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Unsymmetrically Substituted Leuco-Triarylmethane Molecules Formed from the Reaction of a Fischer's Base and α,β-Unsaturated Iminium Salts *via* a Michael-Type Reaction

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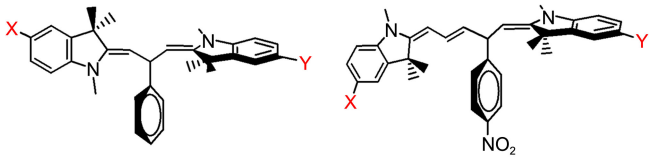
Triarylmethane (TAM) compounds, also known as "leuco-TAM" (LTAM), are used in a variety of chemical, pharmaceutical, and life science industries, including thermal imaging and carbonless copying materials.[1-3] In addition, they are used as either building blocks or blocking groups in the synthesis of many functional groups in organic compounds.[4-7] Furthermore, the oxidized species TAM^+ has many biological and medicinal functions.[8,9] For example, Malachite green (MG, 4-[(4-dimethylaminophenyl)-phenylmethyl]-*N*,*N*-dimethylaniline)—a TAM^+ molecule—is used primarily as a dye in the textile industry; it is also useful in treating fungal and bacterial infections in fish and fish eggs. Although it has been prohibited for use to control fungal infections in commercial fisheries,[10,11] MG continues to be used worldwide because of its ready accessibility and low cost. Consequently, there is a strong demand for the substitutes of MG compounds.

Many research groups[12-14] have examined the structural modification of LTAM molecules. We previously reported the synthesis and characterization of the Fisher's base (FB) analogs of LTAM molecules such as symmetrically substituted LTAM, (2*Z*, 2'*E*)-2,2'-(2-phenylpropane-1,3-diylidene)-*bis*(1,3,3-trimethylindoline) derivatives and unsymmetric LTAM (Un-LTAM), (2*E*, 2'*E*)-2,2'-{(*E*)-4-phenylpent-2-ene-1,5-diylidene}*bis*(1,3,3-trimethylindoline) molecules.[15-19] These LTAM molecules have a central carbon that has two symmetrically substituted FB fragments and one phenyl ring.

Although significant progress has been made toward the synthesis of the FB analogs of LTAM and Un-LTAM dyes, the synthesis of unsymmetrically substituted LTAM dyes has not been reported so far. As part of an ongoing study on the structural modification of LTAM molecules, we report the synthesis and structural elucidation of unsymmetrically substituted LTAM and Un-LTAM molecules, Us-LTAM1-2. Unsymmetrically substituted dyes contain two different substituents X and Y (*viz*. X ≠ Y) of the LTAM molecules. Chemical structures of symmetrically and unsymmetrically substituted LTAM and Un-LTAM dyes are shown in Scheme 1.

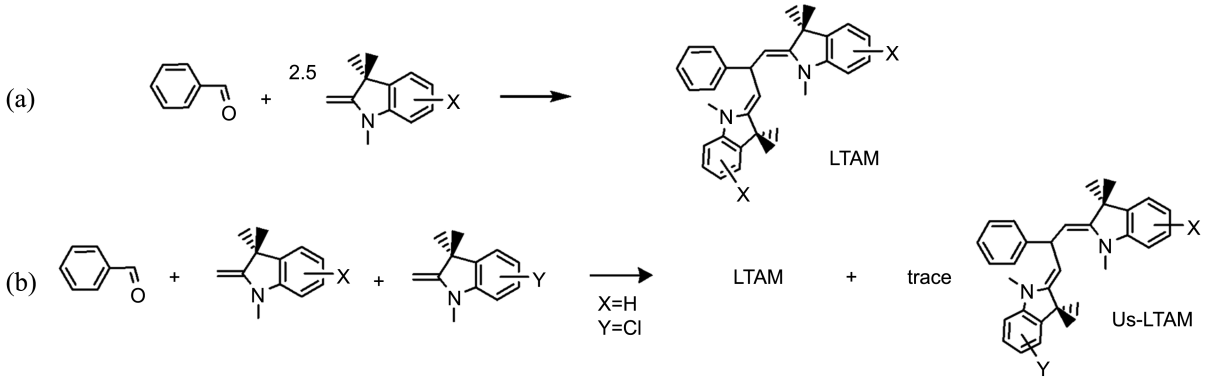
In general, the FB analogs of symmetrically substituted LTAM dyes were obtained from a reaction of an excess molar of FB with substituted aryl aldehydes.[15,16] In the first step, an enamine moiety of FB attacks the carbonyl carbon to form a carbinol anion, which then protonates from the reaction media (or solvent) in the second step. The third step is characterized by the dehydration of the carbinol forming an α,β-unsaturated iminium salt as a crucial intermediate. This iminium salt, an analog of the α,β-unsaturated carbonyl compound, reacts with an FB molecule as a nucleophile by a so-called Michael-type reaction.[20,21]

We first attempted to obtain unsymmetrically substituted LTAM dyes from the reaction of benzaldehyde derivatives

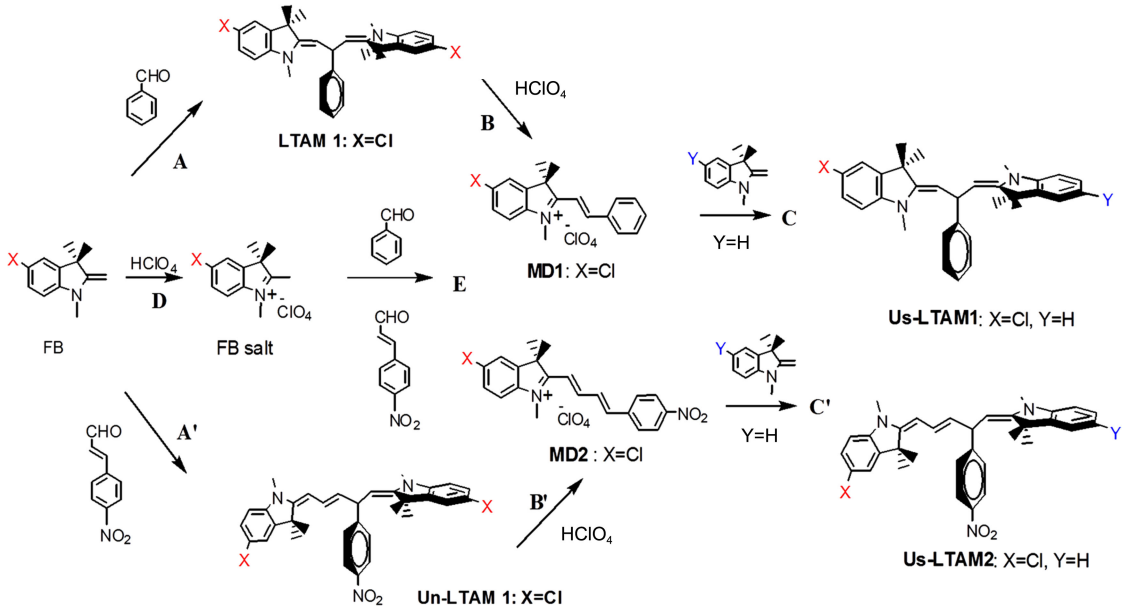


Us-LTAM (X≠Y) 1 Us-LTAM (X≠Y) 2

Scheme 1. Chemical structures of unsymmetrically substituted LTAM and Un-LTAM molecules.



Scheme 2. Formation of LTAM molecules from the reaction of benzaldehyde derivatives with either excess FB (a) or two different FB analogs (b).



Scheme 3. Synthetic scheme for the unsymmetrically substituted Us-LTAM1 and 2.

with two different FB molecules. Only a trace amount of unsymmetrically substituted LTAM molecule was obtained whereas symmetrically substituted LTAMs were surprisingly dominant, as shown in Scheme 2.

Since unsymmetrically substituted LTAM has two different FB groups and one phenyl ring on the central carbon, two consecutive processes are necessary. Thus, α,β-unsaturated iminium salts (MD1 and MD2 in Scheme 3) can be potent intermediates that can react with the other FB molecule *via* a Michael-type addition to synthesize unsymmetrically substituted LTAM molecules. Scheme 3 shows the complete synthetic scheme for the unsymmetrically substituted Us-LTAM1 and 2.

(*E*)-1,3,3-trimethyl-2-styryl-3*H*-indolinium perchlorate MD1 and 1,3,3-trimethyl-2-((1*E*,3*E*)-4-(4-nitrophenyl)buta-1,3-dienyl)-3*H*-indolinium perchlorate MD2 were prepared from the reaction of 1,2,3,3-tetramethyl-3*H*-indolinium perchlorate and the corresponding aldehydes in ethanol.

Alternatively, MD1 and MD2 were also obtained from the acid-catalyzed decomposition of the corresponding LTAM and Un-LTAM molecules in the ethanolic solutions of hydroperchloric acid (Steps B and B'). Both MD1 and MD2 have the maximum wavelength at 390 and 431 nm, and ε = 4.11×10^4 and 5.22×10^5 $Lmol^{-1}cm^{-1}$, respectively, in ethanol. As a representative example, Us-LTAM1 is formed from the reaction of an FB molecule with MD1, which was obtained from the reaction of 1,2,3,3-tetramethyl-3*H*-indolinium perchlorate with benzaldehyde. The LTAM (5-Cl) was linearly decomposed in acidic alcohol to yield MD1 and was then reacted with another molecule of FB to form an Us-LTAM1.

The chemical structures of MD1 and MD2 have been determined by one-dimensional ^1H and ^1H–^1H 2D COSY NMR experiments. The ^1H NMR spectra of MD1 displayed characteristic H_α and H_β central-ethylene signals at 7.85 and 8.30 ppm, respectively, and an aromatic AX system, H_A and H_B, in the 8.40-8.43 ppm range, in addition to *N*-methyl at 4.16 ppm and two identical gem-methyl groups at 1.81 ppm. The spectrum of MD2 is more complicated than that of MD1 because of the spectral overlap of the resonances corresponding to H_δ, H_6 and H_A, and H_B and H_γ. ^1H–^1H COSY was used to identify protons belonging to the central carbons, Hα–Hδ, linking the two aromatic rings. COSY signals in the 7.0-8.5 ppm range showed three correlations (H_α–H_β, H_β–H_γ, H_γ–H_δ) for the central protons of MD2.

The final step in the formation of Us-LTAM1 and 2 is the Michael-type reaction of an α,β-unsaturated iminium salt (MD1 and MD2) with the substituted FB molecule. Concerning the mechanism, general LTAM molecules can be formed from the Michael-type addition of the second FB molecule on the β carbon of α,β-unsaturated iminium salts (*e.g.*, MD1). On the other hand, unsymmetrical LTAM molecules are originated from a δ carbon attack of α, β, γ, δ-

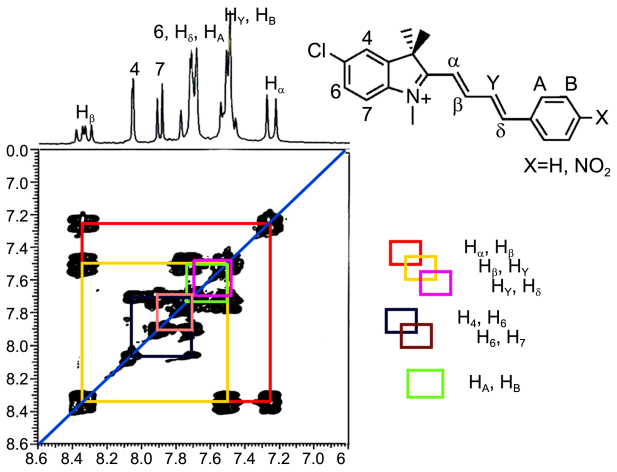


Figure 1. COSY spectrum of MD2 in the 7.0-8.5 ppm range showing three correlations (H_α–H_β, H_β–H_γ, H_γ–H_δ) for the central protons.

unsaturated iminium salts (*e.g.*, MD2). Experimentally, unsymmetrical LTAM molecules were formed as the sole product. This suggests that the Michael-type addition of an FB molecule occurs on the δ-carbon and not on the β-carbon of the α,β,γ,δ-unsaturated iminium salts.

Figure 2 shows the comparison of ^{1}H NMR spectra of Un-LTAM1 (X = Y = Cl), Un-LTAM2 (X = Y = H), and Us-LTAM2 (X = Cl, Y = H) in the 5.0-8.5 ppm region. The characteristic ^{1}H NMR resonances of these LTAM molecules were identical, except for the 5H of Un-LTAM1, which is absent at 6.75 ppm (see Figure 2(a)).

As a representative example, the chemical structure of Us-LTAM2 was determined by ^{1}H NMR, 2D COSY, HETCOR, and NOESY experiments.

As reported earlier,[14] Malachite green FB analogs (LTAM), (2*Z*, 2'*E*)-2,2-(2-phenylpropane-1,3-diylidene)-*bis*(1,3,3-trimethylindoline) derivatives show the characteristic ^{1}H NMR resonance patterns of the three adjacent protons, two *N*-methyl, and diastereotopic gem-dimethyl groups. Therefore, these *N*-methyl and three consecutive protons (H_α, H_β, and H_γ) were used to characterize the LTAM molecules. The methylene protons H_α and H_β resonate as two doublets at ~4.3 and ~4.4 ppm, respectively, while the central proton H_γ is observed as a doublet of doublets at 5.4 ppm. Two *N*-methyl groups are well separated at 1.3-1.4 and 1.5-1.7 ppm ranges, and correspond to the *E*- and *Z*-indoline groups, respectively. The four diastereotopic methyl groups are also well separated and resonate as *E*- and *Z*-indoline groups at 1.32-1.44 and 1.50-1.70 ppm ranges, respectively.

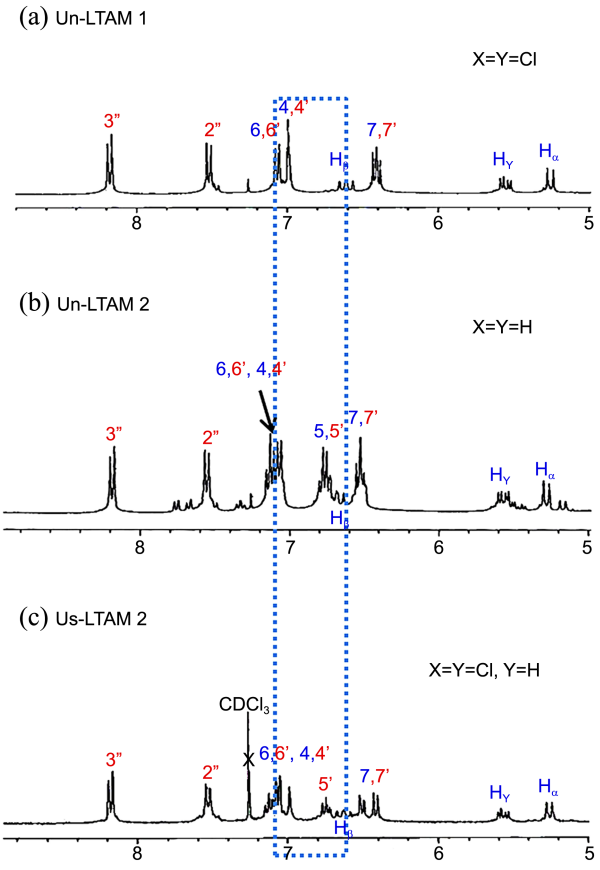


Figure 2. Comparison of ^{1}H NMR spectroscopy of (a) Un-LTAM1 (X = Y = 5-Cl), (b) Un-LTAM2 (X = Y = H), and (c) Us-LTAM2 (X = 5-Cl, Y = H) in the 5.0-8.5 ppm range.

In contrast, the ^{1}H NMR spectra of Un-LTAM molecules display very different signals for the five closely correlated protons H_α–H_ε. They are well separated over a wide region (~4.4-6.8 ppm).

COSY was used to identify the protons belonging to the aromatic rings, particularly the five consecutive protons on the connecting carbon chain between the two indoline groups. H_β was simultaneously correlated with the two H_α and H_γ protons. Similarly, H_γ was also correlated with H_γ and H_ε.

2D NOESY spectrum of Us-LTAM2 gives information about the spatial correlations. Some selective correlation data of H_α–H_ε are collected in Table 1. These spatial correlations are particularly crucial for the protons of interest such as H_α (H_α-*N*Me, H_α–H_β, and H_α–H_γ) and H_ε (H_ε-*N*Me', H_ε–H_δ, and H_ε–H_γ), which are indicated in red and blue dashed lines, respectively, in Table 1.

In conclusion, novel unsymmetrically substituted LTAM molecules are successfully synthesized from the Michael-type reaction of α,β-unsaturated iminium salts (MD1 and MD2) with substituted FB molecules.

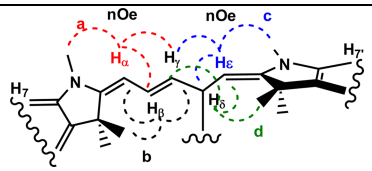
Experimental Section

General Procedures. Melting points were determined on a Nikon Labophot-2 polarizing microscope equipped with a Mettler FP82HT hot stage. The ^{1}H NMR spectra were obtained in deuterated chloroform on a Varian Mercury 300 NMR instrument. Chemical shifts were reported in δ (ppm) relative to tetramethylsilane as the internal standard. The UV–Vis absorption spectra were recorded using a Varian Cary 1E UV–Vis spectrometer.

^{1}H NMR Experiment. All NMR data were acquired on a Varian Mercury 300 NMR spectrometer operating at 300.07 MHz for ^{1}H and 75.46 MHz for ^{13}C. Sample solutions with 0.1 M concentration in DMSO-d_6 were placed in 5-mm

Table 1. The spatial correlations of H_α, H_β, H_γ, H_δ, and H_ε with other related protons of the NOESY spectrum of Us-LTAM**2** in the 1.0-7.0 ppm region in $CDCl_3$

Structure showing selective nOe



Us-LTAM 2

proton		nOe	note
Symbols	δ (ppm)		
H_α	5.28	H_γ, *N*-Me	a
H_β	6.66	H_α, H_γ, H_δ, H_8, H_9	b
H_γ	5.59	H_α, H_β, H_δ, H_ε	-
H_δ	4.82	H_β, H_γ, H_ε, $H_{8'}$, $H_{9'}$	d
H_ε	4.39	H_γ, H_δ, *N*-Me	c

Particularly crucial nOe to determine the diasteromeric configuration

NMR tubes, and the spectra were recorded at 298 K. ^{1}H and ^{13}C chemical shifts were referenced with $SiMe_4$ in $CDCl_3$ as the internal standard or with the residual solvent signal in DMSO-d_6 (^{1}H, 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: attached proton test, ^{1}H–^{1}H COSY, ^{1}H–^{1}H NOESY, and ^{1}H–^{13}C HETCOR. The ^{1}H–^{1}H COSY spectra were obtained 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 measured with one-bond ^{1}H–^{13}C coupling constant set to 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 was 20,000 Hz in the F2 and 4500 Hz in the F1 dimension. The resulting resolution was 19.53 Hz per point in the F2 and 17.6 Hz per point in the F1 dimension. All 2D experiments were performed by the standard pulse sequences using the Mercury Data System software Version V NMR 6.1B. For proton decoupling, the Waltz 16 modulation was used.

Materials. The required FB derivatives 2-methylene-1,3,3-trimethylindoline, 5-chloro-2-methylene-1,3,3-trimethylindoline and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were purchased from Aldrich and used without further purification.

The methine dyes, (*E*)-1,3,3-trimethyl-2-styryl-3*H*-indolinium perchlorate (MD1) and 1,3,3-trimethyl-2-((1*E*,3*E*)-4-(4-nitrophenyl)buta-1,3-dienyl)-3*H*-indolinium perchlorate (MD2) were obtained from the reaction of 1,2,3,3-tetramethyl-3*H*-indolinium perchlorate (FB-$HClO_4$) with benzaldehyde and (*E*)-3-(4-nitrophenyl)acrylaldehyde derivatives, respectively. These materials were recrystalyzed in hot EtOH. Us-LTAM1 and 2 is formed from the reaction of an α,β-unsaturated iminium salt (MD1 and MD2) with the substituted FB molecule and recrystalized in acetone.

(*E*)-5-Chloro-1,3,3-trimethyl-2-((*Z*)-2-phenyl-3-(1,3,3-trimethylindolin-2-ylidene)propylidene)indoline, Us-LTAM1: Greenish yellow; yield, 21%; melting point, 170-171 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.05 (s, 3H), 1.32 (s, 3H), 1.41 (s, 3H), 1.68 (s, 3H), 2.95 (s, 3H), 3.26 (s, 3H), 4.36 (d, J = 9.3 Hz, 1H), 4.42 (d, J = 9.9 Hz, 1H), 5.22 (t, J = 9.0, 10.2 Hz, 1H), 6.35 (d, J = 7.8 Hz, 1H), 6.42 (d, J = 7.5 Hz, 1H), 6.70 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 7.02 (s, 1H), 7.05 (t, J = 7.8 Hz, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.22 (t, J = 7.2 Hz, 1H), 7.33 (dd, J = 7.2, 7.5 Hz, 2H), 7.46 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.5, 28.9, 29.3, 30.6, 30.8, 33.5, 38.6, 44.3, 44.8, 97.3, 101.9, 105.3, 105.5, 118.5, 122.5, 123.0, 123.1, 126.0, 126.8, 127.4, 127.8, 128.5, 139.4, 139.9, 145.0, 146.4, 147.7, 151.5, 151.6; EI mass spectra for $C_{31}H_{33}ClN_2$, Mw: 469.06; C, 79.38; H, 7.09; Cl, 7.56; N, 5.97 obtained C, 79.33; H, 7.21; Cl, 7.64; N, 5.82.

(*E*)-5-Chloro-1,3,3-trimethyl-2-((3*E*,5*E*)-2-(4-nitrophenyl)-5-(1,3,3-trimethylindolin-2-ylidene)pent-3-enylidene)-indoline, Us-LTAM2: Brown; yield, 44%; melting point, 257-259 °C; 1H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 3H), 1.49 (s, 3H), 1.55 (s, 3H), 1.61 (s, 3H), 3.03 (s, 3H), 3.06 (s, 3H), 4.39 (d, J = 11.0, 1H), 4.82 (dd, J = 6.0, 10.2 Hz, 1H), 5.28 (d, J = 11.0 Hz, 1H), 5.59 (dd, J = 11.0, 6.0 Hz, 1H), 6.43 (d, J = 7.5 Hz, 1H), 6.52 (d, J = 7.8 Hz, 1H), 6.66 (dd, J = 11.0, 11.0 Hz, 1H), 6.75 (dd, J = 8.3, 7.5 Hz, 1H), 7.00 (d, J = 2.1 Hz 1H), 7.05 (d, J = Hz, 1H), 7.07 (dd, J = 7.8, 2.1 Hz, 1H), 7.11 (t, J = 7.5 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 8.19 (d, J = 8.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2, 28.4, 28.5, 28.7, 29.0, 29.4, 44.4, 45.1, 45.1, 94.9, 95.6, 144.7, 145.7, 105.4, 105.6, 118.8, 121.6, 122.1, 123.1, 123.9, 126.9, 127.5, 127.8, 128.6, 128.8, 138.0, 140.1, 146.3, 153.8, 153.9, 155.6; ES mass spectra for $C_{33}H_{34}ClN_3O_2$, Mw: 540.09; C, 73.39; H, 6.35; Cl, 6.56; N, 7.78 obtained C, 73.47; H, 6.43; Cl, 6.70; N, 7.69.

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