Synthesis of 5,8- and 5,6-Quinolinediones Using Oxidative Demethylation with Cerium(IV) Ammonium Nitrate

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4-Phenyl-5,8-quinolinediones (7, 8, 12, 13), 4-phenyl-5,6-quinolinediones (9, 14), and 2-dialkylamino-4-phenyl-5,8-quinolinediones (17, 18), were synthesized by oxidative demethylation of the corresponding 5,8-dimethoxy- or 5,6,8-trimethoxy-4-phenylquinolines with cerium(IV) ammonium nitrate. Sulfur-containing quinolinequinones (21, 24) were prepared by oxidation of the corresponding 5,8-dimethoxy- or 5,6,8-trimethoxy-2(1H)-quinolinethiones (20, 23).

Key words quinolinequinone; oxidative demethylation; cerium(IV) ammonium nitrate

Streptonigrin, a highly substituted 5,8-quinolinedione, is one of the most potent inhibitors of avian myeloblastosis virus reverse transcriptase (AMV-RT), and the 7-amino-6-methoxy-5,8-quinolinedione moiety of streptonigrin is the minimum structure for inhibition of AMV-RT.¹⁾ Reverse transcriptase is considered to be an excellent target for the chemotherapy of retroviral diseases, such as human acquired immunodeficiency syndrome (AIDS). We observed that 6-methoxy-5,8-quinolinediones and 8-methoxy-5,6-quinolinediones were as potent (as inhibitors of AMV-RT) as streptonigrin, and much less toxic.²⁾ We also prepared various quinolinequinones, 2(1H)-quinolinequinones, and isoquinolinequinones by oxidative demethylation of the corresponding 5,8-dimethoxy- or 5,6,8-trimethoxy(iso)quinolines with cerium(IV) ammonium nitrate (CAN) or silver(II) oxide, and examined their inhibitory activities.^{2b,3)} Here we report the synthesis of 4-phenylquinolinequinones and sulfur-containing quinolinequinones by oxidative demethylation of 4-phenylquinolines and 2(1H)-quinolinethiones.

4-Phenyl-5,8-quinolinediones (**7, 8, 12, 13, 17, 18**) and 4-phenyl-5,6-quinolinediones (**9, 14**) were prepared from 4-phenyl-2(1H)-quinolinones (**1, 2**).^{3c)} 4-Phenyl-2-trifluoromethanesulfonyloxyquinolines (**3, 4**), prepared from 2(1H)-quinolinones (**1, 2**), were reduced with triethylammonium formate in the presence of palladium acetate and 1,1'-bis(diphenylphosphino)ferrocene (DPPF)⁴⁾ to afford the 2-unsubstituted quinolines (**5, 6**) in 88—99% yields. 2-Chloro-4-phenylquinolines (**10, 11**) prepared by chlorination of the 2(1H)-quinolinones (**1, 2**) with phosphorus oxychloride, were treated with cyclic secondary amines (piperidine, pyrrolidine, morpholine, 1-methylpiperazine) to afford 2-dialkylaminoquinolines (**15, 16**) in 94—99% yields.

Oxidative demethylation of 5,8-dimethoxy-4-phenylquinolines (**5, 10, 15**) with CAN in acetonitrile-water at 0—5 °C furnished the corresponding *p*-quinones (**7, 12, 17**) in 45—94% yields. Treatment of 5,6,8-trimethoxy-4-phenylquinolines (**6, 11**) with CAN furnished *p*-quinones (**8, 13; 24—33% yields**) and *o*-quinones (**9, 14; 24—75% yields**). In contrast, 2-dialkylamino-5,6,8-trimethoxy-4-phenylquinolines (**16**) were oxidized with CAN to furnish exclusively *p*-quinones (**18**) in 43—87% yields.

Sulfur-containing quinolinequinones (**21, 24**) were pre-

pared from 2(1H)-quinolinones (**19, 22**).^{3c)} Treatment of **19** (or **22**) with Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) in 1,2-dimethoxyethane afforded the corresponding 2(1H)-quinolinethiones (**20, 23**) in 91—99% yields. Oxidative demethylation of *N*-unsubstituted 2(1H)-quinolinethiones (**20**) with CAN in acetonitrile-water at 0—5 °C furnished "dimeric" quinones (**21**) in 56—76% yields. The *N*-methyl-2(1H)-quinolinethione (**23a**) was oxidatively demethylated with CAN to afford the expected quinone (**24a**) in 15% yield. However, attempted oxidation of **23b** with CAN failed, giving a complex mixture. The quinone (**24b**) was obtained by oxidative demethylation of **23b** with silver(II) oxide-nitric acid⁵⁾ in 49% yield.

Analytical and spectral data for the quinones (**7—9, 12—14, 17, 18, 21, 24**) are given in Table I. These quinones showed no activity against human immunodeficiency virus.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ¹H-NMR spectra were measured at 270 MHz in CDCl₃ with tetramethylsilane as an internal standard. 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 chromatography (flash chromatography) was performed with Silica gel 60 (230—400 mesh).

2-Trifluoromethanesulfonyloxy-4-phenylquinolines (3, 4) Trifluoromethanesulfonic anhydride (0.1 ml, 0.6 mmol) was added to a solution of 4-phenyl-2(1H)-quinolinone (**1, 2**) (0.5 mmol) in dry CH₂Cl₂ (10 ml) containing triethylamine (0.2 ml, 1.4 mmol) at 0—5 °C. The mixture was stirred at 0—5 °C for 30 min, poured into ice-water (20 ml), and extracted with CH₂Cl₂ (3 × 20 ml). The extract was washed with water, dried, and evaporated. The residue was chromatographed (eluting with CH₂Cl₂ or ethyl acetate-hexane (1:19)) to afford **3** (or **4**).

3: Yield 99%. mp 119—121 °C (ether). MS *m/z* (%): 413 (M⁺, 100), 280 (71), 264 (16). Anal. Calcd for C₁₈H₁₄F₃NO₅S: C, 52.30; H, 3.41; N, 3.39. Found: C, 52.34; H, 3.44; N, 3.34. ¹H-NMR δ: 3.46 (3H, s, C₅-OCH₃), 4.04 (3H, s, C₈-OCH₃), 6.84 (1H, d, *J* = 8.6 Hz, C₆-H), 7.09 (1H, s, C₃-H), 7.12 (1H, d, *J* = 8.6 Hz, C₇-H), 7.25—7.45 (5H, m, C₆H₅).

4: Yield 99%. mp 73—74 °C (ether-hexane). MS *m/z* (%): 457 (M⁺, 100), 442 (43), 324 (53). Anal. Calcd for C₂₀H₁₈F₃NO₆S: C, 52.52; H, 3.97; N, 3.06. Found: C, 52.44; H, 3.95; N, 3.01. ¹H-NMR δ: 2.41 (3H, s, C₇-CH₃), 3.19 (3H, s, C₅-OCH₃), 3.87 (3H, s, C₆-OCH₃), 4.07 (3H, s, C₈-OCH₃), 6.97 (1H, s, C₃-H), 7.3—7.5 (5H, m, C₆H₅).

4-Phenylquinolines (5, 6) Formic acid (0.11 ml, 3 mmol) was added to a mixture of **3** (or **4**) (0.5 mmol), triethylamine (0.56 ml, 4 mmol), palladium acetate (30 mg, 0.13 mmol), and DPPF (140 mg, 0.25 mmol)

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Chart 1

in *N,N*-dimethylformamide (5 ml). The mixture was stirred at 25 °C for 1 h, and then at 60 °C for 2 h. The reaction mixture was diluted with 1% $NaHCO_3$ solution (30 ml), and extracted with CH_2Cl_2 (3 × 20 ml). The extract was washed with water, dried and evaporated. The residue was chromatographed (eluting with CH_2Cl_2 -ethyl acetate (19:1) or ethyl acetate-hexane (1:4)) to afford **5** (or **6**).

5: Yield 99%. mp 177–178 °C (CH_2Cl_2 -ether). MS m/z (%): 265 (M^+ , 69), 250 (100), 236 (16), 220 (20). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.90; H, 5.73; N, 5.23. 1H -NMR δ : 3.45 (3H, s, C_5 -OCH₃), 4.08 (3H, s, C_8 -OCH₃), 6.77 (1H, d, $J = 8.6$ Hz, C_6 -H), 7.00 (1H, d, $J = 8.6$ Hz, C_7 -H), 7.24 (1H, d, $J = 4.3$ Hz, C_3 -H),

7.25–7.45 (5H, m, C_6H_5), 8.91 (1H, d, $J = 4.3$ Hz, C_2 -H).

6: Yield 88%. mp 104–105 °C (hexane). MS m/z (%): 309 (M^+ , 51), 294 (100). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.53; H, 6.21; N, 4.48. 1H -NMR δ : 2.43 (3H, s, C_7 -CH₃), 3.19 (3H, s, C_5 -OCH₃), 3.87 (3H, s, C_6 -OCH₃), 4.07 (3H, s, C_8 -OCH₃), 7.13 (1H, d, $J = 4.3$ Hz, C_3 -H), 7.3–7.5 (5H, m, C_6H_5), 8.82 (1H, d, $J = 4.3$ Hz, C_2 -H).

2-Chloro-4-phenylquinolines (10, 11) A mixture of 4-phenyl-2(1H)-quinolinone (**1**, **2**) (1 mmol) and phosphorus oxychloride (2 ml, 21.5 mmol) was heated at 60–70 °C for 30 min. The reaction mixture was cooled, poured into ice-water (50 ml), neutralized with $NaHCO_3$, and

Table 1. Analytical and Spectral Data for Quinolinequinones (7—9, 12—14, 17, 18, 21, 24)

	Yield (%)	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis or HRMS ^{a)} Calcd (Found)			MS <i>m/z</i> (%)	IR (KBr) $\nu_{\text{C=O}}$ (cm ⁻¹)	¹ H-NMR (270 MHz) δ (CDCl ₃ , <i>J</i> =Hz)
					C	H	N			
7	74	Orange prisms (CH ₂ Cl ₂ -ether)	135—138	C ₁₅ H ₉ NO ₂	76.59 (76.55)	3.86 3.94	5.95 5.79	235 (M ⁺ , 85) 234 (100) 206 (21)	1666	6.93, 7.13 (each 1H, d, <i>J</i> =10.2, C ₆ -H, C ₇ -H), 7.25—7.55 (6H, m, C ₃ -H, C ₆ H ₅), 9.01 (1H, d, <i>J</i> =5.0, C ₂ -H)
8	33	Yellow plates (ethyl acetate-ether)	172—176	C ₁₇ H ₁₃ NO ₃	73.11 (72.88)	4.69 4.75	5.02 4.93	279 (M ⁺ , 100) 264 (28) 249 (30)	1672 1652	2.15 (3H, s, C ₇ -CH ₃), 4.01 (3H, s, OCH ₃), 7.25—7.55 (5H, m, C ₆ H ₅), 7.42 (1H, d, <i>J</i> =5.0, C ₃ -H), 8.94 (1H, d, <i>J</i> =5.0, C ₂ -H)
9	24	Orange needles (ether-hexane)	154—155	C ₁₇ H ₁₃ NO ₃	73.11 (72.97)	4.69 4.75	5.02 4.89	279 (M ⁺ , 12) 251 (74) 250 (55) 222 (100)	1700 1656	2.10 (3H, s, C ₇ -CH ₃), 4.20 (3H, s, OCH ₃), 7.2—7.5 (6H, m, C ₃ -H, C ₆ H ₅), 8.93 (1H, d, <i>J</i> =5.3, C ₂ -H)
12	94	Yellow plates (CH ₂ Cl ₂ -hexane)	176—177	C ₁₅ H ₈ ClNO ₂	66.81 (66.46)	2.99 2.76	5.19 5.17	271 (M ⁺ + 2, 34) 269 (M ⁺ , 71) 268 (100)	1666	6.93, 7.13 (each 1H, d, <i>J</i> =10.2, C ₆ -H, C ₇ -H), 7.54 (1H, s, C ₃ -H), 7.25—7.55 (5H, m, C ₆ H ₅)
13	24	Yellow needles (CH ₂ Cl ₂ -hexane)	166—169	C ₁₇ H ₁₂ ClNO ₃	65.08 (64.93)	3.86 3.88	4.46 4.40	315 (M ⁺ + 2, 35) 313 (M ⁺ , 100) 300 (11), 298 (32) 286 (17), 284 (44)	1668	2.13 (3H, s, C ₇ -CH ₃), 4.01 (3H, s, OCH ₃), 7.20—7.55 (6H, m, C ₃ -H, C ₆ H ₅)
14	75	Orange needles (ether)	162—163	C ₁₇ H ₁₂ ClNO ₃	65.08 (64.91)	3.86 4.06	4.46 4.32	315 (M ⁺ + 2, 3) 313 (M ⁺ , 7) 287 (26), 285 (76) 258 (37), 256 (100)	1696 1666	2.09 (3H, s, C ₇ -CH ₃), 4.21 (3H, s, OCH ₃), 7.2—7.5 (6H, m, C ₃ -H, C ₆ H ₅)
17a	45	Dark red prisms (CH ₂ Cl ₂ -hexane)	179—181 (dec.)	C ₂₀ H ₁₈ N ₂ O ₂ ·1/3H ₂ O	74.05 (73.93)	5.80 5.50	8.64 8.60	318 (M ⁺ , 100) 317 (79) 289 (29)	1678 1644	1.6—1.8 (6H, m, CH ₂ (CH ₂) ₃ CH ₂), 3.7—3.9 (4H, m, CH ₂ NCH ₂), 6.60 (1H, s, C ₃ -H), 6.71, 6.88 (each 1H, d, <i>J</i> =10.2, C ₆ -H, C ₇ -H), 7.2—7.5 (5H, m, C ₆ H ₅)
17b	48	Red prisms (CH ₂ Cl ₂ -hexane)	181—182	C ₁₉ H ₁₆ N ₂ O ₂	74.98 (74.85)	5.30 5.14	9.20 9.23	304 (M ⁺ , 100) 303 (67) 275 (64)	1676 1646	2.0—2.1 (4H, m, CH ₂ (CH ₂) ₂ CH ₂), 3.66 (4H, br s, CH ₂ NCH ₂), 6.38 (1H, s, C ₃ -H), 6.71, 6.88 (each 1H, d, <i>J</i> =10.3, C ₆ -H, C ₇ -H), 7.2—7.5 (5H, m, C ₆ H ₅)
17c	47	Red prisms (CH ₂ Cl ₂ -hexane)	177—178	C ₁₉ H ₁₆ N ₂ O ₃	71.23 (70.84)	5.03 4.85	8.74 8.70	320 (M ⁺ , 100) 319 (85) 263 (14)	1676 1650	3.82 (8H, br s, (CH ₂) ₂ O(CH ₂) ₂), 6.62 (1H, s, C ₃ -H), 6.74, 6.91 (each 1H, d, <i>J</i> =10.3, C ₆ -H, C ₇ -H), 7.2—7.5 (5H, m, C ₆ H ₅)
17d	71	Dark red prisms (CH ₂ Cl ₂ -hexane)	187—189	C ₂₀ H ₁₈ N ₃ O ₂ ·1/3H ₂ O	70.78 (70.69)	5.84 5.61	12.38 12.29	333 (M ⁺ , 100) 332 (42) 265 (37) 263 (37)	1674 1648	2.36 (3H, s, NCH ₃), 2.54 (4H, t, <i>J</i> =5.0, CH ₂ -N(CH ₃)-CH ₂), 3.85 (4H, t, <i>J</i> =5.0, CH ₂ NCH ₂), 6.62 (1H, s, C ₃ -H), 6.73, 6.90 (each 1H, d, <i>J</i> =10.3, C ₆ -H, C ₇ -H), 7.2—7.5 (5H, m, C ₆ H ₅)
18a	43	Dark red prisms (CH ₂ Cl ₂ -ether)	187—188	C ₂₂ H ₂₂ N ₂ O ₃ ·1/10H ₂ O	72.55 (72.43)	6.14 6.10	7.69 7.55	362 (M ⁺ , 100) 347 (78) 319 (19)	1660	1.6—1.8 (6H, m, CH ₂ (CH ₂) ₃ CH ₂), 2.05 (3H, s, C ₇ -CH ₃), 3.75—3.85 (4H, m, CH ₂ NCH ₂), 3.96 (3H, s, OCH ₃), 6.52 (1H, s, C ₃ -H), 7.2—7.5 (5H, m, C ₆ H ₅)
18b	55	Red needles (CH ₂ Cl ₂ -ether)	187—189	C ₂₁ H ₂₀ N ₂ O ₃	72.40 (72.05)	5.79 5.84	8.04 7.94	348 (M ⁺ , 100) 333 (70) 319 (22) 305 (29)	1648	1.95—2.10 (4H, m, CH ₂ (CH ₂) ₂ CH ₂), 2.05 (3H, s, C ₇ -CH ₃), 3.64 (4H, br s, CH ₂ NCH ₂), 3.95 (3H, s, OCH ₃), 6.29 (1H, s, C ₃ -H), 7.2—7.5 (5H, m, C ₆ H ₅)
18c	68	Red needles (CH ₂ Cl ₂ -hexane)	196—200	C ₂₁ H ₂₀ N ₂ O ₄	69.22 (69.00)	5.53 5.60	7.69 7.49	364 (M ⁺ , 100) 349 (50) 307 (48)	1664	2.06 (3H, s, C ₇ -CH ₃), 3.81 (8H, s, (CH ₂) ₂ O(CH ₂) ₂), 3.97 (3H, s, OCH ₃), 6.54 (1H, s, C ₃ -H), 7.2—7.5 (5H, m, C ₆ H ₅)
18d	87	Dark red prisms (ethyl acetate-ether)	192—193	C ₂₂ H ₂₃ N ₃ O ₃	70.01 (69.65)	6.14 6.14	11.13 10.99	377 (M ⁺ , 100) 362 (29) 307 (59)	1658	2.06 (3H, s, C ₇ -CH ₃), 2.35 (3H, s, NCH ₃), 2.51 (4H, t, <i>J</i> =5.0, CH ₂ -N(CH ₃)-CH ₂), 3.84 (4H, t, <i>J</i> =5.0, CH ₂ NCH ₂), 3.96 (3H, s, OCH ₃), 6.55 (1H, s, C ₃ -H), 7.2—7.5 (5H, m, C ₆ H ₅)
21a	76	Yellow needles (CHCl ₃ -hexane)	210	C ₁₈ H ₈ N ₂ O ₄ S ₂	379.9925 (379.9930)			380 (M ⁺ , 34) 191 (100)	1664	7.05, 7.14 (each 2H, d, <i>J</i> =10.2, 2C ₆ -H, 2C ₇ -H), 8.04 (2H, d, <i>J</i> =8.6, 2C ₃ -H), 8.32 (2H, d, <i>J</i> =8.6, 2C ₄ -H)
21b	56	Yellow needles (CHCl ₃ -hexane)	245 (dec.)	C ₃₀ H ₁₆ N ₂ O ₄ S ₂	67.66 (67.28)	3.03 3.24	5.26 5.14	532 (M ⁺ , 8) 267 (100)	1662	6.89, 7.07 (each 2H, d, <i>J</i> =10.2, 2C ₆ -H, 2C ₇ -H), 7.15—7.50 (10H, m, 2C ₆ H ₅), 7.82 (2H, s, 2C ₃ -H)
21c	60	Pale yellow needles (ethyl acetate)	201 (dec.)	C ₂₀ H ₁₂ N ₂ O ₄ S ₂	408.0238 (408.0248)			408 (M ⁺ , 38) 205 (100)	1664	2.74 (6H, s, 2C ₄ -CH ₃), 6.97, 7.07 (each 2H, d, <i>J</i> =10.6, 2C ₆ -H, 2C ₇ -H), 7.83 (2H, s, 2C ₃ -H)
21d	72	Yellow needles (ethyl acetate)	210	C ₂₂ H ₁₆ N ₂ O ₆ S ₂ ·H ₂ O	54.31 (54.36)	3.73 3.37	5.76 5.73	468 (M ⁺ , 2) 235 (100)	1680 1663	2.74 (6H, s, 2C ₄ -CH ₃), 3.93 (6H, s, 2OCH ₃), 6.29 (2H, s, 2C ₇ -H), 7.79 (2H, s, 2C ₃ -H)
24a	15	Dark red powder (ether-hexane)	137—142 (dec.)	C ₁₁ H ₉ NO ₂ S	219.0354 (219.0352)			219 (M ⁺ , 100)	1660	2.52 (3H, s, C ₄ -CH ₃), 4.23 (3H, s, NCH ₃), 6.81, 6.89 (each 1H, d, <i>J</i> =10.2, C ₆ -H, C ₇ -H), 7.78 (1H, s, C ₃ -H)
24b	49	Dark red needles (ethyl acetate-hexane)	185—190 (dec.)	C ₁₂ H ₁₁ NO ₃ S ·1/10H ₂ O	57.40 (57.37)	4.50 4.46	5.58 5.40	249 (M ⁺ , 100) 234 (76)	1674	2.53 (3H, d, <i>J</i> =1.0, C ₄ -CH ₃), 3.91 (3H, s, OCH ₃), 4.25 (3H, s, NCH ₃), 6.04 (1H, s, C ₇ -H), 7.74 (1H, q, <i>J</i> =1.0, C ₃ -H)

a) High-resolution MS.

extracted with CH_2Cl_2 (3×20 ml). The extract was washed with water, dried, and evaporated. The residue was chromatographed (eluting with ethyl acetate–hexane (1:9)) to afford 2-chloro-4-phenylquinoline (**10**, **11**).

10: Yield 99%. mp 186–187 °C (CH_2Cl_2 –hexane). MS m/z (%): 301 ($\text{M}^+ + 2$, 19), 299 (M^+ , 57), 286 (34), 284 (100). *Anal.* Calcd for $\text{C}_{17}\text{H}_{14}\text{ClNO}_2$: C, 68.12; H, 4.71; N, 4.67. Found: C, 68.16; H, 4.51; N, 4.68. $^1\text{H-NMR}$ δ : 3.44 (3H, s, $\text{C}_5\text{-OCH}_3$), 4.05 (3H, s, $\text{C}_8\text{-OCH}_3$), 6.77 (1H, d, $J=8.6$ Hz, $\text{C}_6\text{-H}$), 7.03 (1H, d, $J=8.6$ Hz, $\text{C}_7\text{-H}$), 7.2–7.5 (6H, m, $\text{C}_3\text{-H}$, C_6H_5).

11: Yield 98%. mp 131–133 °C (ether–hexane). MS m/z (%): 345 ($\text{M}^+ + 2$, 21), 343 (M^+ , 57), 330 (36), 328 (100). *Anal.* Calcd for $\text{C}_{19}\text{H}_{18}\text{ClNO}_3$: C, 66.38; H, 5.28; N, 4.07. Found: C, 66.25; H, 5.24; N, 4.03. $^1\text{H-NMR}$ δ : 2.41 (3H, s, $\text{C}_7\text{-CH}_3$), 3.18 (3H, s, $\text{C}_5\text{-OCH}_3$), 3.85 (3H, s, $\text{C}_6\text{-OCH}_3$), 4.07 (3H, s, $\text{C}_8\text{-OCH}_3$), 7.12 (1H, s, $\text{C}_3\text{-H}$), 7.30–7.45 (5H, m, C_6H_5).

2-Dialkylaminoquinolines (15, 16) A mixture of a 2-chloroquinoline (**10**, **11**) (1 mmol) and 1-methylpiperazine (or piperidine, pyrrolidine, or morpholine; 2 ml) was refluxed for 2–3 h, and then evaporated. The residue was chromatographed using ethyl acetate–methanol (19:1–7:3) (or ethyl acetate–hexane (1:19–2:3)) as the eluent to afford 2-(4-methyl-1-piperazinyl)quinoline (or 2-(1-piperidinyl)quinoline, 2-(1-pyrrolidinyl)quinoline, or 2-morpholinoquinoline; **15**, **16**).

15a: Yield 99%. mp 114–115 °C (CH_2Cl_2 –hexane). MS m/z (%): 348 (M^+ , 100), 333 (26), 319 (48), 265 (44). *Anal.* Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 76.05; H, 7.02; N, 7.99. $^1\text{H-NMR}$ δ : 1.67 (6H, brs, $\text{CH}_2(\text{CH}_2)_3\text{CH}_2$), 3.37 (3H, s, $\text{C}_5\text{-OCH}_3$), 3.74 (4H, brs, CH_2NCH_2), 4.01 (3H, s, $\text{C}_8\text{-OCH}_3$), 6.44 (1H, d, $J=8.6$ Hz, $\text{C}_6\text{-H}$), 6.73 (1H, s, $\text{C}_3\text{-H}$), 6.88 (1H, d, $J=8.6$ Hz, $\text{C}_7\text{-H}$), 7.2–7.5 (5H, m, C_6H_5).

15b: Yield 99%. mp 182–183 °C (CH_2Cl_2 –hexane). MS m/z (%): 334 (M^+ , 100), 319 (54), 305 (37). *Anal.* Calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.21; H, 6.60; N, 8.37. $^1\text{H-NMR}$ δ : 2.02 (4H, brs, $\text{CH}_2(\text{CH}_2)_2\text{CH}_2$), 3.37 (3H, s, $\text{C}_5\text{-OCH}_3$), 3.65 (4H, brs, CH_2NCH_2), 4.02 (3H, s, $\text{C}_8\text{-OCH}_3$), 6.41 (1H, d, $J=8.3$ Hz, $\text{C}_6\text{-H}$), 6.49 (1H, s, $\text{C}_3\text{-H}$), 6.89 (1H, d, $J=8.6$ Hz, $\text{C}_7\text{-H}$), 7.25–7.45 (5H, m, C_6H_5).

15c: Yield 98%. mp 139–140 °C (CH_2Cl_2 –hexane). MS m/z (%): 350 (M^+ , 100), 319 (53), 293 (42). *Anal.* Calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.87; H, 6.29; N, 7.98. $^1\text{H-NMR}$ δ : 3.39 (3H, s, $\text{C}_5\text{-OCH}_3$), 3.74 (4H, t, $J=5.0$ Hz, CH_2NCH_2), 3.85 (4H, t, $J=5.0$ Hz, CH_2OCH_2), 4.01 (3H, s, $\text{C}_8\text{-OCH}_3$), 6.49 (1H, d, $J=8.6$ Hz, $\text{C}_6\text{-H}$), 6.71 (1H, s, $\text{C}_3\text{-H}$), 6.92 (1H, d, $J=8.6$ Hz, $\text{C}_7\text{-H}$), 7.2–7.5 (5H, m, C_6H_5).

15d: Yield 99%. mp 172–174 °C (CH_2Cl_2 –hexane). MS m/z (%): 363 (M^+ , 7), 293 (100), 280 (23), 263 (22). *Anal.* Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_2$: C, 72.70; H, 6.93; N, 11.56. Found: C, 72.49; H, 6.96; N, 11.55. $^1\text{H-NMR}$ δ : 2.36 (3H, s, NCH_3), 2.56 (4H, t, $J=5.0$ Hz, $\text{CH}_2\text{-N}(\text{CH}_3)\text{-CH}_2$), 3.38 (3H, s, $\text{C}_5\text{-OCH}_3$), 3.80 (4H, t, $J=5.0$ Hz, CH_2NCH_2), 4.01 (3H, s, $\text{C}_8\text{-OCH}_3$), 6.47 (1H, d, $J=8.6$ Hz, $\text{C}_6\text{-H}$), 6.73 (1H, s, $\text{C}_3\text{-H}$), 6.90 (1H, d, $J=8.6$ Hz, $\text{C}_7\text{-H}$), 7.2–7.5 (5H, m, C_6H_5).

16a: Yield 94%. mp 106–107 °C (hexane). MS m/z (%): 392 (M^+ , 100), 377 (67), 363 (18). *Anal.* Calcd for $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_3$: C, 73.44; H, 7.19; N, 7.14. Found: C, 73.22; H, 7.25; N, 7.07. $^1\text{H-NMR}$ δ : 1.67 (6H, brs, $\text{CH}_2(\text{CH}_2)_3\text{CH}_2$), 2.35 (3H, s, $\text{C}_7\text{-CH}_3$), 3.17 (3H, s, $\text{C}_5\text{-OCH}_3$), 3.72 (4H, brs, CH_2NCH_2), 3.78 (3H, s, $\text{C}_6\text{-OCH}_3$), 4.08 (3H, s, $\text{C}_8\text{-OCH}_3$), 6.70 (1H, s, $\text{C}_3\text{-H}$), 7.3–7.5 (5H, m, C_6H_5).

16b: Yield 96%. mp 119–120 °C (hexane). MS m/z (%): 378 (M^+ , 100), 363 (90), 335 (25). *Anal.* Calcd for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.89; H, 7.05; N, 7.25. $^1\text{H-NMR}$ δ : 1.95–2.10 (4H, m, $\text{CH}_2(\text{CH}_2)_2\text{CH}_2$), 2.35 (3H, s, $\text{C}_7\text{-CH}_3$), 3.16 (3H, s, $\text{C}_5\text{-OCH}_3$), 3.55–3.70 (4H, m, CH_2NCH_2), 3.77 (3H, s, $\text{C}_6\text{-OCH}_3$), 4.11 (3H, s, $\text{C}_8\text{-OCH}_3$), 6.44 (1H, s, $\text{C}_3\text{-H}$), 7.30–7.45 (5H, m, C_6H_5).

16c: Yield 99%. mp 154–156 °C (ether). MS m/z (%): 394 (M^+ , 100), 379 (63). *Anal.* Calcd for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 70.03; H, 6.76; N, 6.91. $^1\text{H-NMR}$ δ : 2.36 (3H, s, $\text{C}_7\text{-CH}_3$), 3.17 (3H, s, $\text{C}_5\text{-OCH}_3$), 3.70 (4H, t, $J=5.0$ Hz, CH_2NCH_2), 3.79 (3H, s, $\text{C}_6\text{-OCH}_3$), 3.85 (4H, t, $J=5.0$ Hz, CH_2OCH_2), 4.06 (3H, s, $\text{C}_8\text{-OCH}_3$), 6.67 (1H, s, $\text{C}_3\text{-H}$), 7.3–7.5 (5H, m, C_6H_5).

16d: Yield 96%. oil. MS m/z (%): 407 (M^+ , 9), 337 (100), 324 (25), 307 (18). High-resolution MS Calcd for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_3$: 407.2209. Found: 407.2209. $^1\text{H-NMR}$ δ : 2.35 (6H, s, $\text{C}_7\text{-CH}_3$, NCH_3), 2.55 (4H, t, $J=5.0$ Hz, $\text{CH}_2\text{-N}(\text{CH}_3)\text{-CH}_2$), 3.17 (3H, s, $\text{C}_5\text{-OCH}_3$), 3.76 (4H, t, $J=5.0$ Hz, CH_2NCH_2), 3.78 (3H, s, $\text{C}_6\text{-OCH}_3$), 4.07 (3H, s, $\text{C}_8\text{-OCH}_3$), 6.69 (1H, s, $\text{C}_3\text{-H}$), 7.30–7.45 (5H, m, C_6H_5).

(4-Phenyl)-2(1H)-quinolinethiones (20a, b) Lawesson's reagent (809 mg, 2 mmol) was added to a solution of 2(1H)-quinolinone (**19a**, **b**) (2 mmol) in 1,2-dimethoxyethane (40 ml). The resulting solution was refluxed for 1 h, and then evaporated. The residue was chromatographed (eluting with CH_2Cl_2) to afford **20a**, **b**.

20a: Yield 96%. mp 212–214 °C (ethyl acetate). MS m/z (%): 221 (M^+ , 100), 206 (88), 191 (43). *Anal.* Calcd for $\text{C}_{11}\text{H}_{11}\text{NO}_2\text{S}$: C, 59.71; H, 5.01; N, 6.33. Found: C, 59.45; H, 5.11; N, 6.04. $^1\text{H-NMR}$ δ : 3.91, 3.95 (each 3H, s, 2OCH_3), 6.59 (1H, d, $J=8.6$ Hz, $\text{C}_6\text{-H}$), 6.91 (1H, d, $J=8.6$ Hz, $\text{C}_7\text{-H}$), 7.43 (1H, dd, $J=9.2$, 1.3 Hz, $\text{C}_3\text{-H}$), 7.96 (1H, d, $J=9.2$ Hz, $\text{C}_4\text{-H}$), 10.85 (1H, br, NH).

20b: Yield 94%. mp 217–221 °C (decomp.) (CH_2Cl_2 –hexane). MS m/z (%): 297 (M^+ , 100), 282 (83), 267 (16). *Anal.* Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_3\text{S}$: C, 68.66; H, 5.08; N, 4.71. Found: C, 68.53; H, 4.94; N, 4.72. $^1\text{H-NMR}$ δ : 3.41 (3H, s, $\text{C}_5\text{-OCH}_3$), 3.99 (3H, s, $\text{C}_8\text{-OCH}_3$), 6.58 (1H, d, $J=8.6$ Hz, $\text{C}_6\text{-H}$), 6.97 (1H, d, $J=8.6$ Hz, $\text{C}_7\text{-H}$), 7.20–7.45 (6H, m, $\text{C}_3\text{-H}$, C_6H_5), 11.04 (1H, br, NH).

4-Methyl-2(1H)-quinolinethiones (20c, d) Lawesson's reagent (2.0 g, 5 mmol) was added to a solution of 2(1H)-quinolinone (**19c**, **d**) (4 mmol) in 1,2-dimethoxyethane (50 ml). The resulting solution was stirred at 25 °C for 3 h, and evaporated. The residue was chromatographed (eluting with CH_2Cl_2 –ethyl acetate (3:2) or CH_2Cl_2) to afford **20c**, **d**.

20c: Yield 99%. mp 201 °C (ethyl acetate). MS m/z (%): 235 (M^+ , 94), 220 (100), 205 (37). *Anal.* Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_2\text{S}$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.29; H, 5.57; N, 5.91. $^1\text{H-NMR}$ δ : 2.64 (3H, s, $\text{C}_4\text{-CH}_3$), 3.86, 3.95 (each 3H, s, 2OCH_3), 6.61 (1H, d, $J=8.9$ Hz, $\text{C}_6\text{-H}$), 6.92 (1H, d, $J=8.9$ Hz, $\text{C}_7\text{-H}$), 7.27 (1H, s, $\text{C}_3\text{-H}$), 10.82 (1H, br, NH).

20d: Yield 96%. mp 213–216 °C (CH_2Cl_2 –ether). MS m/z (%): 265 (M^+ , 90), 250 (100). *Anal.* Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_3\text{S}$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.66; H, 5.62; N, 5.28. $^1\text{H-NMR}$ δ : 2.66 (3H, s, $\text{C}_4\text{-CH}_3$), 3.84, 3.96, 4.00 (each 3H, s, 3OCH_3), 6.79 (1H, s, $\text{C}_3\text{-H}$), 7.28 (1H, s, $\text{C}_3\text{-H}$), 10.72 (1H, br, NH).

1,4-Dimethyl-2(1H)-quinolinethiones (23) Lawesson's reagent (1.0 g, 2.5 mmol) was added to a solution of 2(1H)-quinolinone (**22**) (2 mmol) in 1,2-dimethoxyethane (50 ml). The resulting solution was refluxed for 3 h, and then evaporated. The residue was chromatographed (eluting with CH_2Cl_2 or ethyl acetate–hexane (1:2)) to afford **23**.

23a: Yield 91%. mp 136–139 °C (ethyl acetate). MS m/z (%): 249 (M^+ , 100), 234 (94), 219 (39). *Anal.* Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_2\text{S}$: C, 62.62; H, 6.06; N, 5.62. Found: C, 62.69; H, 6.05; N, 5.61. $^1\text{H-NMR}$ δ : 2.58 (3H, s, $\text{C}_4\text{-CH}_3$), 3.85, 3.87 (each 3H, s, 2OCH_3), 4.25 (3H, s, NCH_3), 6.73 (1H, d, $J=8.9$ Hz, $\text{C}_6\text{-H}$), 7.06 (1H, d, $J=8.9$ Hz, $\text{C}_7\text{-H}$), 7.47 (1H, s, $\text{C}_3\text{-H}$).

23b: Yield 91%. mp 164–166 °C (ethyl acetate). MS m/z (%): 279 (M^+ , 100), 264 (65), 249 (19), 234 (22). *Anal.* Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_3\text{S}$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.01; H, 6.11; N, 4.97. $^1\text{H-NMR}$ δ : 2.60 (3H, d, $J=0.7$ Hz, $\text{C}_4\text{-CH}_3$), 3.83, 3.91, 3.96 (each 3H, s, 3OCH_3), 4.24 (3H, s, NCH_3), 6.85 (1H, s, $\text{C}_7\text{-H}$), 7.45 (1H, q, $J=0.7$ Hz, $\text{C}_3\text{-H}$).

Oxidative Demethylation of 5,8-Dimethoxy- and 5,6,8-Trimethoxy-4-phenylquinolines (5, 6, 10, 11, 15, 16) Method A: A solution of CAN (1370 mg, 2.5 mmol) in acetonitrile–water (1:1, 5 ml) was added dropwise to 4-phenylquinoline (**5**, **11**) (0.5 mmol) dissolved in acetonitrile–water (4:1, 20 ml) containing pyridine-2,6-dicarboxylic acid *N*-oxide⁶⁾ (458 mg, 2.5 mmol) at 0–5 °C. The mixture was stirred at 0–5 °C for 30 min, diluted with water (60 ml), and extracted with CH_2Cl_2 (4×40 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate–hexane (1:9–3:7)) to afford *p*-quinone (**7**, **13**) and/or *o*-quinone (**14**).

Method B: A solution of CAN (4.11 g, 7.5 mmol) in acetonitrile–water (1:1, 20 ml) was added dropwise to 4-phenylquinoline (**6**) (157 mg, 0.5 mmol) dissolved in acetonitrile–water (4:1, 40 ml) containing pyridine-2,6-dicarboxylic acid *N*-oxide (1373 mg, 7.5 mmol) at 0–5 °C. The mixture was stirred at 0–5 °C for 30 min, diluted with water (100 ml), and extracted with CH_2Cl_2 (4×40 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed. Elution with ethyl acetate–hexane (3:7) afforded the less polar *o*-quinone (**9**, 34 mg, 24%), and further elution with ethyl acetate–hexane (1:1) afforded the more polar *p*-quinone (**8**, 46 mg, 33%).

Method C: A solution of CAN (685 mg, 1.25 mmol) in acetonitrile–water (1:1, 5 ml) was added dropwise to 2-chloro-, 2-(1-piperidinyl)-, 2-(1-pyrrolidinyl)-, or 2-morpholinoquinoline (**10**, **15a–c**, **16a–c**) (0.5 mmol) dissolved in acetonitrile–water (4:1, 10 ml) containing pyridine-2,6-dicarboxylic acid *N*-oxide (229 mg, 1.25 mmol) at 0–5 °C. The mixture was stirred at 0–5 °C for 15–30 min, diluted with water

(60 ml), and extracted with CH_2Cl_2 (4×40 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate–hexane (1 : 4—1 : 1)) to afford the corresponding *p*-quinone (**12**, **17a—c**, **18a—c**).

Method D: A solution of CAN (685 mg, 1.25 mmol) in acetonitrile–water (1 : 1, 5 ml) was added dropwise to 2-(4-methyl-1-piperazinyl)-quinoline (**15d**, **16d**) (0.5 mmol) dissolved in acetonitrile–water (4 : 1, 10 ml) containing pyridine-2,6-dicarboxylic acid *N*-oxide (229 mg, 1.25 mmol) at 0–5 °C. The mixture was stirred at 0–5 °C for 15–30 min, diluted with water (60 ml), neutralized with NaHCO_3 and extracted with CH_2Cl_2 (4×40 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate–methanol (9 : 1—7 : 3)) to afford the corresponding *p*-quinone (**17d**, **18d**).

Oxidative Demethylation of 2(1*H*)-Quinolinethiones (20**, **23**)** **Method A:** A solution of CAN (822 mg, 1.5 mmol) in water (6 ml) was added dropwise to a 2(1*H*)-quinolinethione (**20**, **23a**) (0.5 mmol) dissolved in acetonitrile (30 ml) at 0–5 °C. The mixture was stirred at 0–5 °C for 30 min, diluted with water (100 ml), and extracted with CH_2Cl_2 (3×100 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with CH_2Cl_2 –methanol (99 : 1, **21a**), ethyl acetate–hexane (3 : 7—1 : 1, **21b**), CHCl_3 –acetone (49 : 1, **21c**), CH_2Cl_2 –ethyl acetate (17 : 3, **21d**), and CHCl_3 –acetone (99 : 1, **24a**)) to afford the corresponding *p*-quinone (**21**, **24a**).

Method B: Nitric acid (6*N*, 7.5 ml) and AgO (248 mg, 2 mmol) were added to a solution of **23b** (56 mg, 0.2 mmol) in 1,4-dioxane (15 ml). The mixture was stirred at 25 °C for 1 h, diluted with water (100 ml), and extracted with CH_2Cl_2 (3×100 ml). The extract was washed with brine,

dried and evaporated. The residue was chromatographed (eluting with CHCl_3 –acetone (99 : 1)) to afford **24b** (24 mg, 49%).

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