Regioselective Synthesis of a Potent Src Kinase Inhibitor: 4-(2,4-Dichloro-5-methoxyphenylamino)-7-methoxy-8-(2-morpholin-4-ylethoxy)benzo[*g*]quinoline-3-carbonitrile

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Abstract: The regioselective synthesis of compound **3**, a potent Src kinase inhibitor is described. A key step in this synthesis is the regioselective thermal rearrangement of a substituted benzocyclobutene to provide a 2,3,6,7-tetrasubstituted naphthalene. An efficient route to the uniquely substituted benzocyclobutene is reported.

Key words: drugs, regioselectivity, rearrangements, heterocycles, ring closure

Protein tyrosine kinases catalyze the phosphorylation of a tyrosine residue on a substrate protein, a process resulting in cell growth and differentiation. Src is a cytoplasmic non-receptor kinase that participates in signaling pathways controlling proliferation, migration and angiogenesis.[1] Thus, a small molecule Src kinase inhibitor may prove useful for therapeutic intervention in cancer[2a,b] as well as other disease states affected by this signaling pathway.[3a–c] We had identified a series of substituted 4-anilino-6,7-dialkoxy-3-quinolinecarbonitriles to be very potent Src kinase inhibitors (e.g. compound **1**, Figure 1).[4a–c] Further exploration of this series lead to the discovery of 4-anilino-7,8-dialkoxybenzo[*g*]quinoline-3-carbonitriles such as **2** (Figure 1), which was a more potent Src kinase inhibitor than the corresponding 3-quinolinecarbonitrile.[5] Since the C-7 water-solubilizing group provided enhanced cellular activity, and improved the physical properties of compounds such as **1**, our goal was to synthesize the analogously substituted benzo[*g*]quinoline-3-carbonitrile **3**. However, the chemistry utilized to synthesize **2** was not suitable for the synthesis of **3**, as this would provide products possessing a mixture of C-7 and C-8 substituents. Since any non-regioselective synthesis would generate a mixture of products requiring purification by chromatographic separation,[6] a synthetic strategy was devised to unambiguously provide compound **3** as a single regioisomer.

Scheme 1 outlines the retrosynthetic analysis of the approach for compound **3**. The 2,3,6,7-tetrasubstituted naphthalene **A** (P = protecting group, E = alkyl group) was the key intermediate from which existing methodology could be utilized to construct the target compound.[7] The regioselective synthesis of this intermediate was therefore our major challenge, as existing literature procedures would have provided the 2,3,6,7-tetrasubstituted naphthalene precursor **A** as a regioisomeric mixture.[8a–c]

It had been reported that 3-amino-6,7-dimethoxynaphthalene-2-carboxylic acid *tert*-butyl ester (**A**: wherein P = Me, E = *tert*-butyl) was synthesized via the thermal rearrangement of a substituted benzocyclobutene.[9] This approach provided a route to the regioselective synthesis of key intermediate **A**, which could therefore be obtained from the thermal rearrangement of uniquely substituted benzocyclobutene **B** (R = alkyl or substituted aryl). Our strategy was to construct intermediate **B** via a benzyne-

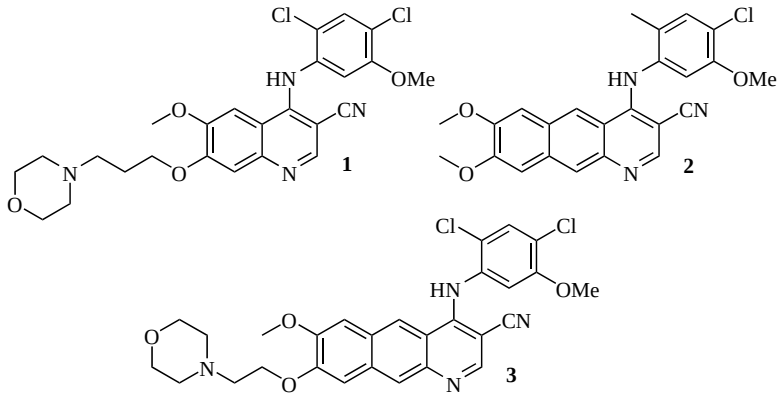

Figure 1

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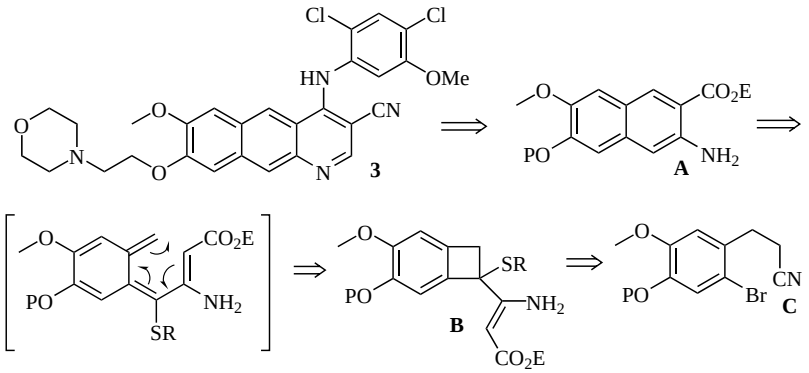
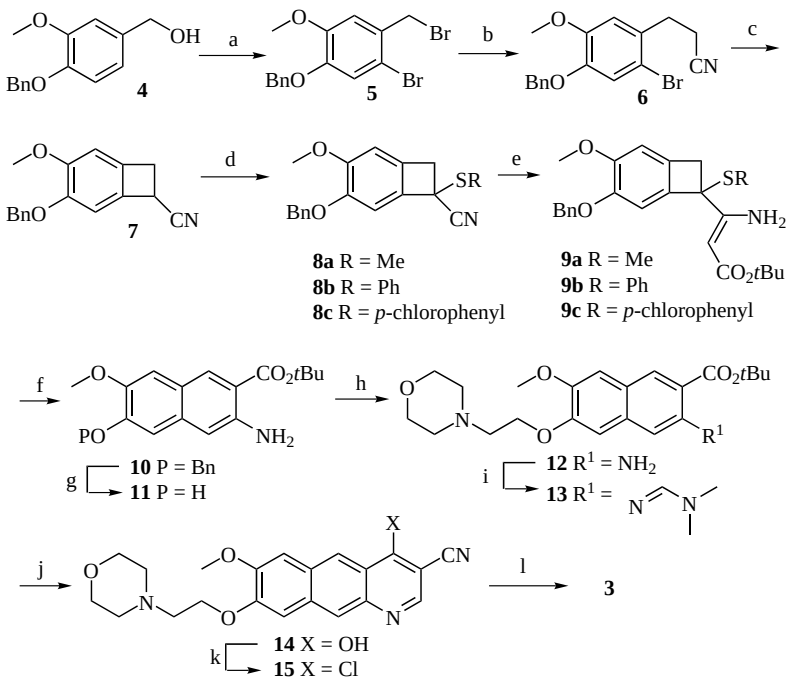


Scheme 1

mediated annulation of **C**,[10] followed by installation of the appropriate SR leaving group, and addition of an alkyl acetate anion to the nitrile group. We describe herein our optimized reaction sequence to provide target compound **3**.

Of key importance to the success of this synthesis was the choice of protecting group for the C-4 oxygen substituent of intermediate **C**. This protecting group would have to be compatible with the strongly basic conditions of the benzyne-mediated cyclization step, but readily removable in the presence of the functional groups on intermediate **A**. Since the benzyloxy substituted benzocyclobutene **7** had previously been prepared via benzyne-mediated cyclization, the benzyl group was the logical choice.[11] In this work,[11] **7** (Scheme 2) was prepared by a five-step sequence from 5-bromovanillin. As part of our effort to maximize the efficiency of this synthesis, a three-step reaction sequence was devised to provide compound **7**. Thus, 4-benzyloxy-3-methoxybenzyl alcohol **4** was brominated in acetic acid to provide **5** in 86% yield.[12] The substituted benzyl bromide **5** was converted to nitrile **6** by reaction with the lithium salt of acetonitrile (45%).[13] Compound **6** was converted to benzocyclobutene **7** in 65% yield by treatment with $NaNH_2$ in liquid NH_3.[10]

Benzocyclobutene **7** was readily converted to **8a** in 76% yield by treatment with $NaN(TMS)_2$ at –78 °C, followed by the rapid addition of dimethyl disulfide. The addition of the magnesium bromide anion of *tert*-butyl acetate to **8a** at 0 °C provided **9a** in 87% yield.[9] The cyclization re-



Scheme 2 Reagents and conditions: (a) Br_2, HOAc, 10 °C to r.t, 2 h (87%); (b) BuLi, MeCN, THF, –78 °C, 1 h (45%); (c) $NaNH_2$ (4 equiv), NH_3, –33 °C, 45 min (65%); (d) (1) $Na(TMS)_2$, THF, –78 °C, 5 min; (2) RSSR, –78 °C to r.t., 1 h (R = Me,76%; R = Ph, 92%; R = *p*-chlorophenyl, 86%); (e) EtMgBr, HN*i*-Pr_2, $MeCO_2t$-Bu, THF, 0 °C, 1 h (R = Me, 87%; R = Ph, 87%; R = *p*-chlorophenyl, 85%); (f) 1,2-dichlorobenzene, reflux, 1 h (67%); (g) H_2 (40 psi), Pd/C, THF, 24 h (95%); (h) DEAD, diphenyl-2-pyridylphosphine, 2-morpholinoethanol, THF, 1.5 h (70%); (i) DMF-dimethylacetal, reflux, 1.5 h (used directly in step j); (j) BuLi, MeCN, THF, –78 °C, 1 h (59% from steps i and j); (k) $POCl_3$, reflux, 1 h (used directly in step l); (l) 2,4-dichloro-5-methoxyaniline, ethoxyethanol, $Pd_2(dba)_3$, K_3PO_4, ligand, DME, reflux, 4 h (56% from steps k and l).

action of **9a** was carried out in refluxing 1,2-dichlorobenzene which was carefully de-gassed with N_2 prior to heating.[9] However, a modest yield (32%) of **10** was obtained, along with 22% of C-4 methylsulfide substituted product (derived from air oxidation of the initial cyclized intermediate[9]). Since elimination of the methylsulfide substituent was incomplete, we set out to install a more labile leaving group, such as thiophenyl, or a thiophenyl group with electron-withdrawing substituents. Compounds **8b** and **9b** were prepared by the same methods described for the preparation of **8a** and **9a**. The cyclization of **9b** gave improved results as compared to **9a**, providing **10** in 52–69% yields. The major naphthalene by-product identified in these reactions possessed a C-2 carboxylic acid (7–9%), presumably due to the thermal cleavage of the *tert*-butyl ester group of **10**. Additionally, C-4 thiophenyl substituted product (ca. 5%) was isolated. A cleaner reaction was achieved with **9c**, possessing the more labile *p*-chlorophenyl sulfide leaving group. Purification of the crude product was readily achieved by trituration with diethyl ether to provide **10** in good yield (typically 67–73%). Since the best yields were obtained under very dilute conditions (≤0.6 g/100 mL), it was necessary to modify the reaction conditions for large-scale reactions. This was achieved by adding **9c** slowly to a heated solution of 1,2-dichlorobenzene to maintain a higher dilution of the starting material throughout the reaction period. In this way, multigram quantities of the 2,3,6,7-tetrasubstituted naphthalene **10** were readily prepared.

Debenzylation of **10** cleanly provided **11** (95%) when hydrogenated at 40 psi in a Parr shaker in the presence of Pd/C. The coupling reaction of **11** with 4-(2-hydroxyethyl)morpholine was carried out under Mitsunobu reaction conditions[14] to provide **12** in 70% yield. Compound **12** was converted to the amidine **13** in refluxing DMF dimethyl acetal. Subsequent treatment of compound **13** with the lithium anion of MeCN afforded the cyclized intermediate **14** in 59% yield from **12**.[7] The reaction of **14** with refluxing $POCl_3$ generated the 4-chloro intermediate **15**, which was used in the subsequent step without purification. Addition of 2,4-dichloro-5-methoxyaniline[15] to **15** under standard conditions[7] (ethoxyethanol, pyridine·HCl, 120 °C, 90 min) provided modest yields of **3** (40–45% overall from **14**). An improved yield of **3** was obtained using $Pd_2(dba)_3$, 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)-1,1′-biphenyl[16] and K_3PO_4 in refluxing DME (56% overall from **14**).[17]

In summary, target compound **3** was prepared as a single regioisomer via a 12-step reaction sequence from a commercially available starting material. Methodology was elucidated for the regioselective construction of 2,3,6,7-tetrasubstituted naphthalenes bearing four different substituents. With this synthesis, we prepared multigram quantities of **3**, which allowed us to carry out extensive testing of this compound as an Src kinase inhibitor. As was anticipated, this compound proved to be significantly more potent than **l**. A preliminary report of the activity of **3** has been presented.[18] A more detailed discussion of the activity of **3**, and a number of analogs, will be described elsewhere.[19]

Mps are uncorrected. These were determined in open capillary tubes using a Meltemp mpt apparatus. ^{1}H NMR spectra were recorded on a NT-300 WB NMR spectrometer. ^{13}C NMR were recorded on a Bruker DRX 400 MHz spectrometer. Chemical shifts (δ) are in parts per million referenced to Me_4Si. Electrospray (ES) mass spectra were recorded in positive mode on a Micromass Platform spectrometer. Chemical ionization (CI) mass spectra were determined by atmospheric pressure chemical ionization (APCI) using H_2O–MeCN–HCO_2H (1:1:0.0025) as a carrier solvent system on the same spectrometer. Flash chromatography was performed using Baker 40 μM silica gel. Unless otherwise mentioned, reactions were carried out under nitrogen.

5-(Benzyloxy)-1-bromo-2-(bromomethyl)-4-methoxybenzene (5)

4-Benzyloxy-3-methoxybenzyl alcohol (**4**) (4.8 g, 19.65 mmol) was dissolved in HOAc (30 mL) and cooled to 10 °C in a H_2O–ice bath. A solution of Br_2 (1.25 mL, 24.39 mmol) in HOAc (10 mL) was added dropwise to the reaction mixture while stirring. The reaction was allowed to warm to r.t. and was stirred for 2 h. The reaction was diluted with H_2O and the resulting precipitate collected by filtration. The precipitate was washed with H_2O and purified by flash chromatography (silica gel; hexanes–EtOAc, 93:7) to provide **5**.

Yield: 6.61 g (87%); white solid; mp 103–105 °C (Lit 110 °C).

The analytical data were consistent with the data given in the literature.[20]

3-(4-Benzyloxy-2-bromo-5-methoxyphenyl)propionitrile (6)

To a solution of BuLi (20.3 mL of a 1.6 M solution in hexane, 32.38 mmol) in anhyd THF (20 mL) was added a solution of MeCN (1.8 mL, 32.38 mmol) in THF (15 mL). The reaction mixture was stirred at –78 °C for 1 h. A solution of **5** (0.7 g, 1.8 mmol) in anhyd THF (30 mL) was added in one portion and stirring was continued for 1 h at –78 °C. The reaction was quenched by the addition of H_2O (25 mL), and the mixture was allowed to warm to r.t. To this was added EtOAc (50 mL). An insoluble by-product was removed by filtration. Following separation of the layers, the organic layer was dried ($MgSO_4$). After reducing in vacuo, the crude product was purified by flash chromatography (silica gel; hexanes–EtOAc, 95:5 to 87:13) to provide **6**.

Yield: 2.0 g (45%); white solid; mp 52–53 °C.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.39 (m, 5 H), 7.33 (s,1 H), 7.08 (s, 1 H), 5.09 (s, 2 H), 3.77 (s, 3 H), 2.92 (t, *J* = 5.5 Hz, 2 H), 2.78 (t, *J* = 5.1 Hz, 2 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 148.52, 147.34, 136.56, 129.88, 128.33, 127.86, 127.76, 119.67, 116.95, 114.09, 113.02, 70.06, 55.72, 30.35, 17.03.

MS (CI): *m*/*z* = 346.2, 348.2 (M + 1).

Anal. Calcd for $C_{17}H_{16}BrNO_2$: C, 58.98; H, 4.66; N, 4.05. Found: C, 58.77; H, 4.71; N, 3.89.

4-Benzyloxy-3-methoxybicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile (7)

A suspension of $NaNH_2$ was prepared from liquid NH_3 (100 mL), Na (0.52 g, 22.8 mmol) and a catalytic amount of ferric nitrate. To this was added **6** (2 g, 5.7 mmol) in portions and the reaction was stirred at –33 °C for 45 min. The reaction was then cooled down to –78 °C and quenched with aq NH_4Cl. The liquid NH_3 was allowed to evaporate and the resulting solid residue was washed with H_2O. Purification by flash chromatography (silica gel; hexanes–EtOAc, 4:1) provided **7**.

Yield: 1.0 g (65%); white solid; mp 85–87 °C (Lit: 90–92 °C).

The analytical data were consistent with the data given in the literature.[11]

4-Benzyloxy-7-(4-chlorophenylsulfanyl)-3-methoxybicyclo-[4.2.0]octa-1,3,5-triene-7-carbonitrile (8c)

To a solution of **7** (1.0 g, 3.70 mmol) in anhyd THF (10 mL) at –78 °C was added sodium $NaN(TMS)_2$ (5.65 mL of a 1 M solution in THF, 5.60 mmol) over a period of 4 min, followed by the addition of 4,4′-dichlorodiphenyl disulfide in one portion. The mixture was stirred at –78 °C for 15 min and then at r.t. for 1 h. The reaction was quenched with H_2O (20 mL), and EtOAc (20 mL) was subsequently added. Following separation of the layers, the aq layer was extracted twice more with EtOAc. The organic layers were combined and dried (Na_2SO_4). After reducing in vacuo, the crude material was purified by flash chromatography (silica gel; hexanes–EtOAc, 4:1) to give **8c**.

Yield: 1.3 g (86%); off-white solid; mp 114–115 °C.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.62–7.54 (m, 4 H), 7.41 (m, 4 H), 7.36 (m, 1 H), 6.97 (s,1 H), 6.83 (s, 1 H), 5.08 (dd, *J* = 9.1, 10.5 Hz, 2 H), 3.98 (d, *J* = 10.5 Hz, 1 H), 3.78 (s, 3 H), 3.60 (d, *J* = 10.5 Hz, 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 152.80, 149.20, 136.69, 135.87, 134.92, 132.48, 131.05, 129.55, 129.39, 128.32, 127.81, 127.65, 118.91, 108.30, 107.14, 70.15, 55.94, 45.48, 43.71.

MS (CI) : *m*/*z* = 408.1, 410.2 (M + 1).

Anal. Calcd for $C_{23}H_{18}ClNO_2S$: C, 67.72; H, 4.45; N, 3.43. Found: C, 67.99; H, 4.63; N, 3.33.

3-Amino-3-[4-benzyloxy-7-(4-chlorophenylsulfanyl)-3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]acrylic Acid *tert*-Butyl Ester (9c)

To a stirred solution of EtMgBr (3.26 mL of a 3 M solution in Et_2O, 9.8 mmol) in anhyd THF (10 mL) at 0 °C under N_2 was added diisopropylamine (2.75 mL, 19.6 mmol). The mixture was stirred at 0 °C for 1 h. *tert*-Butyl acetate (0.5 mL, 3.6 mmol) and a solution of **8c** (1.0 g, 2.45 mmol) in anhyd THF (10 mL) were added successively, and the resulting mixture was stirred for 1 h. The reaction was quenched with aq NH_4Cl and the product mixture was extracted with EtOAc. The EtOAc extract was washed with brine, dried (Na_2SO_4) and passed through a plug of silica gel (EtOAc) to give **9c**.

Yield: 1.194 g (85%); white solid; mp 112–115 °C.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.60–7.29 (m, 9 H), 6.81 (s, 1 H), 6.72 (s, 1 H), 5.08 (dd, *J* = 9.1, 11.8 Hz, 2 H), 4.15 (s, 1 H), 3.73 (s, 3 H), 3.48 (d, *J* = 10.7 Hz, 1 H), 3.30 (d, *J* = 10.6 Hz, 1 H), 1.36 (s, 9 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 168.84, 161.41, 151.58, 148.16, 136.95, 136.21, 136.07, 133.82, 132.55, 130.88, 128.64, 128.25, 127.69, 127.62, 108.89, 108.10, 84.56, 77.54, 70.21, 60.07, 55.84, 44.87, 28.11.

MS (ES): *m*/*z* = 523.9, 525.9 (M + 1).

Anal. Calcd for $C_{29}H_{30}ClNO_4S$: C, 66.46; H, 5.77; N, 2.67. Found: C, 66.31; H, 5.91; N, 2.61.

3-Amino-6-benzyloxy-7-methoxynaphthalene-2-carboxylic Acid *tert*-Butyl Ester (10)

N_2 was bubbled through a solution of 1,2-dichlorobenzene (150 mL) for 1 h and the reaction was heated to 179 °C. A solution of **9c** (3.0 g, 5.72 mmol) was added dropwise over a period of 30 min. After heating for a further 1 h, the reaction was cooled and reduced in vacuo. The residue was triturated with Et_2O, collected by filtration and washed with Et_2O to give **10**.

Yield: 1.46 g (67%); yellow solid; mp 179–180 °C.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.18 (s, 1 H), 7.4 (m, 5 H), 7.18 (s, 1 H), 7.01 (s, 1 H), 6.85 (s, 1 H), 6.21 (s, 2 H), 5.17 (s, 2 H), 3.74 (s, 3 H), 1.58 (s, 9 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 166.93, 150.74, 146.71, 145.95, 136.64, 133.51, 130.50, 128.35, 127.92, 127.86, 120.10, 112.66, 108.29, 107.43, 104.57, 80.32, 69.53, 55.28, 27.89.

MS (ES): *m*/*z* = 379.9 (M + 1).

Anal. Calcd for $C_{23}H_{25}NO_4 \cdot 0.7\ H_2O$: C, 70.50; H, 6.08; N, 3.57. Found: C, 70.45; H, 6.24; N, 3.40.

3-Amino-6-hydroxy-7-methoxynaphthalene-2-carboxylic Acid *tert*-Butyl Ester (11)

A solution of **10** (4.7 g, 12.39 mmol) was dissolved in DMF (40 mL). To this was added MeOH (100 mL) and 10% Pd/C (2.0 g). The reaction mixture was hydrogenated on a Parr shaker at 40 psi for 20 h. The catalyst was removed by filtration through a pad of Celite, and the filltrate was concentrated in vacuo. To complete the reaction, the resulting residue was again hydrogenated as described above for 4 h. After removal of the catalyst through Celite, the solvent was evaporated. The resulting residue was dissolved in CH_2Cl_2 and passed through a plug of magnesol, eluting with CH_2Cl_2 and EtOAc. The filtrate was reduced in vacuo to provide **11**.

Yield: 3.40 g (95%); yellow solid; mp 262–263 °C.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 9.61 (br s, 1 H), 8.15 (s, 1 H), 7.13 (s, 1 H), 6.74 (d, *J* = 2.7 Hz, 2 H), 6.12 (s, 2 H), 3.82 (s, 3 H), 1.58 (s, 9 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 166.99, 149.87, 146.42, 145.71, 133.97, 130.65, 119.94, 112.11, 10.47, 107.27, 106.17, 80.17, 55.25, 27.90.

MS (ES): *m*/*z* = 289.9 (M + 1).

Anal. Calcd for $C_{16}H_{19}NO_4 \cdot 0.1$ EtOAc: C, 66.06; H, 6.69; N, 4.70. Found: C, 66.30; H, 6.96; N, 4.30.

3-Amino-7-methoxy-6-(2-morpholin-4-ylethoxy)naphthalene-2-carboxylic Acid *tert*-Butyl Ester (12)

To a solution of **11** (0.72 g, 2.49 mmol) in THF (7.5 mL) was added 4-(2-hydroxyethyl)morpholine (0.46 mL, 3.74 mmol), followed by the addition of diphenyl-2-pyridylphosphine (1.34 g, 4.98 mmol) and DEAD (0.6 mL, 3.87 mmol). The resulting mixture was stirred at r. t. for 1.5 h, quenched with H_2O, diluted with EtOAc and the two layers were separated. The organic layer was extracted with aq HCl (0.2 N). After neutralizing the aqueous layer with sat. aq $NaHCO_3$, it was extracted with EtOAc. The EtOAc extract was dried (Na_2SO_4), filtered and evaporated to yield a brown oil. The oil was purified by flash chromatography (silica gel; EtOAc–hexane, 85:15 to 100:0) to give **12**.

Yield: 0.70 g (70%); orange solid; mp 125–127 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.24 (s, 1 H), 7.00 (s, 1 H), 6.81 (d, *J* = 2.34 Hz, 2 H), 5.47 (br s, 2 H), 4.26 (t, *J* = 4.5 Hz, 2 H), 3.92 (s, 3 H), 3.75 (t, *J* = 3.5 Hz, 4 H), 2.93 (t, *J* = 4.5 Hz, 2 H), 2.65 (br s, 4 H), 1.63 (s, 9 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 166.94, 150.92, 146.62, 145.91, 133.62, 130.46, 120.05, 112.57, 108.29, 107.37, 104.15, 80.29, 66.09, 65.79, 56.77, 55.29, 53.60, 27.88.

MS (ES): *m*/*z* = 403.3 (M + 1).

Anal. Calcd for $C_{22}H_{30}N_2O_5$: C, 65.65; H, 7.51; N, 6.96. Found: C, 65.65; H, 7.30; N, 6.98.

4-Hydroxy-7-methoxy-8-(2-morpholin-4-ylethoxy)benzo[*g*]-quinoline-3-carbonitrile (14)

A mixture of **12** (0.69 g, 1.70 mmol) and DMF dimethyl acetal (2.4 mL) in toluene (7.0 mL) was heated under reflux for 1.5 h. The sol-

vent was evaporated and the residue was dried under high vacuum to yield **13** as a light purple foam. This material was used immediately in the next step.

To THF (15 mL) at –78 °C was added BuLi (2.6 mL of a 1.6 M solution in hexane, 1.63 mmol) and the mixture was stirred for 5 min. To this was added MeCN (0.36 mL, 6.8 mmol) dropwise, followed by stirring for 1 h. Then a solution of **13** in THF (5 mL) was added dropwise over a period of 15 min. The mixture was stirred at –78 °C for 1 h, then at r.t. for 1 h. After cooling again to –78 °C, the reaction was quenched with $MeCO_2H$ (0.5 mL), then warmed to r.t. and stirred for 1 h. The resulting solid was collected by filtration, washed with EtOAc and dried in vacuo. Purification was carried out by flash chromatography (silica gel; CH_2Cl_2–MeOH, 95:5 to 89:11) to give **14**.

Yield: 0.38 g (59%); yellow solid; mp 275 °C (decomp).

^{1}H NMR (DMSO-d_6–TFA-d_1, 300 MHz): δ = 8.74 (s, 1 H), 8.69 (s, 1 H), 8.00 (s, 1 H), 7.65 (s, 1 H), 7.59 (s, 1 H), 4.59 (t, *J* = 3.3 Hz, 2 H), 4.1 (d, *J* = 9.2 Hz, 2 H), 3.97 (s, 3 H), 3.75 (m, 4 H), 3.66 (d, *J* = 9.3 Hz, 2 H), 3.34 (t, *J* = 7.0 Hz, 2 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 175.11, 151.12, 149. 89, 146.87, 134.69, 131.98, 126.64, 123.37, 122.30, 117.33, 114.01, 106.88, 105.74, 90.30, 66.14, 66.10, 56.66, 55.58, 53.58.

MS (ES): *m*/*z* = 380.2 (M + 1).

Anal. Calcd for $C_{21}H_{21}N_3O_4 \cdot 2.5\ H_2O$: C, 60.71; H, 6.07; N, 10.12. Found: C, 60.93; H, 6.11; N, 9.76.

4-Chloro-7-methoxy-8-(2-morpholin-4-ylethoxy)benzo[*g*]quinoline-3-carbonitrile (15)

A mixture of **14** (2.32 g, 6.11 mmol) in $POCl_3$ (35 mL) was heated under reflux for 1 h, then cooled to r.t. Excess $POCl_3$ was evaporated to yield a residue, to which toluene was added and the resulting solution was reduced in vacuo. Toluene was added and evaporated twice more. The resulting residue was cooled in an ice bath, neutralized with cold aq $NaHCO_3$ and stirred. The solid was collected by filtration, washed with cold H_2O and dried in vacuo to yield 1.99 g of **15** as a yellow solid. This was used without further purification in the next step.

4-(2,4-Dichloro-5-methoxyanilino)-7-methoxy-8-[2-(4-morpholinyl)ethoxy]benzo[*g*]quinoline-3-carbonitrile (3)

To a mixture of $Pd_2(dba)_3$ (354 mg, 0.387 mmol), K_3PO_4 (1.23 g, 5.80 mmol) and 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)-1,1′-biphenyl[16] (471 mg, 1.20 mmol) in DME (20 mL) were added **15** (1.54 g, 3.87 mmol) and 2, 4-dichloro-5-methoxyaniline[15] (0.896 g, 4.64 mmol). The resulting mixture was heated at reflux for 4 h, cooled to r.t. and diluted with sat. aq $NaHCO_3$ (300 mL). The precipitated solids were collected by filtration, washed with H_2O thoroughly and purified by flash chromatography (silica gel; CH_2Cl_2–MeOH, 99:1 to 97:3) to give **3**.

Yield: 1.45 g (56% from **14**); off-white solid; 231–234 °C.

^{1}H NMR (DMSO-d_6 + TFA-d_1, 300 MHz): δ = 9.35 (s, 1 H), 9.24 (s 1 H), 8.42 (s, 1 H), 7.91 (s, 1 H), 7.82 (s 1 H), 7.61 (s, 1 H), 7.48 (s, 1 H), 4.66 (m, 2 H), 4.07 (s, 3 H), 4.04-3.97 (m, 2 H), 3.90 (s, 3 H), 3.83–3.63 (m, 6 H), 3.34 (m, 2 H).

^{13}C NMR (DMSO-d_6 –TFA-d_1, 100 MHz): δ = 158.84, 158.48, 158.11, 157.75, 153.89, 151.01, 150.82, 149.21, 133.83, 132.31, 129.69, 128.32, 122.65, 117.07, 116.68, 114.95, 114.16, 106.67, 106.31, 82.94, 63.53, 63.29, 56.75, 55.92, 54.77, 52.03.

MS (ES) *m*/*z* = 553.3, 555.3 (M + 1).

Anal. Calcd for $C_{28}H_{26}Cl_2N_4O_4 \cdot 2.0\ H_2O$: C, 57.05; H, 5.13; N, 9.50. Found: C, 56.88; H, 4.96; N, 9.10.

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