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Competition between two intramolecular domino Knoevenagel hetero Diels–Alder reactions: a new entry into novel pyranoquinolinone derivatives

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Abstract—4-Hydroxy-1,2-dihydro-2-quinolinones undergo facile intramolecular domino Knoevenagel hetero Diels–Alder reactions with o-prenylated aromatic aldehydes and the aliphatic aldehyde citronellal, to afford novel pyranoquinolinone derivatives. A high degree of chemoselectivity has been achieved under microwave irradiation condition.

1. Introduction

The pyranoquinolinone skeleton constitutes a fundamental part of numerous natural products and has distinct properties of general interest.[1] Naturally occurring compounds such as flindersine, simulenoline, melicobisquinolone A, melicobisquinolone B, huajiaosimuline, zanthodioline, khaplofoline, etc. were found to possess the pyranoquinolinone ring system.[2] Structures incorporating this moiety have shown marked psychotropic, antiallergenic, anti-inflammatory, antihistaminic and estronegic activities and are thus of prime interest for biological applications.[3] Hence, novel and efficient syntheses of such compounds still represents a highly pursued target. While numerous synthetic methodologies for the synthesis of pyranoquinolinone have been reported,[4] only a few reports are known using the Diels–Alder reaction.[5] In recent years, the application of microwave irradiation in organic synthesis has attracted much interest due to their shorter reaction times and operational simplicity, coupled with the higher conversions with a high degree of selectivity.[6]

The domino Knoevenagel intramolecular hetero Diels–Alder (IMHDA) reaction is one of the most powerful weapons in organic synthesis, especially in the area of heterocycles and natural products.[7] The most widely used heterodienes are usually those where the olefinic bond is flanked between the symmetrical 1,3-dicarbonyl compounds.[8] Recently, we reported a chemoselective synthesis of pyrano[3,2-*c*]coumarin derivatives by the competition between two intramolecular domino Knoevenagel hetero Diels–Alder reactions.[9] Our continuous interest in the area of cycloaddition reactions,[10,11] prompted us to examine the mode of cycloaddition of a heterodiene wherein the olefinic segment is flanked between a keto carbonyl on the one side and a lactam carbonyl on the other side. Herein, we wish to report the successful application of the cycloaddition chemistry to the synthesis of novel pyranoquinolinone derivatives.

2. Results and discussion

We initially examined the reaction of 4-hydroxy-1,2-dihydro-2-quinolinone **1a** with 2-(3-methyl-2-butenyloxy) benzaldehyde **2** in the presence of ethylene diammonium diacetate (EDDA) in refluxing ethanol for 10 h (Scheme 1). The reaction proceeded via a domino Knoevenagel hetero Diels–Alder pathway, wherein both the keto carbonyl and the lactam carbonyl were involved in the cycloaddition to give a 53:47 mixture of the corresponding angular pyranoquinolinone **4a** and linear pyranoquinolinone **5a** derivatives in 60% yield (Table 1, entry 1). No intermediate **3a** was isolated. The use of triethylamine or piperidine in place of EDDA afforded a mixture of **4a** and **5a** in 50 and 67% of yields, with no significant change in chemoselectivity (entries 2 and 3). In an effort to improve the chemoselectivity, the same reaction was carried out under microwave conditions. The use of EDDA or triethylamine under microwave conditions gave better chemoselectivity with improved chemical yields as compared to thermal conditions (entries 4 and 5). To our delight, the use of

Keywords: hetero Diels–Alder reaction; quinolones; chemoselectivity; microwaves.

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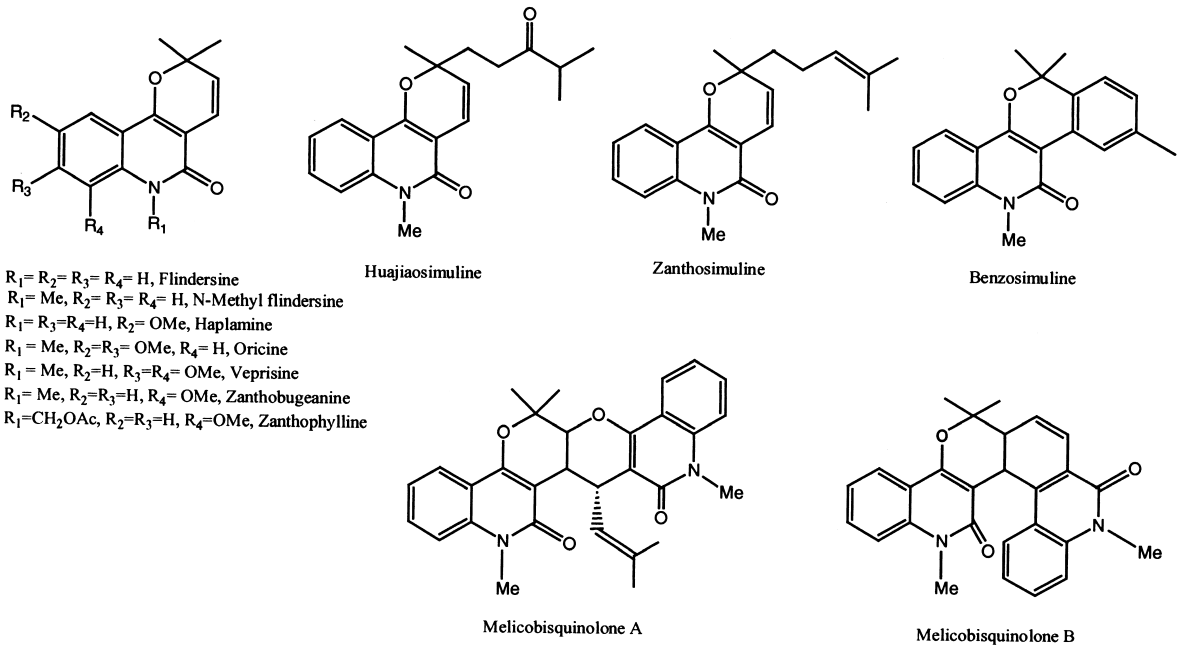
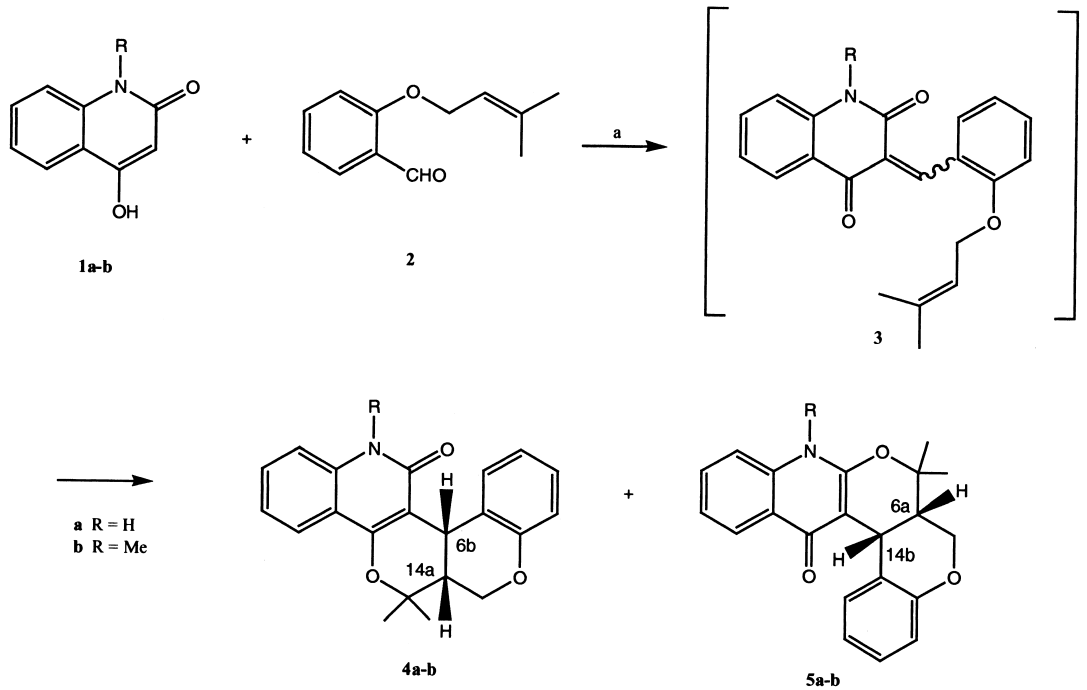


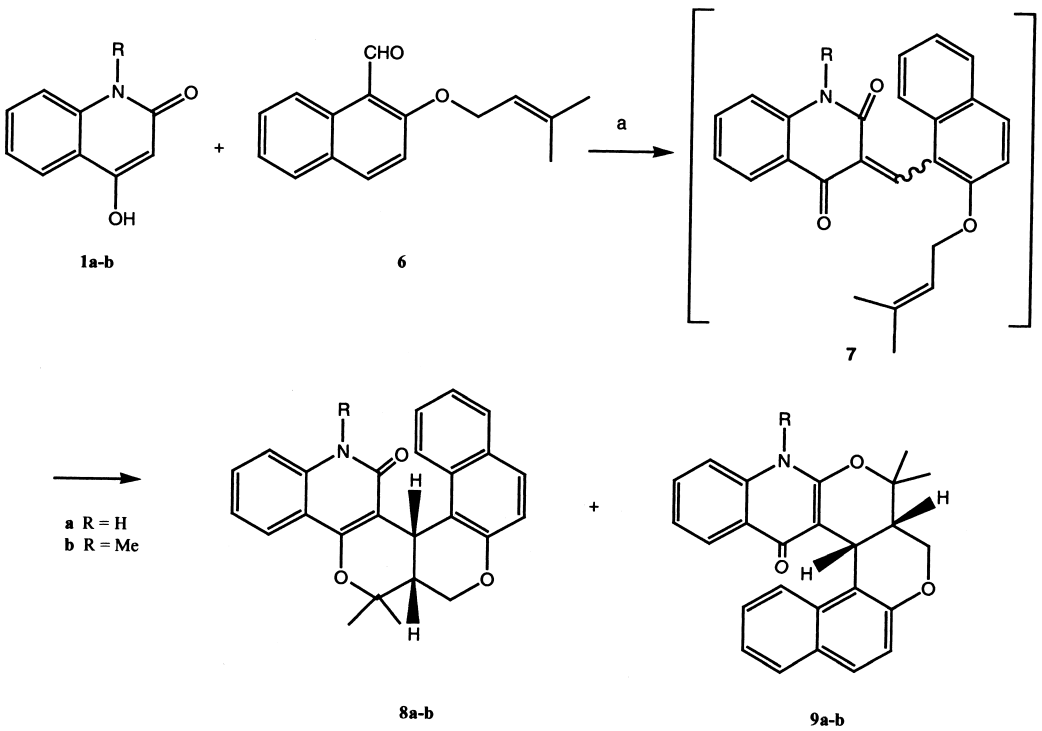


Scheme 1. (a) Base, ethanol, reflux or MW irradiation.

Table 1. Reactions of **1a**,**b** with aromatic aldehyde **2**

Entry	Substrate	Reaction condition	Reaction time	Base	**4**/**5**[a]	Overall yield[b] (%)
1	**1a**	Reflux	10 h	EDDA	53:47	60
2	**1a**	Reflux	10 h	Triethylamine	56:44	50
3	**1a**	Reflux	14 h	Piperidine	55:45	67
4	**1a**	MW	3 min	EDDA	79:21	78
5	**1a**	MW	2 min	Triethylamine	82:18	70
6	**1a**	MW	3 min	Piperidine	88:12	79
7	**1b**	Reflux	10 h	EDDA	55:45	42
8	**1b**	Reflux	12 h	Triethylamine	65:35	51
9	**1b**	Reflux	9.5 h	Piperidine	58:42	50
10	**1b**	MW	6 min	EDDA	84:16	65
11	**1b**	MW	5.5 min	Triethylamine	81:19	59
12	**1b**	MW	3.5 min	Piperidine	86:14	66

[a] Ratio determined by the integration of the ^{1}H NMR spectrum.
[b] Combined isolated yield of products.



Scheme 2. (a) Base, ethanol, reflux or MW irradiation.

piperidine as the base provided the highest chemoselectivity of 88:12 with an enhanced chemical yield of 79% (entry 6). The structure of the products **4a** and **5a** were completely characterized by IR, ^{1}H and ^{13}C NMR and mass spectral data. The IR spectrum of **4a** exhibited carbonyl absorption at 1665 cm^{-1}, whereas the compound **5a** exhibited absorption at 1634 cm^{-1}. The most distinguishing features of the ^{13}C NMR spectrum of **4a** and **5a** are due to the signals for the carbonyl carbons. In the case of **4a**, the carbonyl carbon resonated at δ 164.22 ppm and in the case of **5a**, the carbonyl carbon resonated at δ 173.21 ppm. The *cis* fusion of the two pyran rings in **4a** and **5a** was discerned by the coupling constant J_{14a}=4.6 Hz and J_{6a}=4.8 Hz, respectively.

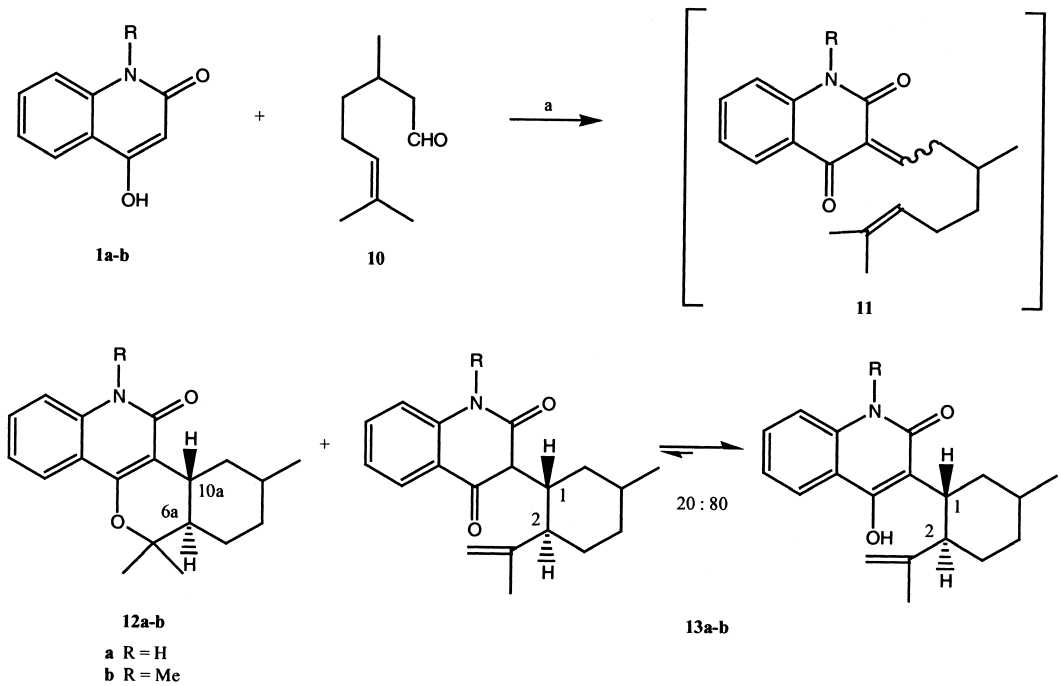
Next, the reaction of 4-hydroxy-1-methyl-1,2-dihydro-2-quinolinone **1b** with aldehyde **2** in the presence of base under various conditions was examined that afforded a mixture of **4b** and **5b**. High chemoselectivity of 86:14 with 66% yield was achieved under microwave conditions employing piperidine as base (entry 12).

To explore this reaction in a synthetically useful context, we examined the reactions of **1a**,**b** with 2-(3-methyl-2-butenyloxy) naphthaldehyde **6**. In a similar fashion, the reaction proceeded via the domino Knoevenagel hetero Diels–Alder pathway to afford a mixture of angular pyranoquinolinone **8a**,**b** and linear pyranoquinolinone **9a**,**b** derivatives (Scheme 2). Once again, the best results were obtained when the reaction was carried out under microwave conditions using piperidine as base (Table 2, entries 6 and 12). The structure and the stereochemistry of the polycyclic derivatives **8a**,**b** and **9a**,**b** were confirmed by the spectroscopic data. It is noteworthy that the above reactions assemble six rings with two stereocentres in a stereoselective fashion by a one pot strategy.

Table 2. Reactions of **1a**,**b** with aromatic aldehyde **6**

Entry	Substrate	Reaction condition	Reaction time	Base	**8**/**9**[a]	Overall yield[b] (%)
1	**1a**	Reflux	14 h	EDDA	54:46	51
2	**1a**	Reflux	16 h	Triethylamine	46:54	41
3	**1a**	Reflux	12 h	Piperidine	53:47	43
4	**1a**	MW	5 min	EDDA	84:16	70
5	**1a**	MW	3 min	Triethylamine	85:15	68
6	**1a**	MW	5 min	Piperidine	91:9	70
7	**1b**	Reflux	22 h	EDDA	55:45	63
8	**1b**	Reflux	18 h	Triethylamine	60:40	62
9	**1b**	Reflux	12 h	Piperidine	68:32	67
10	**1b**	MW	8 min	EDDA	69:31	64
11	**1b**	MW	6.5 min	Triethylamine	78:22	50
12	**1b**	MW	5 min	Piperidine	81:19	67

[a] Ratio determined by the integration of the ^{1}H NMR spectrum.
[b] Combined isolated yield.



Scheme 3. (a) Base, ethanol, reflux or MW irradiation.

In light of our results with the aromatic aldehydes **2** and **6**, we were interested in a study of the reactivity of aliphatic aldehyde viz. citronellal. The reaction of **1a** with **10** in refluxing ethanol in the presence of base under various conditions furnished a mixture of **12a** and **13a** (Scheme 3). A close examination of the spectral data revealed that the product **12a** arises as a result of domino Knoevenagel intramolecular hetero Diels–Alder reaction and the product **13a** results by an intramolecular ene (IER) reaction. Similarly, treatment of **1b** with **10** afforded a mixture of domino Knoevenagel IMHDA product **12b** and IER product **13b**. Unlike aromatic aldehydes, aliphatic aldehyde gave highest chemoselectivity and chemical yield using triethylamine as base. (Table 3 entries 5 and 11). The *trans* annelation of pyran derivatives **12a**,**b** is determined by the coupling pattern for 6a-H with two large coupling constants. The 6a-H of **12a** resonates at δ 2.38 as a triplet of a doublet with J=11.0, 2.6 Hz. The ene products **13a**,**b**, isolated as solids showed tautomeric mixtures of the lactam-enol and keto-lactam forms in the ratio of 80:20 as evidenced by ^{1}H NMR spectra in DMSO-d_6. The protons 1-H and 2-H involved in the ring closure of the intramolecular ene reaction, are *trans* as assigned by the coupling pattern for 1-H and 2-H protons. The 2-H proton of **13a** resonates as a triplet of a doublet at δ 3.22 with J=11.6, 3.1 Hz.

In summary, we have developed a simple and efficient route to the novel polycyclic derivatives by intramolecular domino Knoevenagel hetero Diels–Alder reaction of **1a**,**b** with aromatic aldehydes **2**, **6** and aliphatic aldehyde **10**. A high degree of chemoselectivity has been achieved by the application of microwave conditions. We are presently studying further applications of this protocol into natural product synthesis.

3. Experimental

3.1. General

All melting points are uncorrected. IR spectra were recorded on a SHIMADZU FT-IR 8300 instrument. ^{1}H and ^{13}C NMR

Table 3. Reactions of **1a**,**b** with citronellal **10**

Entry	Substrate	Reaction condition	Reaction time	Base	**12/13**[a]	Overall yield[b] (%)
1	**1a**	Reflux	5 h	EDDA	54:46	44
2	**1a**	Reflux	4.5 h	Triethylamine	58:42	51
3	**1a**	Reflux	6 h	Piperidine	56:44	41
4	**1a**	MW	2 min	EDDA	79:21	68
5	**1a**	MW	3 min	Triethylamine	84:16	68
6	**1a**	MW	2 min	Piperidine	83:17	54
7	**1b**	Reflux	9 h	EDDA	58:42	55
8	**1b**	Reflux	8.5 h	Triethylamine	57:43	49
9	**1b**	Reflux	10 h	Piperidine	55:45	50
10	**1b**	MW	5 min	EDDA	82:18	67
11	**1b**	MW	4.5 min	Triethylamine	83:17	80
12	**1b**	MW	3.5 min	Piperidine	77:23	70

[a] Ratio determined by the integration of the ^{1}H NMR spectrum.
[b] Combined isolated yield of products.

spectra were recorded in $CDCl_3$ using TMS as an internal standard on a Bruker DPX200 at 200 and 50.3 MHz, respectively. Elemental analyses were carried out on a CEST 1106 instrument. MS spectra were recorded on a Finnigan MAT-8230 GC-Mass spectrometer. Microwave irradiation experiments were carried out in a domestic microwave oven of power 800 W. Flash column chromatography was performed on silica gel (SISCO 230–400 mesh). The starting materials **1a**,**b** were prepared according to the literature procedure.[12]

3.2. General procedure for the intramolecular domino Knoevenagel hetero Diels–Alder reaction

To the solution of 4-hydroxy quinolinone **1a**,**b** (1 mmol) in dry ethanol (10 mL), the corresponding aldehyde (1 mmol) and the base (1 mmol) were added and the reaction mixture was refluxed (or) irradiated under microwave conditions. After completion of the reaction, the solvent was evaporated under reduced pressure and the residue was subjected to flash column chromatography using hexane/ethyl acetate (9:1) as eluent.

3.2.1. [6*b*,14*a*]-*cis*-14,14-Dimethyl-7,8,14,14*a*-tetrahydro-1*H*,6*bH*-chromeno[4^1,3^1:4,5]pyrano[3,2-*c*]quinolin-7-one (4a). Colorless crystals, mp 194°C; IR (KBr): 1665 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.18 (s, 3H), 1.64 (s, 3H), 2.34 (m, 1H), 4.42 (d, J=4.6 Hz, 1H), 4.46 (dd, J=11.6, 10.5 Hz, 1H), 4.62 (dd, J=11.6, 6.4 Hz, 1H), 6.81 (d, J=8.1 Hz, 1H), 6.94–7.62 (m, 6H), 7.91 (d, J=8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 23.94, 28.16, 29.18, 40.42, 65.26, 80.86, 101.62, 115.31, 115.62, 115.91, 120.92, 121.58, 123.02, 123.81, 127.92, 129.71, 131.89, 152.14, 153.62, 159.24, 164.22; MS (*m*/*z*): 333 (M^+). Anal. calcd for $C_{21}H_{19}O_3N$: C, 75.66; H, 5.75; N, 4.20. Found: C, 75.61; H, 5.77; N, 4.20.

3.2.2. [6*a*,14*b*]-*cis*-7,7-Dimethyl-6*a*,9,14,14*b*-tetrahydro-6*H*,7*H*-chromeno[4^1,3^1:4,5]pyrano[2,3-*b*]quinolin-14-one (5a). Colorless crystals, mp 188°C; IR (KBr): 1634 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.16 (s, 3H), 1.64 (s, 3H), 2.32 (m, 1H), 4.34 (dd, J=11.8, 6.0 Hz, 1H), 4.52 (d, J=4.8 Hz, 1H), 4.73 (dd, J=11.8, 10.6 Hz, 1H), 6.82–7.74 (m, 7H), 8.24 (d, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 23.84, 29.42, 30.46, 38.62, 66.24, 82.14, 96.94, 115.81, 116.62, 121.07, 122.16, 122.97, 125.04, 125.94, 126.99, 129.42, 133.12, 152.62, 153.57, 163.42, 173.21; MS (*m*/*z*): 333 (M^+). Anal. calcd for $C_{21}H_{19}O_3N$: C, 75.66; H, 5.75; N, 4.20. Found: C, 75.63; H, 5.76; N, 4.21.

3.2.3. [6*b*,14*a*]-*cis*-8,14,14-Trimethyl-7,8,14,14*a*-tetrahydro1*H*,6*bH*chromeno[4^1,3^1:4,5]pyrano[3,2-*c*]quinolin-7-one (4b). Colorless crystals, mp 190°C; IR (KBr): 1659 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.17 (s, 3H), 1.65 (s, 3H), 2.15 (s, 3H), 2.36 (m, 1H), 4.42 (d, J=4.2 Hz, 1H), 4.48 (dd, J=11.4, 10.8 Hz, 1H), 4.62 (dd, J=11.6, 6.4 Hz, 1H), 6.82 (d, J=8.4 Hz, 1H), 6.89–7.64 (m, 6H), 7.94 (d, J=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.10, 23.64, 28.16, 30.41, 41.64, 65.24, 80.86, 101.32, 115.61, 115.81, 116.04, 120.48, 121.62, 123.04, 123.72, 128.04, 129.39, 131.81, 152.71, 153.66, 159.22, 169.44; MS (*m*/*z*): 347 (M^+). Anal. calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.03; H, 6.08; N, 3.99.

3.2.4. [6*a*,14*b*]-*cis*-7,7,9-Trimethyl-6*a*,9,14,14*b*-tetrahydro-6*H*,7*H*-chromeno[4^1,3^1:4,5]pyrano[2,3-*b*]quinolin-14-one (5b). Colorless crystals, mp 201°C; IR (KBr): 1632 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.18 (s, 3H), 1.69 (s, 3H), 2.16 (s, 3H), 2.38 (m, 1H), 4.32 (dd, J=11.8, 6.4 Hz, 1H), 4.56 (d, J=4.8 Hz, 1H), 4.81 (dd, J=11.8, 10.6 Hz, 1H), 6.77–7.81 (m, 7H), 8.26 (d, J=8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.00, 23.91, 30.11, 30.64, 39.41, 66.32, 82.14, 96.71, 115.81, 116.09, 121.23, 122.16, 123.41, 125.61, 126.01, 127.32, 129.45, 133.24, 152.41, 153.21, 163.08, 173.41; MS (*m*/*z*): 347 (M^+). Anal. calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.07; H, 6.09; N, 4.01.

3.2.5. [8*c*,16*a*]-*cis*-16,16-Dimethyl-9,10,16,16*a*-tetrahydro-1*H*,8*cH*-benzo[5^1,6^1]chromeno[4^1,3^1:4,5]pyrano-[3,2-*c*]quinolin-9-one (8a). Colorless crystals, mp 202°C; IR (KBr): 1663 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.57 (s, 3H), 1.62 (s, 3H), 2.38 (m, 1H), 4.31 (t, J=11.4 Hz, 1H), 4.56 (ddd, J=11.2, 6.4, 1.6 Hz, 1H), 4.89 (d, J=4.2 Hz, 1H), 6.89 (d, J=8.6 Hz, 1H), 7.25–7.81 (m, 7H), 7.88 (dd, J=8.2, 1.8 Hz, 1H), 8.24 (d, J=8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 24.84, 26.26, 27.89, 38.32, 62.72, 78.54, 102.4, 111.82, 114.55, 115.31, 116.20, 119.24, 122.39, 123.41, 124.02, 125.41, 128.12, 128.34, 129.31, 132.43, 134.71, 151.21, 152.62, 158.62, 169.32; MS (*m*/*z*): 383 (M^+). Anal. calcd for $C_{25}H_{21}NO_3$: C, 78.31; H, 5.52; N, 3.65. Found: C, 78.31; H, 5.54; N, 3.60.

3.2.6. [4*a*,12*b*]-*cis*-5,5-Dimethyl-4*a*,7,12,12*b*-tetrahydro-4*H*,5*H*-benzo[5^1,6^1]chromeno[4^1,3^1:4,5]pyrano[2,3-*b*]quinolin-12-one (9a). Colorless crystals, mp 212°C; IR (KBr): 1631 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.58 (s, 3H), 1.63 (s, 3H), 2.43 (m, 1H), 3.81 (dd, J=11.6, 6.0 Hz, 1H), 4.21 (t, J=11.4 Hz, 1H), 4.86 (d, J=4.3 Hz, 1H), 7.18–7.84 (m, 8H), 8.46 (dd, J=8.1, 1.6 Hz, 1H), 8.52 (d, J=7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 25.21, 26.04, 26.81, 39.10, 63.41, 81.12, 100.12, 115.44, 116.50, 118.20, 123.21, 124.22, 124.64, 125.51, 126.16, 128.29, 128.82, 129.92, 130.61, 131.62, 132.64, 151.01, 152.49, 162.11, 173.41; MS (*m*/*z*): 383 (M^+). Anal. calcd for $C_{25}H_{21}NO_3$: C, 78.31; H, 5.52; N, 3.65. Found: C, 78.29; H, 5.50; N, 3.63.

3.2.7. [8*c*,16*a*]-*cis*-10,16,16-Trimethyl-9,10,16,16*a*-tetrahydro-1*H*,8*H*-benzo[5^1,6^1]chromeno [4^1,3^1:4,5]pyrano-[3,2-*c*]quinolin-9-one (8b). Colorless crystals, mp 220°C; IR (KBr): 1666 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.56 (s, 3H), 1.66 (s, 3H), 2.16 (s, 3H), 2.43 (m, 1H), 4.32 (t, J=11.2 Hz, 1H), 4.60 (ddd, J=11.2, 6.1, 1.3 Hz, 1H), 5.01 (d, J=4.1 Hz, 1H), 6.83 (d, J=8.1 Hz, 1H), 7.35–7.81 (m, 7H), 7.92 (dd, J=8.2, 1.6 Hz, 1H), 8.26 (d, J=8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.21, 24.92, 26.21, 27.89, 39.42, 62.81, 78.61, 102.6, 111.81, 114.61, 115.32, 116.32, 119.30, 122.49, 123.62, 123.89, 124.91, 128.21, 128.36, 129.42, 132.44, 135.81, 151.63, 152.63, 158.71, 169.06; MS (*m*/*z*): 397 (M^+). Anal. calcd for $C_{26}H_{23}NO_3$: C, 78.57; H, 5.83; N, 3.52. Found: C, 78.59; H, 5.85; N, 3.51.

3.2.8. [4*a*,12*b*]-5,6,7-Trimethyl-4*a*,7,12,12*b*-tetrahydro-4*H*,5*H*-benzo[5^1,6^1]chromeno[4^1,3^1:4,5]pyrano[2,3-*b*]quinolin-12-one (9b). Colorless crystals, mp 224°C; IR (KBr): 1634 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.43 (s, 3H), 1.62 (s, 3H), 2.14 (s, 3H), 2.48 (m, 1H), 3.79 (dd, J=11.6, 6.0 Hz, 1H), 4.24 (t, J=11.2 Hz, 1H), 4.88 (d, J=4.3 Hz, 1H), 7.24–

7.81 (m, 8H), 8.42 (dd, J=8.0, 1.4 Hz, 1H), 8.52 (d, J=7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.04, 25.24, 26.31, 27.04, 39.31, 64.64, 81.12, 99.94, 116.04, 116.51, 118.31, 123.41, 124.31, 124.62, 125.61, 126.16, 128.28, 128.91, 129.32, 130.62, 131.68, 132.68, 151.41, 151.98, 163.11, 173.26; MS (*m*/*z*): 397 (M^+). Anal. calcd for $C_{26}H_{23}NO_3$: C, 78.57; H, 5.83; N, 3.52. Found: C, 78.55; H, 5.83; N, 3.54.

3.2.9. [6*a*,10*a*]-*trans*-6,6,9-Trimethyl-6*a*,7,8,9,10,10*a*,11,12-octahydro-6*H*-isochromeno[4,3-*c*] quinolin-11-one (12a). Colorless crystals, mp 209°C; IR (KBr): 1667 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.53 (m, 1H), 0.92 (d, J=6.2 Hz, 3H), 1.21 (s, 3H), 1.12–1.28 (m, 2H), 1.38 (m, 1H), 1.53 (s, 3H), 1.68 (m, 1H), 1.91 (m, 2H), 2.38 (td, J=11.0, 2.6 Hz, 1H), 3.26 (m, 1H), 7.26–7.51 (m, 3H), 7.91 (dd, J=8.0, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 20.12, 23.14, 28.64, 28.91, 33.04, 34.62, 34.99, 36.81, 50.32, 83.14, 104.65, 116.52, 116.60, 123.41, 124.10, 132.21, 154.31, 160.42, 163.41; MS (*m*/*z*): 297 (M^+). Anal. calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.79; N, 4.71. Found: C, 76.74; H, 7.79; N, 4.74.

3.2.10. Intramolecular ene product (13a). Colorless crystals, mp 167°C; IR (KBr): 3298, 1645 cm^{-1}; MS (*m*/*z*): 297 (M^+). Anal. calcd for $C_{19}H_{23}NO_2$: C, 76.72; H, 7.80; N, 4.71. Found: C, 76.74; H, 7.69; N, 4.76. *Lactam-enol form*: ^{1}H NMR (DMSO-d_6): δ 0.88 (d, J=6.6 Hz, 3H), 0.92–2.1 (m, 7H), 1.66 (s, 3H), 3.01 (td, J=11.6, 3.1 Hz, 1H), 3.22 (td, J=11.6, 3.1 Hz, 1H), 4.61 (bs, 1H), 4.72 (bs, 1H), 7.31–7.52 (m, 3H), 8.06 (dd, J=8.4, 1.6 Hz, 1H), 11.31 (bs, 2H); ^{13}C NMR (DMSO-d_6): δ 19.21, 20.91, 31.94, 32.64, 34.61, 37.99, 38.81, 46.21, 111.32, 116.35, 123.05, 123.61, 124.46, 132.04, 132.46, 148.81, 150.99, 160.24, 163.01. *Keto-lactam form*: ^{1}H NMR (DMSO-d_6): δ 0.91 (d, J=6.4 Hz, 3H), 1.12–1.98 (m, 7H), 1.68 (s, 3H), 2.34 (m, 1H), 3.21 (td, J=11.8, 2.6 Hz, 1H), 4.02 (bs, 1H), 4.61 (bs, 1H), 4.94 (bs, 1H), 7.32–7.51 (m, 3H), 8.04 (dd, J=8.1, 1.8 Hz, 1H).

3.2.11. [6*a*,10*a*]-*trans*-6,6,9,12-Tetramethyl-6*a*,8,9,10,10*a*,11,12-octahydro-6*H*-isochromeno[4,3-*c*]quinolin-11-one (12b). Colorless crystals, mp 226°C; IR (KBr): 1664 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.61 (m, 1H), 0.98 (d, J=6.3 Hz, 3H), 1.26 (s, 3H), 1.21–1.31 (m, 2H), 1.38 (m, 1H), 1.58 (s, 3H), 1.71–1.92 (m, 3H), 2.16 (s, 3H), 2.36 (td, J=11.0, 2.8 Hz, 1H), 3.31 (m, 1H), 7.24–7.41 (m, 3H), 7.78 (dd, J=7.7, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 19.61, 21.12, 23.61, 27.92, 28.82, 34.01, 34.71, 34.98, 35.98, 51.61, 83, 24, 104.61, 117.81, 118.32, 123.16, 125.61, 132.61, 154.32, 160.41, 163.04; MS (*m*/*z*): 311 (M^+). Anal. calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.08; H, 7.99; N, 4.51.

3.2.12. Intramolecular ene product (13b). Colorless crystals, mp 233°C; IR (KBr): 3289, 1644 cm^{-1}. MS (*m*/*z*): 311 (M^+). Anal. calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.08; H, 7.99; N, 4.61. *Lactam-enol form*: ^{1}H NMR (DMSO-d_6): δ 0.91 (d, J=6.8 Hz, 3H), 1.01–2.1 (m, 7H), 1.65 (s, 3H), 2.21 (s, 3H), 3.21 (td, J=11.8, 3.1 Hz, 1H), 3.41 (td, J=11.8, 3.1 Hz, 1H), 4.62 (bs, 1H), 4.81 (bs, 1H), 7.26–7.61 (m, 3H), 7.94 (dd, J=8.4, 1.6 Hz, 1H), 11.32 (bs, 1H); ^{13}C NMR (DMSO-d_6): δ 19.31, 20.88, 21.21, 32.01, 32.66, 35.31, 38.04, 38.91, 47.04, 111.33, 117.01, 123.64, 124.01, 124.61, 132.06, 132.61, 149.21, 150.91, 161.12, 163.81. *Keto-lactam form*: ^{1}H NMR (DMSO-d_6): δ 0.90 (d, J=6.6 Hz, 3H), 1.13–2.01 (m, 7H), 1.62 (s, 3H), 2.18 (s, 3H), 2.35 (m, 1H), 3.42 (td, J=11.6, 2.6 Hz, 1H), 4.12 (bs, 1H), 4.67 (bs, 1H), 5.02 (bs, 1H), 7.31–7.67 (m, 3H), 7.99 (dd, J=8.2, 1.6 Hz, 1H).

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