A Diels–Alder Strategy for the Building of Imidazo[4,5-*g*]quinoline-4,9-dione Derivatives

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Benzimidazole-4,7-diones **3a** and **3b** were synthesized and submitted to hetero Diels–Alder reactions with azadienes **4** and **5** to afford imidazo[4,5-*g*]quinoline-4,9-diones **6**–**9**. The structure of the latter was assigned by X-ray diffraction, ^{1}H NMR NOE DIFF experiments or by a molecular dynamics study.

Introduction

We are engaged in a program directed at searching for new antiparasitic compounds. Recently,[1] we described the activity of some benzimidazole-4,7-diones of general formula **I** (Figure 1) as *Toxoplasma gondii* purine nucleoside phosphorylase inhibitors. In order to determine structure-activity relationships, we planned the synthesis of imidazoquinolinediones **II** and **III** as tricyclic derivatives of quinones **I**.

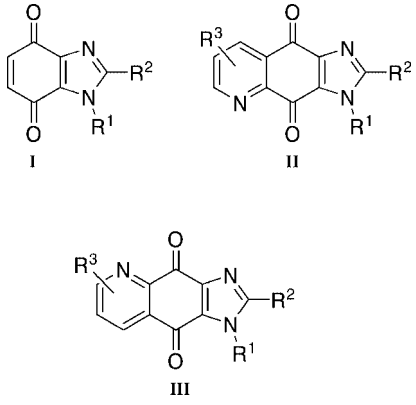
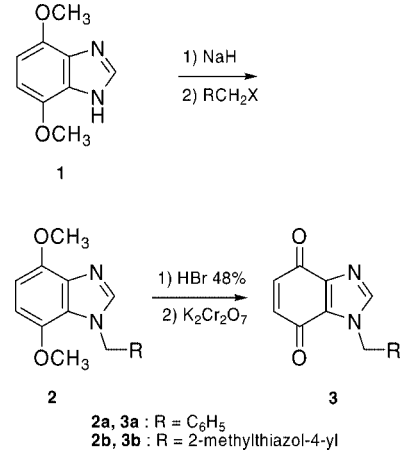


Figure 1. Benzimidazolediones **I** and imidazoquinolinediones **II**–**III**.

All the syntheses of the few imidazoquinolinediones described in the literature[2,3] start from a quinoline-5,8-dione derivative and require the building of the imidazole ring. However, quinoline derivatives can be obtained by a Diels–Alder reaction of 1-azadienes[4] with a dienophile.[5–9] We wish to report here our results concerning this alternative strategy based on hetero Diels–Alder reactions between benzimidazole-4,7-diones **I** as dienophiles and α,β-unsaturated *N*,*N*-dimethylhydrazones.

Results and Discussion

The synthesis of the benzimidazolequinones **3a** and **3b** was carried out as outlined in Scheme 1.



Scheme 1. Synthesis of benzimidazoledione derivatives **3**.

Thus, treatment of 4,7-dimethoxybenzimidazole (**1**)[10] with NaH in DMF and subsequent addition of the appropriate alkylating agent afforded the *N*-substituted benzimidazoles **2a**[11] and **2b**. Attempts to transform compound **2a** directly into quinone **3a** by treatment with ceric ammonium nitrate (CAN) failed because a dimerization process oc-

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curred, a phenomenon already described for dimethoxybenzene derivatives.[12] The use of AgO/HNO_3 as oxidant[13] was also unsuccessful as a 40% yield of the desired quinone was obtained mixed with a dimerized product. Finally, quinones **3a** and **3b** were obtained by demethylation of compounds **2a** and **2b** with hydrogen bromide followed by oxidation with $K_2Cr_2O_7$. This method provided quinones **3a** and **3b** in good overall yields (58 and 62% respectively, calculated from **2a** and **2b**).

The hetero Diels–Alder reactions of **3a** and **3b** with azadienes **4**[14] and **5**[15] are described in Scheme 2 and Table 1. In all cases, the primary tetrahydro cycloadducts were not detected.

Starting from azadiene **4**, the Diels–Alder reaction with quinone **3a**, carried out in acetonitrile in the presence of acetic anhydride,[16] gave a mixture of dihydro cycloadducts and fully aromatized products. A further addition of manganese dioxide to the reaction mixture provided the regioisomeric compounds **6** and **7** in good yields with a poor regioselectivity (46:54).

On the other hand, the reaction of azadiene **5** with quinones **3a** or **3b** in ethanol afforded directly a mixture of the aromatized compounds **8a** + **9a** or **8b** + **9b**, respectively, with better regioselectivities than observed with azadiene **4** and quinone **3a**. All the regioisomers were separated by column chromatography on silica gel and identified.

The regiochemistry of the Diels–Alder reaction can be predicted by frontier molecular orbital (FMO) theory. Therefore, we calculated the primary orbital coefficients for quinones **3a** and **3b** by the semi-empirical PM3 method.[17] The calculations (Scheme 2) indicate that the largest LUMO orbital coefficients of quinones **3** are located at C-5 in both cases. As for azadienes **4** and **5**, we have previously reported that the largest values of the HOMO orbital coefficients (Scheme 2) are situated at C-4.[18] Therefore, compounds **6** and **8** would be the major regioisomers. Moreover, the small difference between the orbital coefficient values for azadiene **4** could explain the weak regioselectivity observed in its reaction with quinone **3a**.

In order to unambiguously establish the structure of the different regioisomers, we first envisaged an X-ray diffraction study. Unfortunately, attempts to obtain suitable crystals of **6**–**9** only succeeded for **8b** (Figure 2), which only allowed us to assign the structure of regioisomers **8b** and **9b**.

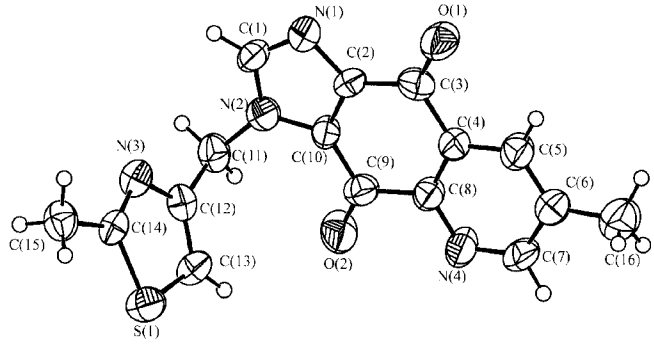
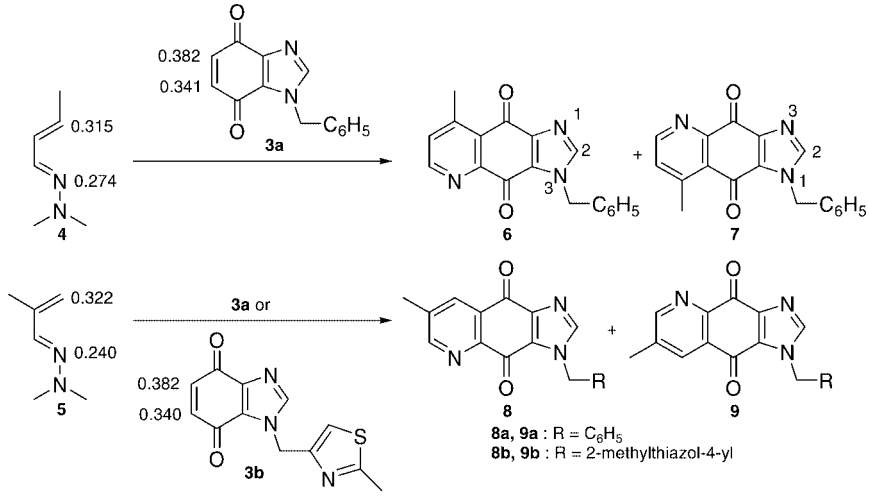


Figure 2. X-ray crystal structure of **8b** (anisotropically refined atoms shown as 50% displacement ellipsoids).

A 2D ^1H-^{13}C NMR HMBC correlation experiment was performed on compound **8a** but the detected ^1H-^{13}C couplings were not helpful for a structural determination.

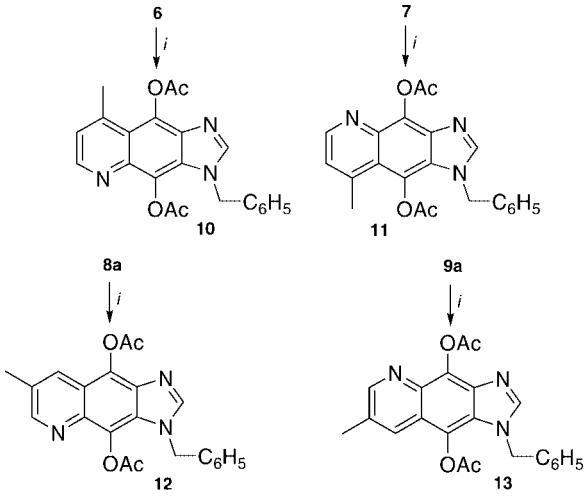


Scheme 2. Synthesis of imidazoquinolinediones **6**–**9**.

Table 1. Synthesis of imidazoquinolinediones **6**–**9**.

Quinone	Azadiene	Conditions	Products	Yield [%]	Ratio
3a	**4**	MeCN, Ac_2O, room temp., 48 h then MnO_2, room temp., 24 h	**6** + **7**	63	**6/7** = 46:54
3a	**5**	EtOH, room temp., 4 h	**8a** + **9a**	59	**8a/9a** = 69:31
3b	**5**	EtOH, room temp., 4 h	**8b** + **9b**	85	**8b/9b** = 68:32

We then carried out ^{1}H NMR NOE DIFF experiments on the diacetoxy derivatives **10**–**13**, which were obtained following a known procedure[19] (Scheme 3).



Scheme 3. Synthesis of the diacetoxy derivatives of compounds **6**, **7**, **8a**, **9a**. (*i*): Ac_2O, Zn/AcONa.

Using this methodology, we were able to assign only the structure of compound **13** (Figure 3), and therefore those of **8a** and **9a**. For the others, the NOE DIFF experiments were inconclusive.

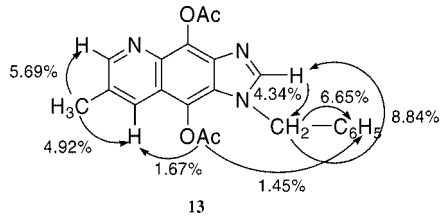


Figure 3. ^{1}H NMR NOE DIFF experiments performed on **13**.

We next turned our attention to the ^{1}H NMR spectra of the diacetoxy derivatives **10** and **11**, where the benzylic protons show different signals for these regioisomers: a singlet at δ = 5.58 ppm for one of them, and two doublets at δ = 5.44 and 5.59 ppm for the other. This different behavior was assumed to come from a conformational restriction in **11**, leading to a nonchemical equivalence of the benzylic protons. In order to confirm this hypothesis, we performed a comparative molecular dynamic study on **10** and **11** (Figure 4). As expected, compound **11** shows a weaker oscillation of the dihedral angle $\psi 2$ compared to that of compound **10**, thereby establishing the structural assignment.

Conclusions

An effective procedure using a Diels–Alder methodology has been developed for the synthesis of imidazoquinoline-dione derivatives. The regiochemistry of the cycloadditions

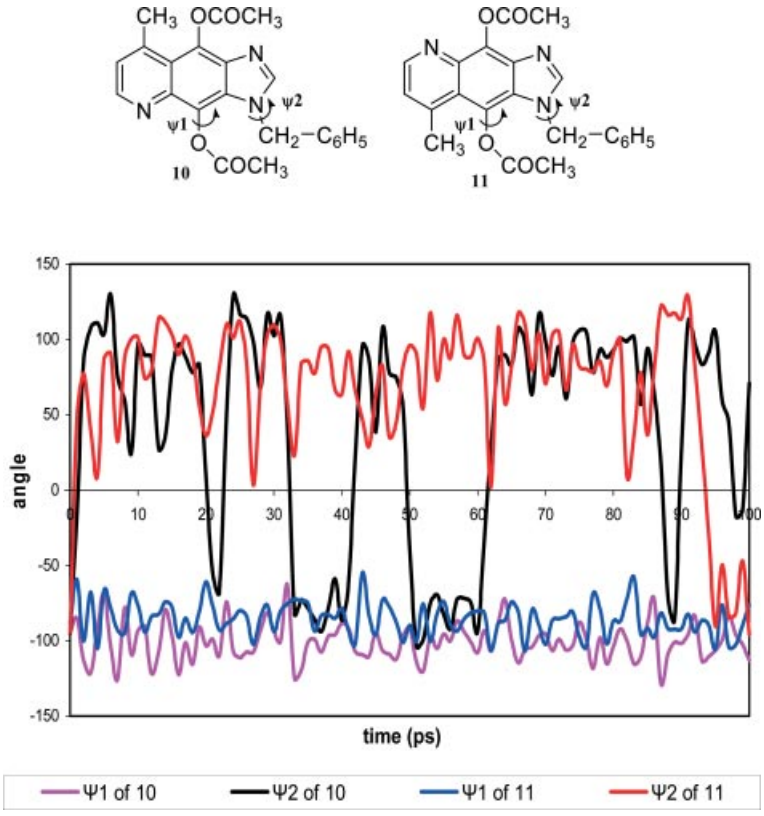


Figure 4. Plotting of dihedral angle (ψ) values vs. time for compound **10** and **11** during molecular modelling simulation.

of azadiene **5** with quinones **3** agrees with the calculations of the semi-empirical method PM3, but that of azadiene **4** with quinone **3a** seems to be in contradiction. The difference between the orbital coefficient values of N-1 and C-4 for azadiene **4** is smaller than that for azadiene **5**, which could explain this result. A biological evaluation of imidazoquinolinediones **6**–**9** and efforts to improve the regioselectivity of the [4+2] cycloadditions between benzimidazole-4,7-diones and azadienes are underway.

Experimental Section

General Remarks: Melting points were measured with a Büchi apparatus (capillary tube). The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with a Bruker AM 300 spectrophotometer. The chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) as an internal reference. The infrared spectra were recorded with a Perkin–Elmer 1310 spectrometer. Mass spectra (EI) were recorded with a GC/MS Nermag R10–10 spectrometer. Elemental analyses were performed at the Centre de Microanalyse du CNRS at Solaize (France). The coefficients of the molecular frontier orbitals and the conformational energy were computed with the PM3 semi-empirical method of the Sybyl[20] molecular modelling package. The global charge of the molecule was set to neutral, and the electronic configuration was set to the ground state. Starting from a PM3 energetically minimized conformation, a short molecular dynamics (100 ps) was made at constant energy and volume (NVE) using the molecular mechanics method. Calculations were carried out with the Merck Force Field (MMFF94)[21] and a conformation was sampled every 0.5 ps. The electrostatic cut-off was set to 16 Å and the dielectric constant was set to 80 and varies with distance. Atomic partial charges were calculated using the algorithm included with the MFF94 force field. All calculations were carried on an SGI O_2 workstation.

1-Benzyl-4,7-dimethoxy-1*H*-benzimidazole (2a): A solution of 4,7-dimethoxy-1*H*-benzimidazole (**1**; 1.78 g, 10 mmol) in dry DMF (250 mL) was added dropwise, over 15 min, to a suspension of NaH (60% in mineral oil; 0.425 g, 10.6 mmol) in the same solvent (10 mL). The reaction mixture was stirred for 15 min and benzyl bromide (1.62 g, 9.47 mmol) was added. After stirring for 12 h, DMF was removed under vacuum. The residue was then dissolved in dichloromethane (250 mL), washed with a saturated aqueous K_2CO_3 solution (3 × 250 mL), and dried with Na_2SO_4. Evaporation of the solvent led to a residue which was purified by column chromatography (ethyl acetate) to afford **2a** (2.06 g, 81%). M.p. 166 °C. IR (KBr): $\tilde{\nu}$ = 2800, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.78 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3) 5.65 (s, 2 H, CH_2N), 6.54 (d, J = 8.5 Hz, 1 H, 5-H or 6-H), 6.59 (d, J = 8.5 Hz, 1 H, 5-H or 6-H), 6.99–7.11 (m, 3 H, ArH), 7.14–7.23 (m, 1 H, ArH), 7.81 (s, 1 H, 2-H) ppm.

4,7-Dimethoxy-1-[(2-methylthiazol-4-yl)methyl]-1*H*-benzimidazole (2b): Compound **2b** was obtained as described for compound **2a** (alkylating agent: 4-chloromethyl-2-methylthiazole) and purified by column chromatography (ethyl acetate/methanol, 9:1). The product was isolated as a brownish oil (1.89 g, 69%). IR (film): $\tilde{\nu}$ = 2800, 1510 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.65 (s, 3 H, 2′-CH_3), 3.82 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 5.62 (s, 2 H, CH_2N), 6.50 (d, J = 8.5 Hz, 1 H, 5-H or 6-H), 6.55 (d, J = 8.5 Hz, 1 H, 5-H or 6-H), 6.70 (s, 1 H, 5′-H), 7.88 (s, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.08, 46.44, 55.89, 56.00, 102.21, 103.79, 115.43, 124.64, 135.58, 141.69, 142.75, 146.11, 152.14, 166.73 ppm. EI-MS: m/z = 289.0885 [M$^+$]; $C_{14}H_{15}N_3O_2S$ requires 289.0885. $C_{14}H_{15}N_3O_2S$·0.2 H_2O (292.96): calcd. C 57.40, H 5.29, N 14.34, S 10.94; found C 57.36, H 4.96, N 14.63, S 11.06.

1-Benzyl-1*H*-benzimidazole-4,7-dione (3a): A solution of 1-benzyl-4,7-dimethoxy-1*H*-benzimidazole (**2a**; 1.61 g, 6 mmol) in aqueous 48% HBr (40 mL) was heated to reflux for 4 h. After cooling to 4 °C over 12 h, the precipitate was filtered off and dissolved in water (50 mL). Then, an aqueous solution of 6.7 N HCl (1.05 mL), an aqueous solution of 0.3 M $K_2Cr_2O_7$ (4.8 mL), sodium acetate (1.61 g, 19.6 mmol), and CH_2Cl_2 (100 mL) were added successively. Stirring was maintained for 30 min. The aqueous layer was then extracted with $CHCl_3$ (5 × 30 mL) and the combined organic layers were dried with Na_2SO_4. After removing the solvents, the residue was purified by column chromatography (ethyl acetate). Quinone **3a** was obtained in 58% yield (0.83 g). M.p. 163 °C. IR (KBr): $\tilde{\nu}$ = 1660 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 5.53 (s, 2 H, CH_2N), 6.64 (d, J = 10.3 Hz, 1 H, 5-H or 6-H), 6.71 (d, J = 10.3 Hz, 1 H, 5-H or 6-H), 7.28–7.31 (m, 2 H, ArH), 7.35–7.39 (m, 3 H, ArH), 7.78 (s, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 50.32, 128.02, 128.96, 129.27, 130.07, 134.57, 136.22, 136.75, 142.54, 143.08, 178.49, 180.81 ppm. $C_{14}H_{10}N_2O_2$ (238.24): calcd. C 70.58, H 4.23, N 11.76; found C 70.48, H 4.27, N 11.86

1-[(2-Methylthiazol-4-yl)methyl]-1*H*-benzimidazole-4,7-dione (3b): Compound **3b** was obtained from **2b** as described for **3a**. Yield: 0.96 g (62%) after purification by column chromatography (ethyl acetate/methanol, 9:1). M.p. 152–153 °C (dec.). IR(KBr): $\tilde{\nu}$ = 1680 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.68 (s, 3 H, 2′-CH_3), 5.57 (s, 2 H, CH_2N), 6.63 (d, J = 10.4 Hz, 1 H, 5-H or 6-H), 6.70 (d, J = 10.4 Hz, 1 H, 5-H or 6-H), 7.24 (s, 1 H, 5′-H), 7.99 (s, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.21, 45.75, 118.07, 136.11, 136.79, 143.63 (2 C), 148.79 (2 C), 167.53, 178.59, 180.82 ppm. EI-MS: m/z = 259.0413 [M$^+$]; $C_{12}H_9N_3O_2S$ requires 259.0415. $C_{12}H_9N_3O_2S$·0.1 H_2O (261.08): calcd. C 55.20, H 3.55, N 16.09, S 12.36; found C 54.88, H 3.09, N 15.98, S 12.50.

3-Benzyl-8-methyl-3*H*-imidazo[4,5-*g*]quinoline-4,9-dione (6) and 1-Benzyl-8-methyl-1*H*-imidazo[4,5-*g*]quinoline-4,9-dione (7): Acetic anhydride (1.02 g, 9.95 mmol) and a solution of azadiene **4** (0.70 g, 6.3 mmol) in dry acetonitrile (5 mL) were added dropwise to a solution of quinone **3a** (1 g, 4.2 mmol) in the same solvent (140 mL). The reaction mixture was stirred for 48 h. Manganese dioxide (3.60 g, 41.6 mmol) was then added and stirring was maintained for 24 h. This mixture was filtered and concentrated. The residue was purified by column chromatography (dichloromethane/acetone, 67:33) to give **6** and **7** (0.8 g, 63% overall yield).

6: Yield: 0.37 g (29%). M.p. 278–280 °C. IR (KBr): $\tilde{\nu}$ = 1680 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.90 (d, J = 0.6 Hz, 3 H, 8-CH_3), 5.67 (s, 2 H, CH_2N), 7.36–7.39 (m, 5 H, ArH), 7.89 (s, 1 H, 2-H), 7.43 (dq, J = 4.9 and 0.6 Hz, 1 H, 7-H), 8.80 (d, J = 4.9 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.62, 50.72, 128.31, 128.89, 129.18, 130.73, 131.12, 134.53, 144.30, 144.85, 150.08, 151.57, 152.24, 155.04, 174.37, 180.05 ppm. $C_{18}H_{13}N_3O_2$ (303.31): calcd. C 71.27, H 4.32, N 13.85; found C 70.85, H 4.46, N 13.60.

7: Yield: 0.43 g (34%). M.p. 243–245 °C. IR (KBr): $\tilde{\nu}$ = 1660, 1690 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.85 (d, J = 0.6 Hz, 3 H, 8-CH_3), 5.67 (s, 2 H, CH_2N), 7.31–7.39 (m, 5 H, ArH), 7.85 (s, 1 H, 2-H), 7.41 (dq, J = 2.1 and 0.6 Hz, 1 H, 7-H), 8.83 (d, J = 2.1 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.48, 50.36, 127.78, 127.90, 128.61, 129.01, 130.72, 132.06, 134.60, 143.03, 144.50, 149.99, 150.95, 152.46, 176.65, 177.95 ppm. $C_{18}H_{13}N_3O_2$ (303.31): calcd. C 71.27, H 4.32, N 13.85; found C 71.02, H 4.50, N 13.57.

3-Benzyl-7-methyl-3*H*-imidazo[4,5-*g*]quinoline-4,9-dione (8a) and 1-Benzyl-7-methyl-1*H*-imidazo[4,5-*g*]quinoline-4,9-dione (9a): A solu-

tion of azadiene **5** (0.252 g, 2.25 mmol) in dry ethanol (2.2 mL) was added dropwise to a solution of quinone **3a** (0.357 g, 1.5 mmol) in the same solvent (11 mL). Stirring was maintained for 4 h. The precipitate was then filtered off, washed with ethanol, and purified by column chromatography (ethyl acetate/petroleum ether, 9:1) to afford **8a** and **9a** (0.27g, 59% overall yield).

8a: Yield: 0.187 g (41%). M.p. 258–260 °C. IR (KBr): $\tilde{\nu}$ = 1665 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.53 (d, J = 0.6 Hz, 3 H, 7-CH_3), 5.69 (s, 2 H, CH_2N), 7.28–7.40 (m, 5 H, ArH), 7.90 (s, 1 H, 2-H), 8.35 (dq, J = 1 and 0.6 Hz, 1 H, 8-H), 8.81 (d, J = 2.1 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.20, 51.23, 128.78, 129.36, 129.63, 129.95, 132.63, 134.88, 135.52, 139.00, 144.43, 144.67, 147.04, 154.87, 175.15, 178.34 ppm. $C_{18}H_{13}N_3O_2$ (303.31): calcd. C 71.27, H 4.32, N 13.85; found C 71.05, H 4.29, N 13.79.

9a: Yield: 0.083 g (18%). M.p. 298–300 °C. IR (KBr): $\tilde{\nu}$ = 1680, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.53 (d, J = 0.6 Hz, 3 H, 7-CH_3), 5.66 (s, 2 H, CH_2N), 7.32–7.43 (m, 5 H, ArH), 7.90 (s, 1 H, 2-H), 8.27 (dq, J = 2.3 Hz and 0.6 Hz, 1 H, 8-H), 8.85 (d, J = 2.3 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.76, 50.65, 127.91, 128.92, 129.25, 129.56, 131.32, 134.48, 134.52, 138.02, 144.47, 144.87, 146.75, 154.83, 175.70, 176.99 ppm. EI-MS: m/z = 303.1008 [M$^+$]; $C_{18}H_{13}N_3O_2$ requires 303.1008. $C_{18}H_{13}N_3O_2 \cdot 0.2\,H_2O$ (306.91): calcd. C 70.43, H 4.40, N 13.69; found C 70.31, H 4.21, N 13.64.

7-Methyl-3-[(2-methylthiazol-4-yl)methyl]-3*H*-imidazo[4,5-*g*]quinoline-4,9-dione (8b) and 7-Methyl-1-[(2-methylthiazol-4-yl)methyl]-1*H*-imidazo[4,5-*g*]quinoline-4,9-dione (9b): Compounds **8b** and **9b** were obtained from quinone **3b** and azadiene **5** (0.413 g, 85% overall yield) as described above for compounds **8a** and **9a**. They were purified by column chromatography (dichloromethane/acetone, 1:1).

8b: Yield: 0.282 g (58%). M.p. 208–210 °C. IR (KBr): $\tilde{\nu}$ = 1670 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.53 (d, J = 0.6 Hz, 3 H, 7-CH_3), 2.67 (s, 3 H, 2′-CH_3), 5.72 (s, 2 H, CH_2N), 7.42 (s, 1 H, 5′-H), 8.13 (s, 1 H, 2-H), 8.37 (dq, J = 2.1 and 0.6 Hz, 1 H, 8-H), 8.82 (d, J = 2.1 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.73, 19.05, 46.08, 118.70, 129.49, 131.84, 135.04, 138.52, 143.80, 144.93, 146.52, 148.45, 154.32, 167.22, 174.71, 177.82 ppm. $C_{16}H_{12}N_4O_2S$ (324.35): calcd. C 59.25, H 3.73, N 17.27, S 9.88; found C 58.78, H 3.76, N 17.08, S 9.99.

9b: Yield: 0.131 g (27%). M.p. 246–248 °C. IR (KBr): $\tilde{\nu}$ = 1650, 1730 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.53 (s, 3 H, 7-CH_3), 2.68 (s, 3 H, 2′-CH_3), 5.69 (s, 2 H, CH_2N), 7.27 (s, 1 H, 5′-H), 8.09 (s, 1 H, 2-H), 8.25 (d, J = 1.7 Hz, 1 H, 8-H), 8.84 (d, J = 1.7 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.74, 19.14, 46.05, 117.99, 129.49, 131.00, 134.41, 137.94, 144.60, 145.02, 146.71, 148.69, 154.75, 167.48, 175.70, 176.96 ppm. EI-MS: m/z = 324.0681 [M$^+$]; $C_{16}H_{12}N_4O_2S$ requires 324.0681). $C_{16}H_{12}N_4O_2S$ (324.35): calcd. C 59.25, H 3.73, N 17.27, S 9.88; found C 59.10, H 3.65, N 17.08, S 9.69.

4-(Acetyloxy)-3-benzyl-8-methyl-3*H*-imidazo[4,5-*g*]quinolin-9-yl Acetate (10): A mixture of **6** (0.020 g, 0.066 mmol), zinc powder (0.064 mg, 0.98 mmol), sodium acetate (0.023 g, 0.28 mmol), and acetic anhydride (2.75 mL) was stirred for 5 h. After removing the solvent, the residue was extracted with hot $CHCl_3$ (3 × 50 mL) and the combined organic extracts were dried (Na_2SO_4). The solvent was removed and the residue was purified by column chromatography (dichloromethane/acetone, 50:50) to give **10** (0.017 g, 69% yield). IR (KBr): $\tilde{\nu}$ = 1765 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.29 (s, 3 H, 4-$OCOCH_3$), 2.58 (s, 3 H, 9-$OCOCH_3$), 2.89 (d, J = 0.8 Hz, 3 H, 8-CH_3), 5.58 (s, 2 H, CH_2N), 7.13 (dq, J = 4 and 0.8 Hz, 1 H, 7-H), 7.17–7.36 (m, 5 H, ArH), 8.03 (s, 1 H, 2-H), 8.68 (d, J = 4 Hz, 1 H, 6-H^{13}C NMR ($CDCl_3$): δ = 21.08, 21.33, 21.66, 50.56, 119.31, 126.37 (2 C), 126.94, 128.57, 128.64, 128.81, 129.53, 129.58 (2 C), 134.54, 136.09, 136.36, 140.01, 148.81, 149.65; 169.62, 169.97 ppm. EI-MS: m/z = 389.1375 [M$^+$]; $C_{22}H_{19}N_3O_4$ requires 389.1375.

4-(Acetyloxy)-1-benzyl-8-methyl-1*H*-imidazo[4,5-*g*]quinolin-9-yl Acetate (11): Compound **11** was prepared as above from **7** (0.019 g, 76% yield). IR (KBr): $\tilde{\nu}$ = 1765 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.19 (s, 3 H, 4-$OCOCH_3$), 2.65 (s, 3 H, 9-$OCOCH_3$), 2.75 (d, J = 0.7 Hz, 3 H, 8-CH_3), 5.44 (d, J = 16.1 Hz, 1 H, CH_2N), 5.59 (d, J = 16.1 Hz, 1 H, CH_2N), 7.38 (dq, J = 4 and 0.7 Hz, 1 H, 7-H), 7.13–7.41 (m, 5 H, ArH), 7.98 (s, 1 H, 2-H), 8.75 (d, J = 4 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.38, 23.29 (2 C), 50.29, 120.71, 123.71, 126.76 (2 C), 127.97, 128.33, 128.87, 129.64 (2C), 135.78, 136.04, 137.70, 139.35, 142.56, 149.24, 149.61; 169.85, 170.13 ppm. EI-MS: m/z = 389.1372 [M$^+$]; $C_{22}H_{19}N_3O_4$ requires 389.1375.

4-(Acetyloxy)-3-benzyl-7-methyl-3*H*-imidazo[4,5-*g*]quinolin-9-yl Acetate (12): Compound **12** was prepared as above from **8a** (0.012 g, 47% yield). IR (KBr): $\tilde{\nu}$ = 1770 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.29 (s, 3 H, 4-$OCOCH_3$), 2.54 (d, J = 0.6 Hz, 3 H, 7-CH_3), 2.62 (s, 3 H, 9-$OCOCH_3$), 5.59 (s, 2 H, CH_2N), 7.17–7.35 (m, 5 H, ArH), 8.04 (s, 1 H, 2-H), 8.09 (dq, J = 2.2 and 0.6 Hz, 1 H, 8-H), 8.74 (d, J = 2.2 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.35, 20.79, 21.41, 50.32, 119.90, 126.53, 126.66 (2 C), 127.37, 127.99, 128.85 (2 C), 129.63 (2 C), 130.28, 134.38, 135.68, 135.97, 149.02, 152.12, 168.86, 169.42 ppm. EI-MS: m/z = 389.1378 [M$^+$]; $C_{22}H_{19}N_3O_4$ requires 389.1375.

4-(Acetyloxy)-1-benzyl-7-methyl-1*H*-imidazo[4,5-*g*]quinolin-9-yl Acetate (13): Compound **13** was prepared as above from **9a** (0.017 g, 69% yield). IR (KBr): $\tilde{\nu}$ = 1770 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.24 (s, 3 H, 4-$OCOCH_3$), 2.52 (d, J = 0.6 Hz, 3 H, 7-CH_3), 2.65 (s, 3 H, 9-$OCOCH_3$), 5.52 (s, 2 H, CH_2N), 7.11–7.39 (m, 5 H, ArH), 7.75 (dq, J = 2 and 0.6 Hz, 1 H, 8-H), 7.98 (s, 1 H, 2-H), 8.77 (d, J = 2 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.35, 21.06, 21.17, 50.61, 118.92, 126.92 (2 C), 128.50, 128.76, 128.83, 129.45, 129.60 (2 C), 129.67, 132.97, 135.91, 136.08, 137.30, 148.89, 152.53; 169.36, 169.40 ppm. EI-MS: m/z = 389.1378 [M$^+$]; $C_{22}H_{19}N_3O_4$ requires 389.1375.

X-ray Crystallographic Study: Single crystals suitable for X-ray analysis were obtained by recrystallisation from anhydrous ethanol. Crystal data for compound **8b**: $C_{16}H_{12}N_4O_2S$; M = 324.36 g mol^{-1}; triclinic, space group $P\bar{1}$, a = 4.7768(4) Å, b = 9.0378(8) Å, c = 21.575(4) Å, α = 92.121(3)°, β = 94.092(3)°, γ = 96.668(7)°, V = 736.0(1) Å^3, T = 293(2) K, Z = 2, $d_{calcd.}$ = 1.463 Mg m^{-3}, μ(Mo-K_α) = 0.24 mm^{-1}, 4015 reflections collected, 2892 unique (R_{int} = 0.082), 850 observed reflections [$I > 2\sigma(I)$]. Images were measured on a Nonius Kappa CCD diffractometer[22] (graphite monochromator, λ = 0.71073 Å) and data extracted using the DENZO[23] package. Structural solution was effected using SHELXS-86[24] and refinement completed with SHELXL-97.[25]

CCDC-205609 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[1] F. Alvarez, A. Ghérardi, P. Nebois, M.-E. Sarciron, A.-F. Pétavy, N. Walchshofer, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 977–979.

[2] C.-W. Schellhammer, S. Petersen, G. Domagk, US 3084165/1963 (*Chem. Abstr.* **1963**, *59*, 75 262).

[3] M.-E. Suh, M.-J. Kang, H.-W. Yoo, S.-Y. Park, C.-O. Lee, *Bioorg. Med. Chem.* **2000**, *8*, 2079–2083.

[4] The synthetic usefulness of azadienes has been established: B. Serckx-Poncin, A.-M. Hesbain-Frisque, L. Ghosez, *Tetrahedron Lett.* **1982**, *23*, 3261–3264.
[5] For some recent reviews on the synthesis of nitrogen-containing heterocycles by hetero Diels–Alder reactions see: a) F. Pautet, P. Nebois, Z. Bouaziz, H. Fillion, *Heterocycles* **2001**, *54*, 1095–1138; b) P. Buonora, J.-C. Olsen, T. Oh, *Tetrahedron* **2001**, *57*, 6099–6138; c) S. Jayakumar, M. P. S. Ishar, M. P. Mahajan, *Tetrahedron* **2002**, *58*, 379–471.
[6] M. Alvarez, L. Feliu, W. Ajana, J. A. Joule, J. L. Fernandez-Puentes, *Eur. J. Org. Chem.* **2000**, 849–855.
[7] Y. A. Jackson, S. A. Hepburn, W. F. Reynolds, *J. Chem. Soc., Perkin Trans. 1* **2001**, 2237–2239.
[8] Z. Bouaziz, A. Ghérardi, F. Régnier, M.-E. Sarciron, X. Bertheau, B. Fenet, N. Walchshofer, H. Fillion, *Eur. J. Org. Chem.* **2002**, 1834–1838.
[9] L. Legentil, J. Bastide, E. Delfourne, *Tetrahedron Lett.* **2003**, *44*, 2473–2475.
[10] L. Weinberger, A. R. Day, *J. Org. Chem.* **1959**, *24*, 1451–1455.
[11] A. F. Pozharskii, V. V. Kuz'menko, A. M. Simonov, *Chem. Heterocycl. Comp.* **1971**, *7*, 1036–1042.
[12] P. Jacob, P. S. Callery, A. T. Shulgin, N. Castagnoli, *J. Org. Chem.* **1976**, *41*, 3627–3629.
[13] C. Flader, J. Liu, R. F. Borch, *J. Med. Chem.* **2000**, *43*, 3157–3167.
[14] T. Severin, G. Wanninger, H. Lerche, *Chem. Ber.* **1984**, *117*, 2875–2885.
[15] A. Waldner, *Helv. Chim. Acta* **1988**, *71*, 486–492.
[16] M. Chigr, H. Fillion, A. Rougny, *Tetrahedron Lett.* **1988**, *29*, 5913–5916.
[17] J. J. P. Stewart, *J. Comput. Chem.* **1989**, *10*, 209–221.
[18] O. Cherkaoui, P. Nebois, H. Fillion, M. Domard, B. Fenet, *Tetrahedron* **1996**, *52*, 9499–9508.
[19] J. Lee, J. K. Snyder, *J. Org. Chem.* **1990**, *55*, 4995–5008.
[20] SYBYL® 6.9.2, Tripos Inc., 1699 South Hanley Rd., St. Louis, Missouri, 63144, USA.
[21] T. A. Halgren, *J. Am. Chem. Soc.* **1992**, *114*, 7827–7843.
[22] Collect data collection software, Nonius B. V., **1998**.
[23] DENZO-SMN: Z. Otwinowski, W. Minor, in *Methods in Enzymology*, vol. 276: Macromolecular Crystallography, part A (Eds.: C. W. Carter, Jr., R. M. Sweet), Academic Press, **1997**, pp. 307–326.
[24] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **1990**, *46*, 467.
[25] G. M. Sheldrick, SHELXL-97, a computer program for crystal structure refinement, University of Göttingen, Germany, **1997**.
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