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Synthesis of 3(1,2-dihydro-4-hydroxy-2-oxo-3-quinolyl) furo[3,2-c] quinolin-4 (5H) ones

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ABSTRACT

3,3′-acetonylidene/ ethanalidene/ acetophynylidene bis [4-hydroxyquinolin-2(1H) one] s are formed when 4-hydroxyquinolin-2(1H)ones are reacted with glyoxals. These Compounds underwent smooth cyclodehydration in PPA to give 3(1,2-dihydro-4-hydroxy-2-oxo-3-quinolyl) furo [3,2-c] quinolin-4(5H)ones in facile manner.

KEYWORDS

4-hydroxyquinolin-2(1H)ones;
3,3′-acetonylidene/ ethanalidene/ acetophynylidene bis [4-hydroxyquinolin-2(1H) one] s;
Glyoxals;
3-quinolyl furo [3,2-c] quinolin-4(5H)ones.

INTRODUCTION

Furo [3,2-c] quinolin-4-ones are widely distributed in nature among rutaceae family and posses a wide range of pharmacological properties like analgesic, antiphlogistic and sedative properties[1]. Recently chemistry of quinolones is gaining importance[2-7] because of their diverse biological activities[8-14]. Some candidates with quinolone scaffolds are already in market as drugs and some are in clinical trials[15-19]. In view of these potential features it was felt worthwhile to synthesize 2,3-disubstituted furo quinolones and study their spectral and physiological properties. For this purpose substituted 4-hydroxyquinolin-2 (1H)ones[20,21] have been selected as convenient starting materials. The present investigation involves a discussion of the synthesis of 3,3′-acetonylidenebis [4-hydroxy-1-methylquinolin-2 (1H)-one] and their subsequent dehydrative cyclisation to the corresponding furo quinolones, and their spectral characteristics.

EXPERIMENTAL

All the melting points are uncorrected and determined in sulphuric acid bath. The ultra-violet spectra are taken in $CHCl_3$ on Shimadzu 160 ultraviolet visible spectrophotometer. The absorption maxima λ_{max} are presented in nm along with log ε. the infrared spectra were obtained in KBr on shimadzu 435 instrument. NMR spectra were recorded on bruker (300MHz) spectro photometer with TMS as internal standard. ^{13}CNMR spectra were recorded on (75MHz) spectrophotometer. The chemical shift values are reported in δppm. The mass spectra were recorded on VG-Micro Mass 7070H instrument of direct inlet probe.

Synthesis of 3(1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolyl) 2,5-dimethylfuro [3,2-c] quinolin-4 (5H) one (5a). (General procedure)

Synthesis of 3,3'-acetonylidenebis [4-hydroxy-1-methylquinolin-2(1H)one] (4a)

As a representative case a solution of 4-hydroxy-1-methylquinolin-2 (1H) one (1a, 0.875g, 5m moles) and pyruvicaldehyde (**(2a)**, 0.3ml, 2.5 mole) in absolute ethanol (10ml) was refluxed on steam bath for 5 h. After completion of the reaction as inferred by TLC, the reaction mixture was cooled and the colorless solid was filtered, washed with a little cold ethanol. TLC of the product showed two spots. To effect separation of the two compounds the product was chromatographed over a silica gel (finer that 200 mesh) column. 3,3′-Methylenebis [4-hydroxy-1-methylquinolin-2 (1H)-one] **(3a)** was eluted with pet. ether: benzene (9:1) solvent mixture in the first fraction, yield 0.28g (31%), m.p. >300°C. 3,3′-Acetonylidenebis[4-hydroxy-1-methyl quinolin-2 (1H) one] **(4a)** was obtained in the second fraction with pet. ether: benzene (1:4) as eluent. Yield 0.495g (49%), m.p.240-241°C; UV: λ_{max} nm (log ε) 248 (4.46), 301 (4.32), 319 (4.35); IR: ν max 2900, 2600, 1720, 1640, 1605, 1530, 1450, 1340, 1240, 1160, 1030, 910, 750cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 2.23 (d, 3H, $COCH_3$), 3.73 (d, 6H, 2N-CH_3) 5.50 (d, 1H, CH), 7.20-7.70 (m, 6H, arom. H), 8.17 (d, 2H, H-5, H-5′) and δ 12.30 (s, 2H, D_2O exchangeable, OH); ^{13}C NMR: ($CDCl_3$) (APT) δ 28.43 (CH_3), 31.53 (CH_3), 31.72 (CH_3), 49.25 (CH) 115.49 (CH), 115.64 (CH), 118.94 (tertiary), 119.17 (tertiary), 126.10 (CH),126.26 (CH), 132.80 (CH), 132.80 (CH) 139.85 (tertiary), 162.70 (tertiary), 163.51 (tertiary), 166.25 (tertiary), 167.91 (tertiary) and δ 202.93 (tert.). Mass: m/z (rel.int.%) 404 (M^+, 13), 387 (62), 370 (11), 362(50), 361 (100), 344 (10), 254 (97), 229 (5), 228 (13), 226 (10), 212 (10), 200 (11), 188 (7), 187, 186, 175 (36), 147 (5), 146 (6).

Synthesis of 3 (1, 2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolyl) 2,5-dimethyl furo [3,2-c] quinolin-4 (5H) one (5a) (General procedure)

As a representative case 3,3′-acetonylidenebis[4-hydroxy-1-methylquinolin-2 (1H) one] (**(4a)**, 0.404g, 1 mmole) in PPA (10g P_2O_5 and 6 ml H_3PO_4) was heated on a steam bath for 3 h. The solution was then poured onto crushed ice, filtered, dried and chromatographed over silica gel (60-120 mesh) eluting with benzene. The colorless compound on TLC showed single spot. Yield 0.243g (63%), m.p. 191-192°C. UV: λ_{max} nm (loge) 247 (4.57), 288 (4.07), 338 (4.41); IR: ν_{max} 2940, 1640, 1625, 1600, 1550, 1310, 1240, 1150, 1100, 990, 880, 755cm^{-1} ; ^{1}H NMR: ($CDCl_3$) δ 2.33 (s, 3H, CH_3), 3.70 (s, 3H, $N^{1'}$-CH_3), 3.75 (s, 3H, N^5-CH_3), 6.84-7.50 (m, 6H, arom. H), 7.7 (d, 2H, H-9, H-5') and 10.30 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR: ($CDCl_3$) (APT) δ 13.26 (CH_3) 29.54 (CH_3), 29.69 (CH_3), 103.137 (tertiary). 110.90 (tertiary), 112.68 (tertiary), 113.80 (CH), 114.84 (CH), 116.33 (tertiary), 117.33 (tertiary), 120.37 (CH), 121.43 (CH), 122.76 (CH), 123.95 (CH), 128.99 (CH), 130.54 (CH), 136.59 (tertiary), 139.22 (tertiary), 153.85 (tertiary), 154.03 (tertiary), 158.40 (tertiary), 160.24 (tertiary) and δ 162.45 (tertiary). Mass: m/z (rel.int.%) 386 (M^+, 14), 212 (50), 184(20), 183 (11), 175 (100), 174 (40), 169 (9), 168 (8), 157 (8), 156 (7), 155 (8), 146 (23), 134 (10), 133 (26), 132 (15), 105 (87), 104 (25), 77 (46).

Similarly, other compounds **(4b-4l)** and **(5b-5l)** are synthesized and their characteristic data is given below.

Synthesis of 3 (1,2-dihydro-1-ethyl-4-hydroxy-2-oxo-3-quinolyl) 2-ethyl-5-methylfuro [3,2-c] quinolin-4 (5H) one (5b)

Synthesis of 3,3′-acetonylidenebis [1-ethyl-4-hydroxyquinolin-2 (1H)-one] (4b)

Yield 40%; m.p. 228-229°C; UV: λ_{max} nm (log ε) 245 (4.31), 308 (4.17), 320 (4.28); IR: ν_{max} 2900, 2560, 1715, 1630, 1600, 1540, 1410, 1370, 1240, 1170, 1030, 860, 760cm$^{-1;}$ ^{1}H NMR: ($CDCl_3$) δ 1.40 (t, 3H, N-CH_2-CH_3), 2.25(s, 3H, CO-CH_3), 4.38(q, 2H, N-CH_2- CH_3), 5.50 (s, 1H,CH), 7.22-7.71 (m 6H, arom. H), 8.20 (dd, 2H, arom. H-5, H-5′) and δ 12.13 (s, 2H, D_2O exchangeable, OH); Mass: m/z (rel.int.%) 432 (M^+, 10), 415 (70), 404 (30), 398 (7), 390 (40), 389 (100), 376 (41), 268 (60), 189 (28). Elemental analysis: Found : C,69.57%; H, 5.41%; N, 6.21%; calculated for $C_{25}H_{24}N_2O_5$; C, 69.43%; H, 5.59%; N,6.48%.

Synthesis of 3(1,2-dihydro-1-ethyl-4-hydroxy-2-oxo-3-quinolyl) 2-ethyl-5-methylfuro [3,2-c] quinolin-4 (5H) one (5b)

Yield 60%; m.p. 182-183°C; UV: λ_{max} nm (log ε) 246 (4.47), 391 (4.09), 341 (4.19); IR: ν_{max} 2900(broad), 1635, 1625, 1580, 1480, 1420, 1360, 1240, 1160, 1000, 910, 760cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 1.32-1.42 (m, 6H,N-CH_2-CH_3), 2.20 (s, 3H,CH_3),

4.09-4.31 (m, 4H, N-CH_2-CH_3), 6.98-8.10 (m, 8H, arom. H) and δ 10.20 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR: ($CDCl_3$) δ 11.32 (CH_3, N-CH_2-CH_3), 11.60 (CH_3, N_5-CH_2-CH_3), 13.71 (CH_3,C-10), 37.14 (CH_2, N-CH_2-CH_3), 39.22 (CH_2, N_5-CH_2-CH_3), 103.46 (tertiary, C-3), 110.78 (tertiary, C-3′), 112.96 (tertiary, C-3a), 113.0 (CH, C-8′), 114.98 (CH, C-6),115.95 (tertiary, C-4′a),117.61 (tertiary, C-9a), 119.97 (CH, C-5′), 122.09 (CH, C-9) 122.98 (CH, C-6'), 125.86 (CH, C-8), 127.64 (CH, C-7'), 129.46 (CH, C-7), 137.58 (tertiary, C-8′a), 139.0 (tertiary, C-5a), 154.01 (tertiary, C-2), 155.03 (tertiary, C-4′), 158.01 (tertiary, C-9b), 160.21 (tertiary, C-2′), 162.07 (tertiary, C-4); Mass: m/z (rel.int.%) 414 (M^+, 8), 386(13), 358(19), 226(46), 198(18), 183(13), 189 (100),188 (41), 169(7), 155 (10); Elemental analysis: Found : C, 72.55%; H, 5.26%; N, 6.91%; Calculated for $C_{25}H_{22}N_2O_4$; C, 72.45 %; H, 5.35 %; N,6.76%.

Synthesis of 3 (1,2-dihydro-4-hydroxy-2-oxo-1-phenyl-3-quinolyl) 2-methyl-5-phenylfuro [3,2-c]quinolin-4 (5H)one (5c)

Synthesis of 3,3'-acetonylidenebis [4-hydroxy-1-phenylquinolin-2 (1H)-one] (4c)

Yield 41%; m.p. 310-312°C; UV: λ_{max} nm (log ε) 247 (4.44), 301 (4.28), 319 (4.27); IR: ν_{max} 2850, 2580, 1715, 1635, 1605, 1520, 1495, 1380, 1330, 1280, 1250, 1180, 1210, 750cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 2.30 (s, 3H, CO-CH_3), 5.52 (s, 1H, CH), 6.64-7.68 (m, 16H, arom. H), 8.20(d, 2H, H-5, H-5^1) and δ 12.10 (D_2O exchangeable, s, 2H, OH); Mass: m/z (rel.int.%) 528 (M+, 9), 511 (68), 486 (66), 485 (100), 316 (70), 250 (9), 249 (15), 237 (42); Elemental analysis: C, 75.10%; H, 4.44%; N, 5.09%; Calculated for $C_{33}H_2N_2O_5$: C, 74.99%; H, 4.58%; N. 5.03%.

Synthesis of 3(1,2-dihydro-4-hyroxy-2-oxo-1-phenyl-3-quinolyl) 2-methyl-5-phenylfuro [3,2-c] quinolin-4 (5H) one (5c)

Yield 60%; m.p. 265-266°C; UV: λ_{max} nm (log ε) 247 (4.57), 288 (4.07), 338 (4.28). IR: ν_{max} 2925, 1640, 1625, 1600, 1580, 1460, 1360, 1240, 1160, 1010, 840, 760cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 2.33 (s, 3H, C-CH_3), 6.58-8.22 (m, 18H, arom. H) and δ 10.56 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR: ($CDCl_3$) δ 14.57 (CH_3), 106.15 (tertiary), 109.55 (tertiary), 113.02 (tertiary), 115.14 (CH), 116.39 (tertiary), 117.04 (CH), 118.23 (tertiary), 120.68 (CH), 121.81 (CH), 123.48 (CH), 124.60 (CH), 128.57 (CH), 128.91(CH), 128.97 (CH), 129.24(CH), 129.32(CH), 129.46(CH),129.94(CH), 130.03(CH), 130.11(CH), 130.33(CH), 130.55(CH), 137.27 (tertiary), 137.96 (tertiary), 138.40 (tertiary), 140.26 (tertiary), 154.69 (tertiary), 155.91 (tertiary), 160.77 (tertiary), 161.99 (tertiary) and δ 162.14 (tertiary); Mass: m/z (rel.int%) 510 (M^+, 22), 274 (39), 246 (27), 236 (48), 237 (100); Elemental analysis: Found; C, 77.78%; H, 4.21%; N, 5.33%; Calculated for $C_{33}H_{22}N_2O_4$: C, 77.63%; H, 4.34%; N, 5.49%.

Synthesis of 3(1,2-dihydro-6-bromo-4-hydroxy-1-methyl-2-oxo-3-quinolyl) 8-bromo-2, 5-dimethylfuro [3,2-c] quinolin-4 (5H) one (5d)

3,3′-Acetonylidenebis [6-bromo-4-hydroxy-1-methylquinolin-2 (1H) one] (4d)

Yield 40%; m.p. >315°C; UV: λ_{max} nm (log ε) 238 (4.46), 304 (4.28), 331 (4.33); IR: ν_{max} 2850, 2550, 1720, 1635, 1605, 1495, 1450, 1320, 1260, 1100, 840, 750cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 2.15 (d, 3H, CO-CH_3), 3.78 (d, 3H, N-CH_3), 5.55 (d, 1H, CH), 7.3-8.1 (m, 6H, arom. H) and δ 12.34 (s, 2H, OH); Elemental analysis found: C, 49.28%; H, 3.07%; N, 4.81%; calculated for $C_{23}H_{18}N_2O_5Br_2$: C, 49.13%; H, 3.23%; N, 4.98%.

3(1,2-Dihydro-6-bromo-4-hydroxy-1-methyl-2-oxo-3-quinolyl)8-bromo-2,5-dimethyl furo [3,2-c]quinolin-4(5H)one (5d)

Yield 69; m.p. 287-287°C; UV: λ_{max} nm (log ε) 246 (4.41), 288 (4.06), 336 (4.11); IR: $_{max}$ 2950, 1635, 1625, 1600, 1560, 1450, 1250, 1100, 1070, 1005, 860, 745cm^{-1} ; ^{1}H NMR: ($CDCl_3$) δ 2.30 (s.3H, C-CH_3), 3.72 (s, 3H, 1N-CH_3), 3.79 (s, 3H, N^5-CH_3), 7.10-8.02 (m, 6H, arom. H) and δ 10.50 (s, 1H, D_2O exchangealble, OH) Elemental analysis: Found : C, 50.91%; H, 2.78%; N, 5.24%; Calculated for $C_{23}H_{16}N_2O_4Br_2$: C, 50.74%; H, 2.96%; N, 5.15%.

Synthesis of 3(1,2-dihydro-4-hydroxy-1-methyl-7-nitro-2-oxo-3-quinolyl)7-nitro-2,5-dimethylfuro [3,2-c]quinolin-4(5H)one (5e)

(a) 3,3′-Acetonylidenebis [4-hydroxy-1-methyl-7-nitroquinolin-2 (1H) one] (4e)

Yield 40%; m.p. 305-307°C; UV: λ_{max} nm (log ε) 247(4.40), 300(4.30), 321(4.33); IR: ν_{max} 2900, 2550,

1720, 1640, 1605, 1520, 1340, 1260, 1105, 870, 820, 790, 750cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 2.22 (s, 3H, CO-CH_3), 3.81 (s, 6H, 2N-CH_3) 5.43 (s, 1H, CH), 7.10-8.11 (m, 6H, arom. H) and δ 12.125 (s, 2H, OH); Elemental analysis: Found :C, 55.79%; H, 3.76%; N, 11.11%; Calculated for $C_{23}H_{18}N_4O_9$: C, 55.87%; H, 3.67%; N, 11.23%.

Synthesis of 3(1,2-dihydro-4-hydroxy-1-methyl-7-nitro-2-oxo-3-quinolyl) 2,5-dimethyl-7-nitrofuro [3,2-c] quinolin-4(5H) one (5e)

Yield 52%; m.p. 220-221°C; UV: λ_{max} nm (log ε) 246 (4.31), 280 (3.86), 338 (4.01); IR: ν_{max} 2875, 1640, 1625, 1520, 1340, 1240, 1120, 1000, 750cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 2.26 (s, 3H, C-CH_3), 3.62 (s, 3H, N^1-CH_3), 3.77 (s, 3H, N^5-CH_3) and δ 7.20-8.20 (m, 6H, arom. H); Elemental analysis: Found: C, 57.86%; H, 3.51%; N, 11.67%; Calculated for $C_{23}H_{16}N_4O_8$: C, 57.98%; H, 3.39%; N, 11.76%.

Synthesis of 3(1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolyl)5-methylfuro [3,2-c]quinolin-4(5H)one (5f)

3,3'-Ethanalidenebis[4-hydroxy-1-methylquinolin-2 (1H) one] (4f)

Yield 52%; m.p. 246-247°C; UV: λ_{max} nm (log ε) 246 (4.58), 297 (4.31), 319 (4.34); IR: ν_{max} 2850, 2550, 1725, 1630, 1605, 1580, 1500, 1450, 1420, 1370, 1270, 1160, 840, 760cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 3.87 (s, 6H, N-CH_3), 5.37 (s, 1H, CH), 7.23-7.74(m, 6H, arom. H), 8.18 (dd, 2H, H-5, H-5′), 9.83 (s, 1H, CH = O) and δ 12.30 (s, 2H, OH); Mass: m/z (rel.int.%) 390 (M^+, 40), 389 (49), 372 (26), 362 (100), 361 (82), 240 (36), 188 (15), 175 (38); Elemental analysis: Found: C, 67.55%; H, 4.52%; N, 7.27%; Calculated for $C_{22}H_{18}N_2O_5$: C, 67.68%; H, 4.65%; N, 7.18%.

3(1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolyl) 5-methylfuro [3,2-c] quinolin-4 (5H) one (5f)

Yield 68%; m.p. 172-3°C; UV: λ_{max} nm (log ε) 239 (4.48), 279 (3.99), 347 (4.14); IR: ν_{max} 2940 (broad), 1640, 1625, 1600, 1550, 1340, 1250, 1140, 1010, 960, 750cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 3.72 (s, 3H, N1-CH_3), 3.78 (s, 3H, N5-CH_3), 6.92-7.80 (m, 7H, arom. H), 8.20 (d, 2H, H-5′, H-9) and δ 10.82 (s, 1H, D_2O exchangeable, OH); Mass: m/z (rel.int.%) 372 (M^+, 18), 198 (20), 174 (28), 170 (15), 175 (100), 146 (32), 134 (12), 133 (19), 157 (11), 155 (13); Elemental analysis: Found: C, 71.09%; H, 4.26%; N, 7.41%; Calculated for $C_{22}H_{16}N_2O_4$: C, 70.96%; H, 4.33%; N, 7.52%.

Synthesis of 3(1,2-dihydro-1-ethyl-4-hydroxy-2-oxo-3-quinolyl)5-ethylfuro [3,2-c] quinolin-4(5H) one (5g)

3,3′-ethanalidenebis [1-ethyl-4-hydroxyquino- lin-2(1H)-one] (4g)

Yield 30%; m.p. >300°C; UV: λ_{max} nm (log ε) 246 (4.47), 298 (4.21), 330 (4.39); IR: ν_{max} 2850, 2600, 1715, 1630, 1540, 1450, 1300, 1240, 1200, 760cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 1.40 (t, 3H, N-CH_2-CH_3), 4.40 (q, 2H, N-CH_2-CH_3), 5.41 (s, 1H, CH), 7.10-8.16 (m, 8H, arom. H), 9.79 (s, 1H, CH=O), 12.40 (s, 2H, OH); Elemental analysis: Found: C, 68.77%; H, 5.36%; N, 6.81%; Calculated for $C_{24}H_{22}N_2O_5$: C, 68.89%; H, 5.30%; N, 6.70%.

Synthesis of 3(1,2-dihydro-1-ethyl-4-hydroxy-2-oxo-3-quinolyl) 5-ethylfuro [3,2-c] quinolin-4 (5H) one (5g)

Yield 71%; m.p. 170-171°C; UV: λ_{max} nm (log ε) 248 (4.42), 287 (4.00), 341 (4.03); IR: ν_{max} 2900 (broad), 1635, 1620, 1590, 1510, 1300, 1260, 1140, 1070, 755cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 1.30 (m, 6H, N-CH_2-CH_3), 4.32 (m, 4H,N-CH_2-CH_3), 6.98-7.70 (m, 7H, arom. H), 8.15 (d, 2H, H-5′, H-9) and δ 10.70 (s, 1H, OH); Elemental analysis: Found: C, 71.72%; H, 5.17%; N, 7.09%; Calculated for $C_{24}H_{20}N_2O_4$: C, 71.98%; H, 5.03%; N, 7.00%.

Synthesis of 3 (1,2-dihydro-4-hydroxy-2-oxo-1-phenyl-3-quinolyl) 5-phenylfuro [3,2-c] quinolin-4 (5H) one (5h)

3,3′-Ethanalidenebis [4-hydroxy-1-phenylquinolin-2(1H)one (4h)

Yield 39%; m.p. 270-271°C; UV: λ_{max} nm (log ε) 229 (4.31), 301 (4.26), 321 (4.21); IR: ν_{max} 2900, 2650, 1720, 1640, 1570, 1490, 1340, 1270, 760cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 5.51 (s, 1H, CH), 6.60 (d, 2H, H-8, H-8′), 7.17-8.22, (m, 16H, arom. H), 9.98 (s, 1H, CH = O) and δ 12.41 (s, 2H, OH); Elemental analysis: Found: C, 74.56%; H, 4.48%; N, 5.38%; Calculated for $C_{32}H_{22}N_2O_5$: C, 74.70%; H, 4.31%; N, 5.45%.

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Synthesis of 3(1,2-dihydro-4-hydroxy-1phenyl-2-oxo-3-quinolyl) 5-phenyl furo [3,2-c] quinolin-4 (5H) one (5h)

Yield 64%; m.p. 202-204°C; UV: λ_{max} nm (log ε) 248 (4.41), 287 (4.06), 340 (4.30); IR: ν_{max} 2920(broad), 1640, 1625, 1570, 1500, 1300, 1260, 1140, 1060, 950, 760cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 6.56 (d, 2H, H-6, H-8′), 7.10-8.22 (m, 17H, arom. H), 10.12, (s, 1H, OH); Elemental analysis: Found: C, 77.49%; H, 4.15%; N, 5.39%; Calculated for $C_{32}H_{20}N_2O_4$: C, 77.40%; H, 4.06%; N, 5.64%.

Synthesis of 3 (1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolyl) 5-methyl-2-phenylfuro [3,2-c] quinolin-4 (5H) one (5i)

3,3′-Acetophenylidenebis[4-hydroxy-1-methylquinolin-2(1H)-one](4i)

Yield 78%; m.p. 248-249°C; UV: λ_{max} nm (log ε) 247 (4.38), 297 (4.31), 319 (4.33) IR: ν_{max} 2875, 2575, 1710, 1635, 1605, 1540, 1495, 1440, 1370, 1290, 1220, 1100, 1040, 860, 760cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 3.57 (s, 3H, N-CH_3), 3.78 (s, 3H, N-CH_3), 6.37 (s, 1H, CH), 7.23-7.83 (m, 13H, arom. H), 8.22 (d, 2H, H-5, H-5′), 12.13 (s, 1H, D_2O exchangeable, OH) and δ 12.49 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR: ($CDCl_3$) δ 30.10 (CH_3, N-CH_3), 30.17 (CH_3, N-CH_3), 43.72 (CH), 107.68 (CH), 111.48 (tertiary), 114.17 (CH), 117.87 (tertiary), 122.66 (CH), 124.84 (CH), 127.82(CH), 128.04(CH), 131.36 (CH), 131.94 (CH), 136.93 (tertiary), 138.42 (tertiary), 161.01 (tertiary), 161.95 (tertiary), 164.89 (tertiary), 166.16 (tertiary), 195.02 (tertiary); Mass: m/z (rel.int.%) 466 (M^+,3), 449 (4), 431 (2), 362 (20), 361 (53), 344 (9), 254 (100), 175 (31); Elemental analysis: Found: C, 72.21%; H, 4.56%; N, 6.17%; Calculated for $C_{28}H_{22}N_2O_5$: C, 72.09%; H, 4.75%; N, 6.01%.

Synthesis of 3(1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolyl) 5-methyl-2-phenylfuro [3,2-c] quinolin-4 (5H) one (5i)

Yield 70%; m.p. 141-142°C; UV: λ_{max} nm (log ε) 246 (4.24), 286 (3.87), 340 (4.03); IR: ν_{max} 2950 (broad), 1635, 1625, 1580, 1330, 1240, 1150, 1100, 1010, 760cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 3.66 (s, 3H, N-CH_3), 3.78 (s, 3H, N-CH_3), 7.20-7.78 (m, 11H, arom. H), 8.15 (d, 2H, H-5′, H-9), δ 10.20 (s, 1H, OH); Elemental analysis: Found: C, 75.20%; H, 4.30%; N, 6.06%; Calculated for $C_{28}H_{20}N_2O_4$: C, 74.99%; H, 4.50%; N, 6.25%.

Synthesis of 3(1,2-dihydro-1-ethyl-4hydroxy-2-oxo-3-quinolyl) 5-ethyl-2-phenylfuro [3,2-c] quinolin-4 (5H) one (5j)

3,3′-Acetophenylidenebis[4-hydroxy-1-ethylquinolin-2 (1H)-one](4j)

Yield 80%; m.p. 281-282°C; UV: λ_{max} nm (log ε) 246 (4.55), 301 (4.11), 327 (3.97); IR: ν_{max} 2850, 2550, 1720, 1630, 1470, 1300, 1280, 1220, 750cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 1.20 (t, 3H, N-CH_2 CH_3), 4.32 (q, 2H, N-CH_2-CH_3), 5.83 (s, 1H, CH), 7.10-8.20 (m, 13H, arom. H) and δ 12.22 (s, 2H, OH); Elemental analysis: Found : C, 73.06%; H, 5.00%; N, 5.78%; Calculated for $C_{30}H_{26}N_2O_5$: C, 72.86%; H, 5.30%; N, 5.67%.

Synthesis of 3(1,2-dihydro-1-ethyl-4hydroxy-2-oxo-3-quinolyl) 5-ethyl-2-phenylfuro [3,2-c] quinolin-4 (5H) one (5j)

Yield 80%; m.p. 281-282°C; UV: λ_{max} nm (log ε) 248 (4.42), 287 (4.01), 3.47 (4.33); IR: ν_{max} 2900 (broad), 1640, 1625, 1510, 1300, 1260, 1140, 1070, 1020, 755cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 1.42 (m, 6H, N-CH_2 CH_3), 4.48 (m, 4H, N-CH_2, CH_3), 7.12-7.8 (m, 11H, arom. H), 8.2 (d, 2H, H-5′, H-9), 10.24 (D_2O exchangeable, s, 1H, OH); Elemental analysis: Found: C, 75.46%; H, 5.30%; N, 5.61%; Calculated for $C_{30}H_{24}N_2O_4$: C, 75.61%; H, 5.08%; N, 5.88%.

Synthesis of 3-(1,2-dihydro-4-hydroxy-2-oxo-1-phenyl-3-quinolyl)-2,5-phenylfuro [3,2-c]quinolin-4(5H)one(5k)

3,3′-Acetophynelidenebis[4-hydroxy-1-phyenyl-quinolin-2 (1H)-one](4k)

Yield 82%; m.p.>300°C; UV: λ_{max} nm (log ε) 247 (4.47), 302 (4.07), 320 (4.19); IR: ν_{max} 2900, 2600, 1710, 1620, 1495, 1450, 1395, 1320, 1100, 760cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 5.62 (s, 1H, CH), 6.59 (D, 2H, H-8, H-8′), 6.96-8.18 (M, 21H, arom. H), 12.32 (s, 2H, OH); ^{13}C NMR: ($CDCl_3$) δ 42.01, 113.41, 114.91, 116.12, 11.00, 122.51, 123.00, 124.77, 124.84, 128.01, 128.83, 129.30, 130.06, 130.30, 131.08, 131.83, 137.59, 139.71, 156.01, 160.91, 161.03,195.60; Mass: m/z (rel.int.%) 590 (M^+, not recorded), 573 (16), 485 (40), 324 (14), 336 (30),

257 (50), 209 (11), 208 (7); Elemental analysis: Found: C, 77.01%; H, 4.49%; N, 4.96%; Calculated for $C_{38}H_{26}N_2O_5$: C, 77.27%; H, 4.44%; N, 4.74%.

3(1,2-Dihydro-4-hydroxy-2-oxo-1-phenyl-3-quinolyl)-2,5-diphenyl furo [3,2-c] quinolin-4 (5H)-one (5k)

Yield 83%; m.p.286-287°C; UV: λ_{max} nm (log ε) 238 (4.58), 288 (4.11), 339 (4.36); IR: ν_{max} 2950 (broad), 1635, 1625, 1580, 1560, 1450, 1250, 1100, 1060, 860cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ 6.66 (dd, 2H, arom. H-6, H-8′) 7.06-8.12 (m, arom. H), and 10.62 (D_2O exchangeable, s, OH); ^{13}C NMR : ($CDCl_3$) δ 115.53, 117.30, 121.23, 122.00,123.65, 124.83, 126.36, 128.65, 128.97, 129.18, 129.36,129.62, 129.66, 129.92, 130.36, 130.53, 130.53, 130.95, 131.95, 138.36, 138.89, 140.71, 156.78, 160.77, 161.51; Elemental analysis: Found: C, 79.51%; H, 4.32%; N, 4.76%; Calculated for $C_{38}H_{24}N_2O_4$: C, 79.70%; H, 4.23%; N, 4.89%.

Synthesis of 3(1,2-dihydro-6-bromo-4-hydroxy-1methyl-2-oxo-3-quinolyl) 8-bromo-5-methyl-2-phenylfuro [3,2-c] quinolin-4 (5H) one (5l)

3,3′-Acetophenylidenebis[6-bromo-4-hydroxy-1-methylquinolin-2(1H)-one](41)

Yield 75%; m.p. >300°C; UV: λ_{max} nm (log ε) 249 (4.51), 301 (4.29), 319 (4.39); IR : ν_{max} 2900, 2650, 1725, 1640, 1590, 1495, 1430, 1300, 1240, 760cm^{-1}; ^{1}H NMR : ($CDCl_3$) δ 3.73 (s, 6H, 2N-CH_3), 5.81 (s, 1H, CH), 7.03-8.22 (m, 13H, arom. H), 12.17 (s, 1H, OH); Elemental analysis: Found: C, 53.68%; H, 3.35%; N, 4.54%; Calculated for $C_{28}H_{20}N_2O_5$; C, 53.86%; H, 3.23%; N, 4.49%.

(b) Synthesis of 3-(1,2-dihydro-6-bromo-4-hydroxy-1-methyl-2-oxo-3-quinolyl)-8-bromo-5-methyl-2-phenylfuro[3,2-c]quinolin-2(1H)-one (51)

Yield 61%; m.p. 301-302°C; UV: λ_{max} nm (log ε) 247 (4.49), 286 (4.01), 344 (4.31); IR: ν_{max} 2950 (broad), 1640, 1625, 1560, 1480, 1420, 1360, 1260, 1100, 1060, 910, 750cm^{-1}; ^{1}H NMR : ($CDCl_3$) δ 3.70 (s, 3H, N-CH_3), 3.82 (s, 3H, N-CH_3), 6.96-8.18 (M, 1 1H, arom. H), 10.7 (s, 1H, OH); Elemental analysis: Found: C, 55.27%; H, 3.08%; N, 4.77%; Calculated for $C_{28}H_{18}Br_2O_4$: C, 55.45%; H, 2.99%; N, 4.62%.

RESULTS AND DISCUSSION

As a representative case 1-methyl-4-hydroxyquinolin-2(1H) one **(1a)** and pyruvicaldehyde **(2a)** were refluxed in dry ethanol for four hours. The colorless solid that separated out was filtered. TLC of the crude product showed two spots in benzene- ethyl acetate (9:1) solvent system, which were separated over a silica gel column. The first fraction of colorless crystalline needles eluted with petroleum ether-benzene (9:1) solvent mixture was sparingly soluble in 10% sodium hydroxide with a high melting point (>300°C). The compound was identified as 3,3′-methylenebis [4-hydroxy-1-methylquinolin-2(1H) one] **(3a)** which was further confirmed by obtaining undepressed mixed melting point with an authentic sample[10a].

The second compound **(4a)** was eluted with petroleum ether-benzene (1:9) solvent mixture, m.p. 241-2°C. The compound was soluble in 5% sodium hydroxide and gave a positive ferric chloride test for the hydroxyl group. Positive 2,4-DNP test indicated the presence of a carbonyl group other than the amide group. Mass spectrum of the compound displayed molecular ion peak at m/z 404. Mass spectrum and micro analytical data of the compound suggested the molecular formula $C_{23}H_{30}N_2O_5$. The IR spectrum (KBr) of the product showed two different carbonyl absorptions, at 1640cm^{-1} (amide carbonyl) and at 1720cm^{-1}(methyl ketone). Broad peaks centered around 2900 and 2600cm^{-1} are due to the stretching frequencies of the hydroxyl groups. The ^{1}H NMR spectrum in $CDC1_3$ displayed signal at δ 12.30 as a singlet integrating for two protons, exchangeable with D_2O, revealing the presence of two hydroxyl groups. The signal at δ 8.19 doublet, integrating for two protons was assigned to the periprotons at C-5and C-5′ and another broad multiplet at δ 7.20-7.70 integrating for six aromatic protons (C-6, C-7, C-8, C-6′, C-7′, C-8′). The doublet peaks at δ 5.50 (1H), 3.73 (6H) and 2.23(3H) were assigned to the C^{10}-H, N-CH_3 and $COCH_3$ respectively. The doublet nature of these peaks could not possibly be due to any coupling because of the absence of protons α to these groups. The possibility of any long-range couplings is also ruled out. These facts led us to conclude that the spectrum could possibly be a combination spectrum of a mixture consisting of the keto and enol forms of the com-

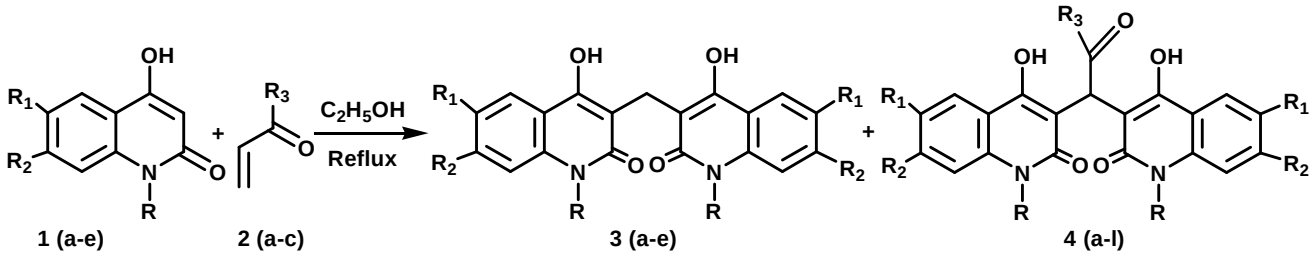
pound **(4a)**. The chemical as well as the magnetic environment of the protons on the C^{10}, N-CH_3 and $COCH_3$ carbons are expected to be different slightly leading to a small chemical shift variation. The addition of D_2O has changed the spectrum profile. The doublet peaks mentioned above have now been shown as singlets. This confirms that the compound exists in keto-enol tautomerism, which is highly sensitive to solvent polarity, and one of the tautomers could be predominant in the solvent system $CDC1_3$+D_2O. In UV spectrum the absorption maxima at λ_{max} 248 (log ε 4.46), 301 (4.32), 319nm (4.35) revealed the presence of the benzenoid and quinolone chromophores. On the basis of the above spectral data the structure of the compound has been assigned as 3,3′-acetonylidene-bis [1-methyl-4-hydroxyquinolin-2(1H)one] **(4a)** (Scheme 1).

Further the fragmentation pattern in the mass spectrum supports the assigned structure. The molecular ion (m/z 404) furnished a prominent ion at m/z 361 (100%), which forms the base peak, by loss of an acetyl group. The latter by expulsion of 186amu resulted in the ion at m/z 175, which by further loss of CO and H resulted in ions at m/z 147 and m/z 146 respectively. The other fragments formed are consistent with the assigned structure.

EXPERIMENTAL

The structure assigned for the compound **(4a)** is further substantiated by ^{13}C NMR spectrum. The ^{13}C NMR spectrum with attached proton test (APT) revealed the presence of 18 different types of carbon in the compound. A signal at δ 28.43 is assigned to the carbon C-12. The two N-methyl carbons C-9 and C-9′ are resonating at δ 31.53 and 31.72. The signal at δ 49.25 is due to the carbon at C-10. The signals at δ 115.49, 115.64, 126.10 and 126.26 have been assigned to the aromatic carbons C-8′, C-8, C-6′ and C-6 respectively. Carbons C-5 and C-5′ are resonating at δ 124.12 and carbons C-7 and C-7′ at δ 132.80. The tertiary carbons C-4a and C-4′a are represented by a signal at δ 118.94. The signal at δ 119.17 can be accounted by the two tertiary carbons C-3 and C-3′ and the signal at δ 139.85 is due to C-8a and C-8′a. The two carbons bearing hydroxyl groups viz., C-4 and C-4′ resonated at δ 162.70 and δ 163.51. The downfield signals at δ 166.25 and 167.91 are due to the carbonyl carbons C-2 and C-2′ of the quinolone ring. The bridge carbonyl C-11 resonated at δ 202.93.

The above reaction has been extended to the other substituted quinolin-2(1H)ones **(1a-e)** and glyoxals **(2a-c)** (Scheme 1).



Scheme 1

1 & 3	a	b	c	d	e
R	CH_3	C_2H_5	C_6H_5	CH_3	CH_3
R^1	H	H	H	Br	H
R^2	H	H	H	H	NO_2

2	R^3
a	CH_3
b	H
c	C_6H_5

4	a	b	c	d	e	f	g	h	i	j	k	l
R	CH_3	C_2H_5	C_6H_5	CH_3	CH_3	CH_3	C_2H_5	C_6H_5	CH_3	C_2H_5	C_6H_5	CH_3
R^1	H	H	Br	H	H	H	H	H	H	H	H	Br
R^2	H	H	H	H	NO_2	H	H	H	H	H	H	H
R^3	CH_3	CH_3	CH_3	CH_3	CH_3	H	H	H	C_6H_5	C_6H_5	C_6H_5	C_6H_5

It was observed that when reacted with pyruvic aldehyde **(2a)** and glyoxal **(2b)**, the 4-hydroxyquinolin-2(1H)-ones **(1a-e)** gave two products namely the corresponding 3,3′-methylenebis [4-hydroxyquinolin-

2(1H)ones] **(3a-e)** and 3,3′-acetonylidenebis [4-hydroxyquinolin-2 (1H)ones] **(4a-l)**, where as with phenylglyoxals **(2c)** only one product was obtained i.e. 3,3′-acetophenylidenebis [4-hydroxyquinolin-2(1H)-one] **(4i-l)**. The yields are in the range of 40-80%. The structure of these compounds **(4b-1)** has been assigned by analogy with **(4a)** and their spectral characteristics (experimental).

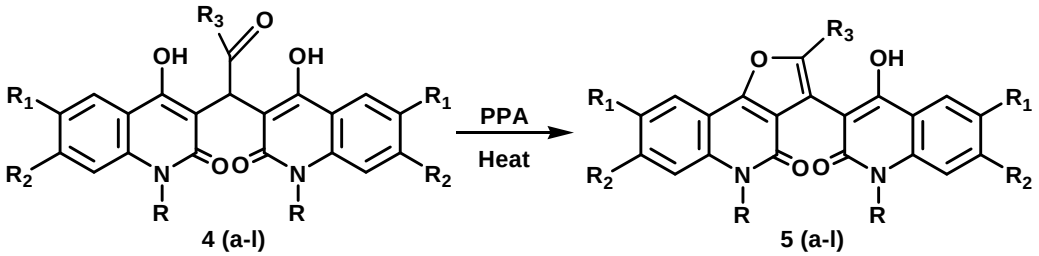
The mechanism of formation of compounds **(4a-l)** can be explained by the nucleophilic addition of 4-hydroxyquinolin-2(1H)one(1) on the aldehyde carbon of glyoxal (2) leading to an unstable dione intermediate which could add an another molecule of 4-hydroxyquinolin-2(1H)one by nucleophilic addition at the double bond forming 3,3′-acetonylidene/ ethanalidene/ acetophenylidenebis [4-hydroxyquinolin-2(1H)-ones] (4). The formation of formaldehyde from pyruvicaldehyde and glyoxal under reaction conditions could be the reason for the formation of 3,3-methylenebis [4-hydroxyquinolin-2 (1H) ones] **(3a-e)**. (Scheme 1).

3,3′-acetonylidenebis [4-hydroxy-1-methylquinolin-2(1H) one] **(4a)** smoothly underwent cyclodehydration in PPA when heated on a steam bath for 8 hours which resulted in a single colorless compound with m.p. 191-92°C. The compound was sparingly soluble in base and gave a negative 2,4-DNP test, indicating the presence of hydroxyl group and the absence of the carbonyl group. Mass spectrum furnished the molecular ion at m/z 386 suggesting the loss of a water molecule from **(4a)**, which is confirmed by micro analytical data (M.F. $C_{23}H_{18}N_2O_4$). UV spectrum ($CHCl_3$) showed absorption maxima at λ_{max} 247 (log ε 4.57), 288 (4.07), 338nm (4.41) indicating the presence of carbostyril. The IR spectrum (KBr) indicated the presence of only amide carbonyls at 1640 and 1625cm^{-1} and a hydroxyl group at 2940cm^{-1}. The ^1H NMR ($CDCl_3$) displayed signals at δ 10.30 (s, 1H D_2O exchangeable) was assigned to the OH proton, a signal at δ 7.70 (d, 2H) is due to the periprotons H-9 and H-5′. The multiplet at δ 7.50-6.84 is assigned to the aromatic protons H-6, H-7, H-8, H-6′, H-7′ and H-8′. The N-CH_3 protons at C-11 and C-12 are resonating at δ 3.75 and 3.70 respectively as two sharp singlets. The signal at δ 2.33 (s, 3H) is attributed to the methyl protons at C-10. From the foregoing spectral data, the structure of the compound has been assigned 1 as 3(1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolyl) 2,5-dimethylfuro **(3,2-c)** quinolin-4(5H)one **(5a)**.

Further the fragmentation pattern in the mass spectrum supports the above assigned structure. The molecular ion M^+ at m/z 386 (14%) fragmented to give two major fragments at m/z 212 (50%) and at m/z 174 (40%). A base peak is formed at m/z 175(100%) and the other ions formed are consistent with the assigned structure (experimental). The above conclusions are further substantiated by ^{13}C NMR (APT) ($CDCl_3$) spectrum, which indicated the presence of 23 different carbons. A signal at δ 13.26 was assigned to C-13, the peaks at δ 29.54 and δ 29.69 are due to N-methyl groups at C-11 and C-12 respectively. The chemical shifts at δ 113.08, 114.84, 120.37, 121.43, 122.76, 123.95, 128.99 and δ 130.54 are assigned to the aromatic carbons C-8′, C-6, C-5′, C-9′, C-6′, C-9, C-7′ and C-7 of the two quinolone rings in that order. The signals at δ 136.59 and δ 139.22 are attributed to C-8′a and C-5a. The downfield signals at δ 162.45 and δ 160.24 are accounted by the two amide carbonyl carbons C-4 and C-2′. The three carbons C-9b, C-4′ and C-2 which are directly linked to the oxygen atom are resonating at δ 158.40, 154.03 and δ 153.85 respectively. A peak at δ 103.13 is due to C-3, the signals at δ 112.68 and 110.90 may be related to C-3a and C-3′ and the tertiary carbons at C-4′a and C-9a are giving signals at δ 116.33 and δ 117.33 respectively.

The cyclisation of **(4a)** to 3(1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolyl) 2,5-dimethylfuro [3,2-c] quinolin-2(1H)one **(5a)** can be rationalized as follows. The first step involves the protonation of the carbonyl oxygen in the acidic medium followed by nucleophilic attack of the enolic -OH on the protonated carbonyl resulting in O-C bond formation. Finally elimination of a water molecule results in the formation of **(5a)**. Cyclodehydration of **(4a)** in concentrated sulphuric acid and polyphosphate ester (PPE) was also attempted at different temperatures. However with these reagents the desired product **(5a)** could not be obtained. In H_2SO_4 an inseparable mixture was obtained, whereas in PPE the starting material was recovered. Therefore the 3,3′-acetonylidene /ethanalidene/ acetophynylidene bis [4-hydroxyquinolin-2(1H)ones] **(4a-l)** were cyclised to the corresponding furoquinolones **(5a-l)** in PPA. In all the cases the title compounds **(5a-l)** were obtained

in good yields proving the generality of the reaction. (Scheme 2).



Scheme 2

5	a	b	c	d	e	f	g	h	i	j	k	l
R	CH_3	C_2H_5	C_6H_5	CH_3	CH_3	CH_3	C_2H_5	C_6H_5	CH_3	C_2H_5	C_6H_5	CH_3
R^1	H	H	Br	H	H	H	H	H	H	H	H	Br
R^2	H	H	H	H	NO_2	H	H	H	H	H	H	H
R^3	CH_3	CH_3	CH_3	CH_3	CH_3	H	H	H	C_6H_5	C_6H_5	C_6H_5	C_6H_5

The structures assigned for these compounds **(5a-l)** are well supported by the spectral properties (results and discussion and experimental).

CONCLUSIONS

When two moles of 4-hydroxyquinolin-2 (1H) ones were condensed with one mole of glyoxals substituted methylenebisquinolones are formed which were subjected to cyclisation in PPA, to give furoquinolones. The process provides a facile procedure for the preparation of furoquinolones in good yields.

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