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Synthesis of Eupomatidines 1, 2 and 3 and Related Compounds Including Iminoquinolinequinone Structure

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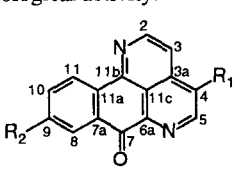
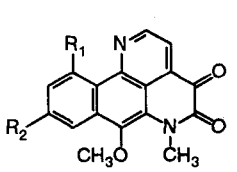
Abstract: Three aromatic alkaloids, eupomatidines 1 (**1**), 2 (**2**), and 3 (**3**), and two related compounds (**27**, **28**) were synthesized from (6-methoxy-)1,4-naphthoquinone by hetero Diels-Alder reaction with (2-methoxy-)2-butenal dimethylhydrazone.

In recent years a series of structurally related and biologically active polycyclic aromatic alkaloids including iminoquinolinequinone structure have been isolated from natural resources.[1] In 1991 Carroll and Taylor reported the isolation and structural elucidation of new aromatic alkaloids, eupomatidines 1 (**1**), 2 (**2**) and 3 (**3**), and imbilines 1 (**5**), 2 (**6**) and 3 (**7**) from *Eupomatia bennetti* and *E. laurina* (Eupomatiaceae).[2] Eupomatidines 1-3 are (di)methoxy derivatives of sampangine (naphtho[1,2,3-*ij*][2,7]naphthyridin-7(7*H*)-one, **4**) isolated from *Cananga odorata* (Annonaceae).[3] Imbilines 1-3 possess the common structure, 4,5-dihydronaphtho[1,2,3-*ij*][2,7]naphthyridine-4,5(6*H*)-dione.

In connnection with our synthetic studies on heterocyclic quinones and related compounds,[4] we achieved total synthesis of eupomatidines 1 (**1**), 2 (**2**) and 3 (**3**) including the iminoquinolinequinone structure.[5] Now we report the full details of the synthesis of eupomatidines 1-3 and their isomers (**27**, **28**) by hetero Diels-Alder reaction, and their biological activity.



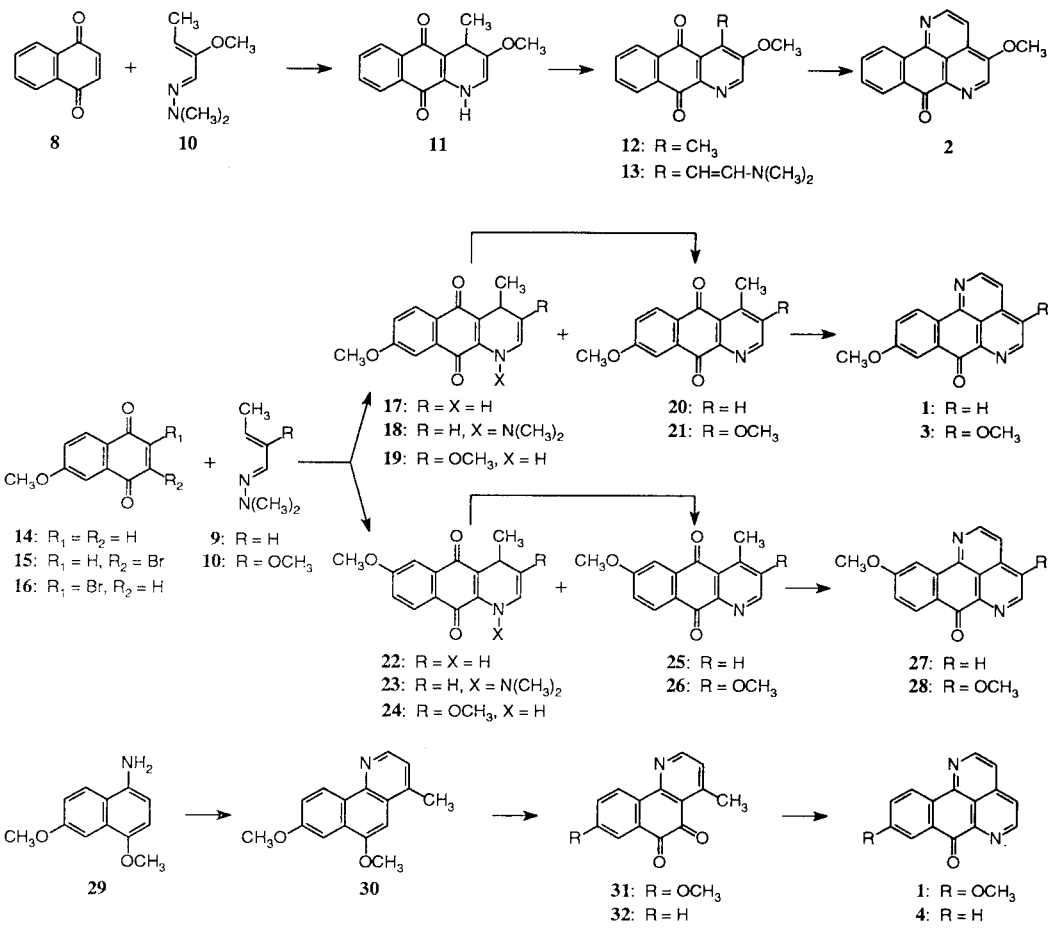
1: $R_1 = H$, $R_2 = OCH_3$
2: $R_1 = OCH_3$, $R_2 = H$
3: $R_1 = R_2 = OCH_3$
4: $R_1 = R_2 = H$



5: $R_1 = R_2 = H$
6: $R_1 = OH$, $R_2 = H$
7: $R_1 = H$, $R_2 = OCH_3$

The hetero Diels-Alder cycloaddition[6] of 1,4-naphthoquinone (**8**) with 2-methoxy-2-butenal dimethylhydrazone (**10**, prepared from 2-butenal dimethylhydrazone[7] (**9**)) was carried out in chloroform at 25°C for 5 h to give the corresponding adduct (**11**) in 79% yield. Oxidation of **11** with manganese(IV) oxide[6] in chloroform

gave 3-methoxy-4-methylbenzo[*g*]quinoline-5,10-dione (**12**) in 75% yield. The aza-anthraquinone (**12**) was condensed with *N*,*N*-dimethylformamide (DMF) diethyl acetal[8] in DMF to give the enamine (**13**). Treatment of the crude enamine (**13**) with ammonium chloride and acetic acid[8] in DMF at 110°C furnished the desired 4-methoxynaphtho[1,2,3-*ij*][2,7]naphthyridin-7(7*H*)-one (**2**), *i.e.* eupomatidine 2 in 88% yield from **12**.



Next, we synthesized eupomatidine 1 (**1**). The hetero Diels-Alder reaction of 6-methoxy-1,4-naphthoquinone[9] (**14**) with 2-butenal dimethylhydrazone (**9**) in acetonitrile at 80°C for 3 h in the presence of acetic anhydride[6] afforded 4-methyl-1,4-dihydrobenzo[*g*]quinoline-5,10-diones (**17** and **22**) as an inseparable mixture in 71% yield. Oxidation of the mixture of **17** and **22** with manganese(IV) oxide in chloroform gave 4-methylbenzo[*g*]quinoline-5,10-diones (**20** and **25**) in 40% and 14% yields from **14**, respectively. Treatment of **20** with DMF diethyl acetal in DMF followed by ammonium chloride and acetic acid gave 9-methoxy-naphtho[1,2,3-*ij*][2,7]naphthyridin-7(7*H*)-one (**1**), *i.e.* eupomatidine 1 in 91% yield. Similarly, 10-methoxy-naphtho[1,2,3-*ij*][2,7]naphthyridin-7(7*H*)-one (**27**) was obtained from **25** in 51% yield.

In order to achieve regioselective hetero Diels-Alder reaction,[10] we used 2-bromo-7-methoxy-1,4-naphthoquinone[11] (**15**) and 2-bromo-6-methoxy-1,4-naphthoquinone[11] (**16**) instead of **14**. The reaction of **15** with **9** in acetonitrile at 80°C for 4 h proceeded regioselectively and gave **17** (56%), **18** (8.6%) and **20** (21%). The 1,4-dihydro compounds, **17** and **18**, were aromatized to form **20** by treatment with manganese(IV) oxide in chloroform at 25°C and palladium on carbon in toluene at 110°C, respectively. Similarly, 7-methoxy-4-methylbenzo[*g*]quinoline-5,10-dione (**25**) was obtained from **16** and **9**.

The structure **1** was further confirmed by the following independent synthesis. 6,8-Dimethoxy-4-methylbenzo[*h*]quinoline (**30**) prepared from 4,6-dimethoxy-1-naphthylamine[12] (**29**), was oxidized by fuming nitric acid in acetic acid at 40-50°C to give benzo[*h*]quinoline-5,6-dione (**31**, 25% yield) in addition to 6,8-dimethoxy-4-methyl-7-nitrobenzo[*h*]quinoline (59% yield). The *o*-quinone (**31**) was treated with DMF diethyl acetal in toluene at 100°C followed by ammonium chloride and acetic acid to furnish **1** in 62% yield. Similarly, sampangine (**4**) was obtained from **32**[13] in 54% yield.

Finally, eupomatidine 3 (**3**) was synthesized. The hetero Diels-Alder cycloaddition of 6-methoxy-1,4-naphthoquinone (**14**) with 2-methoxy-2-butenal dimethylhydrazone (**10**) in chloroform at 25°C for 2 h afforded dimethoxy-4-methyl-1,4-dihydrobenzo[*g*]quinoline-5,10-diones (**19** and **24**) as an inseparable mixture in 70% yield. The mixture of **19** and **24** was oxidized with manganese(IV) oxide in chloroform to give 4-methylbenzo[*g*]quinoline-5,10-diones (**21** and **26**) in 42% and 9.2% yields from **14**, respectively. In contrast, the hetero Diels-Alder reaction of 2-bromo-7-methoxy-1,4-naphthoquinone (**15**) and 2-bromo-6-methoxy-1,4-naphthoquinone (**16**) with **10** proceeded regioselectively and gave 4-methylbenzo[*g*]quinoline-5,10-diones (**21**

Table 1. ^{13}C-NMR Chemical Shift Data for Eupomatidines 1 (**1**), 2 (**2**) and 3 (**3**), Sampangine (**4**), **27** and **28**.[a)]

Carbon	**1**	**2**	**3**	**4**	**27**	**28**
C_2	147.39	146.54	146.76	147.31	147.21	146.51
C_3	118.19	114.25	113.32	119.17	119.49	114.61
C_{3a}	138.78	130.37	130.32	138.63	138.64	130.40
C_4	123.45	152.69	152.91	123.45	123.02	152.43
C_5	148.46	128.97	128.94	148.44	148.41	128.70
C_{6a}	148.25	141.02	141.19	147.83	148.32	141.30
C_7	181.89	180.97	181.10	181.87	180.82	180.14
C_{7a}	134.05	132.85	134.39	132.27	126.26	126.64
C_8	110.85	128.41	110.54	128.44	131.14	130.98
C_9	162.46	131.21	162.27	131.35	118.66	118.60
C_{10}	122.52	134.11	122.26	134.64	164.92	164.57
C_{11}	127.53	125.41	127.35	125.37	108.33	108.19
C_{11a}	128.77	135.56	129.03	135.31	137.82	137.98
C_{11b}	151.47	150.39	150.56	151.07	151.16	150.34
C_{11c}	119.19	120.04	119.45	119.62	119.97	120.26
C_4-O$\underline{C}H_3$		56.86	56.86			56.84
C_9-O$\underline{C}H_3$	55.89		55.92			
C_{10}-O$\underline{C}H_3$					55.93	55.90

a) Assignment confirmed by direct and long-range C-H correlations.

and **26**) in 32% and 53% yields, respectively. Treatment of **21** with DMF diethyl acetal in DMF followed by ammonium chloride and acetic acid gave 4,9-dimethoxynaphtho[1,2,3-*ij*][2,7]naphthyridin-7(7*H*)-one (**3**), *i.e.* eupomatidine 3 in 68% yield. Similarly, 4,10-dimethoxynaphtho[1,2,3-*ij*][2,7]naphthyridin-7(7*H*)-one (**28**) was obtained from **26** in 63% yield.

The spectroscopic data obtained for **1**-**4** were identical to the values reported for the corresponding natural products, eupomatidines 1, 2, and 3, and sampangine, respectively. The ^{13}C-NMR chemical shift data for **1**-**4**, **27**, and **28** are given in Table 1.

With naphtho[1,2,3-*ij*][2,7]naphthyridin-7(7*H*)-ones (**1**-**4**, **27**, **28**) in hand, antifungal activity against *Candida albicans*, *Paecilomyces variotii*, and *Trichophyton mentagrophytes* was studied. The result is summarized in Table 2. Sampangine (**4**) and eupomatidine 1 (**1**), no substituent at C_4, exhibit activity against these three fungi. Eupomatidines 2 (**2**) and 3 (**3**), **27**, and **28** bearing methoxyl group at C_4 and/or C_{10} exhibit activity against *T. mentagrophytes*; no activity against *C. albicans* and *P. variotii*. Extensive biological studies are in progress.

Table 2. Antifungal Activity of Eupomatidines 1 (**1**), 2 (**2**) and 3 (**3**), Sampangine (**4**), **27** and **28** (EC_{50}, μg/ml).

Compound	**1**	**2**	**3**	**4**	**27**	**28**
C. albicans	50	>100	>100	1.6	>100	>100
P. variotii	6.25	>100	>100	0.2	>100	>100
T. mentagrophytes	0.4	3.1	6.25	0.2	12.5	6.25

Experimental Section

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. UV spectra were determined with a Hitachi 340 spectrometer. IR spectra were obtained with a Hitachi 260-10 spectrophotometer. ^{1}H-NMR spectra were recorded at 270.05 MHz with a JEOL JNM-EX 270 spectrometer. ^{13}C-NMR spectra were recorded at 125.65 MHz with a JEOL JNM-LA 500 spectrometer. ^{1}H- and ^{13}C-NMR spectra were measured in $CDCl_3$, and chemical shifts were recorded in δ values relative to an internal standard, tetramethylsilane. Mass spectra were recorded on a JMS-DX 302 mass spectrometer. Elemental analyses were obtained by a Perkin-Elmer Model 240B elemental analyzer. All reactions were run with magnetic stirring. Anhydrous sodium sulfate was used for drying organic solvent extracts, and the solvent was removed with a rotary evaporator and finally under high vacuum. Column (or flash) chromatography was performed with E. Merck silica gel 60 (230–400 mesh).

2-Methoxy-2-butenal Dimethylhydrazone (10) Bromine (1.28 g, 8 mmol) in methanol (10 ml) was added dropwise to a solution of 2-butenal dimethylhydrazone (**9**, 560 mg, 5 mmol) in methanol (10 ml) at -30°C with stirring. After stirring for 5 min, the solution was warmed to 5°C for 15 min, diluted with CH_2Cl_2 (100 ml) and neutralized with saturated aqueous $NaHCO_3$ solution. The organic layer was separated, washed with water (2 x 30 ml), dried and evaporated. The residue was purified by flash chromatography (CH_2Cl_2) to give 3-bromo-2-methoxybutanal dimethylhydrazone (**9'**) as a pale yellow oil. Sodium methoxide (28% methanol solution, 3 ml) was added to **9'** and the mixture was refluxed for 30 min. After cooling, the mixture was diluted with water (50 ml) and extracted with CH_2Cl_2 (3 x 30 ml). The extract was washed with water (40 ml), dried and evaporated to give **10** (240 mg, 34% from **9**) as a pale yellow oil.

9' (diastereomeric mixture): MS *m/z* (%): 224 (M^++2, 7), 222 (M^+, 7), 192 (6), 190 (6), 115 (100). High-resolution MS Calcd for $C_7H_{15}{}^{79}BrN_2O$: 222.0368. Found: 222.0367. ^{1}H-NMR δ: 1.675 and 1.724 (3H, d, J = 6.9 Hz, C<u>H</u>$_3$-CH), 2.849 and 2.843 (6H, s, $N(CH_3)_2$), 3.380 and 3.383 (3H, s, OCH_3), 3.65-4.30 (2H, m, CH-CH), 6.417 and 6.394 (1H, d, J = 6.3 Hz, CH=N).

10 (*E-Z* mixture): MS *m/z* (%): 142 (M^+, 100), 127 (57), 98 (24), 83 (24), 44 (42). High-resolution MS Calcd for $C_7H_{14}N_2O$: 142.1106. Found: 142.1109. ^{1}H-NMR δ: 1.770 and 1.742 (3H, d, J = 7.3 Hz, C<u>H</u>$_3$-CH-), 2.939 and 2.854 (6H, s, $N(CH_3)_2$), 3.707 and 3.623 (3H, s, OCH_3), 5.105 and 4.792 (1H, q, J = 7.3 Hz, CH=C), 7.030 and 6.704 (1H, s, CH=N).

3-Methoxy-4-methyl-1,4-dihydrobenzo[*g*]quinoline-5,10-dione (11) A solution of **10** (142 mg, 1 mmol) in $CHCl_3$ (2 ml) was added to a solution of 1,4-naphthoquinone (**8**, 79 mg, 0.5 mmol) in $CHCl_3$ (2 ml). After stirring at 25°C for 5 h, the solution was subjected to flash chromatography (CH_2Cl_2) to give **11** (100 mg, 79%) as a deep blue solid. mp 172-173°C (ether-hexane). MS *m/z* (%): 255 (M^+, 9), 240 (100). *Anal.* Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.19; N, 5.49. Found: C, 70.45; H, 5.20; N, 5.52. IR (KBr): 3356, 1672, 1658, 1594, 1562, 1504, 1368, 1338, 1312, 1288, 1264, 1232, 1194, 1154, 1104, 1004, 794, 724 cm^{-1}. ^{1}H-NMR δ: 1.280 (3H, d, J = 6.3 Hz, C_4-CH_3), 3.616 (3H, s, OCH_3), 3.970 (1H, q, J = 6.3 Hz, C_4-H), 5.662 (1H, d, J = 5.0 Hz, C_2-H), 6.703 (1H, br, NH), 7.593 and 7.714 (each 1H, td, J = 7.6, 1.3 Hz, C_7-H, C_8-H), 8.017 and 8.113 (each 1H, dd, J = 7.6, 1.3 Hz, C_6-H, C_9-H).

3-Methoxy-4-methylbenzo[*g*]quinoline-5,10-dione (12) Manganese(IV) oxide (521 mg, 6 mmol) was added to a solution of **11** (51 mg, 0.2 mmol) in $CHCl_3$ (30 ml). The mixture was stirred at 25°C for 1 h, and then filtered. The filtrate was evaporated and the residure was purified by flash chromatography (ethyl acetate-CH_2Cl_2, 4:1) to give **12** (38 mg, 75%) as a pale yellow solid. mp 272-275°C (CH_2Cl_2-ether). MS *m/z* (%): 253 (M^+, 100), 235 (42). *Anal.* Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 70.86; H, 4.45; N, 5.59. IR (KBr): 1676, 1592, 1546, 1468, 1300, 1282, 1212, 1038, 1018, 950, 798, 720 cm^{-1}. ^{1}H-NMR δ: 2.788 (3H, s, C_4-CH_3), 4.107 (3H, s, OCH_3), 7.75-7.85 (2H, m, C_7-H, C_8-H), 8.20-8.40 (2H, m, C_6-H, C_9-H), 8.658 (1H, s, C_2-H).

Eupomatidine 2 (2) A suspension of **12** (34 mg, 0.13 mmol) in dry DMF (0.3 ml) and DMF diethyl acetal (59 mg, 0.4 mmol) under N_2 was heated at 120°C for 30 min. Ammonium chloride (450 mg, 8.4 mmol) and acetic acid (1.5 ml) were added and the mixture was heated at 110°C for 30 min. After cooling, the mixture was diluted with water (20 ml) and extracted with $CHCl_3$ (3 x 15 ml). The extract was washed with water (30 ml), dried and evaporated. The residue was purified by flash chromatography (ethyl acetate-CH_2Cl_2, 4:1) to give **2** (31 mg, 88%) as a yellow solid. mp 262-265°C (decomp.) (CH_2Cl_2-ether) [lit.,[2] mp 262-265°C (decomp.)]. MS *m/z* (%): 262 (M^+, 100), 247 (18), 219 (33), 164 (13). High-resolution MS Calcd for $C_{16}H_{10}N_2O_2$: 262.0742. Found: 262.0747. IR (KBr): 1666, 1596, 1570, 1502, 1410, 1378, 1324, 1294, 1280, 1238, 1100, 1040, 1026, 990, 922, 722 cm^{-1}. UV (C_2H_5OH) λ_{max} nm (log ε): 243 (4.51), 265 (4.25), 333 (3.71), 390 (4.16), 407 (4.14). ^{1}H-NMR δ: 4.249 (3H, s, OCH_3), 7.690 (1H, ddd, J = 7.9, 7.6, 1.3 Hz, C_9-H), 7.821 (1H, ddd, J = 7.9, 7.6, 1.3 Hz, C_{10}-H), 8.016 (1H, d, J = 5.6 Hz, C_3-H), 8.487 (1H, dd, J = 7.9, 1.3 Hz, C_8-H), 8.669 (1H, s, C_5-H), 8.879 (1H, dd, J = 7.9, 1.3 Hz, C_{11}-H), 8.895 (1H, d, J = 5.6 Hz, C_2-H).

8-Methoxy-4-methylbenzo[*g*]quinoline-5,10-dione (20) and 7-Methoxy-4-methylbenzo[*g*]quinoline-5,10-dione (25) from 6-Methoxy-1,4-naphthoquinone (14) and 2-Butenal Dimethylhydrazone (9) Aza-diene **9** (280 mg, 2.5 mmol) and acetic anhydride (51 mg, 0.5 mmol) were added to a solution of **14** (47 mg, 0.25 mmol) in CH_3CN (2.5 ml). The solution was refluxed for 3 h, and then evaporated. The residue

was purified by flash chromatography (ethyl acetate-hexane, 1:9) to give an approximately 3:1 mixture of **17** and **22** (45 mg, 71%) as a deep blue oil. Manganese(IV) oxide (612 mg, 7 mmol) was added to a solution of the isomeric mixture in $CHCl_3$ (20 ml). The whole was stirred at 25°C for 1 h, and then filtered. The filtrate was evaporated and the residue was purified by flash chromatography (ethyl acetate-CH_2Cl_2, 1:49) to give **20** (25 mg, 40% from **14**) and **25** (8.7 mg, 14% from **14**) as a pale yellow solid, respectively.

20: mp 212-214°C (CH_2Cl_2-ether). MS *m/z* (%): 253 (M^+, 100), 225 (29). *Anal.* Calcd for $C_{15}H_{11}NO_3 \cdot 1/5\ H_2O$: C, 70.14; H, 4.47; N, 5.45. Found: C, 70.03; H, 4.43; N, 5.59. IR (KBr): 1686, 1660, 1598, 1578, 1494, 1352, 1306, 1274, 1250, 1162, 1022, 750 cm^{-1}. ^1H-NMR δ: 2.928 (3H, s, C_4-CH_3), 4.008 (3H, s, OCH_3), 7.317 (1H, dd, J = 8.9, 2.6 Hz, C_7-H), 7.508 (1H, d, J = 4.6 Hz, C_3-H), 7.773 (1H, d, J = 2.6 Hz, C_9-H), 8.222 (1H, d, J = 8.9 Hz, C_6-H), 8.895 (1H, d, J = 4.6 Hz, C_2-H).

25: mp 214-217°C (CH_2Cl_2-ether). MS *m/z* (%): 253 (M^+, 100), 225 (29), 222 (39). *Anal.* Calcd for $C_{15}H_{11}NO_3 \cdot 1/10\ H_2O$: C, 70.64; H, 4.43; N, 5.49. Found: C, 70.72; H, 4.41; N, 5.46. IR (KBr): 1674, 1594, 1580, 1494, 1314, 1300, 1272, 1232, 1084, 1018, 978, 862, 750 cm^{-1}. ^1H-NMR δ: 2.915 (3H, s, C_4-CH_3), 3.999 (3H, s, OCH_3), 7.292 (1H, dd, J = 8.6, 2.6 Hz, C_8-H), 7.490 (1H, d, J = 4.9 Hz, C_3-H), 7.690 (1H, d, J = 2.6 Hz, C_6-H), 8.328 (1H, d, J = 8.6 Hz, C_9-H), 8.908 (1H, d, J = 4.9 Hz, C_2-H).

8-Methoxy-4-methyl-1,4-dihydrobenzo[*g*]quinoline-5,10-dione (17), 1-(Dimethylamino)-8-methoxy-4-methyl-1,4-dihydrobenzo[*g*]quinoline-5,10-dione (18) and 8-Methoxy-4-methylbenzo[*g*]quinoline-5,10-dione (20) from 2-Bromo-7-methoxy-1,4-naphthoquinone (15) and 2-Butenal Dimethylhydrazone (9)

(a) Aza-diene **9** (350 mg, 3.1 mmol) was added to a solution of **15** (80 mg, 0.3 mmol) in CH_3CN (3 ml). The solution was refluxed for 4 h, and then evaporated. The residue was purified by column chromatography (CH_2Cl_2) to give **17** (43 mg, 56%), **18** (7.7 mg, 8.6%) and **20** (16 mg, 21%).

17: mp 149-152°C (ether-hexane). MS *m/z* (%): 255 (M^+, 8), 240 (100). *Anal.* Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.31; H, 5.16; N, 5.44. IR (KBr): 3352, 1678, 1654, 1618, 1594, 1572, 1478, 1444, 1372, 1338, 1322, 1266, 1194, 1030, 750, 734 cm^{-1}. ^1H-NMR δ: 1.118 (3H, d, J = 6.6 Hz, C_4-CH_3), 3.7-3.8 (1H, m, C_4-H), 3.921 (3H, s, OCH_3), 4.9-5.0 (1H, m, C_3-H), 6.163 (1H, dd, J = 7.6, 4.3 Hz, C_2-H), 6.72 (1H, br, NH), 7.181 (1H, dd, J = 8.6, 2.6 Hz, C_7-H), 7.480 (1H, d, J = 2.6 Hz, C_9-H), 8.029 (1H, d, J = 8.6 Hz, C_6-H).

18: mp 90-91°C (hexane). MS *m/z* (%): 298 (M^+, 9), 283 (26), 240 (100). High-resolution MS Calcd for $C_{17}H_{18}N_2O_3$: 298.1317. Found: 298.1317. IR (KBr): 2952, 2920, 1680, 1656, 1630, 1600, 1584, 1560, 1456, 1382, 1352, 1338, 1286, 1232, 744 cm^{-1}. ^1H-NMR δ: 1.171 (3H, d, J = 6.6 Hz, C_4-CH_3), 2.727 (6H, s, $N(CH_3)_2$), 3.699 (1H, dq, J = 5.3, 6.6 Hz, C_4-H), 3.904 (3H, s, OCH_3), 5.191 (1H, dd, J = 7.9, 5.3 Hz, C_3-H), 6.251 (1H, d, J = 7.9 Hz, C_2-H), 7.132 (1H, dd, J = 8.6, 2.6 Hz, C_7-H), 7.451 (1H, d, J = 2.6 Hz, C_9-H), 7.964 (1H, d, J = 8.6 Hz, C_6-H).

(b) Manganese(IV) oxide (643 mg, 7.4 mmol) was added to a solution of **17** (31 mg, 0.12 mmol) in $CHCl_3$ (5 ml). The mixture was stirred at 25°C for 15 h, and then filtered. The filtrate was evaporated and the residue was purified by flash chromatography (ethyl acetate-hexane, 2:1) to give **20** (28 mg, 91%).

(c) Palladium on carbon (10%, 60 mg) was added to a solution of **18** (30 mg, 0.1 mmol) in toluene (3 ml). The mixture was refluxed for 6 h, and then filtered. The filtrate was evaporated and the residue was purified by flash chromatography (CH_2Cl_2) to give **20** (23 mg, 90%).

7-Methoxy-4-methyl-1,4-dihydrobenzo[*g*]quinoline-5,10-dione (22), 1-(Dimethylamino)-7-methoxy-4-methyl-1,4-dihydrobenzo[*g*]quinoline-5,10-dione (23) and 7-Methoxy-4-methylbenzo[*g*]quinoline-5,10-

dione (25) from 2-Bromo-6-methoxy-1,4-naphthoquinone (16) and 2-Butenal Dimethylhydrazone (9) (a) Aza-diene **9** (224 mg, 2 mmol) was added to a solution of **16** (53 mg, 0.2 mmol) in CH_3CN (5 ml). The solution was refluxed for 1 h, and then evaporated. The residue was purified by column chromatography (CH_2Cl_2-hexane, 3:7-1:1, then CH_2Cl_2-ethyl acetate, 49:1-24:1) to give **22** (8.4 mg, 17%), **23** (23 mg, 39%) and **25** (11 mg, 22%).

22: mp 156-159°C (ether-hexane). MS *m/z* (%): 255 (M^+, 8), 240 (100). *Anal.* Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.46; H, 5.13; N, 5.45. IR (KBr): 3348, 1672, 1646, 1620, 1580, 1486, 1448, 1366, 1344, 1322, 1288, 1254, 1186, 1146, 1064, 1024, 754, 734 cm^{-1}. ^1H-NMR δ: 1.196 (3H, d, J = 6.9 Hz, C_4-CH_3), 3.7-3.8 (1H, m, C_4-H), 3.947 (3H, s, OCH_3), 4.9-5.0 (1H, m, C_3-H), 6.161 (1H, dd, J = 7.6, 4.3 Hz, C_2-H), 6.85 (1H, br, NH), 7.067 (1H, dd, J = 8.6, 2.6 Hz, C_8-H), 7.571 (1H, d, J = 2.6 Hz, C_6-H), 7.973 (1H, d, J = 8.6 Hz, C_9-H).

23: mp 108-109°C (hexane). MS *m/z* (%): 298 (M^+, 14), 283 (36), 240 (100). High-resolution MS Calcd for $C_{17}H_{18}N_2O_3$: 298.1317. Found: 298.1314. IR (KBr): 2924, 2856, 1672, 1660, 1626, 1600, 1586, 1554, 1468, 1386, 1350, 1300, 1292, 1278, 1228, 1118, 736 cm^{-1}. ^1H-NMR δ: 1.165 (3H, d, J = 6.6 Hz, C_4-CH_3), 2.729 (6H, s, $N(CH_3)_2$), 3.709 (1H, dq, J = 5.3, 6.6 Hz, C_4-H), 3.924 (3H, s, OCH_3), 5.213 (1H, dd, J = 7.6, 5.3 Hz, C_3-H), 6.260 (1H, d, J = 7.6 Hz, C_2-H), 7.091 (1H, dd, J = 8.6, 2.6 Hz, C_8-H), 7.491 (1H, d, J = 2.6 Hz, C_6-H), 7.929 (1H, d, J = 8.6 Hz, C_9-H).

(b) Manganese(IV) oxide (130 mg, 1.5 mmol) was added to a solution of **22** (13 mg, 0.05 mmol) in $CHCl_3$ (2 ml). The mixture was stirred at 25°C for 2 h, and then filtered. The filtrate was evaporated and the residue was purified by flash chromatography (CH_2Cl_2-ethyl acetate, 19:1) to give **25** (11 mg, 85%).

(c) Palladium on carbon (10%, 60 mg) was added to a solution of **23** (30 mg, 0.1 mmol) in toluene (3 ml). The mixture was refluxed for 6 h, and then filtered. The filtrate was evaporated and the residue was purified by flash chromatography (CH_2Cl_2-ethyl acetate, 19:1) to give **25** (16 mg, 63%).

Eupomatidine 1 (1) and 10-Methoxynaphtho[1,2,3-*ij*][2,7]naphthyridin-7(7*H*)-one (27) A suspension of **20** (or **25**) (34 mg, 0.13 mmol) in dry DMF (0.6 ml) and DMF diethyl acetal (59 mg, 0.4 mmol) under N_2 was heated at 120°C for 30 min. Ammonium chloride (450 mg, 8.4 mmol) and acetic acid (1.5 ml) were added, and the mixture was heated at 110°C for 30 min. After cooling, the mixture was diluted with water (20 ml) and extracted with $CHCl_3$ (3 x 20 ml). The extract was washed with water (30 ml), dried and evaporated. The residue was purified by flash chromatography (ethyl acetate-CH_2Cl_2, 1:49-1:24 (or 1:9-1:4)) to give **1** (32 mg, 91%) (or **27**, 18 mg, 51%) as a yellow solid.

1: mp 228-231°C (CH_3OH) [lit.,[2] mp 195-197°C]. MS *m/z* (%): 262 (M^+, 100), 232 (11), 191 (22). High-resolution MS Calcd for $C_{16}H_{10}N_2O_2$: 262.0742. Found: 262.0728. IR (KBr): 1674, 1602, 1496, 1404, 1380, 1350, 1282, 1022, 838 cm^{-1}. UV (C_2H_5OH) λ_{max} nm (log ε): 216 (4.48), 221 (4.48), 231 (4.42), 261 (4.26), 286 (4.25), 350 (3.52), 437 (3.76). ^1H-NMR δ: 4.015 (3H, s, OCH_3), 7.372 (1H, dd, J = 8.9, 2.6 Hz, C_{10}-H), 7.665 (1H, d, J = 5.9 Hz, C_3-H), 7.916 (1H, d, J = 5.6 Hz, C_4-H), 7.916 (1H, d, J = 2.6 Hz, C_8-H), 8.779 (1H, d, J = 8.9 Hz, C_{11}-H), 8.838 (1H, d, J = 5.9 Hz, C_2-H), 9.134 (1H, d, J = 5.6 Hz, C_5-H).

27: mp 272-274°C (CH_2Cl_2-ether). MS *m/z* (%): 262 (M^+, 100), 232 (36), 191 (18). High-resolution MS Calcd for $C_{16}H_{10}N_2O_2$: 262.0742. Found: 262.0733. IR (KBr): 1658, 1592, 1374, 1352, 1286, 1274, 1234, 1220, 1024, 868 cm^{-1}. ^1H-NMR δ: 4.070 (3H, s, OCH_3), 7.200 (1H, dd, J = 8.6, 2.6 Hz, C_9-H), 7.751 (1H, d, J = 5.9 Hz, C_3-H), 7.907 (1H, d, J = 5.6 Hz, C_4-H), 8.346 (1H, d, J = 2.6 Hz, C_{11}-H), 8.438 (1H, d, J = 8.6 Hz, C_8-H), 8.884 (1H, d, J = 5.9 Hz, C_2-H), 9.133 (1H, d, J = 5.6 Hz, C_5-H).

6,8-Dimethoxy-4-methylbenzo[*h*]quinoline (30) Methyl vinyl ketone (490 mg, 7 mmol), *m*-nitrobenzenesulfonic acid (366 mg, 1.8 mmol), zinc chloride (34 mg, 0.25 mmol) and concentrated HCl (0.4 ml) were added to a solution of 4,6-dimethoxy-1-naphthylamine (**29**, 203 mg, 1 mmol) in ethanol (24 ml). The mixture was refluxed for 1 h, and then evaporated. After the addition of water (60 ml), the mixture was neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (3 x 40 ml). The extract was washed with water (60 ml), dried and evaporated. The residue was purified by flash chromatography (ethyl acetate-hexane, 1:4) to give **30** (136 mg, 54%). mp 130-131°C (colorless needles from ether-hexane). MS *m/z* (%): 253 (M^+, 100), 238 (21), 210 (44). *Anal.* Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.94; H, 5.99; N, 5.51. IR (KBr): 1606, 1520, 1452, 1438, 1422, 1264, 1252, 1230, 1204, 1178, 1068, 1028, 830 cm^{-1}. ^1H-NMR δ: 2.701 (3H, s, C_4-CH_3), 4.001 (3H, s, OCH_3), 4.130 (3H, s, OCH_3), 7.017 (1H, s, C_5-H), 7.259 (1H, d, J = 4.6 Hz, C_3-H), 7.358 (1H, dd, J = 9.2, 2.6 Hz, C_9-H), 7.687 (1H, d, J = 2.6 Hz, C_7-H), 8.680 (1H, d, J = 4.6 Hz, C_2-H), 9.167 (1H, d, J = 9.2 Hz, C_{10}-H).

8-Methoxy-4-methylbenzo[*h*]quinoline-5,6-dione (31) Fuming nitric acid (2.0 ml) was added dropwise to a solution of **30** (126 mg, 0.5 mmol) in acetic acid (5 ml) at 20-25°C and the solution was heated at 40-50°C for 1.5 h. After cooling, the solution was diluted with water (70 ml), neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (3 x 70 ml). The extract was washed with water (100 ml), dried and evaporated. The residue was purified by flash chromatography (ethyl acetate-hexane, 1:3) to give **31** (31 mg, 25%). Further elution with ethyl acetate-hexane (7:3) afforded 6,8-dimethoxy-4-methyl-7-nitrobenzo[*h*]quinoline (**31'**) (87 mg, 59%).

31: mp 200-203°C (red needles from CH_2Cl_2-hexane). MS *m/z* (%): 253 (M^+, 41), 225 (100), 210 (50), 182 (22). *Anal.* Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.25; H, 4.44; N, 5.55. IR (KBr): 1678, 1602, 1586, 1568, 1552, 1456, 1434, 1394, 1380, 1298, 1230, 1020, 820, 756 cm^{-1}. ^1H-NMR δ: 2.740 (3H, s, C_4-CH_3), 3.937 (3H, s, OCH_3), 7.125 (1H, d, J = 5.3 Hz, C_3-H), 7.306 (1H, dd, J = 8.9, 2.6 Hz, C_9-H), 7.599 (1H, d, J = 2.6 Hz, C_7-H), 8.617 (1H, d, J = 5.3 Hz, C_2-H), 8.620 (1H, d, J = 8.9 Hz, C_{10}-H).

31': mp 235-236°C (pale yellow needles from CH_2Cl_2-ether). MS *m/z* (%): 298 (M^+, 100), 252 (16). *Anal.* Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.17; H, 4.74; N, 9.28. IR (KBr): 1622, 1612, 1530, 1470, 1454, 1432, 1372, 1294, 1276, 1258, 1238, 1146, 1070, 846, 834, 786 cm^{-1}. ^1H-NMR δ: 2.699 (3H, s, C_4-CH_3), 4.014 (3H, s, OCH_3), 4.063 (3H, s, OCH_3), 7.100 (1H, s, C_5-H), 7.328 (1H, d, J = 4.3 Hz, C_3-H), 7.500 (1H, d, J = 9.2 Hz, C_9-H), 8.709 (1H, d, J = 4.3 Hz, C_2-H), 9.447 (1H, d, J = 9.2 Hz, C_{10}-H).

Eupomatidine 1 (1) from 31 A suspension of **31** (25 mg, 0.1 mmol) in dry toluene (6 ml) and DMF diethyl acetal (59 mg, 0.4 mmol) under N_2 was heated at 100°C for 1.5 h. Ammonium chloride (16 mg, 0.3 mmol) and acetic acid (0.2 ml) were added, and the mixture was heated at 100°C for 1 h. After cooling, the mixture was diluted with water (15 ml) and extracted with $CHCl_3$ (3 x 15 ml). The extract was washed with water (30 ml), dried and evaporated. The residue was purified by flash chromatography (CH_2Cl_2) to give **1** (16 mg, 62%).

Sampangine (4) A solution of **32** (100 mg, 0.45 mmol) in dry toluene (4 ml) and DMF diethyl acetal (345 mg, 2.34 mmol) under N_2 was heated at 100°C for 1 h. Ammonium chloride (460 mg, 8.6 mmol) and acetic acid (1.6 ml) were added, and the mixture was heated at 100°C for 15 min. After cooling, the mixture was basified with ammonia solution and extracted with $CHCl_3$ (3 x 100 ml). The extract was washed with water (150 ml), dried and evaporated. The residue was purified by flash chromatography (ethyl acetate) to give **4** (56 mg, 54%) as a yellow solid. mp 228-231°C (CH_2Cl_2-ether) [lit.,[3] mp 210°C]. MS *m/z* (%): 232 (M^+, 100),

204 (51). High-resolution MS Calcd for $C_{15}H_8N_2O$: 232.0637. Found: 232.0640. IR (KBr): 1670, 1612, 1594, 1574, 1404, 1384, 1274, 1228, 954, 870, 788, 754, 720, 594 cm^{-1}. ^1H-NMR δ: 7.656 (1H, td, J = 7.6, 1.3 Hz, C_9-H), 7.667 (1H, d, J = 5.9 Hz, C_3-H), 7.785 (1H, td, J = 7.6, 1.3 Hz, C_{10}-H), 7.886 (1H, d, J = 5.6 Hz, C_4-H), 8.403 (1H, dd, J = 7.6, 1.3 Hz, C_8-H), 8.718 (1H, dd, J = 7.6, 1.3 Hz, C_{11}-H), 8.802 (1H, d, J = 5.9 Hz, C_2-H), 9.088 (1H, d, J = 5.6 Hz, C_5-H).

3,8-Dimethoxy-4-methylbenzo[*g*]quinoline-5,10-dione (21) and 3,7-Dimethoxy-4-methylbenzo[*g*]-quinoline-5,10-dione (26) (a) A solution of **10** (142 mg, 1 mmol) in $CHCl_3$ (2 ml) was added to a solution of **14** (94 mg, 0.5 mmol) in $CHCl_3$ (2 ml). After stirring at 25°C for 2 h, the solution was subjected to flash chromatography (CH_2Cl_2) to give an approximately 4:1 mixture of **19** and **24** (99 mg, 70%) as a deep blue oil. Manganese(IV) oxide (304 mg, 3.5 mmol) was added to a solution of the isomeric mixture in $CHCl_3$ (20 ml). The whole was stirred at 25°C for 1.5 h, and then filtered. The filtrate was evaporated and the residue was purified by flash chromatography (ethyl acetate-CH_2Cl_2, 1:4) to give **21** (60 mg, 42% from **14**) and **26** (13 mg, 9.2% from **14**) as a pale yellow solid, respectively.

19: ^1H-NMR δ: 1.266 (3H, d, J = 6.6 Hz, C_4-CH_3), 3.607 (3H, s, C_3-OCH_3), 3.915 (3H, s, C_8-OCH_3), 3.948 (1H, q, J = 6.6 Hz, C_4-H), 5.652 (1H, d, J= 5.0 Hz, C_2-H), 6.60 (1H, br, NH), 7.181 (1H, dd, J = 8.6, 2.6 Hz, C_7-H), 7.472 (1H, d, J = 2.6 Hz, C_9-H), 8.043 (1H, d, J = 8.6 Hz, C_6-H).

24: ^1H-NMR δ: 1.276 (3H, d, J = 6.6 Hz, C_4-CH_3), 3.615 (3H, s, C_3-OCH_3), 3.947 (3H, s, C_7-OCH_3), 3.955 (1H, q, J = 6.6 Hz, C_4-H), 5.652 (1H, d, J= 5.0 Hz, C_2-H), 6.77 (1H, br, NH), 7.044 (1H, dd, J = 8.6, 2.6 Hz, C_8-H), 7.595 (1H, d, J = 2.6 Hz, C_6-H), 7.965 (1H, d, J = 8.6 Hz, C_9-H).

21: mp 285-288°C (decomp.) (CH_2Cl_2-ether). MS *m/z* (%): 283 (M^+, 100), 268 (22). *Anal.* Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.78; H, 4.66; N, 4.87. IR (KBr): 1680, 1656, 1598, 1564, 1468, 1440, 1298, 1206, 1102, 1016, 952, 752 cm^{-1}. ^1H-NMR δ: 2.779 (3H, s, C_4-CH_3), 3.998 (3H, s, OCH_3), 4.098 (3H, s, OCH_3), 7.283 (1H, dd, J = 8.6, 2.6 Hz, C_7-H), 7.762 (1H, d, J = 2.6 Hz, C_9-H), 8.201 (1H, d, J = 8.6 Hz, C_6-H), 8.618 (1H, s, C_2-H).

26: mp 266-269°C (CH_2Cl_2-ether). MS *m/z* (%): 283 (M^+, 100), 252 (24). *Anal.* Calcd for $C_{16}H_{13}NO_4 \cdot 1/10$ H_2O: C, 67.41; H, 4.67; N, 4.91. Found: C, 67.16; H, 4.54; N, 4.82. IR (KBr): 1676, 1598, 1564, 1470, 1348, 1298, 1276, 1126, 1016, 970, 912, 844 cm^{-1}. ^1H-NMR δ: 2.773 (3H, s, C_4-CH_3), 3.990 (3H, s, OCH_3), 4.101 (3H, s, OCH_3), 7.275 (1H, dd, J = 8.6, 2.6 Hz, C_8-H), 7.673 (1H, d, J = 2.6 Hz, C_6-H), 8.308 (1H, d, J = 8.6 Hz, C_9-H), 8.644 (1H, s, C_2-H).

(b) A solution of **10** (142 mg, 1 mmol) in $CHCl_3$ (1 ml) was added to a solution of **15** (or **16**) (53 mg, 0.2 mmol) in $CHCl_3$ (3 ml). The solution was stirred at 25°C for 2 h, and then evaporated. The residue was purified by flash chromatography (ethyl acetate-$CHCl_3$, 1:9-1:4) to give **21** (18 mg, 32%) (or **26**, 30 mg, 53%).

Eupomatidine 3 (3) and 4,10-Dimethoxynaphtho[1,2,3-*ij*][2,7]naphthyridin-7(7*H*)-one (28) A suspension of **21** (or **26**) (20 mg, 0.07 mmol) in dry DMF (0.6 ml) and DMF diethyl acetal (41 mg, 0.28 mmol) under N_2 was heated at 120°C for 30 min. Ammonium chloride (450 mg, 8.4 mmol) and acetic acid (1.5 ml) were added, and the mixture was heated at 110°C for 30 min. After cooling, the mixture was diluted with water (20 ml) and extracted with $CHCl_3$ (3 x 20 ml). The extract was washed with water (30 ml), dried and evaporated. The residue was purified by flash chromatography (ethyl acetate-CH_2Cl_2, 3:17 (or 3:7)) to give **3** (14 mg, 68%) (or **28**, 13 mg, 63%) as a yellow solid.

3: mp 278-281°C (decomp.) (CH_2Cl_2-CH_3OH) [lit.,[2] mp 245-248°C (decomp.)]. MS *m/z* (%): 292 (M^+, 100), 262 (14), 249 (21). High-resolution MS Calcd for $C_{17}H_{12}N_2O_3$: 292.0848. Found: 272.0845. IR

(KBr): 1672, 1600, 1574, 1502, 1436, 1410, 1378, 1322, 1288, 1240, 1098, 1030, 992, 954, 826 cm^{-1}. UV (C_2H_5OH) λ_{max} nm (log ε): 218 (4.34), 229 (4.31), 247 (4.42), 269 (4.10), 284 (4.12), 324 (3.67), 335 (3.75), 381 (3.86), 418 (3.87). ^{1}H-NMR δ: 4.008 (3H, s, C_9-OCH_3), 4.244 (3H, s, C_4-OCH_3), 7.346 (1H, dd, J = 8.9, 2.6 Hz, C_{10}-H), 7.925 (1H, d, J = 2.6 Hz, C_8-H), 7.941 (1H, d, J = 5.9 Hz, C_3-H), 8.651 (1H, s, C_5-H), 8.780 (1H, d, J = 8.9 Hz, C_{11}-H), 8.834 (1H, d, J = 5.9 Hz, C_2-H).

28: mp 282-285°C (decomp.) (ethyl acetate-ether). MS *m/z* (%): 292 (M^+, 100), 262 (29). High-resolution MS Calcd for $C_{17}H_{12}N_2O_3$: 292.0848. Found: 272.0849. IR (KBr): 1664, 1594, 1572, 1502, 1466, 1454, 1402, 1374, 1328, 1250, 1026, 992, 924 cm^{-1}. ^{1}H-NMR δ: 4.056 (3H, s, C_{10}-OCH_3), 4.238 (3H, s, C_4-OCH_3), 7.182 (1H, dd, J = 8.9, 2.6 Hz, C_9-H), 8.024 (1H, d, J = 5.9 Hz, C_3-H), 8.348 (1H, d, J = 2.6 Hz, C_{11}-H), 8.428 (1H, d, J = 8.9 Hz, C_8-H), 8.642 (1H, s, C_5-H), 8.872 (1H, d, J = 5.9 Hz, C_2-H).

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