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Molecular recognition: studies on the synthesis of some bis thiophene carboxamide derivatives as ditopic receptors for long chain dicarboxylic acids

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Abstract—New molecular receptors **6**, **7** and **8** with diphenyl ether/diphenyl sulphide as spacer having functional groups complementary to long chain dicarboxylic acids have been developed. Binding studies with different dicarboxylic acids showed high association constants with the receptor **6**.

The science of assembling heterocyclic rings has made enormous strides in recent years. The proper arrangement of such assemblies has generated novel molecular species such as molecular clefts, molecular knots, heterohelicenes, molecular cavities.[1] Supramolecular chemistry[2–5] based on molecular recognition has added a new dimension to chemistry and stereochemistry and is a fast growing subject. It has potential application in different areas like (i) drug design and targeted drug delivery,[6] (ii) synthesis of enzyme models and artificial enzymes,[7] (iii) development of molecular sensors[8] etc. During the last decade, considerable efforts directed toward modeling biological non-covalent binding in chemical systems, resulted in the synthesis of numerous artificial receptors and also the development of innovative approaches for the generation of selective non-covalent binders.[9] Both mono- and dicarboxylic acids and carboxylates are important targets in the area of molecular recognition because a large number of antibiotics, analgesics, anti-inflammatory agents and other biologically active molecules, e.g. folic acid, bile acid, prostaglandin, billirubin, etc. contain the carboxylic acid moiety. Di- and tri-carboxylates are essential components of numerous metabolic processes, including for instance, the citric acid glyoxalate cycle.[10] The binding of carboxyl or carboxylate groups is involved in many biological recognition process such as peptide recognition[11] by Vancomycin (in which amide-carboxylate binding is crucial) and biotin dependent carboxylate catalyzed reactions (which proceed through a carboxylated enzyme complex intermediate in which the covalently bound biotinyl prosthetic group acts as a mobile carboxyl carrier between the remote catalytic sites).[12]

Thus the host–guest complexation studies of the carboxylic acids and their derivatives with suitable receptors are of prime importance to mimic the biochemical process. As a result of this during the last decade, a large number of synthetic receptors, with hydrogen bonding groups, have been designed by various workers[13–15] to recognize suitable mono- and bis- dicarboxylic acids and their derivatives. The hydrogen bonding groups include, simple amides and phosphamides,[12] urea derivatives,[13,14] and amides derived from amino pyridines.[15] We have designed one of the more promising types of ditopic receptor molecule in the form of clip shaped forceps where the oxygen/sulphur atom is the pivot directing the guest molecule through the array of benzene and thiophene rings having amide functionalities at the end for proper complementary hydrogen bonding.

Here we report the synthesis and their binding studies of some bisthiophene-5-carboxamide derivatives **6**(**a**,**b**) and **7**(**a**,**b**) and **8**(**a**,**b**) as novel receptors for long chain dicarboxylic acids, where diphenyl ether or diphenyl sulphide moiety has been used as a spacer between the two-thiophene units. The molecules are designed for the selective recognition of dicarboxylic acids. Based on DTMM[16] energy minimization calculation, it has been found that suberic acid, benzene-1,3-dipropanoic acid and benzene-1,3-dibutanoic acid may fit into the cavities of our designed receptors. The distances between the two amide protons and the two pyridine nitrogen atoms in receptor **6a** are 12.51 and 14.59 Å, respectively (Fig. 1) while the distances between the amide protons for **7a** and **8a** are 12.42 and 16.02 Å, respectively.

The compounds have been synthesized in six steps starting from diphenylether (**1a**) or diphenylsulphide (**1b**). Friedel Craft acylation of **1a** with an excess of acetyl

Keywords: dicarboxylic acids; diphenyl ether; diphenyl sulphide; host–guest complexation.

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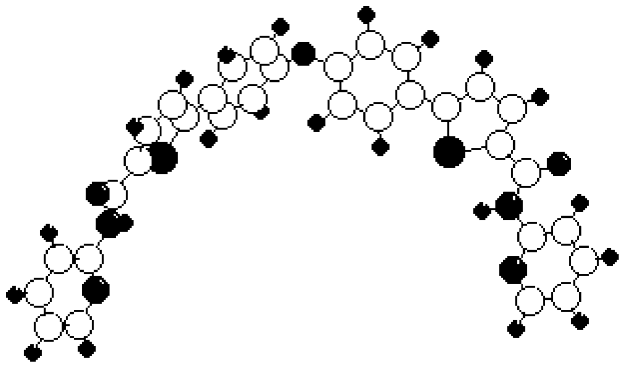


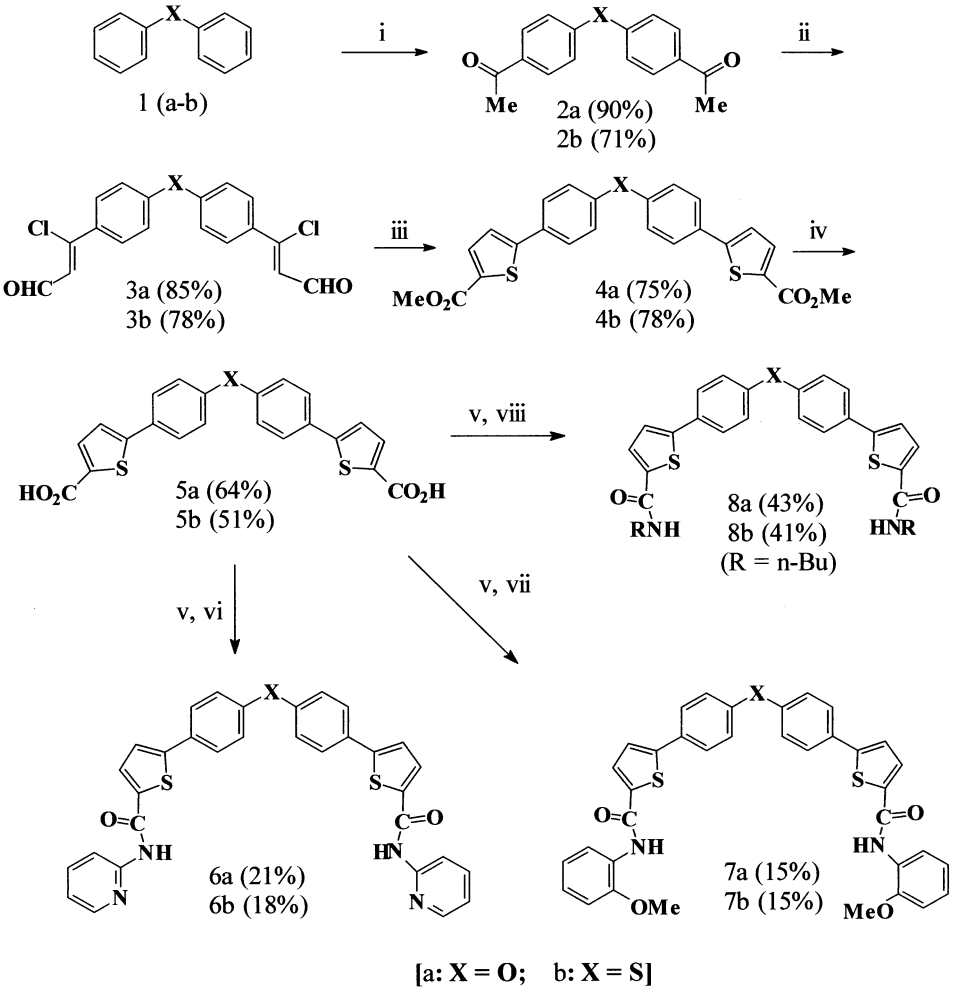
Figure 1. DTMM energy minimised structure of receptor **6a**.

chloride/anhydrous $AlCl_3$ produced the diketone **2a** in 90% yield (Scheme 1).

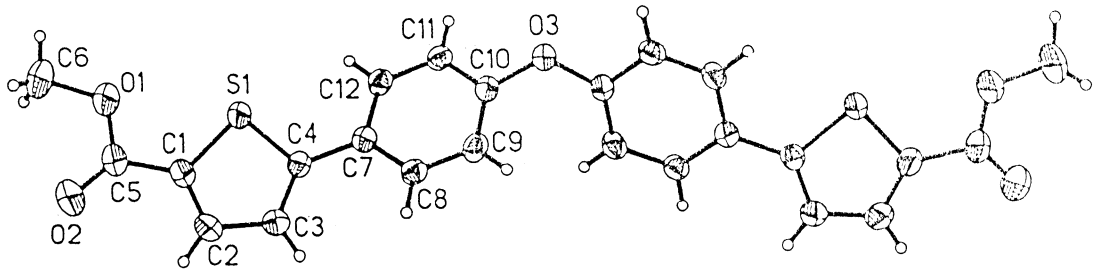
The diketone **2a** on treatment with $POCl_3$/DMF at 0–5°C for 4–5 days afforded the bis-chloroaldehyde 4,4′-bis (1-chloro-2-formylethenyl)phenylether (**3a**) as a light yellow solid in excellent yield. Under identical condition compound **3b** was obtained in 78% yield from **2b**, which in turn was prepared from diphenyl sulphide (**1b**) using Friedel Craft's acylation reaction as used for the synthesis of **2a**.

The bis-chloroaldehydes **3a** or **3b** separately on condensation with ~2 equiv. of methyl thioglycolate/Et_3N in pyridine followed by ring closure with 50% KOH produced the bis thiophene-5-carboxylic ester derivatives **4a** and **4b**, respectively. Subsequent hydrolysis with aqueous ethanolic KOH produced bis acid **5** in 64–69% yield. Reaction of the bis acids (**5**) with oxalyl chloride afforded the bis acid chloride derivative which on subsequent treatment with two equivalents of 2-amino pyridine and Et_3N in CH_2Cl_2 resulted in the formation of the receptor **6** in moderate yield. Following a similar sequence, reaction of **5** with *o*-anisidine or *n*-butyl amine afforded the bisthiophene carboxamide derivatives **7** and **8**, respectively. All the compounds have been characterized by the usual spectroscopic methods as well as by analysis. In addition the structure of compound **4a** and **4b** has also been confirmed by X-ray crystallographic studies (Fig. 2).[17]

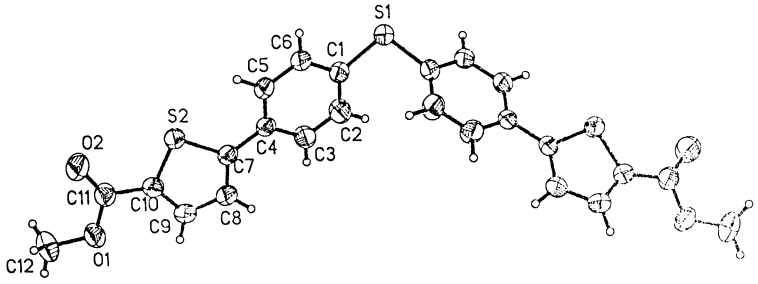
Association constants (K_a)[14] for different dicarboxylic acids with receptor **6a** or **6b** were evaluated by NMR titration[18] in



Scheme 1. *Reagents and conditions:* (i) CH_3COCl, anhyd. $AlCl_3$, CS_2, rt, overnight then reflux, 2 h. (ii) $POCl_3$, DMF, 0–5°C, 5 days. (iii) Methyl thioglycolate, pyridine, Et_3N, 50°C, 45 min, then KOH (50%), 20 min. (iv) KOH, EtOH–H_2O, reflux, 5–6 h. (v) Oxalyl chloride, DMF (cat.), CH_2Cl_2, rt, overnight. (vi) 2-Aminopyridine, Et_3N, CH_2Cl_2, rt, 24 h, then reflux, 2 h. (vii) *o*-Anisidine, Et_3N, CH_2Cl_2, rt, 24 h, then reflux, 2 h. (viii) *n*-Butylamine, Et_3N, CH_2Cl_2, rt, 24 h.



4a



4b

Figure 2. ORTEP diagrams of compound **4a** and **4b** derived from X-ray crystallographic data.

dry $CDCl_3$ at 298 K by adding increasing amounts of guest in dry $CDCl_3$ containing ~2% DMSO-d_6 (Table 1). From the ^{1}H NMR spectra, it was observed that the NH resonance of **6a** and **6b** showed a downfield chemical shift upon addition of the guest. But the effect of addition of these acids to the receptor **7a**, **7b**, **8a** or **8b** led to no change of NH resonance. Thus receptor **6a** form strong complexes (Fig. 3) with all three dicarboxylic acids (K_a 10^2–10^3 M^{-1}) (Table 1) however complexation between receptor **6a** and suberic acid was found to be maximum (K_a=5.87×103 M^{-1}). This was expected as in receptor **6a**, suberic acid is well arranged with hydrogen bonding sites into the cavity compared to other dicarboxylic acids (as per DTMM energy minimization study, Fig. 4). Receptor **6b** also forms strong host–guest complex with these acids (K_a from 10^2–10^3 M^{-1}) (Table 1) though the binding of **6b** with the guest carboxylic acids are slightly lower as compared to that of host **6a**. However, receptors **7** or **8** could not take part in recognition even though they have four binding centers, it has no basic hydrogen bonding acceptor site (as in **6**) in the form of amidopyridine. Thus, once again it is proved that the positioning of pyridine amides by a suitable spacer is important for binding dicarboxylic acids.

Table 1. Binding constants of receptor **6** and dicarboxylic acids

Dicarboxylic acid	Receptor	Association constant K_a (at 25°C), M^{-1}	ΔG^a at 25°C, kcal mol^{-1}
Suberic acid	**6a**	5.87×10^3	−5.12
	6b	3.14×10^3	−4.75
Benzene-1,3-dipropanoic acid	**6a**	2.34×10^3	−4.58
	6b	1.79×10^3	−4.42
Benzene-1,3-dibutanoic acid	**6a**	7.45×10^2	−3.90
	6b	5.26×10^2	−3.69

[a] ΔG was calculated from the relation $\Delta G=-RT \ln K_a$.

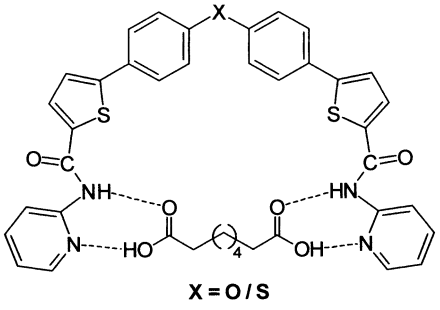


Figure 3. Possible mode of complexation of **6**(**a**,**b**) with suberic acid.

^{1}H NMR titrations with the host **6** were carried out by increasing addition of a solution of the guest dicarboxylic

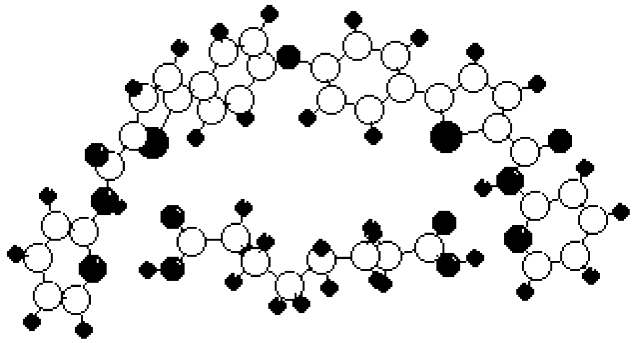


Figure 4. DTMM energy minimised structure of receptor **6a** with suberic acid.

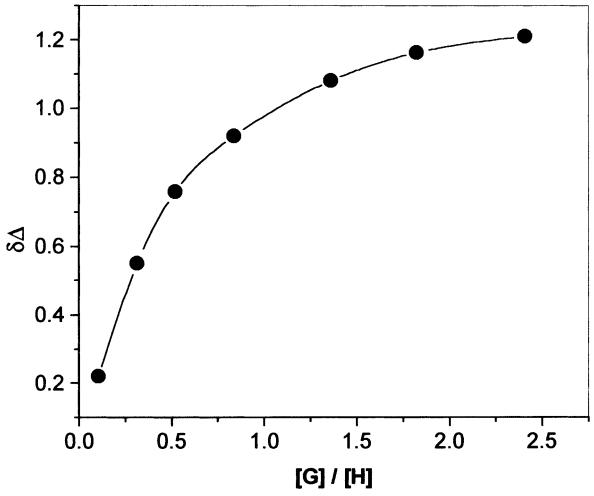


Figure 5. ^{1}H NMR titration curve for suberic acid with receptor **6a**.

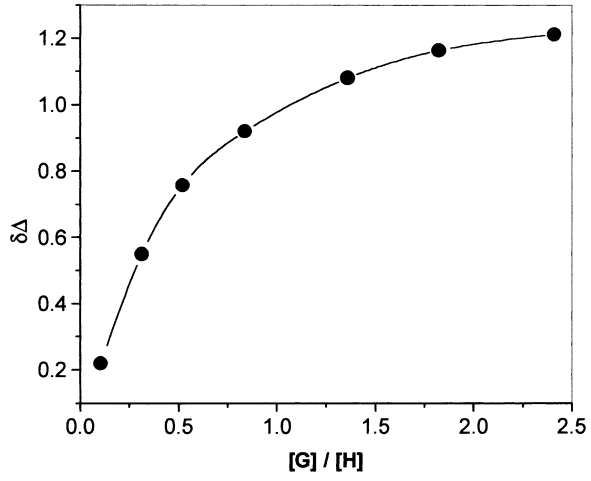


Figure 6. ^{1}H NMR titration curve for suberic acid with receptor **6b**.

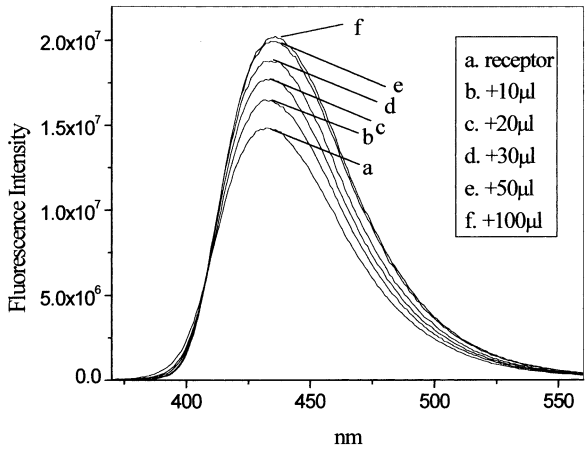


Figure 7. Fluorescence titration spectra of **6a** at excitation at 330 nm with suberic acid at 25°C.

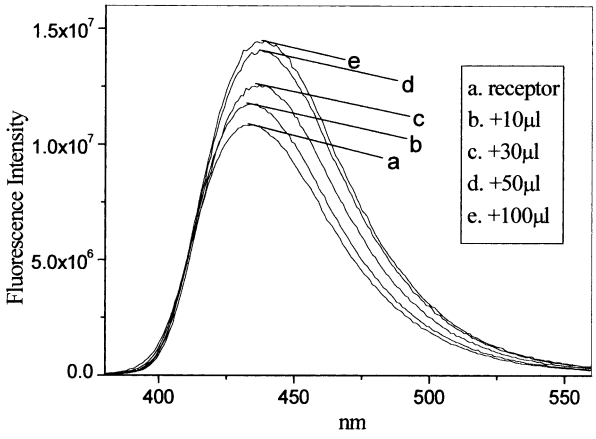


Figure 8. Fluorescence titration spectra of **6b** at excitation at 330 nm with suberic acid at 25°C.

acid (in dry $CDCl_3$ containing about 2% of DMSO-d_6) to a solution of **6** (in dry $CDCl_3$) followed by recording the NMR spectra after each addition. Such addition was continued until the complexation is completed, i.e. no further change of the amide proton was observed. The chemical shift for the amide protons of **6a** and **6b** at the saturation point was δ=9.43 and 9.36 ppm, respectively. The change in chemical shift ($\Delta\delta$) values were calculated by subtracting the chemical shift at each titration point from the chemical shift value of pure host. Thus a titration curve of $\Delta\delta$ vs concentration ratio of guest [*G*] and host [*H*] is plotted (Figs. 5 and 6).

Integration of the proton signals of the 1:1 complex in the ^{1}H NMR spectrum as well as the break in the titration curve (Fig. 5) ($\Delta\delta$ vs [*G*]/[*H*])[18] at 1.0 establishes a 1:1 stoichiometry for the dicarboxylic acid with **6**. We have also studied the fluorescence spectra of the host molecules **6** and also the influence of the guest molecules in spectral shifts. The fluorescence titrations were carried out by successive addition of guest solution (in $CHCl_3$ containing 2% dry DMSO) to the solution of receptor (in $CHCl_3$). The solution of receptor **6** was excited at 330 nm with the emission being monitored at 433 and 435 nm, respectively for **6a** and **6b**.

Here also a higher affinity for suberic acid was noted with a considerable change in the fluorescence intensity (Figs. 7 and 8). Binding constant (K_a)[19] was calculated from the titration curve (a plot of emission intensity against the concentration of suberic acid) and was found to be 3.45×10^3 and 1.47×10^3 M^{-1}, respectively for receptor **6a** and **6b**. Results are consistent with the binding data obtained from ^{1}H NMR titration experiments.

Thus, we have succeeded in the synthesis of an artificial receptor based on pivotal ether or thioether linkage, hinged with two symmetrical arms of *p*-substituted phenyl with thiophene moiety as core structure; by fine tuning these molecules with amide functionalities, we are able to demonstrate that these synthetic receptors can form strong complexes with appropriate dicarboxylic acids. Although there are many reports of amido pyridine derivatives as carboxylic acid binders,[15] to our knowledge, this type of host without rigid spacer units has not been previously investigated.

1. Experimental

1.1. General

All melting points are uncorrected and recorded in one-side open glass capillaries using a sulphuric acid bath. Solvents and reagents were used as obtained from commercial suppliers or purified according to standard procedures. NMR spectra were recorded on 200, 300 and 500 MHz Bruker spectrometer in $CDCl_3$ (dried with 4 Å molecular sieves) or DMSO-d_6 as solvent with TMS as an internal standard. Coupling constant (J) values are given in Hz. IR spectra were recorded on a Perkin–Elmer 800 machine. Mass spectral and elemental analysis values were obtained from CDRI, Lucknow. Yields of the products refer to spectroscopically homogeneous substances.

1.2. Genearal method for the synthesis of 2 (a, b)

To a stirred solution of **1** (34 mmol) and acetyl chloride (7.3 mL, 102 mmol) in dry carbon disulfide (75 mL), anhydrous $AlCl_3$ (18.2 g, 136 mmol) was added in four batches at 0–5°C. The reaction mixture was allowed to reach room temperature gradually and then stirred at this temperature overnight. Then it was refluxed for 2 h, cooled to room temperature and poured in crushed ice with stirring. The aqueous layer was extracted with $CHCl_3$. The organic layer was successively washed with water and then dried over anhydrous Na_2SO_4. Removal of solvent afforded the crude product **2**. The crude product thus obtained was recrystallized from $CHCl_3$–petroleum ether (60–80°C) mixture to furnish the diketone as a white solid in 71–90% yield.

1.2.1. 4,4′-Diacetylphenyl ether (2a). White solid, mp 89–91°C; yield 90%; IR (KBr) ν_{max} 1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60 (s, 6H), 7.08 (dd, 4H, J=1.9, 6.9 Hz), 7.98 (dd, 4H, J=1.9, 6.9 Hz) ppm. Anal Calcd for $C_{16}H_{14}O_3$: C, 75.59; H, 5.51. Found: C, 75.31; H, 5.36.

1.2.2. 4,4′-Diacetylphenylsulphide (2b). White solid, mp 88–90°C; yield 71%; IR (KBr) ν_{max} 1674 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.59 (s, 6H), 7.41 (ddd merged to td, 4H, J=1.9, 8.5 Hz), 7.90 (ddd merged to td, 4H, J=1.9, 8.5 Hz) ppm. Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.11; H, 5.18. Found: C, 70.85; H, 4.89.

1.3. General method for the synthesis of 3 (a, b)

To an ice cooled solution of DMF (3 mL), $POCl_3$ (0.66 mL, 7.24 mmol) was added dropwise and stirred at 0°C for 10 min. To this stirred solution at 0–5°C, a solution of the ketone **2** (1.8 mmol) in DMF (2–3 mL) was injected slowly. Stirring was continued at 0–5°C for 2 h and then left in the fridge (~4°C) for five days with occasional shaking. Then the reaction mixture was decomposed with an excess of ice-cold sodium acetate solution and extracted with CH_2Cl_2. The organic layer was washed with water, $NaHCO_3$ (5%) solution and finally thoroughly with water and then dried (anhydrous Na_2SO_4). Removal of solvent under reduced pressure afforded compound **3** as a reddish brown oil, which solidified on standing. The crude product thus obtained was recrystallized from CH_2Cl_2–diethyl ether mixture to furnish **3** as a yellow solid.

1.3.1. 4,4′-Bis (1-chloro-2-formylethenyl)phenylether (3a). Yellow solid, mp 120–121°C, yield 85%; IR (KBr) ν_{max} 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.63 (d, 2H, J=6.8 Hz), 7.10 (dd, 4H, J=2.5, 8.8 Hz), 7.78 (dd, 4H, J=2.5, 8.8 Hz), 10.21 (d, 2H, J=6.8 Hz) ppm; MS (m/z) 351 (3.3, M+2+2), 349 (16.3, M+2), 347 (27.9, M+), 312 (9.3, M−Cl), 219 (8.4), 190 (9.9), 167 (35.5), 165 (100), 137 (11.5). Anal. Calcd for $C_{18}H_{12}O_3Cl_2$: C, 62.25; H, 3.46. Found: C, 62.11, H, 3.32.

1.3.2. 4,4′-Bis (1-chloro-2-formylethenyl)phenylsulphide (3b). Yellow solid, mp 120–122°C, yield 78%; IR (KBr) ν_{max} 1672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.67 (d, 2H, J=6.8 Hz), 7.42 (dd, 4H, J=2.0, 8.8 Hz), 7.72 (dd, 4H, J=2.0, 8.8 Hz), 10.22 (d, 2H, J=6.8 Hz). Anal. Calcd for $C_{18}H_{12}O_2SCl_2$: C, 59.50; H, 3.31. Found: C, 59.25; H, 3.12.

1.4. General procedure for the preparation of 4 (a, b)

To a stirred solution of chloroaldehyde **3** (0.58 mmol) and methyl thioglycolate (0.11 mL, 1.27 mmol) in 3–4 mL pyridine at 0°C, triethylamine (0.24 mL, 1.73 mmol) was added dropwise. The reaction mixture was gradually allowed to attain room temperature and then stirred at 45–50°C for an additional 30 min. Then it was cooled to 10–15°C and 6 mL 50% KOH (aq.) was added to it. Stirring was continued at 10–15°C for 20 min more. The reaction mixture was then poured into ice water and extracted with dichloromethane. The organic layer was successively washed with dil HCl and water and then dried over anhydrous Na_2SO_4. Removal of solvent followed by purification with column chromatography (silica gel/benzene) afforded **4** in 75–78% yield.

1.4.1. 4,4′-Bis (5-carbomethoxy-2-thienyl)phenylether (4a). Light yellow solid, yield 75%; mp 203–205°C; IR (KBr) ν_{max} 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (s, 6H), 7.08 (dd, 4H, J=1.9, 6.8 Hz), 7.23 (d, 2H, J=3.9 Hz), 7.62 (dd, 4H, J=1.9, 6.8 Hz), 7.76 (d, 2H, J=3.9 Hz) ppm; MS (m/z) 450 (100, M^+), 419 (29, M−OCH_3), 392 (22.4), 348 (11.8), 289 (9.4), 233 (9.6), 193 (11.6), 158 (34), 148 (14.7). Anal. Calcd for $C_{24}H_{18}O_5S_2$: C, 64.00; H, 4.00. Found: C, 63.82; H, 3.84.

1.4.2. 4,4′-Bis (5-carbomethoxy-2-thienyl)phenylsulphide (4b). Light yellow solid, mp 178–179°C ($CHCl_3$–petroleum ether, 60–80°C), yield 78%; IR (KBr) ν_{max} 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (s, 6H), 7.28 (d, 2H, J=4.0 Hz), 7.39 (ddd merged to td, 4H, J=2.0, 8.6 Hz), 7.58 (ddd merged to td, 4H, J=2.0, 8.6 Hz), 7.75 (d, 2H, J=4.0 Hz) ppm. ^{13}C NMR ($CDCl_3$): 52.49, 124.07, 127.14, 131.74, 132.48, 132.63, 134.68, 136.42, 150.38, 162.78. MS (m/z): 466 (100, M^+), 436 (6.3), 364 (20.3), 233 (13.8), 218 (29.7), 202 (77.2), 166 (50.9), 130 (17.3). Anal Calcd for $C_{24}H_{18}O_4S_3$: C, 61.80; H, 3.86. Found: C, 61.54; H, 3.75.

1.5. General method for the preparation of bis acid 5 (a, b)

To a solution of bisester **4** (0.93 mmol) in 50 mL of ethanol,

KOH (209 mg, 3.72 mmol) in 10 mL of water was added and refluxed for 4 h. Excess ethanol was distilled off and the residue was diluted with water, extracted with ethyl acetate to remove neutral matter (if any). The aqueous part was treated with active charcoal and filtered while hot. Acidification of the cold filtrates with cold and dilute HCl precipitated the desired product, which was isolated by filtration, washed well with water and dried to produce **5** in 51–64% yield.

1.5.1. 4,4′-Bis-(5-carboxy-2-thienyl)phenylether (5a). Yellow solid; mp 233–235°C; yield 64%; IR (KBr) ν_{max} 1672 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.13 (dd, 4H, J=1.9, 6.8 Hz), 7.51 (d, 2H, J=3.9 Hz), 7.70 (d, 2H, J=3.9 Hz), 7.77 (dd, 4H, J=1.9, 6.8 Hz) ppm; MS (m/z) 406 (5, M^-16), 378 (24.5, $M-CO_2$), 336 (24.4), 335 (49.4), 333 (3.9, $M-CO_2$–COOH), 323 (6.6), 296 (61.5), 295 (10.6), 279 (32.5), 241 (16.1), 175 (54.2), 158 (22.3), 147 (54.1).

1.5.2. 4,4′-Bis-(5-carboxy-2-thienyl)phenylsulphide (5b). Yellow solid; mp 237–240°C; yield 51%; IR (KBr) ν_{max} 1673 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.35–7.93 (m, 12H), 12.68–13.0 (broad hump, 2H). (The compound was poorly soluble in DMSO-d_6). Anal Calcd for $C_{22}H_{14}O_4S_3$: C, 60.27; H, 3.19. Found: C, 60.15; H, 3.02.

1.6. General method for the preparation of 6 (a, b)

To a suspension of the bis acid (0.5 mmol) in dry CH_2Cl_2 (30 mL), oxalyl chloride (0.2 mL, 2.25 mmol) and dry DMF (catalytic) was added and stirred at room temperature for 7 h. Solvent was then removed under reduced pressure to furnish the acid chloride as an orange brown solid. It was used without further purification and was immediately dissolved in 50 mL of dry CH_2Cl_2 and cooled to 0–5°C. Now to this stirred solution at 0–5°C was added dropwise a solution of 2-amino pyridine (94 mg, 1.0 mmol) and triethylamine (0.17 mL, 1.25 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred at room temperature for 24 h and then refluxed further for 2 h. The reaction mixture was then cooled to room temperature, decomposed with ice water and extracted thoroughly with ethyl acetate. The organic layer was washed successively with water, 10% $NaHCO_3$ solution, finally with water for several times and dried (anhydrous Na_2SO_4). Removal of solvent followed by purification with preparative TLC (silica gel/benzene–ethyl acetate 2:1) furnished the bisamide **6** in 18–21% yield.

1.6.1. 4,4′-Bis[5-pyridine-2-aminocarboxyl)-2-thienyl]-phenylether (6a). Light yellow solid; yield 21%; mp 220–222°C ($CHCl_3$–petroleum ether, 60–80°C); IR (KBr) ν_{max} 1696, 3398 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00–7.02 (brd, 2H, J=7.2 Hz), 7.03 (dd, 4H, J=1.9, 8.6 Hz), 7.21 (d, 2H, J=3.9 Hz), 7.58 (dd, 4H, J=1.9, 8.6 Hz), 7.59 (d, 2H, J=3.9 Hz), 7.70 (m, 2H), 8.24 (brd, 2H, J=4.3 Hz), 8.27 (d, 2H, 8.4 Hz), 8.45 (brs, 2H) ppm. Anal Calcd for $C_{32}H_{22}N_4O_3S_2$: C, 66.90; H, 3.83; N, 9.76. Found: C, 66.72; H, 3.67; N, 9.57.

1.6.2. 4,4′-Bis[5-pyridine-2-aminocarboxyl)-2-thienyl]-phenylsulphide (6b). Pale yellow solid; yield 18%; mp 186–188°C ($CHCl_3$–petroleum ether, 60–80°C); IR (KBr) ν_{max} 1655, 3435 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.06–7.10 (brm, 2H), 7.33 (d, 2H, J=3.9 Hz), 7.41 (brd, 4H, J=8.3 Hz), 7.61 (brd, 4H, J=8.3 Hz), 7.65 (d, 2H, J=3.9 Hz), 7.73–7.79 (m, 2H), 8.32–8.34 (brm, 4H), 8.50 (brs, 2H) ppm. Anal Calcd for $C_{32}H_{22}N_4O_2S_3$: C, 65.08; H, 3.73; N, 9.49. Found: C, 64.85; H, 3.54; N, 9.31.

1.7. General method for the preparation of 7 (a, b)

The acid **5** (0.71 mmol) in CH_2Cl_2 (20 mL) on reaction with oxalyl chloride (0.31 mL, 3.55 mmol) and DMF (catalytic) at room temperature afforded the bis acid chloride which on subsequent stirring with *o*-anisidine (0.16 mL, 1.42 mmol) and triethylamine (0.3 mL, 2.13 mmol) in CH_2Cl_2 (50 mL) at room temperature overnight and then refluxing (3 h) afforded **7** as a brownish-yellow solid after the usual work up. This was further purified by column chromatography [SiO_2/petroleum ether (60–80°C)–benzene, 1:1] to furnish the bis amide **7** in 15–33% yield.

1.7.1. 4,4′-Bis[5-(2-methoxyanilido)-2-thienyl]phenyl-ether (7a). Yellow solid; yield 15%; mp 202–204°C; IR (KBr) ν_{max} 1649, 3362, 3428 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.94 (s, 3H), 3.95 (s, 3H), 6.92–7.18 (m, 8H), 7.27 (d, 2H, J=4.0 Hz), 7.59 (d, 2H, J=4.0 Hz), 7.65 (brd, 4H, J=8.6 Hz), 8.41–8.49 (m, 4H), 9.96 (brs, 2H) ppm. Anal. Calcd for $C_{36}H_{28}N_2O_5S_2$: C 68.35; H, 4.43; N, 4.43. Found: C, 68.15; H, 4.25; N, 4.23.

1.7.2. 4,4′-Bis[5-(2-methoxyanilido)-2-thienyl]phenylsulphide (7b). Yellow solid; yield 33%; mp 192–194°C; IR (KBr) ν_{max} 1658, 3334, 3367 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.95 (s, 6H), 6.92 (brd, 2H, J=7.9 Hz), 7.01–7.09 (m, 4H), 7.59 (d, 2H, J=4.0 Hz), 7.31 (d, 4H, J=4.0 Hz), 7.39–7.45 (m, 4H), 7.58 (d, 2H, J=4.0 Hz), 7.59–7.64 (m, 4H), 8.41 (brs, 2H), 8.44–8.52 (m, 2H) ppm. Anal Calcd for $C_{36}H_{28}N_2O_4S_3$: C, 66.67; H, 4.32; N, 4.32. Found: C, 66.41; H, 4.15; N, 4.18.

1.8. General method for the preparation of 8 (a, b)

To a cooled (0–5°C) stirred solution of the bis acid chloride (prepared from 100 mg of **5** following the procedure as described under **6**) in CH_2Cl_2 (30 mL), a solution of *n*-butyl amine (0.1 mL, 0.96 mmol) and Et_3N (0.15 mL, 1.08 mmol) was added. The mixture was stirred at room temperature overnight. The reaction mixture was then decomposed with ice water and extracted with dichloromethane. The organic layer was washed successively with 5–10% ice cold 1N HCl, water, 10% $NaHCO_3$ solution and finally again with water for several times. After drying (anhydrous Na_2SO_4) solvent was distilled out to furnish the bisamide **8** as yellow to light yellow solid.

1.8.1. 4,4′-Bis(5-*n*-butylaminocarboxyl-2-thienyl)phenyl ether (8a). Light yellow solid; mp 187–188°C; yield 43%; IR (KBr) ν_{max} 1634, 3356 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (t, 6H, J=7.0 Hz), 1.31–1.50 (m, 4H), 1.46–1.67 (m, 4H), 3.23–3.30 (m, 2H), 3.39–3.49 (m, 2H), 5.94 (br, 2H), 7.06 (brd, 4H, J=8.7 Hz), 7.20 (d, 2H, J=3.9 Hz), 7.43 (d, 2H, J=3.9 Hz), 7.60 (brd, 4H, J=8.7 Hz). MS (m/z) 532 (2.0, M^+), 517 (1.5, $M-15$), 504 (1.9, $M-CO$), 476 (6.8, $M-C_4H_8$), 450 (100), 452 (14.3), 434 (16.4), 433 (36.2), 419 (22.5), 393 (24.3).

Anal. Calcd for $C_{30}H_{32}O_3N_3S_2$: C, 67.67; H, 6.02; N, 5.26. Found: C, 67.51; H, 5.82; N, 5.07.

1.8.2. 4,4′-Bis(5-*n*-butylaminocarboxyl-2-thienyl)phenyl sulphide (8b). Yellow solid; mp 168–170°C; yield 41%; IR (KBr) ν_{max} 1647, 3442 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (t, 6H, J=7.1 Hz), 1.29–1.44 (m, 4H), 1.45–1.65 (brm, 4H), 3.15–3.33 (m, 2H), 3.39–3.49 (m, 2H), 5.94 (br, 2H), 7.20 (d, 2H, J=3.9 Hz), 7.24–7.31 (m, 4H), 7.43 (d, 2H, J=3.9 Hz), 7.53–7.60 (m, 4H) ppm. Anal Calcd for $C_{30}H_{32}O_2N_3S_3$: C, 64.05; H, 5.69; N, 7.47. Found: C, 63.80; H, 5.43; N, 7.22.

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