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A rapid access to indolo[2,1-*a*]pyrrolo[4′,3′:4,5]-pyrano[5,6-*c*]coumarin/[6,5-*c*]chromone derivatives by domino Knoevenagal intramolecular hetero Diels–Alder reactions

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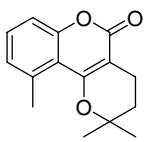
Abstract—Knoevenagal condensation of indole-2-carbaldehyde containing an internal dienophile with coumarins, followed by domino intramolecular hetero Diels–Alder reaction, provides polycyclic heterocycles. Different approaches for stereo- and chemoselective synthesis of indolo[2,1-*a*]pyrrolo[4′,3′:4,5]pyrano[5,6-*c*]coumarin and indolo[2,1-*a*]pyrrolo[4′,3′:4,5]pyrano[6,5-*c*]chromone derivatives are described.

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

Coumarin derivatives are widespread in Nature and are reported to have various biological activities such as anticoagulant, insecticidal, antihelminthic, hypnotic, antifungal, phytoalexin and HIV protease inhibition.[3] Many naturally occurring compounds were found to possess a pyranocoumarin skeleton such as isoethuliacoumarin A, isoethuliacoumarin B, isoethuliacoumarin C, ethuliacoumarin A, ethuliacoumarin B, and pterophyllin 3.[4,5] Similarly, the indole ring system is present in drug candidates having an interesting biological activity and in numerous natural alkaloids that cover a wide range of structural types.[6] Consequently, much effort has been devoted to developing new methods for the construction of indole compounds.[7]



pterophyllin 3

We report here the initial results showing that the solvent-free, microwave assisted domino Knoevenagal intramolecular hetero Diels–Alder reaction is a rapid and expedient way for the preparation of highly pure indolo-pyrrolo-pyrano-coumarin derivatives.

Optimization of the reaction conditions was carried out using the Knoevenagal hetero Diels–Alder reaction of 4-hydroxy coumarin **6** with 1-(3-methylbut-2-enyl)-indole-2-carbaldehyde **5a** as a model reaction. Treatment of ethyl-1*H*-indole-2-carboxylate **1** and 1-bromo-3-methylbut-2-ene **2a** in benzene with 50% aqueous sodium hydroxide in the presence of a catalytic amount of TEBA at room temperature for 2 h furnished ethyl-1-(3-methylbut-2-enyl)-1*H*-indole-2-carboxylate **3a** in a moderate yield, whereas treatment of **1** and **2a** with sodium hydride in DMF resulted in a lower yield of **3a** (40%). Ester **3a** was then reduced to alcohol **4a** with $LiAlH_4$ in dry THF at 0 °C in an 82% yield. Alcohol **4a** was then oxidized with activated MnO_2 in dichloromethane under N_2 at room temperature. However, we found the yield was only 56%, hence we performed the oxidation under Swern conditions to give **5a** in an 85% yield[8] (Scheme 1).

The intended product from the Knoevenagal hetero Diels–Alder reaction, 8a,15b-*cis*-8,8-dimethyl-8,8a,9,15b-tetrahydroindolo[2,1-*a*]pyrrolo[4′,3′:4,5]pyrano[5,6-*c*]coumarin **7a** was always accompanied by 8a,15b-*cis*-8,8-dimethyl-8,8a,9,15b-tetrahydroindolo[2,1-*a*]pyrrolo-[4′,3′:4,5]pyrano[6,5-*c*]chromone derivative **8a**, as shown

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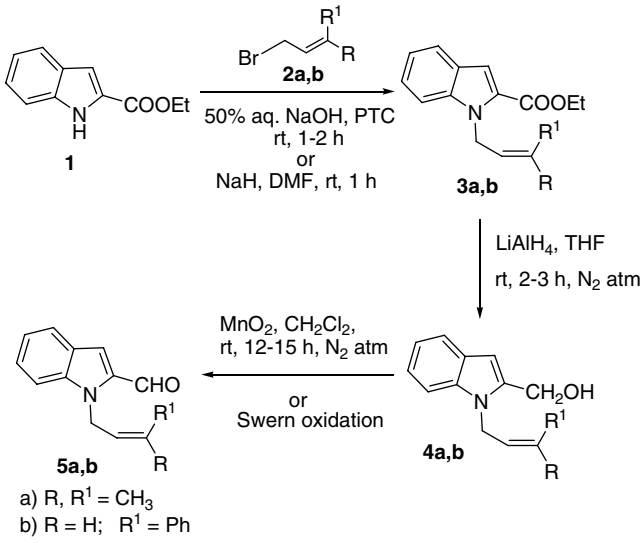


Scheme 1. Preparation of *N*-alkenylindole-2-carbaldehydes.

in Scheme 2.[9] The relative amounts of **7a** and **8a** formed were estimated from the ^{1}H NMR spectrum of the crude mixture.

Table 1 shows how crucial the choice of reaction conditions is in determining the trend of the reaction. A moderate yield of **7a** was obtained by reflux in ethanol, whereas **7a** was formed in a 72% yield under microwave irradiation (entry 1). On the other hand, solvent-free, solid-supported reaction under microwave irradiation afforded a very good yield of **7a** (86%).

The structure of the products was ascertained from spectral data. The IR carbonyl absorption of **7a** was observed at 1634 cm^{-1}, whereas in the case of **8a** it was observed at 1724 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 161.54 ppm for the coumarin and at δ 178.12 ppm for the chromone derivative. The ^{1}H NMR spectrum of **7a** showed a doublet at δ 4.52 for the H_a proton and a multiplet in the region δ 3.38–3.43 for the H_b proton. The cis-stereochemistry of products **7a** and **8a** was confirmed by the coupling constant $J_{Ha,Hb} = 8.0$ Hz. Further, the cis-stereochemistry of derivative **7a** was confirmed by a strong NOE coupling.

The different reactions for the preparation of α-naphtho-coumarin, α-naphtho-chromone, β-naphtho-coumarin and β-naphtho-chromone derivatives are summarized in Schemes 3 and 4. Table 1 shows the isolated yields for the different reaction conditions employed.

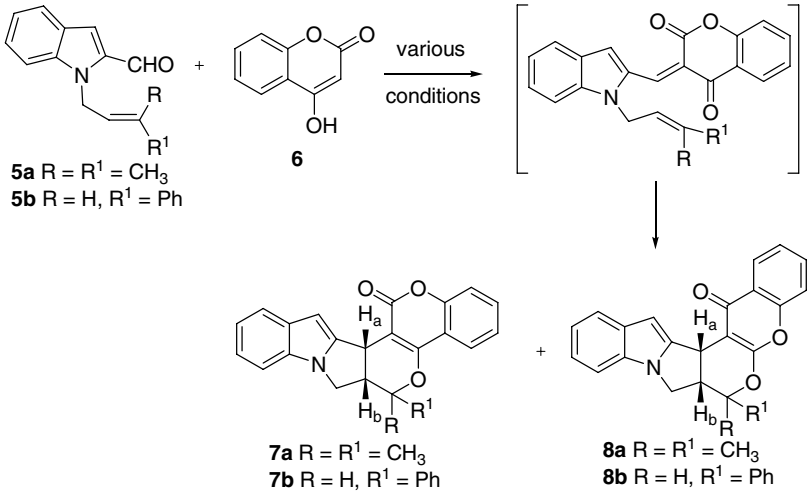
The results reported in Table 1 show that the careful optimization of the conditions leads to short reactions, high yields and mixtures that are easy to separate.

The ^{1}H NMR spectra of compounds **10a**,**b**, **11a**,**b**, **13a**,**b** and **14a**,**b** confirmed the all-cis configuration of the new compounds with vicinal coupling constants of around 7.6 Hz. Moreover, the coumarin and chromone derivatives were distinguished by their carbonyl resonances.

The above results prompted us to extend the methodology to domino Knoevenagal hetero Diels–Alder reaction of compounds **6**, **9** and **12** with aldehyde **5b**. Accordingly, **5b** was readily prepared from ethyl-1*H*-indole-2-carboxylate and cinnamyl bromide as described along the lines for the preparation of **5a** and the results are summarized in Table 2.

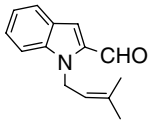
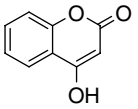
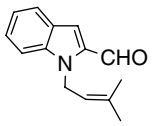
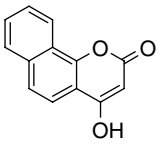
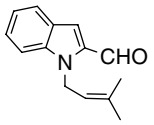
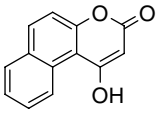
The reactions were successfully carried out with high chemoselectivities under microwave irradiation in ethanol. To improve the chemoselectivity, we further examined the reaction of **6** and **5b** by grinding with K-10 Montmorillonite clay followed by microwave irradiation and obtained a significant reduction in the reaction time with an improved chemoselectivity and yield (Table 2, entry 1).

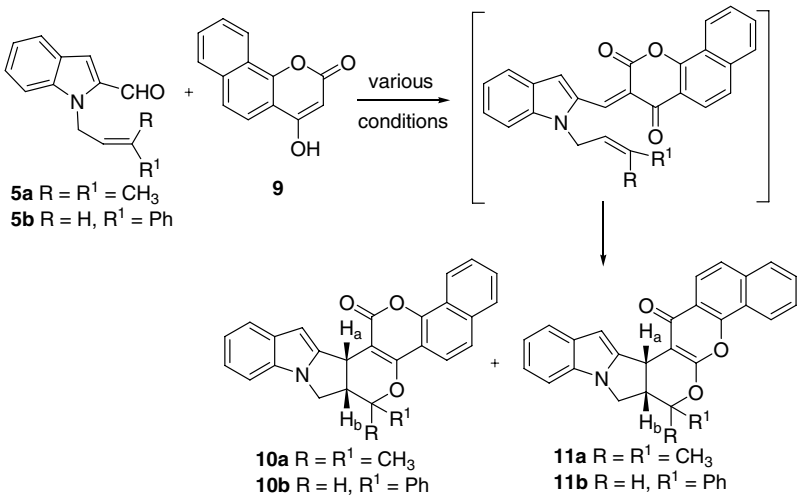
The polycyclic derivatives obtained were readily separated by chromatography on silica gel, and their struc-



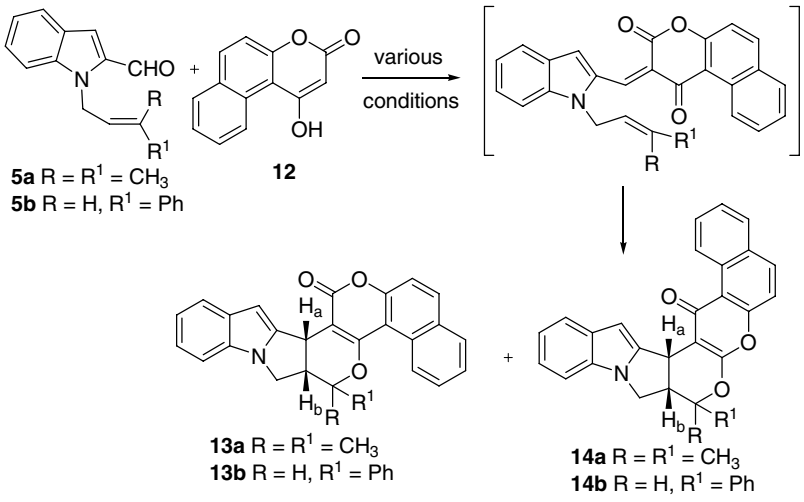
Scheme 2. Reaction of *N*-alkenyl indole-2-carbaldehydes with coumarin.

Table 1. The reaction times and yields of the domino reactions under various conditions

Entry	Aldehyde	1,3-Dione	Conditions	Time	Ratio of products		Overall yield (%)
					Coumarin	Chromone	
1			A Ethanol/reflux	5.5 h	65	35	58
			B Ethanol/MW	10 min	75	25	72
			C K-10 montmorillonite clay/MW	35 min	86	14	86
2			A Ethanol/reflux	6.0 h	51	49	58
			B Ethanol/MW	15 min	70	30	73
			C K-10 montmorillonite clay/MW	4.0 min	88	12	88
3			A Ethanol/reflux	6.0 h	58	42	65
			B Ethanol/MW	13 min	78	22	72
			C K-10 montmorillonite clay/MW	3.5 min	89	11	85

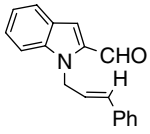
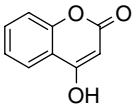
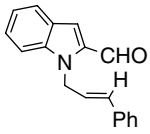
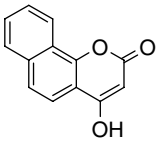
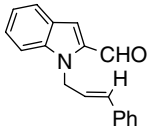
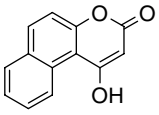


Scheme 3. Reaction of *N*-alkenyl indole-2-carbaldehydes with α-naphtho-coumarin.



Scheme 4. Reaction of *N*-alkenyl indole-2-carbaldehydes with β-naphtho-coumarin.

Table 2. Results obtained from the domino Knoevenagal hetero Diels–Alder reaction of coumarins and **5b** under various conditions

Entry	Aldehyde	1,3-Dione	Conditions	Time	Ratio of products		Overall yield (%)
					Coumarin	Chromone	
1			A Ethanol/reflux	5.5 h	68	32	61
			B Ethanol/MW	12 min	78	22	78
			C K-10 montmorillonite clay/MW	2.5 min	87	13	93
2			A Ethanol/reflux	5.5 h	54	46	62
			B Ethanol/MW	10 min	75	25	76
			C K-10 montmorillonite clay/MW	3.0 min	95	5	94
3			A Ethanol/reflux	6.5 h	60	40	66
			B Ethanol/MW	8 min	76	24	75
			C K-10 montmorillonite clay/MW	3.0 min	84	16	90

tures were assigned by ^{1}H NMR analysis. The cis configuration of the pyrrolo-pyrano ring of the products was assigned by ^{1}H NMR analysis, being significantly supported by the small coupling constant. Similarly, the large coupling constant supports the trans configuration of the benzylic proton (R = H) in **7b**, **8b**, **10b**, **11b**, **13b** and **14b**. Further, the regioisomers were distinguished by their characteristic carbonyl resonances.

In conclusion, the solvent-free microwave assisted synthesis of indolo[2,1-*a*]pyrrolo[4′,3′:4,5]pyrano[5,6-*c*]coumarin and indolo[2,1-*a*]pyrrolo[4′,3′:4,5]pyrano[6,5-*c*]-chromone derivatives through the domino Knoevenagal hetero Diels–Alder reaction presented in this Letter is an environmentally friendly methodology allowing the facile preparation of these important polycyclic materials. These strategies might be a promising tool for developing new routes to natural compounds bearing functionalized coumarin and chromone skeletons.

Acknowledgement

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References and notes

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8. *Experimental procedure for compound* **5a**: *1-(3-Methylbut-2-enyl)-2-carbethoxyindole* **3a**: 1-Bromo-3-methylbut-2-ene (16 mmol), TEBA (0.5 mmol) and 50% NaOH (20 mL) were added to a solution of 2-carbethoxyindole (10 mmol) in benzene (64 mL). The mixture was vigorously stirred at room temperature for 2 h. The organic layer was separated, washed with water and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give a 65% yield (mp 65–67 °C) of **3a**. IR (KBr): 1709 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (t, $J = 7.0$ Hz, 3H), 1.72 (s, 3H), 1.79 (s, 3H), 4.32 (q, $J = 7.0$ Hz, 2H), 5.12 (d, $J = 5.8$ Hz, 2H), 5.20 (t, $J = 5.8$ Hz, 1H), 6.65 (s, 1H), 7.15–7.23 (m, 2H), 7.27 (d, $J = 8.0$ Hz, 1H), 7.30 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.52, 20.10, 22.52, 42.36, 58.91, 110.53, 122.37, 124.59, 124.82, 125.08, 126.99, 128.14, 130.05, 135.52, 140.55, 163.43; MS: $m/z = 257$ (M^+).
1-(3-Methylbut-2-enyl)-2-hydroxymethylindole **4a**: A solution of **3a** (0.73 mmol) in dry THF (5 mL) was added dropwise, under N_2 to a suspension of $LiAlH_4$ (0.88 mmol) in dry THF (40 mL) at 0 °C. The mixture was stirred at room temperature for 3 h. MeOH (1 mL) was slowly added, and the solvent was removed under reduced pressure. After addition of water (2 mL), the aqueous layer was adjusted to pH 7 with 0.1 M HCl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to give an 82% yield (mp 89–91 °C) of **4a**. IR (KBr): 3392 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (br s, 1H), 1.71 (s, 3H), 1.87 (s, 3H), 4.78 (d, $J = 6.0$ Hz, 1H), 4.84 (d, $J = 6.2$ Hz, 2H), 5.23 (t, $J = 6.2$ Hz, 1H), 6.46 (s, 1H), 7.07–7.26 (m,

2H), 7.30 (d, $J = 8.0$ Hz, 1H), 7.58 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.01, 25.46, 41.76, 57.47, 101.57, 109.60, 119.50, 120.82, 120.92, 121.85, 127.46, 134.55, 137.43, 138.45; MS: $m/z = 215$ (M^+).

1-(3-Methylbut-2-enyl)-indole-2-carbaldehyde **5a**: To a solution of oxalyl chloride (76.7 mmol) in CH_2Cl_2 (200 mL) was added DMSO (0.12 mol) at −78 °C. After stirring for 30 min at −78 °C, a solution of **4a** (38.4 mmol) in CH_2Cl_2 (25 mL) was added and stirring continued at −78 °C for 30 min. The reaction mixture was treated with triethylamine(0.23 mol), allowed to warm to room temperature and stirred for a further 30 min. The reaction mixture was diluted with 1 M HCl (20 mL), washed with saturated sodium bicarbonate solution and brine, then dried and concentrated to give **5a** in an 85% yield (mp 80–82 °C). IR (KBr): 1673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75 (s, 3H), 1.82 (s, 3H), 4.87 (d, $J = 6.0$ Hz, 2H), 5.33 (t, $J = 6.0$ Hz, 1H), 6.39 (s, 1H), 7.17–7.24 (m, 2H), 7.29 (d, $J = 7.8$ Hz, 1H), 7.35 (d, $J = 7.8$ Hz, 1H), 9.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.34, 21.56, 37.81, 110.74, 119.53, 121.23, 125.26, 126.13, 126.85, 127.12, 129.05, 129.64, 132.85, 183.09; MS: $m/z = 213$ (M^+).

9. *General procedure for the intramolecular domino Knoevenagel hetero Diels–Alder reaction*:

Method A: To a refluxing solution of 1,3-dione (1 mmol) in 10 mL of dry ethanol, aldehyde **5a** or **5b** (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.

Method B: A solution of 1,3-dione (1 mmol) and the corresponding aldehyde (1 mmol) in dry ethanol was irradiated using a microwave oven (Kenstar, 600 W power) until thin layer chromatography showed the disappearance of the starting material. After removal of the solvent, the crude reaction mixture was subjected to flash column chromatography using hexane:ethyl acetate to yield the products.

Method C: A mixture of activated ketone or 1,3-dione (1 mmol), aldehyde (1 mmol) and K-10 montmorillonite clay (1.0 g) was thoroughly ground in a mortar. The reaction mixture was irradiated using a microwave oven (Kenstar, 600 W power) until complete 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 purification of the crude reaction mixture by flash column chromatography using hexane:ethyl acetate as eluent gave pure products.

8a,15b-cis-8,8-Dimethyl-8,8a,9,15b-tetrahydroindolo[2,1-a]-pyrrolo[4′,3′:4,5]pyrano[5,6-c]coumarin **7a**: Pale yellow solid, mp: 260–262 °C; IR (KBr): 1634 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.54 (s, 3H), 1.57 (s, 3H), 3.38–3.43 (m, $1H_b$), 4.00 (dd, $J = 7.2$, 9.7 Hz, 1H), 4.32 (dd, $J = 8.0$, 9.7 Hz, 1H), 4.52 (d, $J = 8.0$ Hz, $1H_a$), 6.64 (s, 1H), 7.01–7.77 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.43, 26.77, 32.60, 44.72, 50.47, 97.00, 109.20, 119.47, 120.45, 120.87, 121.18, 121.76, 122.83, 123.86, 124.33, 126.78, 128.23, 128.75, 129.45, 130.23, 131.91, 161.54 ppm; mass *m/z*: 357 (M^+). Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.41; H, 5.50; N, 3.80.

8a,15b-cis-8,8-Dimethyl-8,8a,9,15b-tetrahydroindolo[2,1-a]-pyrrolo[4′,3′:4,5]pyrano[6,5-c]chromone **8a**: Yellow solid, mp: 232–234 °C; IR (KBr): 1724 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.72 (s, 3H), 1.76 (s, 3H), 2.92–3.03 (m, $1H_b$), 3.79 (dd, $J = 7.2$, 9.7 Hz, 1H), 4.25 (dd, $J = 8.0$, 9.7 Hz, 1H), 4.44 (d, $J = 8.0$ Hz, $1H_a$), 6.75 (s, 1H), 6.89–7.76 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.26, 26.72, 34.26, 43.18, 48.75, 52.75, 98.10, 111.11, 116.28, 117.76, 118.15, 119.03, 119.82, 120.15, 122.16, 123.03, 123.85, 125.78, 127.00, 128.62, 129.01, 131.73, 178.12 ppm; mass *m/z*: 357 (M^+). Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.43; H, 5.52; N, 4.05.

8a,15b-cis-8-Phenyl-8,8a,9,15b-tetrahydroindolo[2,1-a]pyrrolo[4′,3′:4,5]pyrano[5,6-c]coumarin **7b**: Yellow solid, mp: 220–222 °C; IR (KBr): 1628 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.36–3.40 (m, $1H_b$), 3.92 (dd, $J = 7.0$, 10.1 Hz, 1H), 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 (s, 1H), 7.06–7.73 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 38.53, 44.26, 52.31, 56.07, 109.13, 112.15, 115.26, 121.93, 122.64, 123.23, 124.01, 124.20, 125.33, 126.24, 128.86, 129.52, 131.53, 133.27, 134.28, 137.94, 140.26, 163.90 ppm; mass *m/z*: 405 (M^+). Anal. Calcd for $C_{27}H_{19}NO_3$: C, 79.98; H, 4.72; N, 3.45. Found: C, 80.14; H, 4.83; N, 3.30.

8a,15b-cis-8-Phenyl-8,8a,9,15b-tetrahydroindolo[2,1-a]pyrrolo[4′,3′:4,5]pyrano[6,5-c]chromone **8b**: Yellow solid, mp: 215–217 °C; IR (KBr): 1715 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.48–3.52 (m, $1H_b$), 3.89 (dd, $J = 7.2$, 10.0 Hz, 1H), 4.35 (dd, $J = 8.0$, 10.0 Hz, 1H), 4.55 (d, $J = 8.2$ Hz, $1H_a$), 5.35 (d, $J = 9.6$ Hz, 1H), 6.12 (s, 1H), 6.73–7.68 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.25, 42.76, 58.91, 60.73, 107.26, 113.71, 118.18, 119.23, 121.15, 121.34, 122.45, 124.75, 124.82, 125.24, 126.58, 127.37, 129.21, 130.32, 133.65, 135.52, 136.15, 142.45, 179.89 ppm; mass spectrum *m/z*: 405 (M^+). Anal. Calcd for $C_{27}H_{19}NO_3$: C, 79.98; H, 4.72; N, 3.45. Found: C, 80.10; H, 4.85; N, 3.34.