Synthesis and characterization of alanine functionalized oligo/polythiophenes

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The synthesis and characterization of a series of monothiophenes and terthiophenes bearing amino acids are reported. The reaction of a thiophene, substituted in position 3 by either a carboxylic acid or an acetic acid moiety, with an alanine methyl ester in the presence of hydroxybenzotriazole (HOBt) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) affords several mono/terthiophene-alanine methyl esters. The latter were deprotected to form the corresponding carboxylic acids. Terthiophenes have been prepared in good yields *via* a Stille cross coupling reaction, using a dibromothiophene–alanine methyl ester and tri-butyl stannyl thiophene. The newly prepared monomers are very stable in air and in the presence of organic solvents. The optical and electrochemical properties of the monomers and their corresponding polymers were also examined using cyclic voltammetry and indium tin oxide (ITO) electrodes.

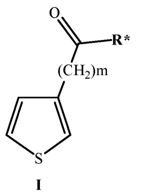
Introduction

Over the past decade, polythiophenes have emerged as an important new category of π-conjugated polymers with applications in both optical devices and sensor materials.[1–11] Their high conductivity, stability and excellent electrochemical response have promoted an increased interest in the synthesis of a variety of new oligothiophenes, which bear exploitable functionalities that can be readily replaced by inorganic, organic, or bioorganic moieties.[12–18] This interest has also resulted in the exploration and development of new synthetic strategies which allow for the tuning of the solubility, conductivity, electroactivity and electrochromic properties of these thiophene-based polymers.[12–18] For example, it has been seen that the introduction of organo main group elements such as divalent sulfur or boron into oligothiophenes yields unusually high conductivities and photoluminescent properties in the corresponding polymers.[19–24]

The biomolecule functionalized oligothiophenes which have been prepared thus far, have had either their electrochemical/optical properties or biological activities probed.[25] Recently, Christopherson and co-workers reported the biological activities of different thiophenes and furans substituted by amino acids. Their study revealed that the amino acid functionalized monomers exhibit an inhibitory effect on Gar transformylase, which is an enzyme responsible for catalyzing the transfer of a formyl group between bioorganic molecules.[25]

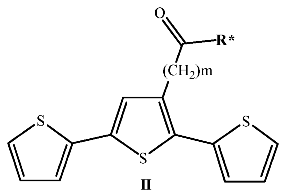
Polythiophenes bearing chiral centers have also been prepared by Nilsson *et al.* using $FeCl_3$ as oxidizing agent. In this study they examined the stereochemical effects of chirality on the polymer backbone.[26–28] They found that the absorption of both stereoisomeric polymers was similar and that the alteration of the stereochemistry of the side chain does not influence the absorption properties of the polymer. Electrochemical oxidation has also been reported to prepare chiral center functionalized polythiophene films on the surface of platinum electrodes.[29,30]

Another strategy, which has been employed to immobilize enzymes, such as glutamate oxidase (GlOx), onto electroactive species such as polythiophenes involves the formation of an amide bond between the polymer and the enzyme.[31] This is usually accomplished by the reaction of the carboxylic groups of the modified polythiophene electrodes and the amino group of the enzyme to create an amide linkage. This strategy has resulted in the design of an amperometric microbiosensor for *in vivo* measurements.[32] Other examples of the systems include reversible electroactive functionalized peptides, namely Fc-Leu-Phe-OMe.[33] In this particular example it was found that the oxidation potential of the Fc moiety was shifted as a consequence of the hydrogen bonding interactions between the amino acids and the 3-aminopyrrazole derivatives. Moreover, a ferrocene peptide containing four amino acids (Fc-Gly-Gly-Tyr-Arg-OH) was found to act as a competitive inhibitor to papain.[34]



I

R* = Amino Acid



II

Our approach toward amino acid modified conducting materials is to investigate the synthesis of new materials with multiple properties: materials combining the high stability and conductivity of polythiophenes, and biological activities of amino acids. This strategy will help control the immobilization process of biological molecules onto conducting and semi-conducting surfaces, which is a key step in the design of efficient electrochemical and biological sensors. So, various

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oligothiophenes bearing an amino acid group (**I** and **II**) will be prepared and polymerized electrochemically to form their corresponding polythiophenes.

Moreover, the amino acid activity may be probed using the redox properties of the conducting materials. The electrical and optical properties will also be examined using indium tin oxide (ITO) electrodes as well as their redox properties.

Result and discussion

Synthesis

A series of oligothiophenes substituted in position 3 with amino acids have been prepared. The 2,5 thiophene end positions are free to allow the chemical or electrochemical polymerization to occur. Amino acid groups and thiophene moieties are attached through a rigid group such as an amide group (thiophene with $n = 0$) or a methylene labile group (thiophenes with $n = 1$).

The influence of these links on the optical and electrochemical properties of amino acid functionalized oligothiophenes and their corresponding polythiophenes will be studied. The amino acid selected in our study is DL-alanine. It is non-polar and has a well established chemistry. Moreover, alanine based enzymes participate in several biochemical reactions. The synthetic procedure of oligothiophenes bearing DL-alanine is summarized in Scheme 1.

The condensation of a 3-thiophene carboxylic acid (**1**) and 3-thiophene acetic acid (**2**) with DL-alanine methyl ester hydrochloride (DL-Ala-OMe HCl) in the presence of hydroxybenzotriazole (HOBT) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) at room temperature in CH_2Cl_2 yields the desired products **3** and **4**, respectively, with a yield of 60–70%. Compounds **1–2** were dibrominated using literature procedures[35] with a small modification (see Experimental section) to form compounds **5** and **6**. The latter were further reacted with DL-Ala-OMe (in the presence of HOBT and DCC) affording products **7–8**. *Via* Stille cross-coupling reactions using tetrakistriphenylphosphine palladium(0) as the catalyst, terthiophenes **9–10** were prepared by reaction of **7–8** and two equivalents of tributyl stannyl thiophene ($ThSnBu_3$) in toluene at 100 °C. The conversion of the methyl esters of **3**, **4**, **9** and **10** to the corresponding carboxylic acids **11–14** was done in methanol with sodium hydroxide and hydrochloric acid. All newly synthesized products are stable in presence of air and organic solvents.

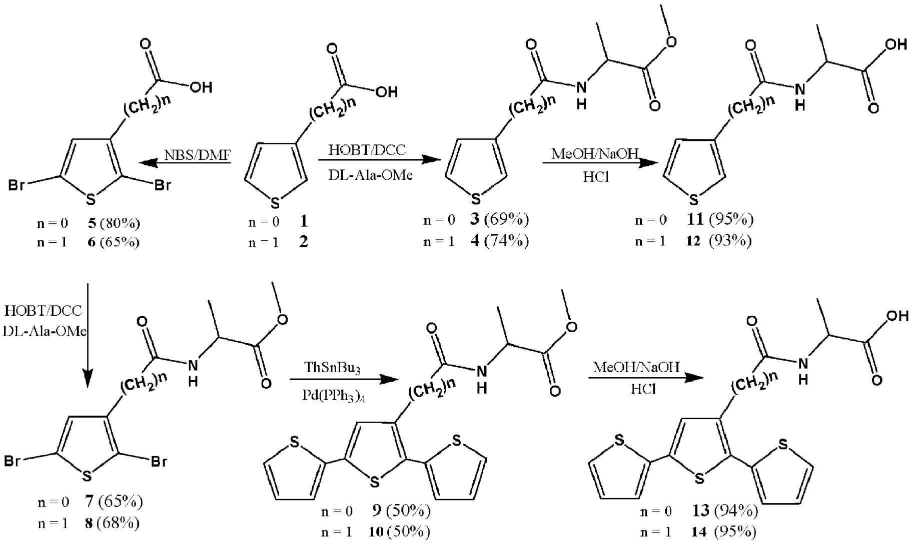
Electrochemistry

The redox properties of all amino acid functionalized oligothiophenes were studied using cyclic voltammetry (CV) or linear sweep voltammetry (LSV). Table 1 summarizes the oxidation peak potentials (irreversible systems) of the prepared monomers.

It is well known that once you increase the degree of conjugation in thiophene monomers, the oxidation peak potential decreases due to the electronic delocalization of the π-system, which explains the low oxidation peak potential of terthiophene monomers.[36–38] Monothiophenes with a methylene group in position 3 have lower oxidation potential because of the electro-donating behavior of this substituent.

Oxidative electropolymerizations of irreversible systems were performed in ACN containing 1 M n-Bu_4NPF_6 by repeated CV cycling beyond the oxidation peak potential of the thiophene component in each monomer (*i.e.* 0.720 and 0.650 V (*vs.* Fc^+/Fc) for **9** and **10**, respectively). As an example of the electrochemical polymerization of amino acid functionalized oligothiophenes, Fig. 1 represents a 10 scan electropolymerization curve of **9** and **10**. In the oxidation process, the peak current increases with increasing number of scans indicating the formation of a polymer film on the surface of the platinum electrode.

Electrochemical properties of the deposited polymer of both poly(**9**)-Pt and poly(**10**)-Pt were studied in a fresh solution of supporting electrolyte that was free of monomer. For both polymers, the peak current depends linearly (Fig. 2) on the scan rate indicating a surface bound species. As an example, poly(**9**)-Pt and poly(**10**)-Pt display a broad reversible oxidation wave with $E_{1/2} = 0.400$ and 0.350 V (*vs.* Fc^+/Fc),



Scheme 1 Synthetic route for amino acid functionalized oligothiophenes.

Table 1 Electrochemical and optical properties of prepared thiophene monomers in ACN

Compound	λ_{max}/nm	E_p/V (*vs.* Fc^+/Fc)^a ± 0.02 V
1	241	2.160^b
2	235	1.640
3	236	2.040^b
4	235	1.500
5	246	1.730
6	250	1.580
7	240	1.850
8	236	1.670
9	347	0.720
10	341	0.650
11	239	1.870
12	243	1.590
13	347	0.720
14	344	0.610

[a] First scan using 0.1 V s^{-1} scan rate. [b] 1 V s^{-1} as scan rate.

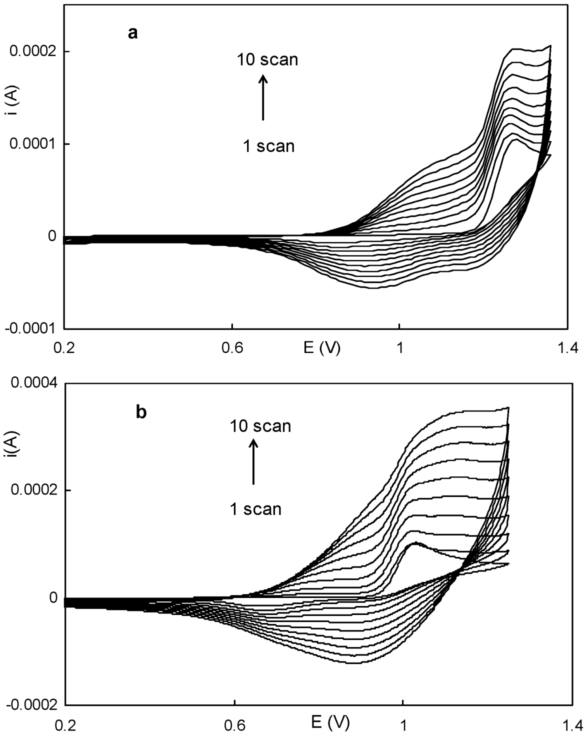


Fig. 1 A 10 scan electrochemical oxidation of **9** (a) and **10** (b) in ACN. Scan rate = 0.1 V s^{-1}. WE = platinum electrode; RE = silver wire and CE = platinum wire.

respectively. All prepared polymers are electrochemically stable. Their doping/undoping is fully reversible and no significant change or degradation of the electrochemical behavior was observed after repeated CV cycling 100 times.

The electropolymerization of compounds **3**, **4**, **11** and **12** was unsuccessful. Although the current increases during the CV cycling, no film was deposited on the surface of the electrode. The solubility or the instability of the produced radical cations of the monomers or the dimers may be the origin of this behaviour. However, **4** and **12** were polymerized chemically using $NOBF_4$ as oxidation agent. As it was expected, polythiophenes with a methylene group (poly(**10**), and (**14**)) have a lower oxidation potential than those with only an amide group (poly(**9**) and (**13**)).

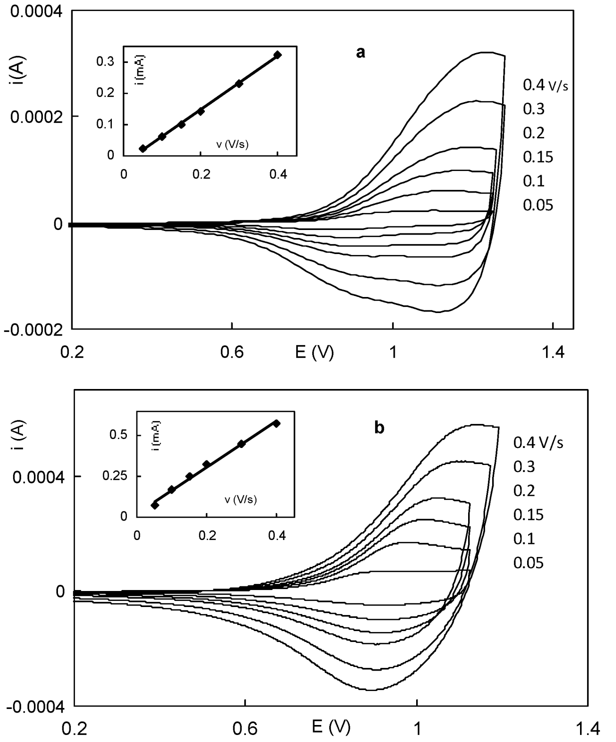


Fig. 2 CV of poly(**9**)-Pt (a) and poly(**10**)-Pt (b) at different scan rates and variation of current with scan rate.

UV-Visible

The optical properties of oligothiophenes and their corresponding polymers are associated with the length of conjugation and the electro-donating/withdrawing behavior of the substituents. As it was expected, the absorption maximum was red shifted for terthiophenes **9**, **10**, **13** and **14** in comparison to monothiophene compounds **1–8**, **11** and **12**.[39] The presence of a methylene or a carbonyl group on either monothiophenes or terthiophenes has no significant effect on the λ_{max}.

Polymers poly(**9**)-Pt and poly(**10**)-Pt prepared *via* anodic oxidation were insoluble in commonly used organic solvents, which makes their characterization *via* classical spectroscopy techniques very difficult. On the other hand, the transparent ITO electrode provides insights into the oxidation/reduction states and structure of the deposited material. At the oxidation peak potential of monomers, polymers were deposited onto the ITO electrodes for 10–20 s. All colored polymers show

Table 2 Electrochemical and optical properties of polythiophenes bearing amino acid moiety [corresponding monomer].

	λ_{max} undoped/nm	λ_{max} doped/nm	$E_{1/2}$/V (*vs.* Fc^+/Fc)
Poly(**9**)-Pt	484 [347]	633	0.400
Poly(**10**)-Pt	430 [341]	627	0.350
Poly(**13**)-Pt	474 [347]	633	0.430
Poly(**14**)-Pt	442 [344]	656	0.300

similar UV-visible behavior (Table 2). They are dark blue in their oxidized state and yellow in their reduced state.

Summary

We have described the synthesis of a variety of mono/oligothiophenes bearing amino acids that are both stable in air and organic solvents. The UV/Vis studies of the mono/oligothiophenes showed that the methylene linker has no significant effect on the λ_{max}, whereas the increased conjugation length in the terthiophenes results in a red shift. As expected, the electrochemical studies of the monomers show that the terthiophene monomers and monomers possessing a methylene group exhibit lower oxidation potentials. The electrochemical oxidation of all terthiophenes successfully yields several polythiophenes bearing chiral centers (amino acids), which display excellent stability in both states (doped and undoped). Their redox potential is low and follows the same tendency as oligothiophene monomers. All deposited polymers exhibit similar optical properties in both states. The synthesis and characterization of new oligo/polythiophenes containing specific chiral centers, L- or D-alanine, are underway. These molecules will be immobilized on solid surfaces and will provide chiral electrodes that will induce electrochemical or biological responses. This concept will be extended to other amino acids such as leucine and glycine.

Experimental section

Generalities

Unless stated otherwise, all reactions and manipulations were carried out under an oxygenated atmosphere using standard Schlenk techniques. Glassware was oven-dried at 100 °C for 24 h prior to use. Solvents were dried using activated (24 h at 100 °C) molecular sieves (4 Å). All reagents were purchased from commercial sources and used as received except where stated otherwise.

^{1}H-proton (^{13}C-carbon) NMR spectra were recorded on a 200 (50) MHz Varian NMR spectrometer. The NMR samples were prepared by using ~20 mg of product dissolved in 1 mL of deuterated solvent (DMSO-d$_6$ or CDCl$_3$). Melting points are uncorrected. IR spectra were recorded on a Michelson BOMEM Fourier-transform infrared spectrophotometer. The KBr pellet method was utilized to obtain all spectra with a ratio of (product : KBr) = 1 : 100. UV-Vis spectra were recorded on an Ultropec 2100 pro spectrophotometer.

The electrochemical experiments were performed using a μAutolab type III (Ecochemie) potentiostat at room temperature (22 ± 2 °C). Voltammetric measurements were performed in acetonitrile (ACN) containing 1 M of n-Bu$_4$NPF$_6$. The platinum electrode (diameter 1.6 mm) was used as the working electrode. Platinum wire was used as auxiliary electrode and silver wire was used as reference electrode. All oxidation peak potentials/oxidation potentials were reported *versus* an internal reference ferrocene/ferrocenium redox (E^0 = 0.390 V *vs.* AgCl/Ag, E^0 = 0.350 V *vs.* SCE). The working electrode was polished on alumina before use. *iR* compensations were applied for all experiments. The bulk electrolyses were performed using a controlled potential in a cell with one compartment using a platinum plate (1.5 cm^2) and ITO electrode as the cathode and anode, respectively.

General synthesis of 3, 4, 7 and 8

DL-Alanine methyl ester hydrochloride (0.417 g, 3 mmol) and triethylamine (0.42 mL, 3 mmol) were added to 40 mL of anhydrous dichloromethane. After stirring for 1 h, this solution was added dropwise to a solution of 2,5-dibromothiophene carboxylic acid (0.858 g, 3 mmol), hydroxybenzotriazole (0.405 g, 3 mmol), and dicyclohexylcarbodiimide (0.615 g, 3 mmol) in 60 mL of anhydrous dichloromethane that had also been stirred for 1 h. The reaction was followed by TLC and was found to be complete after 24 h. After filtration to eliminate the dicyclohexylurea byproduct, the organic reaction mixture was washed 5 times with 100 mL of a NaHCO$_3$ saturated solution followed by 5 × 100 mL washes with water. The organic phase was then dried over MgSO$_4$ and evaporated to dryness. The product was then purified *via* column chromatography on silica gel with a specific eluent.

General synthesis of 9 and 10

2,5-Dibromo-thiophene-3-carbonyl-alanine methyl ester (0.5563 g, 1.5 mmol), 2-tributyl-stannyl-thiophene (1.02 mL, 3.2 mmol), and Pd(Ph$_3$)$_4$ (0.200 g, 0.17 mmol) were added to 25 mL of toluene, which had been dried over 4 Å molecular sieves and degassed for 1 h with N$_2$. The reaction mixture was stirred for 48 h at 90 °C. The reaction was followed by TLC. Once complete the reaction mixture was filtered through celite to remove the catalyst. The mixture was then washed 5 times with 100 mL of a caesium fluoride solution, followed by 5 × 100 mL washes with water. The organic phase was then dried over MgSO$_4$ and evaporated to dryness. The crude product was then purified *via* column chromatography utilizing a solvent system of 30% ethyl acetate and 70% dichloromethane. The pure product was obtained as a white solid. The product was purified *via* column chromatography using a solvent system of 30% ethyl acetate and 70% dichloromethane.

General synthesis of 11–14

Terthiophene-3-alanine methyl ester (0.134 g, 0.343 mmol) and 1 N NaOH (2.2 mL) were added to 2 mL of methanol. The reaction mixture was then stirred at room temperature for 3.5 h, after which 1 N HCl (1 mL) was added. The MeOH was then removed *in vacuo* and the remaining solution was cooled in an ice bath. 1 N HCl (2 mL) was then added dropwise to the solution, which was then allowed to cool in the fridge overnight. The desired product was then filtered off and dried under reduced pressure.

Synthesis of 2-[(thiophene-3-carbonyl)-amino]-propionic acid methyl (3)

The product is a yellow-white solid. The solvent used for the column chromatography on silica gel was ethyl acetate–CH$_2$Cl$_2$ (20 : 90, R_F = 0.65). Yield: 69%. Mp: 130 °C. ^{1}H NMR (200 MHz, CDCl$_3$) δ (ppm) = 1.50 (d, J = 7.0 Hz, 3H, –CH_3), 3.60 (s, 3H, –COOCH_3), 4.70 (m, 1H, –CH–), 6.60 (s br, 1H, –CONH–), 7.20 (m, 1H, Th-H), 7.45 (m, 1H, Th-H), 7.90 (m, 1H, Th-*H*). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) = 17.6, 47.1, 51.5, 125.0, 125.4, 127.6, 135.8, 161.2, 172.3. IR ν/cm^{-1} = 1750 (CO ester), 1624 (CO amide). UV-Vis (CH_2Cl_2), λ_{max} (ε) = 236 nm (1.29 × 10^4 M^{-1} cm^{-1}). HRMS (EI) for $C_9H_{11}NO_3S$ [M$^+$]: calcd. 213.0454; found 213.0463.

Synthesis of 2-(2-thiophen-3-yl-acetylamino)-propionic acid methyl ester (4)

The product is a yellow-white solid. The solvent used for the column chromatography on silica gel was ethyl acetate–CH_2Cl_2 (20 : 90, R_F = 0.70). Yield: 75%. Mp: 85 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) = 1.40 (d, *J* = 7.0 Hz, 3H, –C*H*$_3$), 3.60 (s, 3H, –COOC*H*$_3$), 3.78 (s, 2H, ThC*H*$_2$CO), 4.60 (m, 1H, –C*H*–), 6.15 (s br, 1H, –CON*H*–), 7.05 (m, 1H, Th-*H*), 7.19 (m, 1H, Th-*H*), 7.38 (m, 1H, Th-*H*). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) = 18.5, 38.1, 48.3, 52.7, 123.7, 126.9, 128.6, 134.6, 170.3, 173.5. IR ν/cm^{-1} = 1750 (CO ester), 1647 (CO amide). UV-Vis (CH_2Cl_2), λ_{max} (ε) = 235 nm (4.98 × 10^3 M^{-1} cm^{-1}). HRMS (EI) for $C_{10}H_{13}NO_3S$ [M$^+$]: calcd. 227.0610; found 227.0613.

Synthesis of 2,5-dibromo-thiophene-3-carboxylic acid (5)

Thiophene-3-carboxylic acid (5 g, 39 mmol) and *N*-bromosuccinimide (NBS) (15.1 g, 86 mmol) were added to 80 mL of *N*,*N*′-dimethylformamide (DMF), which had been dried over 4 Å molecular sieves and degassed for 1 h with N_2. The flask was then wrapped with aluminium foil to shield the reaction from light. The reaction mixture was then stirred for 28 h at 50 °C. The reaction was followed by TLC. Once the reaction had reached completion the mixture was allowed to cool to room temperature, after which it was washed with a saturated solution of NaCl. Washing of the reaction mixture with NaCl resulted in the precipitation of the desired product as a white solid. The white solid was then obtained *via* filtration. Yield: 80%. Mp: 178 °C. ^{1}H NMR (200 MHz, DMSO-d$_6$) δ (ppm) = 7.43 (s, 1H, Th-*H*), 13.35 (s, 1H, –COO*H*). ^{13}C NMR (50 MHz, DMSO-d$_6$) δ (ppm) = 111.1, 118.4, 132.1, 133.1, 161.6. IR ν/cm^{-1} = 1693 (CO carboxylic acid). UV-Vis (CH_2Cl_2), λ_{max} (ε) = 246 nm (5.20 × 10^3 M^{-1} cm^{-1}).

Synthesis of 3-(2,5-dibromo-thiophen-3-yl)-acetic acid (6)

Thiophene-3-acetic acid (5 g, 35 mmol) and *N*-bromosuccinimide (NBS) (15.1 g, 86 mmol) were added to 80 mL of *N*,*N*′-dimethylformamide (DMF), which had been dried over 4 Å molecular sieves and degassed for 1 h with N_2. The flask was then wrapped with aluminium foil to shield the reaction from light. The reaction mixture was then stirred for 28 h at 50 °C. The reaction was followed by TLC. Once the reaction had reached completion the mixture was allowed to cool to room temperature, after which it was washed with a saturated solution of NaCl. Washing of the reaction mixture with NaCl resulted in the precipitation of the desired product as a yellow solid. The yellow solid was then obtained *via* filtration. Yield: 65%. Mp: 119 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) = 3.57 (s, 2H, ThC*H*$_2$CO), 6.91 (s, 1H, Th-*H*), 10.85 (s, 1H, –COO*H*). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) = 34.4, 109.7, 110.1, 132.8, 136.4, 170.6. IR ν/cm^{-1} = 1704 (CO carboxylic acid). UV-Vis (CH_2Cl_2), λ_{max} (ε) = 250 nm (8.59 × 10^3 M^{-1} cm^{-1}).

Synthesis of 2-[(2,5-dibromo-thiophene-3-carbonyl)-amino]-propionic acid methyl ester (7)

The product is a white-yellow solid. The solvent used for the column chromatography on silica gel was ethyl acetate–CH_2Cl_2 (30 : 70, R_F = 0.74). Yield: 65%. Mp: 84 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) = 1.25 (d, *J* = 7.0 Hz, 3H, –C*H*$_3$), 3.58 (s, 3H, –COOC*H*$_3$), 4.51 (m, 1H, –C*H*–), 6.83 (d, *J* = 5.9 Hz, 1H, –CON*H*–), 7.10 (s, 1H, Th-*H*) ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) = 18.8, 48.8, 52.9, 112.0, 112.2, 132.1, 136.4, 160.3, 173.4. IR ν/cm^{-1} = 1734 (CO ester) 1644 (CO amide). UV-Vis ((CH_2Cl_2), λ_{max} (ε) = 240 nm (7.84 × 10^3 M^{-1} cm^{-1}).

Synthesis of 2-[2-(2,5-dibromo-thiophen-3-yl)-acetylamino]-alanine methyl ester (8)

The product is a white solid. The solvent used for the column chromatography on silica gel was ethyl acetate–CH_2Cl_2 (30 : 70, R_F = 0.80). Yield: 68%. Mp: 113 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) = 1.39 (d, *J* = 7.0 Hz, 3H, –C*H*$_3$), 3.50 (s, 2H, ThC*H*$_2$CO), 3.75 (s, 3H, –COOC*H*$_3$), 4.58 (m, 1H, –C*H*–), 6.17 (d, *J* = 5.9 Hz, 1H, –CON*H*–), 6.93 (s, 1H, Th-*H*). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) = 17.3, 35.9, 47.2, 51.5, 109.7, 110.6, 130.2, 134.0, 166.9, 172.1. IR ν/cm^{-1} = 1756 (CO ester) 1635 (CO amide). UV-Vis (CH_2Cl_2), λ_{max} (ε) = 236 nm (2.58 × 10^4 M^{-1} cm^{-1}).

Synthesis of 2-[([2,2′;5′,2″]-terthiophene-3′-carbonyl)-amino]-propionic acid methyl ester (9)

The product is a white solid. The solvent used for the column chromatography on silica gel was ethyl acetate–CH_2Cl_2 (30 : 70, R_F = 0.74). Yield: 50%. Mp: 110 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) = 1.59 (d, *J* = 7.0 Hz, 3H, –C*H*$_3$), 3.93 (s, 3H, –COOC*H*$_3$), 4.90 (m, 1H, –C*H*–), 6.59 (d, *J* = 7.0 Hz, 1H, –CON*H*–), 7.25 (m, 1H, Th-*H*), 7.33 (m, 1H, Th-*H*), 7.41 (m, 1H, Th-*H*), 7.47 (m, 1H, Th-*H*), 7.58 (m, 1H, Th-*H*), 7.67 (m, 1H, Th-*H*), 7. 68 (s, 1H, Th-*H*). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) = 18.4, 48.5, 52.7, 124.7, 125.4, 125.6, 127.9, 128.2, 128.3, 129.3, 133.1, 134.1, 135.1, 136.1, 136.9, 163.0, 173.2. IR ν/cm^{-1} = 1755 (CO ester), 1633 (CO amide). UV-Vis (CH_2Cl_2 λ_{max} (ε) = 339 nm (2.04 × 10^4 M^{-1} cm^{-1}). HRMS (EI) for $C_{17}H_{15}NO_3S_3$ [M$^+$]: calcd. 377.0208; found 377.0215.

Synthesis of 2-(2-[2,2′;5′,2″]-terthiophen-3′-yl-acetylamino)-propionic acid methyl ester (10)

The product is a yellow solid. The solvent used for the column chromatography on silica gel was ethyl acetate–CH_2Cl_2 (30 : 70, R_F = 0.60). Yield: 50%. Mp: 136 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) = 1.45 (d, *J* = 7.0 Hz, 3H, –C*H*$_3$), 3.80 (s, 2H, ThC*H*$_2$CO), 3.83 (s, 3H, –COOC*H*$_3$), 4.72 (m, 1H, –C*H*–), 6.26 (d, *J* = 7.0 Hz, 1H, –CON*H*–), 7.3 (m, 7H, Th-*H*). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) = 18.5, 37.3, 48.4, 52.7, 124.3, 125.1, 126.5, 126.9, 128.1, 131.4, 132.7, 134.7, 136.7, 169.5, 173.3. IR ν/cm^{-1} = 1753 (CO ester), 1639 (CO amide). UV-Vis (CH_2Cl_2), λ_{max} (ε) = 343 nm (2.22 × 10^4 M^{-1} cm^{-1}). HRMS (EI) for $C_{18}H_{17}NO_3S_3$ [M$^+$]: calcd. 391.0365; found 391.0368.

2-[(Thiophene-3-carbonyl)-amino]-propionic acid (11)

Thiophene-3-alanine methyl ester (0.213 g, 1 mmol) and 1 N NaOH (2.2 mL) were added to 2 mL of methanol. The reaction mixture was then stirred at room temperature for 3.5 h, after which 1 N HCl (1 mL) was added. The MeOH was then removed *in vacuo* and the remaining solution was cooled in an ice bath. 1 N HCl (2 mL) was then added dropwise to the solution, which was then allowed to cool in the fridge overnight. The desired product was then filtered off and dried under reduced pressure. Product: white solid. Yield: 95%. Mp: 194 °C. ^{1}H NMR (200 MHz, DMSO-d$_6$): δ (ppm) = 1.38 (d, J = 7.4 Hz, 3H, –C*H*$_3$), 4.39 (m, 1H, –C*H*–), 7.58 (m, 2H, Th-*H*), 8.19 (m, 1H, Th-*H*), 8.51 (d, J = 7.0 Hz, 1H, –CON*H*–), 12.55 (s, 1H, –COO*H*). ^{13}C NMR (50 MHz, DMSO-d$_6$): δ (ppm) = 16.9, 47.8, 126.5, 126.9, 128.9, 137.2, 161.8, 174.1. ν/cm^{-1} = 1714 (CO carboxylic acid), 1635 (CO amide). UV-Vis (CH_2Cl_2), $\lambda_{max}(\varepsilon)$ = 243 nm (9.21×10^3 M^{-1} cm^{-1}). HRMS (EI) for $C_8H_9NO_3S$ [M$^+$]: calcd. 199.0297; found 199.0302.

2-(2-Thiophen-3-yl-acetylamino)-propionic acid (12)

Thiophene-3–CH$_2$ alanine methyl ester (0.227 g, 1 mmol) and 1N NaOH (2.2 mL) were added to 2 mL of methanol. The reaction mixture was then allowed to stir at room temperature for 3.5 h, after which 1N HCl (1 mL) was added. The MeOH was then removed *in vacuo* and the remaining solution was cooled in an ice bath. 1N HCl (2 mL) was then added dropwise to the solution, which was then allowed to cool in the fridge overnight. The desired product was then filtered off and dried under reduced pressure. The product is a white solid. Yield: 93%. Mp: 169 °C. ^{1}H NMR (200 MHz, DMSO-d$_6$) δ (ppm) = 1.28 (d, J = 7.4 Hz, 3H, –C*H*$_3$), 3.45 (s, 2H, ThC*H*$_2$CO), 4.25 (m, 1H, –C*H*–), 7.02 (m, 1H, Th-*H*), 7.25 (m, 1H, Th-*H*), 7.45 (m, 1H, Th-*H*), 8.55 (d, J = 7.0 Hz, 1H, –CON*H*–). ^{13}C NMR (DMSO-d$_6$) δ (ppm) = 17.2, 36.6, 47.5, 121.9, 125.4, 128.6, 135.9, 169.5, 174.0 IR ν/cm^{-1} = 1705 (CO carboxylic acid), 1645 (CO amide). UV-Vis (CH_2Cl_2), λ_{max} (ε) = 234 nm (5.56×10^3 M^{-1} cm^{-1}). HRMS (EI) for $C_9H_{11}NO_3S$ [M$^+$]: calcd. 213.0454; found 213.0463.

2-[([2,2′;5′,2′′]-Terthiophene-3′-carbonyl)-amino]-propionic acid (13)

Terthiophene-3-alanine methyl ester (0.134 g, 0.343 mmol) and 1 N NaOH (2.2 mL) were added to 2 mL of methanol. The reaction mixture was then stirred at room temperature for 3.5 h, after which 1 N HCl (1 mL) was added. The MeOH was then removed *in vacuo* and the remaining solution was cooled in an ice bath. 1 N HCl (2 mL) was then added dropwise to the solution, which was then allowed to cool in the fridge overnight. The desired product was then filtered off and dried under reduced pressure. Product: yellow solid. Yield: 94%. Mp: 177 °C. ^{1}H NMR (200 MHz, DMSO-d$_6$): δ (ppm) = 1.38 (d, J = 7.4 Hz, 3H, –C*H*$_3$), 4.38 (m, 1H, –C*H*–), 7.08 (m, 2H, Th-*H*), 7.39 (m, 2H, Th-*H*), 7.41 (m, 1H, Th-*H*), 7.58 (m, 2H, Th-*H*), 8.75 (d, J = 7.0 Hz, 1H, –CON*H*–), 12.59 (s, 1H, –COO*H*). ^{13}C NMR (50 MHz, DMSO-d$_6$): δ (ppm) = 16.7, 48.1. 124.9, 125.0, 126.3, 127.8, 128.5, 133.3, 133.5, 134.2, 134.9, 135.1, 163.3, 173.9. IR ν/cm^{-1} = 1720 (CO carboxylic acid), 1639 (CO amide). UV-Vis (CH_2Cl_2), $\lambda_{max}(\varepsilon)$ = 339 nm (1.19×10^4 M^{-1} cm^{-1}). HRMS (EI) for $C_{16}H_{13}NO_3S_3$ [M$^+$]: calcd. 363.0052; found 363.0054.

2-(2-[2,2′;5′,2′′]Terthiophen-3′-yl-acetylamino)-propionic acid (14)

Terthiophene-3–CH$_2$-alanine methyl ester (0.128 g, 0.315 mmol) and 1N NaOH (2.2 mL) were added to 2 mL of methanol. The reaction mixture was then allowed to stir at room temperature for 3.5 h, after which 1N HCl (1 mL) was added. The MeOH was then removed *in vacuo* and the remaining solution was cooled in an ice bath. 1N HCl (2 mL) was then added dropwise to the solution, which was then allowed to cool in the fridge overnight. The desired product was then filtered off and dried under reduced pressure. The product is a yellow solid. Yield: 95%. Mp: 144 °C. ^{1}H NMR (200 MHz, DMSO-d$_6$) δ (ppm) = 1.28 (d, J = 7.4 Hz, 3H, –C*H*$_3$), 3.59 (s, 2H, ThC*H*$_2$CO), 4.25 (m, 1H, –C*H*–), 7.08 (m, 2H, Th-*H*), 7.39 (m, 2H, Th-*H*), 7.41 (m, 1H, Th-*H*), 7.58 (m, 2H, Th-*H*), 8.58 (d, J = 7.0 Hz, 1H, –CON*H*–), 12.61 (s, 1H, –COO*H*). ^{13}C NMR (50 MHz, DMSO-d$_6$): δ (ppm) = 17.1, 35.5, 47.6, 124.0, 125.6, 126.6, 126.7, 127.3, 128.2, 128.3, 130.5, 133.1, 134.0, 134.2, 135.8, 168.9, 173.9. IR ν/cm^{-1} =1720 (CO carboxylic acid), 1647 (CO amide). UV-Vis (CH_2Cl_2), λ_{max} (ε) = 344 nm, (1.29×10^4 M^{-1} cm^{-1}). HRMS (EI) for $C_{17}H_{15}NO_3S_3$ [M$^+$]: calcd. 377.0208; found 377.0210.

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