Synthesis and Anti-HSV Activity of Methylenedioxy Mappicine Ketone Analogs

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Mappicine ketone (MPK) **1**, a decarboxylated E-ring analog of camptothecin (CPT) (**2**) lacking the lactone portion of CPT, has been identified in our laboratories as an antiviral lead. We have shown that MPK possesses potent activity against the herpesviruses HSV-1, HSV-2, and human cytomegalovirus (HCMV) and appears to be selective since it does not inhibit other DNA or RNA viruses. Unlike CPT, MPK does not have an antitumor activity. Although elucidation of the mechanism of action of MPK is incomplete at the present time, results in our laboratories have shown that it is different from that of Acyclovir (ACV), which inhibits viral replication by inhibition of DNA synthesis.[1] ACV-resistant HSV-1 and HSV-2 viruses are inhibited by MPK and, conversely, MPK resistant mutants are inhibited by ACV.[2]

MPK was initially discovered as a thermolysis product of CPT.[3] However, this method did not prove applicable to the preparation of analogous ring substituted MPK derivatives, making the versatility of this reaction limited. Thus, in order to prepare substituted MPK derivatives for antiviral evaluation, the development of a more general synthetic route became necessary. Impressed by the dramatic enhancement in antitumor activity achieved by the incorporation of the methylenedioxy ring on the A-ring of camptothecin (**3**),[4] we selected methylenedioxy MPK analog **4** as a synthetic target. In this report we describe the total synthesis of the methylenedioxy MPK analog **4**. Since MPK derivatives generally tend to be very insoluble in water, it was also decided to prepare the water-soluble analog **5** to facilitate in vivo antiviral evaluation. We believe that the synthetic methodology reported herein is versatile and should be applicable to a wide variety of mappicine analogs not otherwise available from semisynthesis.

Results and Discussion

Our approach to the synthesis of **4** was based on the Friedlander condensation strategy first described by Wall in the total synthesis of camptothecin.[5] Thus, in the total

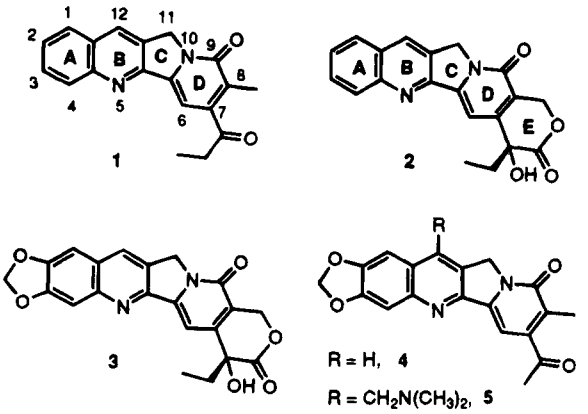
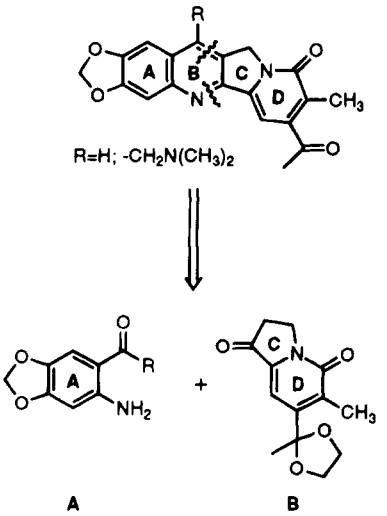


Figure 1.

Scheme 1



synthesis of MPK analogs, condensation of **A** with **B** should produce the desired MPK derivatives (Scheme 1).

The synthesis of **B** presented several challenges. One is the introduction of methyl group into the 8-position of MPK, and the other is the timing of the introduction of methyl ketone into the 7-position of MPK. The synthesis of **B**, illustrated in Scheme 2, represents the optimized sequence of steps. Reaction of 2-pyrrolidinone with dimethyl sulfate afforded methoxypyrroline (**6**) which, on treatment with diethylacetonedicarboxylate and triethylamine, afforded the indolizine **7**.[6] Standard alkylation conditions using methyl iodide and sodium hydride resulted in selective C-alkylation of **7** producing the indolizine **8**. Hydrolysis of **8** to the carboxylic acid and subsequent decarboxylation (trichlorophenol, 220 °C) produced the pyridone **9**. Treatment of compound **9** with *N*-phenyltrifluoromethanesulfonimide gave the corresponding triflate, which was subjected to a palladium-catalyzed Heck coupling[7] with butyl vinyl ether. The resulting enol vinyl ether was hydrolyzed in acid to give methyl ketone **10**. Compound **10** was protected as the ketal **11**, which was oxidized with the Davis reagent (phenyl-2-sulfonyloxaziridine)[8] to yield the alcohol **12**. Oxidation of **12** with pyridinium chlorochromate provided

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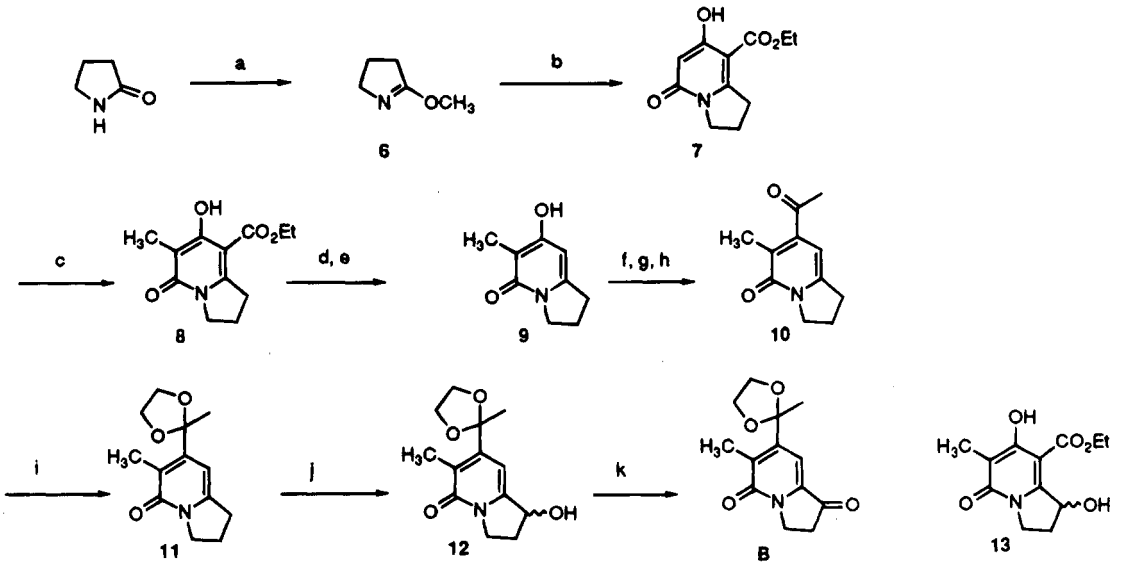
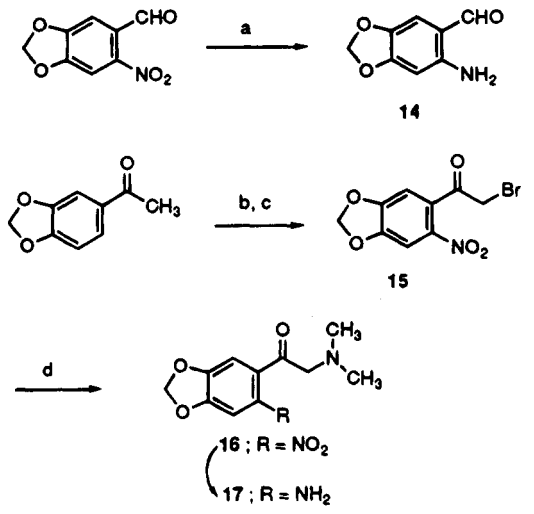
Scheme 2[a]



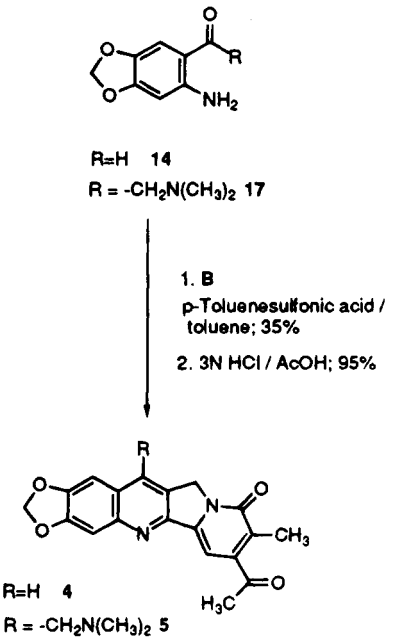
[a] (a) Me_2SO_4, 45 °C (64%); (b) diethylacetonedicarboxylate, Et_3N, rt (45%); (c) NaH, MeI, THF, rt (57%); (d) aqueous LiOH, MeOH, rt, (76%); (e) trichlorophenol, 220 °C, (98%); (f) Tf_2NPh, DMF, rt (68%); (g) butyl vinyl ether, Et_3N, $Pd(OAc)_2$, dppp, DMF (89%); (h) AcOH, HCl, rt (52%); (i) ethylene glycol, HCl, rt (86%); (j) LDA, Davis reagent, THF, −78 °C (51%); (k) PCC, CH_2Cl_2, rt (74%).

Scheme 3[a]



[a] (a) $FeSO_4$, NH_4OH, (45%); (b) HNO_3, 0−40 °C, (76%); (c) Br_2, dioxane, (58%); (d) *N'*-benzylidene-*N,N*-dimethylhydrazine CH_3CN, (27%); (e) Ni_2B, MeOH, HCl (90%).

Scheme 4



the desired indolizinone fragment **B**. It is noteworthy that a route involving hydroxylation earlier in the sequence (i.e., conversion of **8** to **13** to **12**) failed due to poor yields in the decarboxylation step.

The synthesis of fragment **A** (compounds **14** and **17**), used in the Friedlander cyclization with **B**, is illustrated in Scheme 3. Compound **17** was desired because it would lead to a water-soluble MPK derivative. Intermediate **15** was obtained by nitration of the aromatic ring followed by bromination of the ketone moiety. Subsequent conversion of **15** to **16**, however, could not be accomplished by direct displacement of the bromo ketone with dimethylamine. However, we were able to achieve the desired transformation in modest yield by the method of Magnien and Tom[9] in which bromo ketone **15** is treated with *N'*-benzylidene-*N, N*-dimethylhydrazine to form an intermediate quaternary hydrazone. The quaternary hydrazone then undergoes subsequent N−N bond heterolysis to give **16** and benzonitrile. Finally, **16** was reduced to the corresponding aniline **17** by the method of Seltzman and Berrang using nickel boride.[10]

The title compounds **4** and **5** were prepared by Friedlander condensation of **14** and **17** with **B** followed by hydrolysis of the initially formed ketal as illustrated in Scheme 4. Compounds **4** and **5** were evaluated for inhibition of HSV-2. Both compounds were determined to be more potent than the parent **1**; PR_{50}s = 0.25 μM, 0.37 μM, and 1.9 μM, respectively.[2]

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In conclusion, we believe that MPK derivatives demonstrate promising activity against herpesviruses. The synthetic methodology described herein will make access to ring substituted MPK derivatives possible and should lead to a more complete SAR within this series. Research is currently in progress to expand the SAR for this class of compounds.

Experimental Section

General Procedures. Melting points were determined on a capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained in $CDCl_3$ solvent unless otherwise stated; all values are reported in parts per million (δ) from $(CH_3)_4Si$ unless otherwise stated. Elemental analyses were performed in the Analytical and Physical Chemistry Department of SmithKline Beecham Pharmaceuticals. Mass spectra were obtained by the Physical and Structural Chemistry Department at SmithKline Beecham Pharmaceuticals. Analytical thin-layer chromatography (TLC) was carried out with silica gel plates. Column chromatography was performed with silica gel. Compounds were named following IUPAC rules.

2-Methoxypyrroline (6). 2-Pyrrolidinone (850 g, 760 mL, 10 mol) was added dropwise, over a period of 2 h, to a stirred solution of dimethyl sulfate (1260 g, 945 mL, 10 mol) under an argon atmosphere, causing the temperature to rise to 45 °C. When addition was complete, the clear mixture was stirred for 16 h at 60 °C. It was then poured onto ice and saturated K_2CO_3 and extracted with ether (2 × 1 L). The combined organic phase was washed with brine, dried (Na_2SO_4), and removed under vacuum, keeping the heating bath at 20 °C. The residual liquid was distilled under vacuum into a chilled receiver to yield, after a small forerun, 635 g (64%) of **6** as a colorless liquid, bp 35 °C/15 Torr: ^{1}H NMR δ 3.8 (s, 3H), 3.65 (t, 2H), 2.45 (t, 2H), 2.1 (m, 2H).

7-Hydroxy-8-(ethoxycarbonyl)-2,3-dihydro-1*H*-indolizin-5-one (7). To a mixture containing 2-methoxypyrroline (**6**) (100 g, 100 mL, 1 mol) and 1,3-diethyl acetonedicarboxylate (202 g, 182 mL, 1.5 mol) was added triethylamine (10 mL). The resulting mixture was kept at room temperature for 1.5 weeks after which the crystals that formed were separated by filtration and washed with petroleum ether and ethyl ether to give **7** as an off white solid (94 g, 45%), mp 131 °C: ^{1}H NMR δ 5.8 (s, 1H), 4.4 (m, 3H), 4.15 (t, 2H), 3.5 (t, 2H), 2.25 (m, 2H), 1.4 (t, 3H); mp 131 °C (lit.[6] mp 131 °C).

7-Hydroxy-8-(ethoxycarbonyl)-6-methyl-2,3-dihydro-1*H*-indolizin-5-one (8). To a solution of indolizine **7** (10 g, 45 mmol) in dry THF (500 mL) under an argon atmosphere was added NaH (2 g, 49 mmol, 60% dispersion). The resulting mixture was stirred at room temperature for 10 min. Methyl iodide (2.8 mL, 45 mmol) was added, and the mixture was stirred at room temperature for 96 h. The solvent was evaporated, and the residue was purified by flash column chromatography (silica, 0–2% methanol/CH_2Cl_2) to give **8** as a white solid (5.7 g, 57%): ^{1}H NMR δ 11.4 (s, 1H), 4.4 (m, 3H), 4.15 (t, 2H), 3.5 (t, 2H), 2.25 (m, 2H), 2.01 (s, 3H), 1.4 (t, 3H).

7-Hydroxy-6-methyl-2,3-dihydroindolizin-5-one (9). To a solution of **8** (1.2 g, 5 mmol) in methanol (30 mL), THF (20 mL), and H_2O (20 mL) was added LiOH (1g, 25 mmol), and the mixture was stirred at room temperature for 56 h. The reaction mixture was concentrated under vacuum and the resulting mixture was diluted with H_2O and acidified (pH ~ 5) with 3 N HCl. The precipitated solid was filtered and washed with H_2O and dried under vacuum to give 7-hydroxy-8-carboxy-6-methyl-2,3-dihydro-1*H*-indolizin-5-one as a tan solid 0.8 g (76%): ^{1}H NMR (CD_3OD) δ 4.23 (m, 2H), 3.5 (t, 2H), 2.35 (m, 2H), 1.95 (s, 3H). Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.20; H 5.35; N, 6.54.

The 7-hydroxy-8-carboxy-6-methyl-2,3-dihydro-1*H*-indolizin-5-one (0.8 g, 3.75 mmol) and 2,4,6-trichlorophenol (6 g) were heated at 220 °C until the evolution of carbon dioxide stopped. The resulting mixture was cooled to room temperature and diluted with ethyl ether. The precipitated solid was filtered and dried to give **9** as a solid (0.62 g, 98%): ^{1}H NMR (CD_3OD) δ 6.1 (s, 1H), 4.23 (m, 2H), 3.5 (t, 2H), 2.35 (m, 2H), 1.95 (s, 3H).

7-Acetyl-6-methyl-2,3-dihydro-1*H*-indolizin-5-one (10). To a solution of **9** (5 g, 30 mmol) in DMF (100 mL) were added triethylamine (12.6 mL, 90 mmol) and *N*-phenyltrifluoromethanesulfonimide (16 g, 45 mmol). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum and the residue purified by flash column chromatography (silica, 50–100% EtOAc/hexane) to give trifluoromethanesulfonic acid 6-methyl-5-oxo-1,2,3,5-tetrahydroindolizin-7-yl ester as a tan solid (6.15 g, 68%): ^{1}H NMR δ 6.15 (s, 1H), 4.16 (t, 2H), 3.13 (t, 2H), 2.24 (m, 2H), 2.13 (s, 3H).

To a solution of trifluoromethanesulfonic acid 6-methyl-5-oxo-1,2,3,5-tetrahydroindolizin-7-yl ester (6.15 g, 20 mmol) in DMF (100 mL) were added triethylamine (5.5 mL, 40 mmol) and n-butyl vinyl ether (10.3 mL, 80 mmol). To the resulting mixture was added $Pd(OAc)_2$ (0.27 g, 1.2 mmol) along with 1,3-bis-(diphenylphosphino)propane (0.49 g, 1.2 mmol). The resulting mixture was stirred at 60 °C for 5 h. The reaction mixture was concentrated under vacuum and the residue purified by flash column chromatography (silica, 30–60% EtOAc/hexane) to give 7-(1-butoxy-vinyl)-6-methyl-2,3-dihydro-1H-indolizin-5-one as an oil (5 g, 89%): ^{1}H NMR δ 6.15 (s, 1H), 4.35 (d, 1H), 4.16 (m, 3H), 3.79 (t, 2H), 3.1 (t, 2H), 2.2 (m, 5H), 1.72 (m, 2H), 1.48 (m, 2H), 0.95 (t, 3H).

To a solution of 7-(1-butoxyvinyl)-6-methyl-2,3-dihydro-1*H*-indolizin-5-one (5 g, 20 mmol) in glacial acetic acid (10 mL) was added 3 N HCl (3 mL), and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum and the residue resuspended in EtOAc, washed with 5% $NaHCO_3$ and NaCl, and dried (Na_2SO_4). The reaction mixture was concentrated under vacuum and the residue purified by flash column chromatography (silica, 40–100% EtOAc/hexane and 0–5% methanol/CH_2Cl_2) to give **10** as a solid (2.3 g, 52%): mp 101–102 °C; ^{1}H NMR δ 6.07 (s, 1H), 4.15 (t, 2H), 3.08 (t, 2H), 2.47 (s, 3H), 2.24 (m, 3H), 2.16 (s, 3H); MS (ES) 192 (M + H). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.76; H 7.00; N, 7.22.

6-Methyl-7-(2-methyl-1,3-dioxolan-2-yl)-2,3-dihydro-1*H*-indolizin-5-one (11). HCl (g) was bubbled into a solution of ketone **10** (2 g, 10.4 mmol) in ethylene glycol (50 mL) at 0 °C for 10 min. The resulting solution was allowed to warm to room temperature and stirred at room temperature for 14 h. The resulting mixture was poured into a solution of ice cold NH_4OH. This mixture was extracted with CH_2Cl_2, washed with H_2O and NaCl, and dried (Na_2SO_4). The reaction mixture was concentrated under vacuum and the residue purified by flash column chromatography (silica, 0–5% methanol/CH_2Cl_2) to give **11** as a solid (2.13 g, 86%): ^{1}H NMR δ 6.37 (s, 1H), 4.14 (t, 2H), 4.02 (m, 2H), 3.73 (m, 2H), 3.04 (t, 2H), 2.27 (s, 3H), 2.16 (m, 2H), 1.61 (s, 3H).

1-Hydroxy-6-methyl-7-(2-methyl-1,3-dioxolan-2-yl)-2,3-dihydro-1*H*-indolizin-5-one (12). To a solution of diisopropylamine (1.89 mL, 13.6 mmol) in THF (20 mL) at −78 °C was added n-butyllithium (5.4 mL, 13.6 mmol), and the resulting solution was stirred at −78 °C for 10 min. To this was added dropwise a solution of the ketal **11** (2.13 g, 9 mmol) in THF (100 mL), and the resulting mixture was stirred at −78 °C for 10 min. Phenyl-2-sulfonyloxaziridine (Davis reagent)[8] (3.54 g, 18 mmol) in THF (20 mL) was added, and the resulting mixture was stirred at −78 °C, for 1 h. To the reaction mixture was added a saturated solution of NH_4Cl (20 mL) at −78 °C, and the resulting mixture was extracted with CH_2Cl_2. The aqueous layer was acidified with 3 N HCl and extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O and brine and dried (Na_2SO_4). The solvent was removed in vacuo and the residue purified by flash column chromatography (silica, 0–7% methanol: CH_2Cl_2) to give **12** as a foam (1.16 g, 51%): ^{1}H NMR δ 6.66 (s, 1H), 5.21 (br s, 1H), 4.14 (m, 1H), 4.04 (br s, 1H), 3.99 (m, 3H), 3.73 (m, 2H), 2.46 (m, 1H), 2.27 (s, 3H), 2.16 (m, 1H), 1.61 (s, 3H).

6-Methyl-7-(2-methyl-1,3-dioxolan-2-yl)-2,3-dihydro-1*H*-indolizine-1,5-dione (B). To a solution of **12** (1.1g, 4.3 mmol) in CH_2Cl_2 (100 mL) was added pyridinium chlorochromate (1.89 g, 8.7 mmol), and the resulting mixture was stirred at room temperature for 12 h. The reaction was diluted with CH_2Cl_2, and the resulting residue was filtered through a pad of Celite. The reaction mixture was concentrated under vacuum and the residue purified by flash column chromatography (silica, 0–3% methanol/CH_2Cl_2) to give **B** as a foam (0.8 g, 74%): ^{1}H NMR δ

7.20 (s, 1H), 4.28 (br s, 2H), 4.07 (br s, 2H), 3.73 (br s, 2H), 2.89 (br s, 2H), 2.42 (s, 3H), 1.61 (s, 3H).

6-Aminopiperinal (14). A solution of 6-nitropiperinal (25 g, 0.12 mol) and 50:50 EtOH/H_2O (1.3 L) was heated to reflux, and a solution of iron sulfate heptahydrate (250 g, 1.2 mol) and H_2O (1.3 L) was added followed by the addition of ammonium hydroxide (325 mL). The resulting mixture was kept at reflux for 15 min and then was filtered hot. The resulting residue was washed with hot H_2O (1.3 L) to give **14** as a light green solid (9.7 g, 45%): MS (ES) 166 (M + H); mp 107–108 °C (lit.[11] mp 108–109 °C).

2-Bromo-1-(2-nitrophenyl)ethanone (15). HNO_3 (200 mL, 65%) was cooled to 0 °C, and 3,4-(methylenedioxy)acetophenone (41 g, 0.25 mol) was added. The resulting mixture was stirred at 40 °C for 1 h with the evolution of heat. When the evolution of heat ceased, the mixture was poured over ice. The water was decanted and the resulting gum was triturated with methanol. The solidified product was collected by filtration to give 1-(2-nitrophenyl)ethanone as a solid (40g, 76%): ^{1}H NMR δ 7.55 (s, 1H), 6.76 (s, 1H), 6.19 (s, 2H), 2.56 (s, 3H); mp 112 °C.

To a solution of 1-(2-nitrophenyl)ethanone (10 g, 47.8 mmol) in dioxane (30 mL) was added dropwise a solution of bromine (2.5 mL, 48.3 mmol) in dioxane (100 mL). The resulting mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under vacuum, and the mixture was diluted with Et_2O, washed with 5% $NaHCO_3$, H_2O, and brine and dried (Na_2SO_4). The solvent was removed under vacuum and the residue purified by flash column chromatography (silica, 0–60% Et_2O/hexane) to give **15** as a lacrymatory solid (8 g, 58%): ^{1}H NMR δ 7.62 (s, 1H), 6.84 (s, 1H), 6.22 (s, 2H), 4.23 (s, 2H).

2-(Dimethylamino)-1-(2-nitrophenyl)ethanone (16). To a solution containing benzaldehyde (5 g, 47 mmol) and ethanol (250 mL) and cooled to 10 °C was added dropwise a solution containing *N,N*-dimethylhydrazine (5.37 mL, 70.6 mmol) and ethanol (50 mL). The resulting mixture was allowed to warm to room temperature, stirred at room temperature for 30 min, and then heated to reflux and stirred for 20 h. The reaction mixture was concentrated under vacuum and the resulting mixture diluted with H_2O and extracted with Et_2O. The organic layer was washed with brine and dried (Na_2SO_4). The solvent was removed under vacuum to give *N'*-benzylidene-*N,N*-dimethylhydrazine as a light yellow oil (5.2 g, 74%): ^{1}H NMR δ 7.6 (m, 2H), 7.3 (m, 2H), 7.2 (m, 3H), 2.95 (s, 6H).

To a solution of **15** (0.5 g, 1.73 mmol) in CH_3CN (5 mL) was added *N'*-benzylidene-*N,N*-dimethylhydrazine (0.26 g, 1.73 mmol), and the resulting mixture was allowed to stand at room temperature for 24 h. The product precipitated and was filtered to give **16** as a solid (126 mg 27%): ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD): δ 7.65 (s, 1H), 7.19 (s, 1H), 6.27 (s, 2H), 4.67 (s, 2H), 3.09 (s, 6H).

1-(2-Aminophenyl)-2-(dimethylamino)ethanone (17). To a solution of **16** (0.126 g, 0.38 mmol) in methanol (5 mL) was added 1 N HCl (3 mL) and Ni_2B (200 mg). The resulting mixture was heated at 60 °C for 1 h and then diluted with H_2O and extracted with EtOAc. The organic layer was washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo to give **17** as a yellow solid (76 mg, 90%): ^{1}H NMR δ 7.28 (s, 1H), 6.45 (br s, 2H), 6.13 (s, 1H), 5.9 (s, 2H), 3.52 (s, 2H), 2.34 (s, 6H).

(11) Smith, L. I.; Opie, J. W. o-Aminobenzaldehyde. *Organic Syntheses, Wiley: New York;* Coll. Vol. 3, pp 56–58.

7-Acetyl-8-methyldioxolo[4,5-*g*]indolizino[1,2-*b*]quinolin-9(11*H*)-one (4). To a solution of **B** (0.1 g, 0.4 mmol) in toluene (10 mL) were added **14** (73 mg, 0.44 mmol) and *p*-toluenesulfonic acid (2 mg, catalyst). The resulting mixture was heated to reflux using a Dean–Stark trap for 12 h. The mixture was cooled and diluted with hexane/Et_2O (2:1), and the precipitated tan solid was filtered and dried (in vacuo) to give the corresponding ketal (65 mg, 35%): ^{1}H NMR δ 8.1 (s, 1H), 7.57 (s, 1H), 7.48 (s, 1H), 7.14 (s, 1H), 6.18 (s, 2H), 5.19 (s, 2H), 4.09 (m, 2H), 3.84 (m, 2H), 2.45 (s, 3H), 1.72 (s, 3H).

To the ketal (65 mg, 0.17 mmol) dissolved in glacial acetic acid (5 mL) was added 3 N HCl (1 mL), and the resulting mixture was heated to 70 °C for 1 h. The mixture was diluted with H_2O and extracted with CH_2Cl_2, and the organic layer was washed with brine and dried (Na_2SO_4). Solvent was removed under vacuum to give compound **4** as a yellow solid (28 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD) δ 8.23 (s, 1H), 7.49 (s, 1H), 7.35 (s, 1H), 7.19 (s, 1H), 6.20 (s, 2H), 5.23 (s, 2H), 2.64 (s, 3H), 2.32 (s, 3H); MS (ES) 335 (M + H). Anal. Calcd for $C_{19}H_{14}N_2O_4 \cdot 0.5H_2O$: C, 66.47; H, 4.40; N, 8.16. Found: C, 66.41; H 4.20; N, 8.14. mp > 300 °C.

7-Acetyl-12-[(dimethylamino)methyl]-8-methyldioxolo-[4,5-*g*]indolizino[1,2-*b*]quinolin-9(11*H*)-one (5). B (71 mg, 0.28 mmol) and **17** (71 mg; 0.31 mmol) were reacted following the above procedure. The solvent was evaporated, and the residue was purified by flash column chromatography (silica, 0–10% methanol/CH_2Cl_2) to give the corresponding ketal as a yellow solid (25 mg, 35%): ^{1}H NMR δ 7.61 (s, 1H), 7.49 (s, 1H), 7.45 (s, 1H), 6.15 (s, 2H), 5.23 (s, 2H), 4.07 (m, 2H), 3.82 (m, 2H), 3.80 (s, 2H), 2.45 (s, 3H), 2.29 (s, 6H), 1.71 (s, 3H).

The ketal was hydrolyzed following the above procedure. The resulting residue was lyophilized to give compound **5** as a yellow solid (12 mg, 75%): ^{1}H NMR (400 MHz, D_2O) δ 7.4 (s, 1H), 7.2 (s, 1H), 7.01 (s, 1H), 6.3 (s, 2H), 5.18 (s, 2H), 3.65 (s, 2H), 2.98 (s, 6H), 2.66 (s, 3H), 2.17 (s, 3H); MS (ES) 392 (M + H). Anal. Calcd for $C_{22}H_{21}N_3O_4 \cdot HCl$: C, 61.75; H, 4.17; N, 9.82. Found: C, 61.41; H 4.20; N, 9.74.

Plaque Reduction Assays. For HSV-1 and HSV-2 assays, confluent Vero cell monolayers in 24-well plates were infected with 100 pfu/well in Hanks balanced salt solution (HBSS) at 37 °C. Following 1 h of adsorption, EMEM containing 20% FBS, antibiotics, human IgG (50 mg/mL, filter sterilized through 0.45 μm filter and then mixed 1:1 with 4× complete EMEM) and the appropriate amount of compound in HBSS were added to each well. At 24 h post-infection, plaques were visualized and quantified after staining plates with crystal violet. The HCMV assay was carried out on MRC-5 cell monolayers for 7–10 days under the same liquid overlay described above. For all antiviral assays, plaques were counted and compound effectiveness evaluated in terms of percent plaque reduction compared to untreated, infected controls. Calculations for 50% plaque reduction values for antiviral compounds (PR_{50}) were mathematically derived from dose–response data using the Kärber method.

Supplementary Material Available: Copies of ^{1}H NMR spectra of **6–9**, **11–13**, and **15–17** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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