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Synthesis and cyclizations of 1-azapolyene derivatives

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ABSTRACT

Imminium salts of enaminonitriles with polyenals gave stable 1-azapolyenes, which could be readily transformed to benzo- and indoloquinolizines in 1,6-electrocyclizations. Azatrienes and azatetraenes with formaldehyde and primary amines afforded pyrimido[6,1-*a*]isoquinolines.

1. Introduction

The benzoquinolizine framework is a common constituent of various naturally occurring alkaloids and biologically active compounds. Due to the great significance of these heterocycles both from chemical and biological point of view, several methods are known for their preparation.[1] Push–pull enamines, e.g., β-enaminonitriles or esters have also proved to be valuable precursors for the construction of benzoquinolizines, and other bridgehead heterocycles, such as pyrrolizidines, indolizidines, and quinolizidines.[2]

We have reported previously, that 1-cyanomethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline mesylate (**1**) readily reacts with α,β-unsaturated aldehydes **2**, resulting in 1-azatrienes **3**, which could be cyclized to 6,7-dihydro-4*H*-benzo[*a*]quinolizines **4** in good yields (Scheme 1).[3] It is noteworthy, that only few examples can be found in the literature for such 1,6-electrocyclizations of 1-azatrienes providing different dihydropiridines.[4] These results prompted us to investigate the possible extension of the azaelectrocyclization process for 1-azatetraenes and 1-azapentaenes, and to study the synthetic potential of 1-azapolyenes.

2. Results and discussion

We report herein the synthesis, electrocyclizations, and Mannich reactions of 1-azapolyenes **6a**–**f**.

2.1. Synthesis of 1-azatetraenes and 1-azapentaenes

The aromatic polyenals **5a**–**f** were prepared easily in good yields by Wittig-type oxopropenylation of the properly substituted unsaturated aldehyde with 1,3-dioxan-2-yl methyltributyl phosphorane.[5] Azapolyenes **6a**–**f** were obtained in an acid catalyzed Knoevenagel condensation from the mesylate salt **1** and the corresponding polyenals **5a**–**f**. The reactions were carried out in glacial acetic acid at room temperature (Scheme 2).

The mesylate salts of 1-azatetraenes **6a**,**c**,**e** and 1-azapentaenes **6b**,**d**,**f**, formed under mild reaction conditions (Table 1), proved to be stable for extended time at room temperature.

2.2. Cyclizations of azapolyenes

Similarly to the azatrienes the cyclizations of 1-azatetraenes **6a**,**c**,**e** and 1-azapentaenes **6b**,**d**,**f** took place by adding Et_3N in excess, in CH_3CN at reflux to give 4-styryl-6,7-dihydro-4*H*-pyrido[2,1-*a*]isoquinoline **7a**,**c**,**e** and 4-(buta-1,3-dienyl)-6,7-dihydro-4*H*-pyrido[2,1-*a*]isoquinoline **7b**,**d**,**f** derivatives with acceptable yields (Table 2). In contrast to the 1,6-electrocyclizations of 1-azatrienes, no significant difference was observed in reactivity of the differently substituted azapolyene derivatives **6a**–**f**. If the reactions were carried out at lower temperature, in different solvents (CH_3CN, toluene, and ethanol), low conversion and decomposition of the starting material was observed during the prolonged reaction time (2–3 days).

As we described in our earlier study,[3] the computation revealed, that the 6π-cyclization was promoted by a nucleophilic

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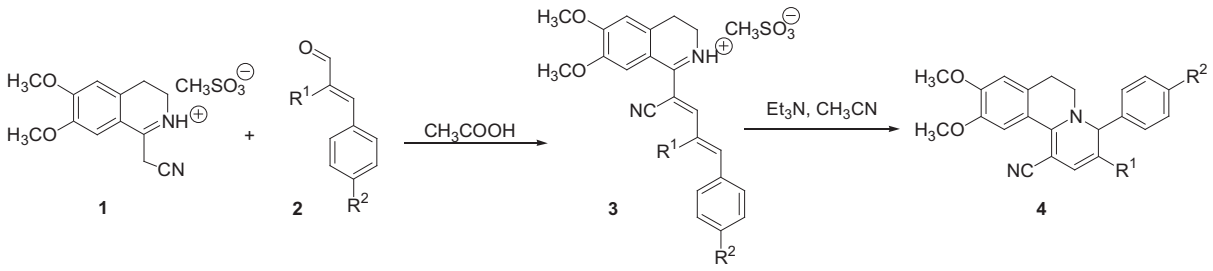
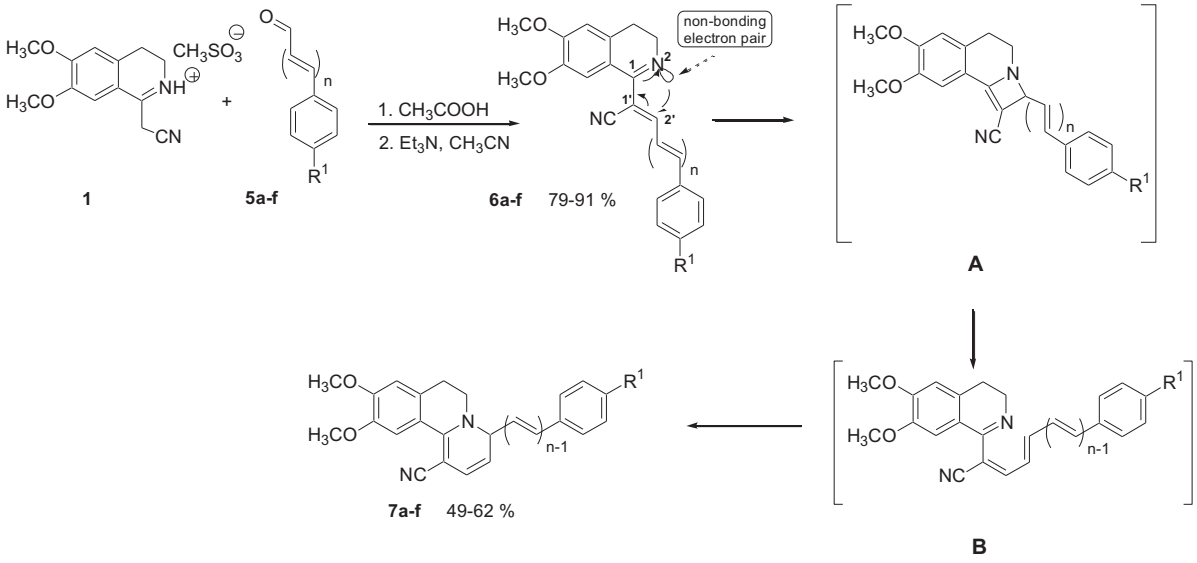


Scheme 1.



Scheme 2.

Table 1
Yields for the 1-azatetraenes and 1-azapentaenes

Entry	R^1	*n*	Reaction time (h)	Yield %
6a	H	2	4	85
6b	H	3	4	89
6c	NO_2	2	3	91
6d	NO_2	3	4	85
6e	NMe_2	2	4	82
6f	NMe_2	3	4	79
10a	NO_2	1	3	92
10b	NO_2	2	3	85
10c	NO_2	3	4	82

Table 2
Yields for the cyclization products

Entry	R^1	*n*	Reaction time (h)	Yield %
7a	H	1	5	56
7b	H	2	6	50
7c	NO_2	1	6	62
7d	NO_2	2	6	53
7e	NMe_2	1	5	60
7f	NMe_2	2	6	49
11a	NO_2	0	5	75
11b	NO_2	1	6	56
11c	NO_2	2	6	48

intramolecular attack of the nitrogen atom on the electron-poor C2′ atom. The formation of the dihydroazete intermediate **A** decrease the activation energy of the rate determining (*E*)→(*Z*) isomerization step affording **B** trough ring opening (Scheme 2). Although, no computations were carried out to date, a similar mechanism could be assumed for these azaelectrocyclizations as well.

2.3. Cyclization of azapolyenes to indoloquinolizines

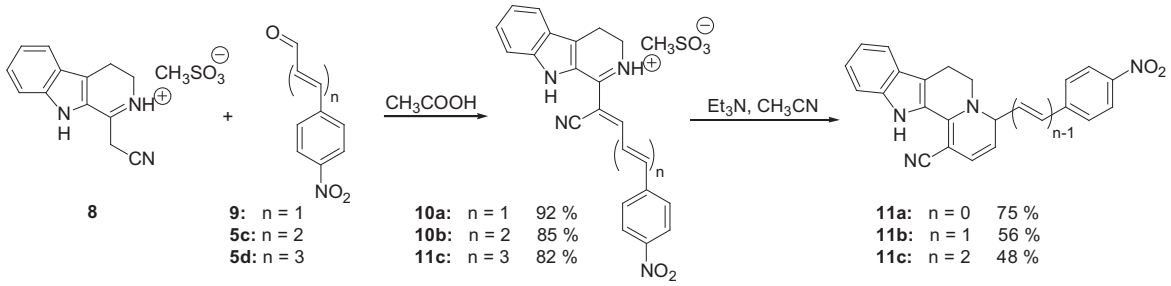
1-Cyanomethylene-1,2,3,4-tetrahydro-β-carboline **8**, a valuable starting material in the synthesis of numerous biologically active compounds, was prepared according to literature procedure starting from *N*-(indol-3-yl-ethyl)-cyanoacetamide.[6,7] The reactions of polyenals (**9**, **5c**,**d**) with the mesylate salt of **8** gave the required 1-azapolyenes **10a**–**c** in good yields (Table 1, Scheme 3).

After deprotonation of **10a**–**c** the 1-azapolyene bases cyclized readily at room temperature in 5–6 h to afford **11a**–**c** indoloquinolizine derivatives. The progress of the cyclization could be followed by ^1H NMR in $CDCl_3$ solution (Fig. 1). The appearance of the new methine H-4 proton of the formed dihydropyridine ring at 4.72 ppm indicates the ring closure unequivocally (Fig. 1).

2.4. C-Acylation of β-enaminonitrile

As we and others published earlier, enaminonitriles, enaminoesters, and nitroenamines are able to undergo regioselective [3+3] cyclizations with α,β-unsaturated carboxylic acid chlorides.[8] These results inspired us to examine the ring closure of the *C*-acylated product (**14**).

1-Cyanomethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**12**) was acylated with 5-phenyl-penta-2,4-dienoic acid chloride (**13**). The reaction took place smoothly at room temperature in acetonitrile in the presence of excess base (K_2CO_3), affording the *C*-acylated product **14** exclusively (Scheme 4). Under the standard reaction conditions (acetonitrile, reflux) however, the formation of the cyclized product could not be observed.



Scheme 3.

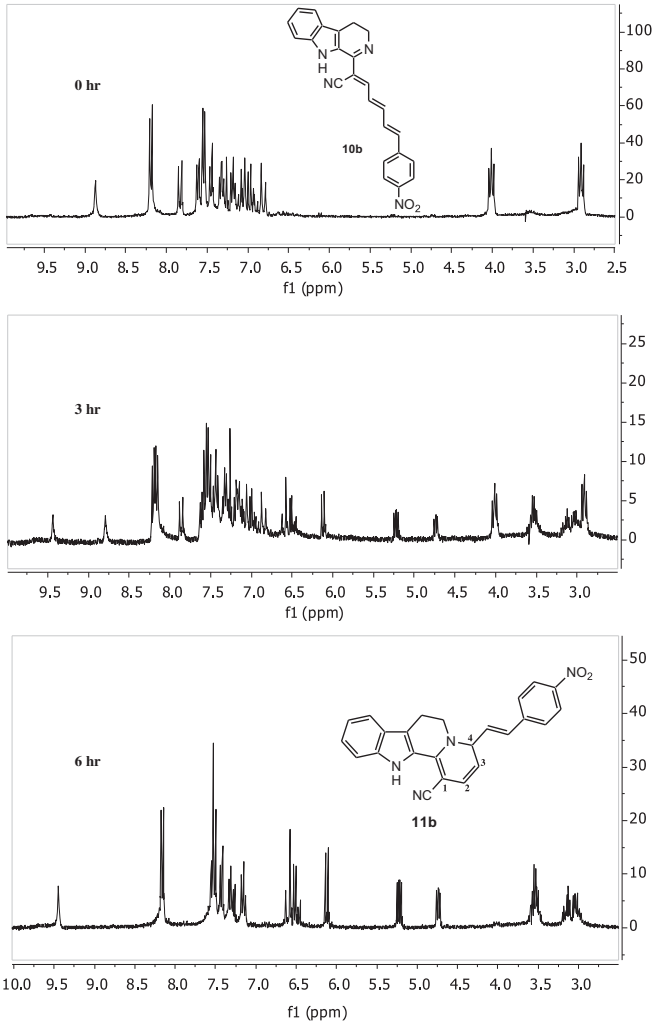
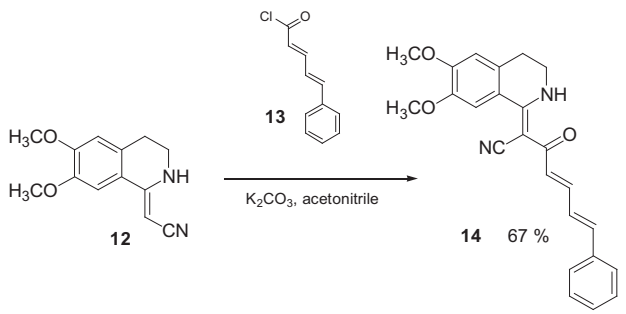


Fig. 1. The progress of the cyclization of **10b** followed by NMR (25 °C, $CDCl_3$).

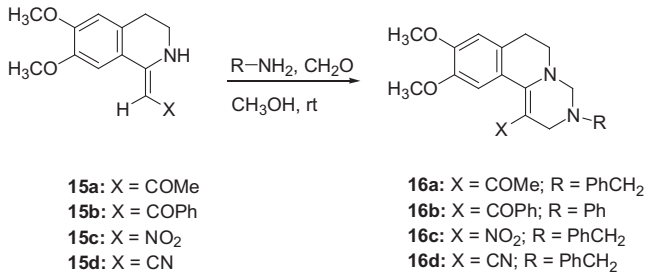


Scheme 4.

Applying high temperature (reflux in xylene) and using different bases as catalysts (Cs_2CO_3, $La(OH)_3$), only the decomposition of the **14** was detected.

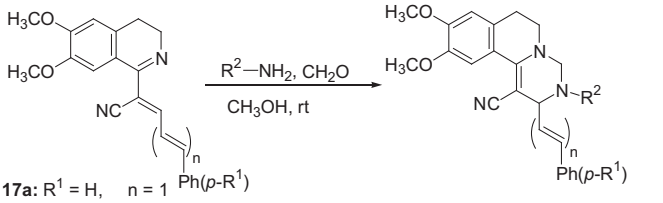
2.5. Aza-annulations of azatrienes

According to earlier publications the aza-annulation reactions of various push–pull enaminones (**15a**,**b**), nitroenamine (**15c**), and enaminonitrile (**15d**) with formaldehyde/amine result in functionalized pyrimido[6,1-*a*]isoquinoline derivatives (**16a**–**c**), (Scheme 5).[9]



Scheme 5.

These results led us to examine the Mannich reactions of enaminonitrile **15d** and the new azapolyenes. According to the described examples the reaction of enaminonitrile with 2 mol of formaldehyde and 1 mol of primary amine afforded tetrahydropyrimido[6,1-*a*]isoquinole **16d** in a double Mannich reaction. Azatrienes **17a**–**d** under similar reaction conditions consumed only 1 mol of formaldehyde to give 2-styryl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolines **18a**–**d** (Scheme 6, Table 3). The products proved to be stable in contrast to 2-(buta-1,3-dienyl)-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline (**18e**), formed in the reaction of the 1-azatatraene (**17e**) under similar conditions. Compound **18e** could be isolated, identified but rapid decomposition was observed at room temperature.



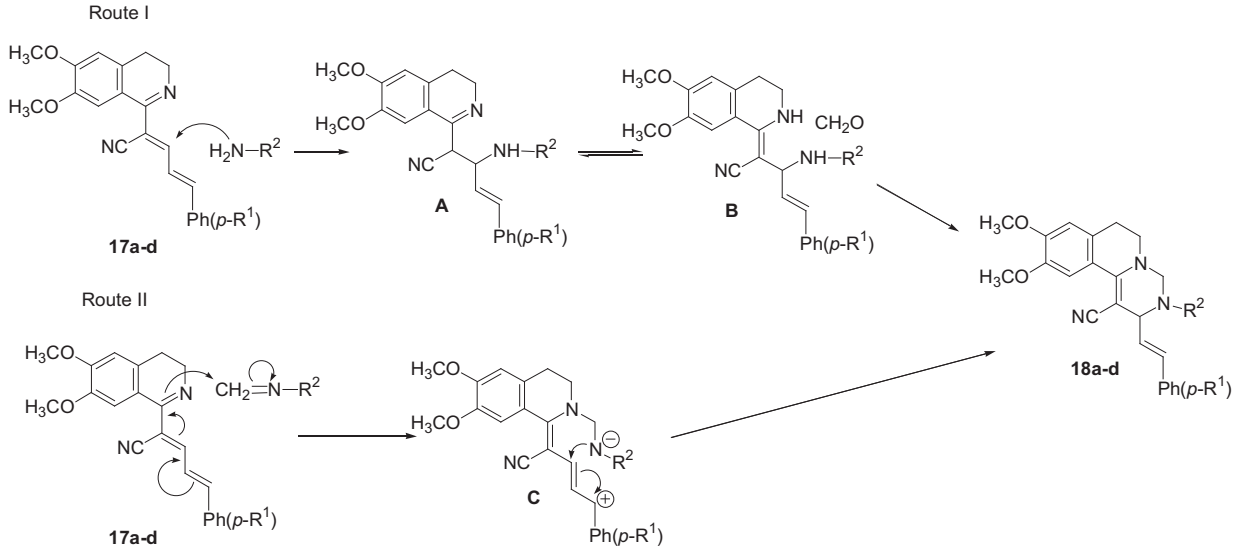
Scheme 6.

Table 3
Yields for the cyclization products

Entry	*n*	R^1	R^2	Reaction time (h)	Yield %
18a	1	H	CH_3	16	79
18b	1	H	CH_2Ph	18	65
18c	1	H	$CH_2CH_2Ph(OMe)_2$	18	83
18d	1	NO_2	CH_2Ph	18	65
18e	2	H	CH_2Ph	18	60

To explain the interesting aza-annulation of azatrienes **17a–d** we made some mechanistic considerations. In earlier publications it was already described that enaminones gave anellated pyrimidine derivatives in Mannich reactions.[10] Surprisingly, the reaction pathway was suggested via first N- rather than C-aminomethylation.

For the reactions of azatrienes two different mechanisms can be considered (Scheme 7). Route I involves the nucleophilic attack of the amine nitrogen resulting in the addition product, which can exist either in the imine (**A**) or the enamine (**B**) form. Subsequent condensation of the enamine with formaldehyde can afford **18a–d**.



Scheme 7.

Route II follows the mechanism of the double Mannich condensation. The N-aminomethylation giving intermediate **C** however is followed by a cyclization/prototropic rearrangement sequence.

To validate either of the two mechanisms depicted in Scheme 7, we attempted the reaction of **17a** with benzyl amine, but no trace of the addition product **A** could be detected. This result may support the formation of the pyrimidine ring according to the Route II.

3. Conclusion

In summary, this work demonstrates the synthetic usefulness of azapolyenes, that are able to undergo 6π-electrocyclization to afford 6,7-dihydro-4*H*-pyrido[2,1-*a*]isoquinolines and indoloquinolizine derivatives. Azatrienes and azatetraenes with formaldehyde and primary amines afford pyrimido[6,1-*a*]isoquinolines. Further investigation of these interesting and novel azaelectrocyclizations and aza-annulations with other azapolyenes is in progress.

4. Experimental section

4.1. General

The structures and the purity of the final products as free bases were confirmed by ^1H, ^{13}C NMR, IR, and microanalysis. NMR Spectra were recorded on a Varian Unity 300 (300 MHz) spectrometer, in $CDCl_3$ solutions. Chemical shifts (δ) are expressed in parts per million relative to the internal standard TMS. IR spectra were recorded on a Perkin Elmer 1600 FT IR spectrometer. The microanalysis was carried out on a Heraeus Micro Rapid CHN. All melting points were measured with a Büchi SMP-20 apparatus and are uncorrected. Column chromatography was conducted with Merck Kieselgel 60 (0.063–0.200 mm). Analytical TLC was carried out on precoated plates (Merck silica gel 60, F_{254}). Solvents were dried and freshly distilled according to the common practice.

4.2. General procedure for the synthesis of 1-azatetraenes and 1-azapentaenes (6a–f, 10a–c)

To the solution of β-enaminonitrile-mesylate (**1**, **8**) (2.0 mmol) in glacial acetic acid (6 mL), the polyenal (**5a–f**, **9**) (3.0 mmol) was added. The mixture was stirred at room temperature for 3–4 h until the reaction was complete. The solution was then poured into diisopropyl ether (30 mL), the formed precipitate was filtered, and washed with diethyl ether.

*4.2.1. 2-(6,7-Dimethoxy-3,4-dihydro-isoquinolin-1-yl)-7-phenyl-hepta-2,4,6-trienenitrile mesylate (**6a**).* Recrystallization (EtOAc) gave **6a** (630 mg, 85%) orange solid, mp 145 °C; R_f (EtOAc) 0.72. [Found: C, 77.62; H, 6.00; N, 7.66. $C_{24}H_{22}N_2O_2$ requires C, 77.81; H, 5.99; N, 7.56%]; ν_{max} (KBr) 2935, 2178, 1600, 1563, 1516, 1280 cm^{-1}; δ_H 7.74 (1H, dd, *J* 14.3, 3.5 Hz, CHCHCH*CH*CHPh), 7.53–7.50 (2H, m, *Ph*), 7.46 (1H, s, H-11), 7.38–7.35 (3H, m, *Ph*), 7.24–7.17 (2H, m, C*H*CHCHCHC*H*Ph), 7.11–6.95 (2H, m, CHC*H*CHCHCHPh), 6.83 (1H, s, H-8), 3.92 (3H, s, O*Me*), 3.88 (3H, s, O*Me*), 3.73 (2H, t, *J* 7.3 Hz, H-6), 2.64 (2H, t, *J* 7.3 Hz, H-7); δ_C (75 MHz, $CDCl_3$) 161.0, 151.7, 147.6, 144.3, 139.5, 136.4, 132.8, 129.1, 128.5, 128.0, 127.4, 119.8, 117.3, 111.6, 110.8, 110.3, 56.5, 56.3, 48.0, 26.0.

*4.2.2. 2-(6,7-Dimethoxy-3,4-dihydro-isoquinolin-1-yl)-9-phenyl-nona-2,4,6,8-tetraenenitrile mesylate (**6b**).* Recrystallization (EtOAc) gave **6b** (705 mg, 89%) dark red solid, mp 105 °C; R_f (EtOAc) 0.74. [Found: C, 78.60; H, 6.23; N, 6.95. $C_{26}H_{24}N_2O_2$ requires C, 78.76; H, 6.10; N, 7.07%]; ν_{max} (KBr) 2934, 2178, 1596, 1560, 1518, 1279 cm^{-1}; δ_H 7.55 (1H, dd, *J* 14.2, 3.9 Hz, CHCHCHCHCH*CH*CHPh), 7.42–7.26 (5H, m, *Ph*), 7.05 (1H, s, H-11), 6.96–6.49 (6H, m, C*H*CHCHCHCHCHC*H*Ph), 6.74 (1H, s, H-8), 3.93 (3H, s, O*Me*), 3.78

(3H, s, O*Me*), 3.73 (2H, t, *J* 7.1 Hz, H-6), 2.65 (2H, t, *J* 7.1 Hz, H-7); δ_C (75 MHz, $CDCl_3$) 161.1, 151.7, 149.1, 147.6, 144.2, 140.1, 136.9, 136.8, 132.8, 132.1, 128.9, 128.7, 128.6, 128.4, 127.1, 119.9, 117.4, 111.2, 110.8, 110.3, 56.5, 56.3, 48.0, 26.1.

*4.2.3. 2-(6,7-Dimethoxy-3,4-dihydro-isoquinolin-1-yl)-7-(4-nitro-phenyl)-hepta-2,4,6-trienenitrile mesylate (**6c**).* Recrystallization (EtOAc) gave **6c** (756 mg, 91%) red solid, mp 164 °C; R_f (EtOAc) 0.66. [Found: C, 69.56; H, 5.04; N, 10.02. $C_{24}H_{21}N_3O_4$ requires C, 69.39; H, 5.10; N, 10.11%]; ν_{max} (KBr) 2938, 2176, 1597, 1514, 1342, 1199, 861 cm^{-1}; δ_H 8.22 (2H, d, *J* 8.8 Hz, *Ph*(*p*-NO_2)), 7.59 (2H, d, *J* 8.8 Hz, *Ph*(*p*-NO_2)), 7.53 (1H, dd, *J* 11.0, 2.9 Hz, CHCHCH*CH*CHPh(*p*-NO_2)), 7.28–7.10 (2H, m, C*H*CHCHCH*CH*Ph(*p*-NO_2)), 7.05 (1H, s, H-11), 6.94–6.84 (2H, m, CHC*HCH*CHCHPh(*p*-NO_2)), 6.78 (1H, s, H-8), 3.95 (3H, s, O*Me*), 3.91 (3H, s, O*Me*), 3.76 (2H, t, *J* 7.5 Hz, H-6), 2.67 (2H, t, *J* 7.5 Hz, H-7); δ_C (75 MHz, $CDCl_3$) 161.0, 151.9, 148.4, 147.8, 142.9, 142.8, 136.3, 132.9, 132.2, 131.3, 127.9, 127.8, 124.6, 119.8, 117.1, 113.7, 111.0, 110.2, 56.7, 56.5, 48.2, 26.1.

*4.2.4. 2-(6,7-Dimethoxy-3,4-dihydro-isoquinolin-1-yl)-9-(4-nitro-phenyl)-nona-2,4,6,8-tetraenenitrile mesylate (**6d**).* Recrystallization (EtOAc) gave **6d** (750 mg, 85%) dark red solid, mp 157 °C; R_f (EtOAc) 0.65. [Found: C, 70.50; H, 5.39; N, 9.36. $C_{26}H_{23}N_3O_4$ requires C, 70.73; H, 5.25; N, 9.52%]; ν_{max} (KBr) 2934, 2200, 1534, 1517, 1393, 1218, 1023, 864 cm^{-1}; δ_H 8.17 (2H, d, *J* 8.1 Hz, *Ph*(*p*-NO_2)), 7.54 (2H, d, *J* 8.1 Hz, *Ph*(*p*-NO_2)), 7.55 (1H, dd, *J* 14.2, 3.9 Hz, CHCHCHCHCH*CH*CHPh(*p*-NO_2)), 7.06 (1H, s, H-11), 6.96–6.52 (6H, m, C*HCHCHCHCH*CHC*H*Ph(*p*-NO_2)), 6.75 (1H, s, H-8), 3.94 (3H, s, O*Me*), 3.89 (3H, s, O*Me*), 3.77 (2H, t, *J* 7.0 Hz, H-6), 2.67 (2H, t, *J* 7.0 Hz, H-7); δ_C (75 MHz, $CDCl_3$) 161.0, 157.4, 151.8, 148.6, 147.7, 147.3, 143.3, 138.6, 134.8, 133.6, 132.8, 129.9, 127.3, 124.4, 121.4, 119.7, 117.2, 110.9, 110.3, 107.9, 56.5, 56.2, 40.0, 26.1.

*4.2.5. 2-(6,7-Dimethoxy-3,4-dihydro-isoquinolin-1-yl)-7-(4-dimethylamino-phenyl)-hepta-2,4,6-trienenitrile mesylate (**6e**).* Recrystallization (EtOAc) gave **6e** (678 mg, 82%) dark blue solid, mp 127 °C; R_f (EtOAc) 0.55. [Found: C, 75.59; H, 6.44; N, 9.98. $C_{26}H_{27}N_3O_2$ requires C, 75.52; H, 6.58; N, 10.16%]; ν_{max} (KBr) 2915, 2178, 1536, 1366, 1160, 808 cm^{-1}; δ_H 7.51 (1H, dd, *J* 7.4, 3.4 Hz, CHCHCH*CH*CHPh(*p*-NMe_2)), 7.37 (2H, d, *J* 8.9 Hz, *Ph*(*p*-NMe_2)), 7.09 (1H, s, H-11), 6.91–6.86 (2H, m, C*H*CHCHCHC*H*Ph(*p*-NMe_2)), 6.81–6.79 (2H, m, CHC*HCH*CHCHPh(*p*-NMe_2)), 6.75 (1H, s, H-8), 6.68 (2H, d, *J* 8.9 Hz, *Ph*(*p*-NMe_2)), 3.94 (3H, s, O*Me*), 3.91 (3H, s, O*Me*), 3.74 (2H, t, *J* 8.5 Hz, H-6), 3.02 (6H, s, NMe_2), 2.66 (2H, t, *J* 8.5 Hz, H-7); δ_C (75 MHz, $CDCl_3$) 161.3, 151.6, 151.2, 149.8, 147.6, 145.8, 140.6, 132.8, 129.0, 126.1, 124.6, 123.6, 120.1, 117.8, 112.3, 110.7, 110.4, 109.2, 56.5, 56.3, 48.0, 40.4, 26.1.

*4.2.6. 2-(4,9-Dihydro-3H-β-carbolin-1-yl)-5-(4-nitro-phenyl)-penta-2,4-dienenitrile mesylate (**10a**).* Recrystallization (EtOAc) gave **10a** (678 mg, 92%) yellow solid, mp 158 °C; R_f (50% EtOAc/hexane) 0.47. [Found: C, 71.88; H, 4.30; N, 15.45. $C_{22}H_{16}N_4O_2$ requires C, 71.73; H, 4.38; N, 15.21%]; ν_{max} (KBr) 3439, 2932, 2176, 1594, 1522, 1344, 1084, 855 cm^{-1}; δ_H 8.97 (1H, br s, N*H*), 8.09 (2H, d, *J* 8.8 Hz, Ph(*p*-NO_2)), 7.83 (1H, d, *J* 11.5 Hz, CHCHC*H*Ph(*p*-NO_2)), 7.57 (1H, d, *J* 14.0 Hz, C*H*CHCHPh(*p*-NO_2)), 7.54 (2H, d, *J* 8.8 Hz, Ph(*p*-NO_2)), 7.47 (1H, dd, *J* 11.5, 14.0 Hz, CHC*H*CHPh(*p*-NO_2)), 7.40 (1H, d, *J* 8.0 Hz, H-5), 7.42 (1H, d, *J* 8.3 Hz, H-8), 7.28 (1H, dd, *J* 8.0, 6.9 Hz, H-7), 7.12 (1H, dd, *J* 8.3, 6.9 Hz, H-6), 3.99 (2H, t, *J* 8.7 Hz, H-3), 2.88 (2H, t, *J* 8.7 Hz, H-4); δ_C (75 MHz, $CDCl_3$) 149.3, 148.1, 145.5, 137.8, 127.5, 125.8, 124.8, 124.6, 123.7, 122.2, 121.0, 119.7, 116.4, 114.9, 112.4, 64.8, 48.6, 21.1.

*4.2.7. 2-(4,9-Dihydro-3H-b-carbolin-1-yl)-7-(4-nitro-phenyl)-hepta-2,4,6-trienenitrile mesylate (**10b**).* Recrystallization (EtOAc) gave **10b** (670 mg, 85%) orange solid, mp 160 °C; R_f (EtOAc) 0.77. [Found: C, 72.87; H, 4.51; N, 14.01. $C_{24}H_{18}N_4O_2$ requires C, 73.08; H, 4.60; N, 14.20%]; ν_{max} (KBr) 3432, 2931, 2180, 1592, 1522, 1341, 1084, 866 cm^{-1}; δ_H 8.87 (1H, br s, N*H*), 8.19 (2H, d, *J* 8.8 Hz, Ph(*p*-NO_2)), 7.83 (1H, d, *J* 11.4 Hz, C*H*CHCHCHPh(*p*-NO_2)), 7.61 (1H, d, *J* 8.0 Hz, H-5), 7.54 (2H, d, *J* 8.8 Hz, Ph(*p*-NO_2)), 7.43 (1H, d, *J* 8.1 Hz, H-8), 7.32 (1H, dd, *J* 8.0, 7.0 Hz, H-7), 7.18 (1H, dd, *J* 8.1, 7.0 Hz, H-6), 7.06 (1H, m, CHCHCH*CH*CHPh(*p*-NO_2)), 6.98–6.84 (2H, m, CHC*HCH*CHCHPh (*p*-NO_2)), 6.80 (1H, d, *J* 15.5 Hz, CHCHCHCHC*H*Ph(*p*-NO_2)), 4.00 (2H, t, *J* 8.9 Hz, H-3), 2.90 (2H, t, *J* 8.9 Hz, H-4); δ_C (75 MHz, $CDCl_3$) 147.8, 143.9, 142.5, 137.1, 136.7, 131.9, 130.7, 127.7, 127.6, 125.6, 125.2, 124.4, 124.2, 121.0, 120.2, 119.5, 115.3, 112.6, 82.3, 49.3, 19.4.

*4.2.8. 2-(4,9-Dihydro-3H-β-carbolin-1-yl)-9-(4-nitro-phenyl)-nona-2,4,6,8-tetraenenitrile mesylate (**10c**).* Recrystallization (EtOAc) gave **10c** (689 mg, 82%) dark red solid, mp 124 °C; R_f (EtOAc) 0.75. [Found: C, 74.37; H, 4.55; N, 13.10. $C_{26}H_{20}N_4O_2$ requires C, 74.27; H, 4.79; N, 13.33%]; ν_{max} (KBr) 3433, 2930, 2179, 1587, 1540, 1338, 1084 cm^{-1}; δ_H 8.89 (1H, br s, N*H*), 8.17 (2H, d, *J* 8.8 Hz, Ph(*p*-NO_2)), 7.82 (1H, d, *J* 11.5 Hz, C*H*CHCHCHCHCHCHPh(*p*-NO_2)), 7.61 (1H, d, *J* 7.6 Hz, H-5), 7.52 (2H, d, *J* 8.8 Hz, Ph(*p*-NO_2)), 7.44 (1H, d, *J* 8.1 Hz, H-8), 7.30 (1H, dd, *J* 7.6, 7.0 Hz, H-7), 7.16 (1H, dd, *J* 8.1, 7.0 Hz, H-6), 7.05–6.49 (6H, m, CHC*HCHCHCHCHCH*Ph(*p*-NO_2)), 3.99 (2H, t, *J* 8.8 Hz, H-3), 2.95 (2H, t, *J* 8.8 Hz, H-4); δ_C (75 MHz, $CDCl_3$) 147.7, 143.8, 142.6, 139.1, 137.1, 136.7, 132.6, 131.9, 130.7, 127.8, 127.6, 127.4, 125.6, 125.4, 124.4, 124.3, 121.0, 120.2, 117.5, 115.3, 112.6, 82.0, 49.3, 19.5.

4.3. General procedure for the cyclization (7a–f, 11a–c)

To the solution of 1-azapolyenes (**6a–f**, **10a–c**) (1 mmol) in acetonitrile (10 mL), Et_3N (2 mmol) was added. The solution was stirred for 6–8 h at reflux or at room temperature (**6a–f** and **10a–c**, respectively). The solvent was removed under reduced pressure, and the residue dissolved in CH_2Cl_2 (10 mL). The CH_2Cl_2 solution was washed with water (2×5 mL), dried over Na_2SO_4, and then evaporated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel using EtOAc/hexane as eluent.

*4.3.1. 9,10-Dimethoxy-4-styryl-6,7-dihydro-4H-pyrido[2,1-a]isoquinoline-1-carbonitrile (**7a**).* Purification by column chromatography (EtOAc/hexane 1:1) gave the title compound **7a** (207 mg, 56%) yellow solid, mp 145 °C; R_f (EtOAc/hexane 1:1) 0.50. [Found: C, 77.85; H, 6.03; N, 7.96. $C_{24}H_{22}N_2O_2$ requires C, 77.81; H, 5.99; N, 7.56%]; ν_{max} (KBr) 2924, 2180, 1636, 1609, 1529, 1288, 1031 cm^{-1}; δ_H 7.91 (1H, s, H-11), 7.28–7.12 (5H, m, *Ph*), 6.64 (1H, s, H-8), 6.46 (1H, d, *J* 15.7 Hz, H-2), 6.27 (1H, dd, *J* 15.7, 8.1 Hz, H-3), 6.12 (1H, d, *J* 9.5 Hz, CHC*H*Ph), 5.17 (1H, dd, *J* 9.5, 5.4 Hz, C*H*CHPh), 4.65 (1H, dd, *J* 8.1, 5.4 Hz, H-4), 3.83 (3H, s, O*Me*), 3.88 (3H, s, O*Me*), 3.44–3.17 (2H, m, H-6), 3.00–2.69 (2H, m, H-7); δ_C (75 MHz, $CDCl_3$) 151.1, 150.8, 147.6, 136.2, 130.8, 129.7, 128.8, 128.4, 127.0, 126.3, 124.6, 124.0, 121.2, 112.3, 111.1, 110.3, 74.7, 64.2, 56.5, 56.2, 47.4, 29.7.

*4.3.2. 9,10-Dimethoxy-4-(4-phenyl-buta-1,3-dienyl)-6,7-dihydro-4H-pyrido[2,1-a]isoquinoline-1-carbonitrile (**7b**).* Purification by column chromatography (EtOAc/hexane 1:1) gave the title compound **7b** (198 mg, 50%) yellow solid, mp 154 °C; R_f (EtOAc/hexane 1:1) 0.67. [Found: C, 78.97; H, 5.89; N, 7.00. $C_{26}H_{24}N_2O_2$ requires C, 78.76; H, 6.10; N, 7.07%]; ν_{max} (KBr) 2937, 2180, 1632, 1465, 1289, 1030 cm^{-1}; δ_H 7.89 (1H, s, H-11), 7.35–7.25 (5H, m, Ph), 6.70 (1H, dd, *J* 15.7, 10.3 Hz, CHCHC*H*CHPh), 6.65 (1H, s, H-8), 6.61 (1H, d, *J* 15.7 Hz, H-2), 6.30 (1H, dd, *J* 15.2, 10.3 Hz, CHC*H*CHCHPh), 6.03 (1H, d, *J* 9.6 Hz, CHCHCHC*H*Ph), 5.85 (1H, dd, *J* 15.1, 7.7 Hz, H-3), 5.14 (1H, dd, *J* 9.6, 5.0 Hz, C*H*CHCHCHPh), 4.57 (1H, dd, *J* 7.7, 5.0 Hz, H-4), 3.93 (3H, s, O*Me*), 3.89 (3H, s, O*Me*), 3.35–3.20 (2H, m, H-6), 2.92–2.50 (2H, m, H-7); δ_C (75 MHz, $CDCl_3$) 151.0, 150.8, 147.5, 137.0, 134.6,

131.2, 130.3, 129.8, 128.9, 128.1, 127.8, 126.6, 124.5, 124.1, 121.2, 112.2, 111.1, 110.3, 74.6, 63.7, 56.5, 56.2, 47.5, 29.7.

*4.3.3. 9,10-Dimethoxy-4-[2-(4-nitro-phenyl)-vinyl]-6,7-dihydro-4H-pyrido[2,1-a]isoquinoline-1-carbonitrile (**7c**).* Purification by column chromatography (EtOAc/hexane 1:1) gave the title compound **7c** (257 mg, 62%) yellow solid, mp 138 °C; R_f (EtOAc/hexane 1:1) 0.61. [Found: C, 69.17; H, 5.11; N, 10.32. $C_{24}H_{21}N_3O_4$ requires C, 69.39; H, 5.10; N, 10.11%]; ν_{max} (KBr) 2933, 2176, 1639, 1488, 1285, 855 cm^{-1}; δ_H 8.07 (2H, d, *J* 8.8 Hz, *Ph*(*p*-NO_2)), 7.83 (1H, s, H-11), 7.43 (2H, d, *J* 8.8 Hz, *Ph*(*p*-NO_2)), 6.64 (1H, s, H-8), 6.48 (1H, d, *J* 15.5 Hz, H-2), 6.40 (1H, dd, *J* 15.5, 7.9 Hz, H-3), 6.09 (1H, d, *J* 9.5 Hz, CHC*H*Ph(*p*-NO_2)), 5.13 (1H, dd, *J* 9.5, 5.3 Hz, C*H*CHPh(*p*-NO_2)), 4.65 (1H, dd, *J* 7.9, 5.3 Hz, H-4), 3.87 (3H, s, O*Me*), 3.83 (3H, s, O*Me*), 3.32–3.18 (2H, m, H-6), 2.87–2.56 (2H, m, H-7); δ_C (75 MHz, $CDCl_3$) 151.3, 151.1, 147.7, 147.6, 142.9, 130.9, 129.8, 128.7, 127.7, 125.5, 124.4, 123.9, 121.1, 111.4, 111.1, 110.4, 75.3, 63.8, 56.6, 56.4, 47.9, 29.9.

*4.3.4. 9,10-Dimethoxy-4-[4-(4-nitro-phenyl)-buta-1,3-dienyl]-6,7-dihydro-4H-pyrido[2,1-a]isoquinoline-1-carbonitrile (**7d**).* Purification by column chromatography (EtOAc/hexane 1:1) gave the title compound **7d** (234 mg, 53%) yellow solid, mp 135 °C; R_f (EtOAc) 0.64. [Found: C, 70.95; H, 5.06; N, 9.51. $C_{26}H_{23}N_3O_4$ requires C, 70.73; H, 5.25; N, 9.52%]; ν_{max} (KBr) 2930, 2176, 1643, 1492, 1280, 860 cm^{-1}; δ_H 8.17 (2H, d, *J* 8.8 Hz, *Ph*(*p*-NO_2)), 7.91 (1H, s, H-11), 7.48 (2H, d, *J* 8.8 Hz, *Ph*(*p*-NO_2)), 6.86 (1H, dd, *J* 15.7, 10.3 Hz, CHCHC*H*CHPh(*p*-NO_2)), 6.67 (1H, s, H-8), 6.61 (1H, d, *J* 15.7 Hz, H-2), 6.31 (1H, dd, *J* 15.2, 10.3 Hz, CHC*H*CHCHPh(*p*-NO_2)), 6.15 (1H, d, *J* 9.5 Hz, CHCHCHC*H*Ph(*p*-NO_2)), 6.01 (1H, dd, *J* 15.1, 7.7 Hz, H-3), 5.16 (1H, dd, *J* 9.5, 5.5 Hz, C*H*CHCHCHPh(*p*-NO_2)), 4.62 (1H, dd, *J* 7.7, 5.5 Hz, H-4), 3.87 (3H, s, O*Me*), 3.83 (3H, s, O*Me*), 3.32–3.18 (2H, m, H-6), 2.87–2.56 (2H, m, H-7); δ_C (75 MHz, $CDCl_3$) 151.2, 151.1, 147.8, 143.7, 133.5, 132.5, 132.1, 130.4, 129.8, 127.1, 126.6, 125.2, 124.5, 121.3, 120.1, 111.76, 111.3, 110.4, 75.2, 63.5, 56.7, 56.4, 47.9, 29.9.

*4.3.5. 4-[2-(4-Dimethylamino-phenyl)-vinyl]-9,10-dimethoxy-6,7-dihydro-4H-pyrido[2,1-a]isoquinoline-1-carbonitrile (**7e**).* Purification by column chromatography (EtOAc/hexane 1:1) gave the title compound **7e** (248 mg, 60%) orange solid, mp 153 °C; R_f (EtOAc/hexane 1:1) 0.48. [Found: C, 75.73; H, 6.60; N, 10.05. $C_{26}H_{27}N_3O_2$ requires C, 75.52; H, 6.58; N, 10.16%]; ν_{max} (KBr) 2930, 2177, 1601, 1530, 1290, 860 cm^{-1}; δ_H 7.91 (1H, s, H-11), 7.26 (2H, d, *J* 6.0 Hz, *Ph*(*p*-NMe_2)), 6.65 (2H, d, *J* 6.0 Hz, *Ph*(*p*-NMe_2)), 6.70 (1H, dd, *J* 16.5, 7.9 Hz, H-3), 6.62 (1H, s, H-8), 6.39 (1H, d, *J* 16.5 Hz, H-2), 6.10 (1H, d, *J* 9.3 Hz, CHC*H*Ph(*p*-NMe_2)), 5.18 (1H, dd, *J* 9.3, 4.3 Hz, C*H*CHPh(*p*-NMe_2)), 4.61 (1H, dd, *J* 7.9, 4.3 Hz, H-4), 3.96 (3H, s, O*Me*), 3.90 (3H, s, O*Me*), 3.35–3.23 (2H, m, H-6), 3.02 (6H, s, NMe_2), 2.90–2.56 (2H, m, H-7); δ_C (75 MHz, $CDCl_3$) 151.2, 150.7, 147.5, 130.9, 129.8, 128.0, 125.7, 124.4, 124.3, 124.1, 122.0, 121.4, 112.9, 112.5, 111.2, 110.3, 75.2, 64.7, 56.5, 56.2, 47.2, 40.6, 27.1.

*4.3.6. 4-[4-(4-Dimethylamino-phenyl)-buta-1,3-dienyl]-9,10-dimethoxy-6,7-dihydro-4H-pyrido[2,1-a]isoquinoline-1-carbonitrile (**7f**).* Purification by column chromatography (EtOAc/hexane 1:1) gave the title compound **7f** (215 mg, 49%) orange solid, mp 146 °C; R_f (EtOAc/hexane 1:1) 0.43. [Found: C, 76.48; H, 6.60; N, 9.39. $C_{28}H_{29}N_3O_2$ requires C, 76.51; H, 6.65; N, 9.56%]; ν_{max} (KBr) 2924, 2179, 1603, 1527, 1290, 859 cm^{-1}; δ_H, 8.03 (1H, s, H-11), 7.46 (2H, d, *J* 8.7 Hz, *Ph*(*p*-NMe_2)), 6.65 (2H, d, *J* 8.7 Hz, *Ph*(*p*-NMe_2)), 6.58 (1H, dd, *J* 15.2, 10.3 Hz, CHCHC*H*CHPh(*p*-NMe_2)), 6.55 (1H, d, *J* 15.2 Hz, H-2), 6.50 (1H, s, H-8), 6.28 (1H, dd, *J* 14.9, 9.5 Hz, CHC*H*CHCHPh(*p*-NMe_2)), 6.11 (1H, d, *J* 9.5 Hz, CHCHCHC*H*Ph(*p*-NMe_2)), 5.79 (1H, dd, *J* 14.9, 8.3 Hz, H-3), 5.15 (1H, dd, *J* 9.5, 5.4 Hz, C*H*CHCHCHPh(*p*-NMe_2)), 4.57 (1H, dd, *J* 8.3, 5.4 Hz, H-4), 3.99 (3H, s, O*Me*), 3.90 (3H, s, O*Me*), 3.35–3.19 (2H, m, H-6), 2.96 (6H, s, Ph(*p*-NMe_2)), 2.88–2.70 (2H, m, H-7); δ_C (75 MHz, $CDCl_3$) 151.0, 150.8, 150.5, 147.6, 135.0, 132.0, 129.8, 129.0, 128.5, 127.8, 125.4, 124.2, 123.5, 121.4, 112.6, 112.5, 111.2, 110.3, 75.3, 64.0, 56.5, 56.2, 47.3, 40.5, 29.9.

*4.3.7. 4-(4-Nitro-phenyl)-4,6,7,12-tetrahydro-indolo[2,3-a]quinolizine-1-carbonitrile (**11a**).* Purification by column chromatography (EtOAc/hexane 1:1) gave the title compound **11a** (276 mg, 75%) yellow solid, mp 129 °C; R_f (EtOAc/hexane 1:1) 0.70. [Found: C, 71.92; H, 4.43; N, 14.99. $C_{22}H_{16}N_4O_2$ requires C, 71.73; H, 4.38; N, 15.21%]; ν_{max} (KBr) 3441, 2930, 2181, 1599, 1513, 1340, 748 cm^{-1}; δ_H 9.46 (1H, br s, N*H*), 8.17 (2H, d, *J* 8.8 Hz, Ph(*p*-NO_2)), 7.56 (2H, d, *J* 8.8 Hz, Ph(*p*-NO_2)), 7.50 (1H, d, *J* 8.0 Hz, H-8), 7.42 (1H, d, *J* 8.3 Hz, H-11), 7.27 (1H, dd, *J* 8.0, 7.0 Hz, H-10), 7.13 (1H, dd, *J* 8.3, 7.0 Hz, H-9), 6.05 (1H, d, *J* 9.6 Hz, H-2), 5.31 (1H, d, *J* 4.7 Hz, H-4), 5.22 (1H, dd, *J* 9.6, 4.7 Hz, H-3), 3.56–3.49 (1H, m, H-6), 3.19–3.12 (1H, m, H-6), 2.98–2.93 (2H, m, H-7); δ_C (75 MHz, $CDCl_3$) 149.3, 148.1, 145.5, 137.8, 129.2, 127.5, 125.8, 124.8, 124.6, 123.7, 122.2, 121.0, 119.7, 116.4, 114.9, 112.4, 82.3, 64.8, 48.6, 21.1.

*4.3.8. 4-[2-(4-Nitro-phenyl)-vinyl]-4,6,7,7a,12,12a-hexahydro-indolo[2,3-a]quinolizine-1-carbonitrile (**11b**).* Purification by column chromatography (EtOAc/hexane 1:1) gave the title compound **11b** (221 mg, 56%) yellow solid, mp 123 °C; R_f (EtOAc/hexane 1:1) 0.68. [Found: C, 73.06; H, 4.85; N, 14.25. $C_{24}H_{18}N_4O_2$ requires C, 73.08; H, 4.60; N, 14.20%]; ν_{max} (KBr) 3440, 2928, 2181, 1595, 1515, 1342, 747 cm^{-1}; δ_H 9.43 (1H, br s, N*H*), 8.15 (2H, d, *J* 8.9 Hz, Ph(*p*-NO_2)), 7.51 (2H, d, *J* 8.9 Hz, Ph(*p*-NO_2)), 7.49 (1H, d, *J* 7.8 Hz, H-8), 7.42 (1H, d, *J* 8.3 Hz, H-11), 7.29 (1H, dd, *J* 7.8, 7.0 Hz, H-10), 7.14 (1H, dd, *J* 8.3, 7.0 Hz, H-9), 6.59 (1H, d, *J* 16.0 Hz, H-2), 6.48 (1H, dd, *J* 16.0, 7.3 Hz, H-3), 6.11 (1H, d, *J* 9.6 Hz, CHC*H*Ph(*p*-NO_2)), 5.21 (1H, dd, *J* 9.6, 5.4 Hz, C*H*CHPh(*p*-NO_2)), 4.72 (1H, dd, *J* 7.3, 5.4 Hz, H-4), 3.63–3.44 (2H, m, H-6), 3.18–2.95 (2H, m, H-7); δ_C (75 MHz, $CDCl_3$) 147.5, 145.5, 142.6, 137.7, 131.2, 128.8, 127.5, 126.3, 125.6, 124.9, 124.2, 123.8, 123.4, 120.9, 119.6, 116.3, 112.8, 112.3, 82.3, 63.0, 48.4, 21.2.

*4.3.9. 4-[4-(4-Nitro-phenyl)-buta-1,3-dienyl]-4,6,7,12-tetrahydro-indolo[2,3-a]quinolizine-1-carbonitrile (**11c**).* Purification by column chromatography (EtOAc/hexane 1:1) gave the title compound **11c** (202 mg, 48%) yellow solid, mp 122 °C; R_f (EtOAc/hexane 1:1) 0.65. [Found: C, 74.43; H, 4.94; N, 13.15. $C_{26}H_{20}N_4O_2$ requires C, 74.27; H, 4.79; N, 13.33%]; ν_{max} (KBr) 3441, 2927, 2180, 1590, 1510, 1342, 750 cm^{-1}; δ_H 9.43 (1H, br s, N*H*), 8.14 (2H, d, *J* 8.8 Hz, Ph(*p*-NO_2)), 7.50 (2H, d, *J* 8.8 Hz, Ph(*p*-NO_2)), 7.47 (1H, d, *J* 7.9 Hz, H-8), 7.43 (1H, d, *J* 8.3 Hz, H-11), 7.27 (1H, dd, *J* 7.9, 7.0 Hz, H-10), 7.13 (1H, dd, *J* 8.3, 7.0 Hz, H-9), 6.84 (1H, dd, *J* 15.2, 9.6 Hz, CHCHC*H*CHPh(*p*-NO_2)), 6.56 (1H, d, *J* 15.8 Hz, H-2), 6.15 (1H, dd, *J* 15.2, 9.5 Hz, CHC*H*CHCHPh(*p*-NO_2)), 6.12 (1H, d, *J* 9.5 Hz, CHCHCHC*H*Ph(*p*-NO_2)), 6.03 (1H, dd, *J* 15.1, 7.7 Hz, H-3), 5.16 (1H, dd, *J* 9.5, 5.4 Hz, C*H*CHCHCHPh(*p*-NO_2)), 4.72 (1H, dd, *J* 7.7, 5.4 Hz, H-4), 3.55–3.49 (2H, m, H-6), 3.10–2.97 (2H, m, H-7); δ_C (75 MHz, $CDCl_3$) 147.6, 145.4, 142.6, 137.7, 133.8, 132.2, 131.9, 128.8, 127.5, 126.9, 125.6, 124.3, 124.2, 123.4, 120.9, 119.6, 116.3, 115.33, 112.81, 112.3, 82.30, 63.0, 48.5, 21.3.

4.4. 2-(6,7-Dimethoxy-3,4-dihydro-2*H*-isoquinolin-1-ylidene)-3-oxo-7-phenyl-hepta-4,6-dienenitrile (14)

Enaminonitrile (**12**) (691 mg, 3 mmol), potassium carbonate (1.66 g, 12 mmol), and carboxylic acid chloride (**13**) (693 mg, 3.6 mmol) were heated to reflux in acetonitrile (50 mL) for 4 h. Potassium carbonate was filtered, and the solvent was removed in vacuo. Purification by column chromatography (EtOAc/hexane 1:1) gave the title compound **14** (777 mg, 67%) yellow solid, mp 210 °C; R_f (EtOAc) 0.67. [Found: C, 74.69; H, 5.32; N, 7.01. $C_{24}H_{22}N_2O_3$ requires C, 74.59; H, 5.74; N, 7.25%]; ν_{max} (KBr) 3450, 2964, 2199, 1692, 1618, 1573, 1265 cm^{-1}; δ_H 8.00 (1H, s, H-8), 7.53–7.43 (3H, m, *Ph*), 7.38–7.33 (2H, m, *Ph*), 7.29 (1H, dd, *J* 14.6, 6.7 Hz, CHC*H*CHCHPh), 7.12 (1H, d, *J* 14.7 Hz, CHCHCHC*H*Ph), 6.99 (1H, d, *J* 14.6 Hz,

C*H*CHCHCHPh), 6.97–6.88 (1H, m, CHCHC*H*CHPh), 6.72 (1H, s, H-5), 3.98 (3H, s, O*Me*), 3.93 (3H, s, O*Me*), 3.49 (2H, td, *J* 6.7, 3.8 Hz, H-3), 2.85 (2H, t, *J* 6.7 Hz, H-4), 1.66 (1H, br s, *NH*); δ_C (75 MHz, $CDCl_3$) 188.0, 164.2, 152.8, 147.8, 141.7, 140.4, 136.6, 132.2, 129.0, 129.0, 128.0, 127.5, 127.3, 123.1, 118.9, 112.2, 110.7, 79.1, 56.6, 56.3, 39.1, 28.2.

4.5. 3-Benzyl-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (16d)

A solution of formaldehyde (37% w/w *aqueous* solution, 0.2 mL, 3.2 mmol), benzyl amine (0.15 mL, 171 mg, 1.6 mmol), and enaminonitrile (**12**) (368 mg, 1.6 mmol) in MeOH (5 mL) was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure and the oily residue was dissolved in CH_2Cl_2 (20 mL). The solution was washed with H_2O (3×10 mL), dried over Na_2SO_4, and then evaporated to give the crude product. Recrystallization (EtOAc) gave **16d** (422 mg, 73%) white solid, mp 172 °C; R_f (EtOAc/hexane 1:1) 0.64. [Found: C, 73.25; H, 6.35; N, 11.60. $C_{22}H_{23}N_3O_2$ requires C, 73.11; H, 6.41; N, 11,63%]; ν_{max} (KBr) 2935, 2175, 1600, 1539, 1525, 1265 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.99 (1H, s, H-11), 7.35–7.29 (5H, m, CH_2*Ph*), 6.65 (1H, s, H-8), 4.10 (2H, s, H-4), 3.95 (3H, s, O*Me*), 3.90 (s, 3H, O*Me*), 3.77 (2H, s, NCH_2Ph), 3.69 (2H, s, H-2), 3.16 (2H, t, *J* 5.8 Hz, H-6), 2.82 (2H, t, *J* 5.8 Hz, H-7); δ_C (75 MHz, $CDCl_3$) 150.5, 150.1, 147.7, 138.0, 129.4, 129.3, 128.8, 127.8, 124.3, 121.0, 110.9, 110.6, 69.0, 65.8, 56.9, 56.5, 56.2, 52.4, 46.5, 29.6.

4.6. General procedure for cyclocondensation of 1-azapolyenes (17a–e) with formaldehyde/amine

A solution of formaldehyde (37% w/w *aqueous* solution, 0.1 mL, 1.6 mmol), amine (1.6 mmol), and 1-azapolyene (**17a–e**) (1.6 mmol) in MeOH (5 mL) was stirred at room temperature for 16–18 h. The reaction mixture was concentrated under reduced pressure and the oily residue was dissolved in CH_2Cl_2 (20 mL). The solution was washed with H_2O (3×10 mL), dried over Na_2SO_4, and then evaporated to give the crude product.

*4.6.1. 9,10-Dimethoxy-3-methyl-2-styryl-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinoline-1-carbonitrile (**18a**).* Recrystallization (EtOAc) gave **18a** (490 mg, 79%) white solid, mp 140 °C; R_f (EtOAc) 0.48. [Found: C, 74.25; H, 6.59; N, 10.58. $C_{24}H_{25}N_3O_2$ requires C, 74.39; H, 6.50; N, 10.84%]; ν_{max} (KBr) 2943, 2162, 1588, 1551, 1525, 1289 cm^{-1}; δ_H (300 MHz $CDC1_3$) 8.03 (1H, s, H-11), 7.41–7.16 (5H, m, *Ph*), 6.65 (1H, s, H-8), 6.57 (1H, d, *J* 16.0 Hz, CHCHPh), 6.26 (1H, dd, *J* 5.1, 16.0 Hz, C*H*CHPh) 4.43 (1H, d, *J* 12.1 Hz, H^a-4), 3.97 (3H, s, O*Me*), 3.88 (s, 3H, O*Me*), 3.80 (1H, d, *J* 5.1 Hz, H-2) 3.68 (1H, d, *J* 12.1 Hz, H^b-4), 3.27–3.22 (2H, m, H-6), 2.82–2.78 (2H, m, H-7), 2.50 (3H, s, NCH_3); δ_C (75 MHz, $CDCl_3$) 150.6, 149.5, 147.6, 136.9, 133.6, 130.2, 129.7, 128.7, 127.9, 126.9, 124.6, 121.0, 111.2, 110.6, 67.1, 63.5, 56.6, 56.2, 46.7, 41.3, 29.4.

*4.6.2. 3-Benzyl-9,10-dimethoxy-2-styryl-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinoline-1-carbonitrile (**18b**).* Recrystallization (EtOAc) gave **18b** (482 mg, 65%) pale yellow solid, mp 133 °C; R_f (EtOAc/hexane 1:1) 0.50. [Found: C, 77.59; H, 6.44; N, 9.00. $C_{30}H_{29}N_3O_2$ requires C, 77.73; H, 6.31; N, 9.06%]; ν_{max} (KBr) 2937, 2172, 1591, 1553, 1290 cm^{-1}; δ_H (300 MHz $CDC1_3$) 8.13 (1H, s, H-11), 7.46–7.23 (10H, m, *Ph*), 6.70 (1H, s, H-8), 6.62 (1H, d, *J* 15.0 Hz, CHC*H*PhNO$_2$), 6.33 (1H, dd, *J* 4.6, 15.0 Hz, C*H*CHPh) 4.47 (1H, d, *J* 12.4 Hz, H^a-4), 4.15 (1H, d, *J* 4.6 Hz, H-2), 4.02 (3H, s, OMe), 3.94 (s, 3H, OMe), 3.82 (1H, d, *J* 13.2 Hz, CH_2Ph), 3.73 (1H, d, *J* 13.2 Hz, CH_2Ph), 3.66 (1H, d, *J* 12.4 Hz, H^b-4), 3.23–3.18 (2H, m, H-6), 2.92–2.82 (2H, m, H-7); δ_C (75 MHz, $CDCl_3$) 150.6, 149.9, 147.8, 138.2, 137.0, 133.3, 130.8, 129.6, 129.2, 128.8, 128.7, 127.8, 127.8, 126.9, 124.6, 121.1, 111.2, 110.7, 67.2, 64.3, 61.4, 57.1, 56.6, 56.3, 46.6, 29.6.

*4.6.3. 3-[2-(3,4-Dimethoxy-phenyl)-ethyl]-9,10-dimethoxy-2-styryl-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinoline-1-carbonitrile (**18c**).* Recrystallization (EtOAc) gave **18c** (714 mg, 83%) pale yellow solid, mp 97 °C; R_f (EtOAc) 0.55. [Found: C, 73.88; H, 6.60; N, 7.99. $C_{33}H_{35}N_3O_4$ requires C, 73.72; H, 6.56; N, 7.82%]; ν_{max} (KBr) 2936, 2168, 1590, 1552, 1514, 1028 cm^{-1}; δ_H (300 MHz $CDC1_3$) 8.06 (1H, s, H-11), 7.44–7.23 (5H, m, *Ph*), 6.80–6.75 (3H, m, *Ph*(OMe)$_2$), 6.66 (1H, s, H-8), 6.57 (1H, d, *J* 16.2 Hz, CHC*H*Ph), 6.30 (1H, dd, *J* 4.8, 16.2 Hz, C*H*CHPh) 4.49 (1H, d, *J* 12.8 Hz, H^a-4), 4.18 (1H, d, *J* 4.8 Hz, H-2), 3.98 (3H, s, O*Me*), 3.91 (s, 3H, O*Me*), 3.87 (3H, s, O*Me*), 3.96 (3H, s, O*Me*), 3.77 (1H, d, *J* 12.8 Hz, H^b-4), 3.26–3.14 (2H, m, H-6), 2.90–2.76 (6H, m, H-7, CH_2CH_2Ph(OMe)$_2$); δ_C (75 MHz, $CDCl_3$) 150.6, 149.9, 149.2, 147.8, 147.7, 137.0, 133.4, 132.7, 130.5, 129.5, 128.7, 127.9, 126.9, 124.6, 121.1, 120.8, 112.4, 111.6, 111.1, 110.6, 82.3, 67.4, 65.7, 61.7, 56.6, 56.2, 56.1, 55.0, 46.7, 34.9, 29.5.

*4.6.4. 3-Benzyl-9,10-dimethoxy-2-[2-(4-nitro-phenyl)-vinyl]-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinoline-1-carbonitrile (**18d**).* Recrystallization (EtOAc) gave **18d** (528 mg, 65%) white solid, mp 114 °C; R_f (EtOAc/hexane 1:1) 0.47. [Found: C, 70.67; H, 5.53; N, 10.89. $C_{30}H_{28}N_4O_4$ requires C, 70.85; H, 5.55; N, 11.02%]; ν_{max} (KBr) 2938, 2169, 1593, 1551, 1483, 1342, 1290 cm^{-1}; δ_H (300 MHz $CDC1_3$) 8.15 (2H, d, *J* 8.7 Hz, *Ph*NO$_2$), 8.09 (1H, s, H-11), 7.55 (2H, d, *J* 8.7 Hz, *Ph*NO$_2$), 7.58–7.34 (5H, m, *Ph*), 6.70 (1H, s, H-8), 6.66 (1H, d, *J* 15.5 Hz, CHC*H*PhNO$_2$), 6.49 (1H, dd, *J* 4.4, 15.5 Hz, C*H*CHPh) 4.45 (1H, d, *J* 12.5 Hz, H^a-4), 4.15 (1H, d, *J* 4.4 Hz, H-2), 3.99 (3H, s, O*Me*), 3.93 (s, 3H, O*Me*), 3.85 (1H, d, *J* 13.0 Hz, CH_2Ph), 3.78 (1H, d, *J* 13.0 Hz, CH_2Ph), 3.73 (1H, d, *J* 12.5 Hz, H^b-4), 3.22–3.20 (2H, m, H-6), 2.90–2.83 (2H, m, H-7); δ_C (75 MHz, $CDCl_3$) 150.8, 150.2, 147.8, 147.2, 143.5, 137.8, 135.7, 131.0, 129.7, 129.2, 128.9, 127.9, 127.4, 124.4, 124.1, 120.8, 111.1, 110.7, 66.5, 64.5, 61.3, 57.2, 56.6, 56.3, 46.7, 29.5.

*4.6.5. 3-Benzyl-9,10-dimethoxy-2-(4-phenyl-buta-1,3-dienyl)-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinoline-1-carbonitrile (**18e**).* Purification by column chromatography (EtOAc/hexane 1:1) gave the title compound **18e** (470 mg, 60%) yellow oil, R_f (EtOAc) 0.63. [Found: C, 78.43; H, 6.30; N, 8.59. $C_{32}H_{31}N_3O_2$ requires C, 78.50; H, 6.38; N, 8.58%]; ν_{max} (KBr) 2935, 2174, 1598, 1522, 1466, 1344, 1277 cm^{-1}; δ_H (300 MHz $CDC1_3$) 8.10 (1H, s, H-11), 7.39–7.18 (10H, m, *Ph*), 6.84 (1H, dd, *J* 10.6, 15.6 Hz, CHCHC*H*CHPh), 6.68 (1H, s, H-8), 6.58 (1H, d, *J* 15.6 Hz, CHCHCHC*H*Ph), 6.44 (1H, dd, *J* 10.6, 15.3 Hz, CHC*H*CHCHPh), 5.94 (1H, dd, *J* 4.6, 15.3 Hz, C*H*CHCHCHPh), 4.42 (1H, d, *J* 12.3 Hz, H^a-4), 4.07 (1H, d, *J* 4.6 Hz, H-2), 4.00 (3H, s, O*Me*), 3.92 (s, 3H, O*Me*), 3.85 (1H, d, *J* 12.3 Hz, H^b-4), 3.79 (1H, d, *J* 13.3 Hz, CH_2Ph), 3.73 (1H, d, *J* 13.3 Hz, CH_2Ph), 3.22–3.13 (2H, m, H-6), 2.92–2.77 (2H, m, H-7); δ_C (75 MHz, $CDCl_3$) 150.6, 149.8, 147.7, 138.1, 137.5, 135.0, 133.7, 133.2, 129.6, 129.2, 129.1, 128.8, 128.7, 128.5, 128.4, 127.8, 127.7, 126.6, 124.6, 121.1, 111.2, 110.6, 68.5, 67.2, 64.3, 61.3, 57.1, 26.6, 26.2, 46.6, 29.6.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.03.058.

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