Synthesis and Photooxygenation of Angular Furoquinolinone

التشييد و الأكسدة الضوئية للفيوروكينولينون الزاوى

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الملخص العربى:

هذا البحث يتناول تحضير بعض مشتقات الفيوروكينولينون الزاوى التى تعد من متشابهات الفيوروكومارين (السورالين) ولهذه المركبات اهمية فى علاج بعض الأمراض الجلدية وذلك لأن لها خاصية ضوئية(متفاعل للضوء)،ونفذ ذلك من خلال تفاعل ويليامسون من ٧-هيدروكسى-٤-ميثيل-٢-كينولينون مع ٣-كلورو-٢-بيوتانون ثم يتبع ذلك بحولقة باستخدام حامض البولى فوسفوريك وتم تحضير أيضا مشتقات من البنزوهيدروكسى كينولينون بواسطة اعادة ترتيب فريز.

Abstract:

Synthesis of 4,8,9-trimethylfuro[2,3-h]quinolin-2(1H)-one as angular furoquinolinone (psoralen analog) was carried out through Williamson reaction of 7-hydroxy-4-methyl-2H-quinolin-2-one with 3-chloro-2-butanone followed by cyclization with polyphosphoric acid (PPA). *o*-Benzoylhydroxy derivative of quinolinone was prepared through the photooxygenation and Fries rearrangement.

Keywords: Furocoumarin, Psoralen, Photooxygenation and Fries rearrangement.

Introduction

Linear furocoumarins (psoralens) and their analogs such as furoquinolinone are active photosensitizers used in PUVA (Psoralen plus UVA) therapy for treatment of several skin diseases.[1-7] The phototherapeutic effects of psoralens are believed to result from intercalation of the drug between adjacent base pairs in the DNA duplex,[8] followed by two successive photocycloaddition reactions that cross-link the DNA.[9] Some undesirable side effects are present such as a persistant erythema[10] genotoxicity,[11] phototoxicity and a possible risk of skin cancer.[12] As these side effects are mostly attributed to psoralen interstrand crosslinks with DNA rather than to monofunctional adducts,[13] a consequence of their bifunctional nature (photoactive α-pyrone and furan sites). To enhance the photobinding properties and reduce side effects, a wide range

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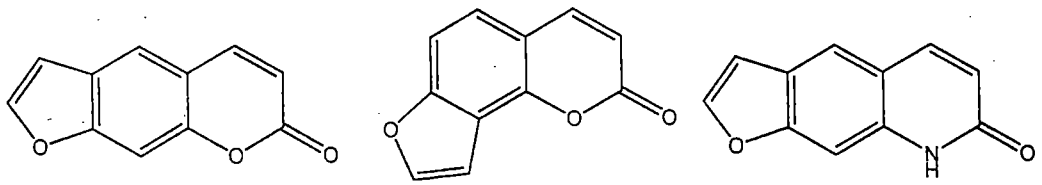
of structural modifications of psoralens have been attempted[14] to obtain furocoumarins able to behave as essentially monofunctional agents. To date, this has been accomplished in three different ways: (a) the use of angular furocoumarins such as angilicin, which on account of their geometry cannot crosslink with DNA,[15](b) blocking of the photoreactive α-pyrone double bond by appropriate substituents[16], or by annelation of an additional aromatic ring,[17] and (c) incorporating an additional benzene ring between active double bonds of the α-pyrone and furan moiety.[18]

In this work we reported the synthesis of 4,8,9-trimethylfuro[2,3-h]quinolin-2(1H)-one as angular furocoumarin analog by constraction furan ring on benzene moiety of quinolinone. The photooxygenation reaction of synthesized furoquinolnone derivative was carried out. The photoproducts (*o*-benzoylhydroxy derivatives) are a convenient intermediate in heteroarene synthesis.

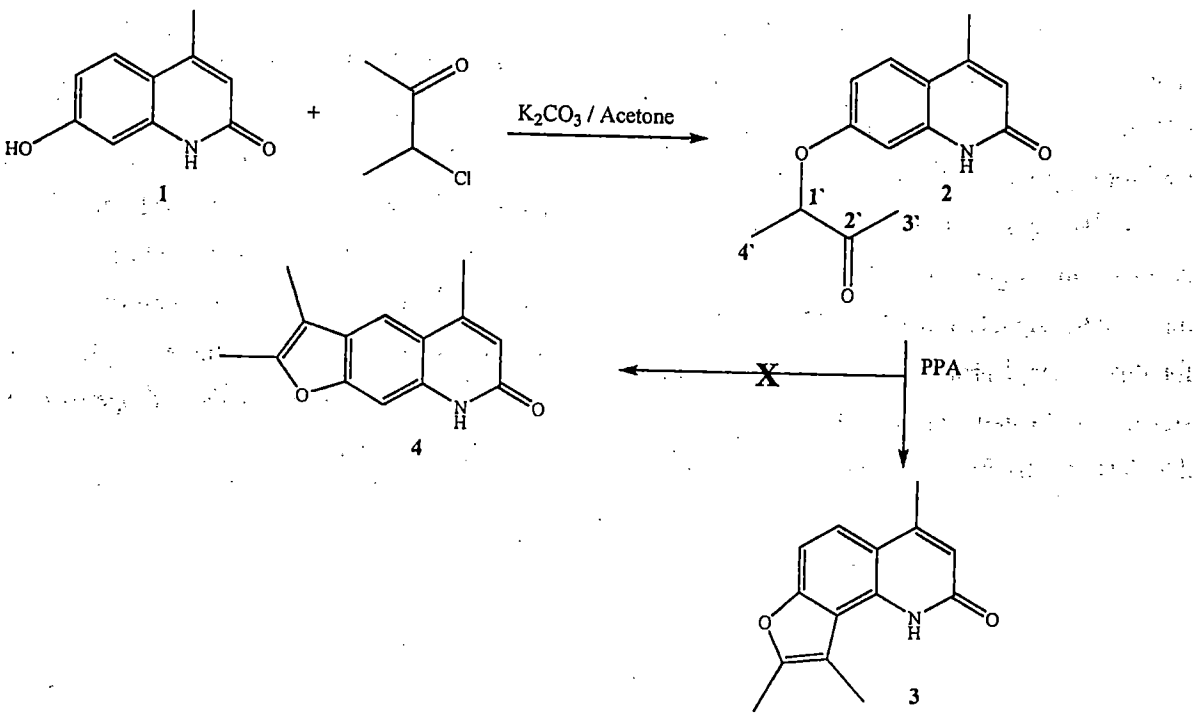


Psoralen **Angelicin** **Furoquinolinone**

Figure 1. Structure of furocoumarins and furoquinolinone

Synthesis of angular furoquinolinone derivatives.

Treatment of m-aminophenol with ethyl acetoacetate in refluxed xylene afforded the corresponding 7-hydroxy-4-methyl-2H-quinolin-2-one (**1**). Williamson reaction of **1** with 3-chloro-2-butanone in refluxing acetone and in the presence of K_2CO_3 for 24 hours gave the keto ether **2** in a moderate yield, scheme 1. The presence of new stretching band for new carbonyl group at 1724 cm^{-1} in **IR** and the aliphatic protons resonances at δ 4.95 (1H, q, J= 6.3 Hz), 2.20 (3H, s), and 1.51 (3H, d, J= 6.3 Hz) for 1`-H, 3`-H, and 4`-H respectively in ^{1}**H-NMR** confirm the ether group in compound **2.** Further confirmation of **2** was detection of molecular ion (M^+) at *m/z* 245 (M^+, 53.64%) in mass spectrum.



Scheme 1

Cyclization of **2** by polyphosphoric acid (PPA) at 80 °C for 4 hours afforded 4,8,9-trimethylfuro[2,3-h]quinolin-2(1H)-one (**3**), scheme 1. The structure of angular furoquinolinone **3** was established for the reaction product based on the spectral (**IR**, **^{1}H-NMR** and **MS**) and elemental analyses, while the structure of linear furoquinolinone **4** was excluded.

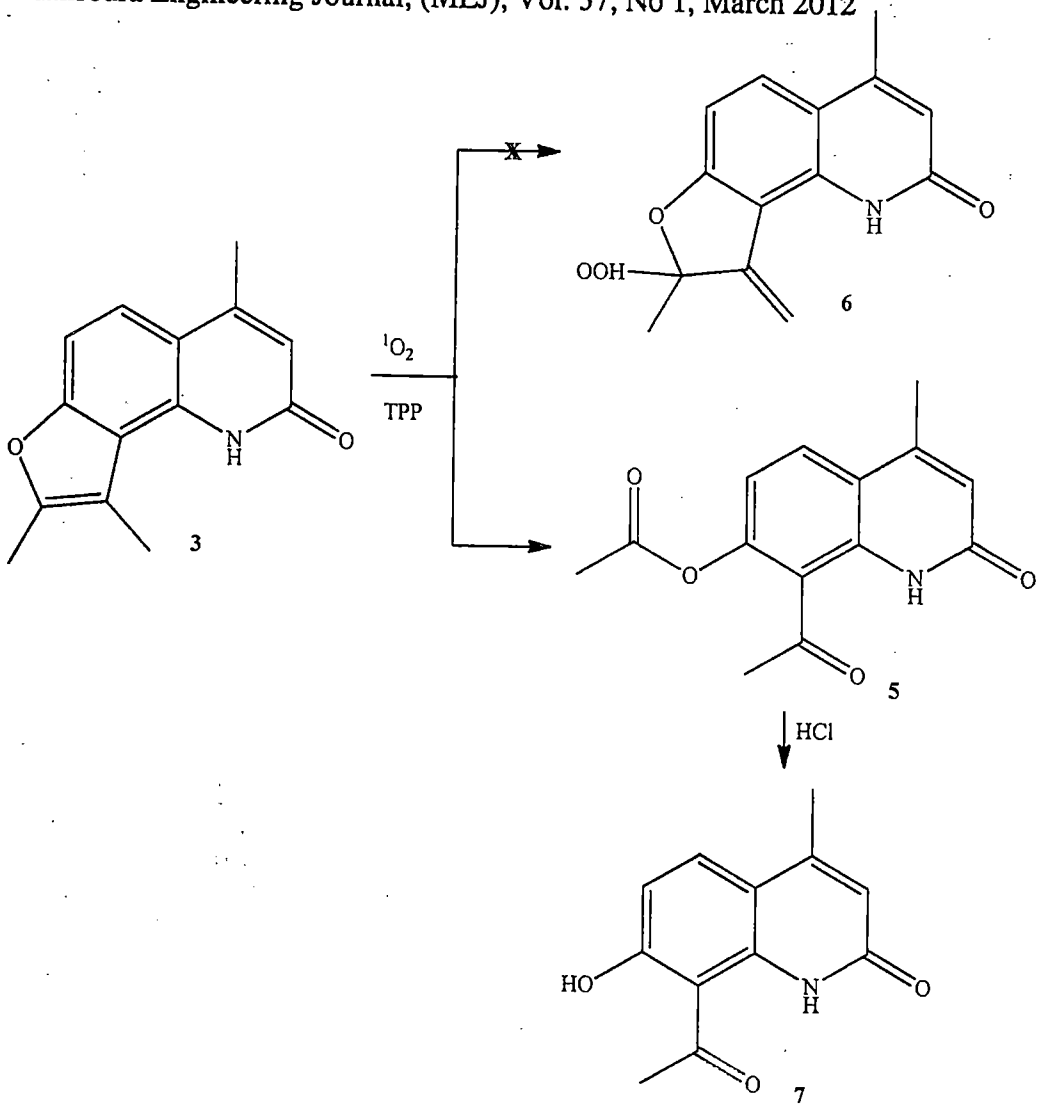
IR spectrum of compound **3** showed a characteristic stretching band at 3305.39 cm^{-1} for NH and characteristic stretching band at 1662.34 cm^{-1} for α-pyridone carbonyl group.

^{1}H-NMR spectrum of **3** showed a characteristic signal for NH at δ 11.67 ppm, three singlet signals at δ 2.67, 2.39 and 2.13 ppm for three methyl groups, a characteristic singlet signal at 6.36 ppm for proton of C-3 and two doublets signals for two aromatic protons (C-5 and C-6) at δ 7.56 and 7.16 ppm with coupling constant J= 8.4 Hz. The multiplicity of the aromatic protons (doublets signals), the presence of *ortho* coupling, confirmed the exclusive cyclization to the angular furoquinolinone skeleton (angelicin analog type).

In **mass** spectrum of compound **3** the molecular ion M^+ was detected as the base peak *m/z* 227 (100%).

Photooxygenation of angular furoquinolinone derivatives 3.

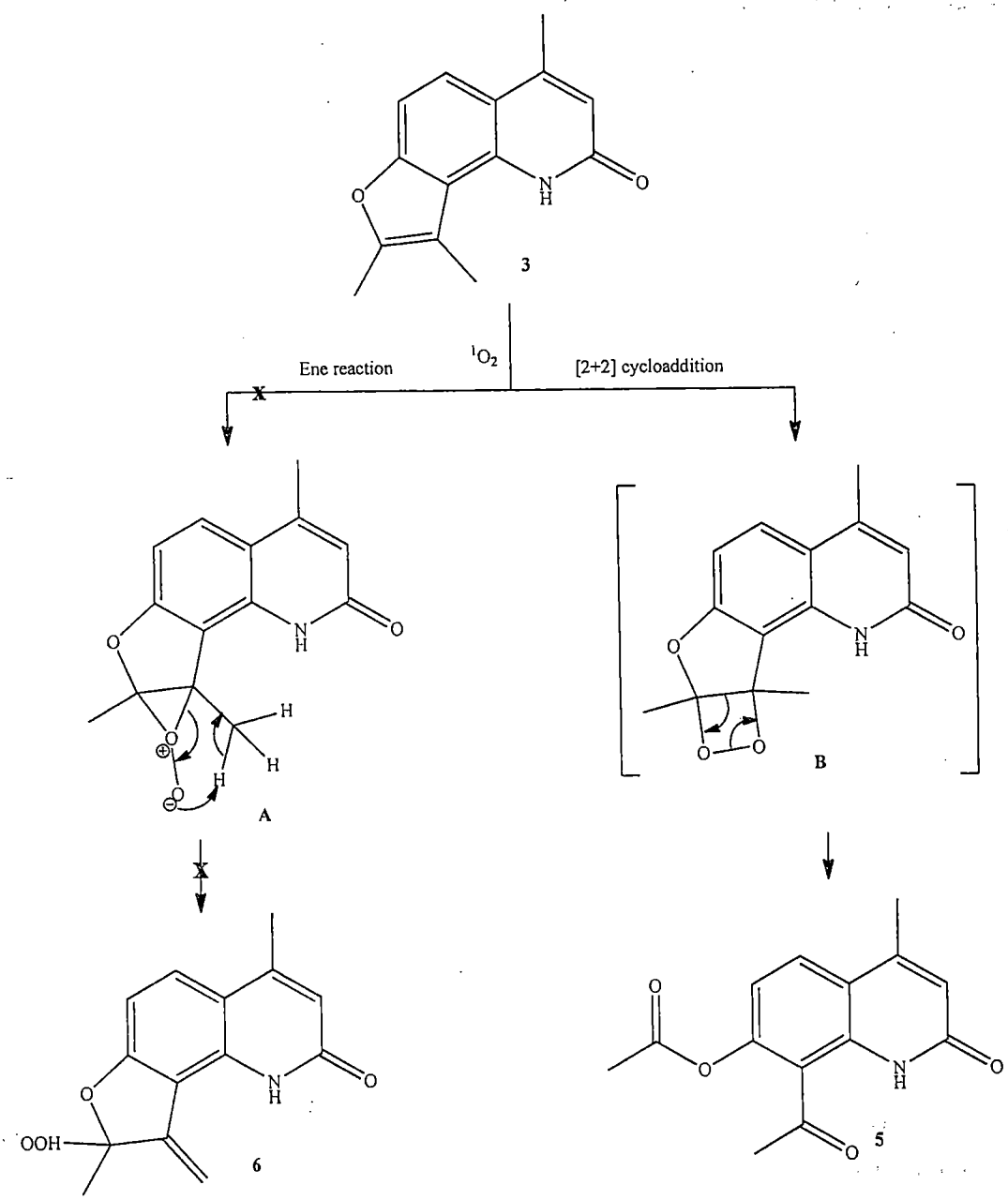
The photooxygenation of the angular furoquinolinone derivative **3** in DMF and in the presence of tetraphenylporphine (TPP) as singlet oxygen sensitizer at room temperature gave 8-acetyl-4-methyl-2-oxo-1, 2-dihydroquinolin -7-yl acetate (**5**) while the allylic hydroperoxide **6** did not form, scheme 2.



Scheme 2

The mechanism of the formation of the allylic hydroperoxide is achieved by the reaction of singlet oxygen ($^1O_2$) with an olefin bearing allylic hydrogens in the so-called Schenck-ene reaction through the ene mechanism from peroxirane transition state (**A**) and leads an allylic Hydroperoxide.[19] On the other hand, the mechanism of the formation of the dioxetane (**B**) is carried out by the [2+2] cycloaddition of singlet oxygen with the double bond of the furan moiety.

dioxetane (**B**) was photolized rapidly under the photooxygenation conditions to give **5** *via* broken O-O and C-C bond, scheme 3.



Scheme 3: Photooxygenation mechanisms of 3.

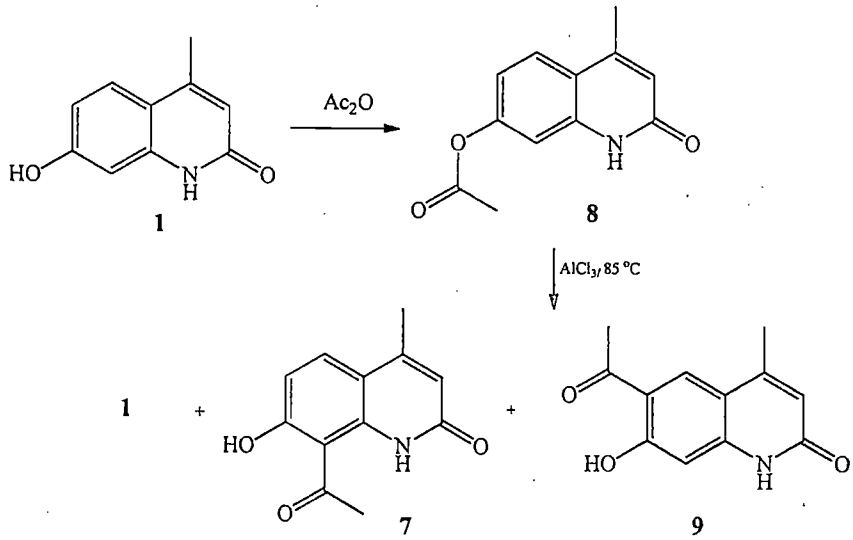
The

The photocleaved product **5** was isolated and fully characterized by **IR**, **^{1}H-NMR** and **mass** spectroscopy (cf. Experimental). **IR** spectrum of **5** showed a new two bands at 1758.76 and 1690 cm^{-1} for two new carbonyl moieties.

^{1}H-NMR spectrum of **5** showed highly downfield signal at δ 11.99 ppm which exchangeable with D_2O assigned to NH proton and a two doublet signals at δ 8.05 and 7.27 ppm with coupling constant J= 8.4 Hz for two aromatic protons (H-5 and H-6), a characteristic

singlet signal at δ 6.44 ppm for H-3 and the three singlet signals of three methyl groups at δ 2.62, 2.47 and 2.34 ppm. In **mass** spectrum of compound **5** the molecular ion M^+ was detected at *m/z* 259 (9.54%). The base peak was (M^+-C_3H_5O), at *m/z* 202 (100%).

Further confirmation of compound **5** was obtained through acid hydrolysis of the photoproduct **5** to afford 8-acetyl-7-hydroxy-4-methyl-2H-quinolin-2-one (**7**), which also obtained through Fries rearrangement of **8**, scheme 4.



Scheme 4

Experimental

Melting points were obtained on a Gallenkamp melting point apparatus (open capillary tubes) and were uncorrected. Silica gel (ADWIC 60 GF_{254}) was used for thin layer chromatography (TLC). Silica gel (ADWIC 60-120 mesh, size 0.13-0.25 nm) was used for column chromatography. **^{1}H-NMR** spectra were performed on a Varian Mercury-VX-300 (300 MHz) at the Micro analytical Unit, Cairo University and a BRUKER (600 MHz) ultra shield Avance III spectrometer at the faculty of science, king Abd-Elaziz University, Jeddah, K.S.A, using (TMS) as an internal stander and DMSO or $CDCl_3$ as solvents. Chemical shifts were expressed as δ ppm. **IR** spectra were performed on a Jasco 4100 FTIR spectrophotometer (KBr pellet) at the department of chemistry, faculty of science at New Damietta, Mansoura University, Damietta branch. The electron impact (EI) **mass** spectra were performed on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV at the Micro analytical Unit, Cairo University. The Elemental analyses were performed on a PERKIN-ELMER 2400 C, H Elemental Analyzer at the Micro analytical Unit, Cairo University, within ± 0.4 deviation form the calculated value.

Synthesis of 7-hydroxy-4-methyl- 2H-quinolin-2-one (1).

A mixture of m-aminophenol (10 g, 90 mmol) and ethyl acetoacetate (11.9 g, 91.7 mmol) was refluxed in xylene at 140° for 4 hour. The solid was filtered off and purified by crystallization from methanol to give white powder of **1** (8 g, 50%) m.p.303°C, (lit[20], 306°C). IR (KBr cm^{-1}): 3430.02 (OH), 3320.82 (N-H), 1662.34 (CO) and 1616.06 (C=C). ^{1}H NMR (DMSO): 11.33 (1H, s), 10.04 (1H, s), 7.49 (1H, s), 6.66 (1H, d, J=8.7 Hz), 6.62(1H, d, J=8.7 Hz), 6.12 (1H, s) and 2.33 (3H, s).

Synthesis of 4-methyl-7-(3-oxobutan-2-yloxy)-2H- quinolin-2-one (2)

To a solution of **1** (2 g, 11.4 mmol) in dry acetone (70 ml), anhydrous potassium carbonate (1.0 molar equiv) and 3-chloro-2-butanone (1.2 g, 11.3 mmol) were added. The resultant mixture was refluxed at 80 °C for 24 hours. The reaction was monitored by TLC for the disappearance of reactants. The inorganic salt was filtered off and the solvent was concentrated under reduced pressure and poured on ice/water. The solid separated was filtered off, washed with excess of water and purified by crystallization from ethanol to afford white crystals of **2** (1.2 g, 60%) m.p.162-164°C. IR (KBr cm^{-1}): 3328.53 (N-H), 2973.74 (=CH), 2915.84 (-CH), 1724 (CO), 1670.05 (CO) and 1620 (C=C). ^{1}H NMR (DMSO): 11.70 (1H, s), 7.61 (1H, s), 7.32 (1H, d, J=8.4 Hz), 6.90 (1H, d, J=8.4 Hz), 6.45 (1H, s), 4.95 (1H, q, J=8.4 Hz), 2.52 (3H, s), 2.20 (3H, s) and 1.51 (3H, d, J=6.3 Hz). MS (m/z, %): 245 (M^+, 53.64), 217 (M^+-CO, 0.48), 203 (M^+-C_2H_2O, 14.09), 202 (M^+-C_2H_3O, 100), 188 (M^+ -C_3H_5O, 2. 056), 174 (M^+

- C_4H_7O, 11.25), 158.05 (M^+ - $C_4H_7O_2$, 5.90) and 105.05 (PhCO, 2.61).

Synthesis of 4,8,9-trimethylfuro[2,3-h]quinolin-2(1H)-one (3)

Compound **2** (1 g, 4.081 mmol) was added to polyphosphoric acid (PPA) (5 g) and the mixture was heated for 4 hours at 80 °C. The reaction mixture was cold and poured onto ice/water. The separated solid was filtered with suction and crystallized from ethanol to afford **3** (0.4 g, 43%) as white crystals, m.p. 230°C. IR (KBr cm^{-1}): 3305.39 (NH), 3135.69 (=CH), 2989.12 (-CH), 1662.34 (CO) and 1560 (C=C). ^1H NMR (DMSO): 11.67(1H, s), 7.56 (1H, d, J=8.4 Hz), 7.16 (1H, d, J=8.4 Hz), 6.36 (1H, s), 2.67 (3H, s), 2.39 (3H, s), and 2.13 (3H, s). MS (m/z, %): 227 (M^+, 100), 212 (M^+-CH_3, 20.87), 198.80 (M^+ -CO, 8.20), 198 (M^+ -CHO, 17.66), 171 (M^+ -C_3H_4O, 5.95) and 170 (M^+ -C_3H_5O, 29.07). Anal.Calcd for $C_{14}H_{13}NO_2$ (227): C, 73.99, H, 5.77, N, 6.16. Found: C, 74.11, H, 5.91, N, 5.83.

Photooxygenation of 4,8,9-trimethylfuro[2,3-h]quinolin-2(1H)-one (3).

A solution of **3** (1 g, 4.4 mmol) and (2 mg) of tetraphenylporphine (TPP) in DMF (30 ml) was irradiated externally by means of a sodium lamp at room temperature. During the irradiation a continuous stream of dry oxygen gas was allowed to pass through the reaction mixture at a slow rate to avoid solvent evaporation. The irradiated solution was monitored by TLC for the disappearance of reactants and the solvent was evaporated at 20 °C/15 torr. The photo-product was purified by column chromatography on silica gel by eluting with a 30% mixture of petroleum ether 40-60 and ethyl acetate to yield 8-acetyl-4-methyl-2-oxo-1, 2-dihydroquinolin -7-yl acetate (**5**). Brown crystal, yield (0.6 g, 63%). m.p. 184°C. IR (KBr cm^{-1}): 3328.53 (N-H), 3077.83 (=CH), 2992.98 (-CH), 1758.76 (CO), 1690(CO), 1666.2 (CO) and 1608.34 (C=C). ^1H NMR (DMSO): 11.99 (1H, s), 8.05 (1H, d, J=8.4), 7.27 (1H, d, J=8.4), 6.44 (1H, s), 2.62 (3H, s), 2.47 (3H, s) and 2.34 (3H, s). MS (m/z, %): 259 (M^+, 9.54), 217 (M^+-C_2H_2O, 73.91), 216 (M^+-C_2H_3O, 1.15) 203 (M^+-C_3H_4O, 12.2), 202 (M^+ -C_3H_5O, 100), 189 (M^+ - $C_3H_2O_2$, 1.99), 174.05 (M^+ - $C_4H_5O_2$, 4.93) and 146 (M^+ - $C_5H_5O_3$, 6.87). Anal.Calcd for $C_{14}H_{13}NO_4$ (259): C, 64.86, H, 5.05, N, 5.40. Found: C, 68.79, H, 6.51, N, 5.83

Synthesis of 8- Acetyl-7-hydroxy- 4- methyl-2H- quinolin-2-one (7)

(Acid hydrolysis of 5).

A solution of **5** (0.5 g,1.93 mmol) in 20 ml hydrochloric acid was refluxed for half an hour and then cool in air to obtain a precipitate which was separated with suction, washed with water, dried and recrystalized from ethanol to give 8-acetyl-7-hydroxy-4-methyl-2H-quinolin-2-one(7), (2.3g,71.6%), m.p.259°C

Synthesis of 4-methyl-2-oxo-1,2-dihydro quinolin -7-yl acetate (8)

A solution of **1** (1 g, 5.7 mmol) in 20 ml acetic anhydride was refluxed for one hour. The reaction mixture was poured onto water and the separated solid was filtered off. The solid was purified by crystallization from ethanol to give white powder of **8** (1.2 g, 97 %) m.p. 257°C. (lit. [20] 257°C)

Synthesis of 6-Acetyl-7-hydroxy-4-methyl-2H-quinolin-2-one (9) and 8-Acetyl-7-hydroxy-4-methyl-2H-quinolin-2-one (7).

Compound **8** (1 g, 4.7 mmol) was mixed with $AlCl_3$ powder (2 g, 15.2 mmol) and the mixture was heated at 85°C the melt is treated with diluted hydrochloric acid (HCl). The separated solid was filtered off, washed with water and purified by column chromatography by eluting with 70% of a mixture of petroleum ether 40-60 and ethyl acetate to give 6-acetyl-7-hydroxy-4-methyl-2H-quinolin-2-one (**9**), 8-acetyl-7-hydroxy-4-methyl-2H-quinolin-2-one (**7**) and **1**. Compoud (**7**), white powder, yield (0.5 g, 50%), m.p. 259-262°C (lit [21]. 259-262°C), compound (**1**), white powder, yield (0.37 g, 45%), m.p. 306°C, and compound **9**, white powder, yield (0.13 g, 5 %), m.p. 191-194°C. (lit. [20] 191-194°C).

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