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Synthesis of Some Novel bis-Spiro[indole-pyrazolinyl-thiazolidine]-2,4′-diones

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Abstract: The reaction of 1*H*-indol-2,3-diones with 1,6-dibromohexane has resulted in the formation of new 1*H*-indol-2,3-diones-1,1′-(1,6-hexanediyl)bis in quantitative yields. These compounds have been used for the synthesis of novel [3′-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)spiro[3*H*-indol-3,2′-thiazolidine]-2,4′-dione]-1,1′-(1,6-hexanediyl)bis via bis Schiff's bases, [3-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl) imino-1*H*-indol-2-one]-1,1′-(1,6-hexanediyl)bis.

Keywords: Antibacterial activity, bis indolyl compounds, bis Schiff's bases, bis-bases, bis-spiro[indole-pyrazolinyl-thiazolidine]-2,4′-diones

The importance of heterocycles in biological systems has stimulated interest in designing and constructing new heterocyclic systems using a molecular modification approach. Among the various heterocyclic systems, indole holds a prominent place because it is present as a core unit in a number of compounds possessing a broad spectrum of biological activities.[1,2] Of these, spiro indoles have attracted our attention because of their enhanced

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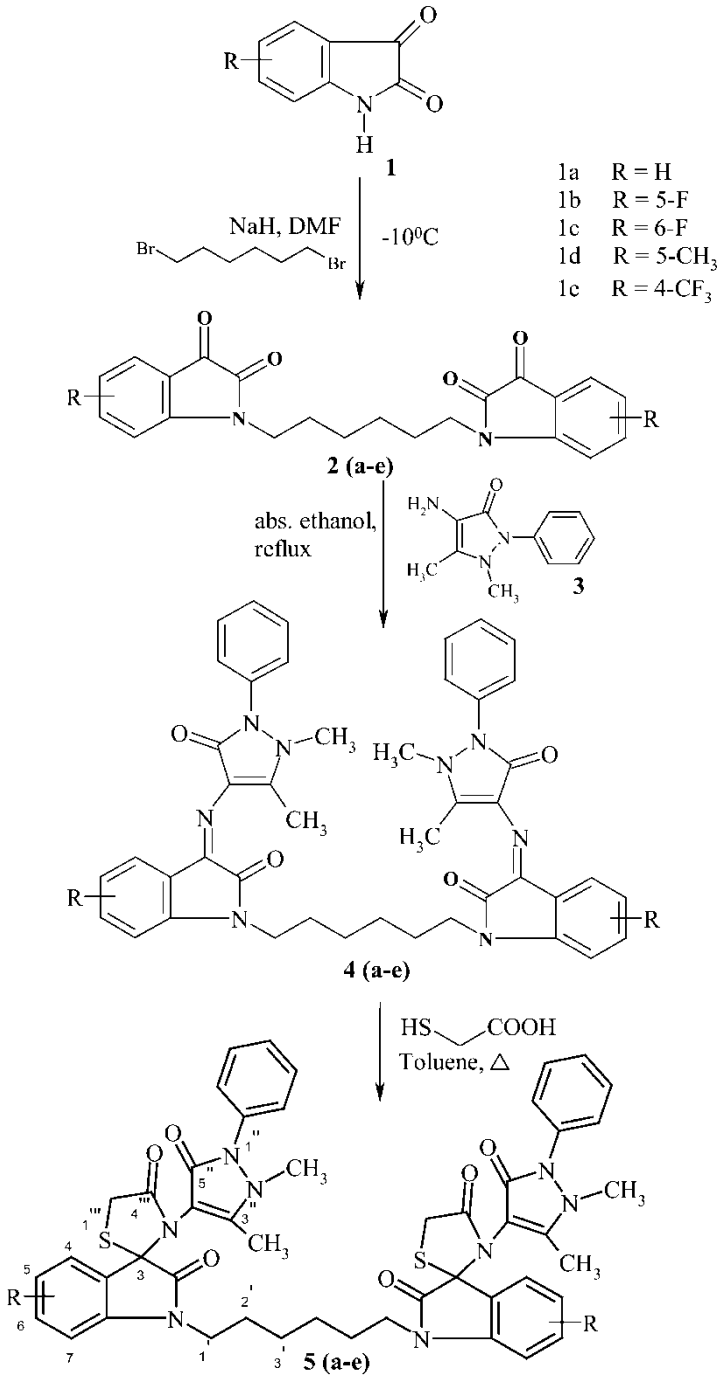
activities.[3,4] In view of this, earlier we developed some new spiro heterocycles[5–10] and their fluorinated analogues. Recently a literature survey has revealed that N-alkylated isatins, because of their lypophilic character, have been used for the synthesis of compounds that possess interesting pharmacological activities such as antimicrobial and antibacterial activities.[11] Besides these, they have also been used as excitatory amino acid antagonists[12] and ulcer inhibitors.[13] If two heterocyclic moieties are joined via a suitable spacer of carbon chain, the resulting bis compound is expected to possess enhanced bioactivity and can be further utilized as an intermediate for constructing new heterocyclic systems. A number of reports have appeared in the literature on the bioactivity of bis heterocyclic compounds containing $>N\text{-}(CH_2)_n\text{-}N<$ linkage,[14,15] but no report, as yet, is available on bis indolyl compounds with such linkages. Realizing the importance of these molecules, we extended our work on spiro indoles in this direction and thought of synthesizing some novel bis spiro indoles containing a suitable spacer. The length of the spacer was decided on the basis of molecular modeling.

In view of this and to understand the combined biological effects of both spiro indoles along with a spacer of alkyl chain between them, we have now developed a facile and elegant synthesis of novel bis-spiro indoles via hitherto unknown bis Schiff's bases, which in turn have been synthesized using bis-indol-2,3-diones.

RESULTS AND DISCUSSION

We have synthesized fifteen novel bis indolyl compounds in all including substituted bis-indol-2,3-diones (**2a**–**e**), bis[imino-indoles] (**4a**–**e**), and bis[spiro (indole-pyrazolinyl-thiazolidinones)] (**5a**–**e**) (Scheme 1).

The reaction of 1*H*-indol-2,3-dione and 1,6-dibromohexane (2:1) in the presence of NaH/DMF at $-10^{\circ}C$ has resulted in the formation of **2a**. The IR spectrum of **2a** showed a characteristic broad absorption band for the presence of a carbonyl group at $1700\,cm^{-1}$. Absence of absorption band in the region $3300-3400\,cm^{-1}$ for >NH indicated that N-alkylation has taken place at the indole moiety. Its ^1H NMR displayed a triplet at δ 3.72, integrating for four protons, thereby showing that two indole moieties have been coupled through nitrogen via an alkyl chain. The methylenes of the hexyl spacer appeared as multiplets at δ 1.44 and 1.73, which was further supported by its ^{13}C NMR spectrum, which showed methylenes carbons at δ 26.4, 28.1, and 40.3. The aromatic protons as expected for the indole moieties appeared at δ 6.87 (H-7), 7.11 (H-5), and 7.61 (H-6 and H-4). C-2 and C-3 carbonyl carbons appeared at δ 175.9 and 183.8 respectively in ^{13}C NMR. Formation of bis product has finally been confirmed on the basis of its EIMS, which showed the molecular ion peak at m/z 376 corresponding to its molecular formula. On the basis of these observations, **2a** has been identified as 1*H*-indol-2,3-diones-1,1′-(1,6-hexanediyl)bis.



Scheme 1.

The reaction of **2a** with 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (**3**) in 1:2 ratio in absolute ethanol yielded an orange-colored Schiff's base, **4a**. It gave a molecular ion peak M^+, at m/z 746 in FAB-MS, suggesting the molecular formula $C_{44}H_{42}O_4N_8$, and indicated that the two pyrazoline moieties have coupled with **2a** with the loss of two water molecules. The IR spectrum showed characteristic absorption band at 1646 (C═N) cm^{-1}. Its ^1H NMR spectrum displayed two singlets at δ 3.24 and 2.44, each integrating for six protons of the two N-CH_3 and two 3″-CH_3 groups of the pyrazoline moieties respectively. Further, multiplets at δ 7.32 integrating for ten protons are due to the presence of two phenyl groups of the pyrazoline moieties. The peaks at δ 6.81 (H-7), 7.05 (H-5), and 7.26 (H-4 and H-6) showed the presence of aromatic protons of the indole moiety. The triplet at δ 3.74 integrating for four protons indicated the presence of two >N-CH_2 linkages. The ^{13}C NMR spectrum of **4a** displayed characteristic carbonyl signals at δ 165.1 (lactam) and 161.3 (pyrazoline), in addition to a signal at δ 146.1 showing the presence of (C═N) in the molecule. These spectral studies confirmed the formation of the desired bis Schiff's base, which was characterized as [3-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl) imino-1*H*-indol-2-one]-1,1′-(1,6-hexanediyl)bis (**4a**).

Compound **4a** was then subjected to the cyclocondensation reaction with mercaptoacetic acid under refluxing conditions using a Dean–Stark apparatus. The new compound **5a** gave a molecular ion peak at m/z 894, corresponding to the molecular formula $C_{48}H_{46}O_6N_8S_2$ as indicated by its FAB-MS. The IR spectrum showed the presence of characteristic absorption peaks at 1720 (thiazolidinone carbonyl), 1700 (lactam carbonyl), and 1684 (pyrazolinyl carbonyl) cm^{-1}, indicating that cycloaddition has occurred. This was further confirmed by its ^1H and ^{13}C NMR data. ^1H NMR spectrum of **5a** showed, as expected, the aromatic protons of indole nucleus as multiplets at δ 6.72 (H-7) and 7.13 (H-4, H-5, and H-6) integrating for eight protons. Two doublets, which integrated for four protons of the two methylenes of the thiazolidinone rings, appeared at δ 3.79 and 4.32 ($J = 15.0$ Hz each). The four methyl groups appeared at δ 2.99 (2 × N-CH_3) and 2.21 (2 × 3″-CH_3). The protons of the two phenyl groups of pyrazoline moieties appeared as multiplets at δ 7.30. Methylenes of the hexyl linker appeared at δ 3.63, 1.69 and 1.40. ^{13}C NMR spectra also showed all expected characteristic peaks at δ 177.1 (thiazolidine carbonyl), 173.1 (lactam carbonyl), 161.0 (pyrazoline carbonyl), and 108.6–134.5 (aromatic carbons). Besides these, methyl carbons at δ 35.4 (-NCH_3) and δ 12.1 (3″-CH_3) of pyrazoline moiety and methylene carbons of the carbon chain at δ 40.7 (C-1′), 30.0 (C-2′) and δ 27.3 (C-3′) and of thiazolidine moiety at δ 35.6 (S-CH_2) were also displayed in ^{13}C NMR. The signals for N-CH_3 and S-CH_2 have been distinguished on the basis of the DEPT-135 experiment.

On the basis of these spectral studies, **5a** was characterized as [3′-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)spiro[3*H*-indol-3,2′-thiazolidine]-2,4′-dione]-1,1′-(1,6-hexanediyl)bis. Using these steps and taking different

substituted indol-2,3-diones, we have synthesized four other new bis-spiro compounds, **5b**–**e**.

Some of the synthetic samples have been evaluated for antibacterial activity against *E. coli* cultures and showed promising results.

EXPERIMENTAL

Melting points were determined in a capillary tube in sulphuric acid bath and are uncorrected. IR spectra were recorded on Shimadzu model IR-435 spectrophotometer using KBr discs. ^{1}H NMR spectra were recorded on Bruker AC (300 MHz) in $CDCl_3$. ^{13}C NMR were recorded on Bruker AC (75.47 MHz) in $CDCl_3$. Mass spectra were recorded on Jeol-JMS-DX 303 mass spectrometer. Substituted indol-2,3-diones (**1b**–**e**) were prepared by literature procedures[8] starting from the corresponding aniline.

1*H*-Indol-2,3-dione-1,1′-(1,6-hexanediyl)bis

A solution of 1*H*-indol-2,3-dione (0.01 mol) in DMF (5 ml) was added dropwise to a stirred soultion of NaH (0.02 mol) in 10 ml of dry DMF during 20 min at −10°C under an inert atmosphere. A deep purple-colored suspension was formed. 1,6-Dibromohexane (0.005 mol) was then added dropwise to the reaction mixture during 30 min at −10°C. The contents were allowed to stir at room temperature for 20 h and then quenched with ice water. A red-colored solid **2a** was purified by column chromatography using silica gel as an adsorbent. Compounds **2b**–**e** were also synthesized using this procedure. The spectral data of compounds **2a**–**e** are recorded in Table 1.

[3-(2,3-Dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)imino-1*H*-indol-2-one]-1,1′-(1,6-hexanediyl)bis

A mixture of **2a** (0.01 mol) and 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (0.02 mol) in absolute ethanol (30 ml) was refluxed at 80°C for about 6 h. An orange-colored solid that separated was filtered, dried, and crystallized from ethanol to give Schiff's base **4a**.

Compounds **4b**–**e** were also synthesized in a similar manner. The spectral data of compounds **4a**–**e** are included in Table 2.

[3′-(2,3-Dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)spiro[3*H*-indol-3,2′-thiazolidine]-2,4′-dione]-1,1′-(1,6-hexanediyl)bis

A mixture of **4a** (0.01 mol) and mercaptoacetic acid (0.022 mol) was refluxed in dry toluene for 8 h with simultaneous removal of water azeotropically,

Table 1. Spectral data of compound 2

Compound	Yield (%)	Mp (°C)	EIMS, m/z	^{1}H NMR (δ, $CDCl_3$)	^{13}C NMR (δ, $CDCl_3$)
2a	80	205	376, 244, 202, 174, 160, 146, 132, 118, 90	1.44 (m, 4H, 2 × H-3′), 1.73 (m, 4H, 2 × H-2′), 3.72 (t, 4H, $J = 6.3$ Hz, 2 × H-1′), 6.87 (d, 2H, $J = 9.0$ Hz, 2 × H-7), 7.11 (t, 2H, $J = 9.3$ Hz, 2 × H-5), 7.61 [m, 4H, 2 × (H-4 & H-6)]	26.4 (C-3′), 28.1 (C-2′), 40.3 (C-1′), 110.4, 124.0, 125.1, 138.0, 151.2, 158.0, 175.9 (C-2), 183.8 (C-3)
2b	76	190	412, 327, 234, 206, 192, 178, 164, 150, 136, 118, 90	1.36 (m, 4H, 2 × H-3′), 1.69 (m, 4H, 2 × H-2′), 3.71 (t, 4H, $J = 7.1$ Hz, 2 × H-1′), 6.86 (d, 2H, $J = 9.1$ Hz, 2 × H-7), 7.30 [m, 4H, 2 × (H-4 & H-6)]	28.2 (C-3′), 30.3 (C-2′), 41.5 (C-1′), 111.2, 127.0, 133.0, 139.9, 150.2, 159.5, 174.8 (C-2), 181.4 (C-3)
2c	75	185	412, 234, 206, 178, 164, 136, 118	1.42 (m, 4H, 2 × H-3′), 1.68 (m, 4H, 2 × H-2′), 3.68 (t, 4H, $J = 6.5$ Hz, 2 × H-1′), 6.77 [m, 4H, 2 × (H-4 & H-7)], 7.39 (m, 2H, 2 × H-5)	27.1 (C-3′), 28.2 (C-2′), 40.1 (C-1′), 110.4, 126.2, 132.9, 139.1, 149.2, 158.0, 174.7 (C-2), 182.2 (C-3)
2d	73	220	404, 278, 198, 174, 160, 146, 132, 118, 104	1.42 (m, 4H, 2 × H-3′), 1.68 (m, 4H, 2 × H-2′), 2.33 (s, 6H, 2 × 5-CH_3), 3.68 (t, 4H, $J = 6.1$ Hz, 2 × H-1′), 6.78 (d, 2H, $J = 9.0$ Hz, 2 × H-7), 7.41 [m, 4H, 2 × (H-4 & H-6)]	20.9 (5-CH_3), 26.7 (C-3′), 27.4 (C-2′), 40.3 (C-1′), 110.4, 126.1, 133.8, 139.0, 149.1, 158.0, 175.2 (C-2), 182.2 (C-3)
2e	70	185	512, 242, 228, 214, 172	1.32 (m, 4H, 2 × H-3′), 1.66 (m, 4H, 2 × H-2′), 3.78 (t, 4H, $J = 6.8$ Hz, 2 × H-1′), 6.89 [m, 6H, 2 × (H-5 & H-7)], 7.23 (m, 2H, 2 × H-6)	25.8 (C-3′), 27.7 (C-2′), 41.7 (C-1′), 110.4, 115.4 (4-**C**F_3), 125.3, 133.1, 140.0, 152.1, 159.8, 174.8 (C-2), 185.1 (C-3)

Table 2. Spectral data of compound 4

Compound	Yield (%)	Mp (°C)	FAB-MS, m/z	^{1}H NMR (δ, $CDCl_3$)	^{13}C NMR (δ, $CDCl_3$)
4a	90	214	746	1.44 (m, 4H, 2 × H-3′), 1.70 (m, 4H, 2 × H-2′), 2.44 (s, 6H, 2 × 3″-CH_3), 3.24 (s, 6H, 2 × N-CH_3), 3.74 (t, 4H, J = 6.1 Hz, 2 × H-1′), 6.81 (d, 2H, J = 9.1 Hz, 2 × H-7), 7.05 (t, 2H, J = 9.1 Hz, 2 × H-5), 7.26 [m, 4H, 2 × (H-4, & H-6)], 7.32 (m, 10H, 2 × N-C_6H_5)	12.8 (3″-CH_3), 27.0 (C-3′), 27.7 (C-2′), 36.3 (N-CH_3), 40.2 (C-1′), 108.9-138.7 (aromatic carbons), 146.1 (C-3), 161.3 (C-5″), 165.1 (C-2)
4b	85	198	782	1.36 (m, 4H, 2 × H-3′), 1.68 (m, 4H, 2 × H-2′), 2.47 (s, 6H, 2 × 3″-CH_3), 3.29 (s, 6H, 2 × N-CH_3), 3.74 (t, 4H, J = 7.3 Hz, 2 × H-1′), 6.74 (d, 2H, J = 9.0 Hz, 2 × H-7), 7.05 [m, 4H, 2 × (H-4 & H-6)], 7.43 (m, 10H, 2 × N-C_6H_5)	14.7 (3″-CH_3), 25.6 (C-3′), 30.4 (C-2′), 32.4 (N-CH_3), 43.4 (C-1′), 110.2-138.4 (aromatic carbons), 141.0 (C-3), 161.3 (C-5″), 167.1 (C-2)
4c	80	190	782	1.26 (m, 4H, 2 × H-3′), 1.65 (m, 4H, 2 × H-2′), 2.46 (s, 6H, 2 × 3″-CH_3), 3.28 (s, 6H, 2 × N-CH_3), 3.75 (t, 4H, J = 7.3 Hz, 2 × H-1′), 6.74 [m, 4H, 2 × (H-4 & H-7)], 7.31 (m, 2H, 2 × H-5), 7.43 (m, 10H, 2 × N-C_6H_5)	13.3 (3″-CH_3), 28.5 (C-3′), 29.2 (C-2′), 32.1 (N-CH_3), 44.0 (C-1′), 110.0-134.3 (aromatic carbons), 142.0 (C-3), 162.2 (C-5″), 166.3 (C-2)
4d	76	215	774	1.42 (m, 4H, 2 × H-3′), 1.67 (m, 4H, 2 × H-2′), 2.14 (s, 6H, 2 × 3″-CH_3), 2.32 (s, 6H, 2 × 5-CH_3), 3.24 (s, 6H, 2× N-CH_3), 3.71 (t, 4H, J = 6.8 Hz, 2 × H-1′), 6.69 (m, 2H, 2 × H-7), 7.14 [m, 2H, 2 × (H-4 & H-6)], 7.35 (m, 10H, 2 × N-C_6H_5)	13.5 (3″-CH_3), 22.5 (5-CH_3), 26.6 (C-3′), 29.9 (C-2′), 30.6 (N-CH_3), 41.2 (C-1′), 111.0-140.2 (aromatic carbons), 141.1 (C-3), 161.4 (C-5″), 165.4 (C-2)
4e	75	190	882	1.43 (m, 4H, 2 × H-3′), 1.66 (m, 4H, 2 × H-2′), 2.45 (s, 6H, 2 × 3″-CH_3), 3.25 (s, 6H, 2 × N-CH_3), 3.74 (t, 4H, J = 6.9 Hz, H-1′), 6.78 [m, 6H, 2 × (H-5, H-6 & H-7)], 7.41 (m, 10H, 2 × N-C_6H_5)	13.3 (3″-CH_3), 28.5 (C-3′), 29.2 (C-2′), 32.8 (N-CH_3), 41.8 (C-1′), 110.0-142.2 (aromatic carbons), 143.0 (C-3), 160.9 (C-5″), 167.2 (C-2)

Table 3. Spectral data of compound 5

Compound	Yield (%)	Mp (°C)	FAB-MS, m/z	^{1}H NMR (δ, $CDCl_3$)	^{13}C NMR (δ, $CDCl_3$)
5a	65	95	894	1.40 (m, 4H, 2 × H-3′), 1.69 (m, 4H, 2 × H-2′), 2.21 (s, 6H, 2 × 3″-CH_3), 2.99 (s, 6H, 2 × N-CH_3), 3.63 (t, 4H, J = 6.0 Hz, 2 × H-1′), 3.79 & 4.32 (dd, 4H, J = 15.0 Hz each, 2 × S-CH_2), 6.72 (d, 2H, J = 9.0 Hz, 2 × H-7), 7.13 [m, 6H, 2 × (H-4, H-5 & H-6)], 7.30 (m, 10H, 2 × N-C_6H_5)	12.1 (3″-CH_3), 27.3 (C-3′), 30.0 (C-2′), 35.4 (N-CH_3), 35.6 (S-CH_2), 40.7 (C-1′), 108.6-134.5 (aromatic carbons), 161.0 (C-5″),173.1 (C-2), 177.1 (C-4‴)
5b	63	80	930	1.30 (m, 4H, 2 × H-3′), 1.65 (m, 4H, 2 × H-2′), 2.35 (s, 6H, 2 × 3″-CH_3), 3.02 (s, 6H, 2 × N-CH_3), 3.70 (t, 4H, J = 7.5 Hz, 2 × H-1′), 3.78 & 4.27 (dd, 4H, J = 15.0 Hz each, 2 × S-CH_2), 6.70 (s, 2H, 2 × H-7), 7.15 [m, 4H, 2 × (H-4 & H-6)], 7.26 (m, 10H, 2 × N-C_6H_5)	14.3 (3″- CH_3), 27.1 (C-3′), 31.1 (C-2′), 33.2 (N-CH_3), 35.5 (S-CH_2), 43.8 (C-1′), 113.0-134.9 (aromatic carbons), 162.4 (C-5″), 171.2 (C-2), 178.0 (C-4‴)
5c	65	85	930	1.38 (m, 4H, 2 × H-3′), 1.64 (m, 4H, 2 × H-2′), 2.24 (s, 6H, 2 × 3″-CH_3), 3.02 (s, 6H, 2 × N-CH_3), 3.64 (t, 4H, J = 7.1 Hz, 2 × H-1′), 3.81 & 4.30 (dd, 4H, J = 15.0 Hz each, 2 × S-CH_2), 6.67 [d, 4H, J = 9.1 Hz, 2 × (H-4 & H-7)], 7.34 (m, 2H, 2 × H-5), 7.48 (m, 10H, 2 × N-C_6H_5)	14.1 (3″-CH_3), 24.2 (C-3′), 30.1 (C-2′), 33.2 (N-CH_3), 34.6 (S-CH_2), 43.8 (C-1′), 110.0-140.2 (aromatic carbons), 161.1 (C-5″), 172.2 (C-2), 177.9 (C-4‴)
5d	55	105	922	1.37 (m, 4H, 2 × H-3′), 1.63 (m, 4H, 2 × H-2′), 2.24 (s, 6H, 2 × 5-CH_3), 2.35 (s, 6H, 2 × 3″-CH_3), 3.11 (s, 6H, 2 × N-CH_3), 3.66 (t, 4H, J = 7.0 Hz, 2 × H-1′), 3.80 & 4.21 (dd, 4H, J = 15.1 Hz each, 2 × S-CH_2), 6.62 (s, 2H, 2 × H-7), 7.15 [m, 4H, 2 × (H-4 & H-6)], 7. 36 (m, 10H, 2 × N-C_6H_5)	14.1 (3″-CH_3), 22.5 (5-CH_3), 29.6 (C-3′), 30.3 (C-2′), 35.1 (N-CH_3), 35.2(S-CH_2), 43.7 (C-1′), 110.0-142.3 (aromatic carbons), 160.9 (C-5″), 171.1 (C-2), 177.5 (C-4‴)
5e	52	101	1030	1.39 (m, 4H, 2 × H-3′), 1.65 (m, 4H, 2 × H-2′), 2.10 (s, 6H, 2 × 3″-CH_3), 2.99 (s, 6H, 2 × N-CH_3), 3.67 (t, 4H, J = 7.2 Hz, 2 × H-1′), 3.81 & 4.23 (dd, 4H, J = 15.1 Hz each, 2 × S-CH_2), 6.72 (m, 2H, 2 × H-7), 7.25 [m, 4H, 2 × (H-5 & H-6)], 7.34 (m, 10H, 2 × N-C_6H_5)	11.2 (3″-CH_3), 27.2 (C-3′), 29.7 (C-2′), 35.5 (S-CH_2), 36.2 (N-CH_3), 43.3 (C-1′), 108.6-141.3 (aromatic carbons), 161.2 (C-5″), 170.1 (C-2), 177.8 (C-4‴)

using a Dean–Stark apparatus. Solution turned light yellow, and a sticky solid was formed. The solvent was removed under reduced pressure, and the residue was treated with a saturated solution of sodium bicarbonate to remove the unreacted acid, if any. The solid left was filtered, dried, and crystallized from a methanol–chloroform mixture to give **5a**.

Compounds **5b–e** were also synthesized following this procedure, and their spectral data are included in Table 3.

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