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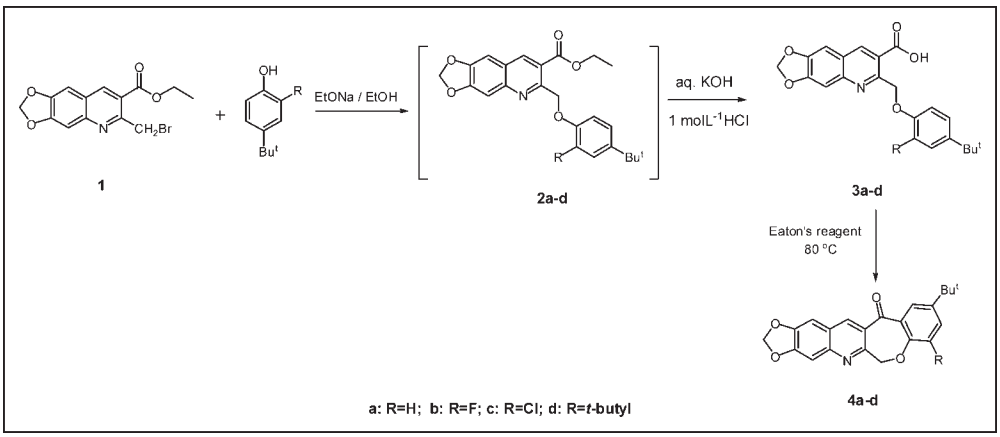

In this study a facile synthesis of novel 10-*tert*-butyl[1]benzoxepino[3,4-*b*][1,3]dioxolo[4, 5-*g*]quinolin-12(6*H*)-ones is described, featuring the one-pot synthesis of 6-[(*tert*-butylphenoxy)methyl][1,3]dioxolo[4,5-*g*]quinoline-7-carboxylic acids from ethyl 6-(bromomethyl)[1,3]dioxolo[4,5-*g*]quinoline-7-carboxylate and their intramolecular Friedel-Crafts acylation reaction by the use of Eaton's reagent (P_2O_5–CH_3 SO_3H) under mild conditions.

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INTRODUCTION

Quinoline-fused ring systems are a backbone of many natural products and pharmacologically significant compounds and display a broad range of biological activities [1–3]. Particularly, five-, six- and seven-membered heterocyclic compounds containing one or two heteroatoms fused to a quinoline ring are found in many natural products as well as in synthetic compounds, which are known to exhibit anticancer [4,5], antiallergenic [6], antibacterial [7], and antiviral properties [8]. The quinoline-fused compounds have been popular targets of synthesis, and a wide variety of protocols have been used. For instance, syntheses have included Friedländer condensation reactions [9], radical cyclization reactions [10], and intramolecular Friedel-Crafts acylation reactions [11,12]. The intramolecular Friedel-Crafts acylation of arylcarboxylic acids is an important route to construct fused ring compounds. Conventionally, intramolecular Friedel-Crafts acylation reaction can be achieved by treating aryl acids with a variety of condensing agents including liquid HF, H_2SO_4, $TiCl_4$, $AlCl_3$, and $AlCl_3$/NaCl [13]. However, using these reagents, not only does the harsh reaction conditions make synthesis and product isolation difficult but also a quantity of acidic waste is inevitably produced, which leads to pollution problems after the reaction. Hence, the development of new synthetic methods would be of considerable importance to the chemistry community.

On the other hand, the introduction of *tert*-butyl group to some compounds can enhance greatly their biological activity. Recently Huy et al. [14] reported that the placement of a metabolically stable *tert*-butyl group at C-2 position of a quinoline ring in primaquine results in a tremendous improvement in blood schizontocidal antimalarial activity (Fig. 1).

In light of these foundings and in view of structural diversity playing a prominent role in medicinal and combinatorial chemistry for a faster and efficient lead generation toward the new drug discovery [15], the synthesis of novel *tert*-butyl substituted quinoline-fused compounds would be much more attractive if a facile and mild broadly applicable synthetic approach could be used. Therefore, we reported herein the simple and effective synthesis of 10-*tert*-butyl[1]benzoxepino[3,4-*b*][1,3]dioxolo[4,5-*g*] quinolin-12(6*H*)-one derivatives by the intramolecular Friedel-Crafts acylation of the arylcarboxylic acids 6-[(*tert*-butyphenoxy)methyl][1,3]dioxolo-[4,5-*g*]quinoline-7-carboxylic acids using Eaton's reagent (P_2O_5–CH_3 SO_3H) as catalyst and solvent as shown in Scheme 1.

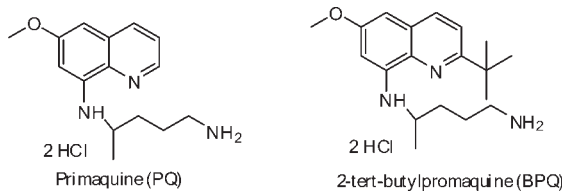


Figure 1. Structures of PQ and BPQ.

RESULT AND DISCUSSION

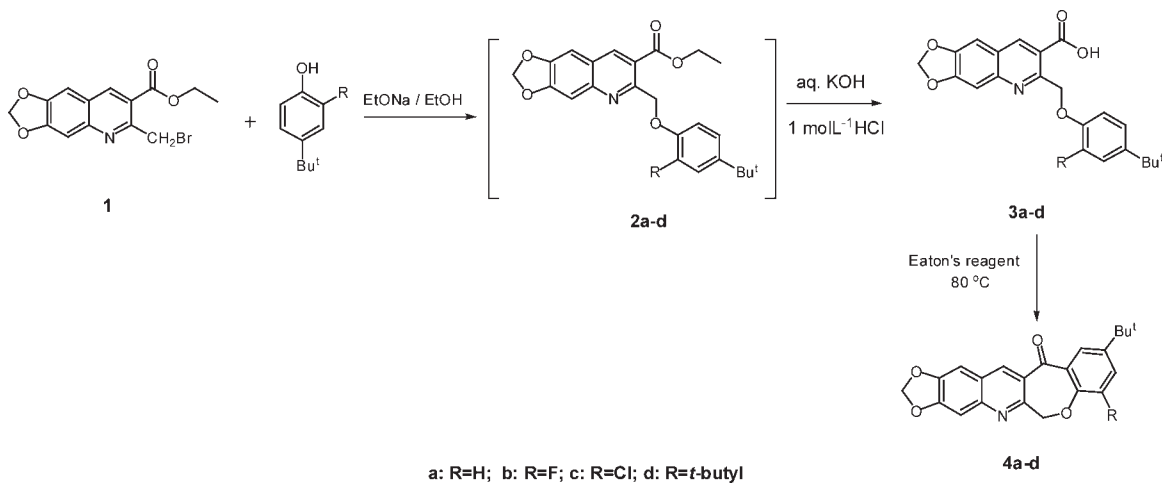
One-pot synthesis 6-[(*tert*-Butyphenoxy)methyl][1,3] dioxolo-[4,5-g]quinoline-7-carboxylic acids. The synthesis starts from readily available ethyl 6-(bromomethyl)[1,3]dioxolo[4,5-*g*]quinoline-7-carboxylate (**1**), which was prepared according to the literature method [11]. The ester ethers ethyl 6-[(*tert*-butylphenoxy)methyl][1,3]dioxolo[4,5-*g*]quinoline-7-carboxylates **(2a–d)** were formed by the Willamson reaction of starting compound **1** and *tert*-butyl substituted phenols. However, the resulting products were difficult to purify from the reaction mixture. Addition some water to the reaction mixture did not have the compounds **2a–d** precipitated out, but instead produced oils. We also tried to chromatograph the reaction mixture on a column to isolate the intermediates but in low yields. Therefore, we developed an efficient one-pot synthesis of the key intermediates 6-[(*tert*-butyphenoxy)methyl][1,3]dioxolo-[4,5-*g*]quinoline-7-carboxylic acids **(3a–d)**, which involved the *in situ* formation of compounds **2a–d** followed by hydrolysis with aqueous ethanolic potassium hydroxide solution. Thus, the two reactions, Williamson reaction and hydrolysis reaction proceeded in one pot, avoiding the tedious isolation of **2a–d**. The value of the one-pot procedure is very obvious: high yields, simple manipulation, and easy purification.

The facile synthesis of the title compounds. Our initial efforts at cyclizing **3a** used polyphosphoric acid as catalyst and solvent. The cyclization reaction could be achieved at 150°C; however, only 37% yield of the cyclized product was isolated. The cyclized product in the obtained mixture was purified by recrystallization from ethanol and was identified as [1]benzoxepino[3,4-*b*][1,3]dioxolo[4,5-*g*]quinolin-12(6*H*)-one (**5**) by spectroscopic methods (Scheme 2). The IR spectrum of **5** exhibited an absence of carboxyl group, which appeared in the substrate **3a** at 3393 cm^{-1}, and the presence of one typical carbonyl absorption for cyclic ketone moiety at 1641 cm^{-1}. Its structure was unequivocal proven by the ^1H NMR spectrum. Particularly, characteristic was the absence of *tert*-butyl protons' resonance at the range of 1.3 to 1.4 ppm, and the presence of seven-proton multiplet in the aromatic region at 7.13 to 8.60 ppm, besides the signals for two methylene protons at 5.41 and 6.16 ppm, respectively. Moreover, the obtained elemental analysis values are also in agreement with theoretical data.

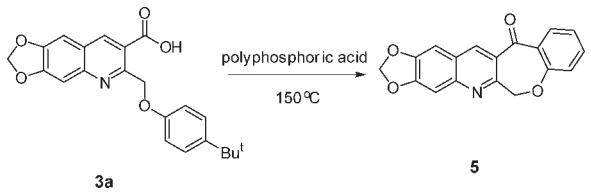
This process involves problem discussed below, which is accompanied by debutylation subsequent to the intramolecular Friedel-Crafts acylation reaction, and it is known that the debutylation reaction is usually carried out in a high-boiling solvent at a high temperature, and the *tert*-butyl substituent is easily removed from aromatic nuclei by Friedel-Crafts reaction using an acid catalyst [16–19]. Hence, we presumed that the high-reaction temperature might lead to the occurrence of debutylation reaction during the cyclization course.

A plausible intramolecular Friedel-Crafts acylation and debutylation mechanism is proposed as shown in Scheme 3. The substrate **3a** was treated with polyphosphoric acid to form the mixed phosphoric-carboxylic anhydride A [20], which further underwent the

Scheme 1



Scheme 2



intramolecular Friedel-Crafts acylation to afford cyclic ketone **4a.** Subsequently, nucleophilic attack of the resulting **4a** to H_3PO_4 under high temperature, followed by loss of isobutene, led to the formation of **5**. The mechanism is analogous to the de-*tert*-butylation of *p-tert*-butylcalix[n]arene in literature [21].

To verify the proposed mechanism, HPLC/MS analysis was selected as a simple and powerful tool, and the reaction was tested as a typical process. Thus, the reaction was monitored with HPLC/MS analysis as follows: portions of the reaction mixture were sampled and were worked up; the qualitative analysis was performed by HPLC/MS. The results revealed that compound **5** existed during the reaction process, and there were no compound **4a** observed during the course of the reaction according to mass spectroscopic detection.

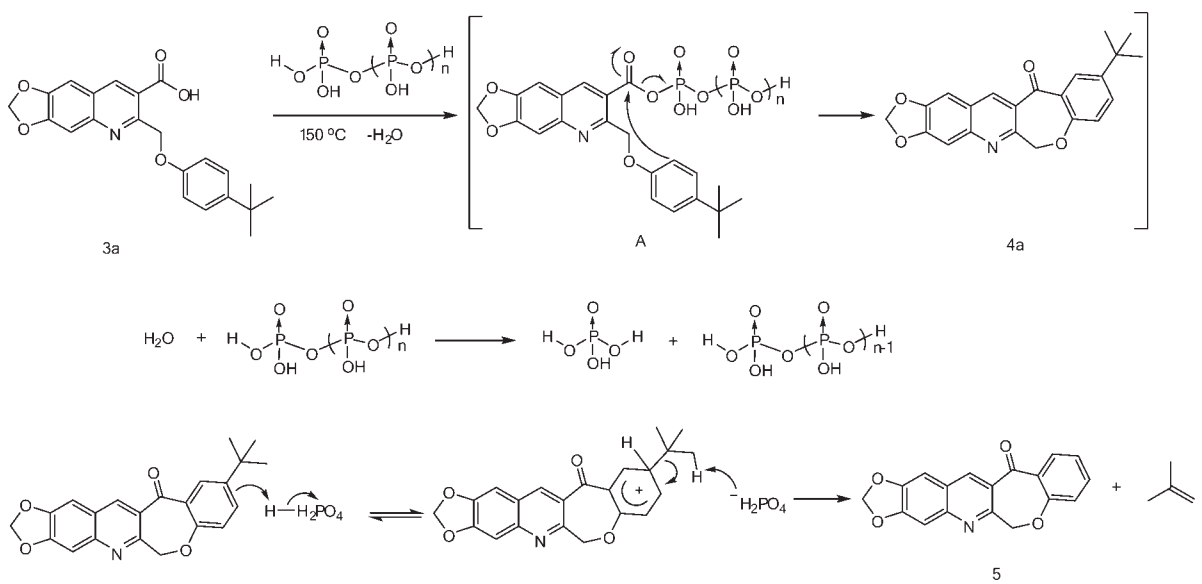
Recently, the inexpensive and commercially available Eaton's reagent, a mixture of P_2O_5 and $MeSO_3H$ [22], has been widely used for effecting intramolecular cyclizations under mild conditions. A number of interesting examples of intramolecular Friedel-Crafts acylation using Eaton's reagent have been published, including the syntheses of quinolone heterocycles [23], 4-hydroxycoumarins [24], and aromatic poly(ether ketone)s [25]. In connection with our studies, we envisioned that the reagent could also be applied to 6-[(*tert*-butylphenoxy)-methyl][1,3]dioxolo[4,5-*g*]quinoline-7-carboxylic acids, from which the desired quinoline-fused ring systems may be synthesized through intramolecular Friedel-Crafts acylation reaction. We were pleased to discover that simply dissolving **3a** in Eaton's reagent and heating to only 80°C resulted in conversion into **4a** in 65% yield within 3 hours. The ease of isolation of **4a** was notable: a simple quench into a basic solution precipitated the product in acceptable purity (94%). The role of P_2O_5 in the reagent mixture $P_2O_5/MeSO_3H$ is as a drying agent. Addition of P_2O_5 decreases the strength of the sulfonic acid. A small amount of water resulting from the cyclization reaction produced a decrease in acidity of $MeSO_3H$ but had little effect on the acid strength of $MeSO_3H$-P_2O_5 acid mixture. Phosphorus pentoxide is, thus, able to delay the deactivation by the water from the cyclization. In neat $MeSO_3H$ substrate **3a** does not give cyclized product after heating at 80°C over 10 hours.

Encouraged by the successful synthesis of compound **4a,** we tested this protocol for the intramolecular cyclization of other substrates **3b–d**. It was found that the method was effective, and all the *tert*-butyl substituted substrates were smoothly converted to the corresponding cyclized products without any evidence for the formation of de-*tert*-butyl products. Thus, the corresponding *tert*-butyl substituted cyclized products **4b–d** were afforded in 49%, 52%, and 58% yield, respectively.

EXPERIMENTAL

General. The melting points were determined by using WRS-1B melting points apparatus. The ^1H NMR was

Scheme 3



measured with a Varian Inova 400 NMR spectrometer at 400 MHz. The reported chemical shifts were against TMS. Elemental analysis was performed using an Elementar Vario EL-III element analyzer. HPLC/MS analysis was performed on a HP 1100 system HPLC/MS spectrometer.

General Procedure for the Preparation of 6-[(*tert*-Butyl phenoxy)methyl][1,3]dioxolo[4,5-*g*]quinoline-7-carboxylic acids (3a–d). To 0.046 g metal sodium (2 mmol) dissolved in 8 mL CH_3CH_2OH *tert*-butyl phenol (2 mmol) and 0.676 g ethyl 6-(bromomethyl)[1,3]dioxolo[4,5-*g*]quinoline-7-carboxylate (**1**) (2 mmol) were added. The mixture was refluxed for 2 hours. Then 60% (v/v) ethanolic potassium hydroxide solution 15 mL was added to the reaction mixture and continued to reflux for 2 hours, cooled, and acidified with 1 M HCl solution. The resulting crude product was recrystalized from 95% ethanol to afford compounds **3a–d**.

6-[(4-*tert*-Butylphenoxy)methyl][1,3]dioxolo[4,5-*g*]quinoline-7-carboxylic acid (3a). Yield 86%; mp 204 to 205°C. IR (KBr): 3393 (COOH), 3058, 2937, 2786, 1712 (C=O), 1610, 1502, 1426, 1245, 1047 (COC), 947 (OCH_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 9H, *t*-butyl), 5.51 (s, 2H, O-CH_2-Ar), 6.10 (s, 2H, OCH_2O), 6.76 to 6.82 (m, 2H, ArH), 6.91 (m, 2H, ArH), 7.38 to 7.41 (m, 2H, ArH), 8.44 (s, 1H, ArH). Anal. Calcd. For $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69 Found: C, 69.72; H, 5.63; N, 3.65%.

6-[(4-*tert*-Butyl-2-fluorophenoxy)methyl][1,3]dioxolo[4,5-*g*]quinoline-7-carboxylic acid (3b). Yield 79%, mp 185 to 187°C. IR (KBr): 3410 (COOH), 3064, 2930, 2853, 1698 (C=O), 1599, 1497, 1410, 1237, 1041 (COC), 948 (OCH_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 9H, *t*-butyl), 5.59 (s, 2H, O-CH_2-Ar), 6.21 (s, 2H, OCH_2O), 6.89 to 7.17 (m, 3H, ArH), 7.31 (s, 1H, ArH), 7.48 (s, 1H, ArH), 8.65 (s, 1H, ArH). Anal. Calcd. For $C_{22}H_{20}FNO_5$: C, 66.49; H 5.07; N 3.52 Found: C 66.53; H 5.12; N 3.59%.

6-[(4-*tert*-Butyl-2-chlorophenoxy)methyl][1,3]dioxolo[4,5-*g*]quinoline-7-carboxylic acid (3c). Yield 77%, mp 216 to 217°C. IR (KBr): 3421 (COOH), 3048, 2936, 2855, 1701 (C=O), 1579, 1514, 1428, 1240, 1035 (COC), 947 (OCH_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 s (9H, *t*-butyl), 5.58 s (2H, O-CH_2-Ar), 6.20 s (2H, OCH_2O), 7.12 to 7.18 m (2H, ArH), 7.32 to 7.35 m (1H, ArH), 7.41 to 7.55 m (2H, ArH), 8.54 s (1H, ArH). Anal. Calcd. For $C_{22}H_{20}ClNO_5$: C, 63.85; H, 4.87; N, 3.38 Found: C, 63.92; H, 4.85; N, 3.48%.

6-[(2,4-Di-*tert*-Butylphenoxy)methyl][1,3]dioxolo[4,5-*g*]quinoline-7-carboxylic acid (3d). Yield 68%, mp 178 to 180°C. IR spectrum (KBr), v, cm^{-1}: 3432 (COOH), 3044, 2939, 2851, 1707 (C=O), 1580, 1507, 1449, 1422, 1243, 1046 (COC), 950 (OCH_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 9H, *t*-butyl), 1.37 (s, 9H, *t*-butyl), 5.55 (s, 2H, O-CH_2-Ar), 6.19 (s, 2H, OCH_2O), 7.08 to 7.21 (m, 3H, ArH), 7.35 to 7.41 (m, 2H, ArH), 8.61 (s, 1H, ArH). Anal. Calcd. For $C_{26}H_{29}NO_5$: C, 71.70; H, 6.71; N, 3.22 Found: C, 71.82; H, 6.69; N, 3.28%.

Synthesis of [1]benzoxepino[3,4-b][1,3]dioxolo[4,5-*g*]quinolin-12(6*H*)-one (5). The 6-[(4-*tert*-butylphenoxy)methyl][1,3]-dioxolo[4,5-*g*]quinoline-7-carboxylic acid (**3a**) (0.38 g, 1 mmol) and polyphosphoric acid (12 g) were added to round flask (25 mL) and stirred at 150°C for 2.5 hours. Then, the reaction mixture was poured into icy water and neutralized with an icy saturated sodium carbonate solution. The crude products were obtained after filtration and washed with water. The pure product **5** was obtained by recrystalization from THF-H_2O. Yield 37%, mp 196 to 197°C. IR (KBr): 3019, 1641 (C=O), 1598, 1559, 1505, 1457, 1400, 1365, 1297,1222, 1168, 1109, 929. ^{1}H NMR (400 MHz, $CDCl_3$): 5.41 (s, 2H, Oxepan-H), 6.16 (s, 2H, OCH_2O), 7.13 to 7.20 (m, 2H, ArH), 7.26 (s, 1H, ArH), 7.40 (s, 1H, ArH), 7.51 to 7.54 (m, 2H, ArH), 8.29 to 8.31 (m, 1H, ArH), 8.60 (s, 1H, ArH). Anal. Calcd. For $C_{18}H_{11}NO4$: C, 70.82; H, 3.63; N, 4.59 Found: C, 70.63; H, 3.78; N, 4.57%.

General Procedure for the Preparation of Title Compounds (4a–d). 6-[(*tert*-Butylphenoxy)methyl][1,3]dioxolo[4,5-*g*]quinolin-7-carboxylic acids **(3a–d)** (1 mmol) and Eaton's reagent (8 mL) were added to round flask (25 mL) and stirred at 80°C for 3 hours. Then, the reaction mixture was poured slowly with stirring into an icy saturated sodium carbonate solution. The crude products were obtained after filtration and washed with water. The pure product **4a–d** was obtained by recrystalization from ethanol.

10-*tert*-Butyl[1]benzoxepino[3,4-b][1,3]dioxolo[4,5-*g*]quinolin-12(6*H*)-one (4a). Yield 65%, mp 201 to 203°C. IR (KBr): 3033, 2925, 2779, 1647 (C=O), 1604, 1586, 1457, 1400, 1249, 1029, 949 (OCH_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 9H, 3-*t*-butyl), 5.43 (s, 2H, Oxepan-H), 6.25 (s, 2H, OCH_2O), 7.24 to 7.27 (m, 1H, ArH), 7.47 (s, 1H, ArH), 7.61 (s, 1H, ArH), 7.83 (s, 1H, ArH), 8.12 to 8.14 (m, 1H, ArH), 8.74 (s, 1H, ArH). Anal. Calcd. For $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88 Found: C, 73.37; H, 5.18; N, 3.92%.

10-*tert*-Butyl-8-fluoro[1]benzoxepino[3,4-b][1,3]dioxolo[4,5-*g*]quinolin-12(6*H*)-one (4b). Yield 49%, mp 215 to 217°C. IR (KBr): 3031, 2927, 2791, 1637 (C=O), 1616, 1471, 1242, 1073, 1028 (COC), 951 (OCH_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 9H, *t*-butyl), 5.58 (s, 2H, Oxepan-H), 6.27 (s, 2H, OCH_2O), 7.29 to 7.31 (m, 1H, ArH), 7.52 (s, 1H, ArH), 7.85 (s, 1H, ArH), 8.13 to 8.16 (m, 1H, ArH), 8.78 (s, 1H, ArH). Anal. Calcd. For $C_{22}H_{18}FNO_4$: C, 69.65; H, 4.78; N, 3.69 Found: C, 69.89; H, 4.61; N, 3.70%.

10-*tert*-Butyl-8-chloro[1]benzoxepino[3,4-b][1,3]dioxolo[4,5-*g*]quinolin-12(6*H*)-one (4c). Yield 52%, mp 226 to 227°C. IR (KBr): 3011, 2920, 2815, 1647 (C=O), 1591, 1461, 1400, 1245, 1038 (COC), 948 (OCH_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 9H, *t*-butyl), 5.57 (s, 2H, Oxepan-H), 6.26 (s, 2H, OCH_2O), 7.19 to 7.23 (m, 1H, ArH), 7.47 (s, 1H, ArH), 7.81 to 7.84 (m, 1H, ArH), 8.11 to 8.13 (m, 1H, ArH), 8.66 (s, 1H, ArH). Anal. Calcd. For $C_{22}H_{18}ClNO_4$: C, 66.75; H, 4.85; N, 3.54 Found: C, 66.46; H, 4.91; N, 3.60%.

8,10-Di-*tert*-Butyl[1]benzoxepino[3,4-b][1,3]dioxolo[4,5-*g*]quinolin-12(6*H*)-one (4d). Yield 58%, mp 241 to 243°C. IR (KBr): 3015, 2923, 2810, 1636 (C=O), 1596, 1462, 1400, 1237, 1036 (COC), 949 (OCH_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9H, *t*-butyl), 1.34 (s, 9H, *t*-butyl), 5.40 (s, 2H, Oxepan-H), 6.23 (s, 2H, OCH_2O), 7.07 to 7.10 (m, 1H, ArH), 7.43 (s, 1H, ArH), 8.01 to 8.03 (m, 1H, ArH), 8.12 (s, 1H, ArH), 8.67 (s, 1H, ArH). Anal. Calcd. For $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35 Found: C, 74.68; H, 6.59; N, 3.29%.

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