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Diels–Alder trapping of 3-methylenequinolin-2,4-dione: a facile synthesis of pyranoquinolinones and spiroquinolinediones

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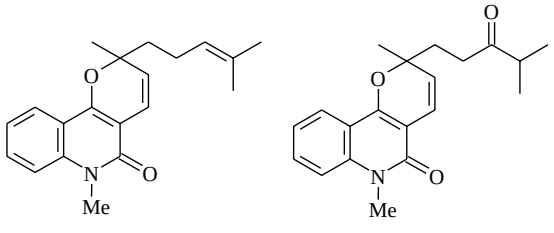
Abstract—3-Methylenequinolin-2,4-dione generated in situ by Knoevenagel condensation of 4-hydroxyquinoline with formaldehyde is trapped by Diels–Alder cycloaddition to provide spiroquinolinediones and pyranoquinolinones.

1. Introduction

The recognition of the synthetic potential of heterocyclic quinone methides has aroused considerable interest in their generation and subsequent transformations.[1] Quinolinone quinone methides constitute such a class of versatile synthons for the synthesis of naturally occurring biologically active pyranoquinolinones, dimeric quinolinone alkaloids and other polycyclic heterocycles. Recently, it was reported that pyranoquinolinones zanthosimuline and huajiaosimuline[2] (Fig. 1) isolated from *Zanthoxylum simulans* exhibit cytotoxic activity against human cancer cells.[3]

The known methods for the generation of quinolinone quinone methides include DDQ oxidation of 3-alkyl-4-hydroxy quinolinone,[4] elimination of a secondary amine from a Mannich base, pyrolysis of flindersine derivatives, or bisquinolinone[5] and Knoevenagel condensation of 4-hydroxyquinolinone with an aldehyde.[6] In spite of the work by various groups to exploit the versatility of quinolinone quinone methides, barring the reports by Grundon and co-workers,[7] no effort has been made to study the cycloaddition profile of this methide. As a part of our general interest in the chemistry of quinonoid compounds and their cycloaddition reactions in particular,[8] we have investigated the cycloaddition profile of this system and the results are presented here.



zanthosimuline huajiaosimuline

Figure 1.

2. Results and discussion

Our investigations began with the reaction of *N*-methyl-3-methylene-quinolin-2,4-dione **3** with cyclopentadiene. When 4-hydroxy-*N*-methylquinolin-2-one **1** was treated with paraformaldehyde in refluxing dioxane in the presence of cyclopentadiene, the in situ generated quinone methide **3** underwent facile hetero Diels–Alder reaction with cyclopentadiene in a chemo- and regioselective manner to afford a colourless product **5a** in 84% yield (Scheme 1).

The structure of the cycloadduct was established by spectroscopic analysis. The IR spectrum of the product showed a strong absorption at 1639 cm^{-1}. In the ^{13}C NMR spectrum, the carbonyl carbon gave a signal at δ 163.41. The signal due to the sp^3 carbon C-1 was discernible at δ 83.03. The regiochemistry of the product was ascertained with the help of ^1H–^1H relayed COSY spectrum. The correlation spectrum clearly showed the connectivity between the different sets of protons. The most diagnostic of these is the connectivity shown by the ring junction proton on C-1 (δ 5.23), which is connected to the olefinic proton on C-2 (δ 6.07) and the ring junction proton on C-5 (δ 2.83).

Keywords: cycloaddition; dienes; enol ethers; quinolines.
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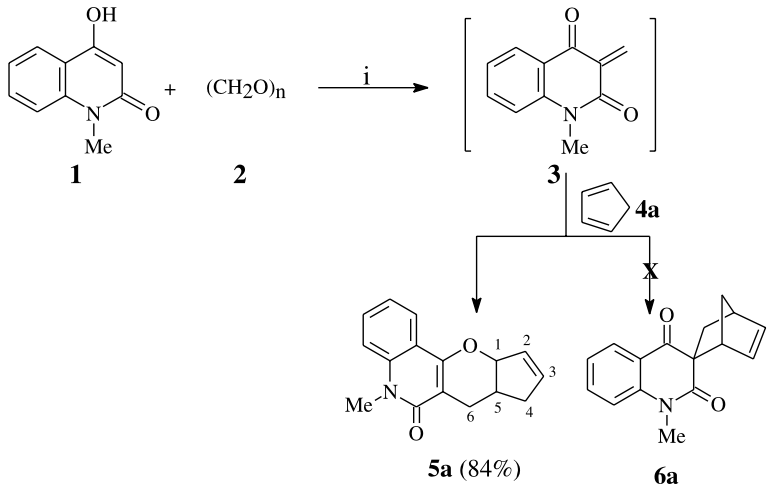
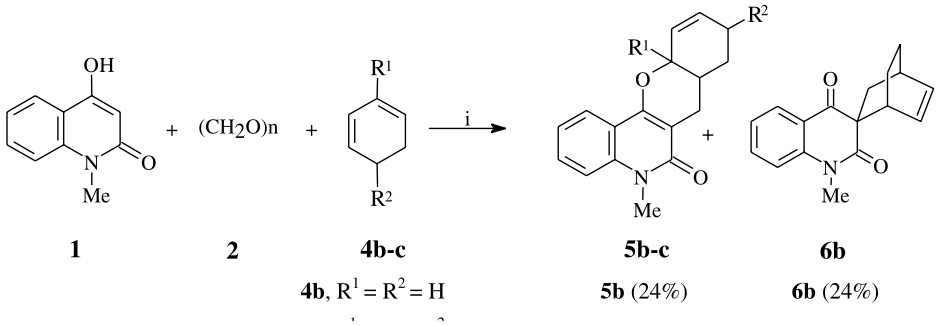


Scheme 1. (i) Dioxane, 100°C, 1 h.



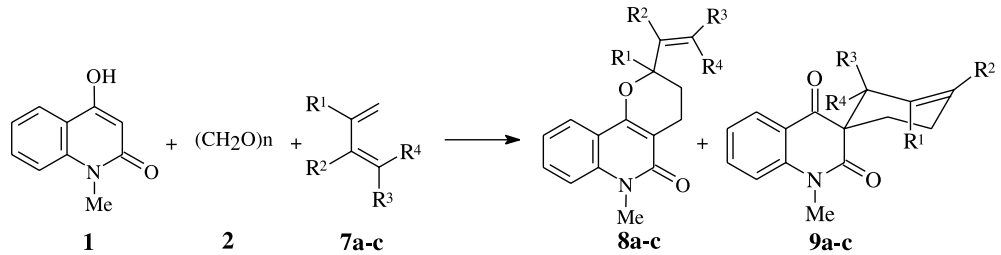
Scheme 2. (i) Dioxane, 100°C, 3 h.

Interestingly, when quinolinone **1** was treated with paraformaldehyde in the presence of cyclohexadiene under similar experimental conditions, spiroquinolinedione, **6b** was also obtained along with the [3,2-*c*]pyranoquinolinone **5b** (Scheme 2). However, α-phellandrene afforded only the corresponding pyranoquinolinone **5c**.

Evidently, the spirocompound is formed by a Diels–Alder reaction where the quinone methide is taking part as a 2π component. It is noteworthy that there has been no report of this quinone methide acting as a 2π system except in the dimerization reproted by Grundon et al.[7]

Subsequently, we decided to explore the reaction of the methide with acyclic dienes. The acyclic dienes **7a–c** when treated with quinolinone **1** under the usual conditions underwent facile cycloaddition with the in situ generated quinone methide **3** (Scheme 3).

The structure of the products was ascertained on the basis of spectroscopic analysis. The IR spectrum of the pyranoquinolinone **8a** showed the absorption due to the amide carbonyl at 1639 cm^{-1}. In the ^{13}C NMR spectrum, the signal due to the lactam carbonyl was seen at δ 163.14. The IR spectrum of the spirocompound **9a** showed two carbonyl



Scheme 3. (i) Dioxane, 100°C, 2–4 h.

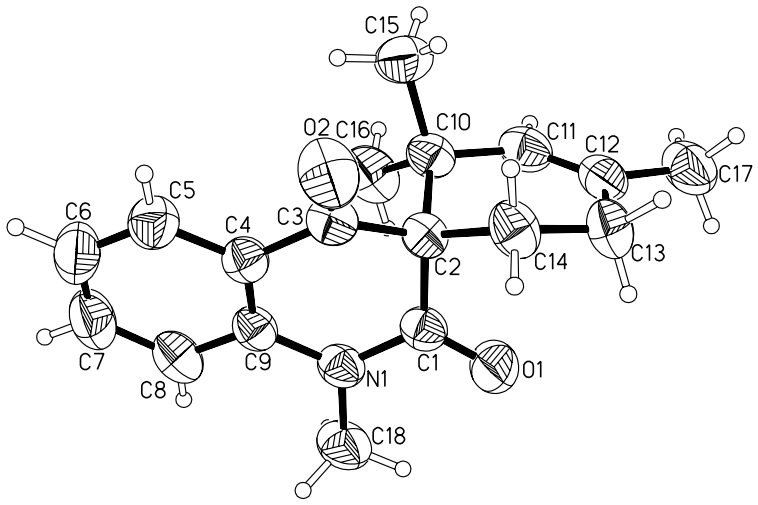
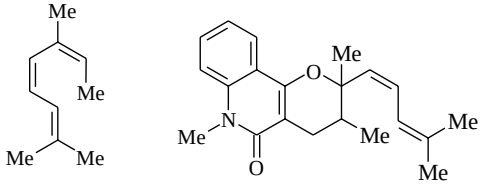


Figure 2. X-Ray structure of **9a**.



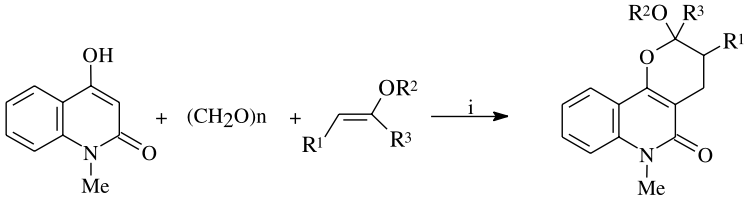
10 **11**

Figure 3.

2,4,6-octatriene (alloocimene) **10** afforded the product **11** in 54% yield (Fig. 3).

In another set of experiments, Diels–Alder trapping of the quinone methide **3** with a series of vinyl ethers was carried out successfully and the results are summarized in Scheme 4.

The foregoing results show that depending on the reaction partner, 3-methylene-quinolin-2,4-dione can act as a 2π and/or 4π component, resulting in Diels–Alder and/or



1 **2** **12a-d** **13a-d**

12a, $R^1 = R^3 = H$, $R^2 = Et$ **13a** (66%)

12b, $R^1 = R^3 = H$, $R^2 = C_4H_9$ **13b** (90%)

12c, $R^1 = H$, $R^2 = R^3 = Me$ **13c** (81%)

12d, $R^1 = Ph$, $R^2 = Me$, $R^3 = H$ **13d** (20%)[#]

Scheme 4. (i) Dioxane, 100°C, 2–3 h. ([#]In the reaction of β-methoxystyrene, most of the quinolinone was converted to bisquinolinone.)

absorption bands at 1689 and 1664 cm^{-1}. In the ^{13}C NMR spectrum, the carbonyl groups were observed at δ 197.26 and 172.02. The signal due to the spirocarbon was discernible at δ 60.23. Finally, the structure of **9a** was unequivocally proved by single crystal X-ray analysis (Fig. 2).[†]

Under the usual experimental conditions 2,6-dimethyl-hetero Diels–Alder adducts. The hetero Diels–Alder reaction exhibited excellent chemoselectivity. The methylene group of the quinone methide **3** is adjacent to two carbonyls, a ketone and a lactam carbonyl. Although not surprising, in all the above hetero Diels–Alder reactions, the ketone carbonyl was found to take part in the reaction. Furthermore, the reaction was regioselective, i.e. in all the adducts the allylic, more substituted or heteroatom substituted carbon of the dienophile bonds to the heterodiene oxygen. This is in analogy with the regioselectivity observed in the [4+2] cycloaddition reactions of 1-oxa-1,3-butadienes, in which the latter act as 4π components in Diels–Alder reactions.[1,9] Theoretical treatment of

[†] Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 161010.

[4+2] cycloaddition reactions of 1-oxa-1,3-butadienes predict the preferential formation of 2-substituted 3,4-dihydro-2*H*-pyrans and accommodate the preferred *endo* approach of the reactants in which the carbon–carbon bond formation is more advanced than carbon–oxygen bond formation, i.e. a concerted but nonsynchronous [4+2] cycloaddition reaction.

In order to explain the observed mode of addition, theoretical calculations were carried out using PC SPARTAN graphical interface package for molecular mechanics and molecular orbital models.[10] The correlation diagram for the reaction of the quinone methide **3** with cyclopentadiene is provided as an illustrative example (Fig. 4).

The correlation diagram indicates that HOMO(**3**)–LUMO(**4**) and HOMO(**4**)–LUMO(**3**) interactions are symmetry allowed. However, HOMO(**4**)–LUMO(**3**) interaction is energetically more favourable compared to the other. Thus, it is an inverse electron demand Diels–Alder reaction. The regioselectivity of the addition can be clearly explained by comparing the size of the orbital coefficients at the reacting centers. The favourable overlap between the orbitals of comparable size leads to the formation of the observed product. The major factor affecting the chemoselectivity is the LUMO coefficient at the carbonyl oxygens of **3**. The larger coefficient at the ketone oxygen (0.33452) compared to that at the lactam carbonyl oxygen (0.21089) accounts for the observed chemoselectivity.

To explain the difference in reactivity of the quinone methide **3** towards different dienes, the heats of formation of the Diels–Alder and hetero Diels–Alder adducts were calculated by PM3 method of semi-empirical calculations using TITAN software (version 1).[11] The heats of formation of some representative examples are given in Table 1.

An examination of the data in Table 1 shows that the hetero Diels–Alder adduct **5a** is more stable than the corresponding normal Diels–Alder adduct **6a** by 14.70 kcal/mol, thus explaining the exclusive formation of **5a** in the reaction of **3** with cyclopentadiene. In the case of hetero Diels–Alder adduct **8a** and normal Diels–Alder adduct **9a** of 2,4-dimethyl pentadiene, the energy difference is only 2.14 kcal/mol which makes their interconversion possible via a 3,3-sigmatropic rearrangement.[12] As evident from the heats of formation of **8b** and **9b**, obtained from 2,3-dimethyl butadiene, calculations predict substantial stability (17.93 kcal/mol) of the normal Diels–Alder adduct over the hetero Diels–Alder adduct. The experimental observation is in complete agreement with the theoretical prediction. The spiro compound **9b** was the only product isolated from this reaction.

In summary, the present investigations have shown that in situ generation and Diels–Alder trapping of quinolinone quinone methide can lead to the formation of a variety of pyranoquinolinones and spiroquinolinediones. It is noteworthy that pyranoquinolinones have important applications in medicinal and synthetic organic chemistry.[1–3] In addition, pyranoquinolines are potentially useful as optical brightners and laser dyes.[13]

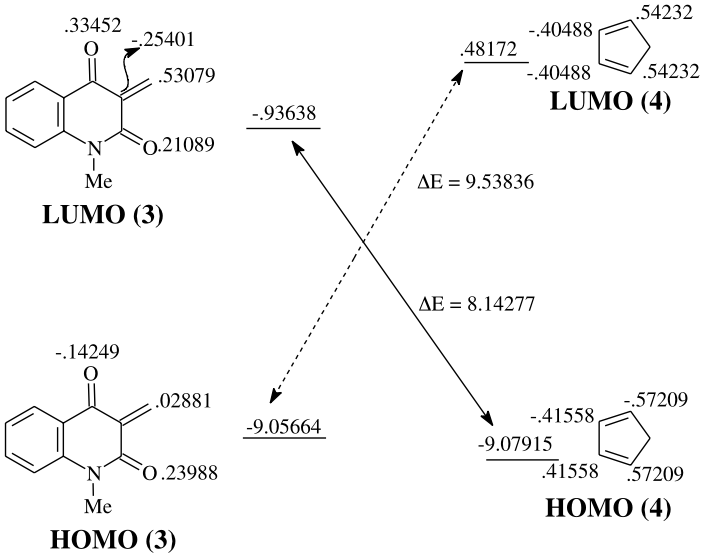


Figure 4. The correlation diagram for the reaction of **3** with **4**.

Table 1. Heats of formation of Diels–Alder and hetero Diels–Alder adducts

Entry	Hetero Diels–Alder adduct	ΔH_f (A) (kcal/mol)	Diels–Alder adduct	ΔH_f (B) (kcal/mol)	Δ(A−B) (kcal/mol)
1	**5a**	−1.671	**6a**	13.209	14.70
2	**8a**	−32.313	**9a**	−30.167	2.14
3	**8b**	−20.434	**9b**	−38.367	17.93

3. Experimental

All reactions were carried out in oven dried glassware (120°C). Analytical thin layer chromatography was performed on silica gel TLC plates. 1-Phenyl butadiene was prepared from cinnamaldehyde by Wittig olefination. All the other dienes, dienophiles, and 2-hydroxynaphthoquinone were purchased from Aldrich. Melting points were recorded on a Fisher Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Bomem MB series FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 MHz NMR spectrometer using chloroform-d as solvent. The chemical shifts are given in δ scale with tetramethylsilane as internal standard. High-resolution mass spectra were run on a Finnigan MAT model 8430 instrument. Elemental analyses were done using Perkin–Elmer 2400 CHN analyser. All solid products were purified by recrystallization from dichloromethane/hexane solvent system.

3.1. General procedure for the reaction of 4-hydroxy-1-methylquinolin-2-one

4-Hydroxy-1-methylquinolin-2-one (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and the diene/dienophile (3 mmol) were suspended in dry dioxane and refluxed under argon. On completion of the reaction, the solvent was removed in vacuo and the residue was taken up in chloroform, washed with saturated sodium carbonate and brine. The extract was dried over anhydrous sodium sulfate and concentrated. The crude product was then purified by column chromatography on silica gel (100–200 mesh). Mixtures of ethyl acetate and hexane were used as eluents.

3.1.1. 7,7a,8,10a-Tetrahydro-5-methyl-6*H*-cyclopenta[5,6]-pyrano[3,2-*c*]quinolin-6-one 5a. 4-Hydroxy-1-methylquinolin-2-one (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and cyclopentadiene (0.264 g, 4 mmol) were suspended in dry dioxane (6 mL) and refluxed (100°C) under argon atmosphere for 1 h. The aqueous work up followed by chromatographic purification on silica gel afforded 0.213 g (84%) of the pyranoquinolinone **5a** as a colourless solid. The product was recrystallized from CH_2Cl_2–hexane, mp 113–115°C. IR (KBr) ν_{max}: 1639, 1496, 1465, 1402, 1303, 1159, 1116 cm^{-1}. ^{1}H NMR: δ 7.93–7.90 (m, 1H), 7.52–7.47 (m, 1H), 7.31–7.26 (m, 1H), 7.21–7.16 (m, 1H), 6.08–6.06 (m, 1H), 6.02–6.00 (m, 1H), 5.23 (d, J=4.9 Hz, 1H), 3.69 (s, 3H), 2.88–2.82 (m, 2H), 2.66–2.55 (m, 2H), 2.28–2.27 (m, 1H). ^{13}C NMR: δ 163.41, 157.54, 138.65, 136.97, 131.57, 130.29, 123.12, 121.67, 116.77, 113.94, 105.92, 83.03, 38.35, 35.49, 29.57, 21.54. HRMS calcd for $C_{16}H_{15}NO_2$: 253.1102. Found: 253.1099.

3.2. Cycloadducts 5b and 6b

4-Hydroxy-1-methylquinolin-2-one (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and cyclohexadiene (0.240 g, 3 mmol) were suspended in dry dioxane (6 mL) and refluxed (100°C) under argon atmosphere for 6 h. The aqueous work up followed by chromatographic purification afforded the product **6b** as a colourless solid (0.064 g, 24%) followed by 0.064 g (24%) of the adduct **5b** as a colourless semi-solid.

3.2.1. 7,7a,8,9-Tetrahydro-5-methyl-6*H*,11a*H*-[1]benzopyrano[3,2-*c*]quinolin-6-one 5b. IR (neat) ν_{max}: 1639, 1496, 1396, 1315, 1166, 1116 cm^{-1}. ^{1}H NMR: δ 7.92–7.90 (m, 1H), 7.46–7.43 (m, 1H), 7.28–7.23 (m, 1H), 7.17–7.13 (m, 1H), 5.99–5.89 (m, 2H), 4.61 (brs, 1H), 3.66 (s, 3H), 2.74 (dd, J=17.7, 6.8 Hz, 1H), 2.52 (dd, J=17.7, 3.9 Hz, 1H), 2.26–2.19 (m, 3H), 1.63 (m, 2H). ^{13}C NMR: δ 163.33, 154.76, 138.51, 133.10, 129.97, 125.63, 122.87, 121.38, 116.19, 113.64, 105.12, 71.59, 29.76, 29.24, 24.77, 24.25, 23.46. HRMS calcd for $C_{17}H_{17}NO_2$: 267.1259. Found: 267.1246.

3.2.2. 1-Methylspiro[2*H*,4*H*-quinoline-3,2′-bicyclo[2.2.2]-oct-5′-ene]-2,4-dione 6b. Recrystallized from CH_2Cl_2–hexane, mp 118–120°C. IR (KBr) ν_{max}: 1698, 1647, 1607, 1555, 1502, 1466, 1366 cm^{-1}. ^{1}H NMR: δ 7.83 (d, J=7.6 Hz, 1H), 7.51–7.48 (m, 1H), 7.10–7.02 (m, 2H), 6.38 (t, J=7.2 Hz, 1H), 5.88 (t, J=7.1 Hz, 1H), 3.35 (s, 3H), 2.73–2.66 (m, 2H), 2.36 (dd, J=12.5, 1.9 Hz, 1H), 2.06–2.01 (m, 1H), 1.59–1.55 (m, 2H), 1.43–1.35 (m, 2H). ^{13}C NMR: δ 196.21, 172.27, 142.84, 136.83, 134.99, 130.71, 128.31, 127.70, 122.70, 114.21, 63.06, 40.41, 30.44, 29.91, 27.76, 22.30, 22.01. EIMS, *m/z*: 267 (M+, 60), 266 (68), 188 (100), 134 (15), 104 (15), 80 (80). HRMS calcd for $C_{17}H_{17}NO_2$: 267.1259. Found: 267.1250.

3.2.3. 7,7a,8,9-Tetrahydro-5,9,11a-trimethyl-6*H*,11*H*-[1]-benzopyrano[3,2-*c*]quinolin-6-one 5c. 4-Hydroxy-1-methylquinolin-2-one (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and *R*-α-phellandrene (0.408 g, 3 mmol) were suspended in dry dioxane (6 mL) and refluxed (100°C) under argon atmosphere for 6 h. The aqueous work up followed by chromatographic purification afforded the product **5c** as a semi-solid (0.236 g, 73%). IR (neat) ν_{max}: 1633, 1596, 1502, 1463, 1397, 1321, 1261, 1183, 1115, 1091, 1048 cm^{-1}. ^{1}H NMR: δ 7.98 (d, J=7.7 Hz, 1H), 7.52–7.47 (m, 1H), 7.31–7.16 (m, 2H), 5.72 (brs, 2H), 3.69 (s, 3H), 2.72 (dd, J=17.6, 6.4 Hz, 1H), 2.47 (dd, J=17.7, 7.2 Hz, 1H), 2.15–2.13 (m, 2H), 1.79–1.61 (m, 3H), 1.52 (s, 3H), 0.95 (d, J=6.7 Hz, 3H), 0.93 (d, J=6.7 Hz, 3H). ^{13}C NMR: δ 163.15, 154.32, 138.42, 132.78, 131.28, 129.79, 122.78, 121.24, 116.36, 113.55, 105.29, 77.33, 38.36, 33.57, 31.54, 29.13, 27.25, 26.85, 22.60, 19.87, 19.47. HRMS calcd for $C_{21}H_{25}NO_2$: 323.1885. Found: 323.1873.

3.3. Cycloadducts 8a and 9a

4-Hydroxy-1-methylquinolin-2-one (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 2,4-dimethylpentadiene (0.288 g, 3 mmol) were suspended in dry dioxane (6 mL) and refluxed (100°C) under argon atmosphere for 6 h. The aqueous work up and chromatography on silica gel afforded 0.136 g (48%) of **9a** as a colourless solid and 0.062 g (22%) of **8a** as a colourless semi-solid.

3.3.1. 2,3,4,6-Tetrahydro-2,6-dimethyl-2-(2-methylpropenyl)-pyrano[3,2-*c*]quinolin-5-one 8a. IR (neat) ν_{max}: 1639, 1502, 1458, 1396, 1315, 1178, 1110, 1072 cm^{-1}. ^{1}H

NMR: δ 7.97 (d, *J*=7.9 Hz, 1H), 7.52–7.46 (m, 1H), 7.30 (d, *J*=8.4 Hz, 1H), 7.18 (t, *J*=7.5 Hz, 1H), 5.20 (s, 1H), 3.69 (s, 3H), 2.66–2.57 (m, 2H), 2.06–2.00 (m, 2H), 1.78 (s, 3H), 1.66 (s, 3H), 1.56 (s, 3H). ^{13}C NMR: δ 163.14, 155.34, 138.60, 136.35, 129.80, 127.62, 122.70, 121.28, 116.59, 113.67, 106.41, 78.08, 32.93, 29.14, 27.12, 26.83, 19.10, 17.92. EIMS, *m/z*: 283 (M+, 50), 268 (40), 228 (22), 200 (100), 188 (80), 134 (15), 96 (45), 81 (40). HRMS calcd for $C_{18}H_{21}NO_2$: 283.1572. Found: 283.1580.

3.3.2. 1,2′,2′,4′-Tetramethylspiro[2*H*,4*H*-quinolin-3,1′-cyclohex-3′-ene]-2,4-dione 9a. Recrystallized from CH_2Cl_2–hexane, mp 83–85°C. IR (neat) ν_{max}: 1689, 1664, 1602, 1465, 1346, 1309 cm^{-1}. ^{1}H NMR: δ 7.85 (dd, *J*=7.6, 1.2 Hz, 1H), 7.58–7.53 (m, 1H), 7.13–7.05 (m, 2H), 4.88 (s, 1H), 3.42 (s, 3H), 2.54–2.22 (m, 3H), 2.09–2.01 (m, 1H), 1.73 (s, 3H), 0.88 (s, 3H), 0.82 (s, 3H). ^{13}C NMR: δ 197.26, 172.02, 143.52, 135.20, 132.65, 127.52, 127.12, 123.22, 122.64, 113.96, 60.23, 39.39, 29.31, 27.91, 27.86, 26.98, 24.19, 23.41. EIMS, *m/z*: 283 (M+, 50), 268 (30), 228 (15), 200 (100), 188 (80), 134 (16), 96 (46), 81 (40). HRMS calcd for $C_{18}H_{21}NO_2$: 283.1572. Found: 283.1579. X-ray crystal data: $C_{18}H_{21}NO_2$. F_w: 283.36. Crystal size: 0.28×0.22×0.20 mm^3, crystal system: monoclinic, space group: $P2_1/c$. Unit cell dimensions a=9.2857(3) Å, α=90°; b=21.7197(7) Å, β=115.619(2)°; c=8.3199(3) Å, γ=90°. R indices (all data) $R1$=0.0844, $wR2$=0.1329. Volume, Z=1109.85(4) Å^3, D_{calcd}=1.244 mg/m^3. $F(000)$=608. Absorption coefficient=0.081 mm^{-1}. Reflections collected=27675. λ=0.71073 Å. (Sheldrick, G.M., Siemens, Analytical X-ray Division, Madison, WI, 1995).

3.3.3. 1,3′,4′-Trimethylspiro[2*H*,4*H*-quinolin-3,1′-cyclohex-3-ene]-2,4-dione 9b. 4-Hydroxy-1-methylquinolin-2-one (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 2,3-dimethylbutadiene (0.246 g, 3 mmol) were suspended in dry dioxane (6 mL) and refluxed (100°C) under argon atmosphere for 2 h. The aqueous work up followed by chromatographic purification afforded **9b** as a colourless solid (0.234 g, 87%). It was recrystallized from CH_2Cl_2–hexane, mp 88–90°C. IR (KBr) ν_{max}: 1696, 1665, 1598, 1470, 1351, 1300, 1096 cm^{-1}. ^{1}H NMR: δ 7.90 (dd, *J*=7.5, 1.2 Hz, 1H), 7.58 (dt, *J*=8.3, 1.5 Hz, 1H), 7.20–7.09 (m, 2H), 3.45 (s, 3H), 2.60 (d, *J*=17.3 Hz, 1H), 2.49 (d, *J*=17.3 Hz, 1H), 1.98–1.85 (m, 4H), 1.73 (s, 3H), 1.64 (s, 3H). ^{13}C NMR: δ 196.57, 173.17, 142.85, 135.16, 128.02, 123.72, 122.91, 120.75, 114.34, 57.74, 32.78, 32.44, 30.09, 28.69, 19.00, 18.96. HRMS calcd for $C_{17}H_{19}NO_2$: 269.1415. Found: 269.1404.

3.4. Cycloadducts 8c and 9c

4-Hydroxy-1-methylquinolin-2-one (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 1-phenyl-1,3-butadiene (0.260 g, 2 mmol) were suspended in dry dioxane (6 mL) and refluxed (100°C) under argon atmosphere for 6 h. The aqueous work up followed by chromatographic purification afforded the product **8c** (0.181 g, 57%) and **9c** (0.133 g, 42%) as semi-solids.

3.4.1. 2,3,4,6-Tetrahydro-6-methyl-2-(phenylvinyl)pyrano[3,2-*c*]quinolin-5-one 8c. IR (neat) ν_{max}: 1633, 1502, 1452, 1408, 1334, 1303 cm^{-1}. ^{1}H NMR: δ 7.97 (d, *J*=7.9 Hz, 1H), 7.49–7.17 (m, 7H), 6.72 (d, *J*=15.9 Hz, 1H), 6.35 (dd, *J*=15.9, 6.2 Hz, 1H), 4.80 (t, *J*=6.3 Hz, 1H), 4.19 (brs, 1H), 3.66 (s, 3H), 2.81–2.57 (m, 2H), 2.23–2.13 (m, 1H), 2.02–1.86 (m, 1H). ^{13}C NMR: δ 162.97, 155.94, 138.40, 136.09, 132.02, 130.06, 128.51, 127.95, 127.45, 126.54, 122.63, 121.43, 116.05, 113.67, 106.60, 81.73, 29.17, 27.08, 19.24. HRMS calcd for $C_{21}H_{19}NO_2$: 317.1416. Found: 317.1401.

3.4.2. 1-Methyl-2′-phenylspiro[2*H*,4*H*-quinolin-3,1′-cyclohex-3′-ene]-2,4-dione 9c. IR (neat) ν_{max}: 1697, 1657, 1595, 1471, 1346, 1303 cm^{-1}. ^{1}H NMR: δ 7.96–7.93 (m, 1H), 7.47–7.41 (m, 1H), 7.09–7.02 (m, 6H), 6.80 (d, *J*=8.2 Hz, 1H), 6.04–6.01 (m, 1H), 5.73–5.70 (m, 1H), 4.17 (s, 1H), 3.10 (s, 3H), 2.61–2.34 (m, 1H), 2.41–2.26 (m, 2H), 2.08–2.01 (m, 1H). ^{13}C NMR: δ 197.49, 169.93, 142.98, 139.86, 135.47, 129.10, 127.79, 127.39, 126.87, 126.75, 122.35, 120.45, 113.96, 59.76, 47.76, 28.96, 28.06, 22.72. HRMS calcd for $C_{21}H_{19}NO_2$: 317.1415. Found: 317.1405.

3.4.3. 2,3,6-Trimethyl-2-(4-methyl-1,3-pentadienyl)-pyrano-[3,2-*c*]quinolin-5-one 11. 4-Hydroxy-1-methylquinolin-2-one (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 2,6-dimethyl-2,4,6-octatriene (0.272 g, 2 mmol) were suspended in dry dioxane (6 mL) and refluxed (100°C) under argon atmosphere for 6 h. The aqueous work up followed by chromatographic purification afforded the product **11** as semi-solid (0.174 g, 54%). IR (neat) ν_{max}: 1637, 1593, 1398, 1180, 1118 cm^{-1}. ^{1}H NMR: δ 8.02–7.99 (m, 1H), 7.54–7.49 (m, 1H), 7.23–7.13 (m, 2H), 6.49 (dd, *J*=15.2, 10.9 Hz, 1H), 5.82 (d, *J*=10.5 Hz, 1H), 5.67 (d, *J*=15.3 Hz, 1H), 3.70 (s, 3H), 2.71 (dd, *J*=17.6, 5.5 Hz, 1H), 2.34 (dd, *J*=17.6, 8.1 Hz, 1H), 2.04–1.97 (m, 1H), 1.77 (s, 3H), 1.70 (s, 3H), 1.38 (s, 3H), 1.04 (d, *J*=9.2 Hz, 3H). ^{13}C NMR: δ 163.16, 154.94, 138.64, 136.08, 133.67, 129.98, 125.93, 124.46, 122.76, 121.43, 116.46, 113.70, 105.72, 81.27, 34.42, 29.79, 26.38, 26.02, 19.81, 18.37, 15.95. HRMS calcd for $C_{21}H_{25}NO_2$: 323.1885. Found: 323.1871.

3.4.4. 2-Ethoxy-2,3,4,6-tetrahydro-6-methylpyrano[3,2-*c*]quinolin-5-one 13a. 4-Hydroxy-1-methylquinolin-2-one (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and ethyl vinyl ether (0.216 g, 3 mmol) were suspended in dry dioxane (6 mL) and refluxed (100°C) under argon atmosphere for 2 h. The aqueous work up followed by chromatographic purification afforded the product **13a** (0.171 g, 66%) as a colourless semi-solid. IR (neat) ν_{max}: 1639, 1595, 1508, 1465, 1402, 1321, 1091, 1054 cm^{-1}. ^{1}H NMR: δ 7.93 (d, *J*=7.9 Hz, 1H), 7.54–7.49 (m, 1H), 7.33 (d, *J*=8.4 Hz, 1H), 7.20 (t, *J*=7.4 Hz, 1H), 5.40 (d, *J*=2.5 Hz, 1H), 3.93–3.90 (m, 1H), 3.74–3.69 (m, 1H), 3.70 (s, 3H), 2.70–2.66 (m, 2H), 2.16–2.08 (m, 1H), 1.99–1.92 (m, 1H), 1.21 (t, *J*=7.0 Hz, 3H). ^{13}C NMR: δ 162.79, 153.58, 138.64, 129.95, 122.33, 121.37, 116.13, 113.68, 107.61, 98.05, 64.36, 29.16, 26.00, 16.01, 15.11. EIMS, *m/z*: 259 (M+, 50), 230 (60), 214 (10), 202 (100), 186 (20), 134 (12), 104 (12), 77 (20). HRMS calcd for $C_{15}H_{17}NO_3$: 259.1208. Found: 259.1207.

3.4.5. 2-Butoxy-2,3,4,6-tetrahydro-6-methylpyrano[3,2-*c*]quinolin-5-one 13b. 4-Hydroxy-1-methylquinolin-2-one

(0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and butyl vinyl ether (0.216 g, 3 mmol) were suspended in dry dioxane (6 mL) and refluxed (100°C) under argon atmosphere for 4 h. The aqueous work up followed by chromatographic purification afforded the product **13b** (0.258 g, 90%) as a colourless oil. IR (neat) ν_{max}: 1640, 1596, 1579, 1502, 1464, 1399, 1354, 1318, 1157, 1092 cm^{-1}. ^1H NMR: δ 7.91 (d, J=7.9 Hz, 1H), 7.51–7.48 (m, 1H), 7.31(d, J=8.4 Hz, 1H), 7.23–7.17 (m, 1H), 5.38 (dd, J=4.5, 2.6 Hz, 1H), 3.88–3.85 (m, 1H), 3.70 (s, 3H), 3.66–3.62 (m, 1H), 2.70–2.65 (m, 2H), 2.11–2.10 (m, 1H), 1.97–1.95 (m, 1H), 1.57–1.52 (m, 2H), 1.35–1.27 (m, 2H), 0.85 (t, J=7.4 Hz, 3H). ^{13}C NMR: δ 162.87, 153.69, 138.70, 130.00, 122.41, 121.44, 116.22, 113.74, 107.67, 98.30, 68.68, 31.66, 29.24, 26.06, 19.22, 16.05, 13.79. HRMS calcd for $C_{17}H_{21}NO_3$: 287.1521. Found 287.1514.

3.4.6. 2,3,4,6-Tetrahydro-2-methoxy-2,6-dimethylpyrano-[3,2-*c*]quinolin-5-one 13c. 4-Hydroxy-1-methylquinolin-2-one (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and methoxypropene (0.216 g, 3 mmol) were suspended in dry dioxane (6 mL) and refluxed (100°C) under argon atmosphere for 2 h. The aqueous work up followed by chromatographic purification afforded the product **13c** (0.210 g, 81%) as a colourless solid. The product was recrystallized from CH_2Cl_2–hexane, mp 118–120°C. IR (KBr) ν_{max}: 1636, 1619, 1593, 1503, 1465, 1396, 1323, 1164, 1063 cm^{-1}. ^1H NMR: δ 7.97 (d, J=7.5 Hz, 1H), 7.51 (t, J=7.2 Hz, 1H), 7.32 (d, J=8.2 Hz, 1H), 7.20 (t, J=7.1 Hz, 1H), 3.71 (s, 3H), 3.30 (s, 3H), 2.68–2.66 (m, 2H), 2.21–2.16 (m, 1H), 1.87–1.76 (m, 1H), 1.65 (s, 3H). ^{13}C NMR: δ 162.88, 153.59, 138.66, 129.90, 122.16, 121.38, 116.05, 113.71, 107.79, 99.72, 49.26, 31.31, 29.17, 22.61, 17.07. EIMS, *m/z*: 259 (M+, 25), 244 (20), 228 (10), 202 (100), 186 (10). HRMS calcd for $C_{15}H_{17}NO_3$: 259.1208. Found: 259.1211.

3.4.7. 2,3,4,6-Tetrahydro-2-methoxy-6-methyl-3-phenyl-pyrano[3,2-*c*]quinolin-5-one 13d. 4-Hydroxy-1-methylquinolin-2-one (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and β-methoxystyrene (0.238 g, 2 mmol) were suspended in dry dioxane (6 mL) and refluxed (100°C) under argon atmosphere for 6 h. The aqueous work up followed by chromatographic purification afforded the product **13d** (0.064 g, 20%) as a colourless solid. The product was recrystallized from CH_2Cl_2–hexane solvent system, mp 117–119°C. IR (KBr) ν_{max}: 1638, 1614, 1592, 1497, 1457, 1412, 1256, 1227, 1137, 1115, 1098 cm^{-1}. ^1H NMR: δ 7.96 (d, J=7.8 Hz, 1H), 7.54 (t, J=7.1 Hz, 1H), 7.36 (d, J=8.3 Hz, 1H), 7.26–7.20 (m, 6H), 5.30 (d, J=3.7 Hz, 1H), 3.73 (s, 3H), 3.56 (s, 3H), 3.37–3.35 (m, 1H), 3.08 (dd, J=17.8, 6.7 Hz, 1H), 2.95 (dd, J=17.8, 4.6 Hz, 1H). ^{13}C NMR: δ 162.52, 153.53, 140.74, 138.72, 128.54, 127.49, 126.93, 122.45, 121.49, 115.80, 113.77, 107.10, 102.81, 56.29, 41.03, 29.23, 23.47. EIMS, *m/z*: 321(M+, 20), 276 (10), 200 (10), 134 (100), 91 (40). HRMS calcd for $C_{20}H_{19}NO_3$: 321.1365. Found: 321.1354.

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