# SYNTHESIS OF CERTAIN QUINOLIN-2(1*H*)-ONE α-METHYLENE-γ-BUTYROLACTONES AS POTENTIAL ANTIPLATELET AGENTS

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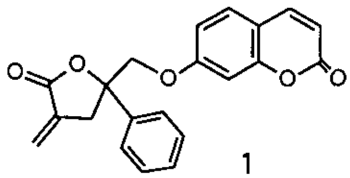
**Abstract-** Certain quinolin-2(1*H*)-one derivatives with various α-methylene-γ-butyrolactones substituted at C(7)-position were synthesized and evaluated for their antiplatelet activity against arachidonic acid (AA)-, and platelet-activating factor (PAF)-induced aggregation in washed rabbit platelets. 7-Hydroxyquinoline 1-oxide was treated with acetic anhydride followed by the hydrolysis of 1.0 N NaOH to afford 7-hydroxyquinolin-2(1*H*)-one (**6**). The desired 7-[(2,3,4,5-tetrahydro-4-methylene-5-oxo-2-furanyl)methoxy]-quinolin-2(1*H*)-ones (**8a-e**) were obtained from **6** *via* alkylation and the Reformatsky-type condensation. These quinolin-2(1*H*)-ones (**8a-e**), exhibited approximately five to seven times more potent than their coumarin counterparts against AA- and PAF-induced aggregation and are approximately two hundred times more potent than aspirin against AA-induced aggregation.

## INTRODUCTION

α-Methylene-γ-butyrolactones containing sesquiterpenes are widely distributed in nature and have been reported to exhibit wide-ranging biological activities, including antitumor, bactericidal, fungicidal, antibiotic and anthelmintic properties.[1-4] Because of their broad range of biological activities and their interesting structural features, α-methylene-γ-butyrolactones present a scientific challenge which is reflected in an increasing number of investigations and syntheses of these heterocycles.[5-10] Recently, we have synthesized certain coumarin containing α-methylene-γ-butyrolactones as potential antiplatelet agents.[11,12] Among them, 7-[(2,3,4,5-tetrahydro-4-methylene-5-oxo-2-phenylfuran-2-yl)methoxy]-2*H*-1-benzopyran-2-one (**1**) showed the most potent inhibition of arachidonic acid (AA)- and platelet-activating factor (PAF)- induced aggregation with $IC_{50}$ values of 3.65 and 16.36 μM respectively.[12] The present report describes the preparation of their bioisosteric quinolin-2(1*H*)-one α-methylene-γ-butyrolactones for the antiplatelet evaluation. A number of quinolin-2(1*H*)-one derivatives such as ethyl 4-(1,2-dihydro-2-oxo-6-quinolyloxy)butyrate,[13] 3,4-dihydro-6-[3-(1-*o*-tolylimidazol-2-yl)sulfinylpropoxy]quinolin-2(1*H*)-one,[14] and 8-[(2,3,4,5-tetrahydro-4-methylene-5-oxo-2-phenylfuranyl)methoxy]quinolin-2(1*H*)-ones[15] had been synthesized and proved to possess antiplatelet activities.



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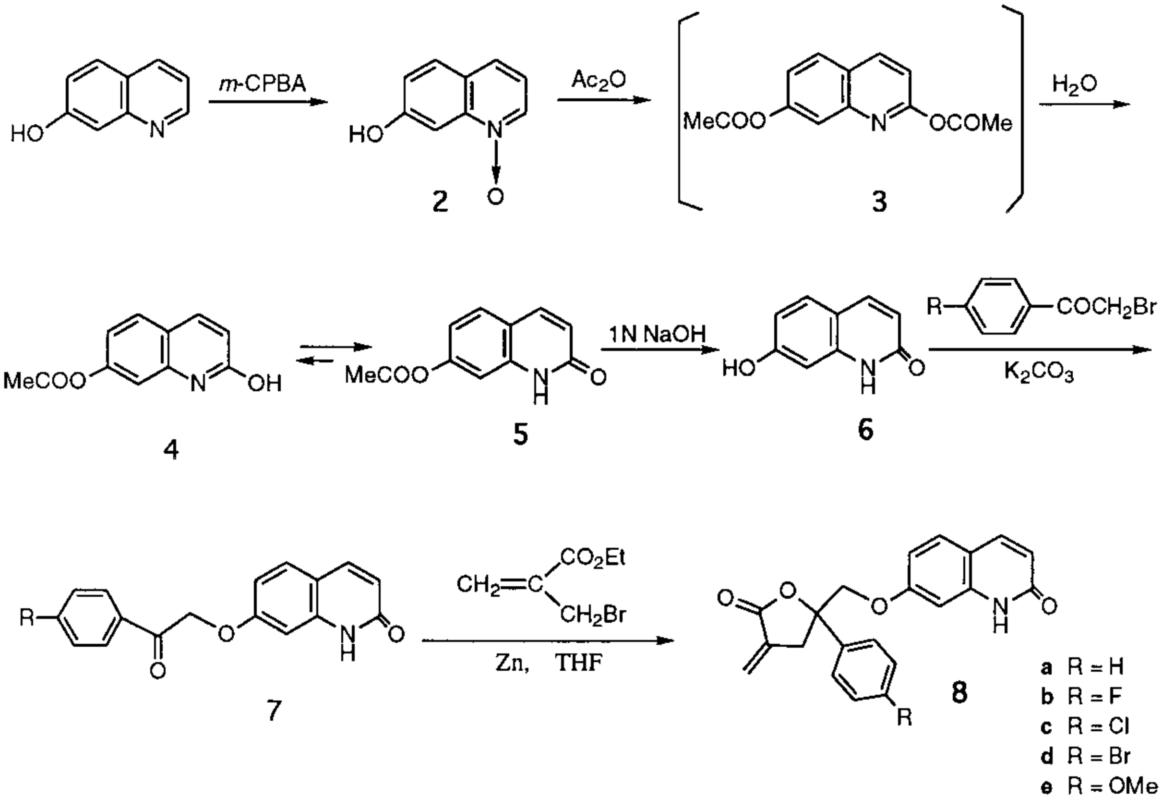
## RESULTS AND DISCUSSION

The preparation of 7-[(2,3,4,5-tetrahydro-4-methylene-5-oxo-2-furanyl)methoxy]quinolin-2(1*H*)-ones (**8a-e**) is illustrated in Scheme 1. 7-Hydroxyquinoline 1-oxide (**2**), obtained by the oxidation of 7-hydroxyquinoline, was treated with acetic anhydride to give 2,7-diacetoxyquinoline (**3**) as an intermediate. The 2-acetoxy group is less stable than the 7-acetoxy one and therefore, is more susceptible to hydrolysis during the work-up process in water, leading to the formation of 7-acetoxy-2-hydroxyquinoline (**4**) which was in equilibrium with its lactam tautomer (**5**). The equilibrium is in favor of **5** based on the X-Ray crystallographic structure of a single molecule (Figure 1) in which the bond length of O(1)-C(2) is 1.246 Å. Hydrogen positions were located from difference-Fourier and positional refined in the last cycle of least-squares refinement. There are a pair of hydrogen bondings [$(N(1)_A$---$O(1)_B$ = 2.843(3) Å; A molecule has coordinates (x, y, z), B molecule has coordinates (2-x, -y, -z)] existed between two molecules, i.e., a hydrogen bonded dimer exists in the unit cell. Hydrolysis of **5** under basic condition afforded 7-hydroxyquinolin-2(1*H*)-one (**6**) which can be alternatively prepared from 3-methoxyaniline.[16] Alkylation of **6** with 2-bromoacetophenone and potassium carbonate to give exclusively 7-(2-oxo-2-phenylethoxy)quinolin-2(1*H*)-one (**7a**) was confirmed by the long-range $^1H$-$^{13}C$-HETCOR NMR spectral evidences in which the singlet C(1') methylene protons (δ at 5.67 ppm) were clearly coupled to carbons with resonances of δ 194.15 (*J*-2), 159.68 (*J*-3), and 70.31 (*J*-1) ppm corresponding to C(2'), C(7), and C(1') respectively. Accordingly, **7b-e** were prepared from **6** and 4-substituted 2-bromoacetophenones. Reformatsky-type condensation of **7a-e** to afford the target **8a-e** proceeded smoothly in a fairly good yield.

**Scheme 1**




The inhibitory concentration for 50% aggregation ($IC_{50}$) induced by AA and PAF are summarized in Table 1. Compound (**8a**) is approximately five to seven times more active than its isosteric isomer (**1**) against AA- and PAF-induced aggregations and are approximately two hundred times more potent than aspirin against AA-induced aggregation. The $IC_{50}$ values of **8a-e** against AA- and PAF-induced aggregation are comparable, indicating that the substituent at C(γ) of the phenyl group do not affect the antiplatelet activity.

**Table 1** $IC_{50}$ Values (μM) of Quinolin-2(1*H*)-ones on the Platelet Aggregation Induced by AA (100 μg/ml) and PAF (2 nM)

| | **8a** | **8b** | **8c** | **8d** | **8e** | Aspirin |
|---|---|---|---|---|---|---|
| AA | 0.5 | 0.4 | 0.7 | 0.9 | 0.7 | 118 |
| PAF | 3.3 | 5.0 | 2.7 | 3.2 | 7.1 | >150 |

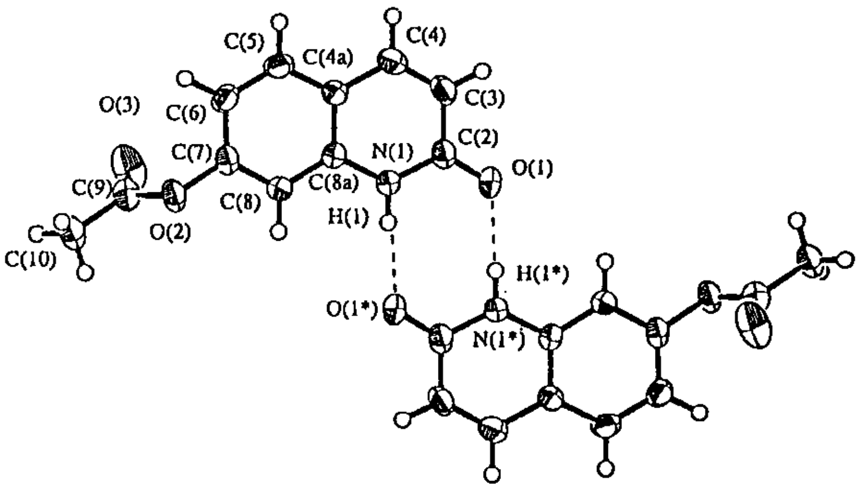



Figure 1. ORTEP drawing of **5**. Selected bond distances (Å) and angles (degree): O(1)-C(2) 1.246(3); C(4)-C(4a) 1.435(3); N(1)-C(8a) 1.382(3); N(1)-C(2) 1.372(3); C(4a)-C(8a) 1.406(3); C(3)-C(4) 1.345(4); C(2)-C(3) 1.444(4); O(1)-C(2)-N(1) 120.3(3); N(1)-C(8a)-C(4a) 118.8(2); O(1)-C(2)-C(3) 124.5(3); N(1)-C(2)-C(3) 115.1(3); C(4a)-C(8a)-C(8) 120.9(3); C(2)-C(3)-C(4) 122.0(3); C(3)-C(4)-C(4a) 121.1(3); C(2)-N(1)-C(8a) 125.2(2); N(1)-C(8a)-C(8) 120.4(2); C(4)-C(4a)-C(8a) 117.7(3).

## EXPERIMENTAL

Melting points were determined on an Electrothermal IA 9000 micromelting point apparatus and are uncorrected. The UV absorption spectra were obtained on a Beckman UV-Visible spectrophotometer. IR spectra were recorded on a Hitachi 260-30 spectrophotometer. $^{1}H$ and $^{13}C$ NMR spectra were obtained with a Varian Gemini-200 spectrometer. Chemical shifts were expressed in parts per million (δ) with tetramethylsilane as an internal standard. Thin-layer chromatography (TLC) was run on precoated (0.2 mm) *Silica gel 60 F-254 plates manufactured* by EM Laboratories, Inc., and short wave UV light (254 nm) was used to detect the UV-absorbing spots. Elemental analyses were carried out on a Heraeus CHN-O-Rapid elemental analyzer.

**7-Hydroxyquinoline 1-oxide (2)**

To a solution of 7-hydroxyquinoline (1.45 g, 10 mmol) in ethyl acetate (300 mL) was added *m*-chloroperoxybenzoic acid (2.24 g, 13 mmol). The mixture was stirred at rt for 30 min. The resulting precipitate was collected, crystallized from methanol/ether 1:10 to afford **2** (1.51 g, 94%). mp 251-252 °C. $^{1}H$-NMR (DMSO-$d_6$) δ: 7.14-8.46 (6H, m, Ar-H). $^{13}C$-NMR (DMSO-$d_6$) δ: 100.71, 117.62, 121.70, 124.01, 125.07, 130.08, 135.18, 142.37, 161.11. Anal. Calcd for $C_9H_7NO_2 \cdot 0.1\ H_2O$: C, 66.34; H, 4.45; N, 8.60. Found: C, 66.62; H, 4.37; N, 8.42.

**7-Acetoxyquinolin-2(1*H*)-one (5)**

A mixture of **2** (0.81 g, 5 mmol) in acetic anhydride (20 mL, 212 mmol) was heated at reflux for 2 h (monitored by TLC). After cooling, it was poured into ice water (100 mL) and extracted with dichloromethane (3 x 60 mL). The dichloromethane extracts were combined and washed with water, dried ($Na_2SO_4$), and then evaporated to give a brown solid which was crystallized from ethyl acetate to give **5** (0.25 g, 24%). mp 247-248 °C. $^{1}H$-NMR (DMSO-$d_6$) δ: 2.30 (3H, s, $CH_3$), 6.47 (1H, d, $J$ = 9.2 Hz, 3-H), 7.04-7.70 (3H, m, Ar-H), 7.90 (1H, d, $J$ = 9.2 Hz, 4-H), 11.82 (1H, br s, OH). $^{13}C$-NMR (DMSO-$d_6$) δ: 20.85 (Me), 107.77, 116.09, 116.96, 121.39, 129.11, 139.69, 139.78, 151.78 (Ar-Cs), 161.92 (C-2), 168.95 (COMe). Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.98; H, 4.59; N, 6.94.

**7-Hydroxyquinolin-2(1*H*)-one (6)[16]**

To a stirred suspension of **5** (0.21 g, 1 mmol) in water (20 mL) was added 1.0 N NaOH (5 mL). After completion of the reaction (*ca.* 1.5 h, monitored by TLC), the mixture was diluted with water (20 mL) and washed with ether. The aqueous layer was acidified with 6 N HCl and the resulting precipitate crystallized from methanol to give **6** (0.13 g, 90%).

**7-(2-Oxo-2-phenylethoxy)quinolin-2(1*H*)-one (7a)**

A mixture of **6** (1.61 g, 10 mmol), $K_2CO_3$ (1.38 g, 10 mmol) and dry DMF (50 mL) was stirred at rt for 30 min and then 2-bromoacetophenone (1.99 g, 10 mmol) in dry DMF (10 mL) was added in one portion. The resulting mixture was further stirred at rt for 24 h (monitored by TLC) and then poured into ice water (100 mL). The white solid thus obtained was collected and crystallized from dichloromethane to afford **7a** (1.76 g, 62%). mp 207-208 °C. $^1$H-NMR (DMSO-$d_6$) δ: 5.67 (2H, s, $OCH_2$), 6.30 (1H, d, $J$ = 9.5 Hz, 3-H), 6.76-8.06 (8H, m, Ar-H), 7.80 (1H, d, $J$ = 9.5 Hz, 4-H), 11.49 (1H, br s, NH). $^{13}$C-NMR (DMSO-$d_6$) δ: 70.31 (C-1'), 99.31, 110.55, 113.64, 118.78, 127.85, 128.88, 129.20, 133.90, 134.26, 139.92, 140.45 (Ar-Cs), 159.68 (C-7), 162.14 (C-2), 194.15 (C-2'). Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 72.82; H, 4.74; N, 5.07.

**7-[2-(4-Fluorophenyl)-2-oxoethoxy]quinolin-2(1*H*)-one (7b)**

Compound (**7b**) was prepared from 2-bromo-4'-fluoroacetophenone by the same procedure as described for **7a** in 75% yield. mp 198-199 °C (dichloromethane). $^1$H-NMR (DMSO-$d_6$) δ: 5.65 (2H, s, $OCH_2$), 6.30 (1H, d, $J$ = 9.4 Hz, 3-H), 6.76-8.16 (7H, m, Ar-H), 7.80 (1H, d, $J$ = 9.5 Hz, 4-H), 11.52 (1H, br s, NH). $^{13}$C-NMR (DMSO-$d_6$) δ: 70.23 (C-1'), 99.37, 110.49, 113.68, 115.83, 116.05, 118.79, 129.20, 130.90, 130.99, 131.05, 139.90, 140.43, 164.12, 166.63 (Ar-Cs), 159.63 (C-7), 162.15 (C-2), 192.84 (C-2'). Anal. Calcd for $C_{17}H_{12}NO_3F$: C, 68.68; H, 4.07; N, 4.71. Found: C, 68.54; H, 4.07; N, 4.71.

**7-[2-(4-Chlorophenyl)-2-oxoethoxy]quinolin-2(1*H*)-one (7c)**

Compound (**7c**) was prepared from 2-bromo-4'-chloroacetophenone by the same procedure as described for **7a** in 70% yield. mp 199-200 °C (dichloromethane). $^1$H-NMR (DMSO-$d_6$) δ: 5.65 (2H, s, $OCH_2$), 6.30 (1H, d, $J$ = 9.2 Hz, 3-H), 6.76-8.06 (7H, m, Ar-H), 7.80 (1H, d, $J$ = 9.6 Hz, 4-H), 11.50 (1H, br s, NH). $^{13}$C-NMR (DMSO-$d_6$) δ: 70.29 (C-1'), 99.38, 110.44, 113.68, 118.82, 128.98, 129.21, 129.79, 132.94, 138.78, 139.88, 140.41 (Ar-Cs), 159.57 (C-7), 162.12 (C-2), 193.32 (C-2'). Anal. Calcd for $C_{17}H_{12}NO_3Cl$: C, 65.08; H, 3.86; N, 4.46. Found: C, 64.82; H, 3.89; N, 4.52.

**7-[2-(4-Bromophenyl)-2-oxoethoxy]quinolin-2(1*H*)-one (7d)**

Compound (**7d**) was prepared from 2-bromo-4'-bromoacetophenone by the same procedure as described for **7a** in 66% yield. mp 205-206 °C (dichloromethane). $^1$H-NMR (DMSO-$d_6$) δ: 5.64 (2H, s, $OCH_2$), 6.30 (1H, d, $J$ = 9.2 Hz, 3-H), 6.75-7.97 (7H, m, Ar-H), 7.80 (1H, d, $J$ = 9.6 Hz, 4-H), 11.65 (1H, br s, NH). $^{13}$C-NMR (DMSO-$d_6$) δ: 70.25 (C-1'), 99.37, 110.44, 113.68, 118.81, 127.97, 129.21, 129.86, 131.92, 133.25, 139.88, 140.41 (Ar-Cs), 159.55 (C-7), 162.11 (C-2), 193.54 (C-2'). Anal. Calcd for $C_{17}H_{12}NO_3Br$: C, 57.00; H, 3.38; N, 3.91. Found: C, 56.73; H, 3.42; N, 3.98.

**7-[2-(4-Methoxyphenyl)-2-oxoethoxy]quinolin-2(1*H*)-one (7e)**

Compound (**7e**) was prepared from 2-bromo-4'-methoxyacetophenone by the same procedure as described for **7a** in 69% yield. mp 189-190 °C (dichloromethane). [1]H-NMR (DMSO-$d_6$) δ: 3.86 (3H, s, $CH_3$), 5.58 (2H, s, $OCH_2$), 6.30 (1H, d, $J$ = 9.4 Hz, 3-H), 6.75-8.03 (7H, m, Ar-H), 7.79 (1H, d, $J$ = 9.5 Hz, 4-H), 11.50 (1H, br s, NH). [13]C-NMR (DMSO-$d_6$) δ: 55.63 (MeO), 70.01 (C-1'), 99.27, 110.54, 113.60, 114.10, 118.73, 127.15, 129.17, 130.22, 139.91, 140.44, 163.66 (Ar-Cs), 159.78 (C-7), 162.14 (C-2), 192.40 (C-2'). Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.62; H, 4.96; N, 4.52.

**7-[(2,3,4,5-Tetrahydro-4-methylene-5-oxo-2-phenyl-2-furanyl)methoxy]quinolin-2(1*H*)-one (8a)**

Activated zinc powder (0.26 g, 3.9 mmol), hydroquinone (6 mg), and ethyl 2-bromomethylacrylate (0.78 g, 4 mmol) were added to a solution of **7a** (0.84 g, 3 mmol) in dry THF (60 mL). The mixture was refluxed under a nitrogen atmosphere for 6 h (monitored by TLC). After cooling, it was poured into an ice-cold 5% HCl solution (300 mL) and extracted with $CH_2Cl_2$ (60 mL x 3). The dichloromethane extracts were combined and washed with water, dried over $Na_2SO_4$, and then evaporated to give a residual solid, which was crystallized from dichloromethane and ether (1:10) to afford **8a** (0.78 g, 75%) as white crystals. mp 183-184 °C. UV $\lambda_{max}$ (log ε): 247 (sh, 4.07), 333 (4.18) (0.1 N HCl in MeOH), 282 (3.76), 324 (4.14), 338 (4.03) (MeOH), 233 (sh, 4.63), 325 (4.05) (0.1 N NaOH in MeOH). [1]H-NMR (DMSO-$d_6$) δ: 3.17 (1H, dt, $J$ = 17.6, 2.8 Hz, 3'-H), 3.63 (1H, dt, $J$ = 17.6, 2.4 Hz, 3'-H), 4.28, 4.41 (2H, AB type, $J$ = 10.6 Hz, $OCH_2$), 5.80 (1H, t, $J$ = 2.4 Hz, $CH_2$=C(4')), 6.12 (1H, t, $J$ = 2.4 Hz, $CH_2$=C(4')), 6.30 (1H, d, $J$ = 9.6 Hz, 3-H), 7.37-7.56 (8H, m, Ar-H), 7.80 (1H, d, $J$ = 9.6 Hz, 4-H), 11.51 (1H, br s, NH). [13]C-NMR (DMSO-$d_6$) δ: 37.12 (C-3'), 73.40 ($OCH_2$), 84.12 (C-2'), 110.38, 113.82, 118.94, 121.51, 125.09, 128.29, 128.62, 129.35, 134.95, 139.94, 140.32, 140.41 (Ar-Cs), 159.59 (C-7), 162.14 (C-2), 168.88 (C-5'). Anal. Calcd for $C_{21}H_{17}NO_4$: C, 72.61; H, 4.93; N, 4.03. Found: C, 72.50; H, 4.94; N, 4.05.

The same procedure was used to convert each of compounds (**7b-e**) to the corresponding (**8b-e**).

**7-[[2-(4-Fluorophenyl)-2,3,4,5-tetrahydro-4-methylene-5-oxo-2-furanyl]methoxy]-quinolin-2(1*H*)-one (8b)**

Yield: 69%. mp 159-160 °C (dichloromethane / ether = 1/10). UV $\lambda_{max}$ (log ε): 250 (sh, 4.10), 332 (4.02) (0.1 N HCl in MeOH), 284 (3.71), 324 (3.95), 338 (3.84) (MeOH), 235 (sh, 4.49), 325 (3.88) (0.1 N NaOH in MeOH). $^1$H-NMR (DMSO-$d_6$) δ: 3.17 (1H, dt, $J$ = 17.4, 2.8 Hz, 3'-H), 3.62 (1H, dt, $J$ = 17.4, 2.6 Hz, 3'-H), 4.27, 4.41 (2H, AB type, $J$ = 10.4 Hz, $OCH_2$), 5.81 (1H, t, $J$ = 2.2 Hz, $CH_2$=C(4')), 6.13 (1H, t, $J$ = 2.8 Hz, $CH_2$=C(4')), 6.30 (1H, d, $J$ = 9.4 Hz, 3-H), 6.72-7.61 (7H, m, Ar-H), 7.80 (1H, d, $J$ = 9.5 Hz, 4-H), 11.50 (1H, br s, NH). $^{13}$C-NMR (DMSO-$d_6$) δ: 37.15 (C-3'), 73.36 ($OCH_2$), 83.85 (C-2'), 99.43, 110.40, 113.87, 115.26, 115.69, 118.99, 121.69, 127.43, 127.59, 129.40, 134.87, 136.52, 136.58, 139.97, 140.44, 159.46, 164.33 (Ar-Cs), 159.57 (C-7), 162.19 (C-2), 168.83 (C-5'). Anal. Calcd for $C_{21}H_{16}NO_4F$: C, 69.03; H, 4.41; N, 3.83. Found: C, 68.81; H, 4.45; N, 3.83.

**7-[[2-(4-Chlorophenyl)-2,3,4,5-tetrahydro-4-methylene-5-oxo-2-furanyl]methoxy]-quinolin-2(1*H*)-one (8c)**

Yield: 79%. mp 193-194 °C (dichloromethane / ether = 1/10). UV $\lambda_{max}$ (log ε): 246 (sh, 4.18), 333 (4.29) (0.1 N HCl in MeOH), 281 (3.87), 324 (4.24), 338 (4.13) (MeOH), 235 (sh, 4.72), 325 (4.12) (0.1 N NaOH in MeOH). $^1$H-NMR (DMSO-$d_6$) δ: 3.15 (1H, dt, $J$ = 17.4, 2.7 Hz, 3'-H), 3.61 (1H, dt, $J$ = 17.4, 2.4 Hz, 3'-H), 4.29, 4.42 (2H, AB type, $J$ = 10.4 Hz, $OCH_2$), 5.81 (1H, t, $J$ = 2.2 Hz, $CH_2$=C(4')), 6.13 (1H, t, $J$ = 2.6 Hz, $CH_2$=C(4')), 6.31 (1H, d, $J$ = 9.5 Hz, 3-H), 6.73-7.58 (7H, m, Ar-H), 7.80 (1H, d, $J$ = 9.5 Hz, 4-H), 11.52 (1H, br s, NH). $^{13}$C-NMR (DMSO-$d_6$) δ: 37.09 (C-3'), 73.18 ($OCH_2$), 83.77 (C-2'), 99.44, 110.34, 113.87, 118.99, 121.81, 127.19, 128.61, 129.38, 133.04, 134.68, 139.32, 139.94, 140.41 (Ar-Cs), 159.53 (C-7), 162.16 (C-2), 168.75 (C-5'). Anal. Calcd for $C_{21}H_{16}NO_4Cl$: C, 66.06; H, 4.22; N, 3.67. Found: C, 66.07; H, 4.27; N, 3.74.

**7-[[2-(4-Bromophenyl)-2,3,4,5-tetrahydro-4-methylene-5-oxo-2-furanyl]methoxy]-quinolin-2(1*H*)-one (8d)**

Yield: 83%. mp 202-203 °C (dichloromethane / ether = 1/10). UV $\lambda_{max}$ (log ε): 246 (sh, 4.09), 332 (4.18) (0.1 N HCl in MeOH), 281 (3.74), 324 (4.11), 338 (4.00) (MeOH), 235 (sh, 4.61), 324 (4.00) (0.1 N NaOH in MeOH). $^1$H-NMR (DMSO-$d_6$) δ: 3.15 (1H, dt, $J$ = 17.2, 2.8 Hz, 3'-H), 3.60 (1H, dt, $J$ = 17.6, 2.4 Hz, 3'-H), 4.29, 4.41 (2H, AB type, $J$ = 10.4 Hz, $OCH_2$), 5.81 (1H, t, $J$ = 2.4 Hz, $CH_2$=C(4')), 6.13 (1H, t, $J$ = 2.8 Hz, $CH_2$=C(4')), 6.31 (1H, d, $J$ = 9.2 Hz, 3-H), 6.73-7.68 (7H, m, Ar-H), 7.80 (1H, d, $J$ = 9.6 Hz, 4-H), 11.53 (1H, br s, NH). $^{13}$C-NMR (DMSO-$d_6$) δ: 37.05 (C-3'), 73.13 ($OCH_2$), 83.80 (C-2'), 99.45, 110.34, 113.88, 118.99, 121.63, 121.83, 127.50, 129.39, 131.53, 134.65, 139.75, 139.94, 140.41 (Ar-Cs), 159.54 (C-7), 162.17 (C-2), 168.74 (C-5'). Anal. Calcd for $C_{21}H_{16}NO_4Br$: C, 59.17; H, 3.78; N, 3.29. Found: C, 59.24; H, 3.90; N, 3.39.

**7-[[2,3,4,5-Tetrahydro-2-(4-methoxyphenyl)-4-methylene-5-oxo-2-furanyl]methoxy]-*quinolin-2(1H)-one* (8e)**

Yield: 86%. mp 182-183 °C (dichloromethane / ether = 1/10). UV $\lambda_{max}$ (log ε): 246 (sh, 4.17), 333 (4.26) (0.1 N HCl in MeOH), 280 (3.90), 324 (4.19), 338 (4.08) (MeOH), 235 (sh, 4.68), 325 (4.08) (0.1 N NaOH in MeOH). $^1$H-NMR (DMSO-$d_6$) δ: 3.15 (1H, dt, $J$ = 17.6, 2.8 Hz, 3'-H), 3.58 (1H, dt, $J$ = 17.2, 2.4 Hz, 3'-H), 3.77 (3H, s, $OCH_3$), 4.24, 4.35 (2H, AB type, $J$ = 10.4 Hz, $OCH_2$), 5.79 (1H, t, $J$ = 2.4 Hz, $CH_2$=C(4')), 6.17 (1H, t, $J$ = 2.8 Hz, $CH_2$=C(4')), 6.31 (1H, d, $J$ = 9.6 Hz, 3-H), 6.74-7.56 (7H, m, Ar-H), 7.80 (1H, d, $J$ = 9.6 Hz, 4-H), 11.52 (1H, br s, NH). $^{13}$C-NMR (DMSO-$d_6$) δ: 37.05 (C-3'), 55.21 (MeO), 73.44 ($OCH_2$), 84.05 (C-2'), 99.36, 110.44, 113.82, 113.99, 118.93, 121.40, 126.54, 129.37, 132.14, 135.19, 139.96, 140.43, 159.15 (Ar-Cs), 159.62 (C-7), 162.17 (C-2), 168.95 (C-5'). Anal. Calcd for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.09; N, 3.71. Found: C, 69.69; H, 5.13; N, 3.75.

**X-Ray Structural Determination of 5** Crystallographic details: $C_{11}H_9NO_3$, $M$ = 203.20, Monoclinic, space group $P2_{1/n}$ (#14), $a$ = 6.748(2) Å, $b$ = 8.091(2) Å, $c$ = 17.654(2) Å, β = 97.06(2)°, $V$ = 956.5(3) Å$^3$, Z = 4. $D_{calc}$ = 1.411 g/cm$^3$. Crystal dimensions 0.45 x 0.55 x 0.55 mm. $F_{000}$ = 424.00. μ(MoKα) = 1.04 cm$^{-1}$. Radiation: MoKα (λ = 0.71069 Å), ω-2θ scanning technique. The crystal structure was solved by direct methods (SIR92). Full-matrix least-squares refinement of atomic positional and thermal parameters (anisotropic C, N, O; fixed H contributions) converged at $R$ = 0.042 ($R_w$ = 0.031) for 1986 reflections.

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