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Synthesis and Cytotoxicity of Methyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione Derivatives

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Abstract—2- and 3-Methyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione and related derivatives were synthesized and evaluated in vitro by NCI against eight cancer types. Compounds **12–15** showed significant activity against melanoma, NCI-H23 non-small cell lung cancer, and MDA-MB-435 and MDA-N breast cancer cell lines; 2-hydroxymethyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (**13**) showed the highest activity against melanoma (mean log $GI_{50} = -7.74$) and the highest overall potency (mean log $GI_{50} = -6.99$).

Introduction

We have previously described the synthesis and potent antineoplastic activity of 4,8-dihydrobenzo[1,2-*b*:4,5-*b*′]-dithiophene-4,8-dione derivatives (**1,2**),[1,2] and 4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (**3**)[2] derivatives. In this continuing structural modification study, we now report the synthesis and cytotoxic evaluation of methyl and substituted methyl derivatives of the latter compound class.

Synthesis of 2-methyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]-dithiophene-4,8-dione (8) and its derivatives

The syntheses of 2-methyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithio-phene-4,8-dione (**8**) derivatives are outlined in Scheme 1. We used 3-methyl-2-thiophene carboxylic acid (**4**) as a starting material. Oxidation of compound **4** to the diacid **5** was accomplished in 45% yield using potassium permanganate in 15% NaOH. The cyclic diacylation of 2-methylthiophene (**7**) using **6** and $AlCl_3$ afforded the dione **8** accompanied by small amounts of other materials. Compound **8** was passed through a chromatographic column with benzene and recrystallized from acetic acid to give pure product (**8**) as yellow needles in 18% yield. Based on mass spectral results [*m*/*z* (234, M^+)] and elemental analysis data, the molecular formula was determined as $C_{11}H_6O_2S$. However, there are three possible structures (**8a, 8b,** and **8**) for this compound.

In the IR spectrum, we found two different carbonyl absorptions at 1640 and 1660 cm^{-1}. In the ^1H NMR spectrum, a CH_3 signal was found at 2.59 ppm, a singlet was observed at 7.27 ppm, and AB type signals were found at 7.57 and 7.68 ppm. In the ^1H-^1H COSY spectrum, we observed allylic coupling between the 2-methyl group and H-3. Accordingly, structure **8a** was ruled out. In the ^{13}C NMR spectrum, we observed two different carbonyl signals at 173 and 176 ppm; therefore, the carbonyl groups are in different chemical environments. However, from the above data, we still could not determine if the structure was **8b** or **8**, and designed the following chemical transformation experiments. This compound was oxidized with CrO_3 in glacial acetic acid to give the 2-carboxylic acid product **9**, which was decarboxylated with a suspension of active copper in quinoline at 190–200 °C to give a 52% yield of compound **10**.

The spectral data (i.e, 1-D and 2-D NMR spectra, mass spectrum, and elemental analysis) of compound **10** were compared with data in a published paper,[3] proving that compound **10** is 4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithio-

Key words: 4,8-Dihydrobenzo[1,2-*b*:4,5-*b*′]dithiophene-4,8-diones; 4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-diones; antineoplastic activity; cytotoxicity; structural modification.

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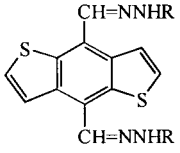

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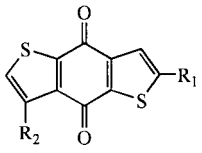

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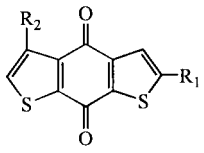

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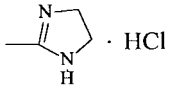
1a, R =  · HCl

1b, R = C(S)NH-*m*-$(CF_3)C_6H_4$

1c, R = C(O)-*p*-$(NH_2)C_6H_4$

2a = **3a**, $R_1 = COCH_3$, $R_2 = H$

2b = **3b**, $R_1 = CH(OH)CH_3$, $R_2 = H$

2c = **3c**, $R_1 = CH(OCOCH_3)CH_3$, $R_2 = H$

2d = **3d**, $R_1 = R_2 = COCH_3$

2e = **3e**, $R_1 = R_2 = CH(OH)CH_3$

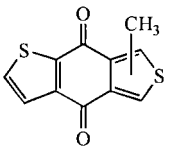
2f = **3f**, $R_1 = R_2 = CH(OCOCH_3)CH_3$

phene-4,8-dione. Therefore, **8** is the major product in the cyclic diacylation reaction and its structure is 2-methyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione.

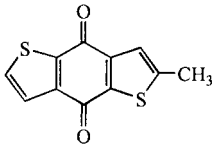
Compound **8** is the key intermediate for the preparation of other anthraquinone derivatives. Oxidation of compound **8** with chromium trioxide in acetic anhydride under mild conditions (5–10 °C) afforded the diacetate intermediate **11**. The crude intermediate **11** was hydrolyzed with dil H_2SO_4 to yield 4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione-2-carboxaldehyde (**12**) with mp 202–203 °C. Since the direct oxidation of **8** gave **9** only in very low (10%) yield, compound **12** was oxidized with silver nitrate in dioxane to give the same 2-carboxylic acid (**9**). Reduction of compound **12** with sodium borohydride in CH_3OH gave a 90% yield of 2-hydroxymethyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (**13**). Treatment of **13** with acetyl chloride or thionyl chloride yielded 2-acetoxymethyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (**14**) in a 92% yield and 2-chloromethyl-4,8-dihydrobenzo-[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (**15**) in an 86% yield, respectively.

Synthesis of 3-methyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (17) and its derivatives

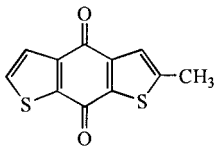
The synthesis of derivatives of 3-methyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (**17**) is outlined in Scheme 2. The cyclic diacylation of 3-methylthiophene (**16**) with **6** and $AlCl_3$ afforded the dione **17** in a 16% yield. Based on mass spectral [*m*/*z* (234, M^+)] and elemental analysis data, the molecular formula was determined as $C_{11}H_6O_2S$. In its ^1H NMR spectrum, in addition to a CH_3 signal found at 2.58 ppm, a singlet was observed at 7.31 ppm, and AB type signals were found at 7.60 and 7.64 ppm. The ^{13}C NMR spectrum showed a CH_3 signal at 16 ppm and two carbonyl carbon signals at 174.5 and 175.8 ppm. From the above data, we confirmed that this product is 3-methyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (**17**). In the presence of a catalytic amount of benzoyl peroxide and a few drops of hydrobromic acid as an initiator, compound **17** underwent free radical bromination with 1.5–1.8 equiv of *N*-bromosuccinimide to afford the 2-(bromomethyl) analogue **18**. In its ^1H NMR spectrum, in addition to a CH_2 signal at 4.88 ppm, AB type signals were found at 7.61 and 7.67 ppm, and a singlet was observed at 7.71 ppm. The ^{13}C NMR spectrum showed a CH_2 signal at 26.5 ppm and two carbonyl carbon signals at 174 and 175 ppm. The mass spectrum showed two molecular ion peaks [*m*/*z* (312, M^+)] and [*m*/*z*(314, $M^+ + 2$)] in a 1:1 ratio, which is characteristic of monobromine substitution, we thus concluded that this product is 3-bromomethyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (**18**). Hydrolysis of compound **18** used silver nitrate in 70% acetone to give a 42% yield of 3-hydroxymethyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (**19**).



8a



8b



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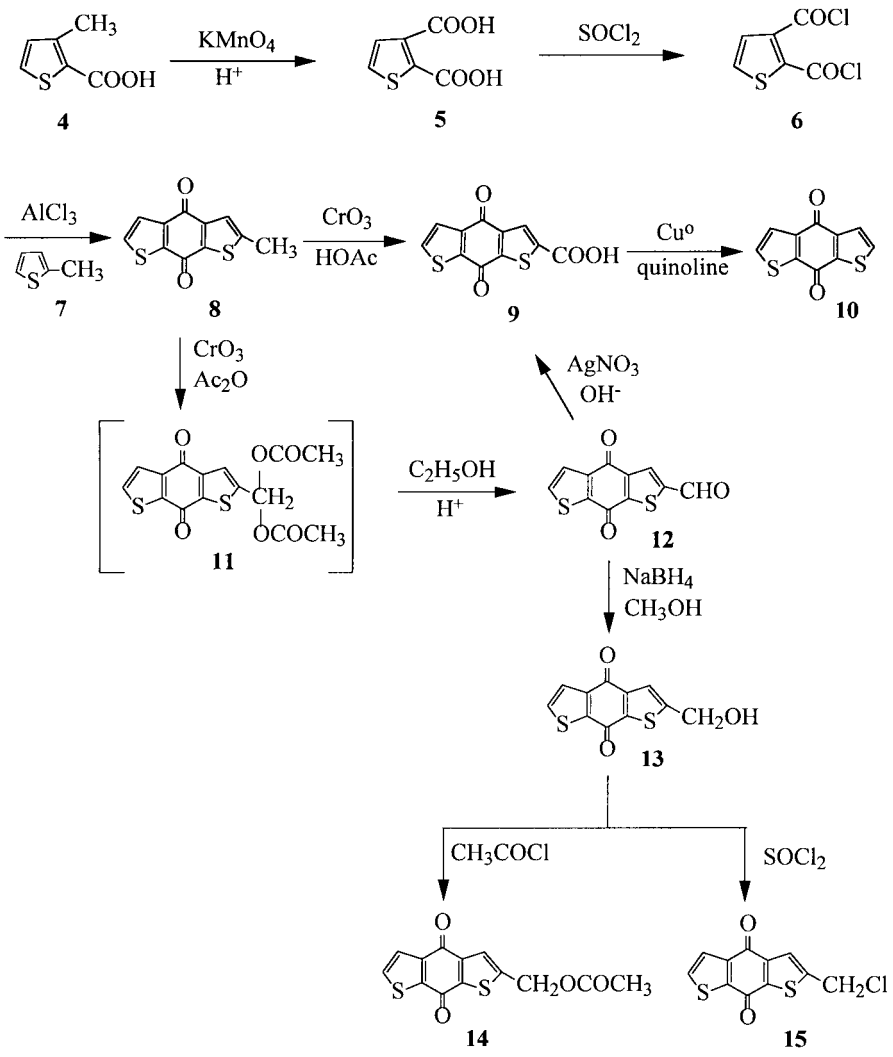
Results and Discussion

Compounds **8–9, 12–15, 17**, and **19** were submitted to NCI for in vitro testing[4–6] against 58 human tumor cell lines derived from leukemia, small and non-small cell lung cancers, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, and breast cancer. All compounds were active against all cell lines with mean log GI_{50} values ranging from −5.18 (compound **9**) to −6.99 (compound **13**). (Activity is defined as $\log GI_{50} < -4$ where GI_{50} is the molar concentration causing 50% cell growth inhibition). Table 1 shows the biological data in selected cell lines. COMPARE computations[4] were performed on all NCI screening data from the test compounds, and all were negative (Pearson correlation coefficients < 0.6) against the NCI "Standard Agent" database. Therefore, these compounds probably act by a mechanism differing from those of the standard agents.

The 2-carboxylic acid (**9**) was less active than either the 2-methyl (**8**) or 2-carboxaldehyde (**12**). The 3-methyl (**17**) and 3-hydroxymethyl (**19**) compounds were less active than the corresponding 2-substituted **8** and **13**. Compounds **13** (2-hydroxymethyl), **14** (2-acetoxymethyl),



Scheme 1. Synthesis of 2-methyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (**8**) and its derivatives.

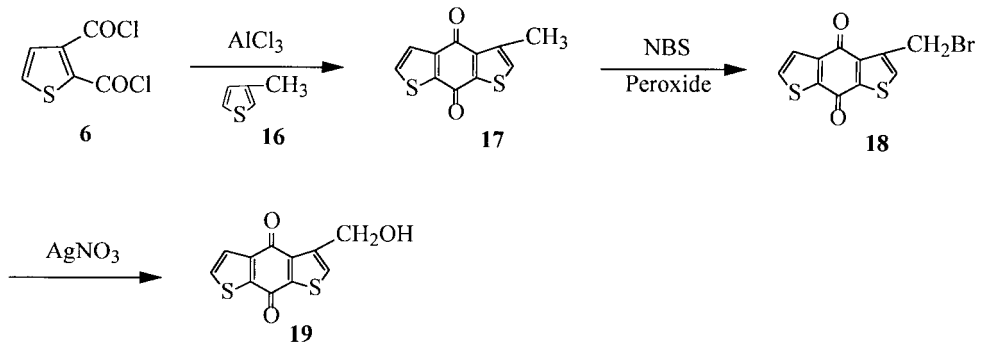
and **15** (2-chloromethyl) displayed striking potency in the melanoma cell panel with GI_{50} values < -8 in several cell lines. 2-Hydroxymethyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (**13**) had the highest activity over all cell lines with a mean log GI_{50} value less than -6.99. This compound is the most promising candidate for further in vivo testing.

Synthetic Methods

General experimental procedures

All melting points were determined on a Yanaco MP-500D apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-440 and Nicolet Impact 400 FT-IR spectrophotometers as KBr pellets. NMR spectra were obtained on Bruker ARX-300 FT-NMR and Varian VXR-300 FT-NMR spectrometers with tetramethylsilane (TMS) as an internal standard. The chemical shift values are expressed in δ values (parts per million). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Mass spectra (MS) were measured with HP 5995 GC–MS and JEOL JMS-Hx 110 spectrometers. Ultraviolet spectra were recorded on a Shimadzu UV-160A spectrophotometer. Elemental analyses were performed by National Cheng Kung University and National Chung Hsing University, Taiwan. Flash column chromatography was performed on silica gel (mesh 25–150 μm). Precoated silica gel plates (Kieselgel 60 F254 0.25 mm, Merck) were used for TLC analysis.

Thiophene-2,3-dicarboxylic acid (5). A stirred solution of 3-methyl-2-thiophene carboxylic acid (**4**) (21.3 g, 150 mmol) in 15% NaOH (700 mL) was heated to 70–80 °C. Potassium permanganate (100 g) was added portionwise over 3 h. Then the mixture was heated to reflux for 3 h, allowed to cool and acidified with excess HCl (12 *M*) in an ice bath. The white precipitate was filtered, then was recrystallized from water to give colorless needles of **5** (mp 270–272 °C) in a 45% yield. IR (KBr): 1700 (C=O), 3400–3600 (OH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.38 (d, $J = 5.2$ Hz, 1H, H-4), 7.79 (d, $J = 5.2$ Hz, 1H, H-5); ^{13}C NMR (DMSO-d_6): δ 130.1 (C-4), 130.9



Scheme 2. Synthesis of 3-methyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (**17**) and its derivatives.

Table 1. Inhibition of in vitro cancer cell lines by compounds **8, 9, 12–15, 17,** and **19**

Cell line	Cytotoxicity $\log GI_{50}(M)$[a,b]							
	8	**9**	**12**	**13**	**14**	**15**	**17**	**19**
Melanoma								
LOXIMVI	−6.89	−5.87	−7.57	< −8.00	< −8.00	< −8.00	−5.97	−5.50
MALME-3M	−6.80	< −8.00	−6.79	−7.48	−7.42	−7.98	−6.55	−5.61
M14	−6.80	−5.75	−7.43	< −8.00	< −8.00	< −8.00	−6.25	−6.11
SK-MEL-2	−6.44	−5.68	−6.74	−7.50	−7.17	−6.93	−5.76	−5.83
SK-MEL-28	−6.71	−5.71	−6.77	< −8.00	< −8.00	−7.67	−5.83	−5.56
SK-MEL-5	−6.82	−5.77	−7.00	< −8.00	−7.74	−7.92	−6.24	−6.50
UACC-257	−6.74	−5.70	−6.78	−7.64	−7.26	−6.74	−5.83	−5.91
UACC-62	−6.72	−5.76	−6.75	−7.26	−6.79	−6.76	−5.79	−5.79
Leukemia								
HL-60(TB)	−6.48	−5.32	−6.60	−7.14	−6.89	−7.68	−5.61	−6.55
Non-small cell lung cancer								
NCI-H23	−6.77	−5.68	−6.85	−7.84	−7.82	−7.65	−5.95	−5.76
NCI-H522	−6.61	−5.82	−6.24	−6.99	−6.85	−6.77	−5.79	−6.77
Ovarian cancer								
OVCAR-3	−6.28	−4.81	−6.68	−6.74	−6.68	−6.76	−5.77	−5.79
OVCAR-8	−6.39	−5.37	−6.77	−6.97	−6.79	−6.69	−5.55	−5.61
Breast cancer								
HS578T	−6.38	−5.58	−6.75	−6.74	−6.80	−6.63	−5.74	−5.72
MDA-MB-435	−6.75	−5.76	−7.73	−7.76	−7.75	−7.73	−6.67	−5.74
MDA-N	−6.77	−5.73	−7.70	−7.75	−7.73	−7.74	−6.53	−5.84
BT-549	–	–	–	–	–	–	–	−5.76
Mean value[c]	−6.15	−5.18	−6.50	−6.99	−6.66	−6.59	−5.62	−5.78

[a]Data obtained from NCI's in vitro disease-oriented tumor cells screen.
[b]Data are an average of at least two testings.
[c]Mean value over all 58 cell lines tested.

(C-5), 136.9 (C-3), 137.3 (C-2), 162.7 C-3-C=O), 165.3 (C-2-C=O); MS *m*/*z* (relative intensity): 172 (M^+, 32), 128 (55), 111 (100); UV λ_{max} (MeOH) nm (log ε): 256 (4.01).

Thiophene-2,3-dicarbonyl chloride (6). A stirred suspension of thiophene-2,3-dicarboxylic acid (**5**) (8.6 g, 50 mmol) in thionyl chloride (20 mL) was maintained at reflux for 1 h. The dark solution was cooled and the excess thionyl chloride was removed under reduced pressure. The residue was treated with two 10 mL portions of dry benzene, followed by the evaporation of each portion. The tan solid (**6**) was dried in vacuum for 1 h and used without further purification.

2-Methyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (8). A solution of the acid chloride (**6**) obtained above in dry 1,2-dichloroethane (50 mL) was added dropwise to a stirred suspension of $AlCl_3$ (14.6 g, 109 mmol) in dry 1,2-dichloroethane (50 mL) maintained at 4 °C. The mixture was allowed to stir at 4 °C for 10 min and a solution of 2-methylthiophene (**7**) (4.9 g, 50 mmol) in 1,2-dichloroethane (25 mL) was slowly added. The yellow suspension stirred at room temperature for 18 h and then was poured into ice and HCl (50 mL, 2 *M*). $CHCl_3$ (300 mL) was added and the mixture was shaken vigorously. The layers were separated and the aqueous layer was extracted with $CHCl_3$. The combined organic portions were washed with saturated $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The resulting yellow mixture was purified by column chromatography (silica gel, benzene), and a yellow fraction (R_f value = 0.29 in benzene) was collected. After evaporation, the residue was recrystallized from acetic acid to give yellow needles of **8** (mp 193–194 °C) in an 18%

yield. IR (KBr): 1600, 1630 (C=O) cm^{-1}; ^1H NMR (CD_2Cl_2): δ 2.59 (s, 3H, C-2-CH_3), 7.27 (s, 1H, H-3), 7.57 (d, $J = 5.1$ Hz, 1H, H-5), 7.68 (d, $J = 5.1$ Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$): δ 16.1 (C-2-CH_3), 124.9 (C-3), 126.7 (C-5), 133.2 (C-6), 142.4 (C-4a), 142.6 (C-3a), 143.2 (C-7a), 144.9 (C-8a), 150.1 (C-2), 172.9 (C-4), 176.9 (C-8); MS *m*/*z* (relative intensity): 234 (M^+, 100), 177 (31); UV λ_{max} (MeOH) nm (log ε): 237 (4.31), 293 (4.21); Anal. calcd for $C_{11}H_6O_2S_2$: C, 56.39; H, 2.58. Found: C, 56.30; H, 2.65.

4,8-Dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione-2-carboxylic acid (9). Method I: A suspension of compound **8** (1.2 g, 5.1 mmol) and CrO_3 (2 g) in glacial acetic acid (15 mL) was refluxed for 3 h. The remainder of the CrO_3 (1.5 g) was added portionwise over a 5 min period. The dark solution began to reflux vigorously. Reflux was maintained for 4 h after the addition was completed. The mixture was then poured into cool water. The resulting precipitate was filtered, washed with water and recrystallized from acetic acid to give yellow needles of **9** (mp > 350 °C) in a 10% yield. IR (KBr): 1650, 1660 (C=O), 2400–3300 (OH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.52 (d, $J = 5.0$ Hz, 1H, H-5), 7.80 (s, 1H, H-3), 8.14 (d, $J = 5.0$ Hz, 1H, H-6); ^{13}C NMR (DMSO-d_6): δ 126.4×2 (C-3, C-5), 129.6 (C-6), 141.8 (C-4a), 142.4 (C-3a), 143.6 (C-7a), 147.3 (C-8a), 158.0 (C-2), 161.7 (C-2-C=O), 172.5 (C-4), 174.5 (C-8); MS *m*/*z* (relative intensity): 264 (M^+, 100), 247 (51); UV λ_{max} (MeOH) nm (log ε): 253 (4.28), 293 (4.12); Anal. calcd for $C_{11}H_4O_4S_2$: C, 49.99; H, 4.03. Found: C, 50.02; H, 3.88.

Method II: To an aqueous solution of 1 mL of NaOH (0.08 g, 2.0 mmol) was added 1 mL of silver nitrate (0.14 g, 0.8 mmol) aqueous solution; this mixture was stirred until a dark brown suspension appeared. Then a solution of **12** (0.1 g, 0.4 mmol) in 1,4-dioxane (5 mL) was added, and stirring continued for 30 min at room temperature until a black metal silver sediment was produced. The reaction mixture was filtered and washed with hot water several times, then the filtrate was acidified with concd HCl to form a yellow precipitate. The precipitate was filtered, washed with water, and recrystallized from acetic acid to give yellow needles of **9** (mp > 350 °C) in a 47% yield. The spectral data have been described above.

4,8-Dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (10). Compound **9** (0.06 g, 0.22 mmol) and active copper (25 mg, 0.4 mmol) were added to a hot solution of quinoline (5 mL) at 190–200 °C. The mixture was heated at 190–200 °C for 2 h, then 5% HCl (5 mL) was added, and the resulting mixture was extracted with $CHCl_3$. The organic layer was separated, washed with saturated $NaHCO_3$ and water, dried, and evaporated. The residue was subjected to column chromatography (silica gel, benzene) to give **10** as a yellow solid (mp 235–237 °C) in a 52% yield.

Preparation of active copper

To a 80 mL aqueous solution of cupric sulfate pentahydrate (10 g, 40.0 mmol) was added Zn powder (2.6 g, 39.8 mmol). The mixture was stirred for 1 h, then filtered to give red brown metal copper, washed with water and dried in a desiccator.

2-Formyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (12). To a suspension of 2-methyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (**8**) (3.5 g, 15 mmol) in glacial acetic acid (50 mL) was added dropwise concd H_2SO_4 (98%, 2 mL) and CrO_3 (4.5 g, 45 mmo1) at 5–10 °C. The mixture was stirred at below 10 °C for 4 h. Then the mixture was poured into ice water and was extracted with $CHCl_3$. The organic layer was washed with saturated $NaHCO_3$ and water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give crude intermediate **11**. EtOH (95%, 60 mL) and dil. H_2SO_4 (30%, 40 mL) were added to **11**, and the mixture was maintained at reflux for 1 h, then cooled and poured into ice water. The mixture was extracted with $CHCl_3$. The organic layer was washed with saturated $NaHCO_3$ and water, dried, and condensed. The residue was purified by column chromatography (silica gel, benzene) to give yellow 2-formyl-4,8-dihydro-benzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (**12**) (mp 202–203 °C) in a 30% yield. IR (KBr): 1650, 1680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.66 (d, $J = 5.1$/Hz, 1H, H-5), 7.76 (d, $J = 5.1$ Hz, 1H, H-6), 8.21 (s, 1H, H-3), 10.04 (s, 1H, 2-CHO); ^{13}C NMR ($CDCl_3$): δ 127.0 (C-3), 132.9 (C-5), 134.9 (C-6), 142.4 (C-4a), 143.0 (C-3a), 144.6 (C-7a), 148.5 (C-8a), 150.0 (C-2), 172.9 (C-4), 174.9 (C-8), 182.9 (C-2-C=O); MS *m*/*z* (relative intensity): 248 (M^+, 22), 247 (100), 219 (5); UV λ_{max} (acetonitrile) nm (log ε): 244 (4.82), 275 (4.38); Anal. calcd for $C_{11}H_4O_3S_2$: C, 53.21; H, 1.62. Found: C, 52.99, H, 1.68.

2-Hydromethyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (13). To a suspension of compound **12** (1.2 g, 4.8 mmol) in CH_3OH (200 mL) was added sodium borohydride (0.2 g, 5.2 mmol). The mixture was stirred for 2 h. After acidification with 5% hydrochloric acid solution, the solution was extracted with $CHCl_3$. The organic layer was washed with water, dried, and condensed. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$:CH_3OH (10:1) to give **13** as an orange solid (mp 183–184 °C) in a 90% yield. IR (KBr) 1050 (C-O), 1640 (C=O), 3300–3500 (OH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.76 (d, $J = 5.4$ Hz, 2H, 2-CH_2-), 5.99 (t, $J = 5.4$ Hz, OH), 7.42 (s, 1H, H-3), 7.57 (d, $J = 5.1$ Hz, 1H, H-5), 8.09 (d, $J = 5.1$ Hz, 1H, H-6); ^{13}C NMR (DMSO-d_6): δ 58.5 (C-2-CH_2-), 121.8 (C-3), 126.3 (C-5), 135.5 (C-6), 141.9 (C-4a), 142.1 (C-3a), 142.3 (C-7a), 144.1 (C-8a), 158.0 (C-2), 172.7 (C-4), 175.6 (C-8); MS *m*/*z* (relative intensity): 250 (M^+, 100), 221 (24); UV λ_{max} (MeOH) nm (log ε): 237 (4.28), 293 (4.18); Anal. calcd for $C_{11}H_6O_3S_2$: C, 52.79; H, 2.42. Found: C, 52.79; H, 2.54.

2-Acetoxymethyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (14). To a solution of compound **13** (0.3 g, 1.2 mmol) in 1,2-dichloroethane (30 mL) was added dropwise acetyl chloride (0.2 g, 2.5 mmol). The mixture was heated at reflux for 4 h, then the mixture was cooled, poured into ice water, and extracted with

$CHCl_3$. The organic layer was washed with saturated $NaHCO_3$ and water, dried, and evaporated. The residue was purified by column chromatography (silica gel, $CHCl_3$) to give **14** as a yellow solid (mp 140–141 °C) in a 92 % yield. IR (KBr): 1240 (C-O), 1600, 1660, 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.11 (s, 3H, $COCH_3$), 5.25 (s, 2H, 2-CH_2-), 7.49 (s, 1H, H-3), 7.55 (d, $J=5.1$ Hz, 1H, H-5), 7.65 (d, $J=5.1$ Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$): δ 20.6 (C-2-CH_3), 60.2 (C-2-CH_2-), 126.0 (C-3), 126.7 (C-5), 133.8 (C-6), 142.3 (C-4a), 142.4 (C-3a), 144.5 (C-7a), 144.7 (C-8a), 147.4 (C-2), 170.2 (C-2-C=O), 172.8 (C-4), 175.4 (C-8); MS *m/z* (relative intensity): 292 (M^+, 29), 250 (100), 221 (34); UV λ_{max} (MeOH) nm (log ε): 237 (4.30), 292 (4.17); Anal. calcd for $C_{13}H_8O_4S_2$: C, 53.41; H, 2.76. Found: C, 53.20: H, 2.82.

2-Chloromethyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (15). To a suspension of compound **13** (0.3 g, 1.2 mmol) in dry benzene (30/mL) was added thionyl chloride (0.4 g, 3.4 mmol). The mixture was heated at reflux for 1 h and the excess thionyl chloride was removed under reduced pressure. The resulting yellow mixture was purified by column chromatography on silica gel eluting with benzene:$CHCl_3$ (10:1) to give **15** as a yellow solid (mp 165–166 °C) in a 86% yield. IR (KBr): 1650 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.77 (s, 2H, CH_2), 7.55 (s, IH, H-3), 7.59 (d, $J=5.1$ Hz, 1H, H-5), 7.67 (d, $J=5.1$ Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$): δ 39.5 (C-2-CH_2-), 126.1 (C-3), 126.8 (C-5), 133.8 (C-6), 142.5×2 (C-3a, C-4a), 144.5 (C-7a), 144.9 (C-8a), 149.2 (C-2), 172.8 (C-4), 175.5 (C-8); MS *m/z* (relative intensity): 270 ($M^+ + 2$, 20), 268 (M^+, 43), 233 (100); UV λ_{max} (MeOH) nm (log ε): 242 (4.28), 293 (4.16); Anal. calcd for $C_{11}H_5O_2S_2Cl$: C, 49.16; H, 1.88. Found: C, 48.98; H, 1.76.

3-Methyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophen-4,8-dione (17). A solution of the acid chloride (**6**) obtained above in dry 1,2-dichloroethane (50 mL) was added dropwise to a stirred suspension of $AlCl_3$ (14.6 g, 109 mmol) in dry 1,2-dichloroethane (50 mL) maintained at 4 °C. The mixture was allowed to stir at 4 °C for 10 min and a solution of 3-methylthiophene (**16**) (4.9 g, 50 mmol) in 1,2-dichloroethane (25 mL) was slowly added. The yellow suspension was allowed to stir at room temperature for 18 h and was poured into ice and HCl (50 mL, 2 *M*). $CHCl_3$ (300 mL) was added and the mixture was shaken vigorously. The layers were separated and the aqueous layer was extracted with $CHCl_3$. The combined organic portions were washed with saturated $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The resulting yellow mixture was purified by column chromatography (silica gel, benzene) to give the yellow solid **17** (mp 146–147 °C) in a 16% yield. IR (KBr): 1660 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.58 (s, 3H, C-3-CH_3), 7.31 (s, 1H, H-2), 7.60 (d, $J=5.2$ Hz, 1H, H-5), 7.64 (d, $J=5.2$ Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$): 16.0 (C-2-CH_3), 126.3 (C-6), 130.3 (C-2), 133.2 (C-7), 139.2 (C-4a), 140.9 (C-3a), 143.3 (C-7a), 144.4 (C-8a), 146.2 (C-3), 174.6 (C-4), 175.9 (C-8); MS *m/z* (relative intensity): 234 (M^+, 100), 206 (19), 197 (50); UV λ_{max} (MeOH) nm (log ε): 245 (4.23), 281 (4.09); Anal. calcd for $C_{11}H_6O_2S_2$: C, 56.39; H, 2.58. Found: C, 56.45; H, 2.50.

3-Bromomethyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (18). To a solution of compound **17** (1.4 g, 6.0 mmol) and benzoyl peroxide (0.1 g, 0.4 mmol) in dry benzene (30 mL) were added several drops of hydrobromic acid. The mixture was refluxed for 10 min, then *N*-bromosuccinimide (1.2 g, 9.6 mmol) and benzoyl peroxide (0.2 g, 0.8 mmol) were added portionwise. Reflux was then continued for 5 h. After filtration, the dry benzene was removed in vacuum. The residue was purified by column chromatography on silica gel eluting with *n*-hexane:benzene (1:5) to give **18** as a yellow solid (mp 179–180 °C) in a 37% yield. IR (KBr): 1650 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.89 (s, 2H, 3-CH_2-), 7.63 (d, $J=4.9$ Hz, 1H, H-5), 7.69 (d, $J=4.9$ Hz, 1H, H-6), 7.73 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$): δ 26.5 (C-3-CH_2-), 126.4 (C-5), 133.5 (C-2), 133.8 (C-6), 137.6 (C-3a), 140.1 (C-4a), 142.1×2 (C-7a, C-8a), 148.2 (C-3), 174.3 (C-4), 175.2 (C-8); MS *m/z* (relative intensity): 314 ($M^+ + 2$, 9), 312 (M^+, 9), 233 (100); UV λ_{max} (MeOH) nm (log ε): 239 (4.29), 291 (4.17); Anal. calcd for $C_{11}H_5O_2S_2Br$: C, 42.19; H, 1.61. Found: C, 42.30; H, 1,60.

3-Hydroxymethyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione (19). To an aqueous solution of acetone (70%, 65 mL) and silver nitrate (1.4 g, 8.2 mmol) was added compound **18** (0.6 g, 1.9 mmol). The mixture was stirred for 2.5 h at 28–30 °C. After filtration, the filtrate was extracted with diethyl ether. The organic layer was dried, and evaporated. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$:CH_3OH (12:1) to give **19** as a yellow solid (mp 139–140 °C) in a 42% yield. IR (KBr): 1275 (C-O), 1650 (C=O), 3200–3600 (OH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 5.54 (s, 1H, OH), 5.85 (s, 2H, 3-CH_2-), 7.61 (d, $J=5.0$ Hz, 1H, H-5), 8.14 (d, $J=5.0$ Hz, 1H, H-6), 8.24 (s, 1H, H-2); ^{13}C NMR (DMSO-d_6): δ 68.5 (C-3-CH_2-), 126.0 (C-5), 133.3 (C-2), 135.7 (C-6), 135.9×2 (C-7a, C-8a), 136.2 (C-4a), 138.2 (C-3a), 141.7 (C-3), 173.9 (C-4), 174.7 (C-8); MS *m/z* (relative intensity): 250 (M^+, 100), 221 (40); UV λ_{max} (MeOH) nm (log ε): 237 (4.22), 290 (4.16); Anal. calcd for $C_{11}H_6O_3S_2$: C, 52.79: H, 2.42. Found: C, 52.86; H, 2.30.

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