New fluorescent indolizines and bisindolizinylethylenes

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Abstract

Eleven new highly fluorescent indolizines and bisindolizinyl ethylene derivatives were synthesized using azomethine ylides for 1,3-dipolar cycloaddition reactions. An investigation of the optical properties indicated a high tunable fluorescence, both in solid state and solution.

Keywords: Azomethine ylides, 1,3-dipolar cycloaddition, fluorescence, indolizines

Introduction

Pyrroloazines are an important class of N-bridgehead heterocycles due to their interesting biological[1,2] and optical properties,[3,4] as demonstrated by the large volume of literature available on the subject.[5–10] One of the most recent developments is the use of such compounds in optoelectronic devices, mostly as pure-color luminophores in OLEDs (organic light emitting diodes).[11,12] Indolizine, resembling condensed pyridine and pyrrole rings, is the simplest pyrroloazine. The indolizine skeleton offers the possibility of fine tuning certain properties by varying the number and type of substituents.[13–15] An example is the synthesis of highly specific chemosensors obtained by linking 7-substituted indolizines to a cyclodextrine moiety.[16]

Several synthetic methods for obtaining indolizines are known, one of the most versatile being 1,3-dipolar cycloaddition reactions with azomethine ylides.[14–21] N-Ylides are excellent staring materials for obtaining pyrrolo[1,2-*b*]pyridazines[8–13] and other highly fluorescent pyrroloazines.[21–23]

Our interest in pyrroloazines led us to investigate the influence of an ethylene spacer between two indolizine moieties, starting from 1,2-dipyridylethylenes using a sequence of 1,3-dipolar cycloaddition reactions involving azomethine ylides. Herein we report the synthesis and

spectral characterization of a series of 7-[1-(2-pyridyl)vinyl]indolizines and 1,2-bisindolizinyl-ethylenes.

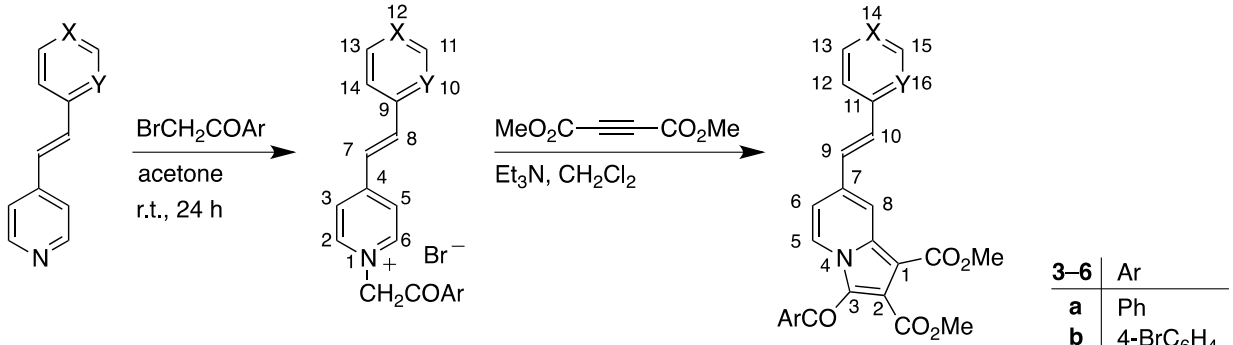
Results and Discussion

Synthesis and structural characterization

The key intermediates, pyridinium salts **3** and **4** were obtained in very high yield from (*E*)-1,2-di(pyridinyl)ethenes **1** and **2** and ω-bromoacetophenone derivatives.

The NMR spectra of compounds **3** and **4** show characteristic signals of the ethylene protons in the range of δ 8.19–7.90 (J = 15.9 Hz) and δ 8.06–7.81 (J = 16.5 Hz), respectively.

Indolizines **5** and **6** were obtained in moderate yields by reacting salts **3** and **4**, respectively, with dimethyl acetylenedicarboxylate (DMAD) in the presence of triethylamine in methylene chloride. Although this method is known to yield 3,8a-dihydroidolizines as byproducts,[5] NMR data indicated only trace amounts of such compounds (Scheme 1).



1 (X=CH, Y=N)
2 (X=N, Y=CH)

3a–d (X=CH, Y=N)
4a–d (X=N, Y=CH)

5a–d (X=CH, Y=N)
6a–d (X=N, Y=CH)

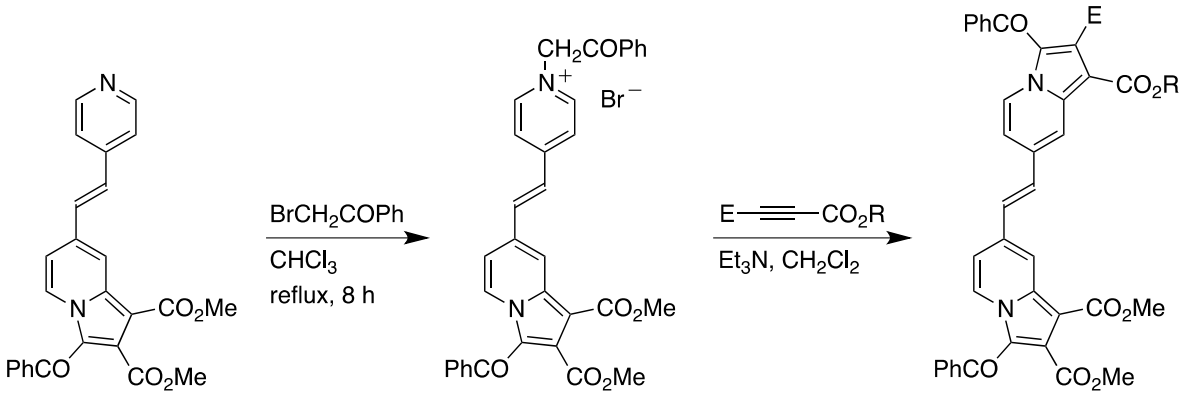
Scheme 1. Synthesis of indolizines **5** and **6**.

In salts **3** and **4**, the chemical shifts of the ethylene protons are shifted upfield to δ 8.10–8.16 for H-7 and δ 7.89–8.01 for H-8 ($J_{7,8}$ = 15.9 Hz) compared to the chemical shifts in compounds **5** and **6** at around δ 7.75 for H-9 and δ 7.20 for H-10 ($J_{9,10}$ = 16.5 Hz). In both compounds **5** and **6**, the characteristic proton signals of the indolizine moiety, H-5, H-6, and H-8 appear at around δ 9.50 ($J_{5,6}$ = 7.7 Hz), δ 7.25 and 8.45 ($J_{6,8}$ = 1.9 Hz), respectively. The ^{13}C-NMR data for compounds **5** and **6** are in accordance with the proposed structures.

The attempt to quaternize the pyridyl nitrogen atom in compounds **5** with ω-bromoacetophenone proved unsuccessful, probably due to the increased steric hindrance caused by the vinyl group in 2-position.

However, refluxing compound **6a** and ω-bromoacetophenone in chloroform furnished compound **7** in excellent yield (Scheme 2). The pyridinium moiety in compound **7** entails the deshielding of H-10 to δ 8.27 (J = 16.2 Hz).

Compounds **8** were obtained in moderate yields using the same method as applied for **5** and **6** (Scheme 2). With ethyl propiolate as dipolarophile, the yield of **8b** was slightly lower than with DMAD, and NMR data proved the reaction to be completely regioselective.



Scheme 2. Synthesis of (*E*)-1,2-di(indolizin-7-yl)ethanes **8**.

Spectral characterization

Five representative compounds were subjected to spectroscopic and fluorimetric measurements and compared with our previous study.[3] No significant difference was observed between the two main absorption bands of compounds **5a** and **6a**. Compounds **8a,b** show a bathochromic shift as compared to the latter, **8a** showing the highest absorbance of the series. The main absorption band of compound **7** has a distinct appearance, due to the presence of the pyridinium moiety.

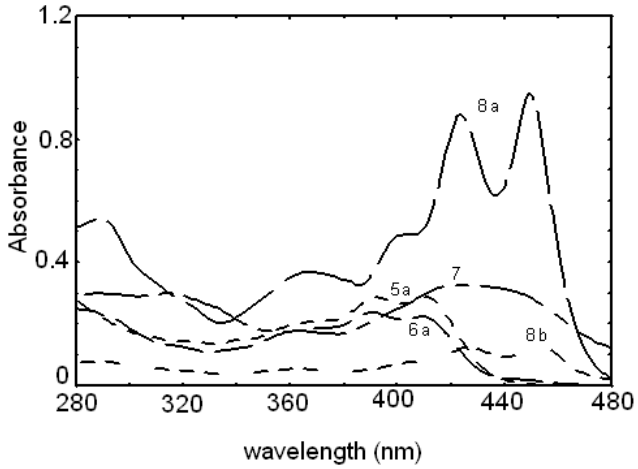


Figure 1. Absorption spectra of the indolizine derivatives **5a**, **6a**, **7**, **8a**,**b** (c = 1x10^{-5} M) in DMSO.

The fluorescence spectra show a clear distinction between compounds **5a**, **7** and **6a**, and **8a,b** indicating that the substituent in position 7 of the indolizine group strongly influences the fluorescent emission through the ethylene spacer. The pyridinium moiety in **7** causes a large bathochromic shift in the fluorescence emission spectra. Also, the 2-pyridyl group in **5** leads to a higher emission wavelength compared to that of **6** with a 4-pyridyl moiety. No significant shift differences were observed between **6a** and **8a,b**, the 4-pyridyl group having a minimal influence on the emission wavelengths. It should be noted that the most intense fluorescence bands correspond to the nonsymmetric **8b**.

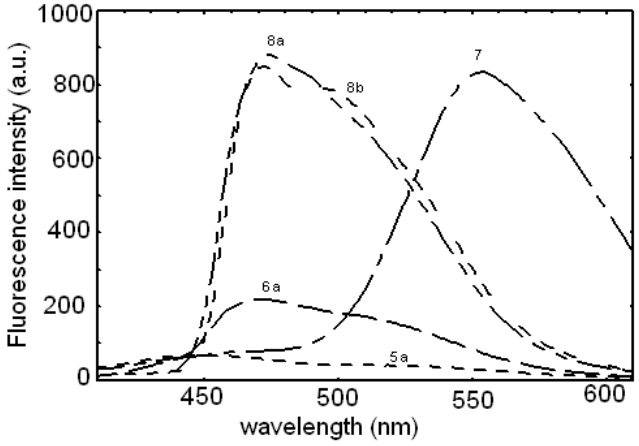


Figure 2. Fluorescence emission spectra of **5a**, **6a**, **7**, **8a**,**b** in DMSO (c = 10^{-5} M). λ_{ex} = 360 nm.

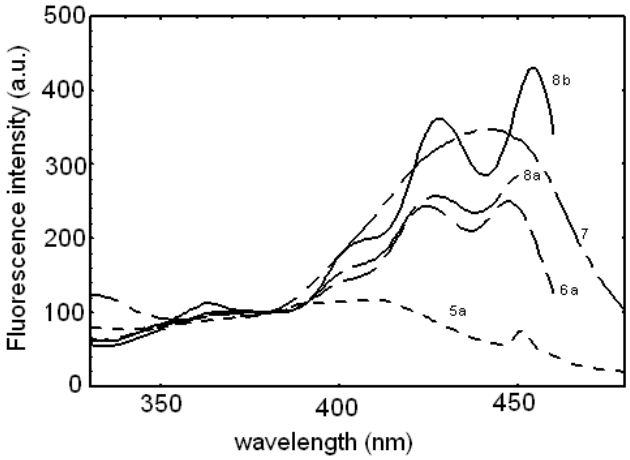


Figure 3. Fluorescence excitation spectra (normalized at 360 nm) of **5a**, **6a**, **7**, **8a**,**b** at different emission wavelengths (λ_{em}): 520 nm **5a**, 470 nm **6a**, 555 nm **7**, 420 nm **8a**, 470 nm **8b**.

Fluorescence quantum yields Φ_f have been calculated compared to quinine bisulfate in 0.1N H_2SO_4, with Φ_f = 0.55. The values observed are generally low, between 0.006 (for **5a**) and

0.061 (for **8b**). An interesting aspect is the large difference (more than double) between the quantum yields of **6a** (0.018) and **8a** (0.060), the two compounds having the same fluorophore.

Table 1. Absorption (λ_{abs} and ε) and fluorescence (λ_{em} and quantum yield, Φ_f) parameters for the indolizines derivatives **5a**, **6a**, **7**, **8a**,**b** in DMSO

Compound	λ_{abs} [nm]	ε [L.mol^{-1} cm^{-1}]10^3	λ_{em} [nm]	Φ_f
5a	366	20.4	480	0.006
	392	28.3	513	
	411	28.7		
6a	363	17.8	514	0.018
	391	23.5		
	409	22.2		
7	316	29.9	554	0.059
	365	17.5		
	421	32.7		
8a	289	54.4	508	0.060
	366	36.6	526	
	403	49.2		
	423	88.8		
	450	94.8		
8b	289	7.70	552	0.061
	363	5.31		
	404	7.30		
	427	12.4		
	454	13.2		

The fluorescence in all the compounds is much more intense in the solid state than in solution. The largest difference between solid and liquid measurements is shown by **5a**, about 24 times more intense in the solid state than in DMSO solution. The similarities observed between **6a** and **8a** in solution can also be seen in the solid state, while compound **8b** has a very similar fluorescence spectrum as compound **7**.

Compared to 4-pyridyl-7-indolizines,[3] the fluorescence spectra in solution of **6** and **8** show similar emission wavelengths and intensities, in spite of the presence of the ethylene spacer. However, when comparing 2-pyridyl-5-indolizines[3] to **5**, a bathochromic shift is noted for the latter, due to the decreased steric strain caused by the ethylene bridge. This is also responsible for the higher fluorescence observed for all the compounds in the solid state, probably due to a different molecular stacking.

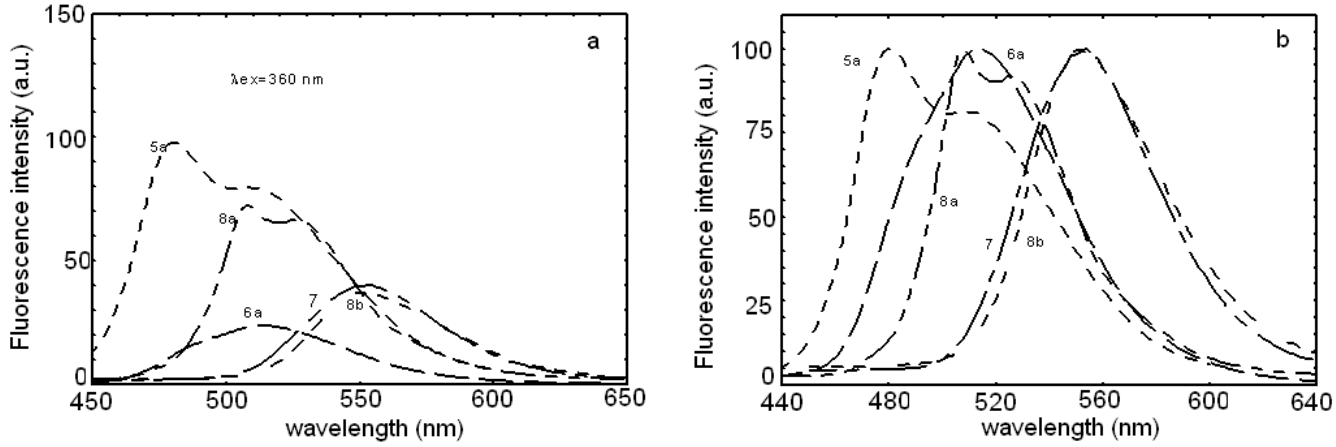


Figure 4. Fluorescence emission spectra of indolizine derivatives powders (a) and the same spectra normalized (b); λ_{ex} = 360 nm.

Conclusions

Eight new pyridinium salts and eleven new indolizine derivatives were synthesized, the latter by 1,3-dipolar cycloaddition reactions with azomethine ylides. The products were characterized using NMR and FT-IR spectroscopy. The fluorescence spectra of representative compounds of the series indicate possible use in optoelectronic or biolabeling applications. The influence of the substituents present on the indolizine ring was highlighted and, in comparison with previous results, the ethylene spacer has little influence in solution, but a significant one in the solid state.

Experimental Section

General. Melting points were determined on a Boëtius hot plate. The NMR spectra were recorded on a Varian Gemini 300 BB instrument (300 MHz for ^{1}H and 75 MHz for ^{13}C). Supplementary evidence was obtained by HETCOR and COSY experiments. The IR spectra (ATR) were recorded on a Vertex 70 Bruker instrument. Elemental analyses were determined on COSTECH Instruments EAS32 (Centre for Organic Chemistry, Spl. Independentei 202B, Bucharest 060023, Romania). Starting materials **1, 2**, and reactants as purchased from Sigma-Aldrich were used without further purification. Spectrophotometric studies have been performed with Perkin Elmer, Lambda 35 absorption spectrophotometer, and fluorescence steady-state emission and excitation spectra were recorded with JASCO FP 6500 spectrofluorimeter at 23 °C. All spectrophotometic measurements have been performed in 1 cm path length quartz cuvettes.

General procedure for the preparation of (3) and (4)

To a solution of (*E*)-1-(2-pyridyl)-2-(4-pyridyl)ethylene **1** (0.91 g, 5 mmol) or (*E*)-1,2-bis(4-pyridyl)ethylene **2** (0.91 g, 5 mmol) in acetone (50 mL) was added the corresponding ω-

bromoacetophenone (6 mmol). The mixture was left in a sealed Erlenmeyer flask for 24 h. The precipitate formed was filtered off and washed with acetone. Salts **3** and **4** were subsequently used without any further purification.

General procedure for the preparation of (5, **6)**, **and (8)**

To a suspension of salt **3**, **4**, or **7 (**2 mmol) in dichloromethane (20 mL) was added DMAD (310 mg, 2.2 mmol) or ethyl propiolate (215 mg, 2.2 mmol). A solution of triethylamine (0.3 mL, 2 mmol) in methylene chloride (5 mL) was added dropwise under vigorous stirring. After 20 min, the reaction mixture was washed with water (50 mL) 3 times, ethanol (96%, 30 mL) was added and the resulting precipitate was filtered off and washed with absolute ethanol. The crude product was purified by column chromatography (short column of standardized aluminum oxide 90, methylene chloride).

(*E*)-4-[2-(3-Benzoyl-1,2-bis(methoxycarbonyl)indolizin-7-yl)-vinyl]-1-(2-oxo-2-phenylethyl) pyridinium bromide (7). A solution of dimethyl (*E*)-3-benzoyl-7-(2-pyridin-4-yl-vinyl) indolizine-1,2-dicarboxylate **6a** (1.32 g, 3 mmol) and ω-bromoacetophenone (0.70 g, 3.5 mmol) in chloroform (30 mL) was refluxed for 8 h. The resulting precipitate was filtered off and washed with chloroform.

(*E*)-1-(2-Oxo-2-phenylethyl)-4-[2-(pyridin-2-yl)vinyl]pyridinium bromide (3a). White powder (1.89 g, 99%); mp 278–282 °C. Anal. Calcd. for $C_{20}H_{17}BrN_2O$: C, 63.01; H, 4.49; N, 7.35. Found: C, 63.38; H, 4.61; N, 7.61. IR: 3030, 2931, 1693, 1630, 1148 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 9.04, 9.02 (2H, AA' H-2,6), 8.75 (1H, dd, *J* = 4.8, 1.8 Hz, H-11), 8.56, 8.54 (2H, BB', H-3,5), 8.19 (1H, d, *J* = 15.9 Hz, H-7) , 8.14–8.11 (2H, m, H-2',6'), 8.01–7.94 (2H, m, H-8,13), 7.83 (1H, m, H-4'), 7.78 (1H, d, *J* = 7.8 Hz, H-14), 7.73–7.68 (2H, m, H-3',5'), 7.49 (1H, ddd, *J* = 7.6, 4.7, 1.8 Hz, H-12), 6.56 (2H, s, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 191.7 (CO), 153.7 (C), 151.0 (CH), 146.8 (CH), 141.1 (CH), 138.2 (CH), 135.5 (CH), 134.5 (C), 134.4 (C), 130.0 (CH), 129.1 (CH), 127.4 (CH), 125.9 (CH), 125.5 (CH), 125.2 (CH), 66.3 (CH_2).

(*E*)-1-[2-(4-Bromophenyl)-2-oxoethyl]-4-[2-(pyridin-2-yl)vinyl]pyridinium bromide (3b). White powder (2.18 g, 95%); mp 200–203 °C. Anal. Calcd. for $C_{20}H_{16}Br_2N_2O$: C, 52.20; H, 3.50; N, 6.09. Found: C, 52.03; H, 3.32; N, 6.50. IR: 3033, 2934, 1692, 1633, 1195 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.99, 8.97 (2H, AA', H-2,6), 8.76 (1H, dd, *J* = 4.8, 1.8 Hz, H-11), 8.55, 8.53 (2H, BB', H-3,5), 8.16 (1H, d, *J* = 15.9 Hz, H-7), 8.07–7.92 (m, 6H, H-8,2',3',5',6'), 7.78 (1H, d, *J*=7.8 Hz, H-14), 7.50 (1H, dd, *J* = 7.6, 4.7 Hz, H-12), 6.49 (2H, s, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 190.8 (CO), 153.8 (C), 153.5 (C), 150.7 (CH), 146.5 (CH), 141.0 (CH), 137.8 (CH), 133.4 (C), 132.8 (CH), 130.7 (CH), 129.3 (C), 127.2 (CH), 125.4 (CH), 125.1 (CH), 125.0 (CH), 65.9 (CH_2).

(*E*)-1-[2-[(1,1'-Biphenyl)-4-yl]-2-oxoethyl]-4-[2-(pyridin-2-yl)vinyl]pyridinium bromide (3c). White powder (2.22 mg, 97%); mp 187–191 °C. Anal. Calcd. for $C_{26}H_{21}BrN_2O$: C, 68.28; H, 4.63; N, 6.12. Found: C, 67.96; H, 4.81; N, 6.25. IR: 3031, 2930, 1687, 1623, 1190 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 9.02, 9.00 (2H, AA', H-2,6), 8.72 (m, 1H, H-11), 8.53, 8.51 (2H,

BB', H-3,5), 8.18–8.12 (3H, m, H-7,2',6'), 8.00–7.92 (4H, m, H-8,13,3',5'), 7.83–7.80 (2H, m, H_{Ph}-2,6), 7.75 (1H, d, *J* = 7.8 Hz, H-14), 7.57–7.43 (4H, m, H_{Ph}-3,4,5, H-4'), 6.54 (2H, s, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 190.5 (CO), 152.9 (C), 152.8 (C), 150.2 (CH), 145.9 (CH), 145.8 (C), 140.2 (CH), 138.4 (C), 137.4 (CH), 132.4 (C), 129.2 (CH), 129.0 (CH), 128.8 (CH), 127.2 (CH), 127.1 (CH), 126.5 (CH), 125.1 (CH), 124.7 (CH), 124.4 (CH), 65.4 (CH_2).

(*E*)-1-[2-(4-Cyanophenyl)-2-oxoethyl]-4-[2-(pyridin-2-yl)vinyl]pyridinium bromide (3d). White powder (1.85 g, 92%); 228–232 °C. Anal. Calcd. for $C_{21}H_{16}BrN_3O$: C, 62.08; H, 3.97; N, 10.34. Found: C, 62.22; H, 4.07; N, 10.26. IR: 3007, 2951, 1699, 1625, 1192 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.00, 8.98 (2H, AA', H-2,6), 8.71 (1H, m, H-11), 8.53, 8.51 (2H, BB', H-3,5), 8.27–8.12 (5H, m, H-7,2',3',5',6'), 7.97–7.89 (2H, m, H-8,13), 7.75 (1H, m, H-14), 7.45 (1H, m, H-12), 6.58 (2H, s, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 190.5 (CO), 153.0 (C), 152.7 (C), 150.1 (CH), 145.9 (CH), 140.3 (CH), 137.4 (CH), 136.9 (C), 133.1 (CH), 128.9 (CH), 126.5 (CH), 125.1 (CH), 124.7 (CH), 124.4 (CH), 117.9 (C), 116.2 (C), 65.6 (CH_2).

(*E*)-1-(2-Oxo-2-phenylethyl)-4-[2-(pyridin-4-yl)vinyl]pyridinium bromide (4a). White powder (1.85 g, 97%); mp 227–230 °C. Anal. Calcd. for $C_{20}H_{17}BrN_2O$: C, 63.01; H, 4.49; N, 7.35. Found: C, 63.17; H, 4.32; N, 7.11. IR: 3018, 2937, 1682, 1623, 1183 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.05, 9.03 (2H, AA', H-2,6), 8.69, 8.67 (2H, AA', H-11,13), 8.39, 8.37 (2H, BB', H-3,5), 8.11 (2H, AA', H-2',6'), 7.98 (1H, d, *J* = 16.5 Hz, H-7), 7.78–7.59 (6H, m, H-8,10,14,3',4',5'), 6.60 (s, 2H, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 190.3 (CO), 152.9 (C), 150.3 (CH), 146.1 (CH), 142.0 (C), 138.9 (CH), 134.6 (CH), 133.6 (C), 129.0 (CH), 128.3 (CH), 127.3 (CH), 124.5 (CH), 121.9 (CH), 65.5 (CH_2).

(*E*)-1-[2-(4-Bromophenyl)-2-oxoethyl]-4-(2-(pyridin-4-yl)vinyl)pyridinium bromide (4b). White powder (2.25 g, 98 %). mp >360 °C. Anal. Calcd. for $C_{20}H_{16}Br_2N_2O$: C, 52.20; H, 3.50; N, 6.09. Found: C, 51.81; H, 3.38; N, 6.15. IR: 3016, 2937, 1695, 1634, 1182 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.95, 8.93 (2H, AA', H-2,6), 8.74, 8.72 (2H, AA', H-11,13), 8.46, 8.44 (2H, BB', H-3,5), 8.08–8.02 (3H, m, H-7,10,14), 7.94–7.83 (5H, m, H-8,2',3',5',6'), 6.41 (s, 2H, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 191.2 (CO), 153.7 (C), 151.5 (CH), 147.1 (CH), 143.1 (C), 139.5 (CH), 133.6 (C), 133.3 (CH), 131.2 (CH), 129.9 (C), 128.7 (CH), 125.4 (CH), 122.9 (CH), 66.4 (CH_2).

(*E*)-1-[2-[(1,1'-Biphenyl)-4-yl]-2-oxoethyl]-4-(2-(pyridin-4-yl)vinyl)pyridinium bromide (4c). White powder (2.22 g, 97%); mp 288–291 °C. Anal. Calcd. for $C_{26}H_{21}BrN_2O$: C, 68.28; H, 4.63; N, 6.12. Found: C, 68.36; H, 4.40; N, 6.16. IR: 3032, 2936, 1684, 1626, 1189 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.99, 8.98 (2H, AA', H-2,6), 8.74, 8.72 (2H, AA', H-11,13), 8.46, 8.44 (2H, BB', H-3,5), 8.17, 8.15 (2H, AA', H-2',6'), 8.06 (1H, d, *J* = 16.5 Hz, H-7), 8.00 (2H, BB', H-3',5'), 7.90–7.81 (3H, m, H-8, H_{Ph}-2,6), 7.74, 7.72 (2H, BB', H-10,14); 7.58–7.45 (m, 3H, H_{Ph}-3,4,5); 6.48 (s, 2H, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 190.4 (CO), 152.6 (C), 150.5 (CH), 146.2 (CH), 145.9 (C), 142.3 (C), 138.4 (CH), 132.4 (C), 129.2 (CH), 129.0 (CH), 128.8 (CH), 127.9 (CH), 127.2 (CH), 127.1 (CH), 65.5 (CH_2).

(*E*)-1-[2-(4-Cyanophenyl)-2-oxoethyl]-4-(2-(pyridin-4-yl)vinyl)pyridinium bromide (4d). White powder (1.90 g, 93%); mp 317–321 °C. Anal. Calcd. for $C_{21}H_{16}BrN_3O$: C, 62.08; H, 3.97;

N, 10.34. Found: C, 61.79; H, 4.17; N, 10.52. IR: 3027, 2911, 2226, 1702, 1627, 1188 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.95, 8.93 (2H, AA', H-2,6), 8.73, 8.71 (2H, AA', H-11,13), 8.47, 8.45 (2H, BB', H-3,5), 8.24, 8.22 (2H, AA', H-2',6'), 8.18, 8.16 (2H, BB', H-3', H-5'), 8.07 (1H, d, *J* = 16.5 Hz, H-7), 7.87 (1H, d, *J* = 16.5 Hz, H-8), 7.74, 7.72 (2H, BB', H-10,14), 6.49 (s, 2H, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 190.4 (CO), 152.7 (C), 150.5 (CH), 146.1 (CH), 142.2 (C), 138.5 (CH), 136.8 (C), 133.1 (CH), 128.8 (CH), 127.8 (CH), 124.4 (CH), 121.9 (CH), 117.9 (C), 116.3 (C), 65.7 (CH_2).

(*E*)-Dimethyl 3-benzoyl-7-(2-pyridin-2-yl-vinyl)indolizine-1,2-dicarboxylate (5a). Bright yellow needles (306 mg, 35%); mp 193–195 °C. Anal. Calcd. for $C_{26}H_{20}N_2O_5$: C, 70.90; H, 4.58; N, 6.36. Found: C, 70.74; H, 4.26; N, 6.40. IR: 3003, 2950, 1696, 1620, 1206 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.57 (1H, d, *J* = 7.7 Hz, H-5), 8.65 (1H, ddd, *J* = 5.0, 1.9, 0.8 Hz, H-13), 8.42 (1H, d, *J* = 1.9 Hz, H-8), 7.75–7.69 (2H, m, H-9,12), 7.62–7.54 (5H, m, H_{Ph}), 7.44 (1H, dt, *J* = 7.7, 1.1 Hz, H-15), 7.38–7.31 (2H, m, H-6,10), 7.22 (1H, ddd, *J* = 7.7, 5.0, 1.1 Hz, H-14), 3.90, 3.40 (6H, 2s, $2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.4 (CO), 165.2, 163.3 (CO_2Me), 154.5 (C), 150.1 (CH), 138.6 (C), 138.4 (C), 137.0 (C), 136.9 (CH), 132.3 (C), 132.1 (CH), 131.4 (CH), 130.3 (CH), 129.9 (CH), 128.4 (C-5), 126.8 (C), 123.1 (CH), 121.0 (CH), 118.7 (C-8), 113.7 (C-6), 105.1 (C-1), 52.5, 51.9 ($2CH_3$).

(*E*)-Dimethyl 3-(4-bromobenzoyl)-7-(2-pyridin-2-ylvinyl)indolizine-1,2-dicarboxylate (5b). Bright yellow needles (384 mg, 37%); mp 186-189 °C. Anal. Calcd.for $C_{26}H_{19}BrN_2O_5$: C, 60.13; H, 3.69; N, 5.39. Found: C, 60.01; H, 3.88; N, 5.12. IR: 3011, 2952, 1692, 1611, 1256 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.54 (1H, d, *J* = 7.4, H-5), 8.65 (1H, dd, *J* = 4.7, 2.4 Hz, H-13), 8.42 (1H, d, *J* = 1.9 Hz, H-8), 7.75–7.66 (3H, m, H-9,12,2',6'), 7.48–7.42 (3H, m, H-3',5',15), 7.37–7.30 (2H, m, H-6,10), 7.22 (1H, ddd, *J* = 7.7, 5.0, 1.1 Hz, H-14), 3.90, 3.40 (6H, 2s, $2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.8 (CO), 165.2 (CO_2Me), 163.5 (CO_2Me), 154.6 (C), 150.1 (CH), 139.6 (C), 138.4 (C), 136.9 (CH), 136.7 (C), 132.2 (C), 132.0 (CH), 131.9 (CH), 130.0 (CH), 128.8 (CH), 128.4 (CH), 128.3 (CH), 123.1 (CH), 121.5 (C), 118.8 (C-8), 113.5 (C-6), 104.9 (C-1), 52.4, 51.9 ($2CH_3$).

(*E*)-Dimethyl 3-[(1,1'-biphenyl]-4-carbonyl]-7-[2-(pyridin-2-yl)vinyl]indolizine-1,2-dicarboxylate (5c). Bright yellow needles (340 mg, 33%); mp 197–199 °C. Anal. Calcd. for $C_{32}H_{24}N_2O_5$: C, 74.41; H, 4.68; N, 5.42. Found: C, 74.46; H, 4.28; N, 5.34. IR: 3046, 2947, 1695, 1604, 1214 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.55 (1H, d, *J* = 7.7 Hz, H-5), 8.66 (1H, dd, *J* = 5.0 Hz, 1.9 Hz, H-13), 8.45 (1H, d, *J* = 1.9 Hz, H-8), 7.80–7.32 (14H, m, $H_{biphenyl}$, H-6,9,10,12,15), 7.23 (1H, ddd, *J* = 7.7, 5.0, 1.9 Hz, H-14), 3.91, 3.35 (6H, 2s, $2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.3 (CO), 165.3, 163.5 ($2CO_2$), 154.6 (C), 150.1 (CH), 144.8 (C), 140.1 (C), 138.5 (C), 138.4 (C), 136.9 (CH), 136.7 (C), 132.1 (C), 131.9 (CH), 130.0 (CH), 129.4 (CH), 129.1 (CH), 128.4 (C-5), 128.3 (CH), 127.4 (CH), 126.9 (CH), 123.1 (CH), 121.6 (C), 118.8 (C-8), 113.5 (C-6), 105.0 (C-1), 52.4, 51.9 ($2CH_3$).

(*E*)-Dimethyl 3-(4-cyanobenzoyl)-7-[2-(pyridin-2-yl)vinyl]indolizine-1,2-dicarboxylate (5d). Bright yellow needles (289 mg, 31%); mp 241–244 °C. Anal. Calcd. for $C_{27}H_{19}N_3O_5$: C, 69.67; H, 4.11; N, 9.03. Found: C, 70.03; H, 3.93; N, 8.85. IR: 2999, 2951, 2228, 1694, 1621, 1212 cm^{-}

[1]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.58 (1H, d, *J* = 7.7 Hz, H-5), 8.59 (1H, dd, *J* = 5.0, 1.9 Hz, H-13), 8.38 (1H, d, *J* = 1.9 Hz, H-8), 7.72 (1H, d, *J* = 16.4 Hz, H-9), 7.69–7.61 (5H, m, H-12,2',3', 5',6'), 7.38 (1H, dt, *J* = 7.7, 1.1 Hz, H-15), 7.34 (1H, dd, *J* = 7.4, 1.9 Hz, H-6), 7.29 (1H, d, *J* = 16.4 Hz, H-10), 7.17 (1H, dd, *J* = 7.7, 5.0 Hz, H-14), 3.83, 3.29 (6H, 2s, $2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.5 (CO), 165.0, 163.1 ($2CO_2$), 154.4 (C), 150.1 (CH), 143.4 (C), 138.9 (C), 137.6 (C), 137.0 (CH), 133.0 (C), 132.6 (C), 132.5 (CH), 132.0 (CH), 129.7 (CH), 129.2 (CH), 128.7 (C-5), 123.3 (CH), 120.3 (C), 118.7 (C-8), 118.2 (C), 114.2 (C-6), 105.7 (C-1), 52.6, 52.0 ($2CH_3$).

(*E*)-Dimethyl 3-benzoyl-7-[2-(pyridin-4-yl)vinyl]indolizine-1,2-dicarboxylate (6a). Yellow powder (231 mg, 27%); mp 232–235 °C. Anal. Calcd. for $C_{26}H_{20}N_2O_5$: C, 70.90; H, 4.58; N, 6.36. Found: C, 70.69; H, 4.70 N, 6.44. IR: 3024, 2949, 1734, 1692, 1220 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.55 (1H, d, *J* = 7.4 Hz, H-5), 8.64–8.63 (2H, AA', H-13,15), 8.41 (1H, d, *J* = 1.8 Hz, H-8), 7.71–7.41 (7H, m, H_{Ph}, H-12,16), 7.38–7.30 (2H, m, H-H-9), 7.20 (1H, d, *J* = 16.4 Hz, H-10), 3.89, 3.31 (6H, 2s, $2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.4 (CO), 165.1 (CO_2), 163.5 (CO_2), 150.6 (CH), 143.6 (C), 140.0 (C), 139.5 (C), 138.4 (C), 132.2 (CH), 132.0 (C), 130.4 (CH), 130.1 (CH), 128.8 (CH), 128.5 (C-5), 128.3 (CH), 121.6 (C), 121.2 (CH), 118.9 (C-8), 113.1 (C-6), 105.0 (C-1), 52.4, 51.9 ($2CH_3$).

(*E*)-Dimethyl 3-(4-bromobenzoyl)-7-[2-(pyridin-4-yl)vinyl]indolizine-1,2-dicarboxylate (6b). Yellow powder (310 mg, 30%); mp 248–251 °C. Anal. Calcd. for $C_{26}H_{19}BrN_2O_5$: C, 60.13; H, 3.69; N, 5.39. Found: C, 60.09; H, 3.46; N, 5.12. IR: 3015, 2950, 1734, 1693, 1222 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.53 (1H, d, *J* = 7.4 Hz, H-5), 8.66, 8.64 (2H, AA', H-13,15), 8.41 (1H, d, *J* = 1.8 Hz; H-8), 7.62–7.54 (4H, m, H-2',3',5',6'), 7.43, 7.41 (2H, BB', H-12,16), 7.38–7.31 (2H, m, H-6,9), 7.21 (1H, d, *J* = 16.4, H-10), 3.90, 3.39 (6H, 2s, $2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.5 (CO), 165.1, 163.3 ($2CO_2$), 150.6 (CH), 143.5 (C), 138.5 (C), 138.3 (C), 136.3 (C), 132.1 (C), 131.5 (CH), 130.3 (CH), 128.5 (C-5), 127.0 (C), 121.2 (CH), 118.9 (C-8), 113.3 (C-6), 105.2 (C-1), 52.6, 52.0 ($2CH_3$).

(*E*)-Dimethyl 3-[(1,1'-biphenyl)-4-carbonyl]-7-[2-(pyridin-4-yl)vinyl]indolizine-1,2-dicarboxylate (6c). Yellow powder (301 mg, 29%); mp 230–232 °C. Anal. Calcd. for $C_{32}H_{24}N_2O_5$: C, 74.41; H, 4.68; N, 5.42. Found: C, 74.23; H, 4.37; N, 5.66. IR: 3029, 2949, 1698, 1592, 1221 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.47 (1H, d, *J* = 7.4 Hz, H-5), 8.58, 8.56 (2H, AA', H-13,15), 8.35 (1H, d, *J* = 1.8 Hz; H-8), 7.73–7.56 (7H, m, H-2,3',5',6',2'',4'',6''), 7.44–7.24 (5H, m, H-6,9,12,16, 5'',3''), 7.14 (1H, d, *J* = 16.4), 3.84, 3.28 (6H, 2s, $2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.4 (CO), 165.2, 163.5 ($2CO_2$), 150.4 (CH), 145.0 (C), 143.9 (C), 140.0 (C), 138.4 (C), 138.2 (C), 135.9 (C), 131.8 (C), 130.7 (CH), 130.0 (CH), 129.5 (CH), 129.1 (CH), 128.5 (CH), 128.4 (CH), 127.4 (CH), 126.9 (CH), 121.3 (CH), 119.0 (C-8), 113.1 (C-6), 105.1 (C-1), 52.5, 52.0 ($2CH_3$).

(*E*)-Dimethyl 3-(4-cyanobenzoyl)-7-[2-(pyridin-4-yl)vinyl]indolizine-1,2-dicarboxylate (6d). Yellow powder (259 mg, 28%); mp 274–277 °C. Anal. Calcd. for $C_{27}H_{19}N_3O_5$: C, 69.67; H, 4.11; N, 9.03. Found: C, 69.39; H, 4.37; N, 9.00. IR: 3013, 2951, 2235, 1695, 1615, 1169 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+TFA): δ 9.67 (1H, d, *J* = 7.4 Hz, H-5), 8.86, 8.84 (2H, AA', H-

13,15), 8.64 (1H, s, H-8), 8.10, 8.08 (2H, BB', H-12,16), 7.82–7.80 (4H, m, 4-CN-C_6H_4), 7.75 (1H, d, *J* = 16.2 Hz, H-10), 7.48–7.42 (2H, m, H-6,9), 3.94, 3.39 (6H, 2s, $2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$+TFA): δ 185.1 (CO), 165.3, 163.5 ($2CO_2$), 154.2 (C), 142.6 (C), 141.7 (CH), 138.4 (C), 138.3 (CH), 135.0 (C), 132.7 (C), 132.2 (CH), 129.2 (C-5), 126.7 (CH), 124.0 (CH), 121.2 (C-8), 117.7 (CN), 115.4 (C), 113.9 (C-6), 106.7 (C-1), 53.0, 52.6 ($2CH_3$).

(*E*)-4-[2-[3-Benzoyl-1,2-bis(methoxycarbonyl)indolizin-7-yl]vinyl]-1-(2-oxo-2-phenylethyl) pyridinium bromide (7). Orange powder (1.59 g, 83%); mp 241–243 °C. Anal. Calcd. for $C_{34}H_{27}BrN_2O_6$: C, 63.86; H, 4.26; N, 4.38. Found: C, 64.19; H, 3.96; N, 4.55. IR: 3007, 2950, 1692, 1615, 1207, 1181 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.38 (1H, d, *J* = 7.4 Hz, H-5), 8.96, 8.94 (2H, AA', H-13,15), 8.54 (1H, s, H-8), 8.47, 8.45 (2H, BB', H-12,16), 8.27 (1H, d, *J* = 16.2 Hz, H-10), 8.10 (2H, d, *J* = 7.4 Hz, H-2'',6''), 7.85–7.64 (8H, m, $H_{Ph'}$, H-3'',4'',5''), 7.55–7.50 (2H, m, H-6,9), 3.85, 3.34 (6H, 2s, $2CH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 190.9 (COPh''), 186.0 (COPh'), 164.1, 162.4 ($2CO_2$), 152.8 (C), 146.0 (CH), 138.6 (C), 138.5 (CH), 137.0 (C), 134.8 (C), 133.7 (C), 130.7 (C), 129.2 (CH), 128.6 (C-5), 128.2 (CH), 128.1 (CH), 126.9 (CH), 124.1 (CH), 121.9 (C), 120.5 (C-8), 112.7 (C-6), 104.7 (C-1), 65.4 (CH_2), 52.0, 51.8 ($2CH_3$).

(*E*)-Tetramethyl 7,7'-(ethene-1,2-diyl)bis(3-benzoylindolizine-1,2-dicarboxylate) (8a). Yellow powder (560 mg, 40%); mp 345–348 °C. Anal. Calcd. for $C_{40}H_{30}N_2O_{10}$: C, 68.76; H, 4.33; N, 4.01. Found: C, 69.13; H, 4.45; N, 4.01. IR: 3159, 2942, 1743, 1693, 1218 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+TFA): δ 9.61 (1H, d, *J* = 7.4 Hz, H-5), 8.47 (1H, d, *J* = 1.9 Hz, H-8), 7.71–7.60 (3H, m, H-2',4',6'), 7.53–7.44 (3H, m, H-6,3',5'), 7.41 (1H, s, H-9), 3.96, 3.34 (6H, 2s, $2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$+TFA): δ 188.0 (CO), 166.3, 164.2 ($2CO_2$), 139.1 (C), 138.6 (C), 137.3 (C), 133.0 (C), 132.9 (CH), 130.4 (CH), 129.1 (CH), 128.9 (CH), 128.6 (C-5), 121.5 (C), 118.8 (C-8), 114.0 (C-6), 105.5 (C-1), 53.1, 52.6 ($2CH_3$).

(*E*)-Dimethyl 3-benzoyl-7-[2-[3-benzoyl-1-(ethoxycarbonyl)indolizin-7-yl]vinyl]indolizine-1,2-dicarboxylate (8b). Pale yellow powder (582 mg, 40%); mp 298–302 °C. Anal. Calcd. for $C_{39}H_{30}N_2O_8$: C, 71.55; H, 4.62; N, 4.28. Found: C, 71.84; H, 4.75; N, 4.03. IR: 3144, 2949, 1745, 1704, 1688, 1218, 1195 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+TFA): δ 9.93 (1H, d, *J* = 7.4 Hz, H-5), 9.63 (1H, d, *J* = 7.4 Hz, H-17), 8.51 (1H, s, H-8), 8.48 (1H, s, H-12), 7.90 (1H, s, H-14), 7.81–7.44 (14H, m, $10H_{COPh}$, H-6,9,10,18), 4.48 (2H, q, *J* = 7.1 Hz, CH_2), 3.98, 3.35 (3H, s, $2CH_3$), 1.48 (3H, t, *J* = 7.1 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$+TFA): δ 188.3, 187.4 (2CO), 166.3, 165.6, 164.4 ($\underline{C}O_2Et$, $2\underline{C}O_2Me$), 141.3 (C), 139.3 (C), 138.3 (C), 138.2 (C), 137.7 (C), 133.3 (C), 133.1 (CH), 132.8 (CH), 132.7 (CH), 130.7 (CH), 130.5 (CH), 130.1 (CH), 129.3 (CH), 129.2 (CH), 128.9 (C-5), 128.7 (CH), 123.1 (C), 121.5 (C), 118.9, 118.4 (2C-8), 114.3 (C-6), 113.8 (C-6), 108.2, 105.7 (2C-1), 62.0 (CH_2), 53.4, 52.8 ($2CH_3$), 14.6 (CH_3).

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References

1. Yue, G.; Wan, Y.; Song, S.; Yang, G.; Chen, Z. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 453.
2. Jones, D. T.; Harris. A. L.; *Mol. Cancer Ther.* **2006**, *5*, 2193.
3. Vasilescu, M.; Bandula, R.; Dumitrascu, F.; Lemmetyinen, H. *J. Fluoresc.* **2006**, *16*, 631.
4. Vasilescu, M.; Bandula, R.; Cramariuc, O.; Hukka, T.; Lemmetyinen, H.; Rantala, T. T.; Dumitrascu F. *J. Photoch. Photobiol. Chemistry*: A **2008**, *194*, 308.
5. Georgescu, E.; Caira, M. R.; Georgescu, F.; Draghici, B.; Popa, M. M.; Dumitrascu, F. *Synlett* **2009**, 1795.
6. Dumitrascu, F.; Mitan, C. I.; Draghici, C.; Caproiu, M. T.; Raileanu D. *Tetrahedron Lett.* **2001**, *42*, 8379.
7. Zbancioc, G.; Mangalagiu, I. *Synlett* **2006**, 804.
8. Zugravescu, I.; Petrovanu, M. *N-Ylid Chemistry*, McGraw-Hill, 1976, p 239.
9. Katritzky, A. R.; Rees, C. W. "Comprehensive Heterocyclic Chemistry", Potts, K., Ed. Pergamon Press, 1984.
10. Dumitrascu, F.; Dumitrescu, D. G. *Arkivoc* **2008**, (*i)*, 232.
11. Mitsumori, T.; Bendikov, M.; Sedó, J.; Wudl, F. *Chem. Mater.* **2003**, *15*, 3759.
12. Mitsumori, T.; Craig, I. M.; Martini, I. B.; Schwartz, B. J.; Wudl, F. *Macromolecules* **2005**, *38*, 4698.
13. Dumitrascu, F.; Draghici, C.; Albulescu, A.; Dumitrescu, D. *Rev. Chim.* (*Bucharest*) **2006**, *57*, 866.
14. Vlahovici, A., Andrei, M., Druta, I. *J. Lumin.* **2002**, *96*, 279.
15. Rotaru, A., Druta, I., Oeser, T., Muler, T. H. *Helv. Chim. Acta* **2005**, *88*, 1798.
16. Delattre, F.; Woisel, P.; Surpateanu, G.; Cazier, F.; Blach, P. *Tetrahedron* **2005**, *61*, 3939.
17. Georgescu, E.; Georgescu, F.; Filip, P.; Popa, M. M.; Dumitrascu, F. *Rev. Chim. (Bucharest)* **2009**, *60*, 480.
18. Rotaru, A.; Druta, I.; Avram, E.; Danac, R. *Arkivoc* **2009**, (*xiii)*, 287.
19. Georgescu, E.; Georgescu, F.; Filip, P.; Miu, B.; Dumitrascu, F. *Rev. Chim. (Bucharest)* **2009,** *60*, 377.
20. Georgescu, E.; Georgescu, F.; Iuhas, P.C.; Draghici, C.; Danila, M. G.; Filip, P. I. *Arkivoc* **2007**,(*x)*, 381.
21. Georgescu, E.; Georgescu, F.; Danila, M. D.; Filip, P. I.; Draghici, C.; Caproiu, M. T. *Arkivoc* **2002**, (*ii)*, 30.

22. Najera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105.
23. Georgescu, E.; Georgescu, F.; Caira, M. R.; Nicolescu, A.; Deleanu, C.; Danila, M.; Petru, F.; Dumitrascu, F. *Arkivoc* **2009**,(*xii)*, 232.

