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Effect of heterocyclic ring system on formation of dimeric quinolones under catalyst-free conditions: a green approach

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Abstract The intermediate-dependent green and efficient synthesis of dimeric quinolones **4a–l** and **7a–l** by the Knoevenagel condensation followed by Michael-type addition of 4-hydroxy-1-methylquinolin-2(1H)-one **1a**, **b** to indole-3-aldehydes **2a–f** and aromatic aldehydes **5a–l** in water through the condensed compound **3a–l** under catalyst-free conditions is described. This reaction was found to be environmentally friendly, has easy-workup and shorter reaction times giving good yields of the product without the need for its isolation using column chromatography.

Keywords Dimeric quinolones · Knoevenagel condensation · Michael addition · Quinine · Luotonin

Introduction

Quinoline and quinolone [1] derivatives have received considerable attention because of their pharmological [2] importance and numerous biological activities [3]. Many of these derivatives are used in a large number of medicinal and pharmaceutical preparations. Some of these quinoline derivatives are known for their antimicrobial [4], antifungal [5], anticancer [6], anti-HIV [7], anti-oxidant [8], enzyme inhibitory [9] and cytotoxic activities [10]. The quinoline ring system also occurs in natural products [11], mainly in alkaloids [12]. Quinine is a quinoline-based alkaloid isolated from the bark of cinchona tree [13] and is used for the treatment of malaria. Luotonin [14] is a cytotoxic alkaloid isolated from *peganum*

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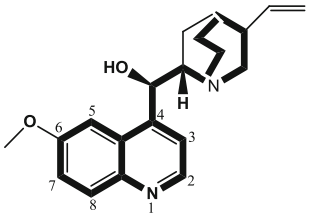
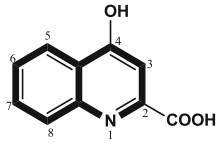
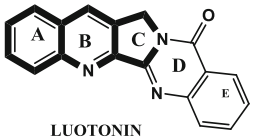
nigellastrum Bunge. This plant is used as a Chinese traditional medicine for the treatment of rheumatism and inflammation. Quinarcine [15] is an acridine-based alkaloid which has been used as an antimalarial agent. Kynurenic acid [16] is a product of quinoline used for the normal metabolism of amino acids and shows neuroactive activity. Especially, antimalarial drugs consist of amino quinoline skeletons (primaquine) extensively used for the treatment of malaria. Pieraquine was the first bis-quinoline-based antimalarial drug and was synthesized in the 1960s from 4-amino quinoline [17].



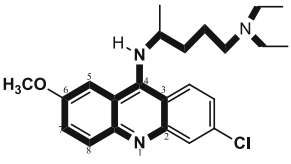
QUININE



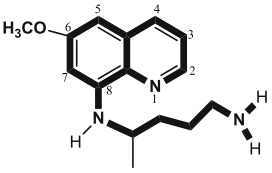
KYNURENIC ACID



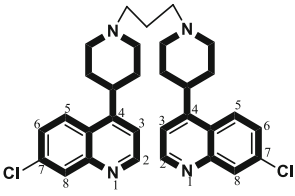
LUOTONIN



Quinarcine



Primaquine



Pieraquine

Indoles are nitrogen-containing heterocyclic compounds widely distributed in nature. Many of these derivatives possess a number of important biological and pharmacological activities [18]. Also, a large number of natural and synthetic indoles have been found in agricultural chemicals [19]. Especially, indolylmethanes and their derivatives are widely recognized as chemical and bioactive metabolites of marine and terrestrial origin [20]. These newly 3-substituted indoles have been prepared by the condensation of indole with carbonyl compounds [21]. If the indole ring system is coupled with other biologically active heterocycles like quinolines and quinolones, the resulting dimeric system is expected to show an increased spectrum of biological activity [22]. Recently, Guo et al. [23].reported the one-pot synthesis of iro- catalyzed bis-indolylmethanes in THF as solvent. Vaghei et al. [24] reported the efficient synthesis of di-, tri- and tetra-bis indolylmethanes under thermal conditions with CTAB as a catalyst. Ramachandiran et al. [25] reported palladium-catalyzed synthesis of indolylmethanes in the presence of $Cu(OAc)_2$ under solvent-free conditions. However, some of the above reported methods suffer from a few drawbacks, such as the toxic catalyst, low yields, lack of cost-effective reagents and prolonged reaction conditions. Hence, to overcome these, a new protocol for the Knoevengel condensation in water has been improved based on green chemistry principles [26] and follows a single way which is indole condensation with carbonyl compounds without catalyst.

Keeping the above results in our mind and in continuation of our earlier work [27], we here report the green and eco-friendly synthesis of indolylmethanes and its comparison study with dimeric quinolones in good yield by condensation of different indole-3-carbaldehydes and aromatic aldehydes with quinolones under green condition, without the need of a catalyst and column chromatography.

Experimental

Materials and methods

Melting points are uncorrected and were determined in open capillary tubes in a sulfuric acid bath. TLC was run on silica gel-G and visualization was carried out using iodine or UV light. IR spectra were recorded using a Perkin-Elmer 1000 instrument in KBr pellets. ^{1}H NMR spectra were recorded in DMSO-d_6 using TMS as internal standard using a 400-MHz spectrometer. Mass spectra were recorded onan Agilent-LCMS instrument under CI conditions and given by Q + 1 values only. The chemical and solvents were purchased either from from Aldrich or Avra laboratories (India) without further purification. Products were purified by recrystallization from ethanol.

General procedure for preparation of 3 from 1 and 2 by step-wise method

A mixture of **1** (10 mmol) and **2** (10 mmol) and water (5 ml) was stirred at room temperature for 30 min. At the end of this period, a pale yellow-colored solid was separated from the reaction mixture which was collected by filtration. The isolated solid was washed with hot water (10 ml × 3), dried, and recrystallized from ethanol to obtain pure **3**.

General procedure for preparation of 4 from 1 and 3 by step-wise method

A mixture of **1** (10 mmol) and **3** (10 mmol) and water (5 ml) was refluxed at 100 °C for 30 min. At the end of this period, an orange-colored solid was separated from the reaction mixture which was collected by filtration. The isolated solid was washed with hot water (10 ml × 3), dried, and recrystallized from ethanol to obtain pure **4**.

General procedure for preparation of 4 from 1 and 2 by one-pot method

A mixture of **1** (20 mmol) and **2** (10 mmol) and water (5 ml) was refluxed at 100 °C 1 h. At the end of this period, an orange-colored solid was separated from the reaction mixture which was collected by filtration. The isolated solid was washed with hot water (10 ml × 3), dried, and recrystallized from ethanol to obtain pure **4**.

General procedure for preparation of 7 from 1 and 5

A mixture of **1** (20 mmol), **5** (10 mmol) and water (5 ml) was refluxed at 100 °C for 1–2 h. The reaction was monitored by checking TLC for the disappearance of the starting material i.e. **1**. At the end of this period, a colorless solid was separated from the reaction mixture and was collected by filtration. The crude product was then washed with water (10 ml) and dried. It was recrystallized from ethanol to obtain pure **7**.

Spectral data

***3a**: 3-((1H-indol-3-yl) methylene)-1-methylquinoline-2,4(1H,3H)-dione*

Pale yellow solid, Yield: 86%, Time: 30 min; M.P.: 210–212 °C; IR (KBr): 3414 cm^{-1} (–NH group, broad and medium), 1660 cm^{-1} (–CO– group, sharp), 1649 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.76 (s, 3H, N–CH_3), 5.68 (s, 1H, –CH–Ar), 6.84–8.25 (m, 9H, four aryl protons of quinoline ring plus five protons of the indole ring), 11.01 (s, 1H, –NH, and D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 29.59, 55.38, 110.46, 111.80, 113.64, 115.42, 117.71, 118.06, 123.39, 124.49, 125.25, 127.62, 133.80, 135.47, 137.48, 152.03, 160.50. *m/z* (M^++1): 303.3 Anal. Calcd for $C_{19}H_{14}N_2O_2$ (302.1): C, 75.48; H, 4.67; N, 9.27; Found: C, 75.44; H, 4.64; N, 9.31.

***3b**: 1-methyl-3-((5-nitro-1H-indol-3-yl) methylene)quinoline-2,4(1H,3H)-dione*

Pale yellow solid, Yield: 91%, Time: 30 min; M.P.: 216–218 °C; IR (KBr): 3425 cm^{-1} (–NH group, broad and medium), 1658 cm^{-1} (–CO– group, sharp), 1641 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.81 (s, 3H, N–CH_3), 5.73 (s, 1H, –CH–Ar), 6.81–8.34 (m, 8H, four aryl protons of quinoline ring plus four protons of the indole ring), 11.05 (s, 1H, –NH, and D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 28.46, 55.29, 110.51, 111.75, 113.58, 115.33, 117.64, 118.12, 123.45, 124.53, 125.19, 127.70, 133.76, 135.54, 137.31, 152.10, 160.58. *m/z* (M^++1): 348.6 Anal. Calcd for $C_{19}H_{13}N_3O_4$ (347.0): C, 65.70; H, 3.77; N, 12.10; Found: C, 65.74; H, 3.73; N, 12.06.

***3c**: 3-((5-chloro-1H-indol-3-yl)methylene)-1-methylquinoline-2,4(1H,3H)-dione*

Pale yellow solid, Yield: 89%, Time: 30 min; M.P.: 209–211 °C; IR (KBr): 3438 cm^{-1} (–NH group, broad and medium), 1662 cm^{-1} (–CO– group, sharp), 1639 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.75 (s, 3H, N–CH_3), 5.69 (s, 1H, –CH–Ar), 6.78–8.31 (m, 8H, four aryl protons of quinoline ring plus four protons of the indole ring), 11.12 (s, 1H, –NH, and D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 28.52, 55.30, 110.58, 111.81, 113.60, 115.28, 117.59, 118.15, 123.37, 124.41, 125.25, 127.67, 133.80, 135.48, 137.36, 152.06, 160.41. *m/z* (M^++1): 337.5 Anal. Calcd for $C_{19}H_{13}ClN_2O_2$ (336.0): C, 67.76; H, 3.89; N, 8.32; Found: C, 67.80; H, 3.85; N, 8.36.

***3d**: 3-((5-bromo-1H-indol-3-yl)methylene)-1-methylquinoline-2,4(1H,3H)-dione*

Pale yellow solid, Yield: 87%, Time: 30 min; M.P.: 206–208 °C; IR (KBr): 3429 cm^{-1} (–NH group, broad and medium), 1653 cm^{-1} (–CO– group, sharp), 1627 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.65 (s, 3H, N–CH_3), 5.53 (s, 1H, –CH–Ar), 6.71–8.29 (m, 8H, four aryl protons of quinoline ring plus four protons of the indole ring), 11.03 (s, 1H, –NH, and D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 28.39, 55.42, 110.34, 111.76, 113.57, 115.21, 117.45, 118.09, 123.28, 124.33, 125.18, 127.53, 133.74, 135.30, 137.24, 152.12, 160.31. *m/z* (M^++1): 381.6 Anal. Calcd for $C_{19}H_{13}BrN_2O_2$ (380.2): C, 59.86; H, 3.44; N, 7.35; Found: C, 59.82; H, 3.48; N, 7.38.

***3e**: 3-((5-methoxy-1H-indol-3-yl)methylene)-1-methylquinoline-2,4(1H,3H)-dione*

Pale yellow solid, Yield: 76%, Time: 30 min; M.P.: 218–220 °C; IR (KBr): 3420 cm^{-1} (–NH group, broad and medium), 1641 cm^{-1} (–CO– group, sharp), 1618 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.20 (s, 3H, –OCH_3), 3.59 (s, 3H, N–CH_3), 5.66 (s, 1H, –CH–Ar), 6.75–8.31 (m, 8H, four aryl protons of quinoline ring plus four protons of the indole ring), 11.14 (s, 1H, –NH, and D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 29.19, 31.26, 55.51, 110.28, 111.65, 113.50, 115.32, 117.53, 118.11, 123.39, 124.41, 125.22, 127.56, 133.68, 135.15, 137.30, 152.23, 160.45. *m/z* (M^++1): 333.4 Anal. Calcd for $C_{20}H_{16}N_2O_3$ (332.1): C, 72.28; H, 4.85; N, 8.43; Found: C, 72.24; H, 4.89; N, 8.47.

***3f**: 1-methyl-3-((5-methyl-1H-indol-3-yl)methylene)quinoline-2,4(1H,3H)-dione*

Pale yellow solid, Yield: 74%, Time: 30 min; M.P.: 216–218 °C; IR (KBr): 3431 cm^{-1} (–NH group, broad and medium), 1648 cm^{-1} (–CO– group, sharp), 1626 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.11 (s, 3H, –CH_3), 3.63 (s, 3H, N–CH_3), 5.48 (s, 1H, –CH–Ar), 6.80–8.49 (m, 8H, four aryl protons of quinoline ring plus four protons of the indole ring), 11.02 (s, 1H, –NH, and D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 29.03, 31.56, 55.61, 110.39, 111.43, 113.60, 115.41, 117.50, 120.37, 124.03, 124.25, 125.38, 134.16, 137.66, 153.05, 160.38. *m/z* (M^++1): 317.0 Anal. Calcd for $C_{20}H_{16}N_2O_2$ (316.1): C, 75.93; H, 5.10; N, 8.86; Found: C, 75.97; H, 5.14; N, 8.89.

***3g**: 3-((1H-indol-3-yl)methylene)-1-ethylquinoline-2,4(1H,3H)-dione*

Pale yellow solid, Yield: 85%, Time: 30 min; M.P.: 212–214 °C; IR (KBr): 3425 cm^{-1} (–NH group, broad and medium), 1656 cm^{-1} (–CO– group, sharp), 1641 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 1.92 (t, 6H, –(N–CH_3)$_2$), 4.25 (q, 4H, (–N–CH_2)$_2$), 5.98 (s, 1H, –CH–Ar), 6.76–8.37 (m, 9H, four aryl protons of quinoline ring plus five protons of the indole ring), 11.16 (s, 1H, –NH, and D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 13.41, 29.50, 55.26, 110.10, 111.72, 113.55, 115.31, 117.68, 118.23, 123.47, 124.53, 125.39, 127.62, 133.87, 135.43, 137.22, 152.13, 160.47. *m/z* (M^++1): 317.5 Anal.

Calcd for $C_{20}H_{16}N_2O_2$ (316.1): C, 75.93; H, 5.10; N, 8.86; Found: C, 75.97; H, 5.14; N, 8.89.

***3h**: 1-ethyl-3-((5-nitro-1H-indol-3-yl)methylene)quinoline-2,4(1H,3H)-dione*

Pale yellow solid, Yield: 91%, Time: 30 min; M.P.: 215–217 °C; IR (KBr): 3418 cm^{-1} (–NH group, broad and medium), 1667 cm^{-1} (–CO– group, sharp), 1638 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 1.86 (t, 6H, –(N–CH_3)$_2$), 4.32 (q, 4H, (–N–CH_2)$_2$), 5.86 (s, 1H, –CH–Ar), 6.71–8.43 (m, 8H, four aryl protons of quinoline ring plus five protons of the indole ring), 11.23 (s, 1H, –NH, and D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 13.34, 28.48, 55.13, 110.18, 111.67, 113.42, 115.53, 117.37, 118.41, 123.50, 124.62, 125.33, 127.70, 133.72, 135.39, 137.18, 152.06, 160.34. *m/z* (M^++1): 362.4 Anal. Calcd for $C_{20}H_{15}N_3O_4$ (361.1): C, 66.48; H, 4.18; N, 11.63; Found: C, 66.45; H, 4.15; N, 11.67.

***3i**: 3-((5-chloro-1H-indol-3-yl)methylene)-1-ethylquinoline-2,4(1H,3H)-dione*

Pale yellow solid, Yield: 86%, Time: 30 min; M.P.: 209–211 °C; IR (KBr): 3420 cm^{-1} (–NH group, broad and medium), 1671 cm^{-1} (–CO– group, sharp), 1628 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 1.67 (t, 6H, –(N–CH_3)$_2$), 4.40 (q, 4H, (–N–CH_2)$_2$), 5.91 (s, 1H, –CH–Ar), 6.65–8.39 (m, 8H, four aryl protons of quinoline ring plus five protons of the indole ring), 11.12 (s, 1H, –NH, and D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 13.29, 28.37, 55.21, 110.34, 111.52, 113.38, 115.46, 117.35, 118.58, 123.12, 124.37, 125.69, 127.63, 133.54, 135.08, 137.23, 152.14, 160.40. *m/z* (M^++1): 351.3 Anal. Calcd for $C_{20}H_{15}ClN_2O_2$ (350.0): C, 68.48; H, 4.31; N, 7.99; Found: C, 68.45; H, 4.34; N, 7.96.

***3j**: 3-((5-bromo-1H-indol-3-yl)methylene)-1-ethylquinoline-2,4(1H,3H)-dione*

Pale yellow solid, Yield: 85%, Time: 30 min; M.P.: 213–215 °C; IR (KBr): 3431 cm^{-1} (–NH group, broad and medium), 1671 cm^{-1} (–CO– group, sharp), 1632 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 1.88 (t, 6H, –(N–CH_3)$_2$), 4.51 (q, 4H, (–N–CH_2)$_2$), 5.83 (s, 1H, –CH–Ar), 6.57–8.48 (m, 8H, four aryl protons of quinoline ring plus five protons of the indole ring), 11.05 (s, 1H, –NH, and D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 13.18, 28.42, 55.33, 110.49, 111.67, 113.03, 115.51, 117.28, 118.45, 123.18, 124.00, 125.57, 127.74, 133.22, 135.11, 137.31, 152.29, 160.08. *m/z* (M^++1): 395.7 Anal. Calcd for $C_{20}H_{15}BrN_2O_2$ (394.1): C, 60.78; H, 3.83; N, 7.09; Found: C, 60.74; H, 3.87; N, 7.05.

***3k**: 1-ethyl-3-((5-methoxy-1H-indol-3-yl)methylene)quinoline-2,4(1H,3H)-dione*

Pale yellow solid, Yield: 74%, Time: 30 min; M.P.: 231–234 °C; IR (KBr): 3427 cm^{-1} (–NH group, broad and medium), 1663 cm^{-1} (–CO– group, sharp),

1628 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 1.77 (t, 6H, –(N–CH_3)$_2$), 3.15 (s, 3H, –OCH_3), 4.64 (q, 4H, (–N–CH_2)$_2$), 5.59 (s, 1H, –CH–Ar), 6.44–8.61 (m, 8H, four aryl protons of quinoline ring plus five protons of the indole ring), 11.21 (s, 1H, –NH, and D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 13.06, 28.17, 31.58, 55.39, 110.35, 111.60, 113.12, 115.47, 117.35, 118.53, 123.26, 124.09, 125.61, 127.82, 133.19, 135.07, 137.28, 152.14, 160.15. *m/z* (M^++1): 345.5 Anal. Calcd for $C_{21}H_{18}N_2O_3$ (346.1): C, 72.82; H, 5.24; N, 8.09; Found: C, 72.86; H, 5.21; N, 8.05.

***3l**: 1-ethyl-3-((5-methyl-1H-indol-3-yl)methylene)quinoline-2,4(1H,3H)-dione*

Pale yellow solid, Yield: 71%, Time: 30 min; M.P.: 228–230 °C; IR (KBr): 3422 cm^{-1} (–NH group, broad and medium), 1658 cm^{-1} (–CO– group, sharp), 1620 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 1.65 (t, 6H, –(N–CH_3)$_2$), 3.02 (s, 3H, –CH_3), 4.57 (q, 4H, (–N–CH_2)$_2$), 5.60 (s, 1H, –CH–Ar), 6.31–8.59 (m, 8H, four aryl protons of quinoline ring plus five protons of the indole ring), 11.17 (s, 1H, –NH, and D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 13.06, 28.01, 31.62, 55.41, 110.27, 111.56, 113.04, 115.41, 117.29, 118.48, 123.35, 124.11, 125.65, 127.75, 133.30, 135.24, 137.28, 152.01, 160.28. *m/z* (M^++1): 331.2 Anal. Calcd for $C_{21}H_{18}N_2O_2$ (330.1): C, 76.34; H, 5.49; N, 8.48; Found: C, 76.38; H, 5.45; N, 8.51.

***4a**: 3,3′-((1H-indol-3-yl)methylene)bis(4-hydroxy-1-methylquinolin-2(1H)-one)*

White solid, Yield: 90%, Time: 60 min; M.P.: 292–294 °C; IR (KBr): 3276 cm^{-1} (–NH group, broad and medium), 2578 (–OH group, broad and medium), 1630 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.65 (s, 6H, –(CH_3)$_2$), 6.40 (s, 1H, –CH), 6.72–8.14 (m, 13H, Ar–H), 10.87 (s, 1H, –NH, D_2O exchangeable)12.97 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 25.32, 51.14, 110.69, 112.01, 115.81, 118.15, 118.80, 121.20, 123.20, 124.08, 127.17, 131.96, 136.83, 138.52, 158.83. *m/z* (M^++1): 478.7 Anal. Calcd for $C_{29}H_{23}N_3O_4$ (477.17): C, 72.94; H, 4.85; N, 8.80; Found: C, 72.90; H, 4.89; N, 8.83.

***4b**: 3,3′-((5-nitro-1H-indol-3-yl)methylene)bis(4-hydroxy-1-methylquinolin-2(1H)-one)*

White solid, Yield: 91%, Time: 60 min; M.P.: 289–291 °C; IR (KBr): 3356 cm^{-1} (–NH group, broad and medium), 2581 (–OH group, broad and medium), 1626 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.79 (s, 6H, –(CH_3)$_2$), 6.43 (s, 1H, –CH), 6.85–8.23 (m, 12H, Ar–H), 11.57 (s, 1H, –NH, D_2O exchangeable)12.59 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 27.44, 51.04, 100.65, 110.25, 110.62, 112.57, 115.71, 123.19, 124.05, 124.78, 127.42, 131.94, 132.06, 138.51, 152.97. *m/z* (M^++1): 523.2 Anal. Calcd for $C_{29}H_{22}N_4O_6$ (522.15): C, 66.66; H, 4.24; N, 10.72; Found: C, 66.62; H, 4.28; N, 10.76.

***4c**: 3,3′-((5-chloro-1H-indol-3-yl)methylene)bis(4-hydroxy-1-methylquinolin-2(1H)-one)*

White solid, Yield: 84%, Time: 60 min; M.P.: 282–284 °C; IR (KBr): 3346 cm^{-1} (–NH group, broad and medium), 2539 (–OH group, broad and medium), 1647 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.64 (s, 6H, –$(CH_3)_2$), 6.71 (s, 1H, –CH), 6.90–8.55 (m, 12H, Ar–H), 11.06 (s, 1H, –NH, D_2O exchangeable)12.27 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 27.38, 51.27, 100.21, 105.32, 110.42, 110.79, 113.83, 115.20, 124.01, 125.07, 127.38, 131.52, 132.06, 135.74, 139.81, 153.47. *m/z* (M^++1): 512.6 Anal. Calcd for $C_{29}H_{22}ClN_3O_4$ (511.13): C, 68.04; H, 4.33; N, 8.21; Found: C, 68.01; H, 4.37; N, 8.24.

***4d**: 3,3′-((5-bromo-1H-indol-3-yl)methylene)bis(4-hydroxy-1-methylquinolin-2(1H)-one)*

White solid, Yield: 83%, Time: 60 min; M.P.: 279–281 °C; IR (KBr): 3339 cm^{-1} (–NH group, broad and medium), 2528 (–OH group, broad and medium), 1637 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.89 (s, 6H, –$(CH_3)_2$), 6.30 (s, 1H, –CH), 6.74–8.23 (m, 12H, Ar–H), 10.86 (s, 1H, –NH, D_2O exchangeable)12.40 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 27.23, 53.02, 100.07, 106.27, 110.18, 110.27, 115.74, 118.50, 124.05, 125.36, 127.49, 131.25, 135.13, 139.63, 140.58, 153.85. *m/z* (M^++1): 556.3 Anal. Calcd for $C_{29}H_{22}BrN_3O_4$ (555.08): C, 62.60; H, 3.99; N, 7.55; Found: C, 62.64; H, 3.95; N, 7.51.

***4e**: 3,3′-((5-methoxy-1H-indol-3-yl)methylene)bis(4-hydroxy-1-methylquinolin-2(1H)one)*

White solid, Yield: 81%, Time: 60 min; M.P.: 296–298 °C; IR (KBr): 3412 cm^{-1} (–NH group, broad and medium), 2569 (–OH group, broad and medium), 1629 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.18 (s, 3H, –OCH_3), 3.90 (s, 6H, –$(CH_3)_2$), 6.22 (s, 1H, –CH), 6.63–8.45 (m, 12H, Ar–H), 11.03 (s, 1H, –NH, D_2O exchangeable)12.74 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 28.79, 31.44, 55.04, 100.65, 110.25, 110.62, 111.94, 112.58, 115.70, 117.16, 117.48, 123.18, 124.04, 124.79, 127.42, 131.93, 132.06, 138.50, 152.97. *m/z* (M^++1): 508.2 Anal. Calcd for $C_{30}H_{25}N_3O_5$ (507.18): C, 70.99; H, 4.96; N, 8.28; Found: C, 70.95; H, 4.92; N, 8.24.

***4f**: 3,3′-((5-methyl-1H-indol-3-yl)methylene)bis(4-hydroxy-1-methylquinolin-2(1H)-one)*

White solid, Yield: 81%, Time: 60 min; M.P.: 297–299 °C; IR (KBr): 3411 cm^{-1} (–NH group, broad and medium), 2552 (–OH group, broad and medium), 1629 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.01 (s, 3H, –CH_3), 3.82 (s, 6H, –$(CH_3)_2$), 6.19 (s, 1H, –CH), 6.59–8.37 (m, 12H, Ar–H),

10.84 (s, 1H, –NH, D_2O exchangeable)12.60 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 28.61, 31.15, 55.21, 110.94, 112.47, 114.01, 115.29, 115.82, 116.70, 117.32, 123.28, 124.17, 126.33, 128.05, 132.15, 138.60, 140.11, 140.31, 153.61. *m/z* (M^++1): 492.3 Anal. Calcd for $C_{30}H_{25}N_3O_4$ (491.1): C, 73.30; H, 5.13; N, 8.55; Found: C, 73.34; H, 5.17; N, 8.51.

***4g**: 3,3′-((1H-indol-3-yl)methylene)bis(1-ethyl-4-hydroxyquinolin-2(1H)-one)*

White solid, Yield: 89%, Time: 60 min; M.P.: 290–292 °C; IR (KBr): 3333 cm^{-1} (–NH group, broad and medium), 2558 (–OH group, broad and medium), 1626 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 1.70 (t, 6H, –(N–CH_3)$_2$), 4.16 (q, 4H, (–N–CH_2)$_2$), 6.25 (s, 1H, –CH), 6.62–8.21 (m, 13H, Ar–H), 11.03 (s, 1H, –NH, D_2O exchangeable)12.74 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 13.37, 27.29, 56.21, 110.66, 112.03, 115.54, 118.11, 118.72, 121.20, 123.09, 123.98, 124.50, 127.09, 132.08, 136.86, 137.38, 153.30. *m/z* (M^+−1): 504.2 Anal. Calcd for $C_{31}H_{27}N_3O_4$ (505.20): C, 73.65; H, 5.38; N, 8.31; Found: C, 73.62; H, 5.35; N, 8.35.

***4h**: 3,3′-((5-nitro-1H-indol-3-yl)methylene)bis(1-ethyl-4-hydroxyquinolin-2(1H)-one)*

White solid, Yield: 91%, Time: 60 min; M.P.: 273–275 °C; IR (KBr): 3341 cm^{-1} (–NH group, broad and medium), 2553 (–OH group, broad and medium), 1632 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 1.74 (t, 6H, –(N–CH_3)$_2$), 4.25 (q, 4H, (–N–CH_2)$_2$), 6.30 (s, 1H, –CH), 6.59–8.18 (m, 12H, Ar–H), 11.14 (s, 1H, –NH, D_2O exchangeable)12.81 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 13.48, 27.36, 56.37, 110.57, 112.31, 115.46, 118.65, 121.19, 123.27, 123.88, 124.46, 127.71, 132.23, 136.78, 137.09, 153.44. *m/z* (M^+−1): 549.7 Anal. Calcd for $C_{31}H_{26}N_4O_6$ (550.19): C, 67.63; H, 4.76; N, 10.18; Found: C, 67.67; H, 4.73; N, 10.14.

***4i**: 3,3′-((5-chloro-1H-indol-3-yl)methylene)bis(1-ethyl-4-hydroxyquinolin-2(1H)-one)*

White solid, Yield: 87%, Time: 60 min; M.P.: 260–262 °C; IR (KBr): 3352 cm^{-1} (–NH group, broad and medium), 2560 (–OH group, broad and medium), 1645 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 1.63 (t, 6H, –(N–CH_3)$_2$), 4.16 (q, 4H, (–N–CH_2)$_2$), 6.44 (s, 1H, –CH), 6.71–8.40 (m, 12H, Ar–H), 11.29 (s, 1H, –NH, D_2O exchangeable)12.39 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 13.22, 27.29, 56.09, 110.83, 112.74, 115.61, 118.47, 121.21, 123.35, 123.92, 124.58, 127.80, 132.41, 136.59, 137.16, 153.50. *m/z* (M^+−1): 540.5 Anal. Calcd for $C_{31}H_{26}ClN_3O_4$ (539.16): C, 68.95; H, 4.85; N, 7.78; Found: C, 68.91; H, 4.89; N, 7.74.

***4j**: 3,3′-((5-bromo-1H-indol-3-yl)methylene)bis(1-ethyl-4-hydroxyquinolin-2(1H)-one)*

White solid, Yield: 85%, Time: 60 min; M.P.: 257–259 °C; IR (KBr): 3348 cm^{-1} (–NH group, broad and medium), 2557 (–OH group, broad and medium), 1641 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 1.48 (t, 6H, –(N–CH_3)$_2$), 4.36 (q, 4H, (–N–CH_2)$_2$), 6.35 (s, 1H, –CH), 6.64–8.37 (m, 12H, Ar–H), 11.06 (s, 1H, –NH, D_2O exchangeable)12.47 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 13.78, 27.26, 56.14, 110.75, 112.69, 115.77, 118.56, 121.31, 123.40, 123.83, 124.66, 127.74, 132.81, 136.72, 137.09, 153.67. *m/z* (M^+-1): 582.6 Anal. Calcd for $C_{31}H_{26}BrN_3O_4$ (583.11): C, 63.71; H, 4.48; N, 7.19; Found: C, 63.74; H, 4.44; N, 7.16.

***4k**: 3,3′-((5-methoxy-1H-indol-3-yl)methylene)bis(1-ethyl-4-hydroxyquinolin-2(1H)-one)*

White solid, Yield: 84%, Time: 60 min; M.P.: 291–293 °C; IR (KBr): 3353 cm^{-1} (–NH group, broad and medium), 2542 (–OH group, broad and medium), 1637 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 1.42 (t, 6H, –(N–CH_3)$_2$), 3.28 (s, 3H, –OCH_3), 4.51 (q, 4H, (–N–CH_2)$_2$), 6.40 (s, 1H, –CH), 6.58–8.24 (m, 12H, Ar–H), 11.15 (s, 1H, –NH, D_2O exchangeable)12.31 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 13.78, 28.65, 31.79, 56.38, 110.67, 112.72, 115.50, 118.83, 121.22, 123.13, 123.44, 124.34, 127.56, 132.19, 136.25, 137.13, 153.82. *m/z* (M^++1): 536.4 Anal. Calcd for $C_{32}H_{29}N_3O_5$ (535.2): C, 71.76; H, 5.46; N, 7.85; Found: C, 71.72; H, 5.49; N, 7.81.

***4l**: 3,3′-((5-methyl-1H-indol-3-yl)methylene)bis(1-ethyl-4-hydroxyquinolin-2(1H)-one)*

White solid, Yield: 82%, Time: 60 min; M.P.: 288–290 °C; IR (KBr): 3326 cm^{-1} (–NH group, broad and medium), 2535 (–OH group, broad and medium), 1629 cm^{-1} (–CO– group, sharp); ^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 1.54 (t, 6H, –(N–CH_3)$_2$), 3.35 (s, 3H, –CH_3), 4.29 (q, 4H, (–N–CH_2)$_2$), 6.38 (s, 1H, –CH), 6.41–8.65 (m, 12H, Ar–H), 11.01 (s, 1H, –NH, D_2O exchangeable)12.63 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 13.28, 28.91, 31.35, 56.10, 110.54, 112.36, 115.62, 118.79, 121.34, 123.19, 123.55, 124.41, 127.67, 132.23, 136.40, 137.25, 154.07. *m/z* (M^++1): 520.2 Anal. Calcd for $C_{32}H_{29}N_3O_4$ (519.5): C, 73.97; H, 5.63; N, 8.09; Found: C, 73.95; H, 5.67; N, 8.06.

***7a**: 3,3′-(phenylmethylene) bis (4-hydroxy-1-methylquinolin-2(1H)-one)*

White solid, Yield: 91% Time: 60 min; M.P.: 287–289 °C; IR (KBr): 2970 (–OH group, broad), 1627 cm^{-1} (–CO– group, sharp);^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.72 (s, 6H, –(CH_3)$_2$), 6.28 (s, 1H, –CH), 7.06–8.07 (m, 13H, Ar–H), 12.60 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 18.88, 55.36, 115.71, 117.26, 123.12, 123.99, 126.02, 126.57, 128.43, 131.97,

137.99, 138.51, 160.87. *m/z* (M^++1): 439. Anal. Calcd for $C_{27}H_{22}N_2O_4$ (438.47): C, 73.96; H, 5.06; N, 6.39; Found: C, 73.84; H, 5.03; N, 6.28.

***7b**: 3,3′-((3-chlorophenyl) methylene) bis (4-hydroxy-1-methylquinolin-2(1H)-one)*

White solid, Yield: 84% Time: 90 min; M.P.: 190–192 °C; IR (KBr): 2975 (–OH group, broad), 1673 cm^{-1} (–CO– group, sharp);^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.83 (s, 6H, –$(CH_3)_2$), 6.46 (s, 1H, –CH), 7.41–8.72 (m, 12H, Ar–H), 12.13 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 18.19, 55.28, 115.63, 117.26, 123.28, 123.72, 126.38, 126.75, 128.18, 131.82, 137.37, 137.81, 138.01, 138.28, 160.46. *m/z* (M^++1): 473. Anal. Calcd for $C_{27}H_{21}ClN_2O_4$ (472.95): C, 68.54; H, 4.49; N, 5.96; Found: C, 68.52; H, 4.48; N, 5.94.

***7c**: 3,3′-((4-chlorophenyl) methylene) bis (4-hydroxy-1-methylquinolin-2(1H)-one)*

White solid, Yield: 83% Time: 90 min; M.P.: 174–175 °C; IR (KBr): 2979 (–OH group, broad), 1683 cm^{-1} (–CO– group, sharp);^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.48 (s, 6H, –$(CH_3)_2$), 6.96 (s, 1H, –CH), 7.23–8.61 (m, 12H, Ar–H), 12.36 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 18.62, 55.31, 115.81, 117.26, 123.62, 123.83, 126.36, 126.71, 128.76, 131.28, 137.51, 138.76, 160.69. *m/z* (M^++1): 473. Anal. Calcd for $C_{27}H_{21}ClN_2O_4$ (472.92): C, 68.57; H, 4.48; N, 5.92; Found: C, 68.53; H, 4.45; N, 5.98.

***7d**: 3,3′-((2-hydroxyphenyl) methylene) bis (4-hydroxy-1-methylquinolin-2(1H)-one)*

White solid, Yield: 72% Time: 120 min; M.P.: 220–222 °C; IR (KBr): 2972 (–OH group, broad), 2968 (–OH group, broad), 1638, cm^{-1} (–CO– group, sharp);^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.79 (s, 6H, –$(CH_3)_2$), 6.35 (s, 1H, –CH), 7.12–8.32 (m, 12H, Ar–H), 12.16 (s, 1H, –OH, D_2O exchangeable); 12.38 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 18.71, 55.24, 115.62, 117.51, 123.24, 123.83, 126.11, 126.72, 128.24, 131.95, 137.14, 138.63, 160.69. *m/z* (M^++1): 455. Anal. Calcd for $C_{27}H_{22}N_2O_5$ (454.47): C, 71.35; H, 4.88; N, 6.16; Found: C, 71.28; H, 4.91; N, 6.18.

***7e**: 3,3′-((4-hydroxyphenyl) methylene) bis (4-hydroxy-1-methylquinolin-2(1H)-one)*

White solid, Yield: 76% Time: 120 min; M.P.: 209–211 °C; IR (KBr): 2985 (–OH group, broad), 2925 (–OH group, broad), 1664, cm^{-1} (–CO– group, sharp);^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.68 (s, 6H, –$(CH_3)_2$), 6.29 (s, 1H, –CH), 7.20–8.44 (m, 12H, Ar–H), 12.23 (s, 1H, –OH, D_2O exchangeable); 12.40 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 18.71, 55.42, 115.62, 117.47, 123.11, 123.92, 126.24, 126.39, 128.82, 131.73, 137.61, 138.83, 160.75. *m/z* (M^++1): 455. Anal. Calcd for $C_{27}H_{22}N_2O_5$ (454.47): C, 71.31; H, 4.83; N, 6.13; Found: C, 71.22; H, 4.94; N, 6.16.

***7f**: 3,3′-((3-nitrophenyl) methylene) bis (4-hydroxy-1-methylquinolin-2(1H)-one)*

White solid, Yield: 85% Time: 60 min; M.P.: 296–298 °C; IR (KBr): 2986 (–OH group, broad), 1679 cm^{-1} (–CO– group, sharp);^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.82 (s, 6H, –$(CH_3)_2$), 6.46 (s, 1H, –CH), 7.82–8.49 (m, 12H, Aromatic hydrogens), 12.62 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 18.31, 55.36, 115.52, 117.29, 123.38, 123.91, 126.71, 126.79, 128.38, 131.57, 137.35, 137.62, 138.29, 138.58, 160.59. *m/z* (M^++1): 484.2 Anal. Calcd for $C_{27}H_{21}N_3O_6$ (483.43): C, 67.02; H, 4.31; N, 8.69; Found: C, 67.03; H, 4.32; N, 8.61.

***7g**: 3,3′-((4-nitrophenyl) methylene) bis (4-hydroxy-1-methylquinolin-2(1H)-one)*

White solid, Yield: 85% Time: 60 min; M.P.: 293–294 °C; IR (KBr): 2991 (–OH group, broad), 1685 cm^{-1} (–CO– group, sharp);^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.87 (s, 6H, –$(CH_3)_2$), 6.63 (s, 1H, –CH), 7.92–8.41 (m, 12H, Ar–H), 12.83 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR δ_C (100 MHz; DMSO-d_6): 18.27, 55.31, 115.46, 117.69, 123.26, 123.71, 126.53, 126.77, 128.81, 131.68, 137.19, 138.81, 160.93. *m/z* (M^++1): 484.2 Anal. Calcd for $C_{27}H_{21}N_3O_6$ (483.49): C, 67.02; H, 4.36; N, 8.64; Found: C, 67.01; H, 4.32; N, 8.63.

***7h**: 3,3′-((4-methoxyphenyl) methylene) bis (4-hydroxy-1-methylquinolin-2(1H)-one)*

White solid, Yield: 75% Time: 120 min; M.P.: 237–238 °C; IR (KBr): 2976 (–OH group, broad), 1672 cm^{-1} (–CO– group, sharp);^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.51 (s, 6H, –$(CH_3)_2$), 3.83 (s, 3H, –OCH_3), 6.84 (s, 1H, –CH), 7.58–8.72 (m, 12H, Ar–H), 12.91 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 18.11, 42.26, 55.42, 115.61, 117.72, 123.51, 123.85, 126.53, 126.79, 128.67, 131.73, 137.27, 138.66, 160.58. *m/z* (M^++1): 469.3 Anal. Calcd for $C_{28}H_{24}N_2O_5$ (468.50): C, 71.78; H, 5.16; N, 5.98; Found: C, 71.76; H, 5.19; N, 5.95.

***7i**: 3,3′-((3,4-dimethoxyphenyl)methylene)bis(4-hydroxy-1-methylquinolin-2(1H)-one)*

White solid, Yield: 79% Time: 120 min; M.P.: 239–241 °C; IR (KBr): 2974 (–OH group, broad), 1676 cm^{-1} (–CO– group, sharp);^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.46 (s, 6H, –$(CH_3)_2$), 3.68 (s, 3H, –OCH_3), 3.81 (s, 3H, –OCH_3), 6.81 (s, 1H, –CH), 7.46–8.69 (m, 11H, Ar–H), 12.86 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 18.25, 40.35, 42.34, 55.51, 115.73, 117.65, 123.58, 123.77, 126.60, 126.91, 128.56, 131.59, 137.17, 138.64, 160.28. *m/z* (M^++1): 499.2 Anal. Calcd for $C_{29}H_{26}N_2O_6$ (498.10): C, 69.87; H, 5.26; N, 5.62; Found: C, 69.85; H, 5.29; N, 5.66.

***7j**: 3,3′-((3-ethoxy-4-methoxyphenyl)methylene)bis(4-hydroxy-1-methylquinolin-2(1H)-one)*

White solid, Yield: 71% Time: 120 min; M.P.: 240–242 °C; IR (KBr): 2982 (–OH group, broad), 1678 cm^{-1} (–CO– group, sharp);^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.43 (s, 6H, –$(CH_3)_2$), 3.74 (s, 3H, –CH_3), 3.61 (q, 2H, -OCH_2), 2.81 (t, 3H, –CH_2–CH_3), 6.74 (s, 1H, –CH), 7.31–8.62 (m, 11H, Ar–H), 12.91 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 18.23, 33.61, 42.32, 45.63, 55.34, 115.57, 117.78, 123.36, 123.75, 126.44, 126.82, 128.53, 131.39, 137.31, 138.48, 160.48. *m/z* (M^++1): 513 Anal. Calcd for $C_{30}H_{28}N_2O_6$ (512.55): C, 70.30; H, 5.51; N, 5.47; Found: C, 70.34; H, 5.56; N, 5.44.

***7k**: 3,3′-(furan-2-ylmethylene) bis (4-hydroxy-1-methylquinolin-2(1H)-one)*

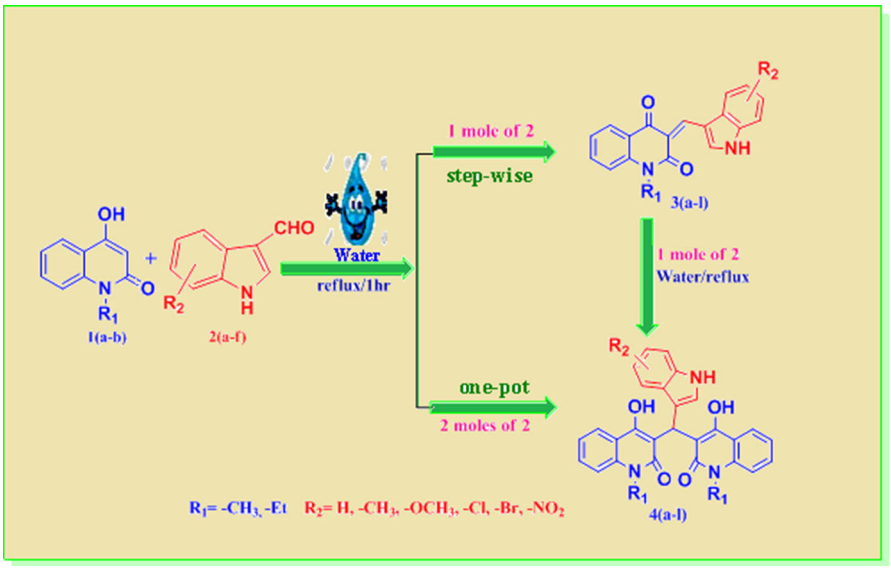
White solid, Yield: 82% Time: 90 min; M.P.: 242–243 °C; IR (KBr): 2973 (–OH group, broad), 1689 cm^{-1} (–CO– group, sharp);^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.52 (s, 6H, –$(CH_3)_2$), 6.83 (s, 1H, –CH), 7.63–8.89 (m, 11H, Ar–H), 12.13 (s, 2H, –OH, D_2O exchangeable); ^{13}C-NMR (100 MHz; DMSO-d_6): δ_C 20.89, 56.45, 119.64, 121.17, 124.33, 125.24, 128.62, 129.51, 132.84, 137.93, 139.73, 160.72. *m/z* (M^++1): 429.3 Anal. Calcd for $C_{25}H_{20}N_2O_5$ (428.44): C, 70.08; H, 4.71; N, 6.54; Found: C, 70.04; H, 4.76; N, 6.58.

***7l**: 3,3′-(phenylmethylene)bis(1-ethyl-4-hydroxyquinolin-2(1H)-one)*

White solid, Yield: 90% Time: 60 min; M.P.: 289–290 °C; IR (KBr): 2968 (–OH group, broad), 1618 cm^{-1} (–CO– group, sharp);^{1}H-NMR (DMSO d_6/TMS, 400 MHZ): δ 3.61 (t, 6H, –$(CH_3)_2$), 4.12 (q, 4H, (–N–CH_2)$_2$), 6.31 (s, 1H, –CH), 7.12–8.24 (m, 13H, Ar–H), 12.58 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 13.89, 18.75, 55.23, 115.57, 117.26, 123.34, 123.87, 126.16, 126.64, 128.39, 131.88, 137.73, 138.41, 160.72. *m/z* (M^++1): 467.4 Anal. Calcd for $C_{29}H_{26}N_2O_4$ (466.1): C, 74.66; H, 5.62; N, 6.00; Found: C, 74.62; H, 5.66; N, 6.04.

Results and discussion

As illustrated in Scheme 1, initially one mole of 4-hydroxy-1-methylquinolin-2(1H)-one **1a** (i.e. **1** , $\mathbf{R_1 = CH_3}$) was reacted with indole-3-carbaldehyde **2a** (i.e. **2**, $\mathbf{R_2 = H}$) to form a condensed compound 3-((1H-indol-3-yl)methylene)-1-methylquinoline-2,4(1H,3H)-dione **3a** (i.e. **3**, $\mathbf{R_1 = CH_3}$, $\mathbf{R_2 = H}$) in water at room temperature for 30 min. The structure of **a** was assigned on the basis of its spectral properties-IR, NMR and Mass. Thus, its IR (KBr) spectrum showed a broad, medium absorption at 3414 cm^{-1} due to the presence of an indole-NH group and a strong, sharp absorptions at 1660 and 1649 cm^{-1} due to the presence of an amide carbonyl group and a carbonyl group at the 4-position. Its ^{1}H NMR, in DMSO-d_6, showed signals at δ 3.76 (s, 3H, N–CH_3), 5.68 (s, 1H, –CH–Ar), 6.84–8.25 (m, 9H,



Scheme 1 Step-wise and one pot synthesis of **4(a–l)**

four aryl protons of quinoline ring plus five protons of the indole ring), 1and 1.01 (s, 1H, –NH, and D_2O exchangeable). Its LC–MS spectrum, when recorded in the Q + 1 mode, showed the molecular ion peak at *m/z* 303 corresponding to a molecular mass of 302.

Later, **3a** was reacted with another mole of **1a** in water under refluxing conditions for 30 min. to form 3,3′-((1H-indol-3-yl)methylene)bis(4-hydroxy-1-methylquinolin-2(1H)-one) **4a** in good yields. The structure of the product was assigned on the basis of its spectral properties-IR, NMR and Mass. Thus, its IR (KBr) spectrum showed a broad, medium absorption at 3276 cm^{-1} due to the presence of an indole-NH group, broad and medium absorption at 2578 cm^{-1} due to the presence of an OH group and a strong, sharp absorption at 1630 cm^{-1} due to the presence of an amide carbonyl group. Its ^1H NMR, in DMSO-d_6, showed signals at δ 3.65 (s, 6H, N–CH_3), 6.40 (s, 1H, –CH–Ar), 6.72–8.14 (m, 13H, four aryl protons of quinoline ring plus five protons of the indole ring), 10.87 (s, 1H, –NH, and D_2O exchangeable), and 12.97 (s, 2H, –OH, and D_2O exchangeable). Its LC–MS spectrum, when recorded in the Q + 1 mode, showed the molecular ion peak at *m/z* 478 corresponding to a molecular mass of 477.

In an alternative method, **4a** could also be prepared in a one-pot method. Thus, a mixture of **1a** (1 mM) and **2a** (2 mM) was refluxed in water for 1 h resulting in the isolation of **4a** in excellent yield and of good purity. The structure of **4a** was confirmed by comparison with an authentic sample which was prepared in the above stepwise method. The reaction of **1a** with **2a** in a one-pot method was examined by carrying out a series of experiments in the presence of different organic and green solvents at different temperatures (Table 1). It was found from these experiments that the formation of **4a** refluxing in water for 1 h, unlike in other solvents such as a

Table 1 Effect of solvent and temperature on formation of **4a** in a one-pot method

Entry	Solvent	Temp.	Time (min)	Yield of **4a**
1	Water	Reflux	60	90
2	Ethanol	Reflux	60	85
3	Methanol	Reflux	60	85
4	PEG-600	Reflux	60	81
5	Glycerol	Reflux	60	78
6	Ethylene glycol	Reflux	60	81
7	Acetic acid	Reflux	60	76
8	1,4-dioxan	Reflux	60	71
9	THF	Reflux	60	68
10	DMF	Reflux	60	62

ethanol, methanol, PEG-600, glycerol, ethylene glycol, acetic acid, 1,4-dioxan, THF, and DMF, gave reasonably high yields (90%) of the product **4a** and in good purity (Table 1, entry-1).

This above model reaction was (compound **3** preparation) performed in water by using different types of electron withdrawing and donating indole aldehydes **2a–f**, **3** was found in good yield (Table 2) in the presence of a heterocyclic ring system having an electron-withdrawing groups (i.e. **5-NO_2**, **5-Cl**, **5-Br**). But after further reaction (i.e. compound **4** preparation), **4** was found in good yield when the heterocyclic ring system having both electron-withdrawing (i.e. **NO_2**, **Cl**, **Br**) and electron-donating groups (i.e. **5-CH_3**, **5-OCH_3**).

Table 2 Synthesis of **3a–l** and **4a–l** in water

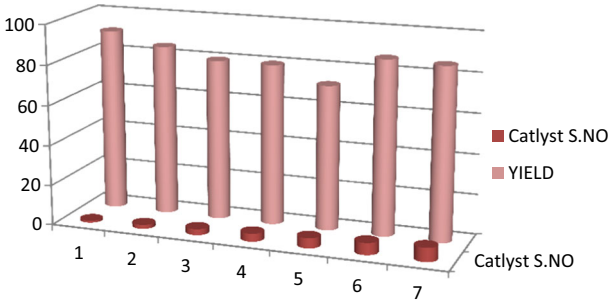
Entry	**1a**, **b** (**R_1**)	**2a–f** (**R_2**)	Product obtained **3a–l**	Yield **3a–l**	Product obtained **4a–l**	Yield **4a–l**	M.P (°C) **3a–l**	M.P (°C) **4a–l**
1	–CH_3	H	**3a**	86	**4a**	90	210–212	292–294
2	–CH_3	5-NO_2	**3b**	91	**4b**	91	216–218	289–291
3	–CH_3	5-Cl	**3c**	89	**4c**	84	209–211	282–284
4	–CH_3	5-Br	**3d**	87	**4d**	83	206–208	279–281
5	–CH_3	5-OCH_3	**3e**	76	**4e**	81	218–220	296–298
6	–CH_3	5-CH_3	**3f**	74	**4f**	81	216–218	297–299
7	–CH_2CH_3	H	**3g**	85	**4g**	89	212–214	290–292
8	–CH_2CH_3	5-NO_2	**3h**	91	**4h**	91	215–217	273–275
9	–CH_2CH_3	5-Cl	**3i**	86	**4i**	87	209–211	260–262
10	–CH_2CH_3	5-Br	**3j**	85	**4j**	85	213–215	257–259
11	–CH_2CH_3	5-OCH_3	**3k**	74	**4k**	84	231–234	291–293
12	–CH_2CH_3	5-CH_3	**3l**	71	**4l**	82	228–230	288–290

Table 3 The effect of solvent for synthesis of compound **7a** (Ref. 27)

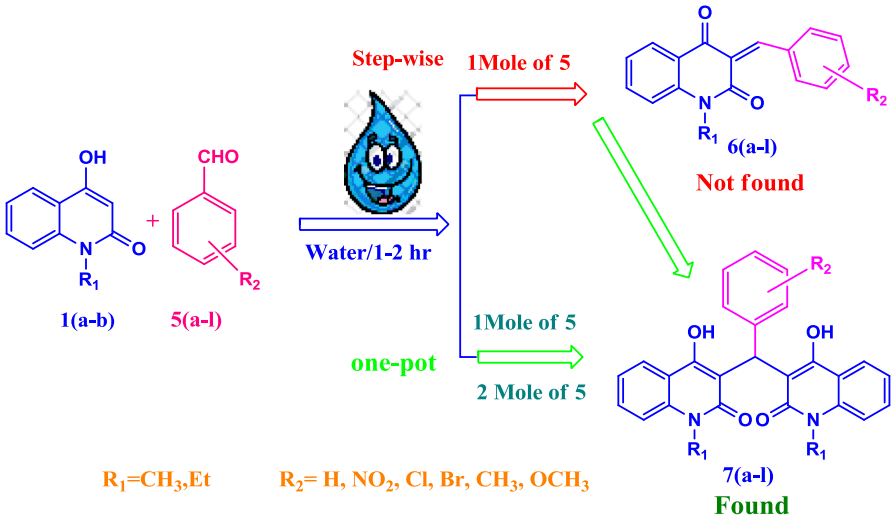
Entry	Solvent	Temp (°C)	Time (min.)	Yield **7a**
1	H_2O	100	60	91
2	Ethylene glycol	100	60	83
3	Glycerol	100	90	79
4	Acetic acid	100	90	80
5	PEG-600	100	120	82
6	DMF	100	90	70
7	H_2O	RT	120	–

After the synthesis of **4a–l** continuing our efforts to carry out the same reaction by taking one mole of 4-hydroxy-1-methylquinolin-2(1H)-one **1a** (i.e. **1**, $\mathbf{R_1 = CH_3}$) with different types of aromatic aldehydes (i.e. benzaldehyde **5a**) (instead of **2a**) in water at room temperature, no product formation was observed (Table 3, entry 1). But the same reaction was performed in water under refluxing conditions for 1 h instead of intermediate compound **6a** the reaction was found to be 3,3[1]-(arylmethylene)-bis-(4-hydroxy-1-methylquinolin-2(1H)-one) **7a** in good yield (91%), the structure having been established on the basis of spectral and analytical data. We checked the reaction every 10 min by using thin layer chromatography. The TLC did not show any intermediate spot of **6a**, showing only the spots corresponding to the **1a**, **5a** and **7a** compounds. Based on the above results, the intermediate **6a** is highly unstable and rapidly reacts with another mole of *N*-methylquinolone **1a** to form the dimeric compound **7a**.

Table 4 Optimization of the reaction conditions (effect of catalyst) (Ref. 27)



Entry	Catalyst	Solvent	Temp (°C)	Yield (**7a**)
1	No catalyst	H_2O	Reflux	91
2	$InCl_3$	H_2O	Reflux	85
3	$ZnCl_2$	H_2O	Reflux	80
4	$FeCl_3$	H_2O	Reflux	80
5	Acetic acid	H_2O	Reflux	72
6	$SnCl_2$	H_2O	Reflux	87
7	L-Proline	H_2O	Reflux	86



Scheme 2 Synthesis of **7(a–l)**

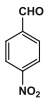
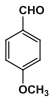
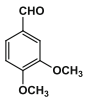
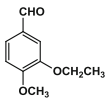
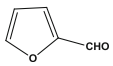
Initially, this transformation was carried out in water under refluxing conditions for 1–2 h in the absence of a catalyst, and **7a** was found in good yield (91%). The reaction conditions were optimized for the above reaction to increase the yield and in order to find the best catalyst and solvent. Thus, the above reaction was carried out in water by using series of catalysts like $InCl_3$, L-Proline, $SnCl_2$, $ZnCl_2$, $FeCl_3$, and even the protic acid like acetic acid. But, unfortunately, in the presence of the catalyst the reaction produced some unreacted starting materials (**1a** and **5a**). Due to that reason, in the presence of the catalyst the reaction produced low yields of **7a**. However, water at 90 °C without a catalyst proved to the best condition. All these results are summarized in Tables 3 and 4 (Scheme 2).

Encouraged by these results, we tested the reaction by using different types of electron-donating and -withdrawing benzaldehyde derivatives to form **7a–l** under optimized conditions to better understand the generality of this method. In these reactions, electron-withdrawing benzaldehyde derivatives gave reasonably better yields. All these results were summarized in Table 5.

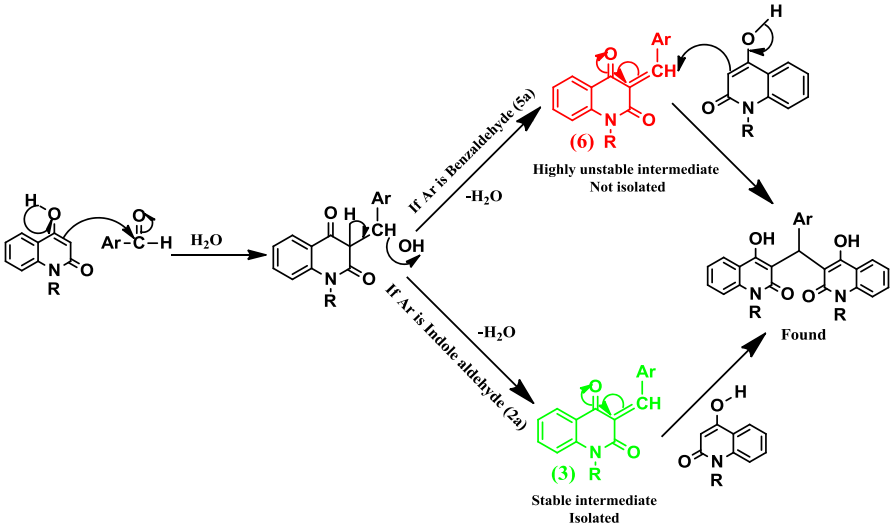
Intermediate-dependent reaction pathway

Based on the above two reactions, a plausible mechanism has been proposed for the formation of **4** and **7**. Initially, one mole of *N*-methyl quinolone **1** reacts with one mole of indole aldehyde **2** in the presence of water to form intermediate compound **3.** This compound further reacts with one mole of *N*-methyl quinolone **1** under refluxing condition to form the final bis-compound. But in the presence of

Table 5 Synthesis of **7a–l** from **1a**, **b** and **5a–l** (Ref. 27)

Entry	**1a**, **b**	**5a–k**	**7a–o**	Yield (%)	M.P (°C)
1	$-CH_3$		**7a**	91	287–289
2	$-CH_3$		**7b**	84	190–192
3	$-CH_3$		**7c**	83	174–175
4	$-CH_3$		**7d**	72	220–222
5	$-CH_3$		**7e**	76	209–211
6	$-CH_3$		**7f**	85	296–298
7	$-CH_3$		**7g**	85	293–294
8	$-CH_3$		**7h**	75	237–238
9	$-CH_3$		**7i**	79	239–241
10	$-CH_3$		**7j**	71	240–242
11	$-CH_3$		**7k**	82	242–243
12	$-CH_2-CH_3$		**7l**	90	289–290

benzaldehyde, the reaction pathway is completely opposite to the first one. In this case, one mole of benzaldehyde **5** in the presence of one mole of *N*-methyl quinolone **1** reacts to give the final bis-compound without any intermediate **6**. Maybe this can happen because the resulting intermediate **6** was highly reactive and rapidly reacts with another mole of N-methyl quinolone **1** to gave the stable dimeric compound **7**.



Conclusions

In summary, we have developed a facile, efficient and green step-wise, one-pot synthesis of dimeric quinolones **4a–l** and **7a–l** by the Knoevenagel condensation followed by Michael-type addition. The effect of heterocyclic (indole ring) and aromatic ring systems on typical intermediate formation can be clearly seen. This reaction was found to be environmentally friendly, has easy-workup and shorter reaction times giving good yields of the product without the need for its isolation using column chromatography.

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