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Synthesis and Biological Activity of 5-Hydroxy-4-quinolones and 5-Methoxy-4-quinolones as Truncated Acridones

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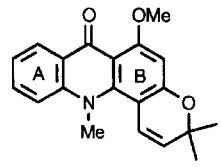
A series of 5-hydroxy-4-quinolone (**3**) and 5-methoxy-4-quinolone (**4**) derivatives were synthesized as truncated acridone analogues and evaluated for antitumor, antiherpes and antituberculosis activities. Among them 5-hydroxy-8-methoxy-quinolone showed potent antitumor activity (IC_{50}=17.7 μM for HL60) which was greater than that of acronycine. However, these compounds didn't show any significant antiherpes or antituberculosis activity.

Key words : Acridone, 5-Hydroxy-4-quinolone, 5-Methoxy-4-quinolone, Antitumor activity, Antiherpes activity, Antituberculosis activity

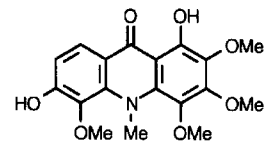
INTRODUCTION

The acridone alkaloid, acronycine (**1**) was isolated from *Acronychia baueri* in 1948 (Hugh *et al.*, 1948) and was found to have potent antitumor activity against a variety of tumor cell lines (Garzen *et al.*, 1983; Elomri *et al.*, 1996). The structure-activity relationships (SAR) of a series of naturally occurring acridone alkaloids have been studied to determine the effects of these compounds on the inhibition of cell growth and macromolecular biosynthesis of human promyelocytic leukemia cells (Price, 1983). Among 50 alkaloids tested, glyfoline (**2**) was found to be the most active compound and 22 alkaloids were found to be more active than acronycine. Further studies of glyfoline congeners by Watanabe and Su revealed that the intramolecular hydrogen bonding between the 1-hydroxy and the peri-carbonyl function of the 1-hydroxy-9-acridone nucleus was an important determinant of their cytotoxicity (Chou *et al.*, 1989 and Su *et al.*, 1989). A positive inductive effect on this hydrogen-bonding by alkyl substitution on the nitrogen (NMe_2> NHMe>NH_2) of 1-hydroxy acridones at 6-position resulted in slightly increased cytotoxicity. Although the derivatives with substituents only on the B ring (i.e., normelicopicine, 1-hydroxy-10-methyl-2,3,4-trimethoxyacridine-9-one) were inactive (Chou *et al.*, 1989), this study did not determine conclusively whether substituents on the A ring affected cytotoxicity. In addition to antitumor activity, quinolone related compounds have shown excellent antiherpes activity aganist HSV-1 and HSV-2 (Wentland *et al.*, 1993).

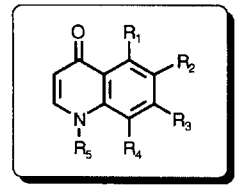
Recently we have reported synthesis and biological activities of several A-ring truncated 1-hydroxy acridone analogs and their methoxy equivalents in order to elucidate further the pharmacophore of acridone congeners and to confirm the importance of the internal hydrogen bonding to cytotoxicity (Chun *et al.*, 1997). In this paper we wish to describe the full synthesis and comprehensive structure activity relationship of 5-hydroxy-1,4-dihydro-4-quinolone analogues



1. Acronycine



2. Glyfoline



3 R = OH
4 R = OMe

Scheme 1.

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(**3**) and 5-methoxy-1,4-dihydro-4-quinolone analogues (**4**) toward antitumor, antiherpes and antituberculosis activity.

MATERIALS AND METHODS

General experimental

All chemical reagents were commercially available. Silica gel column chromatography was performed on silica gel 60, 230-400 mesh (E. Merck). ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-LA 300 at 300 MHz and JEOL JNM-GCX 400 at 400 MHz. Chemical shifts are reported in ppm unit with Me_4Si as standard. Infrared spectra were recorded on a Perkin-Elmer 1710 FT spectrometer. Mass spectra were recorded with VG TRIO-2 GC-MS.

General method of preparation of Meldrum's acid derivatives (6)

Meldrum's acid (0.022 mol) and trimethyl orthoformate (0.024 mol) was added to a stirring solution of substituted aniline (**5**) (0.02 mol) in acetonitrile (30 ml), in succession. The mixture was heated to reflux (70°C) for 2-4 hours and then cooled to room temperature. Solvent was evaporated and the residue was purified by recrystallization from aqueous methanol.

General method for thermolysis of Meldrum's acid derivative (7-27)

Meldrum's acid derivative (**6**) was added in small batches to boiling diphenyl ether (ca. 250°C, 10~20 ml) so as to maintain a concentration of 6 under 20% by weight at any time. Gas evolution was observed instantly upon addition. Heating was continued for 0.5~1 hour after addition and the mixture was then cooled to room temperature. The product mixture was separated by column chromatography using 9% methanol/chloroform as eluant.

[(3-Methoxyanilino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (6a, R_1=H, R_2=H, R_3=H)

^{1}H NMR ($CDCl_3$) δ 11.20 (br. d, 1 H, J=14 Hz, NH), 9.62 (d, 1 H, J=14 Hz), 6.76~7.26 (m, 4 H), 3.95 (s, 3 H, OCH_3), 1.75 (s, 6 H, 2×CH_3); IR (cm^{-1}) 3431, 1720, 1676, 1630, 1590, 1487, 1277, 1221; MS (m/e) 277 (M^+), 233, 188, 174; Yield: 95.4%.

[(2,5-Dimethoxyanilino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (6b, R_1=H, R_2=H, R_3=OCH_3)

^{1}H NMR ($CDCl_3$) δ 11.10 (br. d, 1 H, J=14 Hz, NH), 9.99 (d, 1 H, J=14 Hz), 6.94~7.24 (m, 3 H), 4.18 (s, 3 H, OCH_3), 4.08 (s, 3 H, OCH_3), 1.78 (s, 6 H, 2×CH_3); IR (cm^{-1}) 3452, 1723, 1673, 1636, 1600, 1457, 1300, 1278, 1201; MS (m/e) 307 (M^+), 249, 205, 177, 162; Yield: 95.2%.

[(3,4-Dimethoxyanilino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (6c, R_1=OCH_3, R_2=H, R_3=H)

^{1}H NMR ($CDCl_3$) δ 11.24 (br. d, 1 H, J=14 Hz, NH), 8.58 (d, 1 H, J=14 Hz), 6.72 (m, 3 H), 3.98 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 1.81 (s, 6 H, 2×CH_3), IR (cm^{-1}) 3436, 1733, 1678, 1635, 1592, 1276, 1200, 1157; MS (m/e) 307 (M^+), 249, 205, 177, 162; Yield: 90.2%

[(3,4,5-Trimethoxyanilino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (6d, R_1=OCH_3, R_2=OCH_3, R_3=H)

^{1}H NMR ($CDCl_3$) δ 11.22 (br. d, 1 H, J=14 Hz, NH), 9.55 (d, 1 H, J=14 Hz), 6.44 (s, 2 H), 3.99 (s, 6 H, 2×OCH_3), 3.91 (s, 3 H, OCH_3), 1.68 (s, 6 H, 2×CH_3); IR (cm^{-1}) 3444, 1727, 1681, 1631, 1595, 1515, 1479, 1444, 1417, 1273, 1217, 1124; MS (m/e) 337 (M^+), 279, 234, 204, 192, 177; Yield: 88.8%.

[(2-Chloro-5-methoxyanilino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (6f, R_1=H, R_2=H, R_3=Cl)

^{1}H NMR ($CDCl_3$) δ 11.55 (br. d, 1 H, J=14 Hz, NH), 8.55 (d, 1 H, J=14 Hz), 7.29 (d, 1 H, J=8.8 Hz). 6.84 (d, 1 H, J=3.0 Hz), 6.68 (dd, 1 H, J=8.8, 3.0 Hz), 3.78 (s, 3 H, OCH_3), 1.69 (s, 6 H, 2×CH_3); IR (cm^{-1}) 3421, 1729, 1700, 1688, 1598, 1456, 1430, 1276, 1197; MS (m/e) 313 (M^++2), 311 (M^+), 253, 208, 174; Yield: 85.2 %.

[(3-Methyl-5-methoxyanilino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (6g, R_1=H, R_2=CH_3, R_3=H)

^{1}H NMR ($CDCl_3$) δ 11.10 (br. d, 1 H, J=14 Hz, NH), 8.54 (d, 1 H, J=14 Hz), 7.07 (d, 1 H, J=8.0 Hz). 6.74 (d, 1 H, J=2.4 Hz), 6.66 (dd, 1 H, J=8.0, 2.4 Hz), 3.75 (s, 3 H, OCH_3), 2.51 (s, 3 H, CH_3), 1.68 (s, 6 H, 2×CH_3); IR (cm^{-1}) 3452, 1723, 1673, 1636, 1600, 1457, 1300, 1278, 1201; MS (m/e) 291 (M^+), 233, 188, 174; Yield: 90.1%.

[(3-Methoxy-5-trifluoromethylanilino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (6h, R_1=H, R_2=CF_3, R_3=H)

^{1}H NMR ($CDCl_3$) δ 11.19 (br. d, 1 H, J=14 Hz, NH), 8.57 (d, 1 H, J=14 Hz), 7.01 (s, 1 H). 6.96 (s, 1 H), 6.85 (s, 1 H), 3.82 (s, 3 H, OCH_3), 1.69 (s, 6 H, 2×CH_3); IR (cm^{-1}) 3445, 1726, 1674, 1632, 1611, 1494, 1340, 1283, 1253, 1221, 1166, 1132; MS (m/e) 345 (M^+), 287, 242, 200, 174; Yield: 75.9%.

[(3,5-Dimethoxyanilino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (6i, R_1=H, R_2=OCH_3, R_3=H)

^{1}H NMR ($CDCl_3$) δ 11.25 (br. d, 1 H, J=14 Hz, NH),

8.54 (d, 1 H, J=14 Hz), 6.27-6.34 (m, 3 H), 3.84 (s, 6 H, 2×OCH_3), 1.77 (s, 6 H, 2×CH_3); IR (cm^{-1}) 3448, 1731, 1666, 1627, 1597, 1520, 1469, 1408, 1260, 1211; MS (m/e) 307 (M^+), 249, 205, 174, 162; Yield: 97.5%.

5-Hydroxy-1,4-dihydro-4-quinolone (7)

^1H NMR (DMSO-d_6) δ 7.98 (d, 1 H, J=7.4 Hz, H-2), 7.47 (ps.t, 1 H, J=8.0 Hz, H-7), 6.91 (d, 1 H, J=8.3 Hz, H-6), 6.54 (d, 1 H, J=8.3 Hz, H-8), 6.08 (d, 1 H, J=7.4 Hz, H-3); IR (cm^{-1}) 3436, 2953, 1651, 1614, 1552, 1438, 1270, 1214, 831; MS (m/e) 161 (M^+), 133 (M^+-CO), 104, 78; Anal. Calcd for $C_9H_7O_2N$: C, 67.08; H, 4.35; N, 8.70. Found: C, 67.32; H, 4.31; N, 8.92.

5-Hydroxy-8-methoxy-1,4-dihydro-4-quinolone (8)

^1H NMR ($CDCl_3$) δ 8.50 (br. s, 1 H, NH), 7.64 (ps. t, 1 H, J=6.3 Hz, H-2), 7.00 (d, 1 H, J=8.8 Hz, H-7), 6.61 (d, 1 H, J=8.8 Hz, H-6), 6.25 (d, 1 H, J=6.3 Hz, H-3), 3.94 (s, 3 H, OCH_3); IR (cm^{-1}) 3308, 2832, 1624, 1601, 1566, 1482, 1454, 1231, 1065, MS (m/e) 191 (M^+), 176 (M^+-CH_3), 148; Anal. Calcd for $C_{10}H_9O_3N$: C, 62.83; H, 4.71; N, 7.33. Found: C, 62.96; H, 4.58; N, 7.07.

5-Hydroxy-8-methoxy-1-methyl-1,4-dihydro-4-quinolone (9)

^1H NMR ($CDCl_3$) δ 7.38 (d, 1 H, J=7.3 Hz, H-2), 7. 13 (d, 1 H, J=8.8 Hz, H-7), 6.69 (d, 1 H, J=8.8 Hz, H-6), 6.16 (d, 1 H, J=7.3 Hz, H-3), 4.09 (s, 3 H, OCH_3), 3.84 (s, 3 H, NCH_3); IR (cm^{-1}) 3308, 2832, 1624, 1601, 1566, 1482, 1454, 1231, 1065; MS (m/e) 191 (M^+), 176 (M^+-CH_3), 148; Anal. Calcd for $C_{11}H_{11}O_3N$: C, 64.39; H, 5.37; N, 6.83. Found: C, 64.65; H, 5.21; N, 6.57.

5,8-Dimethoxy-1,4-dihydro-4-quinolone (10)

^1H NMR ($CDCl_3$) δ 7.56 (d, 1 H, J=7.3 Hz, H-2), 7.10 (d, 1 H, J=8.8 Hz, H-7), 6.62 (d, 1 H, J=8.8 Hz, H-6), 5.89 (d, 1 H, J=7.3 Hz, H-3), 3.89 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3); IR (cm^{-1}) 3402, 1622, 1569, 1521, 1262, 1090; MS (m/e) 205 (M^+), 190 (M^+-CH_3), 175, 160, 132; Anal. Calcd for $C_{11}H_{11}O_3N$: C, 64.39; H, 5.37; N, 6.83. Found: C, 64.58; H, 5.52; N, 6.63.

6,7-Dimethoxy-5-hydroxy-1,4-dihydro-4-quinolone (11)

^1H NMR (DMSO-d_6) δ 12.05 (br. s, 1 H, NH), 7.89 (d, 1 H, J=7.3 Hz, H-2), 6.46 (s, 1 H, H-8), 5.99 (d, 1 H, J=7.3 Hz, H-3), 3.84 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3); IR (cm^{-1}) 3293, 1656, 1615, 1472, 1427, 1236, 1122; MS (m/e) 221 (M^+), 206 (M^+-CH_3), 192, 178, 135; Anal. Calcd for $C_{11}H_{11}O_4N$: C, 59.73; H, 4.98; N, 6.34. Found: C, 59.87; H, 4.84; N, 6.62.

5,6,7-Trimethoxy-1,4-dihydro-4-quinolone (12)

^1H NMR ($CDCl_3$) δ 7.79 (d, 1 H, J=7.3 Hz, H-2), 7.18 (s, 1 H, H-8), 6.21 (d, 1 H, J=7.3 Hz, H-3), 3.88 (s, 3 H, OCH_3), 3.85 (s, 6 H, 2×OCH_3); IR (cm^{-1}) 3250, 2971, 1617, 1554, 1478, 1277, 1118; MS (m/e) 235 (M^+), 220 (M^+-CH_3), 192, 177, 162, 149; Anal. Calcd for $C_{12}H_{13}O_4N$: C, 61.28; H, 5.53; N, 5.96. Found: C, 60.96; H, 5.31; N, 6.28.

6,7-Dimethoxy-5-hydroxy-1-methyl-1,4-dihydro-4-quinolone (13)

^1H NMR ($CDCl_3$) δ 14.94 (s, 1 H), 7.42 (d, 1 H, J=7.2 Hz, H-2), 6.11 (s, 1 H, H-8), 6.09 (d, 1 H, J=7.2 Hz, H-3), 3.97 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.73 (s, 3 H, NCH_3); IR (cm^{-1}) 3545, 1651, 1614, 1551, 1425, 1122; MS (m/e) 235 (M^+), 220 (M^+-CH_3), 206, 192, 189, 149; Anal. Calcd for $C_{12}H_{13}O_4N$: C, 61.28; H, 5.53; N, 5.96. Found: C, 61.52; H, 5.34; N, 5.67.

1-Methyl-5,6,7-trimethoxy-1,4-dihydro-4-quinolone (14)

^1H NMR ($CDCl_3$) δ 7.30 (d, 1 H, J=7.8 Hz, H-2), 6.47 (s, 1 H, H-8), 6.09 (d, 1 H, J=7.2 Hz, H-3), 3.98 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.70 (s, 3 H, NCH_3); IR (cm^{-1}) 3435, 1627, 1572, 1486, 1276, 1118; MS (m/e) 249 (M^+), 234 (M^+-CH_3), 216, 191, 163; Anal. Calcd for $C_{13}H_{15}O_4N$: C, 62.65; H, 6.02; N, 5.62. Found: C, 62.88; H, 6.34; N, 5.29.

7-Methoxy-1,4-dihydro-4-quinolone (15)

^1H NMR (DMSO-d_6) δ 11.53 (br. s, 1 H, NH), 7.96 (d, 1 H, J=9.8 Hz, H-2), 7.79 (ps. t, 1 H, J=7.3 Hz, H-5), 6.88 (d, 1 H, J=9.8 Hz, H-3), 6.88 (s, 1 H, H-8), 5.92 (d, 1 H, J=7.3 Hz, H-6), 3.83 (s, 3 H, OCH_3); IR (cm^{-1}) 3435, 3208, 3092, 2978, 1661, 1523, 1478, 1260, 1222; MS (m/e) 175 (M^+), 147, 132; Anal. Calcd for $C_{10}H_9O_2N$: C, 68.57; H, 5.14; N, 8.00. Found: C, 68.32; H, 5.30; N, 7.92.

7,8-Dimethoxy-1,4-dihydro-4-quinolone (16)

^1H NMR (DMSO-d_6) δ 7.77 (ps. t, J=6.8 Hz, H-2), 7.43 (s, 1 H, H-5), 6.95 (s, 1 H, H-8), 5.93 (d, 1 H, J=6.8 Hz, H-3), 3.85 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3); IR (cm^{-1}) 3245, 1605, 1547, 1449, 1273, 1220; MS (m/e) 205 (M^+), 190, 176, 162; Anal. Calcd for $C_{11}H_{11}O_3N$: C, 64.39; H, 5.37; N, 6.83. Found: C, 64.48; H, 5.49; N, 6.77.

7,8-Dimethoxy-1-methyl-1,4-dihydro-4-quinolone (17)

^1H NMR (DMSO-d_6) δ 7.86 (s, 1 H, H-5), 7.75 (d, J= 7.8 Hz, H-2), 6.74 (s, 1 H, H-8), 6.25 (d, 1 H, J=7.8

Hz, H-3), 4.03 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 3.81 (s, 3 H, NCH_3); IR (cm^{-1}) 3401, 1624, 1554, 1499, 1442, 1278, 1068; MS (m/e) 219 (M^+), 204, 188, 173, 159, 148; Anal. Calcd for $C_{12}H_{13}O_3N$: C, 65.75; H, 5.94; N, 6.39. Found: C, 66.09; H, 5.67; N, 6.50.

5,7-Dimethoxy-1,4-dihydro-4-quinolone (18)

^1H NMR (DMSO-d_6) δ 11.23 (br. s, 1 H, NH), 7.56 (d, 1 H, J=7.2 Hz, H-2), 6.44 (s, 1 H, H-8), 6.26 (s, 1 H, H-6), 5.75 (d, J=7.2 Hz, H-3), 3.79 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3); IR (cm^{-1}) 3435, 2964, 1624, 1559, 1523, 1438, 1242; MS (m/e) 205 (M^+), 190, 176, 162; Anal. Calcd for $C_{11}H_{11}O_3N$: C, 64.39; H, 5.37; N, 6.83. Found: C, 64.54; H, 5.14; N, 6.61.

5,7-Dimethoxy-1-methyl-1,4-dihydro-4-quinolone (19)

^1H NMR (DMSO-d_6) δ 7.69 (d, 1 H, J=7.2 Hz, H-2), 6.46 (s, 1 H, H-8), 6.41 (s, 1 H, H-6), 5.80 (d, J=7.2 Hz, H-3), 3.89 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.67 (s, 3 H, NCH_3); IR (cm^{-1}) 3485, 1637, 1572, 1509, 1458, 1201, 1169; MS (m/e) 219 (M^+), 204, 188, 173, 159, 148; Anal. Calcd for $C_{12}H_{13}O_3N$: C, 65.75; H, 5.94; N, 6.39. Found: C, 66.49; H, 6.07; N, 6.20.

5-Hydroxy-7-methoxy-1,4-dihydro-4-quinolone (20)

^1H NMR (DMSO-d_6) δ 11.98 (br. s, 1 H, NH), 8.30 (s, 1 H, OH), 7.88 (d, 1 H, J=7.2 Hz, H-2), 6.37 (s, 1 H, H-6), 6.15 (s, 1 H, H-8), 5.99 (d, 1 H, J=7.2 Hz, H-3), 3.79 (s, 3 H, OCH_3); IR (cm^{-1}) 3436, 1618, 1560, 1456; MS (m/e) 191 (M^+), 162, 146; Anal. Calcd for $C_{10}H_9O_3N$: C, 62.83; H, 4.71; N, 7.33. Found: C, 62.55; H, 4.90; N, 7.11.

5-Hydroxy-8-methyl-1,4-dihydro-4-quinolone (21)

^1H NMR (DMSO-d_6) δ 11.47 (br. s, 1 H, NH), 7.92 (d, 1 H, J=6.8 Hz, H-2), 7.33 (d, 1 H, J=8.0 Hz, H-6), 6.48 (d, 1 H, J=8.0 Hz, H-7), 6,12 (d, 1 H, J=6.8 Hz, H-3), 2.33 (s, 3 H, CH_3); IR (cm^{-1}) 3436, 1616, 1558, 1475, 1455, 1419, 1278, 1210; MS (m/e) 175 (M^+), 146, 130; Anal. Calcd for $C_{10}H_9O_2N$: C, 68.57; H, 5.14; N, 8.00. Found: C, 68.33; H, 5.41; N, 7.73.

5-Methoxy-8-methyl-1,4-dihydro-4-quinolone (22)

^1H NMR (DMSO-d_6) δ 7.64 (br. d, 1 H, H-2), 7.33 (d, 1 H, J=8.0 Hz, H-7), 6.64 (d, 1 H, J=8.0 Hz, H-6), 5.93 (br. d, 1 H, H-3), 3.75 (s, 3 H, OCH_3), 2.33 (s, 3 H, CH_3); IR (cm^{-1}) 3420, 2986, 1631, 1560, 1467, 1412, 1348, 1265; MS (m/e) 189 (M^+), 160, 144; Anal. Calcd for $C_{11}H_{11}O_2N$: C, 69.84; H, 5.82; N, 7.41. Found: C, 70.01; H, 5.59; N, 7.74.

5-Methoxy-8-chloro-1,4-dihydro-4-quinolone (23)

^1H NMR (DMSO-d_6) δ 10.88 (br. s, 1 H, NH), 7.69 (d, 1 H, J=8.8 Hz, H-2), 7.64 (ps. t, 1 H, J=7.6 Hz, H-7), 6.76 (d, 1 H, J=8.8 Hz, H-6), 5.95 (d, 1 H, J=7.6 Hz, H-3), 3.83 (s, 3 H, OCH_3); IR (cm^{-1}) 3435, 3225, 1627, 1605, 1566, 1510, 1352, 1065; MS (m/e) 209 (M^+), 211 (M^++2), 196, 194, 168, 151; Anal. Calcd for $C_{10}H_8O_2NCl$: C, 57.28; H, 3.82; N, 6.68. Found: C, 56.97; H, 3.64; N, 6.39.

5-Methoxy-7-trifluoromethyl-1,4-dihydro-4-quinolone (24)

^1H NMR (DMSO-d_6) δ 11.68 (br. s, 1 H, NH), 7.79 (br. d, 1 H, H-2), 7.36 (s, 1 H, H-6), 6.90 (s, 1 H, H-8), 5.96 (br. d, 1 H, H-3), 3.86 (s, 3 H, OCH_3); IR (cm^{-1}) 3436, 2920, 1647, 1615, 1575, 1388, 1244, 1195, 1116; MS (m/e) 243 (M^+), 228 (M^+-CH_3), 224, 200; Anal. Calcd for $C_{11}H_8O_2NF_3$: C, 54.32; H, 3.29; N, 5.76. Found: C, 54.55; H, 3.01; N, 5.71.

7-Hydroxy-6-methoxy-1,4-dihydro-4-quinolone (25)

^1H NMR (DMSO-d_6) d 7.90 (br.s, 1 H, OH), 7.78 (ps. t, J=6.8 Hz, H-2), 7.44 (s, 1 H, H-5), 6.96 (s, 1 H, H-8), 5.94 (d, 1 H, J=6.8 Hz, H-3), 3.84 (s, 3 H, OCH_3); IR (cm^{-1}) 3436, 3245, 1605, 1547, 1449, 1273, 1220; MS (m/e) 191(M^+), 176, 162, 148; Anal. Calcd for $C_{10}H_9O_3N$: C, 62.83; H, 4.71; N, 7.33. Found: C, 62.67; H, 4.65; N, 7.27.

7-Methoxy-5-trifluoromethyl-1,4-dihydro-4-quinolone (26)

^1H NMR (DMSO-d_6) δ 11.68 (br. s, 1 H, NH), 7.80 (br. d, 1 H, H-2), 7.37 (s, 1 H, H-6), 6.91 (s, 1 H, H-8), 5.97 (br. d, 1 H, H-3), 3.86 (s, 3 H, OCH_3); IR (cm^{-1}) 3436, 2920, 1647, 1615, 1575, 1388, 1244, 1195, 1116; MS (m/e) 243 (M^+), 228 (M^+-CH_3), 224, 200; Anal. Calcd for $C_{11}H_8O_2NF_3$: C, 54.32; H, 3.29; N, 5.76. Found: C, 54.17; H, 3.47; N, 5.58.

5-Hydroxy-7-trifluoromethyl-1,4-dihydro-4-quinolone (27)

^1H NMR (DMSO-d_6) δ 14.97 (s, 1 H, OH), 12.55 (br. s, 1 H, NH), 8.16 (d, 1 H, J=7.2 Hz, H-2), 7.26 (s, 1 H, H-6), 6.80 (s, 1 H, H-8), 6.24 (d, 1 H, J=7.2 Hz, H-3); IR (cm^{-1}) 3436, 1636, 1542, 1457, 1396, 1319, 1248, 1152; MS (m/e) 229 (M^+), 210, 186; Anal. Calcd for $C_{10}H_6O_2NF_3$: C, 52.40; H, 2.62; N, 6.11. Found: C, 52.65; H, 2.57; N, 5.96.

Biological assay

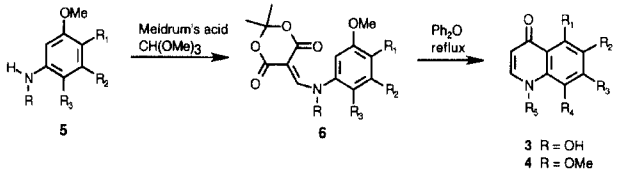
Human leukemia cell line, HL60, was used to measure antitumor activity. Activities against the murine leukemia cell line (L1210) were also tested. Both MTT assays and SRB assays were conducted for the synthesized quinolone compounds. The MTT assay was bas-

ed on the reduction of the yellow colored 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) by mitochondrial dehydrogenases of metabolically-active cells to a blue formazan, as detailed by Carmichael (Carmichael *et al.*, 1987 and Alley *et al.*, 1988). We also determined the antitumor activity of these compounds, following the protocols of the National Cancer Institute, for the sulforhodamine B assay (Skehan *et al.* 1990). Both assays gave similar IC_{50} values for the compounds tested. Antiherpes activity was determined by virus-induced cytopathic effect inhibition assay reported by Lee (Lee *et al.*, 1992). Antituberculosis activity was tested aganinst H37Rv strain and conducted at Southern Research Institute, USA.

RESULTS AND DISCUSSION

Chemistry

We obtained 5-substituted quinolones by thermolysis of 5-arylaminomethylene-2,2-dimethyl-1,3-dioxane-4, 6-diones (**6**, arylaminomethylene Meldrum's acid derivatives, Scheme 2) which was prepared by a reaction of properly-substituted arylamine (**5**) and Meldrum's acid in the presence of trimethyl orthoformate (Cassis *et al.*, 1995). The cyclization of the Meldrum's acid derivatives was carried out in boiling diphenyl ether. Under the reaction conditions, partial demethylation of 5-methoxy-4-quinolones (**4**) resulted in formation of 5-hydroxy-4-quinolones (**3**) in some cases. Since some N-methyl quinolone derivative (R=CH_3) have been isolated from the thermolysis reaction, it is believed that the nitrogen on the quinolone ring is involved in the demethylation process.



Scheme 2.

Antitumor activity

IC_{50} values for the quinolone compounds tested are listed in Table I. None of the quinolones tested had greater cytotoxicity than glyfoline, the most potent cytotoxic compounds of the class. However, 5-hydroxy-8-methoxy-quinolone (**8**) showed potent antitumor activity (IC_{50}=17.7 μM for HL60) which was greater than that of acronycine. Although general structure activity relationship of quinolones to cytotoxicity was not able to be elucidated from these data, the A-ring in the acridone-related compounds did not seem to be indispensible for cytotoxicity and correlationship between internal hydrogen bonding and cytotoxicity in quinolones also was not found.

Antiherpes activity

Antiviral activity of the quinolone compounds was

Table I. Cytotoxicity of the quinolone compounds (μM)

No.	R_1	R_2	R_3	R_4	R_5	L1210	HL-60
Acronycine (**1**)							26.2
Glyfoline (**2**)							1.4 (2.2*)
7	OH	H	H	H	H	26.5	>30.0
8	OH	H	H	OMe	H	>40.0	17.7
9	OH	H	H	OMe	Me	18.9	>30.0
10	OMe	H	H	OMe	H	>40.0	>30.0
11	OH	OMe	OMe	H	H	>40.0	>30.0
12	OMe	OMe	OMe	H	H	>40.0	>30.0
13	OH	OMe	OMe	H	Me	>40.0	>30.0
14	OMe	OMe	OMe	H	Me	>40.0	>30.0
15	H	H	OMe	H	H	>40.0	>30.0
16	H	OMe	OMe	H	H	>40.0	>30.0
17	H	OMe	OMe	H	Me	>40.0	>30.0
18	OMe	H	OMe	H	H	>40.0	>30.0
19	OMe	H	OMe	H	Me	>40.0	>30.0
20	OH	H	OMe	H	H	>40.0	>30.0
21	OH	H	H	Me	H	>40.0	>30.0
22	OMe	H	H	Me	H	>40.0	>30.0
23	OMe	H	H	Cl	H	>40.0	>30.0
24	OMe	H	CF_3	H	H	>40.0	>30.0
25	H	OMe	OH	H	H	>40.0	>30.0
26	CF_3	H	OMe	H	H	>40.0	>30.0
27	OH	H	CF_3	H	H	>40.0	>30.0

*Ref: Su *et al.*, 1992

tested against the herpes simplex virus-1 (HSV-1) and herpes simplex virus-2 (HSV-2). Four of the compounds (**7, 8, 21, 26**) showed moderate activity against HSV-1 (IC_{50} ranged from 27.1 to 82.6 μM, Table II) and two compounds (**7, 26**) showed activity against HSV-2 (IC_{50} =29.4~83 μM). Any of these compounds, however, were not comparable to acyclovir, which is a popular antiviral agent currently in clinical use.

Anti-tuberculosis activity

Anti-tuberculosis activity was assayed against H37Rv of Mtb strain. However, none of tested compounds showed any significant activity.

Table II. Antiherpes activity of the quinolone compounds (μM)

No.	R_1	R_2	R_3	R_4	R_5	HSV-1 (SI)	HSV-2 (SI)
Acyclovir						0.2 (1250)	2.1 (119)
Ara-C						0.3 (33)	2.3 (5)
7	OH	H	H	H	H	54 (1.8)	83 (1.2)
8	OH	H	H	OMe	H	82.6 (1.2)	>100 (NC)
9	OH	H	H	OMe	Me	>100 (NC)	>100 (NC)
10	OMe	H	H	OMe	H	>100 (NC)	>100 (NC)
11	OH	OMe	OMe	H	H	>100 (NC)	>100 (NC)
12	OMe	OMe	OMe	H	H	>100 (NC)	>100 (NC)
13	OH	OMe	OMe	H	Me	>100 (NC)	>100 (NC)
14	OMe	OMe	OMe	H	Me	>100 (NC)	>100 (NC)
15	H	H	OMe	H	H	>100 (NC)	>100 (NC)
16	H	OMe	OMe	H	H	>100 (NC)	>100 (NC)
17	H	OMe	OMe	H	Me	>100 (NC)	>100 (NC)
18	OMe	H	OMe	H	H		
19	OMe	OMe	OMe	H	Me	>100 (NC)	>100 (NC)
20	OH	OMe	OMe	H	H		
21	OH	H	H	Me	H	27.1 (3.7)	>100 (NC)
22	OMe	H	H	Me	H	>100 (NC)	>100 (NC)
23	OMe	H	H	Cl	H	>100 (NC)	>100 (NC)
24	OMe	H	CF_3	H	H	>100 (NC)	>100 (NC)
25	H	OMe	OH	H	H	>100 (NC)	>100 (NC)
26	CF_3	H	OMe	H	H	29.4 (<1)	29.4 (<1)
27	OH	H	CF_3	H	H		

SI: Selectivity, NC: Not calculated

Table III. Anti-Tuberculosis activity of the quinolone compounds

No.	R_1	R_2	R_3	R_4	R_5	MIC (μg/ml)	% inhibition
Rifampin						0.031	96%
7	OH	H	H	H	H	>12.5	3%
8	OH	H	H	OMe	H	>12.5	1%
9	OH	H	H	OMe	Me	>12.5	12%
10	OMe	H	H	OMe	H	>12.5	7%
11	OH	OMe	OMe	H	H	>12.5	17%
12	OMe	OMe	OMe	H	H	>12.5	16%
13	OH	OMe	OMe	H	Me	>12.5	24%
14	OMe	OMe	OMe	H	Me	>12.5	15%
15	H	H	OMe	H	H	>12.5	9%
16	H	OMe	OMe	H	H	>12.5	10%
17	H	OMe	OMe	H	Me	>12.5	0%
18	OMe	H	OMe	H	H	NA	
19	OMe	OMe	OMe	H	Me	NA	
20	OH	OMe	OMe	H	H	NA	
21	OH	H	H	Me	H	>12.5	
22	OMe	H	H	Me	H	>12.5	2%
23	OMe	H	H	Cl	H	NA	4%
24	OMe	H	CF_3	H	H	NA	
25	H	OMe	OH	H	H	NA	
26	CF_3	H	OMe	H	H	NA	
27	OH	H	CF_3	H	H	NA	

NA: Not assayed

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