

3-(3-Chloropropyl)-6-fluorobenzo[*b*]thiophene (**3m**).

The product was purified by column chromatography (*iso*-hexane) to yield 5.67 g (46 %) of a yellow oil; $^1$H nmr (deuteriochloroform): δ 2,20 (m, 2H, $CH_2$), 2.99 (t, J = 5.8 Hz, 2H, $CH_2$), 3.57 (t, J = 4.9 Hz, 2H, $CH_2$), 7.10 (s, 1H, CH), 7.13 (ddd, J (F,H) = 6.8 Hz, J = 6.8 Hz, J = 1.8 Hz, 1H, CH), 7.51 (dd, J (F,H) = 6.8 Hz, J = 1.8 Hz, 1H, CH), 7.67 (dd, J (F,H) = 3.9 Hz, J = 6.8 Hz, 1H, CH).

*Anal.* Calcd. for $C_{11}H_{10}ClFS$ (228.71): C, 57.77; H, 4.41. Found: C, 57.44; H, 4.35.

7-Bromo-3-(4-chlorobutyl)-4-fluorobenzo[*b*]thiophene (**10**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 20:1) to yield 9.44 g (59 %) of a yellow solid; mp 65°; $^1$H nmr (deuteriochloroform): δ 1.85 (m, 2H, CH, $CH_2$), 1.96 (m, 2H, CH, $CH_2$), 3.11 (m, 2H, CH, $CH_2$), 3.57 (m, 2H, CH, $CH_2$), 6.93 (dd, J (F,H) = 8.5 Hz, J = 6.5 Hz, 1H, CH), 7.11 (s, 1H, CH), 7.40 (dd, J (F,H) = 3.0 Hz, J = 6.5 Hz, 1H, CH).

*Anal.* Calcd. for $C_{12}H_{11}BrClFS$ (321.64): C, 44.81; H, 3.45. Found: C, 44.95; H, 3.39.

Methyl 3-(4-Fluorobenzo[*b*]thiophene-3-yl)propionate (**11**).

The product was purified by column chromatography (*iso*-hexane) to yield 0.12 g (3 %) of a yellow oil; $^1$H nmr (deuteriochloroform): δ 2,75 (t, J = 5.7 Hz, 2H, $CH_2$), 3.31 (t, J = 5.7 Hz, 2H, $CH_2$), 3.68 (s, 3H, $CH_3$), 6.99 (dd, J(F,H) = 8.9 Hz, J = 6.2 Hz, 1H, CH), 7.08 (s, 1H, CH), 7.25 (m, 1H, CH), 7.59 (d, J = 6.2 Hz, 1H, CH).

*Anal.* Calcd. for $C_{12}H_{11}FSO_2$ (238.28): C, 60.49; H, 4.65. Found: C, 60.42; H, 4.66.

Methyl 3-(6-Fluorobenzo[*b*]thiophene-3-yl)propionate (**12**).

The product was purified by column chromatography (*iso*-hexane) to yield 0.62 g (14 %) of a yellow oil; $^1$H nmr (deuteriochloroform): δ 2,73 (t, J = 5.7 Hz, 2H, $CH_2$), 3.14 (t, J = 5.7 Hz, 2H, $CH_2$), 3.69 (s, 3H, $CH_3$), 7.06 (s, 1H, CH), 7.12 (ddd, J (F,H) = 6.8 Hz, J = 6.8 Hz, J = 1.9 Hz, 1H, CH), 7.51 (dd, J (F,H) = 6.8 Hz, J = 1.8 Hz, 1H, CH), 7.65 (dd, J (F,H) = 3.9 Hz, J = 6.8 Hz, 1H, CH).

*Anal.* Calcd. for $C_{12}H_{11}FSO_2$ (238.28): C, 60.49; H, 4.65. Found: C, 60.09; H, 4.34.

Methyl 3-(7-Bromo-4-fluorobenzo[*b*]thiophene-3-yl)propionate (**13**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 20:1) to yield 2.32 g (8 %) of a red oil; $^1$H nmr (deuteriochloroform): δ 2,73 (t, J = 5.7 Hz, 2H, $CH_2$), 3.27 (t, J = 5.7 Hz, 2H, $CH_2$), 3.68 (s, 3H, $CH_3$), 6.92 (dd, J (F,H) = 8.5

Hz, J = 6.5 Hz, 1H, CH), 7.16 (s, 1H, CH), 7.38 (dd, J (F,H) = 3.2 Hz, J = 6.5 Hz, 1H, CH).

*Anal.* Calcd. for $C_{12}H_{10}BrFSO_2$ (317.18): C, 45.44; H, 3.18. Found: C, 45.58; H, 3.35.

Methyl 3-(3-Chloropropyl)-6-trifluoromethylbenzo[*b*]thiophene-2-carboxylate (**25**).

3-Fluorobenzotrifluoride (2.52 mL; 20 mmoles) was dissolved in 50 mL dry tetrahydrofurane under nitrogen using a 250 mL 3-necked flask equipped with a stirring bar. The solution was cooled to -78° and *t*-butyl lithium (12 mL of a 1.7 *M* solution in diethyl ether) was added dropwise over 10 minutes to yield a yellow solution. Stirring was continued for 1 hour followed by the dropwise addition of zinc chloride (40 mL of a 1.0 *M* solution in diethyl ether) and the resulting solution was warmed up to room temperature and stirred for 1 hour. Tetrakis(triphenylphosphine)palladium(0) (1.16 g; 0.05 mol %) was added followed by addition of 20 mL of a 1.0 *M* solution of 4-chlorobutanoyl chloride in tetrahydrofuran and the resulting yellow mixture was heated under reflux for 12 hours. The dark hot reaction mixture was poured into water/ethyl acetate (1:1; 100 mL) and the phases separated. After another extraction, the organic phases were combined, washed with water and brine and dried over sodium sulfate. Filtration and concentration under vacuum yielded crude 3-chloropropyl 2-fluoro-4-(trifluoromethyl)phenyl ketone as a brown oil which was dissolved in 20 mL dry toluene and cooled to 0° under nitrogen. After subsequent addition of methyl thioglycolate (1.82 mL; 20 mmoles) and 1,8-diazabicyclo[5.4.0]undec-7-ene (6.0 mL; 40 mmoles), the mixture was stirred at 0° for additional 3 hours, slowly warmed up to room temperature overnight and poured into water /ethyl acetate (1:1; 100 mL). The phases were separated and after another extraction the organic phases were combined, washed with 6 *N* hydrochloric acid, water and brine and dried over sodium sulfate. Filtration, concentration under vacuum and chromatographic purification yielded 1.81 g (58 %) of the target molecule as a colourless oil; $^1$H nmr (deuteriochloroform): δ 2,17 (m, 2H, $CH_2$), 3.48 (t, J = 5.8 Hz, 2H, $CH_2$), 3.63 (t, J = 4.8 Hz, 2H, $CH_2$), 3.96 (s, 3H, $CH_3$), 7.66 (br. d, J = 6.5 Hz, 1H, CH), 8.02 (d, J = 6.5 Hz, 1H, CH), 8.14 (br. s, 1H, CH).

*Anal.* Calcd. for $C_{14}H_{13}ClF_3SO_2 \cdot 0.5\ H_2O$ (336.76): C, 50.07; H, 4.20. Found: C, 50.29; H, 4.12.

General Procedure for the Preparation of 3-(ω-Aminoalkyl)-benzo[*b*]thiophenes (**14**, **16** and **26**) *via* Nucleophilic Substitution of 3-(ω-Chloroalkyl)benzo[*b*]thiophenes (**3**).

At room temperature anhydrous potassium carbonate (3 equivalents) was mixed with the corresponding 3-(ω-chloroalkyl)-benzo[*b*]thiophene (**3**) and the corresponding amine or amine salt (1.1 equivalents) respectively using a round bottomed flask. After flushing with nitrogen, sodium iodide (1.1 equivalents) was added in one portion followed by dry acetonitrile to result in a 1.0 *M* solution of the 3-(ω-chloroalkyl)benzo[*b*]thiophene (**3**). The resulting mixture was heated at 80° while stirring for 18 hours, poured into ice-water and the product was extraced into ethyl acetate. The organic extract was washed with water and brine, dried over anhydrous sodium sulfate and finally filtered and concentrated to yield the crude target compounds, which were adsorbed onto silicagel and purified by column chromatography.

1-[3-(4-Methoxybenzo[*b*]thiophene-3-yl)propyl]-4-(2-methoxyphenyl)-piperazine (**14a**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 0.46 g (62 %) of a yellow oil; $^1$H nmr (deuteriochloroform): δ 1.95 (m, 2H, CH, $CH_2$), 2.50 (m, 2H, $CH_2$), 2.67 (broad s, 4H, $CH_2$), 3.02 - 3.10 (broad s + m, 6H, $CH_2$), 3.84 (s, 3H, $CH_3$), 3.90 (s, 3H, $CH_3$), 6.71 (d, J = 6.0 Hz, 1H, CH), 6.82 - 7.00 (m, 5H, CH), 7.21 (t, J = 6.0 Hz, 1H, CH), 7.39 (d, J = 6.0 Hz, 1H, CH); gc-ms: 14.4 minutes; m/z 396. The oil was dissolved in ethanol (4 mL) and oxalic acid (0.13 g; 1.2 equivalents) was added and the mixture heated up to reflux for 30 minutes. After cooling down to room temperature the obtained solid was collected by filtration, washed with ethanol (2 mL) and dried *in vacuo* to yield 0.41 g (72 %) of a colourless solid; mp 164 - 166°.

*Anal.* Calcd. for $C_{23}H_{28}N_2O_2S{\bullet}C_2O_4H_2{\bullet}C_2H_5OH$: C, 60.88; H, 6.81; N, 5.26. Found: C, 60.58; H, 6.88; N, 4.95.

1-[3-(5-Methoxybenzo[*b*]thiophene-3-yl)propyl]-4-(2-methoxyphenyl)-piperazine (**14b**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 1.48 g (81 %) of a yellow syrup; $^1$H nmr (deuteriochloroform): δ 2.01 (m, 2H, CH, $CH_2$), 2.53 (m, 2H, $CH_2$), 2.67 (broad s, 4H, $CH_2$), 2.85 (m, 2H, $CH_2$), 3.11 (broad s, 4H, $CH_2$), 3.85 (s, 3H, $CH_3$), 3.89 (s, 3H, $CH_3$), 6.84 - 7.01 (m, 5H, CH), 7.11 (s, 1H, CH), 7.19 (d, J = 1.9 Hz, 1H, CH), 7.70 (d, J = 6.7 Hz, 1H, CH); gc-ms: 14.5 minutes; m/z 396; The syrup was dissolved in ethanol (20 mL) and oxalic acid (0.4 g; 1.2 equivalents) was added and the mixture heated up to reflux for 30 minutes. After cooling down to room temperature the obtained solid was collected by filtration, washed with ethanol (10 mL) and dried *in vacuo* to yield 1.47 g (81 %) of a colourless solid; mp 143 - 145°.

*Anal.* Calcd. for $C_{23}H_{28}N_2O_2S{\bullet}C_2O_4H_2{\bullet}C_2H_5OH$: C, 60.88; H, 6.81; N, 5.26. Found: C, 60.72; H, 6.76; N, 5.37.

1-[3-(6-Methoxybenzo[*b*]thiophene-3-yl)propyl]-4-(2-methoxyphenyl)-piperazine (**14c**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 1.11 g (53 %) of a yellow solid which was recrystallised from diethyl ether; $^1$H nmr (deuteriochloroform): δ 1.99 (m, 2H, CH, $CH_2$), 2.50 (m, 2H, $CH_2$), 2.66 (broad s, 4H, $CH_2$), 2.84 (m, 2H, $CH_2$), 3.11 (broad s, 4H, $CH_2$), 3.84 (s, 3H, $CH_3$), 3.86 (s, 3H, $CH_3$), 6.82 - 7.02 (m, 6H, CH), 7.31 (d, J = 1.8 Hz, 1H, CH), 7.63 (d, J = 6.8 Hz, 1H, CH); gc-ms: 14.5 minutes; m/z 396; mp 96 - 97°.

*Anal.* Calcd. for $C_{23}H_{28}N_2O_2S$: C, 69.66; H, 7.12; N, 7.06. Found: C, 69.37; H, 7.20; N, 6.83.

1-[3-(7-Methoxybenzo[*b*]thiophene-3-yl)propyl]-4-(2-methoxyphenyl)-piperazine (**14d**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 0.49 g (71 %) of a yellow syrup; $^1$H nmr (deuteriochloroform): δ 1.99 (m, 2H, CH, $CH_2$), 2.50 (m, 2H, $CH_2$), 2.66 (broad s, 4H, $CH_2$), 2.87 (m, 2H, $CH_2$), 3.10 (broad s, 4H, $CH_2$), 3.78 (s, 3H, $CH_3$), 3.98 (s, 3H, $CH_3$), 6.77 (d, J = 6.1 Hz, 1H, CH), 6.83 - 7.01 (m, 4H, CH), 7.09 (s, 1H, CH), 7.32 (t, J = 6.1 Hz, 1H, CH), 7.38 (d, J = 6.1 Hz, 1H, CH); gc-ms: 14.6 minutes; m/z 396; The syrup was dissolved in ethanol (4 mL) and oxalic acid (0.13 g; 1.2 equivalents) was added and the mixture heated up to reflux for 30 minutes. After cooling down to room temperature the obtained solid was collected by filtration, washed with ethanol (2 mL) and dried *in vacuo* to yield 0.45 g (75 %) of a colourless solid; mp 110 - 113°.

*Anal.* Calcd. for $C_{23}H_{28}N_2O_2S{\bullet}C_2O_4H_2{\bullet}C_2H_5OH$: C, 60.88; H, 6.81; N, 5.26. Found: C, 60.88; H, 6.45; N, 5.27.

### 1-[3-(4-Bromobenzo[*b*]thiophene-3-yl)propyl]-4-(2-methoxyphenyl)piperazine (**14e**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 1.85 g (65 %) of a yellow syrup; $^1$H nmr (deuteriochloroform): δ 2.00 (m, 2H, CH, $CH_2$), 2.54 (m, 2H, $CH_2$), 2.68 (broad s, 4H, $CH_2$), 3.11 (broad s, 4H, $CH_2$), 3.19 (m, 2H, $CH_2$), 3.85 (s, 3H, $CH_3$), 6.84 - 7.01 (m, 4H, CH), 7.11 (t, J = 6.0 Hz, 1H, CH), 7.19 (s, 1H, CH), 7.55 (d, J = 6.0 Hz, 1H, CH), 7.77 (d, J = 6.0 Hz, 1H, CH); gc-ms: 14.7 minutes; m/z 444/446. The syrup was dissolved in ethanol (20 mL) and oxalic acid (0.45 g; 1.2 equivalents) was added and the mixture heated up to reflux for 30 minutes. After cooling down to room temperature the obtained solid was filtered, washed with ethanol (10 mL) and dried *in vacuo* to yield 1.51 g (68 %) of a colourless solid; mp 153 - 155°.

*Anal.* Calcd. for $C_{22}H_{25}N_2OS{\bullet}C_2O_4H_2{\bullet}C_2H_5OH$: C, 53.70; H, 5.72; N, 4.82. Found: C, 53.38; H, 5.76; N, 4.62.

### 1-[3-(5-Bromobenzo[*b*]thiophene-3-yl)propyl]-4-(2-methoxyphenyl)piperazine (**14f**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 1.58 g (78 %) of a yellow solid which was recrystallised from ethyl acetate; $^1$H nmr (deuteriochloroform): δ 1.95 (m, 2H, CH, $CH_2$), 2.48 (t, J = 5.4 Hz, 2H, $CH_2$), 2.66 (broad s, 4H, $CH_2$), 2.86 (t, J = 5.4 Hz, 2H, $CH_2$), 3.12 (broad s, 4H, $CH_2$), 3.86 (s, 3H, $CH_3$), 6.84 - 7.02 (m, 4H, CH), 7.13 (s, 1H, CH), 7.41 (dd, J = 6.5 Hz, J = 1.4 Hz, 1H, CH), 7.68 (d, J = 6.5 Hz, 1H, CH), 7.93 (d, J = 1.4 Hz, 1H, CH); gc-ms: 14.7 minutes; m/z 444/446; mp 97 - 99°.

*Anal.* Calcd. For $C_{22}H_{25}N_2OS{\bullet}0.5\ C_4H_8O_2$: C, 58.89; H, 5.97; N, 5.72. Found: C, 58.71; H, 5.63; N, 5.99.

### 1-[3-(6-Bromobenzo[*b*]thiophene-3-yl)propyl]-4-(2-methoxyphenyl)piperazine (**14g**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 1.32 g (47%) of a white solid which was recrystallised from ethyl acetate; $^1$H nmr (deuteriochloroform): δ 1.95 (m, 2H, CH, $CH_2$), 2.49 (m, 2H, $CH_2$), 2.65 (broad s, 4H, $CH_2$), 2.85 (m, 2H, $CH_2$), 3.10 (broad s, 4H, $CH_2$), 3.85 (s, 3H, $CH_3$), 6.83 - 7.01 (m, 4H, CH), 7.07 (s, 1H, CH), 7.45 (dd, J = 6.7 Hz, J = 1.4 Hz, 1H, CH), 7.60 (d, J = 6.7 Hz, 1H, CH), 7.96 (d, J = 1.4 Hz, 1H, CH); gc-ms: 14.8 minutes; m/z 444/446; mp 116 - 118°.

*Anal.* Calcd. fr $C_{22}H_{25}N_2OS$: C, 59.32; H, 5.66; N, 6.29. Found: C, 59.30; H, 5.57; N, 6.34.

### [3-(4-Fluorobenzo[*b*]thiophene-3-yl)propyl]-[2-(pyridin-2yl-oxy)ethyl]amine (**14i**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 0.15 g (55 %) of a colourless syrup; $^1$H nmr (deuteriochloroform): δ 1.58 (broad s, 1H, NH), 1.86 (m, 2H, $CH_2$), 2.69 (t, J = 5.5 Hz, 2H, $CH_2$), 2.93 (m, 4H, $CH_2$), 4.33 (t, J = 4,0 Hz, 2H, $CH_2$), 6.65 (d, J = 6.5 Hz, 1H, CH), 6.76 (t, J = 4.5 Hz, 1H, CH), 6.89 (dd, J (F,H) = 9.1 Hz, J = 6.0 Hz, 1H, CH), 6.93 (s, 1H, CH), 7.14 (m, 1H, CH), 7.46 (m, 2H, CH), 8.05 (d, J = 3.8 Hz, 1H, CH); ms: m/z 331 ($M^+$) and 236 ($M^+$ - $C_5H_5NO$). The syrup was dissolved in isopropanol (4 mL) and 1 *M* hydrogen chloride in diethyl ether (0.9 mL; 2 equivalents) was added and the mixture heated up to reflux for 30 minutes. After cooling down to room temperature the obtained solid was collected by filtration, washed with isopropanol (2 mL), diethyl ether (2 mL) and dried *in vacuo* to yield 0.13 g (78 %) of a colourless solid; mp 170 - 174°.

*Anal.* Calcd. for $C_{18}H_{19}FN_2OS{\bullet}HCl$: C, 58.93; H, 5.49; N, 7.64. Found: C, 58.82; H, 5.29; N, 7.74.

### 1'-[3-(7-Methoxybenzo[*b*]thiophene-3-yl)propyl]spiro(indene-1,4' (1*H*) piperidine) (**14k**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 0.46 g (90 %) of a white solid which was recrystallised from diethyl ether; $^1$H nmr (deuteriochloroform): δ 1.34 (broad d, J = 10 Hz, 2H, CH), 2.01 (m, 2H, $CH_2$), 2.19 (ddd, J = 10 Hz, J = 9.2 Hz, J = 2.5 Hz, 2H, CH), 2.31 (td, J = 9.2 Hz, J = 1.5 Hz, 2H, CH), 2.54 (m, 2H, $CH_2$), 2.89 (m, 2H, $CH_2$), 2.99 (broad d, J = 9.2 Hz, CH), 3.96 (s, 3H, $CH_3$), 6.71 (d, J = 4.4 Hz, 1H, CH), 6.76 (d, J = 5.9 Hz, 1H, CH), 6.81 (d, J = 4.4 Hz, 1H, CH), 7.10 (s, 1H, CH), 7.21 (m, 2H, CH), 7.29 (d, J = 5.3 Hz, 1H, CH), 7.32 (dd, J = 6.2 Hz, J = 5.9 Hz, 1H, CH), 7.35 (d, J = 5.3 Hz, 1H, CH), 7.40 (d, J = 6.2 Hz, 1H, CH); ms: m/z 390; mp 93 - 94°.

*Anal.* Calcd. for $C_{25}H_{27}NOS$: C, 77.08; H, 6.99; N, 3.60. Found: C, 77.04; H, 7.03; N, 3.83.

### 1-[3-(4-Fluorobenzo[*b*]thiophen-3-yl)propyl]-4-(pyridin-2-yl)piperazine (**14l**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 0.11 g (57 %) of a colourless syrup which was dissolved in isopropanol (4 mL) and 1 *M* hydrogen chloride in diethyl ether (0.62 mL; 2 equivalents) was added and the mixture heated up to reflux for 30 minutes. After cooling down to room temperature the obtained solid was collected by filtration, washed with isopropanol (2 mL), diethyl ether (2 mL) and dried *in vacuo* to yield 0.105 g (85 %) of a colourless solid; $^1$H nmr (deuteriodimethyl sulfoxide): δ 2.18 (m, 2H, $CH_2$), 2.98 - 3.65 (broad m, 10H, $CH_2$), 4.37 (m, 2H, $CH_2$), 4.33 (t, J = 4,0 Hz, 2H, $CH_2$), 6.78 (dd, J = 5.3 Hz, J = 4.0 Hz, 1H, CH), 6.99 (d, J = 6.6 Hz, 1H, CH), 7.19 (dd, J (F,H) = 9.2 Hz, J = 6.1 Hz, 1H, CH), 7.37 (m, 1H, CH), 7.58 (s, 1H, CH), 7.65 (dd, J = 6.6 Hz, J = 5.3 Hz, 1H, CH), 7.82 (d, J = 6.1 Hz, 1H, CH), 8.16 (d, J = 4.0 Hz, 1H, CH); ms: m/z 356 ($M^+$); mp 197 - 198°.

*Anal.* Calcd. for $C_{20}H_{22}FN_3S \cdot HCl \cdot 0.5\ H_2O$: C, 59.91; H, 6.03; N, 10.48. Found: C, 59.94; H, 5.85; N, 10.21.

### 1-[4-(7-Bromo-4-fluorobenzo[*b*]thiophen-3-yl)butyl]-4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)piperazine (**18**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 1.35 g (86 %) of a colourless syrup; $^1$H nmr (deuteriochloroform): δ 1.63 (m, 2H, $CH_2$), 1.75 (m, 2H, $CH_2$), 2.44 (m, 2H, $CH_2$), 2.63 (broad s, 4H, $CH_2$), 2.97 (m, 2H, $CH_2$), 3.08 (broad s, 4H, $CH_2$), 4.24 (m, 2H, $CH_2$), 4.31 (m, 2H, $CH_2$), 6.53 (d, J = 6.2 Hz, 1H, CH), 6.58 (d, J = 6.2 Hz, 1H, CH), 6.77 (t, J = 6.3 Hz, 1H, CH), 6.91 (dd, J (F,H) = 8.5 Hz, J = 6.5 Hz, 1H, CH), 7.09 (s, 1H, CH), 7.37 (dd, J (F,H) = 3.0 Hz, J = 6.5 Hz, 1H, CH); ms: m/z 505/507 ($M^+$ + 1).

The syrup was dissolved in isopropanol (20 mL) and 1 *M* hydrogen chloride in diethyl ether (5.35 mL; 2 equivalents) was added and the mixture heated up to reflux for 30 minutes. After cooling down to room temperature the obtained solid was collected by filtration, washed with isopropanol (4 mL), diethyl ether (4 mL) and dried *in vacuo* to yield 1.16 g (80 %) of a colourless solid; mp 238 - 240°.

*Anal.* Calcd. for $C_{24}H_{26}BrFN_2O_2S$•HCl•0.5 $H_2O$: C, 52.32; H, 5.12; N, 5.08. Found: C, 52.13; H, 4.92; N, 5.10.

### 1-[4-(4-Fluorobenzo[*b*]thiophen-3-yl)butyl]-4-(2,3-dihydrobenzo[1,4]dioxin-5-yl)piperazine (**19**).

1-[4-(7-Bromo-4-fluorobenzo[*b*]thiophen-3-yl)butyl]-4-(2,3-dihydrobenzo[1,4]-dioxin-5-yl)piperazine (**18**) 0.28 g (0.55 mmoles) was dissolved in dry tetrahydrofuran (20 mL) and 1.4 mL of a 1 *M* solution of lithium aluminium hydride was added dropwise under nitrogen while stirring at room temperature. The resulting mixture was heated under reflux for 12 hours, cooled to room temperature and carefully quenched by adding 20 % aqueous potassium hydroxide solution dropwise. The resulting mixture was extracted 3 times with dichloromethane, the organic phases were combined, washed with brine and dried over anhydrous sodium sulfate. Filtration and concentration under reduced pressure yielded the crude target compound which was adsorbed onto silica gel and purified by column chromatography (hexane/ethyl acetate = 3: 1) to yield 0.16 g (67 %) of a colourless syrup; $^1$H nmr (deuteriochloroform): δ 1.64 (m, 2H, $CH_2$), 1.76 (m, 2H, $CH_2$), 2.45 (m, 2H, $CH_2$), 2.64 (broad s, 4H, $CH_2$), 2.99 (m, 2H, $CH_2$), 3.09 (broad s, 4H, $CH_2$), 4.23 (m, 2H, $CH_2$), 4.31 (m, 2H, $CH_2$), 6.53 (d, J = 6.2 Hz, 1H, CH), 6.58 (d, J = 6.2 Hz, 1H, CH), 6.76 (t, J = 6.2 Hz, 1H, CH), 6.98 (dd, J (F,H) = 9.0 Hz, J = 6.1 Hz, 1H, CH), 7.01 (s, 1H, CH), 7.24 (m, 1H, CH), 7.58 (d, J = 6.2 Hz, 1H, CH); ms: m/z 427 ($M^+$ + 1). The syrup was dissolved in isopropanol (4 mL) and 1 *M* hydrogen chloride in diethyl ether (0.38 mL; 2 equivalents) was added and the mixture heated up to reflux for 30 minutes. After cooling down to room temperature the obtained solid was collected by filtration, washed with isopropanol (2 mL), diethyl ether (2 mL) and dried *in vacuo* to yield 0.15 g (85 %) of a colourless solid; mp 220 - 221°.

*Anal.* Calcd. for $C_{24}H_{27}FN_2O_2S$•HCl•0.6$H_2O$: C, 60.68; H, 6.22; N, 5.90. Found: C, 60.32; H, 5.98; N, 6.04.

### Methyl 3-(3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl)-6-(trifluoromethyl)-benzo[*b*]thiophene-2-carboxylate (**26**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 1.37 g (58 %) of a white solid which was recrystallised from ethyl acetate/*n*-hexane (1:1); $^1$H nmr (deuteriochloroform): δ 1.91 (m, 2H, CH, $CH_2$), 2.51 (m, 2H, $CH_2$), 2.63 (broad s, 4H, $CH_2$), 3.09 (broad s, 4H, $CH_2$), 3.38 (m, 2H, $CH_2$), 3.86 (s, 3H, $CH_3$); 3.95 (s, 3H, $CH_3$), 6.85 - 7.02 (m, 4H, CH), 7.62 (dd, J = 6.7 Hz, J = 1.1 Hz, 1H, CH), 8.05 (d, J = 6.7 Hz, 1H, CH); 8.12 (d, J = 1.1 Hz, 1H, CH); ms: m/z 493 ($M^+$+1); mp 109 - 110°.

*Anal.* Calcd. for $C_{25}H_{27}F_3N_2O_3S$: C, 60.96; H, 5.52; N, 5.69. Found: C, 61.26; H, 5.42; N, 5.59.

### 3-(2-Phenylethyl)-9-trifluoromethyl-3,4,5,6-tetrahydro-2*H*-azepino[2,3-*b*]benzo[*d*]thiophene (**27**).

Following the general procedure for the preparation of 3-(ω-aminoalkyl)-benzo[*b*]thiophenes *via* nucleophilic substitution of 3-(ω-chloroalkyl)-benzo[*b*]thiophenes, methyl 3-(3-chloropropyl)-6-(trifluoromethyl)benzo[*b*]thio-phene-2-carboxylate (**25**) 0.16 g (0.48 mmoles) was reacted with 60 mg (0.5 mmoles) 2-phenethylamine to yield, after aqueous work-up, the methyl 3-(3-phenethylaminopropyl)-6-(trifluoromethyl)benzo[*b*]thiophene-2-carboxylate as an oil which was dissolved in 2 mL dichloroethane under nitrogen and 0.5 mL (0.5 mmoles) trimethylaluminium (1 *M* in toluene) was added and the mixture was stirred at 60° for 2 hours. The solution was poured into a water/dichloromethane mixture (5 mL/50 mL) and the mixture adjusted to pH = 2 on addition of 1 *N* hydrochloric acid. The phases were separated and, after an extraction with dichloromethane, the organic phases were combined, washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to result in a yellow syrup. This was dissolved in 3 mL of dry tetrahydrofuran, and 0.5 mL of a 1 *M* solution of lithium aluminium hydride (0.5 mmoles) was added dropwise under nitrogen while stirring at room temperature. After stirring for 15 hours the reaction was carefully quenched by adding 20 % aqueous potassium hydroxide solution dropwise. The resulting mixture was extracted 3 times with dichloromethane and the organic phases were combined, washed with brine and dried over anhydrous potassium carbonate. Filtration and concentration under reduced pressure yielded the crude target compound which was adsorbed onto silica and purified by column chromatography (ethyl acetate/*iso*-hexane = 3:1) to yield 70 mg (40 %) of a colourless syrup; $^1$H nmr (deuteriochloroform): δ 1.80 (m, 2H, CH, $CH_2$), 2.73 (m, 2H, $CH_2$), 2.81 (m, 2H, $CH_2$), 3.00 (m, 2H, $CH_2$), 3.30 (m, 2H, $CH_2$); 4.14 (s, 2H, $CH_2$), 7.16 (m, 3H, CH), 7.24 (m, 2H, CH), 7.56 (d, J = 6.5 Hz, 1H, CH), 7.69 (d, J = 6.5 Hz, 1H, CH), 8.04 (broad s, 1H, CH); ms: m/z 376 ($M^+$+1). The syrup was dissolved in ethanol (4 mL) and 1 *M* hydrogen chloride in diethyl ether (0.37 mL; 2 equivalents) was added and the mixture heated up to reflux for 30 minutes. After cooling down to room temperature the obtained solid was collected by filtration, washed with ethanol (1 mL), diethyl ether (1 mL) and dried *in vacuo* to yield 50 mg (65 %) of a colourless solid; mp > 230° (decomposition).

*Anal.* Calcd. for $C_{21}H_{20}F_3NS$•HCl: C, 61.23; H, 5.14; N, 3.40. Found: C, 61.15; H, 5.02; N, 3.35.

### 1-[4-(4-Fluorobenzo[*b*]thiophen-3-yl)butyl]piperazine (**17**).

Following the general procedure for the preparation of 3-(ω-aminoalkyl)-benzo[*b*]thiophenes *via* nucleophilic substitution of 3-(ω-chloroalkyl)benzo[*b*]-thiophenes, 3.16 g (9.83 mmoles) of 7-bromo-4-fluoro-3-(4-chlorobutyl)-benzo[*b*]thiophene (**10**) was reacted with 2.05 g of *N*-(*t*-butoxy-carbonyl)-piperazine to yield, after aqueous work-up, the required *t*-butyl 4-[4-(7-bromo-4-fluorobenzo[*b*]thiophen-3-yl)piperazine-1-carboxylate as an oil which was dissolved in 100 mL dichloromethane/trifluoroacetic acid (4:1) and stirred at room temperature for 1 hour. The solution was poured into 250 mL of 10 % aqueous sodium hydroxide and the phases separated. After a further extraction with dichloromethane, the organic phases were combined, washed with water and brine, dried over anhydrous potassium carbonate, filtered and concentrated under reduced pressure to result in 1-[4-(7-bromo-4-fluorobenzo[*b*]thiophen-3-yl)butyl]piperazine (**17**) as a yellow oil. This was dissolved in 50 mL of dry tetrahydrofuran, and 20 mL of a 1 *M* solution of lithium aluminium hydride was added dropwise under nitrogen while stirring at room temperature. The resulting mixture was heated under reflux for 12 hours, cooled to room temperature and carefully quenched by adding 20 % aqueous potassium hydroxide solution dropwise. The resulting mixture was extracted 3 times with dichloromethane and the organic phases were combined, washed with brine and dried over anhydrous potassium carbonate. Filtration and concentration under reduced pressure yielded the crude target compound which was adsorbed onto silica and purified by column chromatography (dichloromethane/methanol/ammonia = 100:10:1) to yield 2.28 g (81 %) of a colourless syrup which slowly crystallises; $^1$H nmr (deuteriochloroform): δ 1.59 (m, 2H, $CH_2$), 1.72 (m, 2H, $CH_2$), 1.86 (broad s, 1H, NH), 2.36 (m, 6H, $CH_2$), 2.88 (t, J = 4.0 Hz, 4H, $CH_2$), 2.97 (m, 2H, $CH_2$), 6.98 (dd, J (F,H) = 9.2 Hz, J = 6.1 Hz, 1H, CH), 7.01 (s, 1H, CH), 7.24 (m, 1H, CH), 7.56 (d, J = 6.1 Hz, 1H, CH); ms: m/z 293 ($M^+$ + 1); mp 47 - 50°.

*Anal.* Calcd. for $C_{16}H_{21}FN_2S$: C, 65.72; H, 7.24; N, 9.58. Found: C, 65.98; H, 7.55; N, 9.38.

### General Procedure for the Preparation of 4-, 6- and 7-Arylbenzo[*b*]thiophenes (**15a**, **15c** and **15e**) *via* Suzuki-reaction [11a] of Substitution of 4-, 6- and 7-Bromobenzo[*b*]thiophenes (**14e**, **14g** and **14h**).

At room temperature, tetrakis(triphenylphosphine)palladium(0) (5 mol%) was mixed with the corresponding bromobenzo[*b*]thiophene (**14**) using a two-necked flask under nitrogen and the corresponding boronic acid (1.5 equivalents) was added. After the addition of toluene (5 mL/mmol) and 2 *M* aqueous sodium carbonate solution (2 equivalents), the resulting mixture was heated at 100° while stirring for 18 hours and poured onto ice-water. The product was extracted into ethyl acetate and the organic extract was washed with water and brine. After drying over anhydrous sodium sulfate and filtering, the extract was concentrated to yield the crude target compounds, which were adsorbed onto silica gel and purified by column chromatography.

### 1-(2-Methoxyphenyl)-4-[3-(4-phenylbenzo[*b*]thiophen-3-yl)-propyl]piperazine (**15a**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 0.16 g (89 %) of a yellow syrup; $^1$H nmr (deuteriochloroform): δ 1.97 (m, 2H, $CH_2$), 2.00 (m, 2H, $CH_2$), 2.25 (m, 2H, $CH_2$), 2.48 (broad s, 4H, $CH_2$), 3.03 (broad s, 4H, $CH_2$), 3.83 (s, 3H, $CH_3$), 6.82 - 7.00 (m, 4H, CH), 7.10 (s, 1H, CH), 7.15 (d, J = 5.5 Hz, 1H, CH), 7.33 (dd, J = 6.0 Hz, J = 5.5 Hz, 1H, CH), 7.43 (m, 5H, CH), 7.84 (d, J = 6.0 Hz, 1H, CH); ms: m/z 443 ($M^+$ +1). The syrup was dissolved in ethanol (4 mL) and 1 *M* hydrogen chloride in diethyl ether (0.72 mL; 2 equivalents) was added and the mixture heated up to reflux for 30 minutes. After cooling down to room temperature the obtained solid was collected by filtration, washed with ethanol (1 mL), diethyl ether (1 mL) and dried *in vacuo* to yield 100 mg (57 %) of a colourless solid; mp 154 - 155°.

*Anal.* Calcd. for $C_{28}H_{30}N_2OS{\bullet}HCl{\bullet}0.5\ H_2O$: C, 68.90; H, 6.61; N, 5.74. Found: C, 68.94; H, 6.24; N, 5.98.

### 1-(2-Methoxyphenyl)-4-[3-(6-phenylbenzo[*b*]thiophen-3-yl)-propyl]piperazine (**15c**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 0.13 g (80 %) of a yellow syrup; $^1$H nmr (deuteriochloroform): δ 2.00 (m, 2H, $CH_2$) 2.52 (m, 2H, $CH_2$), 2.67 (broad s, 4H, $CH_2$), 2.90 (m, 2H, $CH_2$), 3.11 (broad s, 4H, $CH_2$), 3.83 (s, 3H, $CH_3$), 6.82 - 6.98 (m, 4H, CH), 7.11 (s, 1H, CH), 7.43 (m, 3H, CH), 7.59 - 7.65 (m, 3H, CH), 7.81 (d, J = 6.4 Hz, 1H, CH), 8.04 (d, J = 1.0 Hz, 1H, CH); ms: m/z 443 ($M^+$ +1). The syrup was dissolved in isopropanol (4 mL) and 1 *M* hydrogen chloride in diethyl ether (0.58 mL; 2 equivalents) was added and the mixture heated up to reflux for 30 minutes. After cooling down to room temperature the obtained solid was collected by filtration, washed with ethanol (1 mL), diethyl ether (1 mL) and dried *in vacuo* to yield 97 mg (69 %) of a colourless solid; mp 232 - 234°.

*Anal.* Calcd. for $C_{28}H_{30}N_2OS \cdot HCl \cdot 0.5\ H_2O$: C, 68.90; H, 6.61; N, 5.74. Found: C, 68.56; H, 6.27; N, 5.73.

### 1-(2-Methoxyphenyl)-4-(3-[7-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl]propyl)-piperazine (**15e**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 0.20 g (85 %) of a white solid; $^1$H nmr (deuteriodimethyl sulfoxide): δ 2.10 (m, 2H, $CH_2$) 3.10 (m, 2H, $CH_2$), 3.10 - 3.38 (broad m, 6H, $CH_2$), 3.79 (s, 3H, $CH_3$), 3.80 - 4.20 (broad m, 7H, $CH_2$, $CH_3$), 6.89 - 7.01 (m, 4H, CH), 7.11 (d, J = 6.8 Hz, 1H, CH), 7.39 (d, J = 5.4 Hz, 1H, CH), 7.53 (m, 2H, CH), 7.64 (d, J = 6.8 Hz, 2H, CH), 7.82 (d, J = 6.1 Hz, 1H, CH); ms: m/z = 473 ($M^+$ +1). The solid was dissolved in isopropanol (4 mL) and oxalic acid (50 mg; 1.2 equivalents) was added and the mixture heated up to reflux for 30 minutes. After cooling down to room temperature the obtained solid was collected by filtration, washed with isopropanol (1 mL), diethyl ether (1 mL) and dried *in vacuo* to yield 170 mg (73 %) of a colourless solid; mp 119 - 120°.

*Anal.* Calcd. for $C_{29}H_{32}N_2O_2S{\bullet}C_2O_4H_2{\bullet}0.5\ H_2O$: C, 65.13; H, 6.17; N, 4.90. Found: C, 65.12; H, 6.13; N, 4.84.

### General Procedure for the Preparation of Substituted Benzo[*b*]thiophenes (**15b**, **15d**, **20**, **21** and **22**) *via* Palladium Mediated Amination-reaction [11b] of Benzo[*b*]thiophenes (**14e**, **14g** and **17**).

At room temperature, palladium (II) acetate (5 mol%), (*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (5 mol%) and cesium carbonate (1.5 equivalents) were mixed with the corresponding bromoarene (**14**) using a two-necked flask under nitrogen, and toluene (5 mL/mmol) was added. After the addition of the corresponding amine (1.2 equivalents), the resulting mixture was heated at 100° while stirring for 18 hours and poured onto ice-water. The product was extraced into ethyl acetate and the organic extract was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated to yield the crude target compounds which were adsorbed onto silica gel and purified by column chromatography.

### 4-[3-(3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl)benzo[*b*]-thiophen-4-yl]-morpholine (**15b**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 0.18 g (71%) of a colourless syrup; $^1$H nmr (deuteriochloroform): δ 1.97 (m, 2H, $CH_2$), 2.54 (m, 2H, $CH_2$), 2.67 (broad s, 4H, $CH_2$), 3.01 (broad m, 4H, $CH_2$), 3.10 (broad s, 4H, $CH_2$), 3.18 (m, 2H, $CH_2$), 3.85 (s, 3H, $CH_3$), 3.94 (m, 4H, $CH_2$), 6.84 - 7.01 (m, 4H, CH), 7.07 (s, 1H, CH), 7.14 (d, J = 5.9 Hz, 1H, CH), 7.27 (dd, J = 6.1 Hz, J = 5.9 Hz, 1H, CH), 7.61 (d, J = 6.1 Hz, 1H, CH); ms: m/z 452 ($M^+$ +1). The syrup was dissolved in ethanol (4 mL) and 1 *M* hydrogen chloride in diethyl ether (0.8 mL; 2 equivalents) was added and the mixture heated up to reflux for 30 minutes. After cooling down to room temperature the obtained solid was collected by filtration, washed with ethanol (1 mL), diethyl ether (1 mL) and dried *in vacuo* to yield 170 mg (89 %) of a colourless solid; mp 235 - 236°.

*Anal.* Calcd. for $C_{26}H_{33}N_3O_2S{\bullet}HCl{\bullet}0.5\ H_2O$: C, 62.82; H, 7.10; N, 8.45. Found: C, 62.89; H, 7.10; N, 8.40.

### 4-[3-(3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl)benzo-[*b*]thiophen-6-yl]-morpholine (**15d**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 0.13 g (80%) of a white solid which was recrystallised from *iso*-hexane/ethyl acetate (1: ); $^1$H nmr (deuteriochloroform): $\delta$ 1.91 (m, 2H, $CH_2$) 2.43 (m, 2H, $CH_2$), 2.59 (broad s, 4H, $CH_2$), 2.76 (m, 2H, $CH_2$), 3.03 (broad s, 4H, $CH_2$), 3.11 (m, 4H, $CH_2$), 3.78 (s, 3H, $CH_3$), 3.81 (m, 4H, $CH_2$), 6.77 - 6.94 (m, 5H, CH), 6.97 (dd, J = 6.8 Hz, J = 1.7 Hz, 1H, CH), 7.23 (d, J = 1.7 Hz, 1H, CH), 7.57 (d, J = 6.8 Hz, 1H, CH); ms: m/z 452 ($M^+$ +1); mp 134 - 135°.

*Anal.* Calcd. for $C_{26}H_{33}N_3O_2S$: C, 69.15; H, 7.36; N, 9.30. Found: C, 69.08; H, 7.21; N, 9.31.

### 1-[4-(4-Fluorobenzo[*b*]thiophene-3-yl)butyl]-4-(2-methoxyphenyl)piperazine (**20**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 0.11 g (27%) of a yellow syrup; $^1$H nmr (deuteriochloroform): $\delta$ 1.64 (m, 2H, $CH_2$), 1.79 (m, 2H, CH, $CH_2$), 2.47 (m, 2H, $CH_2$), 2.67 (broad s, 4H, $CH_2$), 2.99 (m, 2H, $CH_2$), 3.10 (broad s, 4H, $CH_2$), 3.85 (s, 3H, $CH_3$), 6.84 - 6.99 (m, 5H, CH), 7.23 (m, 2H, CH), 7.57 (d, J = 6.2 Hz, 1H, CH); ms: m/z 399 ($M^+$+1). The syrup was dissolved in ethanol (4 mL) and 1 *M* hydrogen chloride in diethyl ether (0.56 mL; 2 equivalents) was added and the mixture heated up to reflux for 30 minutes. After cooling down to room temperature the obtained solid was collected by filtration, washed with ethanol (1 mL), diethyl ether (1 mL) and dried *in vacuo* to yield 90 mg (75 %) of a colourless solid; mp 203 - 204°.

*Anal.* Calcd. for $C_{23}H_{27}FN_2OS_2$•HCl•0.5$H_2O$: C, 62.22; H, 6.58; N, 6.31. Found: C, 62.54; H, 6.48; N, 6.13.

### 1-(Benzo[*b*]thiophen-7-yl)-4-[4-(4-fluorobenzo[*b*]thiophene-3-yl)butyl]-piperazine (**21**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 0.19 g (39%) of a yellow syrup; $^1$H nmr (deuteriochloroform): $\delta$ 1.58 (m, 2H, $CH_2$), 1.71 (m, 2H, CH, $CH_2$), 2.39 (m, 2H, $CH_2$), 2.59 (broad s, 4H, $CH_2$), 2.92 (m, 2H, $CH_2$), 3.17 (broad s, 4H, $CH_2$), 6.83 (d, J = 5.9 Hz, 1H, CH), 6.90 (dd, J = 9.0 Hz, J = 6.1 Hz, 1H, CH), 6.92 (s, 1H, CH), 7.14 (m, 1H, CH), 7.20 - 7.24 (m, 2H, CH), 7.29 (d, J = 4.2 Hz, 1H, CH), 7.41 (d, J = 6.0 Hz, 1H, CH), 7.48 (d, J = 6.2 Hz, 1H, CH); ms: m/z 425 ($M^+$ +1). The syrup was dissolved in ethanol (4 mL) and 1 *M* hydrogen chloride in diethyl ether (0.9 mL; 2 equivalents) was added and the mixture heated up to reflux for 30 minutes. After cooling down to room temperature the obtained solid was collected by filtration, washed with ethanol (1 mL), diethyl ether (1 mL) and dried *in vacuo* to yield 190 mg (92 %) of a colourless solid; mp 237 - 239°.

*Anal.* Calcd. for $C_{24}H_{25}FN_2S_2$•HCl: C, 62.52; H, 5.68; N, 6.08. Found: C, 62.44; H, 5.71; N, 5.98.

### 8-[4-(4-[4-Fluorobenzo[*b*]thiophene-3-yl]butyl)piperazin-1-yl]-quinoline (**22**).

The product was purified by column chromatography (*iso*-hexane/ethyl acetate = 3:1) to yield 0.28 g (74 %) of a yellow syrup; $^1$H nmr (deuteriochloroform): $\delta$ 1.68 (m, 2H, $CH_2$), 1.79 (m, 2H, CH, $CH_2$), 2.52 (m, 2H, $CH_2$), 2.80 (m, 4H, $CH_2$), 3.01 (m, 2H, $CH_2$), 3.45 (broad s, 4H, $CH_2$), 6.98 (dd, J = 9.0 Hz, J = 6.1 Hz, 1H, CH), 7.02 (s, 1H, CH), 7.13 (m, 1H, CH), 7.22 (m, 1H, CH), 7.33 (dd, J = 6.3 Hz, J = 3.2 Hz, 1H, CH), 7.41 (m, 2H, CH), 7.57 (d, J = 6.2 Hz, 1H, CH), 8.07 (d, J = 6.3 Hz, 1H, CH), 8.87 (m, 1H, CH); ms: m/z 420 ($M^+$+1). The syrup was dissolved in ethanol (4 mL) and 1 *M* hydrogen chloride in diethyl ether (1.34 mL; 2 equivalents) was added and the mixture heated up to reflux for 30 minutes. After cooling down to room temperature the obtained solid was collected by filtration, washed with ethanol (2 mL), diethyl ether (2 mL) and dried *in vacuo* to yield 235 mg (77 %) of a colourless solid; mp 232 - 235°.

*Anal.* Calcd. for $C_{25}H_{26}FN_3S$•2 HCl•$H_2O$: C, 58.82; H, 5.92; N, 8.23. Found: C, 58.69; H, 5.97; N, 7.90.

## REFERENCES AND NOTES

[1] Review: T. Y. Zhang, J. O'Toole and P. C. Scott, *Sulfur Rep*., **22**, 1 (1999); For the synthesis of 3-alkyl substituted benzo[*b*]thiophenes see: [a] S. Cabiddu, D. Cancellu, C. Floris, G. Gelli and S. Melis, *Synthesis*, 888 (1988); [b] R. Patra, R. Gosh, S. B. Maiti and A. Chatterjee, *Tetrahedron Lett.*, **30**, 4279 (1989).

[2a] M. R. Cuberes, M. Moreno-Mañas and F. Sánchez-Ferrando, *Magnetic Resonance in Chemistry*, **23**, 814 (1985); [b] P. A. Plé and L. J. Marnett, *J. Heterocyclic Chem.*, **25**, 1271 (1988).

[3] For a similar approach in indole chemistry see: P. R. Brodfuehrer, B.-C. Chen, T. R. Sattelberg, Sr., P. R. Smith, J. P. Reddy, Derron, R. Stark, S. L. Quinlan and J. G. Reid, *J. Org. Chem.*, **62**, 9192 (1997).

[4a] M. S. Newman and H. K. Karnes, *J. Org. Chem.*, **31**, 3980 (1966); [b] H. Kwart and E. R. Evans, *J. Org. Chem.*, **31**, 410 (1966).

[5] D. A. Clibbens and M. Nierenstein, *J. Chem. Soc*., **107**, 1491 (1915).

[6] J. Barluenga, J. R. Fernandez and M. Yus, *Synthesis*, 977 (1985).

[7] D. J. Dumas, *J. Org. Chem*., **53**, 4650 (1988).

[8] J. L. M. Buus, L. Bjaverskov and N. Lassen, German Patent 2426149 (1974); *Chem. Abstr*., 55389-14-5.

[9] For a similar preparation see: S. Krishnamurthy and D. Aimino, *J. Org. Chem.*, **54**, 4458 (1989).

[10] I. Yanagisawa, Y. Hirata and Y. Ishii, *J. Med. Chem*., **27**, 849 (1984).

[11a] Review: A. Suzuki, *J. Organomet. Chem*., **576**, 147 (1999); [b] J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.* **65**, 1144 (2000).

[12] A. J. Bridges, A. Lee, E. C. Maduakor and C. E. Schwartz, *Tetrahedron Lett.*, **33**, 7499 (1992).

[13] G. Terrago, I. Zidane, C. Marzin and A. Tep, *Tetrahedron*, **44**, 91 (1988).

[14] B. E. Evans, J. L. Leighton, K. E. Rittle, K. F. Gilbert, G. F. Lundell, N. P. Gould, D. W. Hobbs, R. M. DiPardo, D. F. Veber, D. J. Pettibone, B. V. Clineschmidt, P. S. Anderson and R. M. Freidinger, *J. Med. Chem*., **35**, 3919 (1992).

[15] J.-L. Peglion, H. Canton, K. Bervoets, V. Audinot, M. Brocco, A. Gobert, S. Le Marouille-Girardon and M. J. Millan, *J. Med. Chem.*, **38**, 4044 (1995).

[16] F.-P. Montforts, U. M. Schwartz, P. Maib and G. Mai, *Liebigs Ann. Chem*., 1037 (1990).