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Synthesis and Cytotoxicity of 2-Methyl-1-substituted-imidazo [4,5-*g*]quinoline-4,9-dione and 7,8-dihydro-10*H*-[1,4]oxazino[3′,4′:2,3]imidazo[4,5-*g*]quinoline-5,12-dione Derivatives

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Abstract—2-Methyl-1-substituted-imidazo[4,5-*g*]quinoline-4,9-diones and 7,8-dihydro-10*H*-[1,4]oxazino -[3′,4′:2,3]imidazo[4,5-*g*]quinoline-5,12-dione (**19**) derivatives have been synthesized from 6,7-dichloro-5,8-quinolinedione for developing the new anticancer drugs. Our study on the cytotoxicity of imidazoquinolinedione derivatives has revealed that 7,8-dihydro-10*H*-[1,4]oxazino-[3′,4′:2,3]imidazo [4,5-*g*]quinoline-5,12-dione (**19**), a tetracyclic heteroquinone analogue, exhibited high cytotoxicity on human colon tumor cell (HCT 15) in vitro SRB assay. The IC_{50} value of this compound was 0.026 μg/mL whereas those of doxorubicin and cisplatin were 0.023 μg/mL and 1.482 μg/mL, respectively. Meanwhile compounds **5**–**7** and **12** in the series of 1-substituted-imidazoquinolinediones showed relatively good activity on human brain tumor cell lines (XF 498).

Introduction

Heterocyclic quinones containing nitrogen atoms showed excellent antitumor[1,2] and other biological activity.[3] Among the active heterocyclic aminoquinones, streptonigrin[4,5] is a member of a group of antitumor agents which possess an aminoquinone moiety, that includes mytomycin C,[6] actinomycin,[7] rifamycin[8] and geldanamycin.[9] In human clinical trials, streptonigrin was active against malignant lymphomas, mycosis fungoids, and Hodgkin's disease, orally or parenterally.

Studies on the activity of heterocyclic quinones containing nitrogen atoms such as quinolinedione revealed that the number and position of nitrogens are considerably important for the cytotoxicity.[10] Some important structure activity relationships (SAR) were reported.[11] Antitumor activity of streptonigrin (**A**) was completely lost when the aminoquinone moiety (**B**) is blocked as in azastreptonigrin (**C**).[10] The methoxy group (quinone ring), the pyridyl and its substituted phenyl rings were not essential for the activity in murine tumors, although they enhanced activities against the human tumor cells.[11] The synthetic analogues without the 7-aminoquinoline-quinone moiety (**B**) were inactive as antitumor agents (Fig. 1). The electron withdrawing groups at 6 and 7 positions of quinolinediones also contributed to the activity[12] and more condensed heterocyclic quinones were reported to increase the antitumor activity.[13] In another article, Kuo et al.[14] concluded 1-ethyl-2-methyl-naphth[2,3-*d*]imidazole-4,9-dione showed excellent cytotoxicity on human ovarian cancer cell lines.

However, most of the imidazonaphthoquinones did not show any good cytotoxicity on human cancer cell lines. This led us to examine the cytotoxicity of imidazoquinolinediones as well as imidazoquinoxalinediones so as to examine the effect of the number of nitrogen in the nucleus of imidazoheterocyclic quinones. We reported previously that some of the imidazoquinoxalinediones showed marked cytotoxicity on human gastric adenocarcinoma cell lines in comparison with cisplatin and adriamycin (doxorubicin).[15]

Many derivatives of quinolinediones have been synthesized and tested antitumor activity,[14] but the synthesis and

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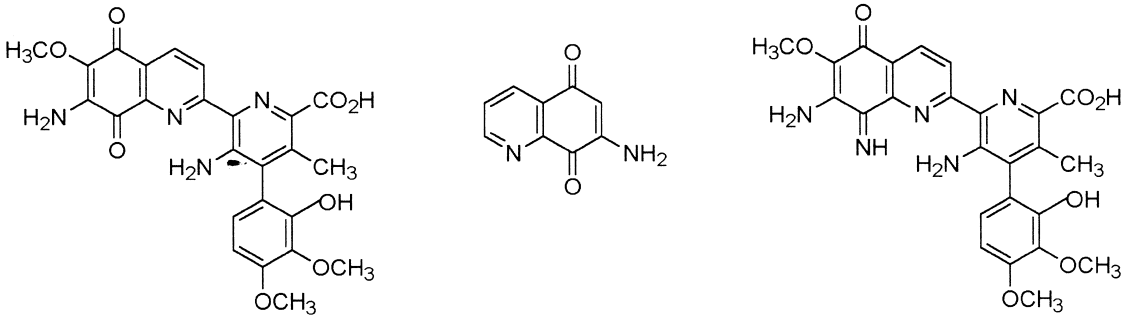

A B C

Figure 1. Streptonigrin structure (A), 7-aminoquinolinequinone moiety (B) that is responsible for the antitumor activity of streptonigrin and azastreptonigrin (C).

cytoxicity of imidazoquinolinediones has not been investigated. The mechanism of the cytotoxicity exhibited by most quinone derivatives was already studied as topoisomerase inhibitor via DNA-intercalation and reduction of quinone moiety by oxidoreductase (DT-diaphorase).[16–19] According to Moore's thesis, [20] the condition of DNA- intercalator are the followings.

1. It is a plane tri or tetracyclic aromatic ring structure.
2. Its surface area is over 28Å^2
3. It has to be *p*-conjugated quinone containing a nitrogen atom, because it makes possible to form hydrogen bonding with DNA.

Based on those considerations, we report here the synthesis of imidazoquinolinediones and examined their cytotoxicity to develop new antitumor imidazoquinones. We could obtain 2-methyl-1-substituted-imidazo[4,5-*g*]quinoline-4,9-diones (**5–17**) and oxazino-[3′,4′:2,3]imidazo-[4,5-*g*]quinoline-5,12-dione analogues (**18–20**) from 6,7-dichloro-5,8-quinolinedione (**1**) as a starting material. Human cancer cell lines of lung (A 549), ovarian (SK-OV-3), melanoma (SK-MEL-2), brain (XF-498), colon (HCT 15) cell lines were used for cytotoxicity test, in comparison with clinically used anticancer agents, cisplatin and adriamycin.

Results

Chemistry

6,7-Dichloro-5,8-quinolinedione (**1**) was prepared according to the literature.[3] 6-Amino-7-chloro-5,8-quinolinedione (**3**) was obtained by treating **1** with sodium azide in acetic acid, followed by reduction of the resulting azide (**2**) with sodium borohydride. Acetylation of **3** with acetic anhydride in the presence of 10% sulfuric acid at 0 °C gave 6-acetamido-7-chloro-5,8-quinolinedione (**4**).[3,21]

4 was reacted with alkylamines or arylamines in the presence of base such as potassium carbonate to yield 1-alkyl-2-methyl-imidazo[4,5-*g*]quinoline-4,9-diones (**5–12**) and 1-aryl-2-methyl-imidazo[4,5-*g*]quinoline-4,9-dione (**13–17**) (Fig. 2).

Reaction **1** with piperidine, morpholine or thiomorpholine in the presence of triethylamine or celium(III) chloride

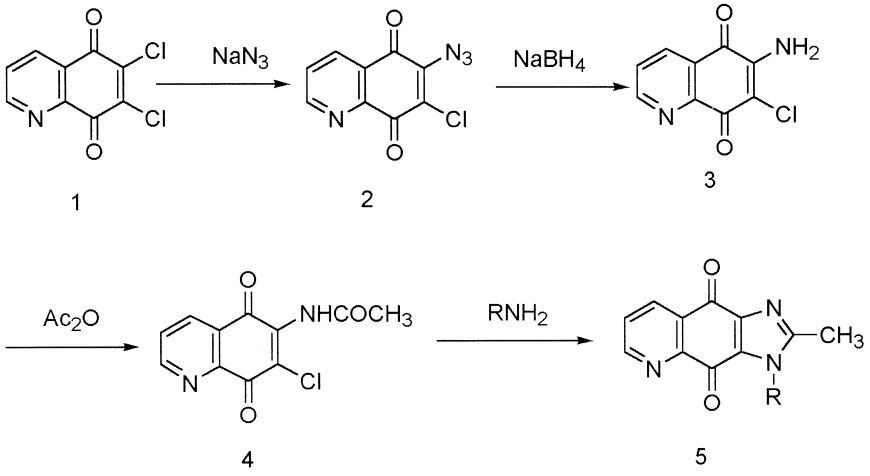

Figure 2. Scheme of the synthetic method of 1-alkyl-imidazoquinoline-4,9-diones (**5–12**) and 1-aryl-imidazoquinoline-4,9-dione(**13–17**). R = **5**; methyl, **6**; ethyl, **7**; propyl, **8**; butyl, **9**; cloroethyl, **10**; *β*-hydroxyethyl, **11**; isopropyl, **12**; benzyl, **13**; phenyyl, **14**; 4-bromophenyl, **15**; 4-ethoxyphentl, **16**; 4-chlorophenyl, **17**; 4-methylphenyl.

followed by cyclization with sodium azide[22] gave the tetracyclic imidazoquinolinedione analogues, **18, 19** and **20** respectively. (Fig. 3).

Cytotoxicity assay by SRB assay

Human cancer cell lines of lung (A 549), ovarian (SK-OV-3), melanoma (SK-MEL-2), brain (XF 498) and colon (HCT 15) were used for cytotoxicity test in vitro using SRB (Sulforhodamine B) assay.[23,24] They were maintained as stocks in RPMI 1640 (Gibco) supplemented with 10% fetal bovine serum (Gibco). Cell cultures were passaged once or twice weekly using trypsin-EDTA to detach the cells from their culture flasks.

The rapidly growing cells were harvested, counted, and inoculate at the appropriate concentrations ($1–2\times10^4$ cells/well) into 96-well microtiter plates. After incubation for 24 h, the compounds dissolved in culture medium were applied to the culture wells in triplicate followed by incubating for 48 h at 37 °C under 5% CO_2 atmosphere. The cultures fixed with cold TCA were stained by 0.4% SRB dissolved in 1% acetic acid. After solubilizing the bound dye with 10 mM unbuffered tris base by gyrotory shaker, the absorbance at 520 nm was measured with a microplate reader (Dynatech Model MR 700). The cytotoxic activity was evaluated by measuring the concentration of compounds required to inhibit the protein synthesis by 50% (IC_{50}) in comparison with those of doxorubicin and cisplatin (Table 1). Each value is the mean of triplicate experiments.

Discussion

The position of the nucleophilic substitution of the compound **1** with amines can be deduced to be at C-6 position based on Pratt's theory[25] and our previous result on the reaction **1** with ethyl acetoacetate, in which the structure of the condensation product was confirmed by X-ray crystallography.[26]

All of the compounds synthesized except for the compounds **8** and **9** exhibited potent cytotoxicity against all the human cancer cell lines tested. Their activities were higher than cisplatin but somewhat lower than doxorubicine (Table 1). The imidazoquinolinedione **8** and **9** having chloroethyl and β-hydroxyethyl respectively had significantly lower activity as compared with cisplatin.

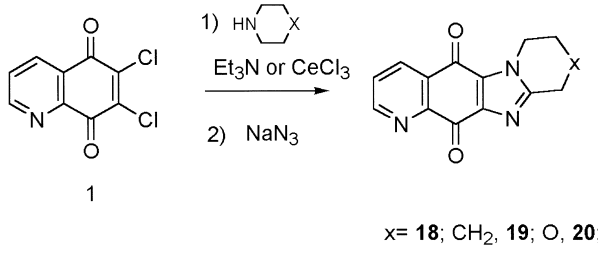

Figure 3. Scheme of the synthetic method of the tetracyclic imidazoquinolinedione derivatives, **18**, **19** and **20**.

Table 1. Cytotoxicity Data on Human Lung Tumor Cell Lines (A 549), Human Ovarian Tumor Cell Lines (SK-OV-3), Human Melanoma Tumor Cell Lines (SK-MEL-2), Human Brain Tumor Cell Lines (XF 498) and Human Colon Tumor Cell Lines (HCT 15)

	IC_{50} (μg/mL)				
Compounds	A549	SK-OV-3	SK-MEL-2	XF 498	HCT 15
Cisplatin	0.276	0.303	0.154	0.106	1.482
Doxorubicin	0.005	0.019	0.010	0.013	0.023
5	0.075	0.295	0.072	0.048	0.251
6	0.085	0.140	0.074	0.031	0.323
7	0.087	0.206	0.147	0.046	0.280
8	0.085	0.197	0.219	0.076	0.278
9	2.800	1.990	1.828	2.366	2.548
10	3.094	1.953	1.075	2.278	2.498
11	0.356	0.600	0.310	0.389	0.433
12	0.049	0.177	0.064	0.037	0.181
13	0.078	0.158	0.097	0.071	0.298
14	0.096	0.241	0.093	0.103	0.153
15	0.217	0.357	0.331	0.244	0.386
16	0.087	0.097	0.076	0.087	0.188
17	0.102	0.129	0.103	0.146	0.277
18	0.032	0.144	0.064	0.032	0.052
19	0.019	0.097	0.052	0.022	0.026
20	0.018	0.347	0.069	0.039	0.061

Conclusion

The 20 derivatives of 2-methyl-1-substituted-imidazo[4,5-*g*]quinoline-4,9-diones and 7,8-dihydro-10*H*-[1,4]oxazino[3′,4′:2,3]imidazo[4,5-*g*]quinoline-5,12-dione derivatives were synthesized. They were tested for cytotoxicity in vitro in comparison with cisplatin and doxorubicin. Most of them showed cytotoxic effect against various human tumor cell lines. They are valuable to be tested for in vivo antitumor activity in human cancer xenograft models.

Experimental

Materials and methods

^{1}H NMR spectra were recorded on a 300 MHz Varian Gemini NMR spectrometer. Samples were dissolved in DMSO-d_6 and $CDCl_3$. Elemental analyses were performed using ThermoQuest (CE Instruments) EA 1110. IR spectra were recorded on a Perkin Elmer 1420 Infrared spectrometer. Melting points were measured by electrothermal digital melting point (Büchi). Most reagents were purchased from Aldrich Chemical Company. 6,7-Dichloro-5,8-quinolinedione (**1**), 6-azido-7-chloro-5,8-quinolinedione (**2**), 6-amino-7-chloro-5,8-quinolinedione (**3**), 6-acetamido-7-chloro-5,8-quinolinedione (**4**) were prepared according to the literature.[21]

General procedure for the preparation of 2-methyl-1-substituted-imidazo[4,5-*g*]quinoline-4,9-diones (5–12 and 14–17)

1-Methyl-2-methyl-imidazo[4,5-*g*]quinoline-4,9-diones (5). Methylamine (40% in water, 0.7 mL) and anhydrous potassium carbonate (1.32 g, 9.55 mmol) were added to a solution of 6-acetamido-7-chloro-5,8-quinolinedione (**4**)

Microanalysis.

	Calculated	Found
5 ($C_{12}H_9N_3O_2$)	C, 63.43; H, 3.99; N, 18.49	C, 63.80; H, 4.09; N, 18.13
6 ($C_{13}H_{11}N_3O_2$)	C, 64.72; H, 4.60; N, 17.42	C, 64.49; H, 4.62; N, 17.38
7 ($C_{14}H_{13}N_3O_2H_2O$)	C, 61.54; H, 4.76; N, 15.38	C, 61.36; H, 4.73; N, 15.79
8 ($C_{15}H_{15}N_3O_2$)	C, 66.90; H, 5.61; N, 15.60	C, 66.54; H, 6.00; N, 15.36
9 ($C_{13}H_{10}ClN_3O_21/5H_2O$)	C, 55.99; H, 3.73 ;N, 15.08	C, 55.96; H, 3.76; N, 14.72
11 ($C_{14}H_{13}N_3O_21/9CH_4O$)	C, 65.49; H, 5.20; N, 16.24	C, 65.89; H, 5.48; N, 15.94
12 ($C_{18}H_{13}N_3O_2$)	C, 71.28; H, 4.32; N, 13.85	C, 70.93; H, 4.45; N, 14.17
14 ($C_{17}H_{10}BrN_3O_2$)	C, 55.46; H, 2.74; N, 11.41	C, 55.17; H, 2.69; N, 11.38
15 ($C_{19}H_{15}N_3O_3.1/6C_2H_6O$)	C, 68.10; H, 4.70; N, 12.33	C, 68.47; H, 4.99; N, 11.93
16 ($C_{17}H_{10}ClN_3O_2$)	C, 63.07; H, 3.11; N, 12.98	C, 63.25; H, 3.16; N, 13.18
17 ($C_{18}H_{13}N_3O_2$)	C, 71.28; H, 4.32; N, 13.85	C, 70.89; H, 4.68; N, 13.79
18 ($C_{14}H_{11}N_3O_2$)	C, 66.40; H, 4.38; N, 16.59	C, 66.24; H, 4.42; N, 16.94
19 ($C_{13}H_9N_3O_3$)	C, 61.18; H, 3.55; N, 16.46	C, 61.56; H, 3.60; N, 16.07
20 ($C_{13}H_9N_3O_2S.1/5C_2H_6O$)	C, 57.39 ;H, 3.64; N, 14.99; S, 11.42	C, 57.74; H, 3.35; N, 14.99; S, 11.65

(500 mg, 1.99mmol) in absolute ethanol (15 mL) and the reaction mixture was refluxed for 5 h. The solvent was evaporated under reduced pressure. Water was added to this residue, the residue was extracted with methylene chloride, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was loaded on a silica gel column (Kieselgel 9385, 230–400 mesh) and eluted with *n*-hexane:ethylacetate (1:3): Yield, 150 mg (33.3%); mp $>268\,^{\circ}C$; ^1H NMR δ 2.52 (s, 3H, CH_3, C2), 3.97 (s, 3H, N-CH_3), 7.6 (dd, 1H, CH, C6), 8.5 (d, 1H, CH, C5), 9.0 (d, 1H, CH, C7); IR 1680 cm^{-1}. Anal. ($C_{12}H_9N_3O_2$) C, H, N.

1-Ethyl-2-methyl-imidazo[4,5-*g*]quinoline-4,9-diones (6). Yield, 220 mg (46%); mp 259 °C; ^1H NMR δ 1.5 (t, 3H, N-$CH_2\underline{CH_3}$), 2.6 (s, 3H, CH_3 C2), 4.5 (q, 2H, N-$\underline{CH_2}CH_3$), 7.5 (dd, 1H, CH, C6), 8.5 (d, 1H, CH, C5), 9.0 (d, 1H, CH, C7); IR 1680 cm^{-1}. Anal. ($C_{13}H_{11}N_3O_2$) C, H, N.

2-Methyl-1-propyl-imidazo[4,5-*g*]quinoline-4,9-diones (7). Yield, 160 mg (32.6%); mp 174 °C; ^1H NMR δ 0.9 (t, 3H, N-$CH_2CH_2\underline{CH_3}$), 1.8 (m, 2H, N-$CH_2\underline{CH_2}CH_3$), 2.5 (s, 3H, CH_3, C2), 4.4 (t, 2H, N-$\underline{CH_2}CH_2CH_3$), 7.8 (dd, 1H, C6), 8.4 (d, 1H, C5), 9.0 (d, 1H, C7); IR 1680 cm^{-1}. Anal. ($C_{14}H_{13}N_3O_2$) C, H, N.

1-Butyl-2-methyl-imidazo[4,5-*g*]quinoline-4,9-diones (8). The general procedure was followed for 12 h using *n*-butylamine (0.41 mL, 3.98 mmol) and purified by chromatography (ethyl acetate:*n*-hexane = 2:1): Yield, 87 mg (20.2%); mp 119 °C; ^1H NMR δ 0.9 (t, 3H, N-$CH_2CH_2CH_2\underline{CH_3}$), 1.4 (m, 2H, N-$CH_2CH_2\underline{CH_2}CH_3$), 1.8 (m, 2H, N-$CH_2\underline{CH_2}CH_2CH_3$), 2.5 (s, 3H, $\underline{CH_3}$, C2), 4.4 (t, 2H, N-$\underline{CH_2}CH_2CH_2CH_3$), 7.8 (dd, 1H, C6), 8.4 (d, 1H, C5), 9.0 (d, 1H, C7); IR 1680 cm^{-1}. Anal. ($C_{15}H_{15}N_3O_2$) C, H, N.

1-(β-Chloroethyl)-2-methyl-imidazo[4,5-*g*]quinoline-4,9-diones (9). The general procedure was followed for 12 h using β-chloroethylamine·HCl (0.47 g, 3.98 mmol) in water (1 mL) and purified by chromatography (ethyl acetate:*n*-hexane = 2:1): Yield, 120 mg (12.5%); mp 247 °C; ^1H NMR δ 2.1 (s, 3H, CH_3, C2), 4.2 (t, 2H, N-$CH_2\underline{CH_2}Cl$), 4.6 (t, 2H, N-$\underline{CH_2}CH_2Cl$), 7.6 (d, 1H, C6), 8.5 (d, 1H, CH, C5), 9.0 (d, 1H, CH, C7); IR 1700 cm^{-1}. Anal. ($C_{13}H_{10}ClN_3O_2$) C, H, N.

1-(β-Hydroxyethyl)-2-methyl-imidazo[4,5-*g*]quinoline-4,9-diones (10). The general procedure was followed for 12 h at rt using ethanolamine (0.24 mL, 3.98 mmol) and recrystallized from ethyl acetate/*n*-hexane: Yield, 280 mg (30.4%); mp 250 °C; ^1H NMR δ 2.5 (s, 3H, CH_3, C2), 3.9 (t, 2H, N-$\underline{CH_2}CH_2OH$), 4.5 (t, 2H, N-$CH_2\underline{CH_2}OH$), 7.6 (dd, 1H, C6), 8.4 (d, 1H, C5), 8.9 (d, 1H, C7); IR 3380, 1680 cm^{-1}, Anal. ($C_{13}H_{11}N_3O_3$) C, H, N

1-Isopropyl-2-methyl-imidazo[4,5-*g*]quinoline-4,9-diones (11). The general procedure was followed for 24 h using isopropylamine (0.24 g, 3.98 mmol) and recrystallized from methanol: Yield, 150 mg (30%); mp $>268\,^{\circ}C$; ^1H NMR δ 1.7 (d, 6H, $CH(\underline{CH_3})_2$), 2.7 (s, 3H, CH_3, C2), 5.2 (m, 1H, $\underline{CH}(CH_3)_2$), 7.8 (dd, 1H, CH, C6), 8.6 (d, 1H, CH, C5), 9.0 (d, 1H, CH, C7); IR 1680 cm^{-1}. Anal. ($C_{14}H_{13}N_3O_2$) C, H, N.

1-Benzyl-2-methyl-imidazo[4,5-*g*]quinoline-4,9-diones (12). The general procedure was followed for 24 h at rt using benzylamine (0.44 mL, 3.98 mmol) and purified by chromatography (ethyl acetate:*n*-hexane = 2:1): Yield, 140 mg (23.3%); mp 171–172 °C; ^1H NMR δ 2.6 (s, 3H, CH_3, C2), 5.7 (s, 2H, $\underline{CH_2}$-Ar), 7.2–7.4 (m, 5H, CH_2-$\underline{Ar}$), 7.6 (dd, 1H, CH, C6), 8.5 (d, 1H, CH, C5), 9.0 (d, 1H, CH, C7); IR 1672 cm^{-1}. Anal. ($C_{18}H_{13}N_3O_2$) C, H, N.

2-Methyl-1-phenyl-imidazo[4,5-*g*]quinoline-4,9-diones (13). The general procedure was followed for 7 h at rt using aniline (0.36 mL, 3.98 mmol): Yield, 160 mg (28%); mp 275 °C.[21] ^1H NMR δ2.5 (s, 3H, CH_3, C2), 7.6 (m, 5H, N-phenyl), 7.8 (dd, 1H, C6), 8.5(d, 1H, C5), 9.0 (d, 1H, C7); IR 1680 cm^{-1}. Anal.($C_{17}H_{11}N_3O_2$) C, H, N.

1-(4-Bromophenyl)-2-methyl-imidazo[4,5-*g*]quinoline-4,9-diones (14). The general procedure was followed for 6 h using 4-bromoaniline 0.68 g (3.98 mmol) and purified by chromatography (ethyl acetate:*n*-hexane = 2:1): Yield, 320 mg (22%); mp 249 °C; ^1H NMR δ 2.4 (s, 3H, CH_3, C2), 7.2 (d, 2H, phenyl), 7.6–7.8 (dd, d, 1H, 2H, C6, phenyl), 8.5 (d, 1H, CH, C5), 9.0 (d, 1H, CH, C7); IR 1680 cm^{-1}. Anal. ($C_{17}H_{10}BrN_3O_2$) C, H, N.

1-(4-Ethoxyphenyl)-2-methyl-imidazo[4,5-*g*]quinoline-4,9-diones (15). The general procedure was followed for 6 h

using *p*-phenetidine (0.55 g, 3.98 mmol) and recrystallized from ethanol: Yield, 550 mg (42%); mp 188–190 °C; ^{1}H NMR δ 1.5 (t, 3H, Ar-O-$CH_2\underline{CH_3}$), 2.4 (s, 3H, CH_3, C2), 4.1 (q, 2H, Ar-O-$\underline{CH_2}CH_3$), 7.0 (d, 2H, phenyl), 7.2 (d, 2H, phenyl), 7.6 (d, 1H, CH, C6), 8.5 (d, 1H, CH, C5), 9.0 (d, 1H, CH, C7); IR 1680 cm^{-1}. Anal. ($C_{19}H_{15}N_3O_3$) C, H, N.

1-(4-Chlorophenyl)-2-methyl-imidazo[4,5-*g*]quinoline-4,9-diones (16). The general procedure was followed for 6 h using 4-chloroaniline (0.51 g, 3.98 mmol) and purified by chromatography (ethyl acetate:*n*-hexane = 2:1): Yield, 250 mg (40%); mp 208 °C; ^{1}H NMR δ 2.5 (s, 3H, CH_3,C2), 7.3, 7.6 (d, d, 4H, phenyl), 7.6 (dd, 1H, CH, C6), 8.6 (d, 1H, CH,C5), 9.0 (d, 1H, CH, C7); IR 1680 cm^{-1}. Anal. ($C_{17}H_{10}ClN_3O_2$) C, H, N.

2-Methyl-1-(4-methylphenyl)-imidazo[4,5-*g*]quinoline-4,9-diones (17). The general procedure was followed for 24 h at 45 °C using *ρ*-toluidine (0.54 g, 3.98 mmol): Yield, 210 mg (40%); mp 262 °C; ^{1}H NMR δ 2.4 (s, 3H, phenyl-$\underline{CH_3}$), 2.5 (s, 3H, CH_3, C2), 7.8 (dd, 1H, C6), 7.2, 7.4 (d, d, 4H, phenyl), 8.4 (d, 1H, C5), 9.0 (d, 1H, C7); IR 1680 cm^{-1}. Anal. ($C_{18}H_{13}N_3O_2$) C, H, N.

7,8,9,10 - tetrahydropyridino[1′,2′:2,3]imidazo[4,5 - *g*]quinoline-5,12-dione(18). Piperidine (0.23 mL, 2.3 mmol) and triethylamine (0.23 mL, 2.3 mmol) were added to a solution of 6,7-dichloro-5,8-quinolinedione (**1**) (500 mg, 1.99 mmol) in acetone (15 mL) and the reaction mixture was stirred for 1 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in DMF (20 mL). Sodium azide (0.16 g, 2.5 mmol) was added to this solution, and the reaction mixture was refluxed for 12 h. The mixture was filtered, the filtrate was extracted methylene chloride, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was treated with active carbon in ethanol: Yield, 260 mg (52%); mp > 268 °C; ^{1}H NMR δ 2.0, 2.2 (m, m, 4H, C9, C8), 3.1 (t, 2H, C10), 4.5 (t, 2H, C7), 7.7 (dd, 1H, C3), 8.4 (d, 1H, C4), 9.0 (d, 1H, C2); IR 1670 cm^{-1}. Anal.($C_{14}H_{11}N_3O_2$) C, H, N.

7,8 - dihydro - 10*H* - [1,4]oxazino[3′,4′:2,3]imidazo[4,5 - *g*]quinoline-5,12-dione (19). 19 was prepared from **1**, cerium chloride (0.2 g, 1.19 mmol) and morpholine (0.21 mL, 2.38 mmol) as described for **18**: Yield, 330 mg (32.7%); mp > 268 °C; ^{1}H NMR δ 4.2 (t, 2H, C7), 4.6 (t, 2H, C8), 5.2 (s, 2H, C10), 7.8 (dd, 1H, C3), 8.4 (d, 1H, C4), 9.0 (d, 1H, C2); IR 1680 cm^{-1}. Anal.($C_{13}H_9N_3O_3$) C, H, N.

7,8 - dihydro - 10*H* - [1,4]thiazino[3′,4′:2,3]imidazo[4,5 - *g*]quinoline-5,12-dione (20). 20 was prepared from **1,** cerium chloride (0.2 g, 1.19 mmol) and thiomorpholine (0.23 mL, 2.38 mmol) as described for **18**: Yield, 450 mg (42%); mp > 268 °C; ^{1}H NMR δ 4.2 (s, 2H, C10), 4.5–4.9 (t, t, 4H, C8, C7), 7.8 (dd, 1H, C3), 8.4 (d, 1H, C4), 9.0 (d, 1H, C2); IR 1680 cm^{-1}. Anal.($C_{13}H_9N_3O_2S.1/5C_2H_6O$) C, H, N.

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