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Synthesis of 4-hydroxy-3-formylideneamino-1*H*/methyl/phenylquinolin-2-ones

B Bhudevi, P Venkata Ramana, Anwita Mudiraj & A Ram Reddy*
Department of Chemistry, University College of Science, Osmania University, Hyderabad 500 007, India
E-mail: ramreou2007@yahoo.co.in

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An efficient method for the synthesis of 4-hydroxy-3-formylideneamino-1*H*/methyl/phenylquinolin-2-ones by the condensation of corresponding 4-hydroxy-3-formyl-1*H*/methyl/phenylquinolin-2-one with substituted anilines/aliphatic primary amines is reported. The carboxaldehyde in turn is prepared starting either from substituted anilines or benzoic acid. The structures of compounds are established by the elemental analysis and spectral data.

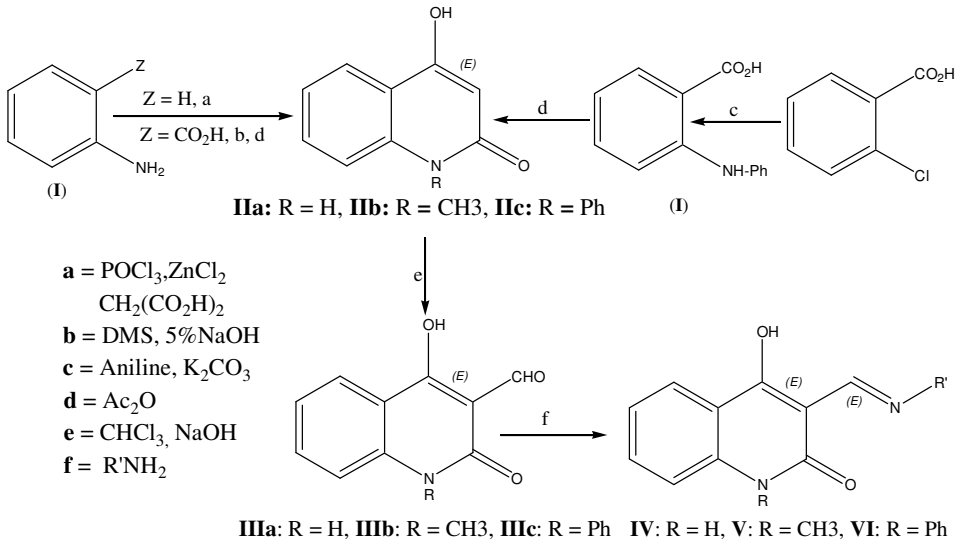
Keywords: 4-Hydroxy-3-formyl-1*H*-quinolin-2-one, Schiff base, 4-hydroxy-3-formylideneamino-1*H*-quinolin-2-one

4-Hydroxy-3-substitutedquinolin-2-ones and their analogues have variety of biological activities[1-3]. 4-Hydroxy-3-formylideneamino-1*H*/methyl/phenyl-quinolin-2-ones generate 4-hydroxy-3-formyl-1*H*/methyl/phenylquinolin-2-ones which show anti-viral and anti-hypertensive[4] activities. Owing to the importance of these imines, it is considered worth-while to prepare a few 4-hydroxy-3-formylidene-amino-1*H*/methyl/phenylquinolin-2-ones and in this paper the synthesis of thirty two different imines starting from substituted anilines or benzoic acid is reported.

Results and Discussion

The synthetic route for the preparation of imines starting from anthranilic acid, *ortho* chlorobenzoic acid and aniline is shown in the **Scheme I** and the compounds in **Table I**. It involves a linear path *via* *N*-methyl/phenylanthranilic acids, 4-hydroxy-1*H*/methyl/phenylquinolin-2-ones and 4-hydroxy-3-formyl-1*H*/methyl/phenylquinolin-2-ones. Anthranilic acid (0.036 mole) on methylation by DMS (0.070 mole) in presence of 5% of NaOH yield *N*-methylanthranilic acid **Ia**. The melting point and spectral data obtained matches with that reported in the literature. A new peak in ^{1}H NMR at δ 3.62 indicates that anthranilic acid is methylated by DMS. *N*-Phenylanthranilic acid **Ib** is prepared by the condensation of *ortho* chlorobenzoic acid (0.1 mole) with aniline (0.1 mole) in basic medium[5]. The structure of the product was confirmed as *N*-phenylanthranilic acid by its melting point. 4-*H*ydroxyquinolin-2-one **IIa** was directly prepared by the condensation of aniline (0.1 mole) with malonic acid (0.1 mole) in presence of $POCl_3$ (0.3 mole) and $ZnCl_2$ (0.2 mole, ref. 6). The *N*-methylanthranilic acid (0.211 mole) and *N*-phenylanthranilic acid (0.3 mole) on cyclocondensation with equal amount of acetic anhydride and acetic acid gave 4-hydroxy-1-methyl/phenylquinolin-2-one (**IIb/IIc**, ref. 7,8). The structure of 4-hydroxy-1*H*/methyl/phenylquinolin-2-one is elucidated by elemental analysis, melting point and spectral data which coincide with reported literature. Synthesis of 4-hydroxy-3-formyl-1*H*/methyl/phenylquinolin-2-one (**IIIa,b,c**) carried out by Reimer-Tiemann reaction with one equivalent of 4-hydroxy-1-*H*/methyl/phenylquinolin-2-one (**IIa,b,c**) (0.0124 mole) using 40 equivalents of $CHCl_3$ (0.5 mole) and 15% NaOH (ref. 9). The structure of the products was confirmed by the disappearance of vinyl proton of (**IIa,b,c**) and appearance of aldehyde signal in the off set region at δ 11.2, 10.3 and 9.4 in **IIIa**, **IIIb** and **IIIc** respectively.

The Schiff bases (**IV,V** and **VI**) were prepared by following reported method[10] with the condensation of one equivalent of each 4-hydroxy-3-formyl-1*H*/methyl/phenylquinolin-2-one (**IIIa,b,c**) and substituted anilines/aliphatic amines in dichloromethane. The melting points of most of the imines are higher than the melting point of their starting material. The electronic absorption spectral study revealed that formation of Schiff base resulted in bathochromic shift in the longer wavelength absorption band. 4-Hydroxy-3-formyl-methyl-quinolin-2-one **IIIb** absorbs

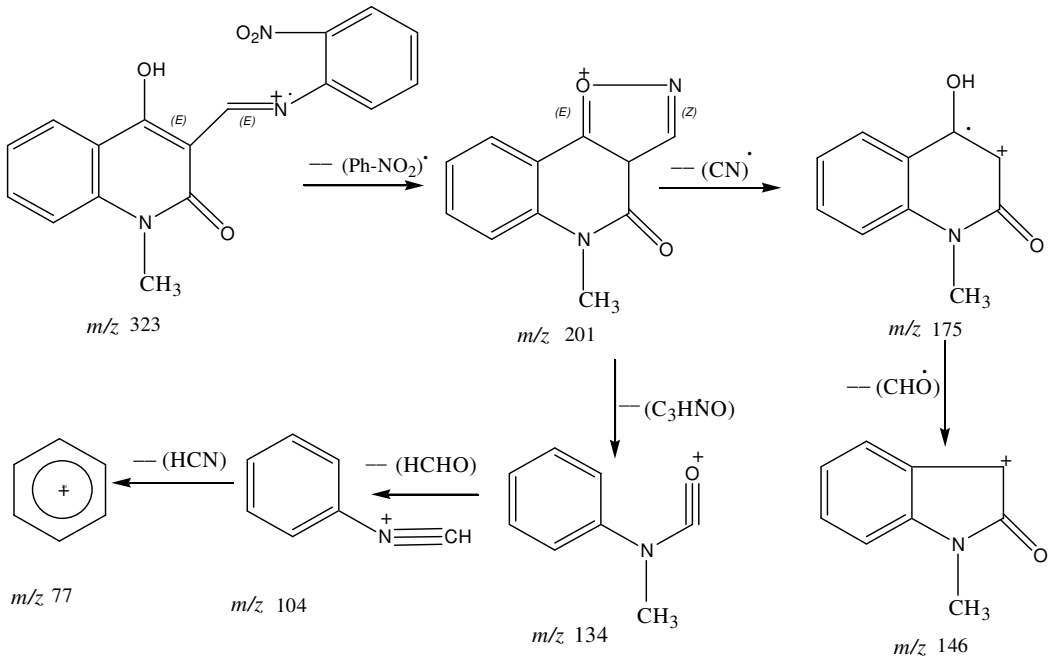


Scheme I — Synthesis of 4-hydroxy-3-formylideneamino-1*H*/methyl/phenylquinolin-2- ones

Table I — List of 4-hydroxy-3-formylideneamino-1*H*/methyl/phenylquinolin-2-ones

Entry	R'	R (m.p. °C)		
		H, **IV**	CH_3, **V**	Ph, **VI**
1	Ph	**IVa** (194-95)	**Va** (148-49)	**VIa** (154-55, ref.10)
2	2-NO_2 Ph	**IVb** (159-60)	**Vb** (232-33)	**VIb** (207-08)
3	4-NO_2 Ph	**IVc** (259-60)	**Vc** (>300)	**VIc** (291-92)
4	2-CH_3 Ph	**IVd** (219-20)	**Vd** (185-86)	**VId** (179-80)
5	4-CH_3 Ph	**IVe** (184-85)	**Ve** (164-65)	**VIe** (214-15)
6	2-OH Ph	-	**Vf**	**VIf** (>300) (ref. 10)
7	4-OH Ph	-	**Vg** (262-63)	**VIg** (176-77)
8	2-Cl Ph	-	**Vh** (191-92)	**VIh** (212-13)
9	3-Cl Ph	-	**Vi** (159-60)	**VIi**
10	4-Cl Ph	-	**Vj** (194-95)	**VIj** (229-30)
11	2-CN Ph	-	**Vk** (259-60)	**VIk** (254-55)
12	3-OCH_3 Ph	-	**Vl** (101-02)	**VIl** (229-31)
13	isopropyl	-	**Vm**	**VIm**
14	*n*-butyl	-	**Vn**	-

at 367 nm (Є 19293) while the absorption spectra of 4-hydroxy-3-formylidene-anilino-1-methylquinolin-2-one **Va** shows the absorption maximum at 382 nm (Є 9508) in $CHCl_3$. Thus there is a 15 nm red shift from starting material **IIIb**. Similarly all the Schiff bases **IV**, **V** and **VI** underwent a red shift of 9-27 nm in their longer wavelength absorption band compared with the respective starting materials (**IIIa,b,c**). The presence of electron withdrawing nitro group at *para* position in aniline moiety (**Vg** and **VIg**) display a new absorption maximum between 400 and 410 nm while at *ortho* position no such new absorption maximum was observed. Aliphatic imines (**Vm**, **Vn** and **VIm**) have not shown such bathochromic shifts. The formation of Schiff bases is further proved by the IR spectral studies. The disappearance of $\upsilon_{C=O}$ stretching frequency of aldehydes in the IR spectrum reveals the formation of **IV**, **V** and **VI**. Similar shifts were reported in the IR spectra of *N*-aryl imines of salicylaldehyde.



Scheme II — Mass spectral fragmentation of 4-Hydroxy-3-formylidene-2'-niroanilino-1-methylquinolin-2-one (**Vb)**

In ^{1}H NMR spectra of 4-hydroxy-3-formyl-1-methylquinolin-2-one **IIIb**, the aldehyde proton gave a signal at δ 10.30. On formation of imine (-CH=N-) the above signal underwent a diatropic shift resonating at δ 9.00 in 4-hydroxy-3-formylidene-4'-hydroxyanilino-1-methylquinolin-2-one **Vg**, while to δ 8.40 in 4-hydroxy-3-formylidene-*n*-butylamino-1-methylquinolin-2-one **Vn**. It is interesting to notice that iminol form is in equilibrium with ketamine in solution which has two coupling vicinal protons. The coupling constants vary between 6.88 and 8.13 Hz. Similar coupling interactions were reported[11]. The mass spectral fragmentation pattern in the mass spectra of these imines further confirmed the condensation of 4-hydroxy-3-formyl-1*H*/methyl/ phenylquinolin-2-one (**IIIa, b, c**) with various anilines and other aliphatic primary amines to yield **IV/V/VI**. The mass spectrum of 4-hydroxy-3-formylidene-2'-nitroanilino-1-methylquinolin-2-one **Vb** intense peak obtained at *m/z* 323 indicates the molecular ion, shows the presence of odd three nitrogens, 201 is the fragmentation due to the loss of $–NO_2C_6H_4$ and the peak at *m/z* 175 is attributed to the loss of -C=N-$C_6H_4NO_2$ group. Similarly the low intensity fragments at *m/z* 146, 134, 104 and 77 are derived from the daughter ions and the mass spectral fragmentation of **Vb** is shown in **Scheme II**.

Experimental Section

All the chemicals were purchased from Loba chemicals. The reagents and solvents were analytical grade and were used without further purification unless otherwise mentioned. Carbon, hydrogen and nitrogen were determined by Perkin-Elmer 240c instrument, IR spectra were recorded as KBr pellet on a Perkin-Elmer-1700 spectrophotometer. Electronic absorbance spectra were recorded on a Shimadzu UV-365 spectrophotometer. ^{1}H NMR spectra were measured on a Varian INOVA-500 spectrometer at RT. Electron spray mass spectra (ES-MS) recorded on a LCQ system (Finngan MAT, USA) using methanol as mobile phase. Melting points were recorded on a Polmon MP 96.

Synthesis of *N*-methylanthranilic acid

N-Methylanthranilic acid was prepared by reported method[7]. Anthranilic acid 5 g (0.036 mole) was dissolved in 13 mL of 5% sodium hydroxide. To this clear solution 1.6 mL (0.070 mole) of dimethyl sulphate was added and stirred for an hr. The reaction-mixture was filtered and washed with cold water and dried. It was recrystallized from ethanol. Yield: 3.5 g (65%); m.p. 187-89°C; ESI-MS, *m/z*: 151; ^{1}H NMR ($CDCl_3$): δ 3.62 (s, 3H, -NH-CH_3), 6.81 (d, 2H, Ar-H, *J* = 7.6 Hz), 7.61 (t, 1H, Ar-H, *J* = 7.8 Hz), 8.11 (d, 1H, Ar-H, *J* = 7.2 Hz), 9.10 (br s, 2H,

-CO_2H and -NH-Me); IR (KBr): 3380 (N-H), 2968 (C-H), 1675 (C=O), 1580 cm^{-1} (C=C).

Synthesis of *N*-phenylanthranilic acid

15.6 g (0.1 mole) of *ortho c*hlorobenzoic acid, 9.3 g (0.1 mole) of aniline, 13.8 g (0.1 mole) of potassium carbonate and 0.5 g (0.006 mole) of cupric oxide were dissolved in 100 mL of *N*,*N*-dimethyl formamide. The reaction-mixture was heated at 80°C on water-bath for 6 hr. After completion of the reaction, the contents were poured into ice-cold water and the unreacted aniline was removed under steam distillation and the residual solution contained potassium *N*-phenyl anthraniliate. Residual solution was extracted with ether and the aqueous layer was acidified with dilute hydrochloric acid. On cooling the solution precipitate of *N*-phenyl anthranilic acid was obtained. It was filtered, washed with water, dried and recrystallized from ethanol. The colourless needles obtained have m.p. 183-84°C; yield: 15.7 g (74%); ESI-MS, *m/z*: 213; ^{1}H NMR ($CDCl_3$): δ 4.76 (br s, 1H, NH), 6.73(dd, 1H, Ar-H, J_1 = 7.2 Hz and J_2 = 7.7Hz), 7.22-7.55 (m, 7H, Ar-H), 7.93 (d, 1H, Ar-H, J = 8.3Hz), 9.21(br s, 1H, COOH); IR (KBr): 3379 (N-H), 3005 (Ar-H), 1669 (C=O), 1593 cm^{-1} (C=C).

Synthesis of 4-hydroxy-quinolin-2-one IIa

A mixture of aniline 9.3 g (0.1 mole) and malonic acid 10.4 g (0.1 mole) was heated at 100°C for 1 hr. with phosphoryl chloride 46 g (0.3 mole) and anhydrous zinc chloride 27.3 g (0.2 mole). The reaction product was decomposed with ice and water, the resulting solid was filtered and washed with water. The solid was treated with 10% sodium hydroxide solution, filtered and the filtrate on acidification with hydrochloric acid gave 4-hydroxy-quinolin-2-one **IIa**. Crystallization from methanol containing a small amount of hydrochloric acid resulted needles of TLC pure **IIa**. yield: 13 g (81%); m.p. >300°C; ^{1}H NMR (DMSO-d_6): δ 5.78 (s, 1H, =CH-), 7.00-7.65 (m, 3H, Ar-H), 7.76 (d, 1H, Ar-H, J = 7.82 Hz), 10.38 (s, 1H, -NH), 10.58 (br s, 1H, -OH); IR (KBr): 3410 (O-H), 2913 (C-H), 1668 (C=O), 1615 (C=C), 1514 cm^{-1} (amide II); ESI-MS, *m/z*: 161; Anal. Calcd. for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.05; H, 4.40; N, 8.68%.

Synthesis of 4-hydroxy-1-methyl/phenylquinolin-2-one IIb/IIc

N-Methyl/phenyl anthranilic acid 41 g (0.3mole)/ 45 g (0.211 mole) was dissolved in 150 mL of acetic acid and 150 mL of acetic anhydride was added. This was heated at 120°C for 6 hr and poured into ice. After basification with sodium hydroxide, the residue was filtered and the filtrate was taken and acidified with hydrochloric acid and cooled. The solid precipitate was filtered and washed with benzene. The compound showed a single spot in TLC, no column chromatography employed for purification. **IIb**: Yield: 19.4 g (37%); m.p. 272°C; ESI-MS, *m/z*: 175. **IIc**: Yield: 17.5 g (35%); m.p. 296°C; ESI-MS, *m/z*: 237.

Synthesis of 4-hydroxy-3-formyl-1*H*/methyl/phenylquinolin-2-one (IIIa/IIIb/IIIc)

Sodium hydroxide (80 mL of 15%) was charged with 0.0124 mole of 4-hydroxy-1-*H*/methyl/ phenylquinolin-2-one (**IIa/IIb/IIc**) and was cooled to 4°C and stirred. Subsequently the temperature inside the flask was maintained at 80°C on a water-bath. At 80°C, 40 mL (0.5 mole) of chloroform was introduced in three portions at intervals of fifteen minutes down the condenser on hot water-bath. Stirring was continued for 12 hr, and the reaction-mixture was cooled to RT. The orange coloured liquid was acidified with dilute sulphuric acid. It was extracted with ethyl acetate and dried with anhydrous sodium sulphate. Ethyl acetate was removed under vacuum and the solid obtained was purified by column chromatography (SiO_2) in hexane, ethyl acetate (7:3) mixture. **IIIa**: Yield: 0.91 g (39%); m.p. >350°C; ESI-MS, *m/z*: 189. **IIIb**: Yield: 0.93 g (37%); m.p. 176°C; ESI-MS, *m/z*: 203. **IIIc**: Yield: 1.15 g (35%); m.p. 234-35°C; ESI-MS, *m/z*: 265.

General procedure for the synthesis of 4-hydroxy-3-formylideneamino-1*H*/methyl/phenylquinolin-2-ones (IV/V/VI)

To a solution of aldehyde (0.1 mmole) (**IIIa/IIIb/IIIc**) in dichloromethane, aniline or substituted aniline or aliphatic amine (0.1 mmole) was added and the reaction-mixture was stirred for 8 hr. The residue obtained on evaporation of the solvent was purified by column chromatography (SiO_2) using pet ether, ethyl acetate (9:1 v/v) as eluent to give Schiff base up to 96% yield as bright yellow solid.

4-Hydroxy-3-formylidene-anilinoquinolin-2-one IVa: ^{1}H NMR ($CDCl_3$): δ 6.70 (s, 1H, -NH-), 7.20-7.60 (m, 9H, Ar-H), 8.20 (s, 1H, -OH), 9.00 (d, 1H, -CH=N-, J = 7.62 Hz); ESI-MS, *m/z*: 264; UV ($CHCl_3$)

λmax: 370 (14960), 245 nm (Є 13950); Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.65; H, 4.51; N, 10.33. Found: C, 72.72; H, 4.58; N, 10.60%.

4-Hydroxy-3-formylidene-2'-nitroanilinoquinolin-2-one IVb: ^{1}H NMR ($CDCl_3$): δ 6.00 (s, 1H, -NH-), 6.80 (m, 1H, Ar-H), 7.20-7.60 (m, 7H, Ar-H), 8.20 (s, 1H, -OH), 9.00 (d, 1H, -CH=N-, *J* = 8.12 Hz); UV ($CHCl_3$): 380 (11033), 346 (7662), 249 nm (Є 20819); Anal. Calcd. for $C_{16}H_{11}N_3O_4$: C, 62.14; H, 3.53; N, 13.5. Found: C, 62.07; H, 3.50; N, 13.55 %.

4-Hydroxy-3-formylidine-2'-ethylanilinoquinolin-2-one IVd: ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3H, -CH_3), 7.00 (s, 1H, -NH-), 7.20-7.60 (m, 8H, Ar-H), 8.20 (s, 1H, -OH), 9.00 (d, 1H, -CH=N-, *J* = 6.88 Hz); UV ($CHCl_3$): 376 (10422), 249 nm (Є 19466); ESI-MS, *m/z*: 278.

4-Hydroxy-3-formylidene-anilino-1-methylquinolin-2-one Va: ^{1}H NMR ($CDCl_3$): δ 3.60 (s, 3H, -N-CH_3), 7.20-7.70 (m, 9H, Ar-H), 8.20-8.30 (s, 1H, -OH), 9.02 (d, 1H, -CH=N-, *J* = 7.16 Hz); UV ($CHCl_3$): 376 (8008), 251 nm (Є 15795); IR (KBr): 1655 (C=O), 1607 cm^{-1} (C=N).

4-Hydroxy-3-formylidene-2'-nitroanilino-1-methylquinolin-2-one Vb: ^{1}H NMR ($CDCl_3$): δ 3.62 (s, 3H, -N-CH_3), 7.20- 7.60 (m, 7H, Ar-H), 7.62 (d, 1H, Ar-H, *J* = 7.66 Hz), 8.22-8.40 (s, 1H, -OH), 9.22 (d, 1H, -CH=N-, *J* = 7.94 Hz); UV ($CHCl_3$): 398 (20741), 346 (12741), 258 nm (Є 18458); IR (KBr): 1655 (C=O), 1599 cm^{-1} (C=N); ESI-MS, *m/z* (%): 323 (100), 201 (70), 175 (13), 146 (11), 134 (12), 104 (21), 77 (18).

4-Hydroxy-3-formylidene-2'-methylanilino-1-methylquinolin-2-one Vd: ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3H, -N-CH_3), 3.62 (s, 3H, -CH_3), 7.20-7.72 (m, 8H, Ar-H), 8.20-8.40 (s, 1H, -OH), 9.20 (d, 1H, -CH=N-, *J* = 8.13 Hz); UV ($CHCl_3$): 384 (64567), 253 nm (Є 58658); IR (KBr): 1651 (C=O), 1600 cm^{-1} (C=N); Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.98; H, 5.49; N, 9.50%.

4-Hydroxy-3-formylideneisopropylamino-1-methylquinolin-2-one Vm: ^{1}H NMR ($CDCl_3$): δ 1.40 (d, 6H, -CH_3, *J* = 4.18 Hz), 3.58 (s, 3H, -N-CH_3), 3.74-3.82 (m, 1H, -CH (CH_3)$_2$), 7.12- 7.20 (m, 2H, Ar-H), 7.48-7.60 (t, 2H, Ar-H, *J* = 7.88 Hz), 8.20-8.42 (s, 1H, -OH), 9.00 (d, 1H, -CH=N-, *J* = 8.21 Hz); UV ($CHCl_3$): 346 (33251), 333 nm (Є 26705); IR (KBr): 1653 (C=O), 1606 cm^{-1} (C=N).

4-Hydroxy-3-formylideneanilino-1-phenylquinolin-2-one VIa: ^{1}H NMR ($CDCl_3$): δ 7.12-7.48 (m, 13H, Ar-H), 7.56 (t, 1H, Ar-H, *J* = 8.18 Hz), 8.22 (s, 1H, -OH), 9.04 (d, 1H, -CH=N, *J* = 6.98 Hz); UV ($CHCl_3$): 382 (20314), 256 nm (Є 16190); IR (KBr): 1655 (C=O), 1607 cm^{-1} (C=N).

4-Hydroxy-3-formylidene-2'-nitroanilino-1-phenylquinolin-2-one VIb: ^{1}H NMR ($CDCl_3$): δ 6.52 (d, 1H, Ar-H, *J* = 7.64 Hz), 7.20 (t, 1H, Ar-H, *J* = 7.72 Hz), 7.28-7.46 (m, 8H, Ar-H), 7.52-7.84 (m, 3H, Ar-H), 8.26-8.40 (s, 1H, -OH), 9.08 (d, 1H, -CH=N-, *J* = 7.38 Hz); UV ($CHCl_3$): 396 (21836), 344 (13552), 254 nm (Є 19263); IR (KBr): 1662 (C=O), 1598 cm^{-1} (C=N); Anal. Calcd. for $C_{22}H_{15}N_3O_4$: C, 68.57; H, 3.92; N, 10.90. Found: C, 68.51; H, 3.90; N, 10.81%.

4-Hydroxy-3-formylidene-2'-methylanilino-1-phenylquinolin-2-one VId: ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 3H, -CH_3), 7.18-7.40 (m, 11H, Ar-H), 7.52 (d, 1H, Ar-H, *J* = 7.68 Hz), 7.60 (t, 1H, Ar-H, *J* = 8.01 Hz), 8.26 (s, 1H, -OH), 9.06 (d, 1H, -CH=N-, *J* = 8.22 Hz); UV ($CHCl_3$): 384 nm (Є2373); IR (KBr): 1649 (C=O), 1601cm^{-1} (C=N); ESI-MS, *m/z*: 354.

4-Hydroxy-3-formylideneisopropylamino-1-phenylquinolin-2-one VIm: ^{1}H NMR ($CDCl_3$): δ 1.52 (d, 6H, -CH_3, *J* = 4.26 Hz), 2.64 (m, 1H, -$CH(CH_3)_2$), 6.62 (d, 1H, Ar-H, *J* = 7.39 Hz), 7.22-7.80 (m, 8H, Ar-H), 8.64-8.68 (s, 1H, -OH), 9.00-9.20 (d, 1H, -CH=N-, *J* = 7.94 Hz).

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