

Synthesis of Some New bis-(*p*-Fluorophenyl)amides of the Thieno[3,2-*b*]thiophene, Thieno[3,2-*b*]furan and 1,2-bis{5-[2-(2-Thienyl)ethenyl]2-thienyl}ethene Series

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Abstract: Three new heterocyclic substituted dianilides, namely 3-chloro-5-[1-(*p*-fluorophenylcarbamoyl)-2-(2-thienyl)ethenyl]thieno-[3,2-*b*]thiophene-2-carboxy-*p*-fluoroanilide (**8**), 1,2-bis{5-[2-(*p*-fluorophenylcarbamoyl)-2-(2-thienyl)ethenyl]-2-thienyl}ethene (**13**) and 6-chloro-2-{2-[3-chloro-2-(*p*-fluorophenyl-carbamoyl)-5-thieno[3,2-*b*]thienyl]-2-ethoxycarbonyl}ethenyl}thieno[3,2-*b*]furan-5-carboxy-*p*-fluoroanilide (**20**) were prepared by multistep synthesis. The prepared dianilides are of particular interest for their potential to serve as the planar heteroaromatic core of DNA intercalators or groove binders.

Keywords: Amides, thieno[3,2-*b*]thienyl- series, potential intercalators or groove binders.

Introduction

There is little recent literature data on the thieno[3,2-*b*]- or thieno[3,4-*b*]thiophenes with different features [1-3] and applications [4,5]. For example, the new class of thienothiophenes, some of which are available from monobromo-, dibromo- or tribromothiophenes [6], was recently described [7]. 3,6-Dimethylthieno[3,2-*b*]thiophene, prepared as the monomer for a polymerization process [8-9], or

thieno[3,2-*b*]thiophenes which are synthesized from phthalimido sulfonyl chloride upon reaction with diaryl (or heteroaryl) acetylenes [10] or as intermediates in the synthesis of heteroarenes which are isoelectric with perylene [11] and various thieno[3,2-*c*]-annelated 1,2-dithiins prepared from appropriate thiophene precursors [12] are also known. The corresponding dianilides of the thieno[3,2-*b*]thiophene and thieno[3,2-*b*]furan types are however unknown. On the other hand, there is patent literature that describes the synthesis of thiophene-3,4-carboxamide derivatives and their application as dopamine receptor blockers [13] or herbicides [14]. Some substituted benzo[*b*]thiophene-carboxamides are used as inhibitors of neutrophil-endothelial cell adhesion [15].

Results and Discussion

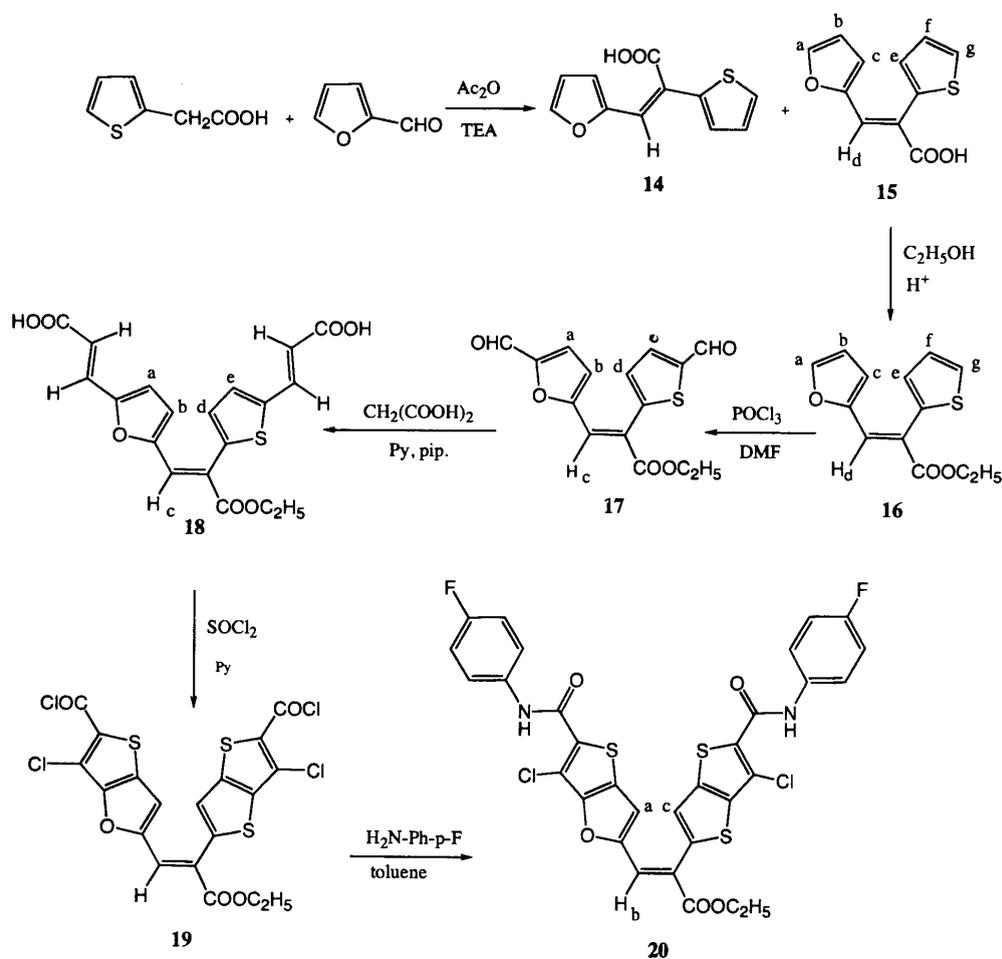
In our previous papers we have reported the synthesis and the photochemistry of some heteropolycyclic anilides of the naphthothieno[3,2-*b*]thiophene series [16], dianilides of the benzo[*b*]thiophene, thieno[2,3-*b*]thiophene [17], benzo[1,2-*b*:4,5-*b'*]dithiophene and dithieno[3,2-*b*:2',3'-*d*]thiophene series [18], and their photochemical reactions leading to the corresponding quinolones. In this paper we describe the synthesis of the dianilides **8**, **13** and **20**, which are interesting polycondensed heteroaromatic compounds as well as potential planar aromatic core of DNA intercalators [20-22].

Dianilides **8** and **13** were prepared in the several steps from (*Z*)-2,3-di-(2-thienyl)acrylic acid (**1**, Scheme 1). Vilsmeier formylation [23] of the methyl ester **3** of acrylic acid **1** afforded methyl *Z*-2-(5-formyl-2-thienyl)-3-(2-thienyl)acrylate (**4**) in 69% yield [16]. Condensation of compound **4** with malonic acid followed by hydrolysis of the ester group afforded 3-{5-[2-(2-thienyl)-1-carboxy]ethenyl}-2-(2-thienyl)acrylic acid (**6**) [16]. Treatment of **6** with thionyl chloride and pyridine [24] provided 3-chloro-5-[1-chlorocarbonyl-2-(2-thienyl)ethenyl]thieno[3,2-*b*]thiophene-2-carbonyl chloride (**7**). The reaction of the chloride **7** with *p*-fluoroaniline in chloroform gave 3-chloro-5-[1-(*p*-fluorophenylcarbamoyl)-2-(2-thienyl)ethenyl]thieno[3,2-*b*]thiophene-2-carboxy-*p*-fluoroanilide (**8**) in 34% yield [16,17].

Compound **1** was decarboxylated [25] to 1,2-di-(2-thienyl)ethene (**9**) and formylated by the Vilsmeier method to afford 1,2-di-[(5-formyl)-2-(2-thienyl)]ethene (**10**) in 42.3% yield. Reaction of compound **10** with 2-thienylacetic acid [26] gave (*Z*)-1,2-bis{5-[2-carboxy-2-(2-thienyl)ethenyl]-2-(2-thienyl)}ethene (**11**), as dark red crystals, in about 30 % yield. The geometry of the molecule was determined from ¹H-NMR data. The corresponding dianilide, (*Z*)-1,2-bis{5-[2-(*p*-fluorophenylcarbamoyl)-2-(2-thienyl)ethenyl]-2-thienyl}ethene (**13**), was prepared in this manner in over 56% yield.

The dianilide 6-chloro-2-{2-[3-chloro-2-(*p*-fluorophenylcarbamoyl)-5-thieno[3,2-*b*]thienyl]-2-ethoxycarbonyl-ethenyl}thieno[3,2-*b*]furan-5-carboxy-*p*-fluoroanilide (**20**), was prepared in several steps. Furan-2-carboxaldehyde reacted with 2-thiopheneacetic acid to give a mixture of the (*E*)- and (*Z*)-3-(2-furyl)-2-(2-thienyl)acrylic acids (**14**) and (**15**) [27]. The (*Z*)-isomer **15** was converted into the corresponding methyl ester **16** which was formylated to give ethyl (*Z*)-3-[5-formyl-(2-furyl)]-2-[5-formyl-(2-thienyl)]acrylate (**17**). Dialdehyde **17** was converted to the corresponding diacrylic acid-ester, ethyl (*Z*)-3-[5-(2-carboxy)ethenyl-2-furyl]-2-[5-(2-carboxy-ethenyl)-(2-thienyl)]acrylate (**18**) upon reaction with malonic acid. The yield was 41%. A double cyclization with SOCl_2 in the presence of the catalytic amount of pyridine afforded 3-chloro-5-{2-ethoxycarbonyl-2-[3'-chlorocarbonyl-5'-thieno[3,2-*b*]thienyl]ethenyl}thieno[3,2-*b*]furancarboxyl chloride (**19**) in 35% yield, which was successfully converted into the corresponding dianilide **20** in 50% yield (Scheme 2).

Scheme 2



The structures of all new compounds were confirmed by $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, IR spectra, elemental analysis and, in the case of compound **5**, its X-ray crystal structure was also determined (Figures 1 and 2) [28].

Figure 1. X-Ray structure of the 3-{5-[1-methoxycarbonyl-2-(2-thienyl)ethenyl]-2-thienyl}acrylic acid (**5**)

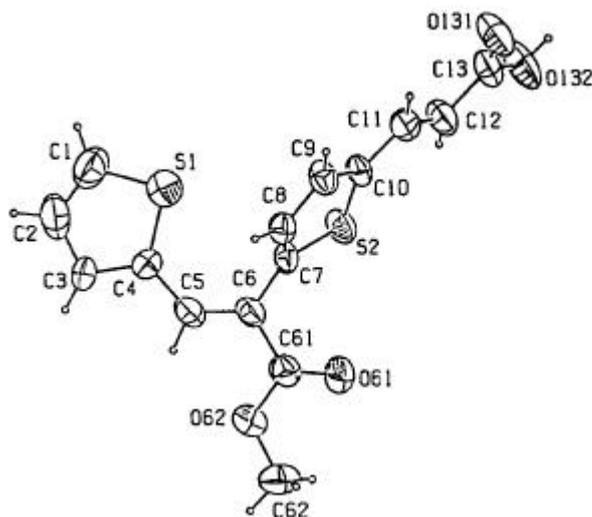
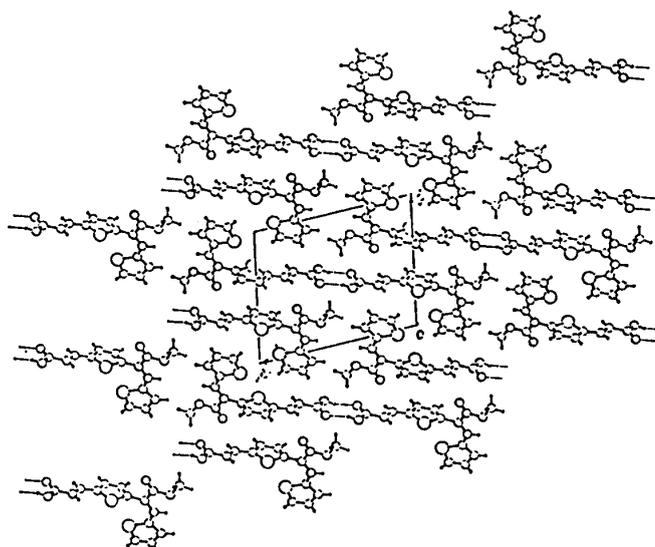


Figure 2. X-Ray structure of 3-{5-[1-methoxycarbonyl-2-(2-thienyl)-ethenyl]-2-thienyl}acrylic acid (**5**) bonded into dimers via H-bonding



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Experimental

General

Melting points were determined on a Koffler hot stage microscope and are uncorrected. IR spectra were recorded on a PERKIN-ELMER Model 257 spectrophotometer in KBr discs or as liquid films between sodium chloride plates. $^1\text{H-NMR}$ (300 MHz) and $^{13}\text{C-NMR}$ (75.46 MHz) spectra were recorded for CDCl_3 or DMSO-d_6 solutions with TMS as internal standard on a Varian Gemini 300. spectrometer. Mass spectra were recorded on a Shimadzu QP-5000 GC/MS instrument at 70 eV using a direct inlet system and with an ion source temperature of 300°C.

(E)- and (Z)-2,3-di-(2-thienyl)acrylic acids (1) and (2) [23].

Compounds **1** and **2** were prepared by heating 2-thienylcarboxaldehyde (23.8 g, 0.21 mol) and thiopheneacetic acid (30 g, 0.21 mol) in triethylamine (31.5 mL) and acetic acid anhydride (31.5 mL) for 1.5 h. After the reaction was complete, the mixture was cooled, acidified with (1:1) conc. hydrochloric acid-water and the two isomers were extracted with ether (350 mL). The organic layer was washed with water and the acids were extracted into 7.5% sodium carbonate solution (1000 mL). The hot alkaline solution of sodium salts was boiled with charcoal, filtered, cooled and acidified to pH 5 with acetic acid. The precipitated (*Z*)- isomer **1** was filtered off and recrystallized from methanol. The yield was 28.10 g, (58.00%), mp 236-239°C (lit. [18], mp 240-241°C). Concentrated hydrochloric acid was added to the filtrate and additional crystalline crops consisting of the (*E*)-isomer **2** were thus obtained. The yield of isomer **2** was 4.5 g (9.02 %), mp 174-175°C (lit.[23] mp 174.5-175.5°C).

Methyl (Z)-2,3-di-(2-thienyl)acrylate (3) [23, 26].

Methyl ester **3** was prepared by refluxing **1** (13 g, 0.055 mol) dissolved in absolute methanol (570 mL) and conc. sulphuric acid (2 mL) for 15 h. The volume of the cooled reaction mixture was reduced to 200 mL and the content was poured into crushed ice (700 g). Crystalline crops were recrystallized from methanol. White crystals (11.3 g, 82.00 %), mp 76-77°C were obtained (lit.[23] mp 75-78.5°C).

Methyl (Z)-2-(5-formyl-2-thienyl)-3-(2-thienyl)acrylate (4) [23]

Methyl ester **3** was formylated by the Vilsmeier method. Phosphorus oxychloride (20.80 mL, 0.227 mol) was added dropwise to a cooled solution of methyl ester **3** (10.80 g, 0.043 mol) in DMF (19.00 mL, 0.246 mol) at such a rate that the temperature of the reaction mixture did not exceed 10°C. After the addition was complete, the mixture was stirred for 1 h at room temperature, then heated at 90-95°C for 1.5 h, cooled and poured into crushed ice (500 g), made weakly alkaline with conc. sodium hydroxide solution and left overnight on ice. The gummy product collected was washed with water and recrystallized from (2:3) benzene-hexane. A yellow crystalline product (8.3 g, 69.10 %) was thus obtained, mp 137-139°C (lit.[23] 141-142°C); ¹³C-NMR (CDCl₃) (d ppm): 52.5, 119.5, 137.8, 144.7, 145.4, 165.8, 184.4.

3-[5-[1-methoxycarbonyl-2-(2-thienyl)ethenyl]-2-thienyl]acrylic acid (5) [18]

Compound **5** was prepared by the condensation of formylated ester **4** (5.00 g, 0.018 mol) with malonic acid (1.9 g, 0.002 mol) in pyridine (60 mL) to which a catalytic amount (a few drops) of piperidine was added. The reaction mixture was heated for 2 h at 45-50°C and for 2.5 h at 100°C. After cooling, the reaction mixture was poured into ice (500 g) and acidified with (1:1) conc. hydrochloric acid-water (130 mL). The yellow crystals formed were filtered off and recrystallized from (2:1) ethanol-dioxane to give 2.9 g (50.40%) of the title compound, mp 196-199°C; IR (cm⁻¹) (KBr): 1705 (COOCH₃), 1660 (COOH), 1600 (C=C); ¹H-NMR (DMSO-d₆) (d ppm): 3.96 (3H, s, CH₃), 6.20 (1H, d, *J* = 15.63 Hz, H_{ethylenic}), 7.04 (1H, d, *J* = 3.36 Hz, H_d), 7.09 (1H, AB_{sys.}, *J* = 3.37 Hz, *J* = 5.07 Hz, H_e), 7.56 (1H, d, *J* = 3.47 Hz, H_b), 7.62 (1H, d, *J* = 3.48 Hz, H_a), 7.76 (1H, d, *J* = 5.07 Hz, H_f), 7.77 (1H, d, *J* = 15.63 Hz, H_{ethylenic}), 8.22 (1H, s, H_c); ¹³C-NMR (DMSO-d₆) (d ppm): 52.5, 118.1, 120.0, 127.3, 130.8, 132.3, 141.4, 166.1, 167.3. Anal. Calcd. for C₁₅H₁₂O₄S₂: C, 56.23; H, 3.75; S, 20.03%; Found: C, 56.65; H, 3.96; S, 20.49%.

3-[5-[2-(2-thienyl)-1-carboxy]ethenyl]-2-(2-thienyl)acrylic acid (6)

Diacid **6** was prepared by hydrolysis of **5** (2.00 g, 0.006 mol) which was added to the solution of 10% NaOH (30 mL) and methanol (30 mL) and refluxed for 2.5 h. Methanol was distilled off *in vacuo*, the residue dissolved in water, acidified with 10% hydrochloric acid and the crude product was recrystallized from (1:1) ethanol-dioxane [16]. The yield was 1.85 g (96.70%), mp 232-235°C; IR (cm⁻¹) (KBr): 1600 (C=C), 1620 (C=C), 1670 (COOH), 1690 (COOH). ¹H-NMR (DMSO-d₆) (d ppm): 5.94 (1H, d, *J* = 15.8 Hz, H_{ethylenic}), 7.04 (1H, d, *J* = 3.36 Hz, H_d), 7.20 (1H, AB_{sys.}, *J* = 3.36 Hz, *J* = 5.12 Hz, H_e), 7.44 (1H, d, *J* = 3.90 Hz, H_b), 7.52 (1H, d, *J* = 3.97 Hz, H_b), 7.58 (1H, d, *J* = 15.9 Hz, H_{ethylenic}), 7.80 (1H, d, *J* = 5.12 Hz, H_f), 8.09 (1H, s, H_c); ¹³C-NMR (DMSO-d₆) (d ppm): 119.1, 128.0, 140.3, 143.7, 167.1, 167.6. Anal. Calcd. for: C₁₄H₁₀O₄S₂: C, 54.88; H, 3.27; S, 20.95%; Found: C, 54.59; H, 3.07; S, 21.40%.

3-Chloro-5-[1-chlorocarbonyl-2-(2-thienyl)ethenyl]thieno[3,2-b]thiophene-2-carbonylchloride (7)

Compound **6** (1.00 g, 0.003 mol) was suspended in thionyl chloride (20 mL, 0.275 mol). The mixture was stirred for 15 min. under external cooling by ice. To this mixture was added dropwise pyridine (1 mL) in SOCl₂ (1 mL). The reaction mixture was stirred for 0.5 h at room temperature and for 45 h at 80-90°C. Excess thionyl chloride was removed under reduced pressure and the remaining material was extracted with hot hexane (20 mL) to give an oily product (0.54 g, 45%) which was used in the next step without further purification.

3-Chloro-5-[1-(p-fluorophenylcarbamoyl)-2-(2-thienyl)ethenyl]thieno[3,2-b]thiophene-2-carboxy-p-fluoroanilide (8)

One equivalent of *p*-fluoroaniline (0.0013 mol) dissolved in chloroform (5 mL) and triethylamine (5 mL) was added dropwise under stirring at room temperature to a solution of dichloride **7** (0.5 g, 0.0013 mol) in chloroform (5 mL). The reaction mixture was refluxed for 1 h. After cooling the *p*-fluoroaniline hydrochloride formed was filtered off, the filtrate was concentrated *in vacuo*, the residue suspended in toluene and the resulting crystals were recrystallized from *N,N*-dimethylformamide [9-10]. Dianilide **8** (0.27 g, 34.10% yield) was thus obtained, mp 252-253°C; IR (cm⁻¹) (KBr): 1615 (C=C), 1660 (CONH), 3400 (NH); ¹H-NMR (DMSO-d₆) (δ ppm): 7.10 (1H, AB_{sys}, *J* = 4.76 Hz, *J* = 3.67 Hz, H_d), 7.15-7.21 (4 H, m, H_{arom.}), 7.48 (1H, d, *J* = 3.67 Hz, H_e), 7.64-7.75 (4H, m, H_{arom.}), 7.71 (1H, *J* = 4.27 Hz, H_e), 7.82 (1H, s, H_a), 7.96 (1H, s, H_b), 9.85 (1H, s, NH), 10.30 (1H, s, NH); ¹³C-NMR (DMSO-d₆) (δ ppm): 115.0, 115.7, 131.0, 134.3, 135.2, 135.7, 142.4, 156.7, 157.1, 159.8, 162.5, 163.1, 164.9; MS (m/z): 556 (M⁺), 382, 205, 177. Anal. Calcd. for: C₂₆H₁₅O₂ClF₂N₂S₃: C, 56.05; H, 2.69; N, 5.05; S, 17.28%; Found: C, 56.35; H, 2.32; N, 4.91; S, 17.60%.

(Z)-1,2-di-(2-thienyl)ethene (9)

Decarboxylation of the corresponding acid **1** (10.00 g, 0.042 mol) was accomplished by a method described earlier [25], by heating with Cu-powder (10 g) in boiling quinoline (50 mL, dried over molecular sieves) for 1 h. The reaction mixture was taken up in ether (100 mL) and washed with 10% hydrochloric acid (150 mL). All ethereal extracts were collected, washed with water, 10% hydrochloric acid, then with water and dried over magnesium sulphate. The residue left after the ether was evaporated, was suspended in methanol (50 mL) and the precipitate filtered. Yellow crystals (4.8 g, 59.00%), mp 130-132°C were thus obtained (lit.[29] mp 133-134°C); ¹H-NMR (CDCl₃) (δ ppm): 6.98 (1H, AB_{sys}, *J* = 5.05 Hz, *J* = 3.65 Hz, H_b or H_e), 7.03 (1H, d, *J* = 3.65 Hz, H_c or H_f), 7.05 (1H, s, H_{ethylenic}), 7.17 (1H, d, *J* = 5.05 Hz, H_a or H_h).

(Z)-1,2-di-[5-formyl-2-(2-thienyl)]ethene (10)

Compound **10** was prepared in the same way as **4**, starting from **9** (5.00 g, 0.026 mol) in DMF (17.5 mL) to which a mixture of POCl_3 (18.5 mL, 0.202 mol) and DMF (17.5 mL) was added dropwise under stirring and cooling. The crude product was recrystallized from chloroform. The yield was 2.75 g (42.30%), mp 210-212°C; IR (cm^{-1}) (KBr): 1640 (COH), 1660 (COH); $^1\text{H-NMR}$ (CDCl_3) (d ppm): 7.22 (1H, d, $J = 3.93$ Hz, H_b), 7.26 (1H, s, $\text{H}_{\text{ethylenic}}$), 7.69 (1H, d, $J = 3.93$ Hz, H_a), 9.94 (1H, s, CHO); $^{13}\text{C-NMR}$ (CDCl_3) (d ppm): 124.6, 129.0, 138.5, 142.5, 149.8 183.9; Anal. Calcd. for: $\text{C}_{12}\text{H}_8\text{O}_2\text{S}_2$: C, 58.49; H, 3.22; S, 25.84%; Found: C, 58.52; H, 3.48; S, 26.12%.

(Z)-1,2-bis[5-[2-carboxy-2-(2-thienyl)ethenyl]-2-thienyl]ethene (11)

Compound **11** was prepared in same way as **1**, using dialdehyde **10** (5.2 g, 0.002 mol) and 2-thiopheneacetic acid (6.3 g, 0.0044 mol) in acetic anhydride (30 mL) and triethylamine (30 mL) [16]. Red crystals (3.2 g, 30.8% yield) were obtained after recrystallization from DMF, mp 254-257°C; IR (cm^{-1}) (KBr): 1590 (C=C), 1670 (COOH); $^1\text{H-NMR}$ (DMSO-d_6) (d ppm): 6.85 (1H, s, H_g), 7.02 (1H, d, $J = 3.66$ Hz, H_c), 7.18 (1H, AB_{sys} , $J = 3.36$ Hz, $J = 3.67$ Hz, H_b), 7.22 (1H, d, $J = 3.97$ Hz, H_e), 7.42 (1H, $J = 3.96$ Hz, H_f), 7.76 (1H, d, $J = 3.67$ Hz, H_a), 8.04 (1H, s, H_d); $^{13}\text{C-NMR}$ (DMSO-d_6) (d ppm): 127.3, 127.8, 132.8, 140.3, 140.8, 141.6, 142.6, 151.5, 172.8; Anal. Calcd. for: $\text{C}_{24}\text{H}_{16}\text{O}_4\text{S}_4$: C, 58.03; H, 3.22; S, 25.84%; Found: C, 57.85; H, 3.53; S, 26.04%.

(Z)-{5,5'-di-[2-(2-thienyl)-2-chlorocarbonylethenyl]}-1,2-di-(2-thienyl)ethene (12)

Dichloride **12** was prepared from diacid **11** (19 g, 0.20 mol) and SOCl_2 (5 mL, 0.07 mol) dissolved in dry toluene (15 mL). The mixture was stirred 30 min. at room temperature and then 2 h at 70°C. Excess SOCl_2 was removed under reduced pressure. The residue was extracted with hexane (50 mL) and dried over magnesium sulphate. After evaporation of the solvent an oily product was obtained which was used without further purification in the next step; IR (cm^{-1}) (KBr): 1740 (COCl), 1590 (C=C).

(Z)-1,2-bis[5-[2-(p-fluorophenylcarbamoyl)-2-(2-thienyl)ethenyl]-2-thienyl]ethene (13)

p-Fluoroaniline (0.36 g, 3.2 mmol) dissolved in chloroform (30 mL) and triethylamine (5 mL) was added dropwise at room temperature to a solution of the oily product **12** (0.8 g, 1.5 mmol) in chloroform. After the addition was complete the mixture was stirred for 1h at room temperature. Excess chloroform was distilled off under reduced pressure and the solid residue was suspended in acetone (15 mL). The precipitate was filtered, the filtrate was concentrated under reduced pressure and the remaining solid residue suspended in toluene (15 mL). After recrystallization from (1:1) DMF-ethanol, orange-brown crystals were obtained in the yield of 0.58 g (56.70%), mp 224-227°C; IR

(cm^{-1}) (KBr): 1600 (C=C), 1662 (CONH), 3295 (NH), 3397 (NH); $^1\text{H-NMR}$ (DMSO- d_6) (d ppm): 6.87 (1H, s, H_g), 7.13-7.19 (4H, m, $\text{H}_{\text{arom.}}$), 7.22 (1H, d, $J = 3.67$ Hz, H_e), 7.26 (1H, $\text{AB}_{\text{sys.}}$, $J = 3.97$ Hz, $J = 4.57$ Hz, H_b), 7.36 (1H, d, $J = 3.97$ Hz, H_f), 7.65 (1H, d, $J = 3.97$ Hz, H_c), 7.82 (1H, s, H_d), 7.84 (1H, d, $J = 5.19$ Hz, H_a); $^{13}\text{C-NMR}$ (DMSO- d_6) (d ppm): 115.2, 115.5, 122.2, 122.5, 122.6, 126.3, 129.9, 131.8, 134.5, 137.7, 145.6, 157.0, 160.2, 165.6; Anal. Calcd. for: $\text{C}_{36}\text{H}_{24}\text{O}_2\text{F}_2\text{N}_2\text{S}_4$: C, 63.32; H, 3.52; N, 4.10; S, 18.80%; Found: C, 63.55; H, 3.96; N, 3.89; S, 18.92%.

(Z)- and (E)-3-(2-furyl)-2-(2-thienyl)acrylic acids (14) and (15).

Compounds **14** and **15** were prepared in a manner described earlier [23, 27] from 2-furancarboxaldehyde (7.54 g, 0.078 mol) and thiophene-2-acetic acid (10 g, 0.07 mol) in acetic anhydride (10 mL) and triethylamine (10 mL). After recrystallization from methanol, 8.3 g (53.90%) of the (*Z*)- isomer, mp 197-200°C and 1.9 g (12.60%) of the (*E*)-isomer, mp 178-184°C were obtained; IR (cm^{-1}) (KBr) for (**15**): 1615 (C=C), 1670 (COOH); $^1\text{H-NMR}$ (DMSO- d_6) (d ppm): 6.22 (1H, d, $J = 3.36$ Hz, H_c), 6.53 (1H, $\text{AB}_{\text{sys.}}$, $J = 3.67$ Hz, $J = 4.88$ Hz, H_b), 7.03 (1H, d, $J = 3.60$ Hz, H_e), 7.12 (1H, $\text{AB}_{\text{sys.}}$, $J = 3.66$ Hz, $J = 4.89$ Hz, H_f), 7.65 (1H, d, $J = 4.58$ Hz, H_g), 7.67 (1H, s, H_d), 7.75 (1H, d, H_a), 12.6 (1H, s, COOH); Anal. Calcd. for: $\text{C}_{11}\text{H}_8\text{O}_3\text{S}$: C, 59.99; H, 3.66; S, 14.56%; Found: C, 59.87; H, 3.61; S, 14.62%.

Ethyl (E)-3-(2-furyl)-2-(2-thienyl)acrylate (16).

Ethyl ester **16** was prepared in the manner described for the preparation of **3** by refluxing acid **15** (14.0 g, 0.064 mol) dissolved in absolute ethanol (250 mL) containing conc. sulphuric acid (2 mL) for 17h. The crude product was recrystallized from ethanol. The yield was 10.8 g, (68.80%), mp 58-59°C; IR (cm^{-1}) (KBr): 1615 (C=C), 1700 (COOEt); $^1\text{H-NMR}$ (DMSO- d_6) (d ppm): 1.20 (3 H, t, $J = 7.32$ Hz, $J = 7.02$ Hz, CH_3), 4.20 (2H, q, $J = 7.02$ Hz, CH_2), 6.25 (1H, d, $J = 3.67$ Hz, H_c), 6.54 (1H, $\text{AB}_{\text{sys.}}$, $J = 3.67$ Hz, $J = 4.88$ Hz, H_b), 7.05 (1H, d, $J = 3.60$ Hz, H_e), 7.14 (1H, $\text{AB}_{\text{sys.}}$, $J = 3.67$ Hz, $J = 4.88$ Hz, H_f), 7.67 (1H, d, $J = 4.57$ Hz, H_g), 7.69 (1H, s, H_d), 7.78 (1H, d, H_a); Anal. Calcd. for: $\text{C}_{13}\text{H}_{12}\text{O}_3\text{S}$: C, 62.89; H, 4.87; S, 12.91%; Found: C, 62.93; H, 4.83; S, 13.02%.

Ethyl (Z)-3-[5-formyl-(2-furyl)]-2-[5-formyl-(2-thienyl)]acrylate (17)

Compound **17** was prepared in a manner similar to the preparation of **4**, but starting from **16** (11.00 g, 0.044 mol) dissolved in DMF (21 mL) to which POCl_3 (22 mL, 0.240 mol) was added dropwise under stirring and cooling at a temperature not exceeding 10°C. The gummy product was recrystallized from (1:2) benzene-hexane to give a yellow crystalline product (5.2 g, 38.60% yield), mp 134-136°C; IR (cm^{-1}) (KBr): 1665 (CHO), 1675 (CHO), 1710 (COOEt); $^1\text{H-NMR}$ (CDCl_3) (d ppm): 1.27 (3H, t, $J = 7.1$ Hz, CH_3), 4.31 (2H, q, $J = 7.05$ Hz, CH_2), 6.30 (1H, d, $J = 3.65$ Hz, H_b), 7.14 (1H, d, $J = 3.93$ Hz, H_d), 7.20 (1H, d, $J = 3.65$ Hz, H_a), 7.80 (1H, d, $J = 3.94$ Hz, H_e), 7.84 (1H, s, H_c), 9.59 (1H, s,

CHO), 9.97 (1H, s, CHO); ^{13}C -NMR (CDCl_3) (d ppm): 14.0, 62.1, 127.0, 144.1, 145.4, 152.7, 153.7, 164.8, 177.7, 182.7; Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{O}_5$: C, 59.21; H, 3.95; S, 10.53%. Found: C, 59.43; H, 3.95; S, 10.20%.

Ethyl (Z)-3-[5-(2-carboxy)ethenyl-(2-furyl)]-2-[5-(2-carboxyethenyl)-(2-thienyl)]acrylate (18)

Dialdehyde **17** (3.00g, 0.01 mol) was condensed with malonic acid (2.25g, 0.02 mol) in pyridine (55 mL) to which a few drops of piperidine were added. The reaction mixture was heated for 1h at 30-40°C and for 2 h at 100°C. After cooling, ice was added (300 g) and the reaction mixture was acidified with 20% hydrochloric acid. Crude product was recrystallized from (2:1) ethanol-dioxane to give 1.6 g (41.70%) of orange crystals, mp 240-244°C; IR (cm^{-1}) (KBr): 1605 (C=C), 1625 (C=C), 1670 (COOH), 1690 (COOH), 1710 (COOEt); ^1H -NMR (DMSO- d_6) (d ppm): 1.23 (3H, t, $J = 7.06$ Hz, CH_3), 4.31 (2H, q, $J = 7.05$ Hz, CH_2), 5.79 (1H, d, $J = 15.87$ Hz, $\text{H}_{\text{ethylenic}}$), 6.18 (1H, d, $J = 15.81$ Hz, $\text{H}_{\text{ethylenic}}$), 6.91 (1H, d, $J = 3.49$ Hz, H_a), 6.96 (1H, d, $J = 3.43$ Hz, H_b), 7.14 (1H, d, $J = 3.67$ Hz, H_d), 7.51 (1H, d, $J = 3.66$ Hz, H_e), 7.25 (1H, d, $J = 15.81$ Hz, $\text{H}_{\text{ethylenic}}$), 7.68 (1H, s, H_c), 7.75 (1H, d, $J = 15.81$ Hz, $\text{H}_{\text{ethylenic}}$), 12.47 (1H, s, COOH); ^{13}C -NMR (DMSO) (d ppm): 14.1, 61.5, 117.6, 117.9, 118.9, 121.0, 122.1, 128.2, 129.8, 130.1, 131.4, 136.6, 138.8, 140.6, 151.3, 152.9, 165.7, 167.1, 167.5; Anal. Calcd. for $\text{C}_{19}\text{H}_{16}\text{O}_7\text{S}$: C, 58.76; H, 4.12; S, 8.25%; Found: C, 58.54; H, 4.41; S, 8.43%.

3-Chloro-5-[2-ethoxycarbonyl-2-[3'-chloro-2'-chlorocarbonyl-5'-thieno[3,2-b]thienyl]ethenyl]thieno[3,2-b]furan-carbonylchloride (19)

Compound **19** was prepared in a manner similar to the preparation of **7**, starting from **18** (1.00 g, 2.6 mmol) and SOCl_2 (14 mL, 0.193 mol), by stirring for 15 min under external cooling on ice. More SOCl_2 (1 mL) and a few drops of pyridine were then added dropwise. The reaction mixture was stirred for 0.5 h at room temperature and for 40 h at 80°C. Excess SOCl_2 was removed under reduced pressure and the remaining material was extracted with hot hexane. After the removal of the solvent an oily product (0.50 g, 35.0%) was obtained which was used without further purification in the next step.

6-Chloro-2-[2-[3-chloro-2-(p-fluorophenylcarbamoyle)-5-thieno[3,2-b]thienyl]-2-{ethoxycarbonyl-ethenyl}thieno[3,2-b]furan-5-carbox-p-fluoroanilide (20)

Compound **20** was prepared from **19** (0.5 g, 0.001 mol) in chloroform (5 mL) and *p*-fluoroaniline (0.25 g, 0.002 mol) dissolved in chloroform (5 mL) in a manner similar to the preparation of **8**. The crude product was recrystallized from DMF. Compound **20**, mp 249-251°C was obtained in 0.38 g (50.60%) yield; IR (cm^{-1}) (KBr): 1615 (C=C), 1673 (CONH), 1720 (COOEt), 3380, 3410 (NH); ^1H -NMR (DMSO- d_6) (d ppm): 1.33 (3H, t, $J = 7.13$ Hz, CH_3), 4.46 (2H, q, $J = 7.09$ Hz, CH_2), 7.22 (1H, s, H_a), 7.15-7.28 (4H, m, H_{arom}), 7.68 (1H, s, H_c), 7.64-7.78 (4H, m, H_{arom}), 8.20 (1H, s, $\text{H}_{\text{ethylenic}}$), 10.3 (2H, s, NH); ^{13}C -NMR (DMSO- d_6) (d ppm): 14.1, 61.9, 115.4, 115.7, 117.6, 119.1, 122.3, 123.1,

123.2, 123.3, 123.4, 126.8, 126.9, 127.5, 134.9, 136.4, 136.7, 144.0, 150.4, 151.8, 157.5, 160.7, 161.0, 166.9; Anal. Calcd. for $C_{31}H_{18}F_2Cl_2N_2O_5S_3$: C, 52.91; H, 2.56; N, 3.98; S, 13.68%; Found: C, 53.57; H, 2.92; N, 4.25; S, 13.45%.

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Sample Availability: Samples of compounds **5** and **13** are available from authors.