Articles

Studies on the Synthesis of *trans*-Dihydrodiols of Polycyclic Aromatic Thiaarenes as Potential Proximate Carcinogenic Metabolites: First Synthesis of *trans*-10,11-Dihydroxy-10,11-dihydroacenaphtho[1,2-*b*]benzo[*d*]thiophene and 6,7-Dihydroxy-6,7-dihydronaphtho[1,2-*b*]thiophene

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Polyaromatic thiophene compounds are found to occur concomitantly with numerous coal-derived products and shale oils and are suspected mutagens and/or carcinogens. The first synthesis of the two title compounds **9** and **16** has been achieved in five or four steps starting from 8,9-dihydroacenaphtho[1,2-*b*]benzo[*d*]thiophene (**1**) and 7-methoxynaphtho[1,2-*b*]thiophene (**12**), respectively. Compound **1** was converted to the *cis*-diol (**11**) (via treatment with OsO_4/pyridine) or to *trans*-diol (**3**) [via Prevost reaction ($PhCOOAg/I_2$) followed by hydrolysis] in 95−98% yield, respectively. Subsequent dehydration (PTS/benzene) of the diol followed by aromatization of the resulting ketone (**5**) produced the phenolic compound **6** in 97% yield. Oxidation of the phenol with phenyl iododiacetate followed by hydrolysis of the *o*-quinone monoketal **7** gave the *o*-quinone (**8**) in 86% yield. Stereoselective reduction of **8** with $NaBH_4$/EtOH under oxygen afforded *trans*-10,11-dihydroxy-10,11-dihydroacenaphtho[1,2-*b*]benzo[*d*]thiophene(**9)** (orange yellow solid) in 55% yield. Compound **16** was obtained as a colorless solid, through the stereoselective reduction of the *o*-quinone **15** (with $NaBH_4$), which in turn was prepared from **12** following the protocol of functional group transformation of methoxy → phenol → *o*-quinone monoketal → *o*-quinone, as used in the previous case. The yields for all the steps are very good. The mutagenicity assay of compound **9** and **16** as well as their parent thiaarenes have been performed. The results showed that **9** may not be the proximate carcinogen of acenaphtho[1,2-*b*]benzo[*d*]thiophene, while it is likely that compound **16** is one of the possible proximate carcinogens for naphtho[1,2-*b*]thiophene.

Introduction

Polycyclic aromatic hydrocarbons (PAH) and polycyclic aromatic azaarenes (PAA) are widespread environmental contaminants that have been extensively studied with regard to their mutagenic and/or carcinogenic activities.[1] It is well-established that metabolism of PAH to *trans*-dihydrodiols is frequently involved in their activation to mutagens.[2] As a consequence of extensive research on the metabolic activation of PAH, a number of papers have detailed the syntheses[3] of *trans*-dihydrodiols and diol epoxides of carcinogenic PAH. Syntheses have included the metabolites of several PAA's including benzacridines,[4−6] acenaphthoquinolines,[6] and benzoquinolines.[7] Only one synthesis of the *trans*-dihydrodiol of a polycyclic aromatic sulfur compound (PASH) has been reported [8] so far, although the term of "bioisosterism" has been coined for analogous thiophene derivatives.[9] Limited data

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suggest that polyaromatic thiophene derivatives are present together with PAHs in coal-derived products[10] and shale oils.[11] PASHs are mutagenic [12] and have also exhibited carcinogenic activity in laboratory animals.[13] On the basis of the concept of "bioisosterism", acenaphtho[1,2-*b*]benzo[*d*]thiophene would be expected to have pharmacological properties similar to those of benzo[*j*]-fluoranthene. Benzo[*j*]fluoranthene is mutagenic and has considerable tumorigenic activity in laboratory animals.[14] Studies with benzo[*j*]fluoranthene have shown that the 9,10-dihydrodiols contribute to its genotoxic activity.[15] We report herein the first stereoselective synthesis of *trans*-10,11-dihydroxy-10,11-dihydroacenaphtho[1,2-*b*]benzo[*d*]-thiophene (**9**) (a bioisoster of benzo[*j*]fluoranthene) and of *trans*-6,7-dihydroxy-6,7-dihydronaphtho[1,2-*b*]thiophene (**16**) as potential proximate carcinogenic metabolites. Those syntheses start from 8,9-dihydroacenaphtho[1,2-*b*]benzo[*d*]thiophene (**1**)[16] and 7-methoxynaphtho[1,2-*b*]-thiophene (**12**),[17] respectively.

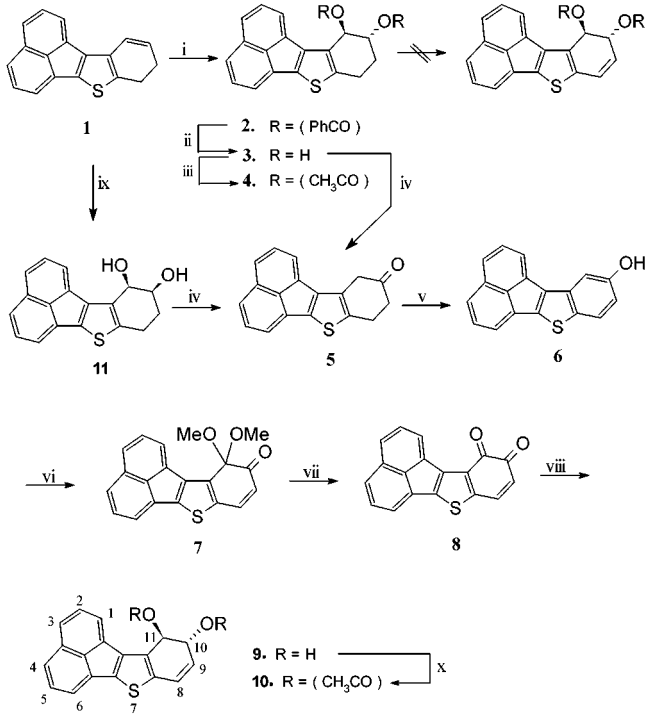
In general, the mutagenicity of PAHs is very indicative of their carcinogenicity. When parent hydrocarbons and their metabolites are assayed comparatively, the results will provide some insight into possible metabolic pathways. Therefore, we tested the mutagenicity of *trans*-10,-11-dihydroxy-10,11-dihydroacenaphtho[1,2-*b*]benzo[*d*]-thiophene (**9**); *trans*-6,7-dihydroxy-6,7-dihydronaphtho[1,2-*b*]thiophene (**16**); their parent thiaarene, acenaphtho[1,2-*b*]benzo[*d*]thiophene; and naphtho[1,2-*b*]thiophene toward *S. typhimurium* strain TA 100.

Results and Discussion

For the synthesis of compound **9** our initial plan was to develop a *trans*-diol functionality via Prevost reaction and then to introduce the unsaturation at position 8. Thus, 8,9-dihydroacenaphtho[1,2-*b*]benzo[*d*]thiophene (**1**), was subjected to Prevost reaction with silver benzoate and iodine in refluxing benzene, which afforded the *trans*-dibenzoate derivative **2** as a yellow solid in 90% yield. Alkaline hydrolysis of the dibenzoate derivative **2** afforded the diol **3** in 98% yield.

On treatment with acetic anhydride/pyridine the diol **3** produced the diacetate derivative **4** in about 98% yield. However, all attempts to dehydrogenate **4** or the dibenzoate derivative **2** with reagents such as (i) DDQ or (ii) *N*-bromosuccinimide, followed by treatment with Li_2CO_3, met with failure.

Scheme 1[a]



[a] Reagents and conditions: (i) $PhCO_2Ag$ (2.4 equiv), I_2 (1.1 equiv), benzene, reflux under argon, 18 h. (ii) KOH, THF, MeOH, H_2O, rt, 2.5 h. (iii) Ac_2O, pyridine, rt, overnight. (iv) PTS, benzene, reflux, 45 min. (v) DDQ, benzene, 90−95 °C, argon, 2 h. (vi) PIDA, MeOH, rt, 5 h. (vii) HCl, AcOH, H_2O, rt, 45 min. (viii) $NaBH_4$, EtOH, rt, oxygen, 12 h. (ix) OsO_4, pyridine, rt, 5 h in dark. (x) Ac_2O, pyridine, 0−5 °C, overnight.

We then directed our efforts toward synthesizing the target molecule via stereoselective reduction of the *o*-quinone derivative. Thus, the *trans*-diol **3** or the *cis*-diol **11** (synthesized in 95% yield by treatment of **1** with OsO_4 in pyridine), on subsequent dehydration (PTS/benzene/reflux) and aromatization (DDQ/benzene/reflux) of the resulting ketone **5**, furnished the 10-hydroxy acenaphtho-[1,2-*b*]benzo[*d*]thiophene (**6**) as a yellow solid in overall excellent yield from the diol. Attempted oxidation of the phenol **6** to ortho quinone **8** with Fremy's salt was unsuccessful. We obtained the *o*-quinone as a dark green solid, in 86% yield, by oxidation[18] of phenol **6** with phenyl iododiacetate (PIDA); this was followed by cleavage of the resulting *o*-quinone monoketal (**7**) with concentrated HCl in acetic acid. Stereoselective reduction[19] of quinone **8** with sodium borohydride in ethanol in an oxygen atmosphere produced the *trans*-dihydrodiol (**9**) in 55% yield. The trans-geometry of the diol moiety was assigned from the $J_{H(10),\ H(11)}$ value (10.3 Hz.) as well as by analogy.[3,4,6,19] It was further characterized by converting it into *trans*-diacetate derivative **10** with Ac_2O and pyridine (Scheme 1).

Following a similar sequence of reactions, *trans*-6,7-dihydroxy-6,7-dihydro-naphtho[1,2-*b*]thiophene (**16**) was synthesized from 7-methoxynaphtho[1,2-*b*]thiophene (**12**) (Scheme 2). Thus, 7-methoxynaphtho[1,2-*b*]thiophene (**12**), subjected to demethylation with BBr_3 in dichloromethane, afforded phenol **13** in 98% yield. On oxidation with PIDA/MeOH, the phenol produced the *o*-quinone

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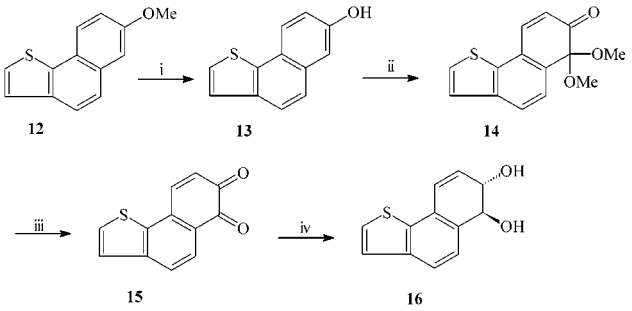
Scheme 2[a]



[a] Reagents and conditions: (i) BBr_3, CH_2Cl_2, rt, 3 h. (ii) PIDA, MeOH, rt, 5 h. (iii) HCl, AcOH, H_2O, rt, 30 min. (iv) $NaBH_4$, EtOH, O_2, 12 h.

Table 1. Mutagenicity Test

test compound	concn, μg/plate	TA100, revertants/ plate	evaluation[a]
DMSO	100	110 ± 5.7	negative
2-aminoacridine	5	858 ± 26	positive
	320	1090 ± 46	positive
acenaphtho[1,2-*b*]-	160	1173 ± 42	positive
benzo[*d*]thiophene	80	969 ± 63	positive
	40	694 ± 38	positive
	20	365 ± 33	positive
	10	186 ± 25	negative
	5	143 ± 2.7	negative
	640	596 ± 48	positive
	320	629 ± 4.5	positive
trans-10,11-dihydroxy-10,11-	160	623 ± 28	positive
dihydroacenaphtho[1,2-*b*]-	80	769 ± 57	positive
benzo[*d*]thiophene	40	625 ± 27	positive
	20	637 ± 23	positive
	10	498 ± 84	positive
	640	117 ± 13	negative
	320	118 ± 3.6	negative
	160	13 ± 7	negative
naphtho[1,2-*b*]thiophene	80	141 ± 7	negative
	40	141 ± 10	negative
	20	128 ± 4.9	negative
	10	130 ± 14	negative
	1280	2.0 ± 1.0	toxic
trans-6,7-dihydroxy-6,7-dihydro-	640	1.3 ± 0.6	toxic
naphtho[1,2-*b*]thiophene	320	1.3 ± 0.6	toxic
	160	76 ± 58	negative
	80	101 ± 9.2	negative
	40	120 ± 2.1	negative
	20	143 ± 15	negative

[a] Positive response (threshold ≥ 2.0 × corresponding solvent).

monoketal **14** as a yellow solid, which was hydrolyzed to the *o*-quinone **15**, as a brick red solid, with 1 N HCl in acetic acid. Reduction of **15** with $NaBH_4$/EtOH under O_2 furnished the *trans*-dihydrodiol (**16**) as a white solid, in 86% yield. All compounds were characterized by the usual spectroscopic data as well as by elemental analysis.

The results of the mutagenicity assays with *trans*-10,-11-dihydroxy-10,11-dihydroacenaphtho[1,2-*b*]benzo[*d*]-thiophene (**9**), *trans*-6,7-dihydroxy-6,7-dihydronaphtho-[1,2-*b*]thiophene (**16**), acenaphtho[1,2-*b*]benzo[*d*]thiophene, and naphtho[1,2-*b*]thiophene are shown in Table 1. Comparison of the mutagenicity of benzo[*j*]fluoranthene reported by LaVoie[20] and that of acenaphtho[1,2-*b*]benzo-[*d*]thiophene suggested that acenaphtho[1,2-*b*]benzo[*d*]-thiophene is more mutagenic. However, the mutagenicity of phenanthrene reported by Oesch[21] appears to be much higher than that of naphtho[1,2-*b*]thiophene. These results suggest that the mutagenicity of PASHs may vary greatly from that of their carbon analogues. At doses above 80 μg per plate, acenaphtho[1,2-*b*]benzo[*d*]thiophene appears to be more mutagenic than its corresponding dihydrodiol (**9**). This suggests that *trans*-10,11-dihydroxy-10,11-dihydroacenaphtho[1,2-*b*]benzo[*d*]thiophene (**9**) may not be the proximate carcinogen of acenaphtho[1,2-*b*]-benzo[*d*]thiophene. On the other hand, naphtho[1,2-*b*]-thiophene shows negative responses at all doses tested. At the same time, *trans*-6,7-dihydroxy-6,7-dihydronaph-tho[1,2-*b*]thiophene (**16**) shows negative response below 160 μg per plate, but is toxic at doses above 320 μg per plate. It is likely that *trans*-6,7-dihydroxy-6,7-dihy-dronaphtho[1,2-*b*]thiophene (**16**) is one of the possible proximate carcinogens, but other metabolic pathways may be involved in its metabolism.

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Experimental Section

All melting points are uncorrected; they were determined in a glass capillary using a sulfuric acid bath. Silver benzoate and DDQ were purchased from Aldrich, while phenyl iododi-acetate and sodium borohydride were purchased from E. Merck. The solvents used were purified and dried as per standard procedures. NMR spectra were recorded on a 300 and 200 MHz NMR spectrometer (except for compound **3**, which was recorded on 90 MHz NMR spectrometer). MS spectra were obtained from CDRI, Lucknow, and RSIC, IIT, Madras, while elemental analyses were obtained from CDRI, Lucknow.

***trans*-10,11-Dibenzoyloxy-8,9,10,11-tetrahydroacenaph-tho[1,2-*b*]benzo[*d*]thiophene (2).** To a suspension of dry silver benzoate (2.53 g, 11.1 mmol) in dry benzene (75 mL) was added iodine (1.3 g, 5.12 mmol), and the mixture was stirred under argon until the color of the iodine disappeared and a white slurry had formed. To this, a solution of compound **1**[16] (1.2 g, 4.62 mmol) in dry benzene (25 mL) was added and the mixture was refluxed with stirring for 18 h in an argon atmosphere. It was then filtered while hot and the residue was washed with a small volume of dry benzene. The combined filtrate was washed successively with 5% sodium thiosulfate solution (1 × 100 mL), cold 5% sodium bicarbonate solution (1 × 100 mL), and finally thoroughly with water. The organic layer was separated and dried (anhydrous Na_2SO_4); the solvent was removed to produce the dibenzoate **2** as a yellow solid (2.1 g, 90.5%): mp 154−155 °C (ether); ^{1}H NMR ($CDCl_3$) δ 2.43−2.52 (m, 2H), 3.10−3.19 (m, 2H), 5.60−5.66 (m, 1H), 6.70 (d, 1H, J = 3.4 Hz), 7.38−7.67 (m, 12H), 7.98−8.08 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$ + CCl_4) δ 22.07, 24.52, 67.34, 70.73, 120.22, 121.67, 125.30, 126.34, 126.64, 127.53, 127.97, 128.42, 129.39, 129.82, 129.96, 130.10, 133.11, 133.25, 133.35, 133.46, 143.72, 143.97, 165.37, 165.87 ppm: IR (KBr) ν_{max} 1706 cm^{-1}; MS (*m*/*z*) 502 (M^+), 105 (B^+). Anal. Calcd for: $C_{32}H_{22}O_4S$: C, 76.49; H, 4.38. Found: C, 76.25; H, 4.21.

***trans*-10,11-Dihydroxy-8,9,10,11-tetrahydroacenaphtho-[1,2-*b*]benzo[*d*]thiophene (3).** To a solution of the dibenzoate **2** (200 mg, 0.398 mmol) in 20 mL of THF and 10 mL of MeOH were added 1 mL of 15% KOH solution and 1.5 mL of water, and the mixture was stirred under argon atmosphere for 2.5 h. The solvent was removed under reduced pressure and the residue was partitioned between water and ethyl acetate. After the usual workup, compound **3** was obtained as a bright yellow solid (115 mg, 98.3%): mp 195−197 °C (ethyl acetate−petroleum ether, 60−80 °C); ^{1}H NMR (90 MHz) (DMSO-d_6) δ 1.75−2.15 (brm, 1H), 2.35−2.50 (m, 1H), 2.70−3.00 (m, 2H), 3.70−4.00 (brm, 1H), 4.50−4.70 (m, 1H), 4.9 (brd, 1H, J = 4.5 Hz), 5.4 (brd, 1H, J = 6.5 Hz), 7.4−7.65 (m, 2H), 7.65−7.80 (m, 3H), 7.93 (d, 1H, J = 6.7 Hz) ppm; IR (KBr) ν_{max} 3300−3600 (br), 3700−3930(br) cm^{-1}. Anal. Calcd for $C_{18}H_{14}O_2S$: C, 73.47; H, 4.76. Found: C, 73.25; H, 4.55.

***cis*-10,11-Dihydroxy-8,9,10,11-tetrahydroacenaphtho-[1,2-*b*]benzo[*d*]thiophene (11).** To a solution of **1** (820 mg,

3.15 mmol) in 30 mL dry pyridine was added a solution of OsO_4 (945 mg, 3.72 mmol) in 5 mL of dry pyridine dropwise with stirring. Stirring was continued at 25 °C in the dark for 5 h. The mixture was then poured into a saturated solution of $NaHSO_3$, stirred overnight, and extracted with ethyl acetate, and the extracts were washed first with ice-cold 1 N HCl and then with water. The organic layer was collected and dried (anhydrous Na_2SO_4), and the solvent was evaporated. The *cis*-diol **11** was obtained as a bright yellow solid (880 mg, 94.9%): mp 204−206 °C (ethyl acetate); ^{1}H NMR (DMSO-d_6) δ 1.70−1.90 (brm, 1H), 1.95−2.15 (brm, 1H), 2.50−3.04 (brm, 2H), 3.80−3.95 (brm, 1H), 4.70 (d, 1H, J = 5.4 Hz, exchangeable with D_2O), 4.72−4.80 (m, 1H), 5.07 (d, 1H, J = 6.7 Hz, exchangeable with D_2O), 7.51−7.61 (m, 2H), 7.73(d, 1H), 7.79 (d, 2H, J = 8.2 Hz), 7.96 (d, 1H, J = 6.7 Hz) ppm; IR (KBr) ν_{max} 3250−3400 (br) cm^{-1}; MS (*m*/*z*) 294 (M$^+$). Anal. Calcd for $C_{18}H_{14}O_2S$: C, 73.47; H, 4.76. Found: C, 73.34; H, 4.52.

***trans*-10,11-Diacetoxy-8,9,10,11-tetrahydroacenaphtho[1,2-*b*]benzo[*d*]thiophene (4).** A mixture of the diol **3** (114 mg, 0.388 mmol), dry pyridine (0.8 mL), and acetic anhydride (4−5 mL) was stirred at room temperature overnight, protected from moisture. The solvent was removed under reduced pressure, then crushed ice was added and the aqueous layer was extracted with ethyl acetate. The organic layer was successively washed thoroughly with ice-cold 0.5 N HCl, 5% $NaHCO_3$ solution and water. After drying (anhydrous Na_2SO_4) and removal of the solvent, the resulting crude diacetate obtained was redissolved in benzene and filtered through a column of silica gel. Removal of the solvent furnished compound **4** as a deep yellow solid (145 mg, 98.4%): mp 185−186 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3H), 2.11 (s, 3H), 2.17−2.35 (m, 2H), 2.96−3.02 (m, 2H), 5.26−5.31 (m, 1H), 6.31 (d, 1H, J = 3.1 Hz), 7.46−7.59 (m, 3H), 7.65 (d, 1H, J = 6.3 Hz), 7.72 (d, 1H, J = 7.8 Hz), 7.73 (d, 1H, J = 8.1 Hz) ppm; IR (KBr) ν_{max} 1738 cm^{-1}. Anal. Calcd for: $C_{22}H_{18}O_4S$: C, 69.84; H, 4.76. Found: C, 69.53; H, 4.49.

10-Oxo-8,9,10,11-tetrahydroacenaphtho[1,2-*b*]benzo[*d*]thiophene (5). A solution of the diol **11** (910 mg) in 250 mL of dry benzene was refluxed with *p*-toluenesulfonic acid (30−40 mg) for 45 min using a Dean−Stark water separator. After the usual workup the crude product was purified by column chromatography (neutral alumina). Elution with benzene−petroleum ether 60−80 °C (4:1) afforded ketone **5** as a deep yellow solid (800 mg, 93.7%): mp 192−194 °C (benzene−petroleum ether, 60−80 °C) (From *trans*-diol **2**, the yield of ketone **5** was 77%); ^{1}H NMR ($CDCl_3$) δ 2.82 (t, 2H, J = 6.8 Hz), 3.26 (t, 2H, J = 6.8 Hz), 3.78 (s, 2H), 7.47−7.59 (m, 3H), 7.66 (d, 1H, J = 6.6 Hz), 7.73 (d, 1H, J = 7.7 Hz), 7.74 (d, 1H, J = 8.0 Hz) ppm; ^{13}C NMR ($CDCl_3$ + CCl_4) δ 24.94, 39.15, 39.57, 120.27, 120.42, 126.32, 126.45, 127.29, 127.46, 127.64, 129.32, 132.86, 133.44, 133.60, 137.18, 139.44, 143.33, 207.29 ppm; IR (KBr) ν_{max} 1706 cm^{-1}; MS (*m*/*z*) 276 (M$^+$), 248 (M − CO). Anal. Calcd for $C_{18}H_{12}OS$: C, 78.26; H, 4.35. Found: C, 78.11; H, 4.20.

10-Hydroxyacenaphtho[1,2-*b*]benzo[*d*]thiophene (6). To a solution of the ketone **5** (180 mg, 0.65 mmol) in dry benzene (10 mL) was added DDQ (163 mg, 0.72 mmol) and the mixture refluxed in an oil bath at 90−95 °C for 2 h under argon. After cooling to room temperature the reaction mixture was washed with 5% Na_2CO_3 solution and then several times with water. The benzene layer was collected and dried (Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography (neutral Al_2O_3). Elution with petroleum ether (60−80 °C)−ethyl acetate mixture (9:1) furnished compound **6** as a yellow solid (174 mg, 97.4%): mp 214−215 °C; ^{1} H NMR ($CDCl_3$) δ 4.90 (brs, 1H), 6.87 (dd, 1H, J = 2.4 and 8.8 Hz), 7.51−7.59 (m, 3H), 7.67−7.80 (m, 3H), 7.73 (d, 1H, J = 8.8 Hz), 7.89 (d, 1H, J = 6.7 Hz) ppm; IR (KBr) ν_{max} 3300 (br) cm^{-1}; MS (*m*/*z*) 274 (M$^+$), 245. Anal. Calcd for $C_{18}H_{10}OS$: C, 78.83; H, 3.65. Found: C, 78.55; H, 3.40.

11,11-Dimethoxy-10-oxo-10,11-dihydroacenaphtho[1,2-*b*]benzo[*d*]thiophene (7). To a stirred solution of phenol **6** (67 mg, 0.245 mmol) in dry methanol (30 mL) was added phenyl iododiacetate (PIDA) (157 mg, 0.489 mmol). Stirring was continued under argon for 5 h. The solvent was then removed in a rotary evaporator, and the residue was subjected to column chromatography (neutral Al_2O_3). Elution with petroleum ether (60−80 °C)−ethyl acetate mixture (9:1) afforded compound **7** as a yellow solid (50 mg, 61.2%): mp 123−125 °C; ^{1}H NMR ($CDCl_3$) δ 3.41 (s, 6H), 6.01 (d, 1H, J = 9.9 Hz), 7.30 (d, 1H, J = 9.9 Hz), 7.55−7.66 (m, 2H), 7.74−7.84 (m, 3H), 8.15 (d, 1H, J = 6.9 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 29.85, 51.85, 99.46, 121.26, 121.72, 124.86, 127.15, 127.60, 127.85, 128.39, 129.52, 132.32, 133.91, 136.32, 137.09, 137.30, 144.57, 146.23, 195.77 ppm; IR (KBr) ν_{max} 1663 cm^{-1}. Anal. Calcd for $C_{20}H_{14}O_3S$: C, 71.86; H, 4.19. Found: C, 71.59; H, 3.98.

10,11-Dioxo-10,11-dihydroacenaphtho[1,2-*b*]benzo[*d*]-thiophene (8). To a solution of compound **7** (40 mg, 0.12 mmol) in acetic acid (3−4 mL) were added 3−4 drops of water and 1−2 drops of concentrated HCl. The mixture was stirred at room temperature for about 45 min. It was then poured into ice water (∼10 mL) and filtered. The quinone was obtained as a dark green solid (30 mg, 85.7%): ^{1}H NMR (DMSO-d_6) δ 6.15 (d,1H, J = 10.0 Hz), 7.39 (d, 1H, J = 10.0 Hz), 7.50−7.63 (m, 2H), 7.77 (d, 1H, J = 6.8 Hz), 7.83 (d, 2H, J = 8.3 Hz), 8.49 (d, 1H, J = 6.9 Hz) ppm; IR (KBr) ν_{max}1648, 1723 cm^{-1}; MS (*m*/*z*) 288 (M$^+$), 260. Anal. Calcd for $C_{18}H_8O_2S$: C, 75.00; H, 2.78. Found: C, 74.68; H, 2.52.

10,11-Dihydroxy-10,11-dihydroacenaphtho[1,2-*b*]benzo[*d*]thiophene (9). To a stirred suspension of the quinone **8** (50 mg, 0.174 mmol) in ethanol (30 mL) under oxygen was added sodium borohydride (79 mg, 2.12 mmol) in four batches over a period of 1 h. Stirring was continued for 12 h at room temperature with slow bubbling of oxygen. The solvent was removed under reduced pressure, and the residue was extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried (anhydrous Na_2SO_4). The solvent was removed under reduced pressure. The crude product thus obtained was purified by preparative TLC (silica gel/ethyl acetate−benzene, 1:1) to afford compound **9** as an orange yellow solid (28 mg, 55.2%): mp 190−192 °C; ^{1}H NMR (DMSO-d_6 + $CDCl_3$) δ 4.39 (brd, 1H, J = 4.8 Hz, exchangeable with D_2O), 4.40−4.60 [m, 1H, changed to a triplet of doublet (J = 2.5 and 10.3 Hz) when treated with D_2O], 4.63 (brd, 1H, J = 5.1 Hz, exchangeable with D_2O), 4.97 (dd, 1H, J = 5.1 and 10.3 Hz, changed to doublet, J = 10.3 Hz, when treated with D_2O), 5.79 (dd, 1H, J = 2.7 and 9.8 Hz), 6.25 (dd, 1H, J = 2.4 and 9.8 Hz), 7.31−7.42 (m, 2H), 7.45−7.57 (m, 3H), 8.07 (d, 1H, J = 6.7 Hz) ppm; IR (KBr) ν_{max} 3270(br), 3403(br). Anal. Calcd for $C_{18}H_{12}O_2S$: C, 73.97; H, 4.11. Found: C, 73.62; H, 3.82.

***trans*-10,11-Diacetoxy-10,11-dihydroacenaphtho[1,2-*b*]-benzo[*d*]thiophene (10).** On reaction of 20 mg (0.068 mmol) of the dihydrodiol **9** with Ac_2O (1 mL) and pyridine (1 drop) at 0−5 °C overnight, and after the usual workup and purification [preparative TLC/silica gel, petroleum ether (60−80 °C)−benzene, 1:1], the diacetate was obtained as a yellow solid (15 mg, 58.3%): mp 175−177 °C [benzene−petroleum ether (60−80 °C)]; ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3H), 2.08 (s, 3H), 5.47 (dd, 1H, J = 2.0 and 5.3 Hz), 6.04 (dd, 1H, J = 5.3 and 9.7 Hz), 6.55 (d, 1H, J = 2.0 Hz), 6.80 (d, 1H, J = 9.7 Hz), 7.50−7.60 (m, 2H), 7.71 (d, 1H, J = 6.7 Hz), 7.77 (d, 2H, J = 8.0 Hz), 7.88 (d, 1H, J = 6.8 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 20.93, 29.66, 66.49, 69.04, 120.18, 122.28, 124.54, 125.27, 126.79, 126.93, 127.70, 127.92, 129.37, 132.62, 132.92, 133.41, 139.44, 140.51, 144.14, 169.93, 170.05 ppm; IR (KBr) ν_{max} 1732 cm^{-1}; FAB MS 376.3 (M$^+$), 316.2. Anal. Calcd for $C_{22}H_{16}O_4S$: C, 70.21; H, 4.26. Found: C, 70.05; H, 4.07.

7-Hydroxynaphtho[1,2-*b*]thiophene (13). To an ice-cooled solution of **12** (690 mg, 3.22 mmol) in dry dichloromethane (60 mL) was added a 1 M solution of BBr_3 in dichloromethane (8 mL) dropwise. It was then allowed to attain room temperature and stirring was continued for 3 h. The reaction mixture was then quenched with 1−2 drops of 1 N HCl and stirred at 5−10 °C for 10 min, water was added, and extraction with ethyl acetate followed. The organic layer was washed several times with water and dried (Na_2SO_4). The solvent was removed to furnish phenol **13** (630 mg, 98%). It was recrystallized from ethyl acetate−petroleum ether (60−

80 °C) to produce the pure phenol as a white solid: mp 138−140 °C; ^{1}H NMR ($CDCl_3$) δ 5.13 (brs, 1H), 7.20 (dd, 1H, J = 2.5 Hz and 8.8 Hz), 7.26 (d, 1H, J = 2.5 Hz), 7.41 (s, 2H), 7.58-(d, 1H, J = 8.6 Hz), 7.77 (d, 1H, J = 8.6 Hz), 8.04 (d, 1H, J = 8.8 Hz) ppm; IR (KBr) ν_{max} 3258 (br) cm^{-1}. Anal. Calcd for $C_{12}H_8OS$: C, 72.00; H, 4.00. Found: C, 71.86; H, 3.88.

6,6-Dimethoxy-7-oxo-6,7-dihydronaphtho[1,2-*b*]-thiophene (14). A mixture of the phenol **13** (220 mg, 1.1 mmol) and PIDA (710 mg, 2.2 mmol) in dry methanol was stirred under argon for 5 h. Removal of the solvent in a rotary evaporator, followed by purification of the residue by column chromatography [neutral alumina Al_2O_3/petroleum ether (60−80 °C)−ethyl acetate (9:1)] afforded the *o*-quinone monoketal **14** as a bright yellow solid (200 mg, 70%): mp 93−95 °C; ^{1}H NMR ($CDCl_3$) δ 3.30(s, 6H), 6.26(d, 1H, J = 10 Hz), 7.40 (d, 1H, J = 5.4 Hz), 7.54(d, 1H, J = 5.4 Hz), 7.63(d, 1H, J = 10 Hz), 7.74 (d, 1H, J = 8.2 Hz), 7.89 (d, 1H, J = 8.2 Hz) ppm; IR (KBr) ν_{max}: 1676 cm^{-1}; MS (*m*/*z*) 260 (M$^+$), 229, 201(B$^+$). Anal. Calcd for $C_{14}H_{12}O_3S$: C, 64.62; H, 4.62. Found: C, 64.50; H, 4.43.

6,7-Dioxo-6,7-dihydronaphtho[1,2-*b*]thiophene (15). To a solution of **14** (160 mg, 0.62 mmol) in acetic acid (4 mL) were added 3−4 drops of 1 N HCl, and the mixture was stirred at room temperature for 30 min. Upon pouring into ice water (10 mL) quinone **15** (brick red solid) precipitated, which was filtered, thoroughly washed with water, and dried to yield 80 mg (61%): mp 200−202 °C; ^{1}H NMR ($CDCl_3$) δ 6.53 (d, 1H, J = 10.1 Hz), 7.66 (d, 1H, J = 5.4 Hz), 7.84 (d, 1H, J = 10.1 Hz), 7.96 (d, 1H, J = 8.2 Hz), 8.03 (d, 1H, J = 8.2 Hz), 8.20 (d, 1H, J = 5.4 Hz) ppm; IR (KBr) ν_{max} 1655 cm^{-1}; MS (*m*/*z*) 214 (M$^+$), 184 (B$^+$). Anal. Calcd for $C_{12}H_6O_2S$: C, 67.29; H, 2.80. Found: C, 66.95; H, 2.55.

***trans*-6,7-Dihydroxy-6,7-dihydronaphtho[1,2-*b*]-thiophene (16).** To a mixture of the quinone **15** (80 mg, 0.37 mmol) in ethanol (50 mL) under oxygen was added sodium borohydride (170 mg, 12 mmol)in three to four batches within 1 h. Stirring was continued for 12 h. The solvent was evaporated under reduced pressure. Water (10 mL) was added and the solution was extracted with ethyl acetate. The organic layer was washed thoroughly with brine and dried (Na_2SO_4) and the solvent removed. The crude dihydrodiol thus obtained was purified by recrystallization from ethyl acetate−petroleum ether mixture to furnish compound **16** as a white solid (70 mg, 86%): mp 168−170° C; ^{1}H NMR ($CDCl_3$) δ 4.29 (brs, 1H), 4.49 (brd, 1H, J = 11.0 Hz), 4.60 (brs, 1H), 4.85 (brd, 1H, J = 11.0 Hz), 6.09 (dd, 1H, J = 2.2 and 9.8 Hz), 6.55 (dd, 1H, J = 2.3 and 9.8 Hz), 7.24 (d, 1H, J = 5.4 Hz), 7.34 (d, 1H, J = 5.4 Hz), 7.59 (d, 1H, J = 8.1 Hz), 7.63 (d, 1H, J = 8.1 Hz) ppm; IR (KBr) ν_{max} 3333 (br) cm^{-1}. Anal. Calcd for $C_{12}H_{10}O_2S$: C, 66.06; H, 4.59. Found: C, 65.81; H, 4.31.

Mutagenicity Assays. Each compound was dissolved in dimethyl sulfoxide. *S. typhimurium* strain TA 100 was used for the mutagenicity assays with preincubation.[22,23] Cytotoxicity was determined by reduction of colonies in nutrient agar plates. Naphtho[1,2-*b*]thiophene was toxic above 320 μg/plate. Reported mutagenicity values are the means of triplicate assays. Background revertants (110/plate) have not been subtracted.

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