First Synthesis of 3,6′- and 3,7′-Biquinoline Derivatives

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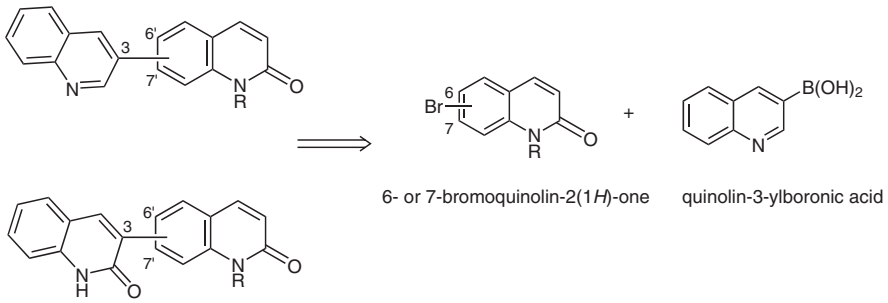
Abstract: The preparation of new 3,6′- and 3,7′-biquinoline derivatives was achieved by microwave-assisted Suzuki cross-coupling between N-protected 6- or 7-bromoquinolin-2(1*H*)-ones and quinolin-3-ylboronic acid. Moreover, a new synthesis of 7-bromoquinolin-2(1*H*)-one leading solely to the 7-substituted isomer was carried out.

Keywords: quinoline, quinolinone, 6-bromoquinolin-2(*1H*)-one, 7-bromoquinolin-2(*1H*)-one, Suzuki cross-coupling

In the course of studies on new compounds with biological activity, we became interested in the synthesis of 3,6′- and 3,7′-biquinoline derivatives by the coupling of a quinoline moiety with a quinolin-2(1*H*)-one derivative bearing a halogen atom in the 6- or 7-position. However, only a few examples of functionalization at the 6- and 7-positions of 6- and 7-haloquinolin-2(1*H*)-ones have been carried out. The reported methods involved either halogen/magnesium exchange,[1] halogen/lithium exchange,[2,3] palladium-catalyzed amino carbonylation,[4] palladium-catalyzed carboxylation,[5] copper-catalyzed aromatic nucleophilic substitution,[6,7] or Heck cross-coupling.[8] To our knowledge, only one example of the Suzuki cross-coupling has been described with an N-unprotected 6-haloquinolin-2(1*H*)-one derivative and various substituted phenylboronic acids in the presence of tetrakis(triphenylphosphine)palladium, lithium chloride, and potassium carbonate.[9]

Thus, for the preparation of 3,6′- and 3,7′-biquinoline derivatives, we decided to follow this latter method by reacting 6- or 7-bromoquinolin-2(1*H*)-one derivatives and quinolin-3-ylboronic acid under Suzuki cross-coupling conditions (Scheme 1).



Scheme 1 Retrosynthetic approach to biquinoline derivatives

6-Bromoquinolin-2(1*H*)-one (**3**) was prepared in three steps according to procedures already described in the literature. Iodination of 4-bromoaniline with benzyltrimethylammonium dichloroiodate in dichloromethane–methanol in the presence of calcium carbonate produced 4-bromo-2-iodoaniline (**1**), which was reacted with methyl acrylate in the presence of palladium(II) acetate and tributylamine under microwave irradiation to give methyl (*E*)-3-(2-amino-5-bromophenyl)prop-2-enoate (**2**). The quinolinone formation to give **3** was achieved by refluxing compound **2** in ethylene glycol (Scheme 2).[9–11]

While already described synthetic methods allowed the preparation of the 6-bromoquinolin-2(1*H*)-one (**3**), to our knowledge, no regioselective preparation of the corresponding 7-isomer has been reported. This compound was previously synthesized in two steps from 3-bromoaniline as an inseparable regioisomeric mixture of 5- and 7-bromoquinolin-2(1*H*)-ones (Scheme 3).[12–17]

Therefore, a new synthesis of 7-bromoquinolin-2(1*H*)-one was carried out that led only to the 7-substituted isomer. We report here a convenient four-step synthesis of this heterocyclic compound in 41% overall yield starting from 4-bromo-2-nitroaniline. Diazotization of 4-bromo-2-nitroaniline followed by iodination as described by Flatt et al.[18] afforded the corresponding aryl iodide **5**. The reduction of the nitro group was carried out in the presence of tin(II) chloride.[19] Literature data reported a reduction yield of 69% using four equivalents of tin(II) chloride. Under these conditions, we observed the formation of a deiodinated product. When the reaction was carried out in the presence of three equivalents of tin(II) chloride, the starting material was partially recovered. This reaction

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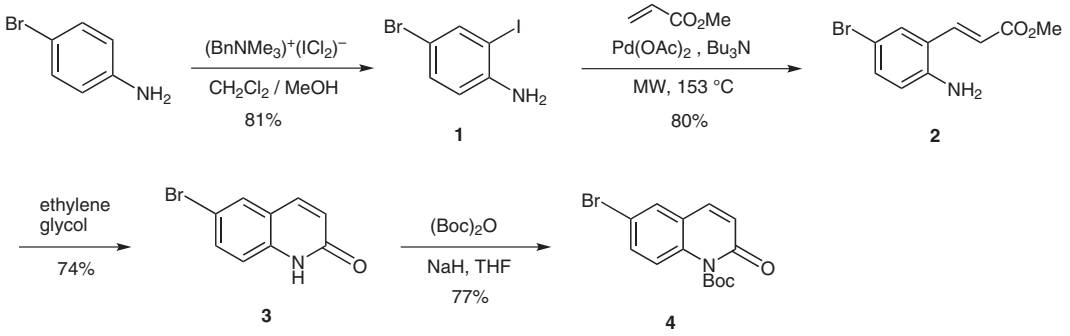
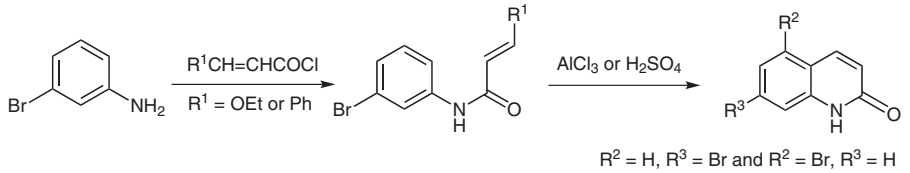


Scheme 2 Synthesis of 6-bromoquinolin-2(1*H*)-one derivatives

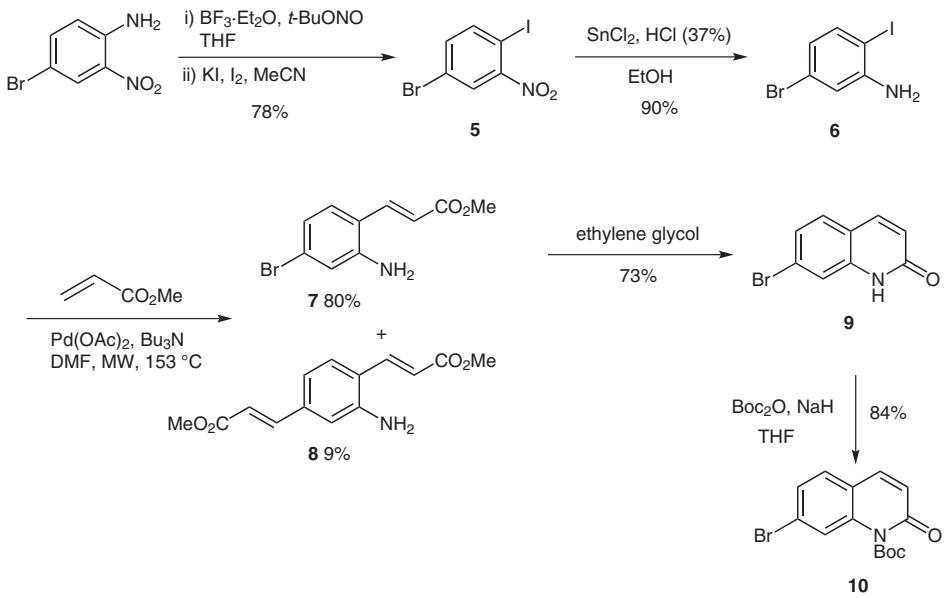


Scheme 3 Preparation of 5- and 7-bromoquinolin-2(1*H*)-ones as a regioisomeric mixture

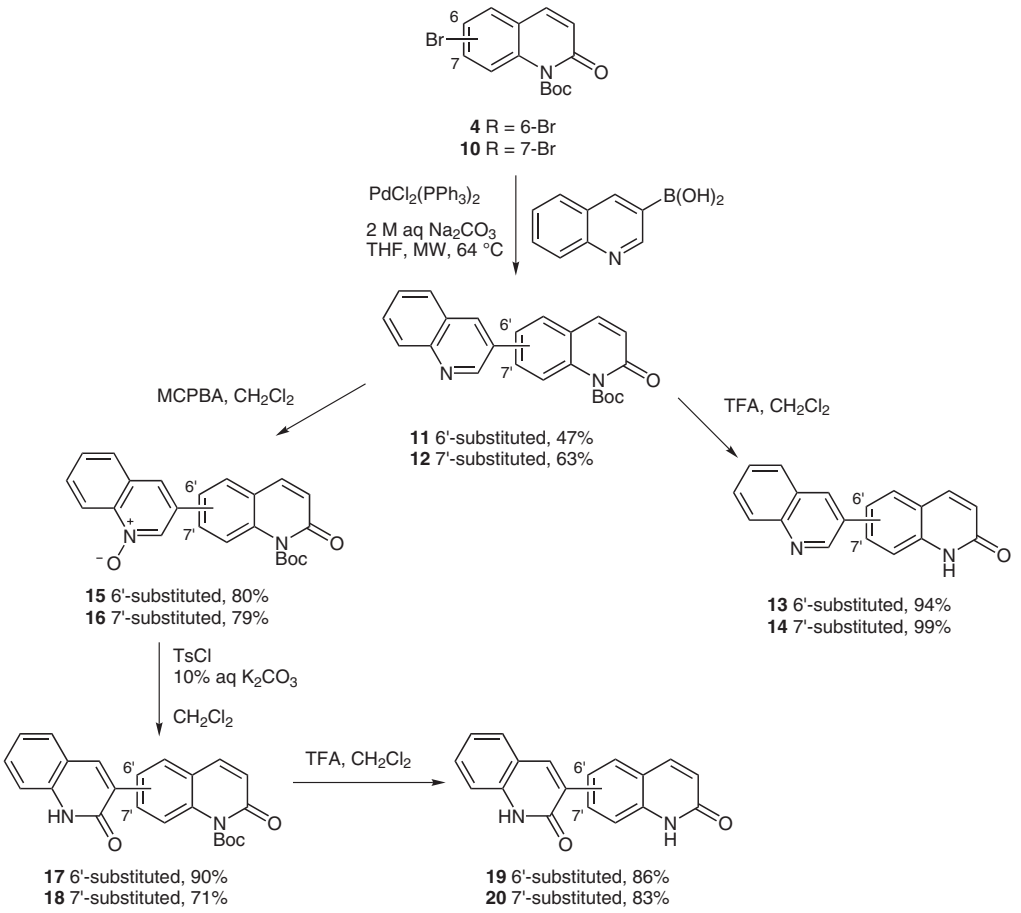
was optimized by using 3.5 equivalents of tin(II) chloride to obtain **6** in 90% yield. The quinolinone formation was achieved in two steps following the procedure described before for the synthesis of the 6-bromo analogue. Compound **6** was treated with methyl acrylate in the presence of palladium acetate and tributylamine under microwave irradiation to give **7** in 80% yield as well as the disubstituted analogue **8** in 9% yield. The cyclization to **9** was performed in 73% yield by refluxing **7** in ethylene glycol (Scheme 4).

For the preparation of biquinoline derivatives, coupling between quinolin-2(1*H*)-ones and quinolin-3-ylboronic acid subunits was achieved by Suzuki cross-coupling (Scheme 5). Quinolin-3-ylboronic acid was prepared as previously described from 3-bromoquinoline.[20]

The coupling reaction was first unsuccessfully conducted on the unprotected 6-bromoquinolin-2(1*H*)-one (**3**) in the presence of tetrakis(triphenylphosphine)palladium, sodium carbonate, and lithium chloride as previously described for an N-unprotected 6-bromoquinolin-2(1*H*)-one derivative with phenylboronic acids.[9] Despite several trials using different catalytic conditions [$Pd(OAc)_2$/NaOMe or $PdCl_2(PPh_3)_2/Na_2CO_3$] the coupling product was not obtained using unprotected 6-bromoquinolin-2(1*H*)-one (**3**). Subsequently, the Suzuki coupling was performed using 6-bromo-1-(*tert*-butoxycarbonyl)quinolin-2(1*H*)-one (**4**), which was prepared by treatment of **3** with di-*tert*-butyl dicarbonate in the presence of sodium hydride in tetrahydrofuran (Scheme 2).



Scheme 4 Preparation of 7-bromoquinolin-2(1*H*)-one



Scheme 5 Preparation of 3,6′- and 3,7′-biquinoline derivatives

Different catalytic systems were tested either in the presence of $Pd(OAc)_2/Na_2CO_3$ or $PdCl_2(PPh_3)_2/Na_2CO_3$. The best result was obtained with $PdCl_2(PPh_3)_2/Na_2CO_3$ under microwave irradiation. When the reaction was performed between **4** and quinolin-3-ylboronic acid in refluxing tetrahydrofuran using $PdCl_2(PPh_3)_2/Na_2CO_3$, the product **11** was obtained in 34% yield after four hours, while product **11** was obtained in 47% yield when the reaction was conducted for ten minutes under microwave irradiation. The same procedure applied to 7-bromo analogue **10**, which was obtained in 84% yield by treating **9** with di-*tert*-butyl dicarbonate in the presence of sodium hydride in tetrahydrofuran (Scheme 4), afforded compound **12** in 63% yield. In this case, the use of microwave irradiation resulted in considerably shortened reaction times (Scheme 5).

Deprotection of compounds **11** and **12** with trifluoroacetic acid in dichloromethane gave the corresponding deprotected products **13** and **14** in 94% and 99% yields, respectively.

The biquinolinone derivatives **17** and **18** were obtained using a classical two-step oxidation procedure to convert the quinoline moiety into the corresponding quinolinone ring. Compounds **11** and **12** were firstly reacted with 3-chloroperoxybenzoic acid in dichloromethane to give the corresponding *N*-oxide derivatives **15** and **16** in 80% and 79% yields, respectively. Treatment of compounds **15** and **16** with tosyl chloride in the presence of potassium carbonate led to the biquinolinone derivatives **17** and **18** in 90% and 71% yields, respectively. The final deprotection step using trifluoroacetic acid in dichloromethane gave 3,6′-biquinoline-2,2′(1*H*,1′*H*)-dione (**19**) and 3,7′-biquinoline-2,2′(1*H*,1′*H*)-dione (**20**) in 86% and 83% yields, respectively (Scheme 5).

In conclusion, the first synthesis of pure 7-bromoquinolin-2(1*H*)-one (**9**) has been described. The preparation of new 3,6′- and 3,7′-biquinoline derivatives was achieved by microwave-assisted Suzuki cross-coupling between N-protected 6- or 7- bromoquinolin-2(1*H*)-ones and quinolin-3-ylboronic acid. Moreover, this is, to our knowledge, the first time that a substitution of 7-haloquinolin-2(1*H*)-one derivative using a Suzuki cross-coupling reaction has been reported.

IR Spectra were recorded on a Perkin-Elmer Paragon 500 spectrophotometer. NMR spectra were performed on a Bruker AVANCE 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz). Mass spectra (ESI+) were determined on a high resolution Waters Micro Q-Toff apparatus. Chromatographic purifications were performed on flash silica gel Geduran SI 60 (Merck) 0.040–0.063 mm column chromatography. TLC were performed on fluorescent silica gel plates (60 F254 from Merck). Experiments under microwave irradiation were performed using a CEM Discover Benchmate microwave apparatus.

6-Bromo-1-(*tert*-butoxycarbonyl)quinolin-2(1*H*)-one (4); Typical Procedure

Compound **3** (1.50 g, 6.69 mmol) was added to a suspension of NaH (60% in a mineral oil, 1.07 g, 26.8 mmol) in anhyd THF (20 mL). The mixture was stirred at 50 °C for 1 h. After cooling, a soln of $(Boc)_2O$ (5.84 g, 26.8 mmol) in anhyd THF (10 mL) was added and the mixture was stirred at 50 °C for 2 h. After cooling, the mixture was poured into sat. aq NH_4Cl (150 mL) and extracted with EtOAc. The organic fractions were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (cyclohexane–EtOAc, 9:1) to give **4** (1.67 g, 77%) as a white solid; mp 98–99 °C.

IR (KBr): 1747, 1592, 1488, 1374, 1280, 1254, 1213, 1145 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.52 (s, 9 H, CH_3), 7.48 (d, J = 8.5 Hz, 1 H), 7.87 (d, J = 9.0 Hz, 1 H), 7.92 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1 H), 8.36 (d, J = 2.0 Hz, 1 H), 8.52 (d, J = 8.5 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.2 (3 CH_3), 116.6, 130.0 (2 C), 133.5, 140.1 (CH), 84.2, 119.5, 128.1, 144.4 (C), 150.2, 156.2 (C=O).

HRMS (ES+): m/z [M + H – CO_2 – C_4H_8]$^+$ calcd for $C_9H_7{}^{79}BrNO$: 223.9711; found: 223.9601.

Methyl (2*E*)-3-(2-Amino-4-bromophenyl)prop-2-enoate (7) and Dimethyl (2*E*,2′*E*)-3,3′-(2-Aminobenzene-1,4-diyl)bisprop-2-enoate (8)

To a soln of compound **6** (4.44 g, 14.9 mmol) in anhyd DMF (30 mL) were added methyl acrylate (1.41 mL, 1.35 g, 15.6 mmol), Bu_3N (3.55 mL, 2.76 g, 14.9 mmol) and $Pd(OAc)_2$ (33.5 mg, 0.149 mmol). The mixture was stirred under microwave irradiation (153 °C, 50 W, P_{atm}) for 5 min then poured into H_2O (300 mL) and extracted with EtOAc. The organic fractions were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (cyclohexane–EtOAc, 8:2) to give **7** (3.07 g, 80%) and **8** (364 mg, 9%) as yellow solids.

Methyl (2*E*)-3-(2-Amino-4-bromophenyl)prop-2-enoate (7)

Mp 112–114 °C.

IR (KBr): 3700–3000, 1713, 1649, 1621 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.70 (s, 3 H, CH_3), 5.87–5.96 (br s, 2 H, NH_2), 6.40 (d, J = 15.5 Hz 1 H), 6.66 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1 H), 6.90 (d, J = 2.0 Hz, 1 H), 7.40 (d, J = 8.5 Hz, 1 H), 7.80 (d, J = 15.5 Hz, 1 H).

^{13}C NMR (400 MHz, DMSO-d_6): δ = 51.3 (CH_3), 115.8, 118.1, 118.8, 129.1, 139.6 (CH), 116.6, 124.5, 149.6 (C_{arom}), 166.9 (C=O).

HRMS (ES+): m/z [M + H]$^+$ for $C_{10}H_{11}{}^{79}BrNO_2$; 255.9973; found: 255.9981.

Dimethyl (2*E*,2′*E*)-3,3′-(2-Aminobenzene-1,4-diyl)bisprop-2-enoate (8)

Mp 148–149 °C.

IR (KBr): 3750–3000, 1700, 1635 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.71 (s, 3 H, CH_3), 3.72 (s, 3 H, CH_3), 5.72–5.78 (br s, 2 H, NH_2), 6.45 (d, J = 16.0 Hz, 1 H), 6.48 (d, J = 16.0 Hz, 1 H), 6.91 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1 H), 6.94 (d, J = 1.5 Hz, 1 H), 7.47 (d, J = 16.0 Hz, 1 H), 7.52 (d, J = 8.0 Hz, 1 H), 7.87 (d, J = 16.0 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 51.2, 51.5 (CH_3), 116.0, 116.1, 116.2, 118.0, 127.9, 139.8, 144.3 (CH), 119.5, 136.4, 148.4 (C_{arom}), 166.5, 166.9 (C=O).

HRMS (ES+): m/z [M + H]$^+$ for $C_{14}H_{16}NO_4$: 262.1079; found: 262.1092.

7-Bromoquinolin-2(1*H*)-one (9)

A soln of **7** (4.58 g, 17.9 mmol) in ethylene glycol (60 mL) was refluxed for 15 h. After cooling, the mixture was poured into H_2O (200 mL) and the solid was filtered and washed with Et_2O and CH_2Cl_2 to give **9** (2.94 g, 73%) as a brown solid; mp 270–272 °C.

IR (KBr): 3100–2800, 1698 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 6.52 (d, J = 9.5 Hz, 1 H), 7.33 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1 H), 7.47 (d, J = 1.5 Hz, 1 H), 7.61 (d, J = 8.5 Hz, 1 H), 7.89 (d, J = 9.5 Hz, 1 H), 11.74–11.86 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 117.3, 122.4, 124.6, 129.8, 139.7 (CH), 118.1, 123.4, 139.9 (C_{arom}), 161.6 (C=O).

HRMS (ES+): m/z [M + H]$^+$ for $C_9H_7{}^{79}BrNO$: 223.9711; found: 223.9711.

7-Bromo-1-(*tert*-butoxycarbonyl)quinolin-2(1*H*)-one (10)

Following the typical procedure for **4** and using **9** (2.10 g, 9.4 mmol), NaH (60% in a mineral oil, 750 mg, 18.8 mmol) in anhyd THF (30 mL) and $(Boc)_2O$ (4.10 g, 18.8 mmol) in anhyd THF (20 mL) with purification by flash chromatography (cyclohexane–EtOAc, 8:2) gave **10** (2.56 g, 84%) as a white solid; mp 95–96 °C.

IR (KBr): 1766, 1610, 1489, 1261, 1215, 1144, 1118 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.52 (s, 9 H, CH_3), 7.47 (d, J = 8.5 Hz, 1 H), 7.80 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1 H), 8.03 (d, J = 8.5 Hz, 1 H), 8.16 (d, J = 2.0 Hz, 1 H), 8.57 (d, J = 8.5 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.2 (3 CH_3), 116.1, 129.8, 129.9 (2 C), 141.1 (CH), 84.3, 123.9, 125.7, 146.4 (C), 150.2, 156.7 (C=O).

HRMS (ES+): m/z [M + Na]$^+$ for $C_{14}H_{14}{}^{79}BrNNaO_3$: 346.0055; found: 346.0058.

1′-(*tert*-Butoxycarbonyl)-3,6′-biquinolin-2′(1′*H*)-one (11); Typical Procedure

To a soln of **4** (200 mg, 0.62 mmol) in THF (7 mL) were added $PdCl_2(PPh_3)_2$ (21.7 mg, 0.031 mmol), aq 2 M Na_2CO_3 (1.54 mL, 3.08 mmol) and quinolin-3-ylboronic acid (160 mg, 0.92 mmol). The mixture was stirred under microwave irradiation (64 °C, 50 W, P_{atm}) for 10 min then poured into H_2O (20 mL) and extracted with EtOAc. The organic fractions were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (cyclohexane–EtOAc, 8:2 then 6:4) to give **11** (109 mg, 47%) as a white solid; mp 143–144 °C.

IR (KBr): 1758, 1213, 1145 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.54 (s, 9 H, CH_3), 7.49 (d, J = 8.5 Hz, 1 H), 7.68 (ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz, 1 H), 7.81 (ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz, 1 H), 8.07–8.12 (m, 3 H), 8.35 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1 H), 8.60–8.65 (m, 2 H), 8.83 (d, J = 2.0 Hz, 1 H), 9.42 (d, J = 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.2 (3 CH_3), 116.2, 126.1, 127.2, 128.5, 128.7, 128.8, 129.6, 129.9, 133.5, 141.2, 149.5 (CH), 84.1, 127.2, 127.6, 131.8, 135.1, 145.4, 147.0 (C), 150.4, 156.2 (C=O).

HRMS (ES+): m/z [M + H]$^+$ for $C_{23}H_{21}N_2O_3$: 373.1552; found: 373.1561.

1′-(*tert*-Butoxycarbonyl)-3,7′-biquinolin-2′(1′*H*)-one (12)

Following the typical procedure for **11** using **10** (100 mg, 0.308 mmol) in THF (5 mL), $PdCl_2(PPh_3)_2$ (10.8 mg, 0.015 mmol), aq 2 M Na_2CO_3 (0.77 mL, 1.54 mmol), and quinolin-3-ylboronic acid (80.0 mg, 0.46 mmol) with microwave irradiation (64 °C, 50 W, P_{atm}) for 5 min. Work up used H_2O (10 mL) and purification was by flash chromatography (cyclohexane–EtOAc, 8:2 then 7:3) to give **12** (72.6 mg, 63%) as a white solid; mp 145–146 °C.

IR (KBr): 1763, 1652, 1219, 1143 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.54 (s, 9 H, CH_3), 7.45 (d, J = 8.5 Hz, 1 H), 7.68 (ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz, 1 H), 7.82 (ddd, J_1 = 8.5 Hz, J_2 = 7.0 Hz, J_3 = 1.5 Hz, 1 H), 8.07–8.13 (m, 2 H), 8.20 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1 H), 8.24 (d, J = 8.5 Hz, 1 H), 8.45–8.46 (m, 1 H), 8.61 (d, J = 8.5 Hz, 1 H), 8.89 (d, J = 2.0 Hz, 1 H), 9.45 (d, J = 2.5 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.2 (3 CH_3), 115.8, 125.8 (2 C), 127.1, 128.6 (2 C), 128.9, 129.9, 133.9, 140.7, 149.5 (CH), 84.0, 126.4, 127.6, 131.7, 139.0, 146.1, 147.1 (C), 150.4, 156.4 (C=O).

HRMS (ES+): m/z $[M + H]^+$ for $C_{23}H_{21}N_2O_3$: 373.1552; found: 373.1571.

3,6′-Biquinolin-2′(1′*H*)-one (13); Typical Procedure

To a soln of **11** (191 mg, 0.51 mmol) in anhyd CH_2Cl_2 (5 mL) was added TFA (0.38 mL, 583 mg, 5.12 mmol). The mixture was stirred at r.t. for 2 h then basified with sat. aq $NaHCO_3$. The solid was filtered and thoroughly washed with H_2O then with Et_2O to give **13** (131 mg, 94%) as a white solid; mp 225 °C.

IR (KBr): 3625–3000, 1675, 1565, 1430 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 6.58 (d, J = 9.5 Hz, 1 H), 7.47 (d, J = 8.5 Hz, 1 H), 7.65 (t, J = 7.5 Hz, 1 H), 7.77 (t, J = 7.5 Hz, 1 H), 8.01 (d, J = 9.5 Hz, 1 H), 8.03–8.08 (m, 3 H), 8.24 (s, 1 H), 8.67 (s, 1 H), 9.30 (d, J = 2.0 Hz, 1 H), 11.69–12.21 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 116.1, 122.6, 126.3, 127.1, 128.3, 128.7, 129.2, 129.4, 132.3, 140.3, 149.3 (CH), 119.7, 127.7, 130.4, 132.0, 138.8, 146.7 (C_{arom}), 161.9 (C=O).

HRMS (ES+): m/z $[M + H]^+$ for $C_{18}H_{13}N_2O$: 273.1028; found: 273.1029.

3,7′-Biquinolin-2′(1′*H*)-one (14)

Following the typical procedure for **13** using **12** (600 mg, 1.61 mmol) in anhyd CH_2Cl_2 (20 mL) and TFA (0.60 mL, 921 mg, 8.1 mmol) gave **14** (437 mg, 99%) as a pale yellow solid; mp 241 °C.

IR (KBr): 3388, 1678 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 6.56 (d, J = 9.5 Hz, 1 H), 7.68–7.73 (m, 3 H), 7.83 (ddd, J_1 = 8.5 Hz, J_2 = 7.0 Hz, J_3 = 1.5 Hz, 1 H), 7.85 (d, J = 8.0 Hz, 1 H), 7.99 (d, J = 9.5 Hz, 1 H), 8.10 (d, J = 8.5 Hz, 1 H), 8.13 (d, J = 8.0 Hz, 1 H), 8.72 (d, J = 2.0 Hz, 1 H), 9.25 (d, J = 2.5 Hz, 1 H), 11.87 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 113.4, 121.0, 122.4, 127.4, 128.3, 128.6, 128.8, 130.2, 133.9, 139.9, 149.0 (CH), 118.9, 127.6, 132.2, 138.8, 139.5, 146.5 (C_{arom}), 162.0 (C=O).

HRMS (ES+): m/z $[M + H]^+$ for $C_{18}H_{13}N_2O$: 273.1028; found: 273.1039.

1′-(*tert*-Butoxycarbonyl)-1-oxido-3,6′-biquinolin-2′(1′*H*)-one (15); Typical Procedure

A soln of **11** (600 mg, 1.61 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a soln of MCPBA (70–75%, 411 mg) in CH_2Cl_2 (10 mL) cooled to 0 °C. The mixture was stirred at r.t. for 62 h then basified with sat. aq K_2CO_3. The aqueous layer was extracted with CH_2Cl_2. The organic fractions were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (EtOAc–MeOH, 98:2) to give **15** (500 mg, 80%) as a yellow solid; mp 168–170 °C.

IR (KBr): 1750, 1574, 1372, 1288, 1218, 1150 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.54 (s, 9 H, CH_3), 7.49 (d, J = 8.5 Hz, 1 H), 7.79 (ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz, 1 H), 7.85 (ddd, J_1 = 8.5 Hz, J_2 = 7.0 Hz, J_3 = 1.5 Hz, 1 H), 8.06 (d, J = 9.0 Hz, 1 H), 8.17 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1 H), 8.32 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1 H), 8.46 (s, 1 H), 8.56 (d, J = 8.5 Hz, 1 H), 8.60 (d, J = 8.5 Hz, 1 H), 8.62 (d, J = 2.0 Hz, 1 H), 9.18 (d, J = 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.2 (3 CH_3), 116.3, 118.8, 122.9, 126.5, 128.7, 129.1, 129.3 (2 C), 130.5, 134.0, 141.3 (CH), 84.2, 127.1, 130.1, 133.1, 133.3, 139.9, 145.7 (C), 150.3, 156.4 (C=O).

HRMS (ES+): m/z $[M + H]^+$ for $C_{23}H_{21}N_2O_4$: 389.1501; found: 389.1503.

1′-(*tert*-Butoxycarbonyl)-1-oxido-3,7′-biquinolin-2′(1′*H*)-one (16)

Following the typical procedure for **15** using **12** (200 mg, 0.537 mmol) in CH_2Cl_2 (3 mL) and MCPBA (70–75%, 185 mg) in CH_2Cl_2 (5 mL); the mixture was stirred at r.t. for 24 h. Purification of the residue obtained after evaporation was carried out by washing with Et_2O, without chromatography, to give **16** (164 mg, 79%) as a beige solid; mp 180–182 °C.

IR (KBr): 1761, 1585, 1370, 1255, 1212, 1141 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.54 (s, 9 H, CH_3), 7.47 (d, J = 8.5 Hz, 1 H), 7.80 (ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz, 1 H), 7.86 (ddd, J_1 = 8.5 Hz, J_2 = 7.0 Hz, J_3 = 1.5 Hz, 1 H), 8.17 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1 H), 8.19 (d, J = 8.0 Hz, 1 H), 8.22 (d, J = 8.5 Hz, 1 H), 8.45 (s, 1 H), 8.54 (s, 1 H), 8.57 (d, J = 8.5 Hz, 1 H), 8.61 (d, J = 8.5 Hz, 1 H), 9.20 (d, J = 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.2 (3 CH_3), 116.2, 118.8, 123.4, 125.6, 126.1, 128.9, 129.2, 129.3, 130.7, 134.1, 140.7 (CH), 84.1, 126.8, 130.0, 133.1, 137.3, 140.0, 146.0 (C), 150.4, 156.5 (C=O).

HRMS (ES+): m/z $[M + H]^+$ for $C_{23}H_{21}N_2O_4$: 389.1501; found: 389.1508.

1′-(*tert*-Butoxycarbonyl)-3,6′-biquinoline-2,2′(1*H*,1′*H*)-dione (17)

To a soln of **15** (300 mg, 0.77 mmol) in CH_2Cl_2 (8 mL) were added 10% w/v aq K_2CO_3 (6 mL) and TsCl (177 mg, 0.93 mmol). The mixture was stirred at r.t. for 4 h. After decantation, the aqueous layer was extracted with EtOAc. The organic fractions were dried ($MgSO_4$) and evaporated. The residue was washed with CH_2Cl_2 to give **17** (270 mg, 90%) as a white solid; mp 284 °C.

IR (KBr): 3650–3175, 1752, 1144 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.54 (s, 9 H, CH_3), 7.23 (ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz, 1 H), 7.38 (d, J = 8.0 Hz, 1 H), 7.43 (d, J = 8.5 Hz, 1 H), 7.54 (ddd, J_1 = 8.5 Hz, J_2 = 7.0 Hz, J_3 = 1.5 Hz, 1 H), 7.78 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1 H), 7.97 (d, J = 9.0 Hz, 1 H), 8.21 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1 H), 8.32 (s, 1 H), 8.50 (d, J = 2.0 Hz, 1 H), 8.59 (d, J = 8.5 Hz, 1 H), 11.99–12.17 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.2 (3 CH_3), 114.8, 115.7, 122.1, 127.2, 127.6, 128.3, 130.5, 131.4, 138.6, 141.1 (CH), 84.0, 119.5, 126.6, 130.4, 134.6, 138.6, 145.2 (C), 150.4, 156.1, 161.0 (C=O).

HRMS (ES+): m/z $[M + H - CO_2 - C_4H_8]^+$ for $C_{18}H_{13}N_2O_2$: 289.0977; found: 289.0984.

1′-(*tert*-Butoxycarbonyl)-3,7′-biquinoline-2,2′(1*H*,1′*H*)-dione (18)

To a soln of **16** (200 mg, 0.515 mmol) in CH_2Cl_2 (5 mL) were added 10% w/v aq K_2CO_3 (4 mL) and TsCl (118 mg, 0.62 mmol). The mixture was stirred at r.t. for 3 h. The solid was washed with Et_2O to give **18** (142 mg, 71%) as a white solid; mp 280 °C.

IR (KBr): 3650–3000, 1763, 1660, 1567, 1430, 1213, 1152 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.53 (s, 9 H, CH_3), 7.23 (t, J = 7.5 Hz, 1 H), 7.37–7.44 (m, 2 H), 7.54 (t, J = 7.5 Hz, 1 H), 7.79

(d, J = 7.5 Hz, 1 H), 8.05 (d, J = 8.5 Hz, 1 H), 8.09 (d, J = 8.5 Hz, 1 H), 8.38 (s, 1 H), 8.39 (s, 1 H), 8.55 (d, J = 8.5 Hz, 1 H), 12.00–12.40 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.3 (3 CH_3), 114.8, 115.5, 122.0, 127.2, 127.4 (2 C), 128.4, 130.7, 139.0, 140.5 (CH), 84.0, 119.5, 126.3, 130.3, 138.4, 138.7, 145.6, 150.5 (C), 156.1, 161.0 (C=O).

HRMS (ES+): m/z [M + H – CO_2 – C_4H_8]$^+$ for $C_{18}H_{13}N_2O_2$: 289.0977; found: 289.0992.

3,6′-Biquinoline-2,2′(1*H*,1′*H*)-dione (19)

Following the typical procedure for **13** using **17** (253 mg, 0.65 mmol) in anhyd CH_2Cl_2 (10 mL) and TFA (0.10 mL, 154 mg, 1.35 mmol) with stirring at r.t. for 2 h gave **19** (161 mg, 86%) as a beige solid; mp 291 °C.

IR (KBr): 3650–3000, 1668, 1570, 1430 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.52 (d, J = 9.5 Hz, 1 H), 7.20 (ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz, 1 H), 7.33–7.37 (m, 2 H), 7.50 (ddd, J_1 = 8.5 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz, 1 H), 7.73 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1 H), 7.92 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1 H), 7.96 (d, J = 9.5 Hz, 1 H), 8.12 (d, J = 2.0 Hz, 1 H), 8.15 (s, 1 H), 11.50–12.30 (br s, 2 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 114.7 (2 C), 121.9, 122.0, 127.9, 128.0, 130.1, 130.9, 137.2, 140.4 (CH), 118.7, 119.6, 129.7, 130.6, 138.3, 138.5 (C), 161.1, 162.0 (C=O).

HRMS (ES+): m/z [M + H]$^+$ for $C_{18}H_{13}N_2O_2$: 289.0977; found: 289.0993.

3,7′-Biquinoline-2,2′(1*H*,1′*H*)-dione (20)

Following the typical procedure for **13** using **18** (90 mg, 0.232 mmol) in anhyd CH_2Cl_2 (4 mL) and TFA (86 μL, 132 mg, 1.16 mmol) with stirring at r.t. for 3 h gave **20** (55.3 mg, 83%) as a pale yellow solid; mp 289 °C.

IR (KBr): 3650–3200, 1662 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.51 (d, J = 9.5 Hz, 1 H), 7.22 (t, J = 7.5 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 1 H), 7.48–7.57 (m, 2 H), 7.71 (d, J = 8.0 Hz, 1 H), 7.77 (d, J = 8.0 Hz, 1 H), 7.80 (s, 1 H), 7.93 (d, J = 9.5 Hz, 1 H), 8.18 (s, 1 H), 11.76 (s, 1 H, NH), 12.03 (s, 1 H, NH).

Due to the insolubility of compound **20**, ^{13}C NMR spectra could not be recorded.

HRMS (ES+): m/z [M + H]$^+$ for $C_{18}H_{13}N_2O_2$: 289.0977; found: 289.0995.

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References

(1) Li, Q.; Woods, K. W.; Wang, W.; Lin, N.-H.; Claiborne, A.; Gu, W.-Z.; Cohen, J.; Stoll, V. S.; Hutchins, C.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2033.
(2) Kelly, T. R.; Bilodeau, M. T.; Bridger, G. J.; Zhao, C. *Tetrahedron Lett.* **1989**, *30*, 2485.
(3) Araki, K.; Tada, K.-I.; Abe, M.; Mutai, T. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1391.
(4) Walsh, T. F.; Toupence, R. B.; Young, J. R.; Huang, S. X.; Ujjainwalla, F.; Devita, R. J.; Goulet, M. T.; Wyvratt, M. J. Jr.; Fisher, M. H.; Lo, J.-L.; Ren, N.; Yudkovitz, J. B.; Yang, Y. T.; Cheng, K.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 443.
(5) Young, J. R.; Huang, S. X.; Chen, I.; Walsh, T. F.; Devita, R. J.; Wyvratt, M. J. Jr.; Goulet, M. T.; Ren, N.; Lo, J.; Yang, Y. T.; Yudkovitz, J. B.; Cheng, K.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1723.
(6) Zimmerman, S. C.; Duerr, B. F. *J. Org. Chem.* **1992**, *57*, 2215.
(7) Zaragoza, F.; Stephensen, H.; Peschke, B.; Rimvall, K. *J. Med. Chem.* **2005**, *48*, 306.
(8) Tedesco, R.; Shaw, A. N.; Bambal, R.; Chai, D.; Concha, N. O.; Darcy, M. G.; Dhanak, D.; Fitch, D. M.; Gates, A.; Gerhardt, W. G.; Halegoua, D. L.; Han, C.; Hofmann, G. A.; Johnston, V. K.; Kaura, A. C.; Liu, N.; Keenan, R. M.; Lin-Goerke, J.; Sarisky, R. T.; Wiggall, K. J.; Zimmerman, M. N.; Duffy, K. J. *J. Med. Chem.* **2006**, *49*, 971.
(9) Huang, S.; Garbaccio, R. M.; Fraley, M. E.; Steen, J.; Kreatsoulas, C.; Hartman, G.; Stirdivant, S.; Drakas, B.; Rickert, K.; Walsh, E.; Hamilton, K.; Buser, C. A.; Hardwick, J.; Mao, X.; Abrams, M.; Beck, S.; Tao, W.; Lobell, R.; Sepp-Lorenzino, L.; Yan, Y.; Ikuta, M.; Murphy, J. Z.; Sardana, V.; Munshi, S.; Kuo, L.; Reilly, M.; Mahan, E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5907.
(10) Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 600.
(11) Plevyak, J. E.; Dickerson, J. E.; Heck, R. F. *J. Org. Chem.* **1979**, *44*, 4078.
(12) Breault, G.; Eyermann, C. J.; Geng, B.; Morningstar, M.; Reck, F. WO 2006,134,378, **2006**; *Chem. Abstr.* **2007**, *146*, 81779.
(13) Horwitz, J. P.; Corbett, T. H.; Palomino, E.; Polin, L.; Hazeldine, S. T. WO 2004,004,651, **2004**; *Chem. Abstr.* **2004**, *140*, 99632.
(14) Roberts, D. A.; Campbell, S. F. CN 85100796, **1986**; *Chem. Abstr.* **1989**, *110*, 114694.
(15) Alabaster, C. T.; Bell, A. S.; Campbell, S. F.; Ellis, P.; Henderson, C. G.; Roberts, D. A.; Ruddock, K. S.; Samuels, G. M. R.; Stefaniak, M. H. *J. Med. Chem.* **1988**, *31*, 2048.
(16) Roberts, D. A. M.; Campbell, S. F. EP 0,148,623, **1985**; *Chem. Abstr.* **1986**, *104*, 19525.
(17) Becker, M. R.; Ewing, W. R.; Davis, R. S.; Pauls, H. W.; Ly, C.; Li, A.; Mason, H. J.; Choi-Sledeski, Y. M.; Spada, A. P.; Chu, V.; Brown, K. D.; Colussi, D. J.; Leadley, R. J.; Bentley, R.; Bostwick, J.; Kasiewski, C.; Morgan, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2753.
(18) Flatt, A. K.; Yao, Y.; Maya, F.; Tour, J. M. *J. Org. Chem.* **2004**, *69*, 1752.
(19) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 1823.
(20) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394.