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An expedient microwave-assisted, solvent-free, solid-supported synthesis of pyrrolo[2,3-*d*]pyrimidine-pyrano[5,6-*c*]coumarin/[6,5-*c*]-chromone derivatives by intramolecular hetero Diels–Alder reaction

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Abstract

A rapid synthesis of pyrrolo[2,3-*d*]pyrimidine annulated pyrano[5,6-*c*]coumarin/[6,5-*c*]chromone derivatives has been accomplished in good yields via an intramolecular domino hetero Diels–Alder reaction using microwave irradiation under solvent-free, solid-supported conditions.

Keywords: Hetero Diels–Alder; Pyrrolopyrimidine; Pyranocoumarin; Microwave

The intramolecular Diels–Alder reaction is a powerful method for the synthesis of many polycyclic compounds, including natural products.[1,2] However, it is a prerequisite that activating groups have to be incorporated into the dienophiles to achieve the desired reactivity.[3,4]

A number of coumarin derivatives have been isolated from natural sources and their pharmacological and biochemical properties depend upon the pattern of substitution. They have attracted considerable interest in recent years because of their diverse pharmacological properties.

Coumarins serve as anti-oxidant, anti-inflammatory, antiallergic, hepatoprotective, antiviral, anticarcinogenic, anticoagulant and antifungal agents in addition to HIV protease inhibitors.[5–9] Many naturally occurring compounds such as isoethuliacoumarin A, isoethuliacoumarin B, isoethuliacoumarin C, ethuliacoumarin A, ethuliacoumarin B, pterophyllin, calonone, isocalonone, (+)-calanoide A, soulattroide and (+)-isoferprenin[10–12] possess a pyrano coumarin skeleton. Similarly, the chromone moiety forms an important component of pharmacophores for number of biologically active molecules of synthetic as well as natural origin and many of them have useful medicinal applications.[13–16]

Pyrrolo[2,3-*a*]pyrimidine nucleoside derivatives are reported to have various biological activities such as anti-HCV, anti-HIV type 1 and anti-HSV as well as being adenosine kinase, aurora-A kinase and cAMP phosphodiesterase inhibitors.[17–20] Naturally occurring mycalisine A, cadeguomycin and 2-deoxycadeguomycin[21,22] (Fig. 1) also possess a pyrrolo[2,3-*a*]pyrimidine moiety.

We disclose here our preliminary investigation on the rapid and expedient synthesis of novel uracil annulated pyrano[5,6-*c*]coumarin and pyrano[6,5-*c*]chromone derivatives

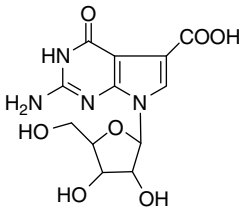

Fig. 1.

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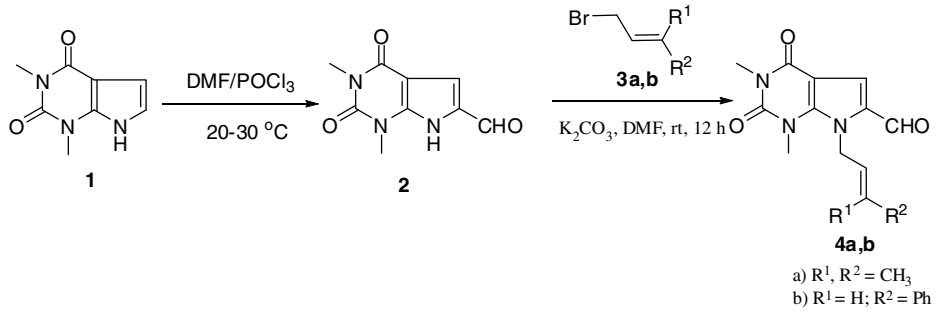
through solvent-free, microwave-assisted, Knoevenagel-intramolecular hetero Diels–Alder reactions. 1,3-Dimethyl-1-pyrrolo[2,3-*a*]pyrimidine-2,4-dione **1** was chosen as the starting material which on treatment with the Vilsmeier reagent (DMF + $POCl_3$) gave 1,3-dimethyl-2,4-dioxo-1*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbaldehyde **2** in excellent yield.[23] Treatment of **2** with 1-bromo-3-methylbut-2-ene **3a**/cinnamyl bromide **3b** in dry DMF in the presence of a K_2CO_3 gave **4a**/**4b** in good yields (70–80%).[24] The same reaction when carried out in 10% aqueous sodium hydroxide in the presence of a catalytic amount of a PTC (TBAS) resulted in a lower yield of the products (40–58%) (Scheme 1).

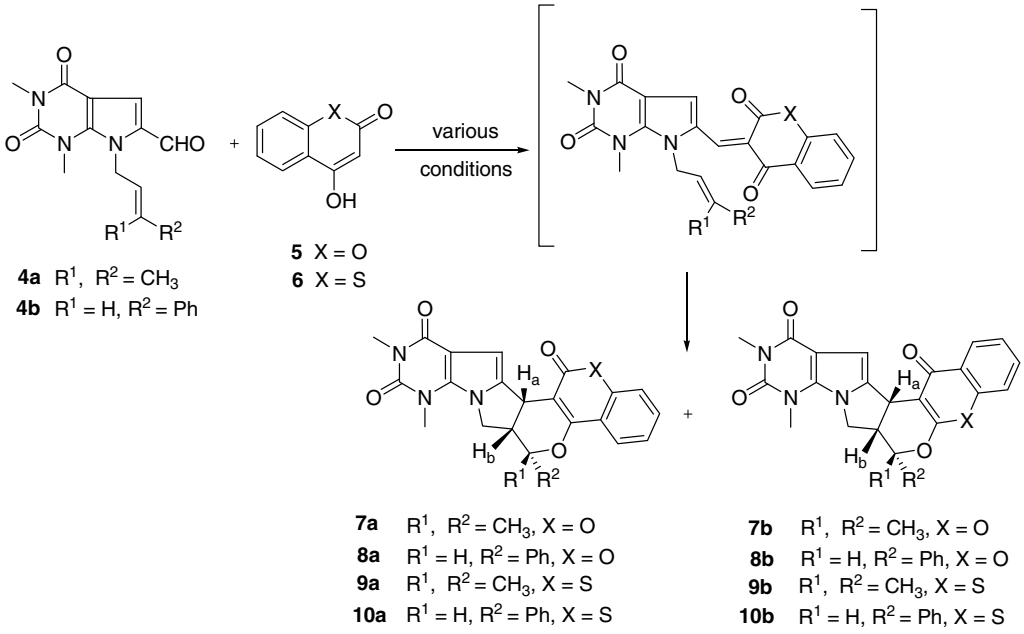
Treatment of 4-hydroxycoumarin **5** with **4a** in refluxing toluene resulted in the formation of the *cis*-fused coumarin **7a** and chromone **7b** with an overall yield of 47% in the ratio 58:42 (Scheme 2). The reaction proceeded via a domino Knoevenagel-intramolecular hetero Diels–Alder pathway in a one-step process.

The relative amounts of **7a** and **7b** formed were estimated from the ^{1}H NMR spectrum of the crude product. The structures of the products were ascertained from spectral data. The IR carbonyl absorption of **7a** was observed at 1640 cm^{-1}, whereas in the case of **7b** it was observed at 1732 cm^{-1}. The formation of coumarin and chromone derivatives was confirmed by the distinguishable carbonyl carbon in the ^{13}C NMR, which appeared at δ 165.5 ppm for the coumarin and at δ 177.1 ppm for the chromone derivative. The ^{1}H NMR spectrum of **7a** exhibited a doublet at δ 4.23 for the H_a proton and a multiplet in the region δ 3.36–3.44 for the H_b proton. The *syn*-stereochemistry of the products was confirmed by the coupling constants $J_{Ha,Hb} = 6.8$ Hz. Further, the *syn*-stereochemistry was confirmed from the strong NOE coupling between the H_a and H_b protons.

The ^{1}H NMR spectrum of **7b** showed a doublet at δ 4.21 for the H_a proton and a multiplet in the region δ 3.28–3.35 for the H_b proton. The *syn*-stereochemistry of the product was confirmed by the coupling constants ($J_{Ha,Hb} = 6.0$ Hz) and a strong NOE coupling between the H_a and H_b protons.



Scheme 1.



Scheme 2.

To improve the reaction yield and the chemoselectivity, we turned our attention to solid-supported microwave conditions as part of our ongoing efforts to apply microwave chemistry to synthesis.[25,26]

When the same reaction was carried out under microwave irradiation for 5 min in toluene, the coumarin and chromone derivatives were obtained in the ratio 65:35 with an overall yield of 52%. We also examined the reaction, under solvent-free conditions, simply by grinding the two components with K-10 montmorillonite clay and irradiating the mixture under microwave conditions which afforded the anticipated cycloadducts in excellent yields with high chemoselectivity. The ratio of the coumarin and chromone derivatives was found to be 74:26 with an improved overall yield of 74% (Table 1).

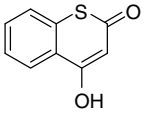
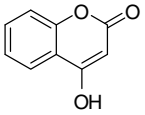
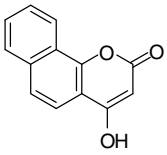
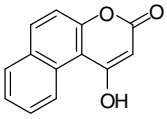
To investigate the synthetic scope of this cycloaddition reaction, we reacted **5,** 4-hydroxy-thiocoumarin **6**, α-naphthocoumarin **11** and β-naphthocoumarin **14**, in refluxing toluene with **4a** and **4b** (Schemes 2–4) and the results are summarized in Tables 1 and 2.

Treatment of 4-hydroxycoumarin **5** with **4b** in refluxing toluene resulted in the formation of cis-fused **8a** and **8b** with an overall yield of 62% and ratio of 54:46.

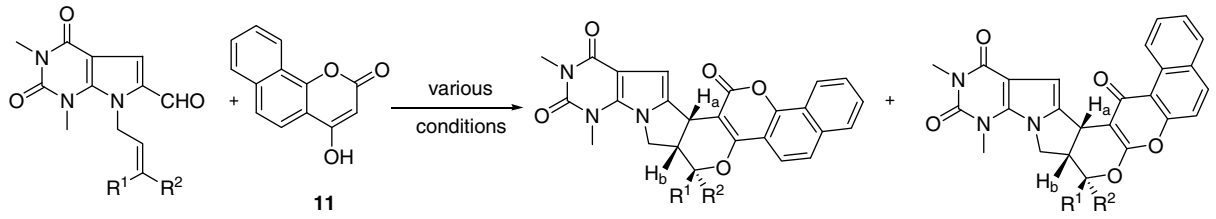
The relative amounts of **8a** and **8b** formed were estimated from the ^{1}H NMR spectra of the crude products. The carbonyl absorption of **8a** was observed at 1644 cm^{-1}, whereas in the case of **8b** it was observed at 1728 cm^{-1} in the IR spectra.

The formation of coumarin and chromone derivatives was confirmed by the distinguishable carbonyl carbon in the ^{13}C NMR, which appeared at δ 162.0 for the coumarin and at δ 178.2 for the chromone derivative. The ^{1}H NMR spectrum of **8a** showed a doublet at δ 4.63 for the H_a proton and a multiplet in the region δ 3.36–3.40 for the H_b

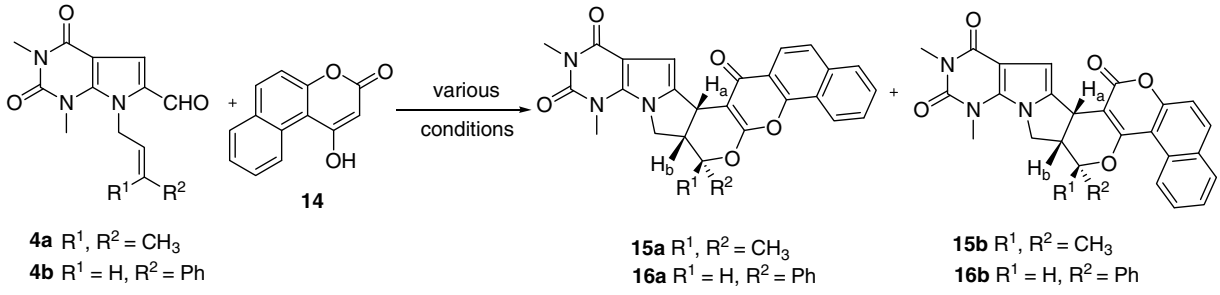
Table 1
Results obtained from the domino Knoevenagel–hetero Diels–Alder reaction of 1,3-diones with **4a** under various conditions

Entry	1,3-Dione	Conditions	Time	Ratio of products		Overall yield (%)
				Coumarin	Chromone	
1		A	4.5 h	55	45	45
		B	5 min	62	38	52
		C	10 min	75	25	75
2		A	5.0 h	58	42	47
		B	5 min	65	35	52
		C	10 min	74	26	74
3		A	5.5 h	54	46	48
		B	10 min	62	38	57
		C	12 min	70	30	77
4		A	5.7 h	50	50	51
		B	12 min	61	39	60
		C	16 min	78	22	77

Method A: toluene reflux; method B: toluene/MW; method C: K-10 montmorillonite clay/MW.

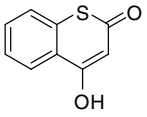
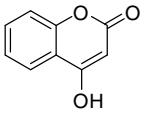
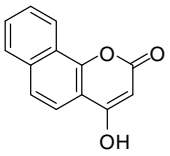
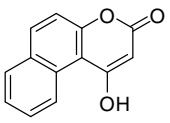


Scheme 3.



Scheme 4.

Table 2
Results obtained from the domino Knoevenagel–hetero Diels–Alder reaction of 1,3-diones with **4b** under various conditions

Entry	1,3-Dione	Conditions	Time	Ratio of products		Overall yield (%)
				Coumarin	Chromone	
1		A	3 h	51	49	65
		B	2 min	64	36	74
		C	30 s	72	28	81
2		A	3.5 h	54	46	62
		B	2.5 min	65	35	77
		C	40 s	75	25	84
3		A	4.5 h	53	47	64
		B	3.0 min	67	33	75
		C	45 s	77	23	89
4		A	4.25 h	64	36	61
		B	3.0 min	75	25	79
		C	47 s	80	20	85

Method A: toluene reflux; method B: toluene/MW; method C: K-10 montmorillonite clay/MW.

proton. The *syn*-stereochemistry of the products was confirmed by the coupling constant $J_{Ha,Hb} = 6.1$ Hz.

In the ^{1}H NMR spectrum of **8b**, a doublet at δ 4.55 appeared for the H_a proton whilst the H_b proton resonated as a multiplet in the region δ 3.48–3.52. The *syn*-stereochemistry of the product was confirmed by the coupling constant $J_{Ha,Hb} = 6.8$ Hz. Further, the *syn*-stereochemistry of the derivative was confirmed by a strong NOE coupling between protons H_a and H_b.

Under microwave irradiation, the reaction proceeded to form **8a** as the major product (65%) and **8b** as the minor product (35%). Better results were obtained when the reaction was performed under microwave irradiation and solvent-free conditions using K-10 montmorillonite clay as a solid support. The ratio of the products formed under these conditions was 75:25 with an overall yield of 84%.

To conclude, we have accomplished the synthesis of novel polycyclic heterocyclic ring systems containing coumarin and chromone moieties under mild conditions.[27] The intramolecular, domino, Knoevenagel–hetero Diels–Alder reaction proved to be a useful protocol to prepare these interesting compounds. Of the various conditions employed, the solvent-free approach on a solid support accelerated by microwaves proved to be synthetically useful in achieving high degrees of chemo- and stereoselectivity with a substantial reduction in reaction time.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.059.

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23. *Experimental procedure for compound* **2**: 2,4-Dioxo-tetrahydropyrrole[2,3-*d*]pyrimidine **1** (0.01 mol) in DMF (10 mL) was added slowly with stirring and exclusion of moisture to a mixture of DMF (0.4 mol) and $POCl_3$ (0.01 mol), keeping the temperature between 20 and 30 °C. After cooling to 0 °C, the resulting yellow solid was filtered and the solid was heated with water (10 mL) at 60–80 °C for 45 min. After cooling, the resulting precipitate was filtered, washed with H_2O and then recrystallized from ethyl acetate. Purple solid, mp: 282 °C ^{1}H NMR (400 MHz, DMSO): 3.30 (s, 3H), 3.57 (s, 3H), 6.81 (s, 1H), 9.32 (s, 1H), 12.2 (s, 1H, br s).; MS (EI) *m/z*: 207 (M^+); Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.90; H, 4.41; N, 20.24.
24. *Experimental procedure for compounds* **4a/4b**: 1,3-Dimethyl-2,4-dioxo-1*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbaldehyde **2** (10 mmol) in DMF (20 mL) was treated with solid K_2CO_3 (16 mmol) and 1-bromo-3-methylbut-2-ene (12 mmol) or cinnamyl bromide (12 mmol) and the mixture was stirred overnight at 20 °C. Water (50 mL) was added to the mixture and the aqueous layer was extracted with ethyl acetate (4 × 20 mL).The combined organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo and the crude product subjected to column chromatography (100–200 mesh) using hexane–ethyl acetate (8:2) as eluent.
    Compound **4a:** Pale yellow solid, mp: 152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 1.75 (s, 3H), 2.01 (s, 3H), 3.41 (s, 3H), 3.78 (s, 3H), 5.18 (d, $J = 4.5$ Hz, 2H), 5.33 (t, $J = 4.5$ Hz, 1H), 7.38 (s, 1H), 9.49 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2, 24.3, 30.4, 30.1, 32.4, 104.8, 117.7, 117.9, 130.9, 132.2, 150.4, 158.8, 147.5, 178.6; MS (EI) *m/z*: 275 (M^+); Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.09; H, 6.18; N, 15.27. Found: C, 60.77; H, 6.14; N,15.23.
    Compound **4b**: Pale yellow solid, mp: 170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.42 (s, 3H), 3.82 (s, 3H), 5.54 (d, $J = 4.8$ Hz, 2H), 6.22 (d, $J = 16.1$ Hz 1H), 6.35 (dt, $J = 16.1$ Hz, 1H), 7.02–7.73 (m, 5H), 7.45 (s, 1H), 9.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.5, 33.6, 31.5, 104.5, 117.7, 126.4 128.0, 128.7, 128.9, 130.5, 131.0, 133.2, 133.4, 135.2, 146.6, 150.1, 157.3, 178.3 ppm; MS (EI) *m/z*: 323 (M^+); Anal. Calcd for $C_{18}H_{17}N_3O_3$: C,66.87; H, 5.26; N, 13.00. Found: C, 66.77; H, 5.23; N, 13.14.
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27. *General procedure for the intramolecular domino Knoevenagel–hetero Diels–Alder reaction*: *Method A*: To a refluxing solution of unsymmetrical 1,3-dione (1 mmol) in 10 mL of dry toluene, aldehyde **4a** or **4b** (1 mmol) was added and the reaction mixture was refluxed until the disappearance of the starting material as evidenced by thin layer chromatography. After completion of the reaction, the solvent was evaporated and the residue was subjected to flash column chromatography using hexane/ethyl acetate (7:3).
    Method B: A mixture of unsymmetrical dione (1 mmol) and the corresponding aldehyde (1 mmol) in dry ethanol was irradiated using a microwave oven (Kenstar, 600 W power) until the disappearance of the starting material. After removal of the solvent, the crude reaction mixture was subjected to flash column chromatography as reported in method A.
    Method C: A mixture of 1,3-dione (1 mmol), the corresponding aldehyde (1 mmol) and K-10 montmorillonite clay (1.0 g) was thoroughly ground in a mortar. The reaction mixture was irradiated with a microwave (600 W) until the disappearance of the starting material as evidenced by thin layer chromatography. After completion of the reaction, the clay was separated by filtration and the product extracted with dichloromethane (2 × 15 mL). Removal of the solvent and the purification of the crude reaction mixture by flash column chromatography gave the pure product.
    7a,15b-cis-6,7-Dihydro-2,4-dioxo-3,5,8,8-tetramethyl-7,7a,8,15b-tetrahydropyrimido[2,3-b]pyrrolizino[4′,3′:4,5] pyrano[5,6-c]coumarin **7a**: Yellow solid, mp: 230–232 °C; IR (KBr): 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (s, 3H), 1.58 (s, 3H), 3.32 (s, 3H), 3.36–3.44 (m, $1H_b$), 3.62 (s, 3H), 4.16 (dd, $J = 7.3$, 9.9 Hz, 1H), 4.23 (d, $J = 6.8$ Hz, $1H_a$), 4.49 (dd, $J = 8.4$, 9.9 Hz, 1H), 6.65 (s, 1H), 7.21–7.27 (m, 2H), 7.45–7.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.36, 26.15, 26.40, 28.05, 30.06, 32.60, 45.09, 49.86, 70.40, 76.60, 104.56, 105.80, 121.28, 123.46, 125.4, 128.80, 132.46, 133.30, 138.5, 149.5, 151.40, 158.80, 165.5 ppm; MS (EI) *m/z*: 419.43 (M^+); Anal. Calcd for $C_{23}H_{21}N_3O_5$: C, 65.86; H, 5.05; N, 10.02. Found: C, 66.00; H, 5.15; N, 9.89.
    7a,15b-cis-6,7-dihydro-2,4-dioxo-3,5,8,8-tetramethyl-7,7a,8,15b-tetrahydropyrimido[2,3-b]pyrrolizino[4′,3′:4,5]pyrano[6,5-c]chromone **7b**: Yellow solid, mp: 247–249 °C; IR (KBr): 1732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (s, 3H), 1.57 (s, 3H), 3.30 (s, 3H), 3.28–3.35 (m, $1H_b$), 3.68 (s, 3H), 4.03 (dd, $J = 7.1$ Hz, 1H), 4.21(d, $J = 6.0$ Hz, $1H_a$), 4.32 (dd, $J = 8.4$ Hz, 1H), 6.62 (s, 1H), 7.22–7.37 (m, 2H), 7.35–7.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.30, 25.05, 24.40, 27.05, 32.16, 31.50, 45.15, 48.80, 69.40, 75.60, 105.50, 111.80, 122.24, 123.36, 125.4, 127.96, 130.46, 134.30, 136.5, 145.5, 153.40, 153.80, 177.1 ppm; MS (EI) *m/z*: 419.43 (M^+); Anal. Calcd for $C_{23}H_{21}N_3O_5$: C, 65.86; H, 5.05; N, 10.02. Found: C, 65.98; H, 5.20; N, 9.87.

7a,15b-cis-6,7-dihydro-3,5-dimethyl-2,4-dioxo-8-phenyl-7,7a,8,15b-tetrahydropyrimido[2,3-b]pyrrolizino[4′,3′:4,5]pyrano[5,6-c]coumarin **8a**: Yellow solid, mp: 241–242 °C; IR (KBr): 1644 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 3.28 (s, 3H), 3.32 (s, 3H), 3.90 (dd, $J = 7.0$, 10.1 Hz, 1H), 3.36–3.40 (m, $1H_b$), 4.16 (dd, $J = 8.0$, 10.1 Hz, 1H), 4.63 (d, $J = 6.1$ Hz, $1H_a$), 4.66 (d, $J = 9.7$ Hz, 1H), 6.56 (d, 1H), 7.03–7.29 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.5, 31.5, 33.6, 37.4, 42.8, 77.9, 91.2, 100.5, 105.7, 117.2, 119.3, 121.5, 125.5, 125.6, 126.8, 127.8, 127.9, 128.4, 128.6, 138.5, 140.9, 150.2, 151.4, 158.3, 162.0 ppm; MS (EI) *m/z*: 467.47 (M^+); Anal. Calcd for $C_{27}H_{21}N_3O_5$: C, 69.37; H, 4.53; N, 8.99. Found: C, 69.51; H, 4.64; N, 8.76.

7a,15b-cis-6,7-dihydro-3,5-dimethyl-2,4-dioxo-8-phenyl-7,7a,8,15b-tetrahydropyrimido[2,3-b]pyrrolizino[4′,3′:4,5]pyrano[6,5-c]chromone **8b**: Yellow solid, mp: 248–249 °C; IR (KBr): 1728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.37 (s, 3H), 3.38 (s, 3H), 3.48–3.52 (m, $1H_b$), 3.89 (dd, $J = 7.2$, 10.0 Hz, 1H), 4.35 (dd, $J = 7.2$, 10.0 Hz, 1H), 4.55 (d, $J = 6.8$ Hz, $1H_a$), 5.35 (d, $J = 9.6$ Hz, 1H), 6.12 (s, 1H), 7.07–7.31 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.1, 31.2, 32.4, 37.6, 42.0, 77.3, 90.9, 100.3, 104.6, 116.2, 118.4, 121.3, 125.2, 125.8, 126.9, 127.1, 130.6, 128.4, 128.5, 138.3, 140.4, 150.8, 151.2, 158.1, 178.2 ppm; MS (EI) *m/z*: 467.47 (M^+); Anal. Calcd for $C_{27}H_{21}N_3O_5$: C, 69.37; H, 4.53; N, 8.99. Found: C, 69.55; H, 4.70; N, 8.80.