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Novel stilbene-based Fischer base analog of leuco-TAM – (2*E*,2′*Z*)-{2-(4-(*E*)-styrylphenyl) propane-1,3-diylidene}bis(1,3,3-trimethylin doline) – derivatives: synthesis and structural consideration by 1D NMR and 2D NMR spectroscopy

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We report the synthesis of a series of novel stilbene-based (St) Fischer base analogs of leuco-triarylmethane (LTAM) dyes by treating Fischer base with (*E*)-4-styrylbenzaldehyde derivatives. All St-LTAM molecules examined herein are characterized by 1D and 2D NMR. They were found to exhibit *ZE* configuration and isomerize to their diastereomers *EE* and *ZZ* in 2–3 h. They exhibit type I behavior of diastereomeric isomerization. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: NMR; ^{1}H; COSY; HMBC; HETCOR; NOESY; Fischer base analogs of leuco-TAM dyes; diastereomeric isomerization; Heck reaction; photochemotherapy agents; malachite green

Introduction

Triarylmethane (TAM) compounds, sometimes referred to as 'leuco-TAMs' (LTAMs) or 'leuco-bases',[1–3] are well known to constitute an important group of intermediates for the synthesis of various functional organic compounds such as polymers and biomolecules.[4,5] Furthermore, the triarylmethyl (trityl) group serves as an excellent protecting group in nucleoside, oligonucleoside, peptide, and carbohydrate chemistry.[6,7] Trityl cations can also act as tools in mass spectrometric analysis because of their facile ionization.[8]

Furthermore, LTAM molecules are regarded to be precursors to TAM^{+} dyes, as the oxidation of LTAM molecules produces the corresponding TAM^{+} dyes. Several TAM^{+} dyes are well known in the dye industry, e.g. malachite green (MG), crystal violet, sunset orange, and pararosaniline. TAM^{+} dyes are categorized as basic dyes, which are extensively used for dyeing silk, wool, and cotton.[9] They also have a wide range of applications, e.g. in textile industries for both dyeing and printing; in ink manufacturing; as coloring agents for papers, toys, and varieties of plastics[10,11]; and in pharmaceutical applications.[12–14] Furthermore, they are used in medicinal applications as photochemotherapy and binding agents.[15,16] Among these dyes, MG is the most interesting. It has long been used to control fungal and protozoan infections in fish.[17,18] Although the use of MG has now been prohibited for the control of fungal infections in commercial fisheries, it is still used worldwide because it is readily accessible and economical.[19] As a result, there is a strong demand for the substitutes for MG compounds.

Previously, we have reported the synthesis and structural study of Fischer base [1,3,3-trimethyl-2-methyleneindoline (FB)] analogs of LTAM dyes, which are derivatives of 2,2′-(2-phenyl propane-1,3-diylidene)bis(1,3,3- trimethylindoline).[20–22] A number of LTAM molecules containing a central carbon bearing two FB fragments and one aryl ring such as phenyl and pyridinyl have been reported previously. The FB moiety, whose skeleton contains a conjugated enamine moiety, is regarded as an active methylene group-containing indole. Indole is an important heterocycle because it contains the skeleton of indole alkaloids, which are biologically active compounds. Thus, the incorporation of an indole nucleus, which is a biologically accepted pharmacophore in medicinal compounds, has made it a versatile heterocyclic system exhibiting a wide spectrum of biological activities.[23–25]

Furthermore, materials exhibiting a novel combination of properties are required. For instance, near-infrared (NIR) absorbing dyes ($_{max} > 700$ nm) can be potentially used in optical imaging systems, thermal writing displays, and infrared photography and as filters for NIR lasers. In this study, we extend the LTAM dyes to stilbene-based (St) FB analogs of LTAM molecules as the stilbene moiety is expected to be a better chromophore because of the extended conjugation from the nitrogen of the FB ring to the central stilbene ring in the corresponding St-TAM^{+} dyes, which are suitable candidates for NIR dyes.[26]

As part of an ongoing study of the structural modification of LTAM molecules, we report herein the synthesis and structural

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characterization of novel St-LTAM FB analogs (Scheme 1) by 1D and 2D ^{1}H and ^{13}C NMR spectroscopy including COSY, HETCOR, HMBC, and NOESY.

Experimental

Materials

The required FB derivatives were 2-methylene-1,3,3-trimethylindoline,5-chloro-2-methylene-1,3,3-trimethylindoline and Cl-FB. 4-Bromobenzaldehydes, 4-substituted styrenes, and other reagents were purchased from Aldrich (Sigma-Aldrich, Korea) and used without further purification.

Synthesis

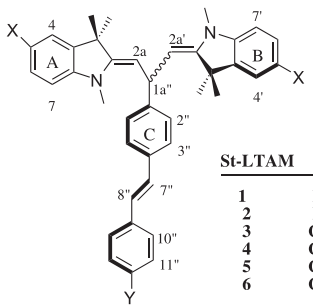
The (*E*)-4-styrylbenzaldehyde [(Y)-SBA] derivatives were prepared from the Heck coupling of substituted styrenes and *p*-bromobenzaldehyde in the presence of palladium acetate [$Pd(OAc)_2$], tri-*o*-tolylphosphine, and triethylamine in a heavy-wall pressure tube.[27,28] After 14 h, the reaction mixture was purified with methanol. Meanwhile, the St-LTAM molecules (hereafter referred to as St-LTAM **1–6**) were synthesized from the reaction of FB derivatives with the (Y)-SBA derivatives prepared in absolute ethanol. The white precipitates obtained from the reaction mixtures were purified with cold ethanol.

*(2E,2′Z)-2,2′-(2-(4-Styrylphenyl)propane-1,3-diylidene)bis(1,3,3-trimethylindoline), St-LTAM (**1**)*

White, yield 58%, mp 177 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.43 (s, 3H), 1.53 (s, 3H), 1.70 (s, 3H), 3.01 (s, 3H), 3.34 (s, 3H), 4.36 (d, J = 9.3 Hz, 1H), 4.43 (d, J = 10.2 Hz, 1H), 5.28 (t, J = 9.3, 10.2 Hz, 1H), 6.49 (d, J = 7.8 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 6.71 (t, 1H), 6.81 (t, 1H), 7.03 (t, 1H), 7.04 (d, J = 16.6), 7.08 (t, 1H), 7.15 (d, J = 16.6), 7.17 (s, 1H), 7.18 (s, 1H), 7.43 (t, 1H), 7.47–7.48 (aromatic, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.9, 29.1, 29.5, 29.7, 31.3, 34.0, 38.9, 44.7, 45.3, 97.5, 101.6, 105.1, 105.9, 118.2, 118.9, 121.8, 122.3, 126.9, 127.0, 127.9, 128.1, 128.5, 128.7, 129.2, 135.4, 138.0, 138.2 138.6, 146.8, 148.5, 149.9, 151.8, 152.5. Anal. Calcd. for $[C_{39}H_{40}N_2]$: C, 87.27; H, 7.51; N, 5.22%; obtained C, 87.22; H, 7.49; N, 5.19%.

*(2E,2′Z)-2,2′-(2-(4-(4-Chlorostyryl)phenyl)propane-1,3-diylidene)bis(1,3,3-trimethylindoline), St-LTAM (**2**)*

White, yield 55%, mp 178 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.40 (s, 3H), 1.48 (s, 3H), 1.66 (s, 3H), 2.94 (s, 3H), 3.26 (s, 3H), 4.35 (d, J = 9.3 Hz, 1H), 4.41 (d, J = 10.1 Hz, 1H), 5.20 (t, J = 9.3, 10.1 Hz, 1H), 6.36 (d, J = 7.9 Hz, 1H), 6.43 (d, J = 8.2 Hz, 1H), 6.97 (d, J = 7.9 Hz, 1H), 6.98 (d, J = 16.5, 1H), 7.01 (d, J = 8.2 Hz, 1H), 7.06 (s, 1H), 7.09 (s, 1H), 7.07 (d, J = 16.5, 1H), 7.35 (t, 1H), 7.47–7.48 (aromatic, 8H).



St-LTAM	X	Y
1	H	H
2	H	Cl
3	Cl	H
4	Cl	Cl
5	Cl	Me
6	Cl	OMe

Scheme 1. Chemical structure of St-LTAM molecules.

^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3, 29.3, 29.4, 30.8, 31.1, 33.7, 35.2, 38.5, 44.4, 45.0, 97.6, 100.0, 101.8, 105.3, 106.3, 121.8, 122.0, 126.5, 126.7, 127.4, 127.6, 127.9, 128.1, 128.2, 128.5, 128.6, 128.8, 135.2, 137.5, 139.8, 144.9, 146.6, 151.0. Anal. Calcd. for $[C_{39}H_{38}Cl_2N_2]$: C, 77.34; H, 6.32; Cl, 11.71; N, 4.63%; obtained C, 77.29; H, 6.30; Cl, 11.68; N, 4.58%.

*(2E,2′Z)-2,2′-(2-(4-Styrylphenyl)propane-1,3-diylidene)bis(5-chloro-1,3,3-trimethylindoline), St-LTAM (**3**)*

White, yield 53%, mp 180 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.41 (s, 3H), 1.51 (s, 3H), 1.68 (s, 3H), 2.91 (s, 3H), 3.29 (s, 3H), 4.43 (d, J = 9.3 Hz, 1H), 4.49 (d, J = 10.1 Hz, 1H), 5.26 (t, J = 9.3, 10.1 Hz, 1H), 6.47 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.75 (d, J = 16.5, 1H), 7.03 (d, J = 7.9 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 7.05 (s, 2H), 7.08 (d, J = 16.7, 1H), 7.11 (d, J = 16.7, 1H), 7.07 (d, J = 16.5, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.44–7.45 (aromatic, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3, 29.3, 29.4, 30.8, 31.1, 33.7, 38.5, 44.4, 45.0, 97.6, 101.8, 105.6, 105.8, 118.7, 119.0, 122.0, 122.4, 127.0, 127.1, 127.9, 128.1, 128.2, 128.5, 129.2, 135.4, 137.5, 138.0, 139.8, 148.7, 146.5, 149.9, 151.0, 151.8. Anal. Calcd. for $[C_{39}H_{39}ClN_2]$: C, 82.01; H, 6.88; Cl, 6.21; N, 4.90%; obtained C, 81.97; H, 6.86; Cl, 6.15; N, 4.88%.

*(2E,2′Z)-2,2′-(2-(4-(4-Chlorostyryl)phenyl)propane-1,3-diylidene)bis(5-chloro-1,3,3-trimethylindoline), St-LTAM (**4**)*

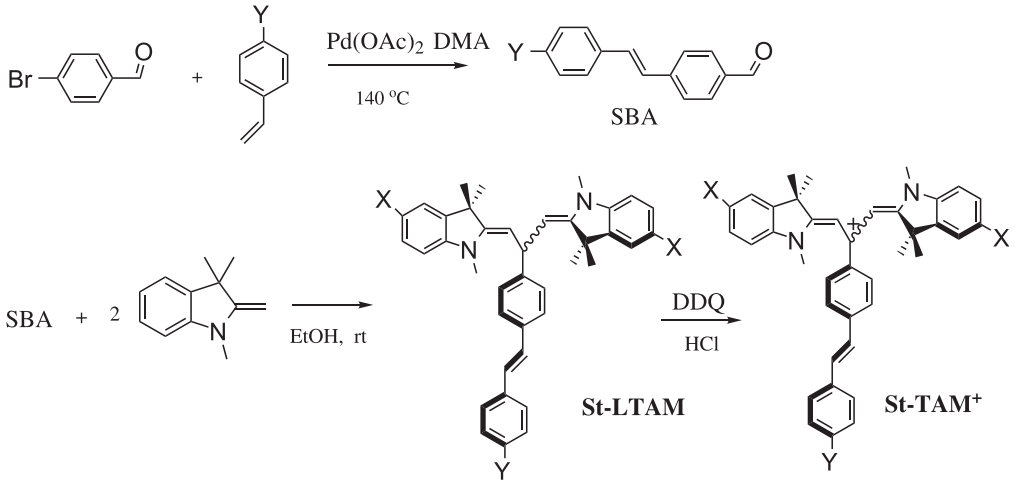
White, yield 57%, mp 217 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.39 (s, 3H), 1.43 (s, 3H), 1.73 (s, 3H), 2.97 (s, 3H), 3.25 (s, 3H), 4.35 (d, J = 9.3 Hz, 1H), 4.40 (d, J = 10.1 Hz, 1H), 5.26 (t, J = 9.3, 10.1 Hz, 1H), 6.36 (d, J = 7.9 Hz, 1H), 6.43 (d, J = 8.2 Hz, 1H), 6.95 (d, J = 16.1, 1H), 7.01 (d, J = 7.9 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 7.05 (s, 1H) 7.06 (s, 1H), 7.11 (d, J = 16.1, 1H), 7.37–7.38 (aromatic, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2, 28.9, 29.3, 30.3, 30.6, 33.6, 38.3, 44.4, 45.0, 95.9, 99.7, 106.5, 121.8, 121.9, 122.3, 122.8, 122.9, 123.1 123.8, 127.3, 127.4, 139.3, 139.5, 139.6, 144.7, 146.3, 149.8, 149.9, 151.9, 152.8, 156.7. Anal. Calcd. for $[C_{39}H_{37}Cl_3N_2]$: C, 73.18; H, 5.83; Cl, 16.62; N, 4.38%; obtained C, 72.88; H, 5.78; Cl, 16.46; N, 4.29%.

*(2E,2′Z)-2,2′-(2-(4-(4-Methoxystyryl)phenyl)propane-1,3-diylidene)bis(5-chloro-1,3,3-trimethylindoline), St-LTAM (**5**)*

Pale yellow, yield 39%, mp 135 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.35 (s, 3H), 1.48 (s, 3H), 1.66 (s, 3H), 2.35 (s, 3H), 2.94 (s, 3H), 3.25 (s, 3H), 4.35 (d, J = 9.4 Hz, 1H), 4.41 (d, J = 10.0 Hz, 1H), 5.20 (t, J = 9.4, 10.0 Hz, 1H), 6.36 (d, J = 7.9 Hz, 1H), 6.42 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 16.1, 1H), 7.00 (d, J = 7.9 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 7.05 (s, 1H), 7.06 (s, 1H), 7.09 (d, J = 16.1, 1H), 7.38–7.39 (aromatic, 6H), 7.14 (d, J = 8.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4, 28.8, 29.4, 30.4, 31.2, 33.6, 38.2, 42.1, 44.4, 45.0, 97.6, 99.9, 100.5, 105.7, 106.3, 121.4, 121.9, 122.2, 122.5, 122.9, 123.5, 126.4, 126.5, 127.5, 128.1, 129.5, 134.7, 135.4, 137.5, 139.6, 139.8, 146.6, 144.9, 147.0, 151.5, 151.8. Anal. Calcd. for $[C_{40}H_{40}Cl_2N_2]$: C, 77.53; H, 6.51; Cl, 11.44; N, 4.52%; obtained C, 77.44; H, 6.46; Cl, 11.36; N, 4.47%.

*(2E,2′Z)-2,2′-(2-(4-(4-Methoxystyryl)phenyl)propane-1,3-diylidene)bis(5-chloro-1,3,3-trimethylindoline), St-LTAM (**6**)*

Pinkish yellow, yield 40%, mp 168 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.40 (s, 3H), 1.48 (s, 3H), 1.66 (s, 3H), 2.94 (s, 3H), 3.28 (s, 3H), 3.83 (s, 3H), 4.35 (d, J = 9.4 Hz, 1H), 4.41 (d, J = 10.0 Hz, 1H), 5.19 (t, J = 9.4, 10.0 Hz, 1H), 6.36 (d, J = 7.9 Hz, 1H), 6.42 (d, J = 8.3 Hz, 1H), 6.90 (d, J = 16.1, 1H), 6.96 (d, J = 7.9 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 7.03 (s, 1H), 7.05 (s, 1H), 7.10 (d, J = 16.1, 1H), 7.43–7.44 (aromatic, 6H), 6.88 (d, J = 8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$)



Scheme 2. Synthetic scheme of St-LTAM/TAM$^+$ molecules.

δ 28.4, 28.9, 29.9, 30.3, 30.6, 33.3, 38.3, 44.4, 45.0, 54.6, 97.7, 99.0, 101.8, 105.5, 106.1, 121.5, 123.1, 123.8 124.8, 125.7, 126.6, 127.5, 128.2, 129.2, 130.3, 135.5, 139.5, 139.8, 146.5, 146.8, 150.1, 151.4, 151.7, 159.2. Anal. Calcd. for [$C_{40}H_{40}Cl_2N_2O$]: C, 75.58; H, 6.34; Cl, 11.15; N, 4.47%; obtained C, 75.43; H, 6.29; Cl, 11.10; N, 4.28%.

Spectral measurements

1D and 2D ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (San Diego, California, USA) NMR spectrometer operating at 300.07 MHz for ^{1}H and 75.46 MHz for ^{13}C. NMR tubes having a diameter of 5 mm contained samples in 0.1 M DMSO-d_6 solutions, and the spectra were recorded at 298 K. ^{1}H and ^{13}C chemical shifts were referenced to $SiMe_4$ in $CDCl_3$ as the internal standard or to the residual solvent signal in DMSO-d_6 (1H, 2.50 ppm; ^{13}C, 39.52 ppm). The digital resolution of the ^{1}H and ^{13}C NMR spectra was 0.25 and 0.6 Hz per point, respectively. Narrower spectral regions of special interest were measured with smaller spectral widths and larger digital resolutions (down to 0.2 Hz). The following techniques were used: BB-1H noise decoupling, attached proton test, ^{1}H–^{1}H COSY, and ^{1}H–^{13}C HETCOR. The ^{1}H–^{1}H COSY spectra were recorded in the magnitude mode with 1024 points in the F2 dimension and 256 increments in the F1 dimension. Each increment was obtained with 16 scans, a spectral width of 4500 Hz, and a relaxation delay of 1 s. The resolutions were 5.4 and 10.7 Hz per point in the F1 and F2 dimensions, respectively. The ^{1}H–^{13}C HETCOR spectra were recorded with one-bond ^{13}C–^{1}H coupling constant maintained at 140 Hz using 2048 points in the F2 dimension and 256 increments in the F1 dimension with a relaxation delay of 1 s. The spectral width in the F2 and F1 dimensions was 20 000 and 4500 Hz, respectively. The resulting resolutions in the F2 and F1 dimensions were 19.53 and 17.6 Hz per point, respectively. All 2D experiments were performed by standard pulse sequences using the Mercury Data System (California, USA) software version v NMR 6.1B. For proton decoupling, the Waltz 16 modulation was

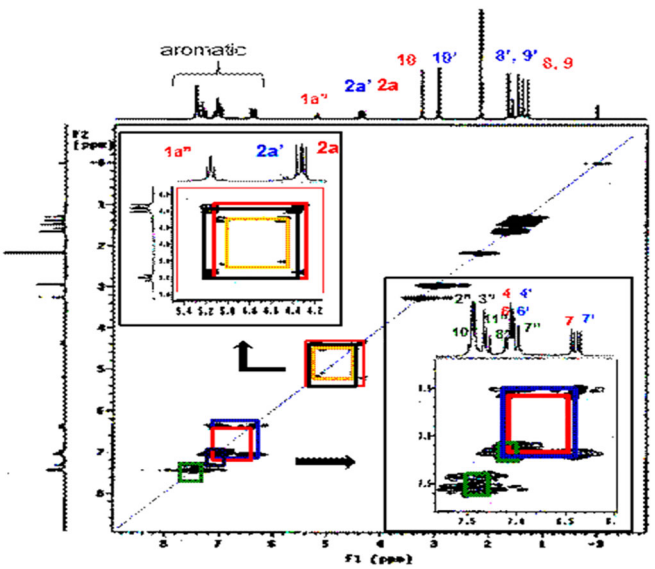


Figure 1. ^{1}H–^{1}H COSY spectrum of St-LTAM **4** (2*E*,2′*Z*)-2,2′-(2-(4-(4-chlorostyryl)phenyl)propane-1,3-diylidene)bis(5-chloro-1,3,3-trimethylindoline). Blue and red numbers denote the left and right rings, respectively.

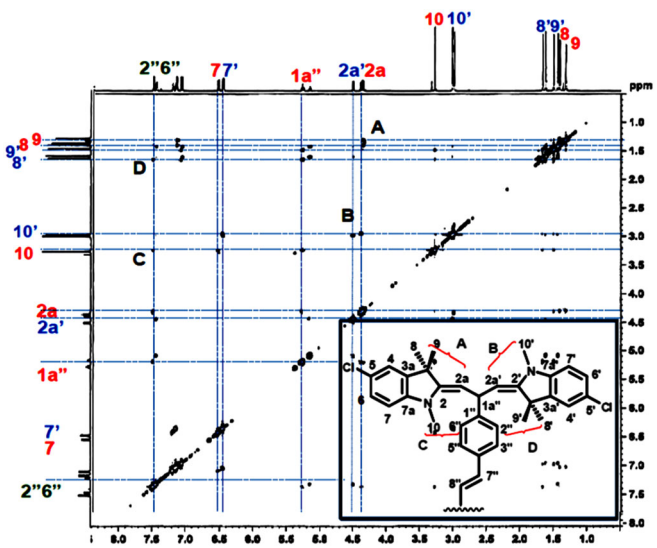


Figure 2. NOE correlation for St-LTAM **4**; spatial correlations of H2a–H8/H9 (A), H2a′–H10′ (B), H10–H2″/H6″ (C), and H9′/H8′–H2″/H6″ (D) are shown.

used. 2D NOESY and HMBC data were obtained from the Korea Research Institute of Chemistry Technology (Daejeon, Korea). The UV–Vis absorption spectra were recorded on a Varian Cary (Mountain View, CA, USA) 1E UV–Vis spectrometer.

Results and discussion

Synthesis of St-LTAM molecules

The (Y)-SBA derivatives were synthesized by the Heck reaction, which is the palladium-catalyzed coupling of olefins with aryl and vinyl halides.[27,28] The coupling of 4-bromobenzaldehydes with 4-substituted styrenes in the presence of 0.1 mol% of $Pd(OAc)_2$ with *N*,*N*-dimethylacetamide as the solvent afforded (Y)-SBA derivatives in isolated yields of 65–71% after 24 h at 140 °C. Most of these derivatives were obtained as white solids.

Next, St-LTAM compounds (St-LTAM) **1–6** were prepared by treating an excess of 5-substituted FB with the SBA derivatives thus prepared, as shown in Scheme 2, by employing the procedure reported by Keum *et al.*[20–22]

For the synthesis of TAM^+ dyes, dichloro dicyano quinone was first added to a solution of St-LTAM in benzene. Second, the solution was stirred for 1.5 h at room temperature. Third, the reaction mixture was poured onto a short column containing aluminum oxide. Next, a mixture of CH_2Cl_2 : methanol (9 : 1) was used as the eluting solvent, and a violet residue was obtained. Then, this residue was treated with 50 ml of methanol containing three drops of concentrated HCl and refluxed for 2.5 h. Finally, the solvent was evaporated, and the resulting dark green solution was purified by silica-gel column chromatography using a mixture of CH_2Cl_2 : methanol (9 : 1) to afford a blue solution, which was used for UV–Vis spectroscopy.

^{1}H NMR spectroscopy

The ^{1}H NMR spectra of all St-LTAMs exhibited characteristic signals in the aliphatic region, namely, a triplet and two doublets in the range of 4.20–5.40 ppm, in addition to two groups of identical singlets at 2.80–3.40 and 1.20–1.70 ppm, respectively.

The detailed ^{1}H and ^{13}C resonances of St-LTAMs **1–6** were assigned by COSY and one-bond ^{1}H–^{13}C correlations obtained by both direct-detection HETCOR and indirect-detection HSQC

Table 1. Selective 1D and 2D correlation NMR data for St-LTAM **4** in $CDCl_3$

Ring	1D and 2D correlation NMR					
	Atom	H (ppm)	C (ppm)	HSQC	HMBC[a]	NOESY
A	2a	4.35	95.9	√	C2, C3, C1″, H2a′	H1a″, Me-8, Me-9
	Me-8	1.43	30.6	√	C2, C3, C3a, C9	2a, 1a″, 4
	Me-9	1.30	30.3	√	C2, C3, C3a, C8	2a, 1a″, 4
	N-Me-10	3.25	33.6	√	C2, C7a	1a″, 2″/6″, 7
B	2a′	4.40	99.7	√	C2′, C3′, C1″, H2a	H2a′, *N*-Me-10′
	Me-8′	1.73	28.9	√	C2′, C3′, C3a′, C9′	1a″, 2″/6″, 4′
	Me-9′	1.39	28.2	√	C2′, C3′, C3a′, C8′	1a″, 2″/6″, 4′
	N-Me-10′	2.97	29.3	√	C2′, C7a′	2a′, 7′
C	1a″	5.26	38.3	√	H2a, H2a′, C2, C2′, C1″, C2″/6″	2a, Me-8, Me-9, *N*-Me-10, 2″/6″
	2″/6″	7.38	123.1	√	C2″/H6″, H2″/C6″, C4″, C3″/C5″, H3″, H5″	Me-8′, Me-9′, *N*-Me-10, 1a″

[a]Each carbon correlates with protons, and vice versa, in HMBC.

Table 2. Selected ^{1}H and ^{13}C NMR spectral data for the comparison between the *Z* and *E* rings for the major *ZE* diastereomer of various St-LTAM molecules in $CDCl_3$

Molecule	Position	δ_{1_H} (ppm)		Δ (ppm)[a] ($\delta_Z - \delta_E$)	δ_{13_C} (ppm)		Δ (ppm)[a] ($\delta_Z - \delta_E$)
		Z	*E*		*Z*	*E*	
St-LTAM **3**	4-/4; —	7.06	7.09	−0.03	122.3	121.8	0.50
	Me-8/Me-8′	1.40	1.66	*−0.26*	31.0	29.2	1.80
	Me-9/Me-9′	1.30	1.48	−0.18	30.9	28.4	2.50
	N-Me/*N*-Me′	3.26	2.94	**0.32**	33.7	29.4	**4.30**
St-LTAM **4**	4-/4; —	7.05	7.06	−0.03	122.3	121.8	0.50
	Me-8/Me-8′	1.43	1.73	*−0.26*	30.6	28.9	1.70
	Me-9/Me-9′	1.30	1.39	−0.18	30.3	28.2	2.10
	N-Me/*N*-Me′	3.25	2.97	**0.32**	33.6	29.3	**4.30**
St-LTAM **6**	4-/4; —	7.03	7.05	−0.02	123.1	121.5	1.60
	Me-8/Me-8′	1.40	1.66	*−0.26*	30.6	28.9	1.70
	Me-9/Me-9′	1.30	1.48	−0.18	30.3	28.4	1.90
	N-Me/*N*-Me′	3.28	2.94	**0.34**	33.3	29.9	**3.40**

[a]Differences of the δ values of *Z* isomers from the corresponding values of *E* isomers.
The *N*-methyl peaks (presented in bold) exhibit the most characteristic peaks.

experiments. COSY was used to identify the peaks from the A (left) and B (right) rings, as well as the central H1a″ of the stilbene unit correlated to the enamine protons, H2a or H2a′ of the two indoline rings.

Figure 1 shows the ^{1}H–^{1}H COSY spectrum of St-LTAM **4** in $CDCl_3$ as a representative example. The figure also shows magnified parts of the spectrum in the range of 4.20–5.40 ppm (upper) and 6.40–7.40 ppm (bottom) for detailed identification.

As shown in the upper region of the ^{1}H–^{1}H COSY spectrum in Fig. 1, a correlation was observed from H1a″ at 5.26 ppm to H2a and H2a′ at 4.35 and 4.40 ppm, respectively. The yellow square denotes a trace of the other isomer formed during the experiment, which is discussed later in this paper. In the aromatic region ranging from 6.40 to 7.40 ppm of the COSY spectrum, four more individual sets of correlations – {H7–H8}, {H7′–H8′}, {H7″–H8″}, and {H10″–H11″} – were observed.

HETCOR and HSQC were employed to identify the carbon shifts of carbons having protons attached by one-bond coupling between ^{1}H and ^{13}C. Some representative correlations such as {H1a″–C1a″}, {H2a–C2a}, and {H2a′–C2a′} were observed.

HMBC was employed for the correlation of the protons to their respective ring components. The remaining chemical shift assignments within the FB rings, A and B, of the molecules were mostly made by employing HMBC and NOESY data. As the A and B rings are not identical, HMBC was employed to differentiate between the two groups of molecules.

Table 3. ^{1}H and ^{13}C NMR data of St-LTAM **1–6** in $CDCl_3$ (300 and 75 MHz, respectively)

Ring[a]	H or C	St-LTAM **1**		St-LTAM **2**		St-LTAM **3**		St-LTAM **4**		St-LTAM **5**		St-LTAM **6**	
		δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
A	2	—	152.5	—	151.0	—	151.8	—	152.8	—	151.8	—	151.7
	2a	4.36	97.5	4.35	97.6	4.43	97.6	4.35	95.9	4.35	97.6	4.35	97.7
	3	—	45.3	—	45.0	—	45.0	—	45.0	—	45.0	—	45.0
	3a	—	138.6	—	139.8	—	137.5	—	139.5	—	139.8	—	139.5
	4	7.17	127.0	7.08	128.1	7.06	127.1	7.05	122.3	7.03	129.5	7.03	129.2
	5	6.81	118.9	6.75	121.8	—	119.0	—	121.9	6.80	121.9	—	123.8
	6	7.08	122.3	7.05	126.5	7.01	122.4	7.01	127.3	7.07	122.5	7.01	125.7
	7	6.55	105.9	6.54	106.3	6.43	105.8	6.42	106.5	6.55	106.3	6.42	106.1
	7a	—	148.5		146.6	—	148.7	—	146.3	—	147.0	—	146.8
	Me-8	1.43	29.5	1.41	29.4	1.40	29.4	1.35	30.3	1.38	29.4	1.40	29.9
	Me-9	1.33	29.7	1.32	30.8	1.30	30.8	1.26	30.6	1.31	30.4	1.30	30.3
	N-Me-10	3.34	34.0	3.29	33.7	3.26	33.7	3.25	33.6	3.33	33.6	3.28	33.3
B	2′	—	151.8	—	151.0	—	151.0	—	151.9	—	151.5	—	151.4
	2a′	4.43	101.6	4.49	101.8	4.41	101.8	4.40	99.7	4.41	99.9	4.41	99.0
	3′	—	44.7	—	44.4	—	44.4	—	44.4	—	44.4	—	44.4
	3a′	—	138.2	—	137.5	—	139.8	—	139.6	—	139.6	—	139.8
	4′	7.18	126.9	7.11	128.2	7.09	127.0	7.06	121.8	7.05	128.1	7.05	128.2
	5′	6.71	118.2	6.69	122.0	—	118.7	—	121.9	6.75	121.4	—	123.1
	6′	7.04	121.8	7.03	126.7	6.97	122.0	7.00	127.4	7.01	122.2	6.96	124.8
	7′	6.49	105.1	6.47	105.3	6.36	105.6	6.36	106.5	6.47	105.7	6.36	105.5
	7a′	—	146.8	—	144.9	—	146.5	—	144.7	—	146.6	—	146.5
	Me-8′	1.70	28.9	1.68	28.3	1.66	28.3	1.66	28.2	1.69	28.4	1.66	28.4
	Me-9′	1.53	29.1	1.51	29.3	1.48	29.3	1.48	28.9	1.46	28.8	1.48	28.9
	N-Me-10′	3.01	31.3	2.91	31.1	2.94	31.1	2.94	29.3	2.97	31.2	2.94	30.6
C	1a″	5.28	38.9	5.26	38.5	5.20	38.5	5.20	38.3	5.25	38.2	5.19	38.3
	1″	—	149.9	—	—	—	149.9	—	156.7	—	144.9	—	150.1
	2″/6″	7.48	128.5	7.44	128.6	7.48	128.5	7.39	123.1	7.42	126.4	7.43	130.3
	3″/5″	7.48	128.1	7.44	127.9	7.48	127.9	7.39	122.9	7.42	123.5	7.43	121.5
	4″	—	135.4	—	128.8	—	135.4	—	149.8	—	134.7	—	135.5
	7″	7.04	127.9	7.05	127.4	6.97	128.1	6.94	123.8	7.09	126.5	6.90	126.6
	8″	7.15	127.9	7.05	127.6	7.07	128.2	7.09	123.8	7.09	127.5	7.10	127.5
	9″	—	138.0	—	135.2	—	138.0	—	149.9	—	135.4	—	128.2
	10″/14″	7.42	128.1	7.44	128.5	7.48	127.9	7.39	122.8	7.42	122.9	7.43	121.5
	11″/13″	7.48	129.2	7.29	100.0	7.43	129.2	7.14	122.8	6.88	100.5	6.88	101.8
	12″	7.43	128.7	—	135.2	7.35	128.1	—	139.3	—	137.5	—	159.2
	(O)Me-12″	—	—	—	—	—		—	—	2.35	42.1	3.83	54.6
$J_{H2a–H1a″}$		9.30		9.30		9.30		9.30		9.40		9.40	
$J_{H2'a–H1a″}$		10.2		10.1		10.1		10.1		10.0		10.0	
$J_{H6–H7}$		8.10		8.20		8.20		8.20		8.30		8.30	
$J_{H6'–H7'}$		7.80		7.90		7.90		7.90		7.90		7.90	

[a]A–C rings are the left, right, and middle rings, respectively.

From HMBC experiments, the following correlations were observed: C-2 at 152.8 ppm to H-1a″ at 5.26 ppm, H-2a at 4.35 ppm, Me-8 at 1.43 ppm, Me-9 at 1.30 ppm, and *N*-Me-10 at 3.25 ppm of the A ring, as well as C-2′ at 151.9 ppm to H-1a″ at 5.26 ppm, H-2a′ at 4.40 ppm, Me-8′ at 1.73 ppm, Me-9′ at 1.39 ppm, and *N*-Me-10′ at 2.97 ppm of the B ring. Similarly, C-3 at 45.0 ppm of the A ring and C-3′ at 44.4 ppm of the B ring were correlated to H-2a at 4.35 ppm, H-4 at 7.05 ppm, Me-8 at 1.43 ppm, Me-9 at 1.30 ppm, H-2a′ at 4.40 ppm, H-4′ at 7.06 ppm, Me-8′ at 1.73 ppm, and Me-9′ at 1.39 ppm. Furthermore, by HMBC, C-3a at 139.5 ppm of the A ring and C-3a′ at 139.6 ppm of the B ring were correlated to H-7 at 6.43 ppm, Me-8 at 1.43 ppm, and Me-9 at 1.30 ppm of the A ring, and C-3a′ at 139.6 ppm was correlated to H-7′ at 6.36 ppm, Me-8′ at 1.73 ppm, and Me-9′ at 1.39 ppm of the B ring, respectively. Two individual sets of HMBC correlations between C3 and the *gem*-dimethyl groups [Me-8 and Me-9] and C3′ and the other *gem*-dimethyl groups [Me-8′ and Me-9′] indicate that they belong to the same subunit, either the A or B ring.

The configuration of the double bonds at positions 2–2a and 2′–2a′ of the enamine moiety of the A and B (FB) rings are either *E* or *Z*. NOE experiments were conducted for the identification of the geometry around the double bonds at positions 2–2a and 2′–2a′ of the enamine moiety of the A and B (FB) rings, respectively, as shown in Fig. 2.

In particular, a strong NOE correlation was observed between H2a at 4.35 ppm (ring-A) and the *gem*-dimethyl protons of the ring-B Me-8′ at 1.73 ppm and Me-9′ at 1.39 ppm (A), while H2a′ at 4.40 ppm (ring-B) exhibited NOE with the *N*-Me-10′ protons (ring-B) at 2.97 ppm (B). In addition, a simultaneous NOE correlation was also observed between ortho-protons H2″/H6″ of the stilbene ring and *N*-Me-10 at 3.25 ppm (ring-A) as well as between the *gem*-dimethyl protons Me-8′ at 1.73 ppm and Me-9′ at 1.39 ppm (ring-B). These NOE observations are compatible with *Z* and *E* arrangements of the double bond of the A and B rings, respectively. Table 1 lists the selective 1D and 2D correlation NMR data for St-LTAM **4** in $CDCl_3$.

The ^1H and ^{13}C chemical shifts of all six compounds were completely assigned. For comparison between the *Z* and *E* rings for the major *ZE* diastereomer of various St-LTAM molecules, Table 2 lists their selected ^1H and ^{13}C NMR spectral data in $CDCl_3$ (300 and 75 MHz, respectively).

The NMR data for the *Z* or *E* ring of the *ZE* isomer suggest that the signals of the *gem*-dimethyl group on the *E* ring were shifted downfield compared with those of the *Z* ring, whereas the signals of the *N*-methyl groups on the *Z* ring were shifted downfield compared with those on the *E* ring. Differences in the δ values of the *Z* and *E* isomers exhibited a decreasing order: *N*-Me peaks > Me-8 > Me-9 for ^1H NMR and *N*-Me peaks > Me-9 > Me-8 for ^{13}C NMR. These results indicated that the *N*-Me protons exhibit the most characteristic resonance peak for the isomeric *Z* or *E* rings.

Now, the following question may arise: 'What causes a difference in the chemical shifts between the protons of the *Z* or *E* ring of the *ZE* isomer'? The considerable deshielding of the *gem*-dimethyl protons 8′ and 9′ of the *E* ring and the *N*-methyl-10 proton of the *Z* ring, as compared with the corresponding protons of the *Z* and *E* ring, can be understood as being largely caused by the local diamagnetic anisotropy of the benzene ring of the stilbene moiety as those protons are in relative proximity to the benzene ring of the stilbene units.[29] In conclusion, the results of the 1D and 2D NMR study conducted herein provide a useful tool for the structural analysis of various St-LTAM molecules.

The detailed ^1H and ^{13}C NMR data of St-LTAM **1–6** are summarized in Table 3.

Diastereomeric isomerization

As shown in Scheme 3, the FB analogs of LTAM molecules are known to have three configurational isomers. However, the *ZE* isomers of the LTAM molecules are typically unstable in organic solvents, and depending on time, they equilibrate into a mixture of other diastereomers without any specific catalytic reagents.[30]

On the other hand, most of the FB analogs of LTAM molecules exhibited a *ZE* configuration in the solid state and equilibrated into a mixture of *EE* and *ZZ* diastereomers within 2–3 h at room temperature. This phenomenon is quiet reasonable as *ZE* would be expected to predominate over *ZZ* and *EE* in all media, based on quantum mechanical calculations.[31] However, the 4-pyryl and 4-nitrophenyl derivatives of the FB analogs of LTAM molecules have been reported to exhibit an *EE* configuration in the solid state and equilibrate into a mixture of *ZE* and *ZZ* diastereomers.[32,33] Thus, the FB analogs of LTAM molecules can be categorized as type 1 (*ZE*) and type 2 (*EE*), as shown in Fig. 3.

The methylene doublets of the *ZZ* isomers for this compound could not be detected because of their low concentration in the equilibrium state. The equilibrium ratios of the *ZZ* isomer, among the diastereomeric isomers, can be determined using the *N*-Me

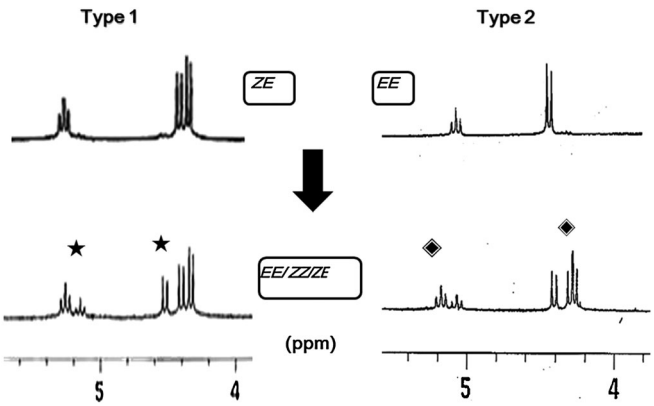
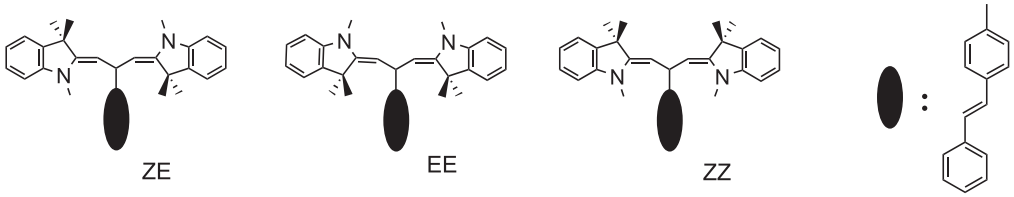


Figure 3. Types (1 and 2) of the configurational isomerization of the FB analogs of LTAM molecule; ★ and ■ denote the *EE* and *ZE* isomers, respectively (the trace amount of *ZZ* isomer is not shown).



Scheme 3. Three configurational isomers of the FB analogs of LTAM molecules.

proton peaks in the ^{1}H NMR spectra. The *N*-Me protons exhibited the most characteristic resonance peak as compared with those of the isomeric *Z* or *E* rings. Hence, the equilibrium ratios of the *ZZ* isomer are based on the intensities of the *N*-methyl protons corresponding to the three diastereomeric isomers at the equilibrium state, as shown in Fig. 4.

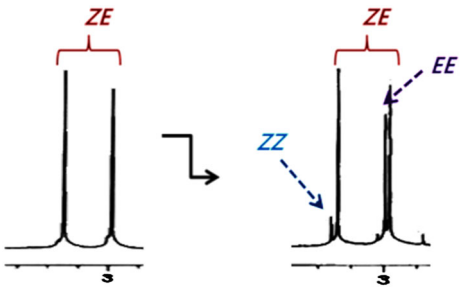


Figure 4. *N*-Methyl peaks from the configurational isomerization of the St FB analogs of LTAM molecules: before (left) and after (right) equilibrium.

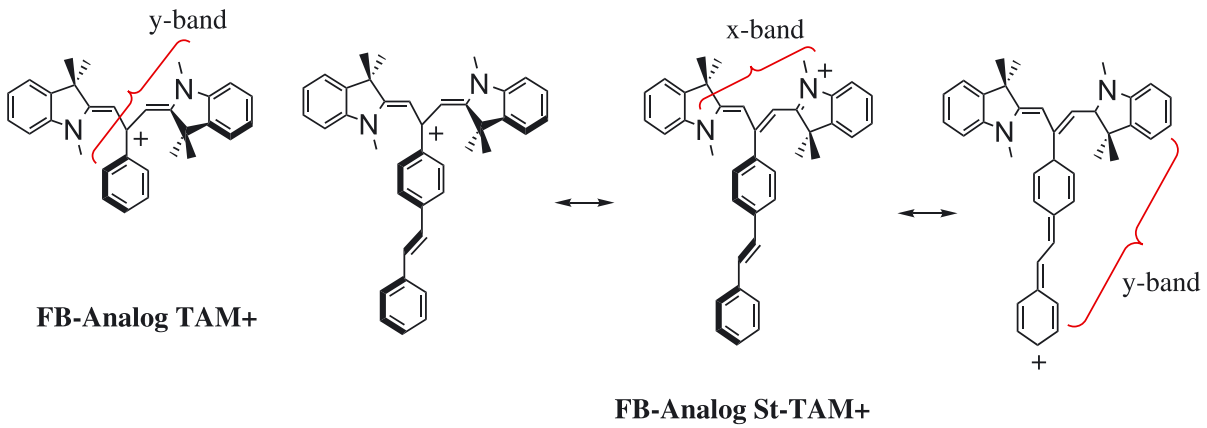
Meanwhile, the configurational stability of the LTAM molecules in the solid state depends on the identity of the aryl moiety, without any specific reason. The LTAM molecules in the shaded columns of Table 3 exhibited *EE* configuration, whereas the others exhibited the *ZE* configuration in the solid state. However, all molecules equilibrated to a mixture of three diastereomers. Irrespective of the types of molecules, the percent ratios among the diastereomeric isomers of the St-LTAM molecules in the thermal equilibrium states exhibited a marginal variation. Table 4 summarizes the percent ratios among the isomers of St-LTAM **1–6**, as well as the data of other LTAM molecules from previous studies for comparison.

Typically, these TAM$^+$ dyes exhibited two absorption bands: x-band and y-band; the x-band corresponds to the promotion of an electron from the nonbonding orbital to the lowest antibonding orbital, resulting in a high electron density on the central carbon atom, while the y-band corresponds to the excitation of an electron from the second-highest occupied bonding orbital to the lowest vacant orbital.[1] The x-bands of the extended TAM$^+$ were comparable with those of the unextended TAM$^+$ dyes, whereas the y-bands were expected to be better chromophores because of the

Table 4. Percent ratios among the isomers of St-LTAM **1–6** in $CDCl_3$ at equilibrium

LTAMs and St-LTAMs			Percent ratios[c]			Type[d]	Ref.
Compound[a]	Aryl group	Substituents[b]	*ZE*	*EE*	*ZZ*		
LTAM	Phenyl	H	60.2	28.3	11.4	1	Keum *et al.*[20,21] and Ma *et al.*[32]
		4-CHO	60.8	34.1	5.10	2	
		3-NO_2	62.9	29.6	7.50	1	
		4-NO_2	61.0	34.1	4.90	2	
	Pyridinyl	3-(N)	64.0	31.1	4.80	1	
		4-(N)	63.3	31.3	5.40	2	
St-LTAM **1**	Styryl	H	63.6	28.9	7.50	1	This study
St-LTAM **2**		4-Cl	62.7	29.7	7.60	1	
St-LTAM **3**		4-H	63.3	28.3	8.40	1	
St-LTAM **4**		4-Cl	62.6	29.8	7.60	1	
St-LTAM **5**		4-Me	63.1	29.4	7.50	1	
St-LTAM **6**		4-OMe	62.2	30.1	7.70	1	

[a]5,5′-Dichlorinated compounds except St-LTAM **1** and **2**.
[b]Substituents on the aryl moiety of LTAM or St-LTAM molecules.
[c]Percent ratios of the configurational isomers at equilibrium
[d]Isomerization types as shown in Fig. 3.



Scheme 4. The y-band in phenyl-based TAM$^+$ *versus* St-TAM$^+$ dyes.

extended conjugation from the nitrogen of the FB ring to the central stilbene ring, as shown in Scheme 4.

Detailed UV–Vis spectroscopic studies of various St-TAM$^+$ dyes in various organic solvents will be presented in the near future.[34]

Conclusion

A series of novel St FB analogs of LTAM – (2*E*,2′*Z*)-2,2′-(2-(4-styrylphenyl)propane-1,3-diylidene)bis(1,3,3-trimethylindoline) – dyes were synthesized and characterized by 1D and 2D NMR. All St-LTAM molecules examined herein exhibited the *ZE* configuration and isomerized to their diastereomers, *EE* and *ZZ*, in 2–3 h. They exhibited type I behavior of diastereomeric isomerization.

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