Palladium-Catalysed Amination of Electron-Deficient or Relatively Electron-Rich Benzo[*b*]thienyl Bromides − Preliminary Studies of Antimicrobial Activity and SARs

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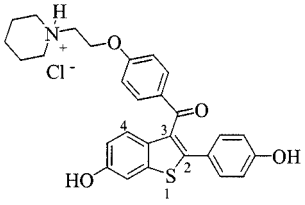
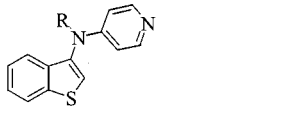
Several diarylamines in the benzo[*b*]thiophene series were prepared in good to high yields by palladium-catalysed amination of ethyl 3-bromobenzo[*b*]thiophene-2-carboxylate with anilines and 5-aminoindole in the presence of $Pd(OAc)_2$, BINAP and Cs_2CO_3 in toluene. The presence of the ester group at the 2-position of the benzo[*b*]thiophene moiety increases the yields and lowers the heating times relative to the reactions performed with 3-bromobenzo[*b*]thiophene. When aminopyridines were used instead of anilines, the ligand and the solvent need to be changed to XANTHPHOS and dioxane in the amination reaction. With 2-aminopyridine a one-pot C–N coupling and intramolecular cyclization involving the nitrogen atom of the pyridine ring occurred, with loss of ethanol, giving an interesting fluorescent tetracyclic heteroaromatic compound. The antimicrobial activity, the minimal inhibitory concentrations (MICs) and the structure-activity relationships (SARs) were evaluated. A selectivity with low MICs was observed against *Bacillus Cereus*, and good results were also obtained against *Candida albicans*. The acids obtained by hydrolysis of the ester group, as non-proteinogenic α,β-unsaturated β-amino acids, can be incorporated into peptide chains to induce conformational constraints.

Introduction

Benzo[*b*]thiophenes are important heterocycles, either as biologically active molecules or as luminescent components used in organic materials.[1] One of the most important drugs based on the benzo[*b*]thiophene system is Raloxifene, approved by the U. S. Food and Drug Administration for the prevention and treatment of osteoporosis in postmenopausal women.[2] Extensive research into other potential applications of this drug, namely for the treatment of Alzheimer's disease, is currently in progress.[3] In the same series, a number of 3-[(4-pyridinyl)amino]benzo[*b*]thiophenes, which are selective serotonin re-uptake inhibitors, have been prepared and may be useful in the treatment of central nervous system disorders, including obsessive compulsive disorders.[4]



Raloxifene



3-(4-pyridinyl)aminobenzo[*b*]thiophenes
R = alkyl

We have recently become interested in palladium-catalysed arylamination of benzo[*b*]thiophenes, either in the benzene or in the thiophene ring, to obtain the corresponding diarylamines and in some cases tetracyclic aromatic compounds resulting from intramolecular cyclizations.[5] We have been able to establish that under the same C−N coupling[6] conditions [$Pd(OAc)_2$ (3mol %), Cs_2CO_3 (1.4 equiv.) and BINAP (4mol %) in toluene] it was possible to obtain either primary amines[5b] or diarylamines[5b,5c] in the benzene ring of the benzo[*b*]thiophene moiety. The same conditions were ineffective for the amination of 3-bromobenzo[*b*]thiophene with *ortho*-bromoanilines, for which *t*BuONa and larger amounts of $Pd(OAc)_2$ and BINAP were required.[5c] In this work we extend the scope of the former conditions to the coupling of ethyl 3-bromobenzo[*b*]thiophene-2-carboxylate (**1a**) (electron-deficient) and 3-bromobenzo[*b*]thiophene (**1b**) (relatively electron-rich) with aro-

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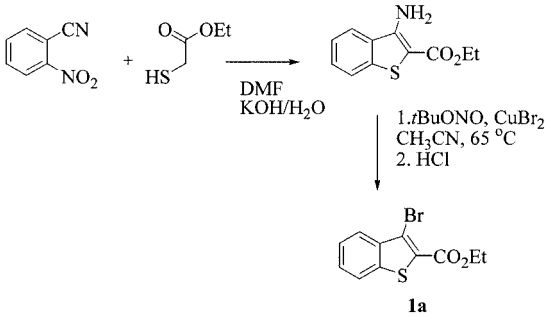
matic amines. Other conditions were required for the coupling with aminopyridines, as already described by other authors for heteroaromatic amines.[7] The antimicrobial activities and minimal inhibitory concentrations (MICs) of some of the prepared compounds against bacteria and against *Candida albicans* were evaluated, together with structure-activity relationships (SARs). The acids obtained by hydrolysis of the ester group, as non-proteinogenic α,β-unsaturated β-amino acids, can be incorporated into peptides to induce conformational constraints, which can help in the study of the structure of proteins.

Results and Discussion

The precursor ethyl 3-bromobenzo[*b*]thiophene-2-carboxylate (**1a**) was prepared from the corresponding 3-amino compound by treatment with *t*BuONO and $CuBr_2$.[8] The 3-amino compound was in turn synthesized by treatment of 2-cyanonitrobenzene with ethylthioglycolate (Scheme 1).[9]

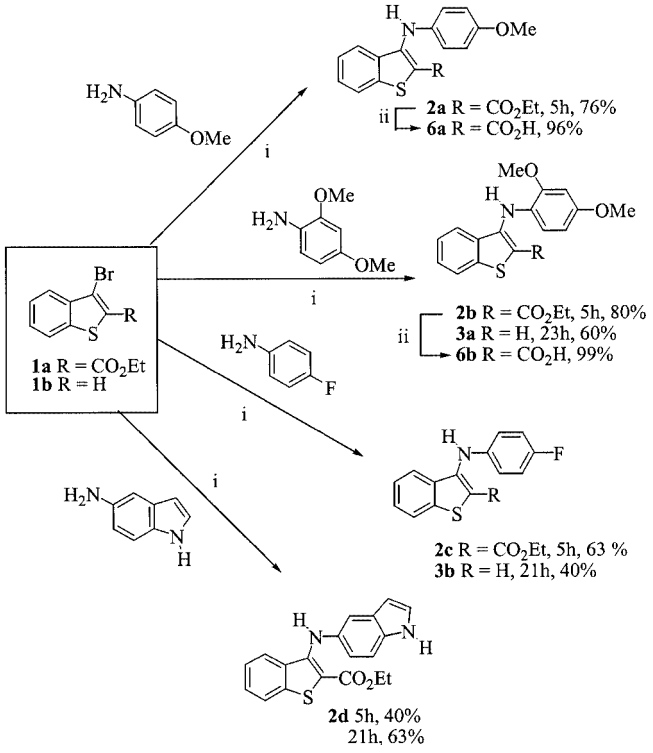


Scheme 1

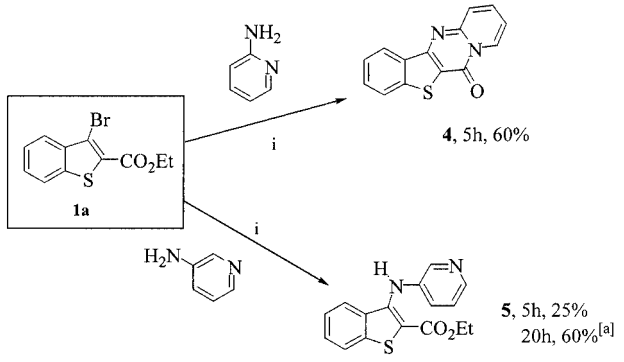
C−N Couplings

Compound **1a** was coupled with several anilines and with 5-aminoindole under the same conditions to give diarylamines **2** in good to high yields (Scheme 2). When 5-aminoindole was used as coupling component, the yield of the coupled product after 5 h of heating was only 40%, while on leaving the reaction overnight the yield was increased to 63%. In order to compare yields, two reactions with 3-bromobenzo[*b*]thiophene (**1b**) were performed. The presence of the ester group in the 2-position increases the reaction yields and lowers the heating times (Scheme 2).

Under the same conditions, 2- and 3-aminopyridines did not react. Changing the conditions to those used by other authors for the coupling of heteroaromatic amines[7] afforded the interesting tetracyclic compound **4** from 2-aminopyridine and the diarylamine **5** from 3-aminopyridine (Scheme 3). The former compound was the result of a C−N coupling followed by an intramolecular cyclization involving the nitrogen atom of the pyridine ring, with loss of ethanol. For the synthesis of compound **5** in good yield more time and greater quantities of Pd were needed, $Pd(OAc)_2$ also being effective as Pd source.



Scheme 2. (i) $Pd(OAc)_2$ (3 mol%), BINAP (4 mol%), Cs_2CO_3 (1.4 equiv.), toluene, 100 °C, Ar; (ii) 1. 30% NaOH, EtOH, Δ, 2. HCl (1N)



Scheme 3. i) Pd_2dba_3 (3 mol% Pd), XANTPHOS (4 mol%), Cs_2CO_3 (1.4 equiv.), dioxane, 100 °C, Ar; [a] $Pd(OAc)_2$ (6 mol%)

Compound **4**, as a planar compound, can intercalate into the DNA bases, acting as an anti-tumour compound and/or as a biomarker, thanks to its fluorescence (Figure 1). It showed a $\lambda_{em(max.)} = 435$ nm and a relative quantum yield of fluorescence in dichloromethane of $\Phi_{dcm} = 0.13$, determined by the standard method[11] with 9,10-diphenylanthracene in ethanol as reference ($\Phi_{EtOH} = 0.95$),[12] at $\lambda_{exc.} = 368$ nm and with application of Equation (1) [A = absorbance at the excitation wavelength of the solutions in dichloromethane (s) and EtOH (r); F = integrated emission area; n = refraction index of the solvents used; subscripts refer to the reference (r) or sample (s) compound].

$$\Phi_s = \frac{A_r F_s n_s^2}{A_s F_r n_r^2} \Phi_r \quad (1)$$

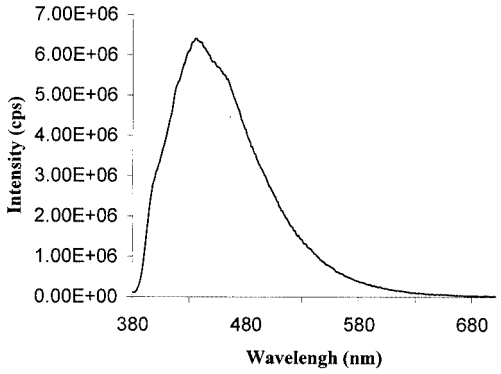


Figure 1. Fluorescence spectrum of compound **4** in dichloromethane (10^{-6} M) ($\lambda_{exc.}$ = 368 nm) showing a λ_{em} = 435 nm

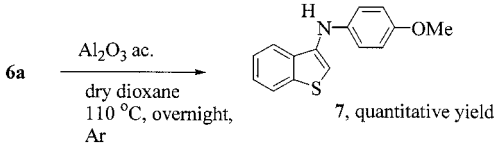
This excitation wavelength ($\lambda_{exc.}$) was chosen from the absorption spectrum of compound **4** (see Exp. Sect.) after verification that when $\lambda_{exc.}$ = 387 nm was used the compound was already emitting at lower wavelengths. The diarylamine **5** showed only a residual fluorescence ($\lambda_{exc.}$ = 362 nm) with a $\lambda_{em(max.)}$ = 431 nm and a negligible quantum yield of fluorescence in dichloromethane (Φ_{dcm} = 0.0008) relative to the same reference compound in ethanol.

Hydrolysis of the Ester Group

The corresponding acids **6a** and **6b** were obtained in almost quantitative yield by hydrolysis of the diarylamines **2a** and **2b** with NaOH in EtOH/H_2O and subsequent acidification with HCl (Scheme 2). The β-amino acids α,β-unsaturated **6a** and **6b** thus obtained can be inserted into peptides to induce conformational constraints, which can help in the study of the structure of proteins.

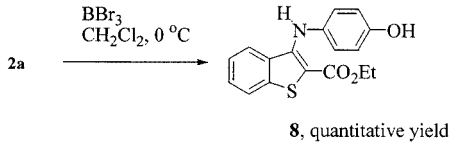
Attempted Cyclization of the Acids and Esters

The acid **6a** was subjected to unsuccessful attempts at cyclization with PPA and acidic Al_2O_3 in order to obtain the corresponding acridinones. The acids are highly polar and did not dissolve in PPA even when it was preheated. When compound **6b** was melted prior to addition, decarboxylation to compound **3a** occurred quantitatively with the heat. With use of acidic Al_2O_3, which some of us have used as an acid catalyst and water retainer in chromenization reactions,[10] in dioxane at 110 °C overnight, decarboxylation from **6a** to **7** took place (Scheme 4). When the reaction was performed at 60 °C for 3 d, starting material and small amounts of compound **7** (formed as time passed) were isolated.



Scheme 4

The ester **2a** was subjected to the Friedel–Crafts conditions described for the synthesis of cyclic constrained analogues of Raloxifene, resulting from diaryl compounds involving the 4-position of the benzo[*b*]thiophene moiety and possessing an ester group in the 3-position,[3] but in our case only demethylation to the hydroxy compound **8** occurred (Scheme 5). The same conditions were applied to the fluoro compound **2c**, but no reaction took place.



Scheme 5

It seems that the diarylamine moiety does not provide suitable activation for the methods examined with the ester compounds. The easy decarboxylation with the temperature is also a problem for the cyclization of the corresponding acids.

In Vitro Antimicrobial Activity and SAR

A screening of antibacterial activities with two Gram-negative (*Escherichia coli* CECT 101 and *Pseudomonas aeruginosa* CECT 108) and two Gram-positive bacteria (*Bacillus subtilis* CECT 498 and *Bacillus cereus* CECT 148) was performed; antifungal activity against *Candida albicans* (CECT 1394) was assessed for some of the compounds obtained, and the minimal inhibitory concentrations (MICs in μg/mL) were determined (Table 1) by an adaptation of the agar streak dilution method based on radial diffusion.[13]

Table 1. Antimicrobial activities of some of the synthesized compounds (CECT-Spanish type culture collection of Valencia University)

Compounds	MIC in μg/mL (zone of inhibition in mm)	
	Bacillus cereus CECT 148	*Candida albicans* CECT 1394
2a	3.13 (14)	100 (8)
8	3.13 (10)	100 (8)
2b	3.13 (11)	100 (5)
6b	3.13 (7)	50 (7)
2c	3.13 (12)	200 (7)
3b	3.13 (14)	50 (8)
4	1.56 (10)	12.5 (10)
5	1.56 (8)	12.5 (8)
Ampicillin	3.13 (13)	–
Chloramphenicol	3.13 (8)	–
Cyclohexamide	–	12.5 (5)

Suspensions of the microorganism containing approximately 10^8 cfu/mL were prepared, and the plates were inoculated. A stock solution of the synthesized compound (1000 μg/mL) in DMSO was prepared, and graded dilutions of the tested compounds were incorporated in cavities

(depth 3 mm, diameter 4 mm) made in the centres of the petri dishes (nutrient agar for antibacterial activity and sabouraud dextrose agar medium for antifungal activity). The plates were incubated in duplicate at 37 °C (for bacteria) and at 30 °C (for fungi) for 24 h. Under the same conditions, different concentrated solutions of ampicillin, chloramphenicol (antibacterial) and cyclohexamide (antifungal) in DMSO were used as standards. The MIC was considered to be the lowest concentration of the tested compound to inhibit growth of bacteria or fungi on the plate. The diameters of the inhibition zones corresponding to the MICs are presented in Table 1. Positive control with use only of inoculation and negative control with use only of DMSO in the cavity were also carried out.

The compounds tested were not active against the Gram-negative bacteria or *Bacillus subtilis* but only against *Bacillus cereus*. Table 1 shows the MICs for *B. cereu*s and *C. albicans* as an evaluation of the antimicrobial activity of the tested compounds.

From inspection of Table 1 it can be concluded that all the compounds exhibit low MICs for *B. cereus* and that compounds **4** and **5**, containing the pyridine ring, show the lowest MICs (1.56 μg/mL), even lower than the MICs for the antibacterial compounds. For the same compounds the lowest MICs (12.5 μg/mL) were also observed against *C. albicans* and are similar to that of cyclohexamide. The presence of the acid group in compound **6b** lowers the MIC against *C. albicans* from 100 to 50 μg/mL in comparison with compound **2b**. Compound **2c** shows the highest MIC against *C. albicans* (200 μg/mL) but without the ester group the corresponding fluoro compound **3b** has a much more lower MIC (50 μg/mL).

Conclusions

Several diarylamines were prepared from electron-deficient or relatively electron-rich bromobenzo[*b*]thiophenes and aromatic amines under the same C−N coupling conditions. The use of XANTHPHOS as ligand was needed for coupling of ethyl 3-bromobenzo[*b*]thiophene-2-carboxylate with aminopyridines. A tetracyclic heteroaromatic fluorescent compound was obtained from the coupling of 2-aminopyridine by a one-pot C−N coupling and intramolecular cyclization with loss of ethanol.

Attempts to cyclize the esters and acids to acridinones have so far been unsuccessful.

In vitro antimicrobial activity, MICs and SARs were evaluated. Selectivity against *B. cereus* was observed, with low MICs. Good results against *C. albicans* were also obtained, especially for the compounds possessing a pyridine ring.

Experimental Section

General Remarks: Melting points were determined with a Gallenkamp apparatus and are uncorrected. The ^{1}H NMR spectra were measured with a Varian Unity Plus instrument at 300 MHz. Spin-spin decoupling techniques were used to assign the signals. The ^{13}C NMR spectra were measured with the same instrument at 75.4 MHz (using DEPT, θ = 45°). The IR spectra were recorded as Nujol mulls with a Perkin−Elmer 1600-FTIR spectrophotometer. The UV spectra were recorded with a Shimadzu UV-250 1PC, UV/Vis recording spectrophotometer. Elemental analyses were determined with a LECO CHNS 932 elemental analyser. Mass spectra (EI) and HRMS data were recorded by the mass spectrometry service of University of Vigo, Spain, or with a Micromass Autospec 3F. The fluorescence studies were performed with a Spex Fluorolog 1680 Double Spectrometer spectrofluorimeter. Column chromatography was performed with Macherey−Nagel silica gel (230−400 mesh). "Petroleum ether" refers to the fraction with boiling range 40−60 °C. "Ether" refers to diethyl ether. When a solvent gradient was used the increase in the polarity was carried out gradually from neat petroleum ether to mixtures of ether/petroleum ether, increasing by 10% of ether until the isolation of the product.

Ethyl 3-Bromobenzo[*b*]thiophene-2 carboxylate (1a): Compound **1a** was obtained according to literature methods[8,9] in 60% overall yield as an orange solid, m.p. 60−62 °C. IR: $\tilde{\nu}_{max.}$ = 1725 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.45 (t, *J* = 7 Hz, 3 H, $CO_2CH_2CH_3$), 4.45 (q, *J* = 7 Hz, 2 H, $CO_2CH_2CH_3$), 7.49−7.58 (m, 2 H, ArH), 7.80−7.86 (m, 1 H, ArH), 7.97−8.02 (m, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.18 (CH_3), 61.77 (CH_2), 114.70 (C), 122.53 (CH), 125.17 (CH), 125. 50 (CH), 127.99 (CH), 138.53 (C), 139.17 (C), 161.34 (C=O) ppm. $C_{11}H_9BrO_2S$ (285.16): calcd. C 46.33, H 3.18, S 11.24; found C 46.69, H 3.56, S 11.48.

General Procedure for C−N Cross Coupling with Anilines and 5-Aminoindole: A dry Schlenk tube was charged under Ar with dry toluene (3−5 mL), compound **1a** or **1b**, $Pd(OAc)_2$ (3 mol %), *rac*BINAP (4 mol %), Cs_2CO_3 (1.4 equiv.) and, finally, the amine. The reaction mixture was stirred and heated at 100 °C for several hours (Scheme 2). After the mixture had cooled, water and ether were added, and the phases were separated. The aqueous phase was extracted with more ether, and the organic phases were collected, dried ($MgSO_4$) and filtered, and removal of the solvent gave an oil, after addition of MeOH to remove traces of toluene. The oil was subjected to column chromatography.

Ethyl 3-[(4-Methoxyphenyl)amino]benzo[*b*]thiophene-2-carboxylate (2a): This compound was produced from compound **1a** (300 mg, 1.05 mmol) and *p*-anisidine (130 mg, 1.05 mmol) and was purified by column chromatography with use of a solvent gradient from neat petroleum ether to 10% ether/petroleum ether. Product **2a** (263 mg, 76%) was obtained as an orange solid. Recrystallization from ether/petroleum ether gave yellow crystals, m.p. 87−89 °C. IR: $\tilde{\nu}_{max.}$ = 3305 (NH), 1667 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.42 (t, *J* = 7 Hz, 3 H, $CO_2CH_2CH_3$), 3.83 (s, 3 H, OCH_3), 4.38 (q, *J* = 7 Hz, 2 H, $CO_2CH_2CH_3$), 6.86 (d, *J* = 8.7 Hz, 2 H, 2 × ArH), 7.06−7.11 (m, 3 H, ArH), 7.22 (d, *J* = 8 Hz, 1 H, ArH), 7.35−7.40 (m, 1 H, Ar-H), 7.73 (d, *J* = 8 Hz, 1 H, ArH), 8.81 (s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.44 (CH_3), 55.46 (OCH_3), 60.69 (CH_2), 103.77 (C), 114.22 (2 × CH), 123.15 (CH), 123.18 (CH), 124.90 (2 × CH), 125.59 (CH), 127.45 (CH), 131.58 (C), 135.01 (C), 140.23 (C), 147.60 (C), 156.69 (C), 165.74 (C=O) ppm. $C_{18}H_{17}NO_3S$ (327.40): calcd. C 66.04, H 5.23, N 4.28, S 9.79; found C 66.00, H 5.43, N 4.48, S 9.79.

Ethyl 3-[(2,4-Dimethoxyphenyl)amino]benzo[*b*]thiophene-2-carboxylate (2b): This compound was produced from compound **1a** (300 mg, 1.05 mmol) and 2,4-dimethoxyaniline (161 mg, 1.05 mmol) and was purified by column chromatography with use

of a solvent gradient from neat petroleum ether to 20% ether/petroleum ether. Product **2b** (300 mg, 80%) was obtained as an orange solid. Recrystallization from ether/petroleum ether gave yellow crystals, m.p. 95−96 °C. IR: $\tilde{\nu}_{max.}$ = 3319 (NH), 1666 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.42 (t, *J* = 7 Hz, 3 H, $CO_2CH_2CH_3$), 3.83 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.38 (q, *J* = 7 Hz, 2 H, $CO_2CH_2CH_3$), 6.37 (dd, *J* = 8.7, 2.7 Hz, 1 H, 5′-H), 6.56 (d, *J* = 2.7 Hz, 1 H, 3′-H), 6.93 (d, *J* = 8.7 Hz, 1 H, 6′-H), 7.08−7.14 (m, 1 H, ArH), 7.34−7.41 (m, 2 H, ArH), 7.72 (d, *J* = 8 Hz, 1 H, ArH), 8.58 (s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.45 (CH_3), 55.55 (OCH_3), 55.69 (OCH_3), 60.66 (CH_2), 99.21 (CH), 103.41 (CH) 104.34 (C), 123.12 (CH), 123.16 (CH), 123.17 (CH), 124.30 (C), 125.35 (CH), 127.40 (CH), 131.91 (C), 140.06 (C), 147.08 (C), 153.19 (C), 157.16 (C), 165.55 (C=O) ppm. $C_{19}H_{19}NO_4S$ (357.42): calcd. C 63.85, H 5.36, N 3.92, S 8.97; found C 63.68, H 5.49, N 4.04, S 8.96.

Ethyl 3-[(4-Fluorophenyl)amino]benzo[*b*]thiophene-2-carboxylate (2c): This compound was produced from compound **1a** (150 mg, 0.526 mmol) and 4-fluoroaniline (64.0 mg, 0.526 mmol) and was purified by column chromatography with use of a solvent gradient from neat petroleum ether to 20% ether/petroleum ether. Product **2c** (105 mg, 63%) was obtained as a yellow solid. Recrystallization from ether/petroleum ether gave light yellow crystals, m.p. 119−121 °C. IR: $\tilde{\nu}_{max.}$ = 3294 (NH), 1668 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): *δ* = 1.42 (t, *J* = 7 Hz, 3 H, $CO_2CH_2CH_3$), 4.39 (q, *J* = 7 Hz, 2 H, $CO_2CH_2CH_3$), 6.97−7.17 (m, 5 H, ArH), 7.25−7.29 (m, 1 H, ArH), 7.38−7.44 (m, 1 H, ArH), 7.76 (d, *J* = 8 Hz, 1 H, ArH), 8.75 (s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.40 (CH_3), 60.90 (CH_2), 106.19 (C) 115.73 (d, *J* = 22.7 Hz, CH-3′ and -5′), 123.27 (CH), 123.39 (CH), 123.80 (d, *J* = 8 Hz, CH-2′ and -6′), 125.37 (CH), 127.57 (CH), 131.60 (C), 138.27 (d, *J* = 2.8 Hz, C-1′), 140.09 (C), 146.41 (C), 159.45 (d, *J* = 242.7 Hz, CF), 165.55 (C=O) ppm. $C_{17}H_{14}FNO_2S$ (315.36): calcd. C 64.75, H 4.47, N 4.44, S 10.17; found C 64.40, H 4.77, N 4.37, S 10.36.

Ethyl 3-[(Indol-5-yl)amino]benzo[*b*]thiophene-2-carboxylate (2d): This compound was produced from compound **1a** (250 mg, 0.877 mmol) and 5-aminoindole (116 mg, 0.877 mmol), with heating for 21 h, and was purified by column chromatography with use of a solvent gradient from neat petroleum ether to 50% ether/petroleum ether. Product **2d** (155 mg, 63%) was obtained as an orange solid. Recrystallization from ether/petroleum ether gave yellow crystals, m.p. 166−168 °C. IR: $\tilde{\nu}_{max.}$ = 3382 (NH), 3307 (NH), 1631 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): *δ* = 1.43 (t, *J* = 7 Hz, 3 H, $CO_2CH_2CH_3$), 4.39 (q, *J* = 7 Hz, 2 H, $CO_2CH_2CH_3$), 6.49−6.51 (m, 1 H, ArH), 6.95−7.00 (m, 1 H, ArH), 7.07 (dd, *J* = 8.4, 2.1 Hz, 1 H, 6′-H), 7.14 (d, *J* = 8 Hz, 1 H, ArH) 7.25−7.27 (m, 1 H, ArH), 7.30−7.34 (m, 2 H, ArH), 7.46 (d, *J* = 2.1 Hz, 1 H, 4′-H), 7.72 (d, *J* = 8 Hz, 1 H, ArH), 8.20 (s, 1 H, indole NH) 9.01 (s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.48 (CH_3), 60.59 (CH_2), 102.56 (C) 102.72 (CH), 111.30 (CH) 115.90 (CH), 119.91 (CH) 123.03 (CH), 123.04 (CH), 125.17 (CH), 125.91 (CH), 127.39 (CH), 128.17 (C), 131.79 (C), 133.58 (C), 134.49 (C) 140.32 (C), 148.52 (C), 165.89 (C=O) ppm. $C_{19}H_{16}N_2O_2S$ (336.41): calcd. C 67.84, H 4.79, N 8.33, S 9.53; found C 67.56, H 4.90, N 8.29, S 9.32.

3-[(2,4-Dimethoxyphenyl)amino]benzo[*b*]thiophene (3a): This compound was produced from compound **1b** (249 mg, 1.17 mmol) and 2,4-dimethoxyaniline (180 mg, 1.17 mmol) and was purified by column chromatography with use of a solvent gradient from neat petroleum ether to 10% ether/petroleum ether. Product **3a** (200 mg, 60%) was obtained as an oil. ^1H NMR ($CDCl_3$): δ = 3.83 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 6.10 (s, 1 H, NH), 6.50 (dd, *J* = 8.7, 2.7 Hz, 1 H, 5′-H), 6.64 (d, *J* = 2.7 Hz, 1 H, 3′-H), 6.90 (s, 1 H, 2-H), 7.22 (d, *J* = 8.7 Hz, 1 H, 6′-H), 7.41−7.44 (m, 2 H, 7- and 4-H), 7.76−7.80 (m, 1 H, ArH), 7.86−7.90 (m, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.53 (OCH_3), 55.56 (OCH_3), 99.24 (CH), 103.74 (CH) 104.11 (C), 116.08 (CH), 120.19 (CH), 123.01 (CH), 123.61 (CH), 124.67 (CH), 127.40 (C), 134.27 (C), 136.08 (C), 138.73 (C), 149.09 (C), 153.96 (C) ppm. MS: *m*/*z* (%) = 287 (7) [M^+ + 2], 286 (20) [M^+ + 1], 285 (100) [M^+], 270 (51) [M^+ − 15], 138 (19). HRMS: calcd. for $C_{16}H_{13}NO_2S$ [M^+] 285.082298, found 285.082351.

3-[(4-Fluorophenyl)amino]benzo[*b*]thiophene (3b): This compound was produced from compound **1b** (300 mg, 1.41 mmol) and 4-fluoroaniline (156 mg, 1.41 mmol) and was purified by column chromatography with use of a solvent gradient from neat petroleum ether to 10% ether/petroleum ether. Product **3b** (127 mg, 40%) was obtained as a white solid. Recrystallization from ether/petroleum ether gave colourless crystals, m.p. 87−89 °C. IR: $\tilde{\nu}_{max.}$ = 3388 (NH) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 5.68 (s, 1 H, NH), 6.91 (s, 1 H, 2-H), 6.98 (s, 4 H, 2′-, 3′-, 5′- and 6′-H), 7.38−7.41 (m, 2 H, ArH), 7.64−7.67 (m, 1 H, ArH), 7.83−7.86 (m, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 107.83 (CH), 115.90 (d, *J* = 22.5 Hz, CH-3′ and -5′), 118.05 (d, *J* = 8 Hz, CH-2′ and -6′), 120.41 (CH), 123.25 (CH), 123.91 (CH), 124.92 (CH), 134.20 (C), 135.77 (C) 138.97 (C), 140.64 (C), 157.37 (d, *J* = 238.7 Hz, CF) ppm. $C_{17}H_{10}FNS$ (243.30): calcd. C 69.11, H 4.14, N 5.76, S 13.18; found C 69.00, H 4.35, N 5.76, S 13.05.

General Procedure for C−N Cross Coupling with Aminopyridines: A dry Schlenk tube was charged under Ar with dry 1,4-dioxane (3−5 mL), compound **1a**, [Pd_2dba_3] (3 mol %Pd) or $Pd(OAc)_2$ (6 mol %), XANTHOPS (4 mol %), Cs_2CO_3 (1.4 equiv.) and, finally, the aminopyridine (1.1 equiv.). The reaction mixture was stirred and heated at 100 °C for several hours (Scheme 3). After it had cooled, water and ether were added and the phases were separated. The aqueous phase was extracted with more ether, the organic phases were collected, dried ($MgSO_4$) and filtered, and removal of solvent gave an oil or a solid. The oil was subjected to column chromatography.

6*H*-Benzo[*b*]thieno[3,2-*d*]pyrido[1,2-*a*]pyrimidin-6-one (4): This compound was produced from compound **1a** (200 mg, 0.702 mmol) and 2-aminopyridine (73.0 mg, 0.772 mmol) and was obtained as a beige solid (100 mg, 60%). Recrystallization from ether gave light beige crystals, m.p. 211−213 °C. IR: $\tilde{\nu}_{max.}$ = 1693 (C=O) cm^{-1}. UV (CH_2Cl_2): $\lambda_{max.}$ (ε, $dm^3 \cdot mol^{-1} \cdot cm^{-1}$) = 387 (6066), 368 (7238), 303 (2062), 276 (14842), 257 (18772) nm. ^1H NMR ([D_6]DMSO): δ = 7.31−7.38 (m, 1 H, ArH), 7.58−765 (m, 1 H, ArH), 7.69−7.76 (m, 1 H, ArH) 7.81−7.93 (m, 2 H, ArH), 8.16 (d, *J* = 8 Hz, 1 H, ArH), 8.37 (br. d, *J* = 8 Hz, 1 H, ArH) 9.01 (br. d, *J* = 8 Hz, 1 H, ArH) ppm. ^{13}C NMR ([D_6]DMSO): δ = 113.21 (C), 115.46 (CH), 123.80 (CH), 124.01 (CH), 125.52 (CH), 125.91 (CH), 126.32 (CH), 130.06 (CH), 133.93 (C), 135.98 (CH), 141.23 (C), 149.28 (C), 153.38 (C), 154.05 (C) ppm. MS (EI): *m*/*z* (%) = 252 (100) [M^+], 224 (35) [M^+ − CO]. HRMS: calcd. for $C_{15}H_{11}N_2OS$ [M^+] 252.035735, found 252.035591.

Ethyl 3-(3-Aminopyridine)benzo[*b*]thiophene-2-carboxylate (5): This compound was produced from compound **1a** (200 mg, 0.702 mmol) and 3-aminopyridine (73.0 mg, 0.772 mmol) and was purified by column chromatography with use of a solvent gradient from neat petroleum ether to neat ether. Product **5** (127 mg, 40%) was obtained as an orange solid. Recrystallization from ether/petroleum ether gave light yellow crystals, m.p. 112−114 °C. IR: $\tilde{\nu}_{max.}$ = 3293 (NH), 1661 (C=O) cm^{-1}. UV (CH_2Cl_2): $\lambda_{max.}$ (ε, $dm^3 \cdot mol^{-1} \cdot cm^{-1}$) 362 (12099), 263 (22764) 225 (13469) nm. ^1H NMR ($CDCl_3$): δ =

1.43 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$), 4.40 (q, J = 7 Hz, 2 H, $CO_2CH_2CH_3$), 7.18−7.24 (m, 2 H, ArH), 7.29−7.38 (m, 2 H, ArH), 7.42−7.48 (m, 1 H, ArH), 7.79 (d, J = 8.1 Hz, 1 H, ArH), 8.33 (br. d, J = 4.5 Hz, 1 H, Ar-H), 8.44 (d, J = 2.4 Hz, 1 H, 2′-H), 8.70 (s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.35 (CH_3), 61.17 (CH_2), 109.34 (C), 123.41(2 × CH), 123.83 (CH), 125.00 (CH), 127.28 (CH), 127.74 (CH), 131.59 (C), 139.01 (C), 139.87 (C), 142.79 (CH), 144.10 (CH), 144.36 (C), 165.26 (C=O) ppm. $C_{16}H_{14}N_2O_2S$ (298.34): calcd. C 64.41, H 4.73, N 9.39, S 10.75; found C 64.09, H 4.95, N 9.24, S 10.70.

General Procedure for the Hydrolysis of the Ester Group: Compounds **2a** or **2b** in ethanol (10−20 mL) were treated with aqueous NaOH solution (30%, 5 equiv.). The mixture was stirred and heated to reflux with a water bath for some hours, the reaction being monitored by TLC. After the mixture had cooled, the ethanol was evaporated under reduced pressure, water was added to the obtained solid, followed by HCl (1 N) until the precipitation of the acids **6a** or **6b** which were obtained by filtration and drying at 50 °C.

3-[(4-Dimethoxyphenyl)amino]benzo[*b*]thiophene-2-carboxylic Acid (6a): This compound was produced from compound **2a** (150 mg, 0.459 mmol), product **6a** (131 mg, 96%) being obtained as yellow solid. Recrystallization from ether gave yellow crystals, m.p. 148−150 °C. IR: $\tilde{\nu}_{max.}$ = 3300 (NH), 1642 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.85 (s, 3 H, OCH_3), 6.89 (d, J = 9 Hz, 2 H, 2 × ArH), 7.05 −7.19 (m, 4 H, ArH), 7.40 (br. t, J = 8 Hz, 1 H, ArH), 7.53 (d, J = 8 Hz, 1 H, ArH), 8.84 (s, 1 H, NH) ppm. $C_{16}H_{13}NO_3S$ (299.35): calcd. C 64.20, H 4.38, N 4.69, S 10.71; found C 64.03, H 4.59, N 4.66, S 10.66.

3-[(2,4-Dimethoxyphenyl)amino]benzo[*b*]thiophene-2-carboxylic Acid (6b): This compound was produced from compound **2b** (360 mg, 1.01 mmol), product **6b** (328 mg, 99%) being obtained as yellow solid. Recrystallization from ether gave yellow crystals, m.p. 152−154 °C. IR: $\tilde{\nu}_{max.}$ = 3354 (NH), 1688 (C=O) cm^{-1}. ^{1}H NMR ([D$_6$]DMSO): δ = 3.76 (s, 6 H, 2 × OCH_3), 6.45 (dd, J = 8.7 and 3 Hz, 1 H, 5′-H), 6.68 (d, J = 3 Hz, 1 H, 3′-H), 6.89 (d, J = 8.7 Hz, 1 H, 6′-H), 7.13−7.17 (m, 2 H, ArH), 7.40−7.45 (m, 1 H, ArH), 7.88 (d, J = 8.1 Hz, 1 H, ArH), 8.53 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 55.42 (OCH_3), 55.76 (OCH_3), 99.45 (CH), 103.75 (C) 104.24 (CH), 123.21(C), 123.63 (CH), 123.67(CH), 123.79 (CH), 124.42 (CH), 127.73 (CH), 131.52 (C), 139.08(C), 146.47 (C), 153.33 (C), 157.33 (C), 166.51 (C=O) ppm. $C_{17}H_{15}NO_4S$ (329.37): calcd. C 61.99, H 4.59, N 4.25, S 9.74; found C 61.99, H 4.83, N 4.31, S 9.60.

Cyclization Attempts

3-[(4-Methoxyphenyl)amino]benzo[*b*]thiophene (7): Al_2O_3 (acidic Brockman I, 10 equiv.) was added to a solution of compound **6a** (50.0 mg, 0.190 mmol) in dry CH_2Cl_2 (3 mL) in a Schlenk tube, and the suspension was stirred at 110 °C under Ar overnight. After the mixture had cooled, the alumina was removed by filtration, and solvent removal gave product **7** (46 mg, quantitative yield) as a solid, m.p. 102−104 °C. ^{1}H NMR ($CDCl_3$): δ = 3.81(s, 3 H, OCH_3), 5.70 (br. s, 1 H, NH), 6.76 (s, 1 H, 2-H), 6.87 (d, J = 9 Hz, 2 H, 2 × ArH), 7.05 (d, J = 9 Hz, 2 H, 2 × ArH), 7.35−7.42 (m, 2 H, ArH), 7.64−7.69 (m, 1 H, ArH), 7.81−7.85 (m, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.62 (OCH_3), 104.60 (CH), 114.74 (2 × CH), 119.44 (2 × CH), 120.19 (CH), 123.20 (CH), 123.74 (CH), 124.79 (CH), 133.95 (C), 136.95 (C), 137.59 (C), 139.01 (C), 154.42 (C) ppm. MS (EI): m/z (%) = 255 (80) [M$^+$], 240 (100) [M$^+$ − Me]. HRMS: calcd. for $C_{15}H_{13}NOS$ [M$^+$] 255.0718, found 255.0726.

Ethyl 3-[(4-Hydroxyphenyl)amino]benzo[*b*]thiophene-2-carboxylate (8): A solution of BBr_3 in CH_2Cl_2 (1 M, 1.6 mmol, 1.6 mL) was added at 0 °C to a solution of compound **2a** (100 mg, 0.301 mmol) in dry CH_2Cl_2 (10 mL). The solution turned green and was stirred at 0 °C for 2 h. A saturated solution of $NaHCO_3$ was slowly added, and extractions were carried out with CH_2Cl_2. The organic phases were collected, dried and filtered, and removal of solvent gave a yellow green solid (95.0 mg, quantitative yield). Recrystallization from ether/petroleum ether gave yellow green crystals, m.p. 152−154 °C. IR: $\tilde{\nu}_{max.}$ = 3330 (NH), 1630 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.41 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$), 4.39 (q, J = 7 Hz, 2 H, $CO_2CH_2CH_3$), 4.90 (br. s, 1 H, OH), 6.81 (d, J = 8.7 Hz, 2 H, 2 × ArH), 7.01−7.20 (m, 3 H, ArH), 7.22 (d, J = 8.2 Hz, 1 H, ArH), 7.35 (br. t, J = 8.2 Hz, 1 H, ArH), 7.72 (d, J = 8.2 Hz, 1 H, ArH), 8.77 (s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.47 (CH_3), 60.78 (CH_2), 115.83 (CH), 123.22 (4 × CH), 123.25 (CH), 125.17 (CH), 125.64 (CH), 127.52 (CH), 131.63 (C), 135.24 (C), 140.32 (C), 147.56 (C), 147.57 (C) 152.71 (C), 165.84 (C=O) ppm. MS (EI): m/z (%) = 313 (50) [M$^+$], 311 (90) [M$^+$ − 2], 267 (100), 239 (80) 210 (90). HRMS: calcd. for $C_{17}H_{15}NO_3S$ [M$^+$] 313.0773, found 313.0760.

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