Synthesis of 5-Aryl- and 5-Heteroaryl-7-carboxyl-8-hydroxyquinaldines through Suzuki Cross-Coupling Reaction with Potassium Organotrifluoroborates

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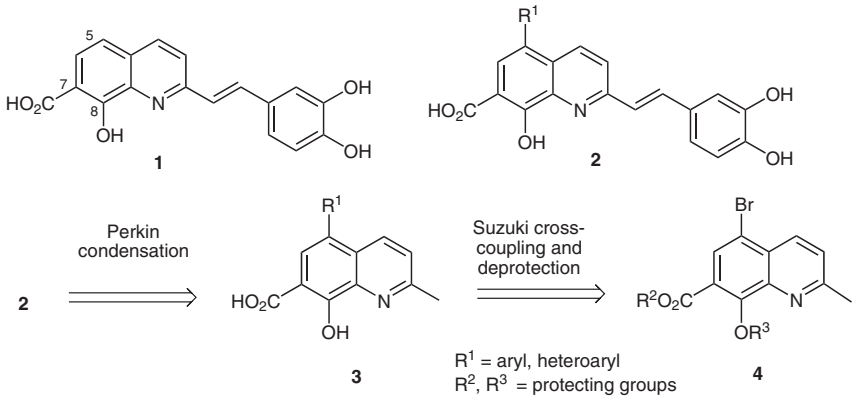
Abstract: A series of 5-aryl- and 5-heteroaryl-7-carboxyl-8-hydroxyquinaldines were prepared from 5-bromo-7-methoxycarbonyl-8-benzyloxyquinaldine based on the Suzuki cross-coupling reaction using potassium organotrifluoroborates. An efficient method of deprotection of the 8-hydroxy group using a microwave-assisted hydrogen transfer reaction is reported.

Key words: quinolines, cross-coupling, boron, palladium, arylations

The 8-hydroxyquinoline framework is a well-known scaffold, which has been decorated with substituents in connection with a variety of applications such as fluorescent sensors,[1] metal chelates,[2] or enzymatic inhibitors.[3] For example, we have reported that polyhydroxylated styrylquinolines (SQLs), exemplified by **1**, are potent HIV-1 integrase inhibitors in in vitro experiments, block the replication of HIV-1 in cell culture, and are devoid of cytotoxicity. Within the framework of SQLs, structure–activity relationship studies have clearly identified the salicylic acid moiety at C-7 and C-8 of the quinoline ring, as critical pharmacophore elements for antiviral activity.[4] In connection with a systematic modulation of the 7-carboxyl-8-hydroxystyrylquinoline scaffold we decided to introduce an additional aromatic or heteroaromatic nucleus at the C-5 position, since previous modulation of this position led to substantial improvement of the biological activity.[5] Owing to the availability of a large array of boronic acid derivatives we chose to explore the Suzuki cross-coupling reaction[6] to access the 5-substituted quinaldines **3**, which could be further elaborated into the corresponding 2-styrylquinoline **2** through Perkin-type condensation with aromatic aldehydes (Scheme 1).[4a] Although several reports emphasized the efficiency of the Suzuki reaction to obtain 5-aryl-8-alkoxyquinolines,[7] none of these substrates displayed a carboxyl or an alkoxycarbonyl group. Suspecting that the need of a strong base in the Suzuki–Miyaura coupling reaction (such as aqueous K_2CO_3) precluded the presence of a hydrolytically unstable ester, we first chose to explore the regioselective Suzuki cross-coupling of 5,7-dibromoquinaldines.

Thus condensation of 5,7-dibromo-8-methoxyquinaldine (**5**) with phenylboronic acid under standard Suzuki reaction conditions afforded the 5-phenylquinaldine **6** in 80% yield along 10% of the 5,7-diphenyl derivative **7**[8] (Scheme 2). Although quite useful, this approach was abandoned since we were unable to achieve efficiently the introduction of the required carboxyl group at C-7 by lithium–bromine exchange reaction. We therefore studied the Suzuki cross-coupling reaction with the fully protected bromo ester **11**. The latter was obtained from hydroxy acid **8**[9] in 82% overall yield by selective methylation of the carboxyl group using MeI/$KHCO_3$,[10] C-5 bromination with NBS in DMF at 0 °C, and benzylation of the phenolic



Scheme 1 Retrosynthetic analysis of styrylquinolines **2**

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hydroxy group. Our initial attempts to couple **10** or **11** with phenylboronic acid using conventional Suzuki reaction conditions met with failure probably due to concomitant hydrolysis of the ester group inducing deactivation of the palladium catalyst and/or decarboxylation.[11] This disappointing results could not be improved despite many attempts to vary the protecting groups and the reaction conditions. After considerable experiments, we found that the desired aryl–aryl cross coupling could be achieved through the trifluoroborate modification of the Suzuki reaction. The use of aryl trifluoroborates in Suzuki-type reactions was first reported by Genet's group using aryldiazonium salts.[12] Subsequently, the reaction of aryl trifluoroborates with aryl halides as coupling partners was developed by Molander et al.[13] Organotrifluoroborates proved to be more reactive than the corresponding boronic acids, but most importantly their coupling can be carried out in the presence of a tertiary amine as base in a non-aqueous solvent. Thus, condensation of **11** with potassium phenyltrifluoroborate using palladium acetate and triphenylphosphine as catalyst and *N*,*N*-diisopropylethylamine as base in refluxing methanol afforded **13a** with 59% isolated yield (Scheme 3). To find out the optimum reaction conditions for an efficient coupling, the reaction was studied by varying several parameters as summarized in Table 1. The nature of the palladium catalyst was first surveyed. Although $Pd(OAc)_2/Ph_3P$, $Pd(PPh_3)_4$, $Pd_2(dba)_3/Ph_3P$, and $PdCl_2(MeCN)_2$ used under ligandless conditions, gave the desired product, the reaction did not go to completion even after an extended period of time. Nanoparticular palladium systems made from a palladium(II) salt and tetrabutylammonium bromide[14] were ineffective (entry 7). Optimal conditions were found to involve the use of $Pd(dppf)Cl_2$, although $Pd(PPh_3)_2Cl_2$ was almost equally effective. Interestingly, other bidendate phosphines such as dppe and dppp were totally unproductive. The reaction was carried out in the presence of 7 mol% of catalyst in combination with Hünig's base in methanol. Attempts to reduce the amount of palladium catalyst gave remaining starting material despite increasing reaction time. The influence of the base was also briefly examined. Although some product was obtained in the absence of base (entry 11) the yield was dramatically reduced.

Furthermore, a mineral base such as Cs_2CO_3 (entry 10) appeared to be less effective than tertiary amines. As depicted in Table 2, a large array of aryl and heteroaryl trifluoroborates reacted with **11** to give the expected coupling products in moderate to good yields when these simple conditions were applied. Electron-rich and electron-poor aryl trifluoroborates are equally efficient. In few cases (entries 2, 12, and 16) a small amount of dehalogenation products (**13**, R^1 = H) was formed together with the desired cross-coupling product. As previously reported, no clear structural factors favoring the reduction process could be defined.[15] A low yield of the coupling product **13q** was obtained using the electron-deficient 3-pyridyl derivative **12q**. Attempts to improve the yield led to no success although previous reports indicated that good yields of cross-coupling products were obtained using this derivative.[13a] As expected, the phenethyl trifluoroborate **12t** gave mainly the reduced product **13** (R^1 = H) presumably through a β-elimination process.

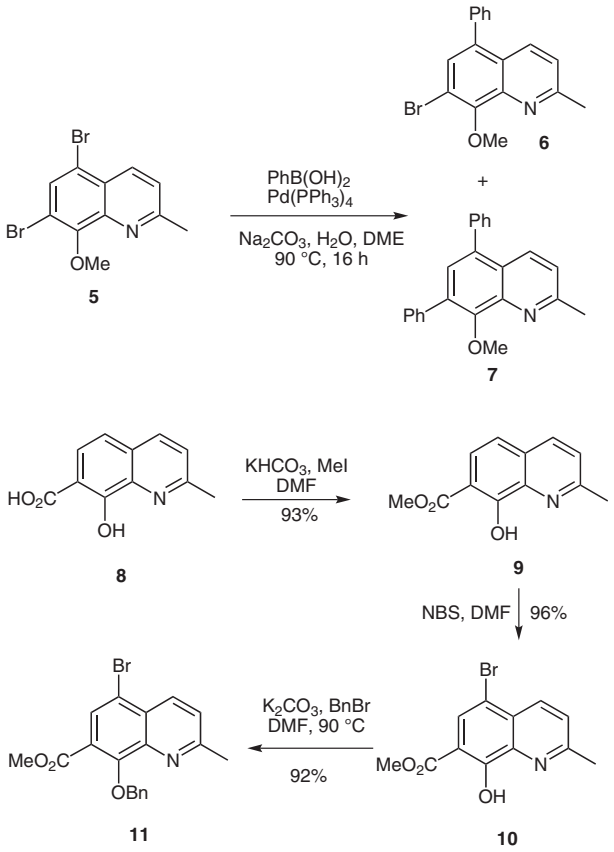
Several methods were investigated to deprotect the quinoline derivatives **13**. Treatment of **13a** with BBr_3 or TMSCl/NaI provided a mixture of partially deprotected products. On the other hand, treatment with 48% aqueous HBr in refluxing AcOH cleanly converted **13a** to **3a**

Table 1 Transformation of **11** to **13a**

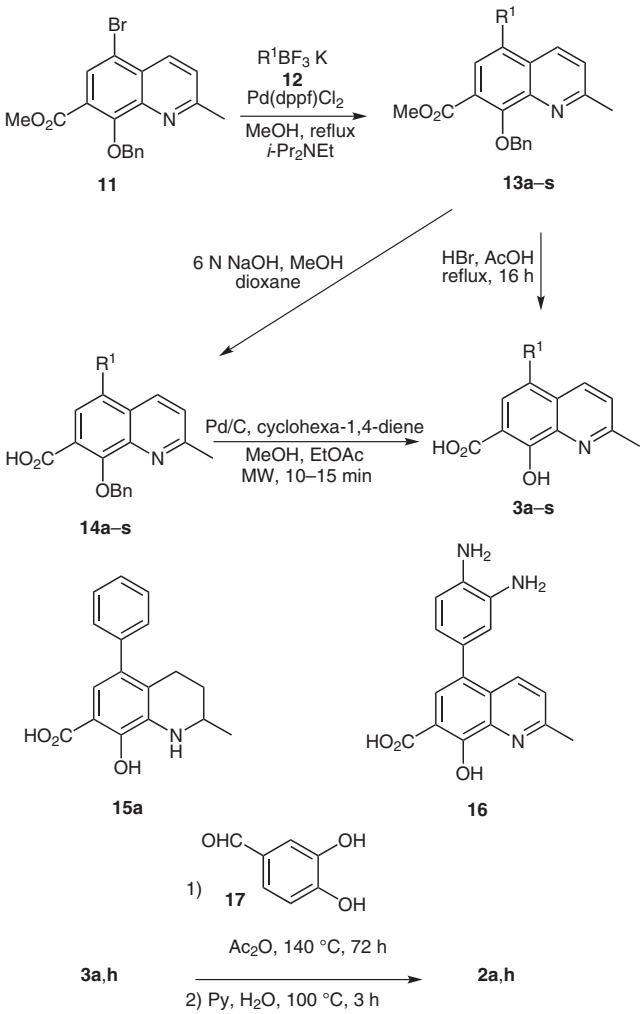
Entry	Palladium (mol%)	Ligand/additive	Base	Yield of **13a** (%)[a,b]	SM (%)	Reduction product **13**: R^1 = H
1	$Pd(OAc)_2$ (12)	Ph_3P	*i*-Pr_2NEt	59	41	–
2	$Pd(PPh_3)_4$ (7)	–	*i*-Pr_2NEt	75	19	–
3	$Pd_2(dba)_3$ (5)	Ph_3P	*i*-Pr_2NEt	40[c]	–	–
4	$Pd(OAc)_2$ (10)	dppe	*i*-Pr_2NEt	0	100	–
	$Pd(OAc)_2$ (10)	dppp	*i*-Pr_2NEt	0	100	–
6	$PdCl_2(MeCN)_2$(7)	–	*i*-Pr_2NEt	50	34	15
7	$PdCl_2$ (6)	Bu_4NBr	*i*-Pr_2NEt	38	50	3
8	$Pd(PPh_3)_2Cl_2$ (7)	–	*i*-Pr_2NEt	85	9	–
9	$Pd(dppf)Cl_2$ (7)	–	*i*-Pr_2NEt	86	–	1
10	$Pd(dppf)Cl_2$ (7)	–	Cs_2CO_3	26	40	–
11	$Pd(dppf)Cl_2$ (7)	–	none	36	59	–

[a] Conditions: **11** (1 equiv), potassium phenyltrifluoroborate (1.35 equiv), base (3 equiv), MeOH, reflux 16 h.
[b] Isolated yields.
[c] Yield established by NMR spectroscopy.

(Scheme 3). Satisfactory yields were obtained in these conditions (Method A) for compounds **13a**,**b**,**c**,**h**,**m**,**r**,**s** (Table 2). In search of milder conditions best suited for sensitive substrates we explored the hydrogenolysis of the acid **14a**.



Scheme 2 Regioselective Suzuki cross-coupling reaction of **5** and synthesis of the 5-bromoquinaldine **11**



Scheme 3 Suzuki cross-coupling reaction of quinoline **11**, deprotection of the adducts **13a**–**s** and synthesis of representative styrylquinolines **2a**,**h**

Table 2 Synthesis of 5-Substituted Quinaldines **13a**–**s** and Deprotection to **3a**–**s**

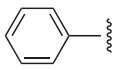
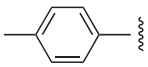
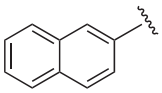
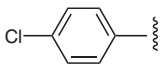
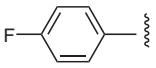
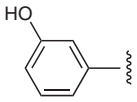
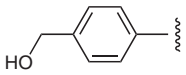
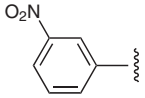
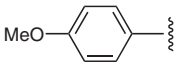
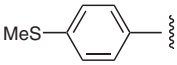
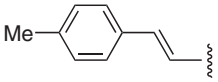
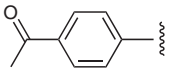
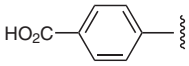
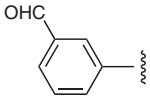
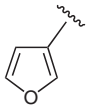
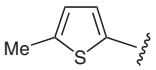
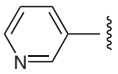
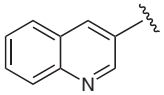
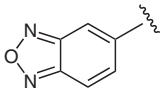
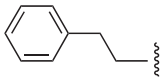
Entry	R^1	Product	Yield (%)	Reduction product **13**: R^1 = H	Deprotection Method A[a] Yield (%)	Method B[b] Yield (%)
1		**13a**	86	3	77	82
2		**13b**	75	7	92	–
3		**13c**	75	–	59	40
4		**13d**	72	–	–	84
5		**13e**	85	–	–	64
6		**13f**	65	–	–	80

Table 2 Synthesis of 5-Substituted Quinaldines **13a–s** and Deprotection to **3a–s** (continued)

Entry	R^1	Product	Yield (%)	Reduction product **13**: R^1 = H	Deprotection Method A[a] Yield (%)	Method B[b] Yield (%)
7		**13g**	95	–	–	85
8		**13h**	78	–	95	80[c]
9		**13i**	85	–	–	93
10		**13j**	84	–	–	61
11		**13k**	87	–	0	–
12		**13l**	87	13		74
13		**13m**	95	–	90	–
14		**13n**	61	–	36	–
15		**13o**	59	–	–	65
16		**13p**	69	9	–	57
17		**13q**	<10	–	–	–
18		**13r**	87	–	76	–
19		**13s**	quant	–	85	76[d]
20		**13t**	<10	45	–	–

[a] Method A: 48% HBr, AcOH, reflux, 16 h.
[b] Method B: *i*. aq 6 N NaOH, MeOH–dioxane, reflux, 16 h; *ii*. Pd/C, cyclohexa-1,4-diene, microwave irradiation, 100 °C, 10 min.
[c] The 3-aminophenyl derivative was obtained.
[d] Compound **16** was obtained.

Unexpectedly, catalytic hydrogenolysis of **14a** using Pd/C or $Pd(OH)_2$ gave rise to the 1,2,3,4- tetrahydroquinoline **15a**. On the other hand catalytic transfer hydrogenation using cyclohexane-1,4-diene and Pd/C catalyst in isopropyl alchohol at reflux[16] was more successful delivering the expected quinoline **3a** in 75% overall yield. The process can be further improved using microwave irradiation.[17] Under standard conditions (MW, 100 °C, 50 equiv cyclohexa-1,4-diene, MeOH–EtOAc) most reactions occurred smoothly in few minutes, with the exception of the sulfur containing quinolines **13j** and **13p** whose reduction required a longer reaction time. When, quinolines **13** were subjected to this simple two-step protocol (Method B), moderate to good yields of the corresponding fully deprotected quinolines **3** were obtained. As expected, concomitant reduction of the nitro group to the corresponding

amino group was observed with quinoline **13h**. Likewise, the major product formed upon reduction of the benzofurazan **14s** was found to be the *o*-phenylenediamine **16** whose synthesis is highly straightforward by using the present method.

Finally, the formation of styrylquinoline derivatives **2** from the 5-arylquinaldines **3** was briefly investigated. In the event, heating **3a** with an excess of 3,4-dihydroxybenzaldehyde (**17**) in acetic anhydride for 3 days followed by hydrolysis with aqueous pyridine afforded the expected styrylquinoline **2a** in 41% yield. Similarly, styrylquinoline **2h** was obtained in 43% yield from the 5-(3-nitrophenyl)quinaldine **3h** (Scheme 3). These results indicated that the 5-aryl substituent did not interfere with the Perkin-type condensation process. The syntheses of the other styryquinolines and their biological evaluation are currently under studies and will be reported in due course.

In conclusion the neutral conditions associated with the trifluoroborate modified Suzuki–Myaura cross-coupling reaction provided a convenient and efficient access to a large variety of 5-aryl- and 5-heteroaryl-7-carboxyl-8-hydroxyquinaldines. We anticipate that such conditions will find application with other hydrolytically sensible materials. This method may be useful for obtaining otherwise difficultly accessible highly decorated quinolines that may afford products of interest for physicochemical and pharmaceutical applications.

Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra were recorded on a Fourier Transform Bruker Vector 22 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer. When diffuse, easily exchangeable protons were not listed. Recognition of methyl, methylene, methine, and quaternary carbon nuclei in ^{13}C NMR spectra rests on the *J*-modulated spin-echo sequence. Mass spectra were recorded on a Bruker Esquire-LC spectrometer. Elemental analyses were performed by the Service de microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France, with a Perkin-Elmer 2400 analyzer. Analytical TLC was performed on Merck silica gel 60 F254 glass precoated plates (0.25 mm layer). Column chromatography was performed on Merck silica gel 60 (230–400 mesh ASTM). MeOH was dried over Mg and distilled. DMF and CH_2Cl_2 were distilled from CaH_2. All reactions involving air- or water-sensitive compounds were routinely conducted in glassware, which was flame-dried under a positive pressure of N_2. Microwave activation was carried out using a CEM Corp Discover LabMate microwave synthesis system. Chemicals obtained from commercial suppliers were used without further purification. $Pd(dppf)Cl_2$ was prepared from $PdCl_2$ and dppf according to literature procedure.[18] Most potassium organotrifluoroborates were purchased from Aldrich or Alpha Aesar (France). Compounds **12o**,**q**,**r** were prepared from the commercially available corresponding boronic acids.[19]

8-Hydroxy-2-methylquinoline-7-carboxylic Acid Methyl Ester (9)

To a stirred solution of 8-hydroxy-2-methylquinoline-7-carboxylic acid[9] (20 g, 98.4 mmol) in anhyd DMF (150 mL) were added $KHCO_3$ (11.8 g, 118.1 mmol) and MeI (20.9 g, 147.6 mmol). The reaction mixture was stirred at 40 °C for 4 h. After concentration in vacuo, the solid residue was taken into H_2O (40 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 19.9 g (93%) of **9**; off-white solid; mp 102–104 °C.

IR (neat): 3200–3000, 2965, 1664, 1622, 1606, 1557, 1435, 1421, 1360, 1334, 1318, 1263, 1238, 1211, 1194, 1153, 1142, 1088, 1037, 981, 849, 820, 763, 722 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.72 (br s, 1 H, OH), 8.24 (d, *J* = 8.5 Hz, 1 H, H-4), 7.61 (d, *J* = 8.7 Hz, 1 H, H-6), 7.56 (d, *J* = 8.5 Hz, 1 H, H-3), 7.38 (d, *J* = 8.7 Hz, 1 H, H-5), 3.92 (s, 3 H, CO_2CH_3), 2.69 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7 (C), 159.1 (C), 158.6 (C), 139.0 (C), 135.7 (CH), 130.4 (C), 124.7 (CH), 124.3 (CH), 117.3 (CH), 109.1 (C), 52.3 (CH_3), 25.3 (CH_3).

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.50; H, 4.97; N, 6.45.

5-Bromo-8-hydroxy-2-methylquinoline-7-carboxylic Acid Methyl Ester (10)

To an ice-cooled solution of quinaldine **9** (10.0 g, 46.3 mmol) in anhyd DMF (150 mL) was added NBS (9.83 g, 55.2 mmol) by portion. The reaction mixture was stirred for 1 h at 0 °C and then 5 h at 40 °C. After concentration in vacuo, the crude product was purified by flash chromatography on silica gel eluting with cyclohexane–EtOAc (85:15) to afford bromoquinoline **10** (13.1 g, 96%); colorless solid; mp 107–108 °C.

IR (neat): 3200–3000, 2958, 1672, 1619, 1603, 1440, 1422, 1404, 1363, 1333, 1310, 1229, 1215, 1204, 1152, 1094, 1042, 985, 921, 893, 836, 777, 746, 728, 670 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.72 (br s, 1 H, OH), 8.32 (d, *J* = 8.7 Hz, 1 H, H-4), 8.08 (s, 1 H, H-6), 7.49 (d, *J* = 8.7 Hz, 1 H, H-3), 4.02 (s, 3 H, CO_2CH_3), 2.83 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6 (C), 159.5 (C), 158.7 (C), 139.8 (C), 135.6 (CH), 129.5 (C), 127.6 (CH), 125.8 (CH), 110.0 (C), 109.9 (C), 52.7 (CH_3), 25.2 (CH_3).

MS (+APCI): *m*/*z* (%) = 298 (100), 296 (100, $[M + H]^+$).

Anal. Calcd for $C_{12}H_{10}BrNO_3$: C, 48.67; H, 3.40; N, 4.73. Found: C, 48.82; H, 3.20; N 4.74.

8-Benzyloxy-5-bromo-2-methylquinoline-7-carboxylic Acid Methyl Ester (11)

To a mixture of bromoquinoline **10** (13.0 g, 43.9 mmol) and K_2CO_3 (15.2 g, 109.7 mmol) in anhyd DMF (120 mL) was added BnBr (18.8 g, 109.7 mmol). The reaction mixture was heated for 18 h at 90 °C. After concentration in vacuo, the residue was taken into H_2O (40 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed by brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by chromatography on silica gel eluting with cyclohexane–EtOAc (90:10) to give of compound **11** (15.6 g, 92%); colorless solid; mp 93–94 °C.

IR (neat): 2949, 1699, 1593, 1497, 1434, 1401, 1316, 1249, 1211, 1210, 1138, 1093, 975, 965, 909, 845, 829, 772, 756, 728, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 8.7 Hz, 1 H, H-4), 8.07 (s, 1 H, H-6), 7.64 (d, *J* = 7.0 Hz, 2 H, $OCH_2C_6H_5$), 7.50–7.25 (m, 4 H, H-3, $OCH_2C_6H_5$), 5.50 (s, 2 H, OCH_2Ph), 3.89 (s, 3 H, CO_2CH_3), 2.83 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8 (C), 159.7 (C), 155.1 (C), 143.7 (C), 137.6 (C), 135.8 (CH), 129.4 (CH), 129.0 (C), 128.8 (2 CH), 128.3 (2 CH), 128.1 (CH), 124.8 (C), 124.6 (CH), 115.8 (C), 77.6 (CH_2), 52.5 (CH_3), 25.4 (CH_3).

MS (+APCI): *m*/*z* (%) = 386 (90), 388 (100, $[M + H]^+$).

Anal. Calcd for $C_{19}H_{16}BrNO_3$: C, 59.08; H, 4.18; N, 3.63. Found: C, 59.25; H, 4.19; N, 3.53.

Cross-Coupling Reaction of Potassium Organotrifluoroborates 12 with 11; General Procedure

A mixture of **11** (1.16 g, 3 mmol), potassium organotrifluoroborate **12** (4.0 mmol), *i*-Pr_2NEt (1.16 g, 9 mmol), and Pd(dppf)Cl_2 (154 mg, 0.21 mmol, 7 mol%) in anhyd MeOH (25 mL) was heated at reflux for 18 h. After cooling to r.t., the mixture was concentrated in vacuo. H_2O (25 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by chromatography on silica gel eluting with EtOAc–cyclohexane to give the title compound.

Methyl 8-(Benzyloxy)-2-methyl-5-phenylquinoline-7-carboxylate (13a)

Colorless solid; mp 129–130 °C.

IR (neat): 2960, 1708, 1606, 1445, 1435, 1375, 1355, 1252, 1204, 1126, 1085, 1031, 982, 915, 898, 853, 833, 786, 772, 744, 702 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.7 Hz, 1 H, H-4), 7.74 (s, 1 H, H-6), 7.72 (d, *J* = 8.7 Hz, 2 H, $OCH_2C_6H_5$), 7.50–7.35 (m, 8 H), 7.31 (d, *J* = 8.7 Hz, 1 H, H-3), 5.56 (s, 2 H, $PhCH_2O$), 3.89 (s, 3 H, CO_2CH_3), 2.81 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0 (C), 158.6 (C), 154.4 (C), 142.9 (C), 138.7 (C), 137.9 (C), 135.5 (C), 134.5 (CH), 129.9 (2 CH), 128.6 (2 CH), 128.4 (2 CH), 128.2 (2 CH), 128.0 (C), 127.8 (CH), 127.6 (CH), 126.4 (CH), 123.7 (C), 123.3 (CH), 77.4 (CH_2), 52.2 (CH_3), 25.5 (CH_3).

MS (+APCI): *m*/*z* (%) = 384.2 (100, $[M + H]^+$).

Anal. Calcd for $C_{26}H_{21}O_3 \cdot H_2O$: C, 77.40; H, 5.59; N, 3.61. Found: C, 77.39; H, 5.73; N, 3.34.

Methyl 8-(Benzyloxy)-2-methyl-5-(4-methylphenyl)quinoline-7-carboxylate (13b)

Yellowish solid; mp 151–152 °C.

IR (neat): 2960, 1711, 1606, 1516, 1496, 1436, 1373, 1355, 1254, 1209, 1172, 1125, 1086, 974, 899, 836, 821, 787, 753, 736 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.7 Hz, 1 H, H-4), 7.72 (s, 1 H, H-6), 7.70 (d, *J* = 8.7 Hz, 2 H, $OCH_2C_6H_5$), 7.40–7.25 (m, 8 H), 5.55 (s, 2 H, $PhCH_2O$), 3.89 (s, 3 H, CO_2CH_3), 2.80 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2 (C), 158.6 (C), 154.3 (C), 143.0 (C), 138.0 (C), 137.4 (C) 135.9 (C), 135.6 (C), 134.6 (CH), 129.8 (2 CH), 129.2 (2 CH), 128.7 (2 CH), 128.3 (2 CH), 128.2 (C), 127.9 (CH), 126.3 (CH), 123.8 (C), 123.3 (CH), 77.4 (CH_2, OCH_2Ph), 52.2 (CH_3), 25.5 (CH_3), 21.2 (CH_3).

MS (+APCI): *m*/*z* (%) = 398 (100, $[M + H]^+$).

Anal. Calcd for $C_{26}H_{23}NO_3 \cdot H_2O$: C, 77.69; H, 5.89; N, 3.48. Found: C, 77.63; H, 5.87; N, 3.40.

Methyl 8-(Benzyloxy)-2-methyl-5-(2-naphthyl)quinoline-7-carboxylate (13c)

Ochred solid; mp 138–140 °C.

IR (neat): 3030, 2947, 1730, 1706, 1607, 1510, 1436, 1401, 1371, 1334, 1257, 1210, 1168, 1136, 1119, 1087, 1040, 983, 909, 861, 835, 816, 784, 752, 730 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.7 Hz, 1 H, H-4), 7.96 (d, *J* = 8.3 Hz, 1 H), 7.95–7.87 (m, 3 H), 7.85 (s, 1 H), 7.73 (d, *J* = 7.2 Hz, 2 H), 7.60–7.50 (m, 3 H), 7.44 (t, *J* = 7.2 Hz, 2 H), 7.43 (d, *J* = 7.2 Hz, 1 H), 7.37 (d, *J* = 7.2 Hz, 1 H), 7.31 (d, *J* = 8.7 Hz, 1 H), 5.60 (s, 2 H, $PhCH_2O$), 3.91 (s, 3 H, CO_2CH_3), 2.82 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1 (C), 158.7 (C), 154.6 (C), 143.0 (C), 137.9 (C), 136.3 (C), 135.5 (C), 134.6 (CH), 133.4 (C), 132.7 (C), 128.9 (CH), 128.7 (2 CH), 128.3 (C), 128.2 (2 CH), 128.0 (2 CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 126.7 (CH), 126.5 (CH), 126.3 (CH), 123.8 (C), 123.4 (CH), 77.5 (CH_2), 52.3 (CH_3), 25.5 (CH_3).

MS (+APCI): *m*/*z* (%) = 434 (100, $[M + H]^+$).

Anal. Calcd for $C_{29}H_{23}NO_3$: C, 80.35; H, 5.35; N, 3.23. Found: C, 80.11; H, 5.44; N, 3.11.

Methyl 8-(Benzyloxy)-5-(4-chlorophenyl)-2-methylquinoline-7-carboxylate (13d)

Colorless solid; mp 181–182 °C.

IR (neat): 2946, 1720, 1607, 1509, 1436, 1373, 1253, 1210, 1127, 1083, 1013, 978, 911, 835, 787, 762, 747 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.7 Hz, 1 H, H-4), 7.72 (s, 1 H, H-6), 7.71 (d, *J* = 7.7 Hz, 2 H, $OCH_2C_6H_5$), 7.49–7.30 (m, 7 H), 7.31 (d, *J* = 8.7 Hz, 1 H, H-3), 5.55 (s, 2 H, $PhCH_2O$), 3.89 (s, 3 H, CO_2CH_3), 2.80 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0 (C), 158.8 (C), 154.7 (C), 143.0 (C), 137.9 (C), 137.2 (C), 134.2 (CH), 133.8 (C), 131.2 (2 CH), 128.7 (2 CH), 128.6 (2 CH), 128.2 (2 CH), 128.0 (C), 127.9 (CH), 126.5 (CH), 123.8 (C), 123.5 (CH), 77.5 (CH_2), 52.3 (CH_3), 25.5 (CH_3).

MS (+APCI): *m*/*z* (%) = 418 (100), 420 (30, $[M + H]^+$).

Anal. Calcd for $C_{25}H_{20}ClNO_3$: C, 71.85; H, 4.82; N, 3.35. Found: C, 71.70; H, 4.90; N, 3.20.

Methyl 8-(Benzyloxy)-5-(4-fluorophenyl)-2-methylquinoline-7-carboxylate (13e)

Beige solid; mp 161–163 °C.

IR (neat): 2950, 1713, 1606, 1512, 1441, 1418, 1371, 1276, 1254, 1218, 1161, 1126, 1089, 985, 910, 850, 782, 758, 738 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.6 Hz, 1 H, H-4), 7.75–7.65 (m, 3 H), 7.47–7.30 (m, 5 H), 7.33 (d, *J* = 8.6 Hz, 1 H, H-3), 7.18 (t, *J* = 8.7 Hz, 2 H, HCCF), 5.54 (s, 2 H, OCH_2Ph), 3.90 (s, 3 H, CO_2CH_3), 2.81 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1 (C), 162.5 (d, $J_{C,F}$ = 247.3 Hz, CF), 158.8 (C), 154.6 (C), 143.0 (C), 137.9 (C), 134.7 (d, $J_{C,F}$ = 3.3 Hz, C), 134.4 (C), 134.3 (CH), 131.6 (d, $J_{C,F}$ = 8.2 Hz, 2 CH), 128.7 (2 CH), 128.3 (2 CH), 128.2 (C), 127.9 (CH), 126.5 (CH), 123.8 (C), 123.5 (CH), 115.6 (d, $J_{C,F}$ = 21.0 Hz, 2 CH), 77.5 (CH_2), 52.3 (CH_3), 25.5 (CH_3).

^{19}F NMR (188 MHz $CDCl_3$): δ = –114.9 (tt, *J* = 7.5 Hz, 5.6 Hz).

MS (+ESI): *m*/*z* (%) = 825.8 (6, $[2 M + Na]^+$), 424 (100, $[M + Na]^+$), 402.3 (7, $[M + H]^+$), 333.2 (8).

Anal. Calcd for $C_{25}H_{20}FNO_3$: C, 74.80; H, 5.02; N, 3.49. Found: C, 74.61; H, 5.07; N, 3.31.

Methyl 8-(Benzyloxy)-5-(3-hydroxyphenyl)-2-methylquinoline-7-carboxylate (13f)

Yellow solid; mp 192–194 °C.

IR (neat): 3500–2900, 1727, 1610, 1580, 1429, 1375, 1351, 1253, 1238, 1203, 1160, 1126, 1096, 988, 972, 839, 776, 744, 731, 694 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.7 Hz, 1 H, H-4), 7.71 (s, 1 H, H-6), 7.69 (d, *J* = 7.8 Hz, 2 H, $OCH_2C_6H_5$), 7.45–7.32 (m, 4 H), 7.29 (d, *J* = 8.7 Hz, 1 H, H-3), 6.98 (d, *J* = 7.8 Hz, 1 H, H-6′), 6.93 (dd, *J* = 8.1, 2.1 Hz, 1 H, H-4′), 6.87 (br s, 1 H, H-2′), 5.54 (s, 2 H, OCH_2Ph), 5.35 (s, 1 H, OH), 3.88 (s, 3 H, CO_2CH_3), 2.79 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.2 (C), 158.6 (C), 157.4 (C), 153.1 (C), 142.0 (C), 139.2 (C), 137.6 (C), 135.2 (C), 134.3 (CH), 129.6 (CH), 128.3 (2 CH), 128.1 (2 CH), 127.8 (CH), 127.2 (C), 125.2 (CH), 123.8 (CH), 123.6 (C), 120.3 (CH), 116.5 (CH), 114.8 (CH), 76.5 (CH_2), 52.4 (CH_3), 25.0 (CH_3).

MS (+APCI): *m*/*z* (%) = 400 (100, $[M + H]^+$).

Anal. Calcd for $C_{25}H_{21}NO_4 \cdot H_2O$: C, 74.33; H, 5.36; N, 3.47. Found: C, 74.01; H, 4.96; N, 3.33.

Methyl 8-(Benzyloxy)-5-(4-hydroxymethylphenyl)-2-methylquinoline-7-carboxylate (13g)
Yellow solid; 114–116 °C.

IR (neat): 3330–2900, 1731, 1708, 1608, 1438, 1372, 1255, 1215, 1130, 1089, 1038, 835, 783, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.7 Hz, 1 H, H-4), 7.72 (s, 1 H, H-6), 7.71 (d, *J* = 7.7 Hz, 2 H), 7.55–7.30 (m, 5 H), 7.31 (d, *J* = 8.7 Hz, 1 H, H-3), 5.55 (s, 2 H, PhCH_2O), 4.80 (s, 2 H, CH_2OH), 3.89 (s, 3 H, CO_2CH_3), 2.80 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 168.7 (C), 160.9 (C), 155.3 (C), 144.2 (C), 143.0 (C), 139.2 (C), 139.1 (C), 137.5 (C), 136.3 (CH), 131.3 (2 CH), 130.2 (2 CH), 129.7 (C), 129.5 (2 CH), 129.4 (CH), 128.5 (2 CH), 127.5 (CH), 125.6 (C), 125.2 (CH), 79.0 (CH_2), 65.2 (CH_2), 53.2 (CH_3), 25.5 (CH_3).

MS (+APCI): *m*/*z* (%) = 414 (100, $[M + H]^+$).

Anal. Calcd for $C_{26}H_{23}NO_4 \cdot H_2O$: C, 74.71; H, 5.67; N, 3.35. Found: C, 74.90; H, 5.68; N, 3.35.

Methyl 8-(Benzyloxy)-5-(3-nitrophenyl)-2-methylquinoline-7-carboxylate (13h)
Yellow solid; mp 131–133 °C.

IR (neat): 2949, 1722, 1607, 1528, 1438, 1347, 1250, 1211, 1137, 1092, 1042, 960, 900, 833, 780, 743, 725, 694 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.33 (s, 1 H, H-2′), 8.32 (d, *J* = 7.8 Hz, 1 H, H-4′), 7.99 (d, *J* = 8.7 Hz, 1 H, H-4), 7.80 (d, *J* = 7.8 Hz, 1 H, H-6′), 7.77 (s, 1 H, H-6), 7.72–7.65 (m, 3 H), 7.50–7.30 (m, 4 H) 5.58 (s, 2 H, OCH_2Ph), 3.91 (s, 3 H, CO_2CH_3), 2.83 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7 (C), 159.2 (C), 155.5 (C), 148.4 (C), 143.1 (C), 140.5 (C), 137.7 (C), 136.0 (CH), 133.6 (CH), 132.6 (C), 129.6 (CH), 128.7 (2 CH), 128.3 (2 CH), 128.0 (CH), 127.7 (C), 127.1 (CH), 124.9 (CH), 124.0 (CH), 123.8 (C), 122.7 (CH), 77.6 (CH_2), 52.4 (CH_3), 25.6 (CH_3).

MS (+APCI): *m*/*z* (%) = 429.3 (100, $[M + H]^+$).

Anal. Calcd for $C_{25}H_{20}N_2O_5$: C, 70.03; H, 4.71; N, 6.54. Found: C, 70.14; H, 4.63; N, 6.42.

Methyl 8-(Benzyloxy)-5-(4-methoxyphenyl)-2-methylquinoline-7-carboxylate (13i)
Colorless solid; mp 180–182 °C.

IR (neat): 2946, 2836, 1721, 1608, 1514, 1456, 1423, 1372, 1346, 1239, 1201, 1171, 1133, 1087, 1032, 988, 971, 936, 914, 839, 794, 780, 756, 734, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.7 Hz, 1 H, H-4), 7.71 (d, *J* = 7.5 Hz, 2 H, $OCH_2C_6H_5$), 7.70 (s, 1 H, H-6), 7.50–7.28 (m, 5 H), 7.30 (d, *J* = 8.7 Hz, 1 H, H-3), 7.03 (d, *J* = 8.5 Hz, 2 H, H-3′, H-5′), 5.55 (s, 2 H, OCH_2Ph), 3.89 (s, 6 H, CO_2CH_3, OCH_3), 2.80 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2 (C), 159.3 (C), 158.6 (C), 154.2 (C), 143.0 (C), 138.0 (C), 135.3 (C), 134.6 (CH), 131.2 (C), 131.1 (2 CH), 128.7 (2 CH), 128.3 (C), 128.2 (2 CH), 127.9 (2 CH), 126.3 (CH), 123.8 (C), 123.2 (CH), 113.9 (2 CH), 77.4 (CH_2), 55.4 (CH_3), 52.3 (CH_3), 25.5 (CH_3).

MS (+APCI): *m*/*z* (%) = 414 (100, $[M + H]^+$).

Anal. Calcd for $C_{26}H_{23}NO_4$: C, 75.53; H, 5.61; N, 3.39. Found: C, 75.43; H, 5.65; N, 3.20.

Methyl 8-(Benzyloxy)-2-methyl-5-[4-(methylthio)phenyl]quinoline-7-carboxylate (13j)
Colorless solid; mp 142–144 °C.

IR (neat): 2914, 1728, 1606, 1556, 1495, 1433, 1369, 1242, 1207, 1169, 1134, 1081, 1036, 1007, 991, 934, 831, 777, 741 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.7 Hz, 1 H, H-4), 7.72 (s, 1 H, H-6), 7.70 (d, *J* = 7.0 Hz, 2 H, $OCH_2C_6H_5$), 7.45–7.35 (m, 7 H), 7.31 (d, *J* = 8.7 Hz, 1 H, H-3), 5.55 (s, 2 H, OCH_2Ph), 3.89 (s, 3 H, CO_2CH_3), 2.80 (s, 3 H, CH_3), 2.56 (s, 3 H, SCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1 (C), 158.7 (C), 154.4 (C), 143.0 (C), 138.2 (C), 137.9 (C), 135.4 (C), 135.0 (C), 134.5 (CH), 130.4 (2 CH), 128.7 (2 CH), 128.3 (2 CH), 128.1 (C), 127.9 (CH), 126.4 (3 CH), 123.8 (C), 123.4 (CH), 77.5 (CH_2), 52.3 (CH_3), 25.5 (CH_3), 15.7 (CH_3).

MS (+APCI): *m*/*z* (%) = 430 (100, $[M + H]^+$).

Anal. Calcd for $C_{26}H_{23}NO_3S$: C, 72.70; H, 5.40; N, 3.26. Found: C, 72.41; H, 5.59; N, 3.19.

Methyl 8-(Benzyloxy)-2-methyl-5-[(*E*)-2-(4-methylphenyl)vinyl]quinoline-7-carboxylate (13k)
Yellow solid; mp 97–99 °C.

IR (neat): 3031, 2943, 1728, 1703, 1630, 1606, 1555, 1502, 1437, 1364, 1248, 1213, 1196, 1156, 1098, 1025, 988, 963, 915, 857, 807, 795, 776, 748, 723, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 8.7 Hz, 1 H, H-4), 8.01 (s, 1 H, H-6), 7.68 (d, *J* = 6.8 Hz, 2 H, $OCH_2C_6H_5$), 7.63 (d, *J* = 16.1 Hz, HC=), 7.48 (d, *J* = 8.0 Hz, 2 H, H-2′, H-6′), 7.47–7.30 (m, 4 H), 7.21 (d, *J* = 8.0 Hz, 2 H, H-3′, H-5′), 7.15 (d, *J* = 16.1 Hz, HC=), 5.52 (s, 2 H, OCH_2Ph), 3.92 (s, 3 H, CO_2CH_3), 2.81 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3 (C), 158.6 (C), 154.4 (C), 143.0 (C), 138.1 (C), 138.0 (C), 134.4 (C), 132.4 (CH), 132.5 (CH), 130.7 (C), 129.5 (2 CH), 128.7 (2 CH), 128.2 (2 CH), 127.9 (CH), 127.7 (C), 126.6 (2 CH), 124.3 (C), 123.2 (CH), 123.1 (CH), 122.4 (CH), 77.4 (CH_2), 52.3 (CH_3), 25.5 (CH_3), 21.8 (CH_3).

MS (+APCI): *m*/*z* (%) = 424 (100, $[M + H]^+$).

Anal. Calcd for $C_{28}H_{25}NO_3$: C, 79.41; H, 5.95; N, 3.31. Found: C, 79.13; H, 5.55; N, 3.11.

Methyl 5-(4-Acetylphenyl)-8-(benzyloxy)-2-methylquinoline-7-carboxylate (13l)
Yellowish solid; 167–169 °C.

IR (neat): 1729, 1680, 1601, 1556, 1498, 1434, 1417, 1372, 1354, 1264, 1246, 1208, 1186, 1169, 1135, 1089, 1036, 988, 935, 867, 842, 780, 746 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.2 Hz, 2 H, H-3′, H-5′), 8.06 (d, *J* = 8.7 Hz, 1 H, H-4), 7.75 (s, 1 H, H-6), 7.70 (d, *J* = 7.0 Hz, 2 H, $OCH_2C_6H_5$), 7.56 (d, *J* = 8.2 Hz, 2 H, H-2′, H-6′), 7.45–7.30 (m, 4 H), 5.57 (s, 2 H, OCH_2Ph), 3.89 (s, 3 H, CO_2CH_3), 2.81 (s, 3 H, CH_3), 2.69 (s, 3 H, $COCH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.7 (C), 167.0 (C) 158.9 (C), 155.1 (C), 143.7 (C), 143.1 (C), 137.8 (C), 136.3 (C), 134.2 (C), 134.1 (CH), 130.3 (2 CH), 128.7 (2 CH), 128.6 (2 CH), 128.3 (2 CH), 128.0 (CH), 127.8 (C), 126.6 (CH), 123.8 (C), 123.7 (CH), 77.6 (CH_2), 52.4 (CH_3), 26.7 (CH_3), 25.5 (CH_3).

MS (+APCI): *m*/*z* (%) = 426 (100, $[M + H]^+$).

Anal. Calcd for $C_{27}H_{23}NO_4$: C, 76.22; H, 5.45; N, 3.29. Found: C, 76.11; H, 5.12; N, 302.

Methyl 5-(4-Carboxyphenyl)-8-(benzyloxy)-2-methylquinoline-7-carboxylate (13m)
Colorless solid; mp 195–196 °C.

IR (neat): 3300–2600, 1723, 1701, 1687, 1609, 1433, 1352, 1254, 1210, 1178, 1093, 914, 780, 727 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 7.8 Hz, 2 H, H-3′), 8.08 (d, *J* = 8.7 Hz, 1 H, H-4), 7.77 (s, 1 H, H-6), 7.70 (d, *J* = 7.8 Hz, 2 H, $OCH_2C_6H_5$), 7.57 (d, *J* = 8.7 Hz, 2 H, H-2′), 7.43 (t, *J* = 7.8 Hz, 2 H, $OCH_2C_6H_5$), 7.39–7.32 (m, 2 H), 5.58 (s, 2 H, OCH_2Ph), 3.90 (s, 3 H, CO_2CH_3), 2.82 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9 (C), 167.0 (C), 159.0 (C), 155.0 (C), 144.3 (C), 143.1 (C), 137.8 (C), 134.3 (C), 134.2 (CH), 130.4 (2 CH), 130.2 (2 CH), 128.7 (2 CH), 128.3 (2 CH), 128.0 (CH), 127.8 (C), 126.7 (CH), 123.8 (C), 123.7 (CH), 77.6 (CH_2), 52.3 (CH_3), 25.5 (CH_3), 1 C undetected.

MS (–ESI): *m*/*z* (%) = 425.9 (100, $[M - H]^-$).

Anal. Calcd for $C_{26}H_{21}NO_5 \cdot H_2O$: C, 71.55; H, 5.08; N, 3.21. Found: C, 71.36; H, 5.09; N, 3.24.

Methyl 5-(3-Formylphenyl)-8-(benzyloxy)-2-methylquinoline-7-carboxylate (13n)
Light brown solid; 167–169 °C.

IR (neat): 2948, 1731, 1700, 1608, 1579, 1556, 1510, 1437, 1401, 1372, 1352, 1312, 1261, 1214, 1158, 1127, 1092, 1040, 983, 914, 838, 803, 781, 740, 698, 648 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 10.11 (s, 1 H, CHO), 8.03 (d, *J* = 8.7 Hz, 1 H, H-4), 7.97 (m, 2 H), 7.76 (s, 1 H, H-6), 7.65–7.72 (m, 4 H), 7.44 (t, *J* = 7.0 Hz, 2 H), 7.38 (t, *J* = 7.0 Hz, 1 H), 7.34 (d, *J* = 8.7 Hz, 1 H, H-3), 5.56 (s, 2 H, OCH_2Ph), 3.90 (s, 3 H, CO_2CH_3), 2.81 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.9 (C), 166.9 (C), 162.9 (C), 158.9 (C), 155.0 (C), 139.8 (C), 137.8 (C), 136.7 (C), 135.9 (CH), 134.0 (CH), 133.9 (C), 131.0 (CH), 129.3 (CH), 129.0 (CH), 128.7 (2 CH), 128.3 (2 CH), 128.0 (CH), 127.9 (C), 126.8 (CH), 123.8 (C), 123.7 (CH), 77.6 (CH_2), 52.4 (CH_3), 25.6 (CH_3).

MS (+ESI): *m*/*z* (%) = 412 (100, $[M + H]^+$).

Anal. Calcd for $C_{26}H_{21}NO_4$: C, 75.90; H, 5.14; N, 3.40. Found: C, 75.58; H, 4.81; N, 3.27.

Methyl 8-(Benzyloxy)-5-(3-furyl)-2-methylquinoline-7-carboxylate (13o)
Colorless solid; mp 158–159 °C.

IR (neat): 2914, 1707, 1611, 1497, 1439, 1424, 1369, 1347, 1273, 1213, 1157, 1136, 1089, 1023, 966, 914, 872, 843, 827, 788, 759, 734, 696 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 8.7 Hz, 1 H, H-4), 7.76 (s, 1 H, H-6), 7.69 (d, *J* = 7.0 Hz, 2 H, $OCH_2C_6H_5$), 7.64 (s, 1 H, H-2′), 7.58 (s, 1 H, H-5′), 7.45–7.34 (m, 4 H), 6.65 (s, 1 H, H-4′), 5.53 (s, 2 H, OCH_2Ph), 3.89 (s, 3 H, CO_2CH_3), 2.81 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0 (C), 158.7 (C), 154.5 (C), 143.2 (CH), 143.1 (C), 140.5 (CH), 137.9 (C), 134.2 (CH), 128.7 (2 CH), 128.3 (2 CH), 127.9 (CH), 126.3 (CH), 126.2 (C), 123.9 (C), 123.5 (CH), 123.1 (C), 112.1 (CH), 77.5 (CH_2), 52.3 (CH_3), 25.5 (CH_3), 1 C undetected.

MS (+APCI): *m*/*z* (%) = 374 (100, $[M + H]^+$).

Anal. Calcd for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75. Found: C, 73.46; H, 5.12; N, 3.91.

Methyl 8-(Benzyloxy)-2-methyl-5-(5-methyl-2-thienyl)quinoline-7-carboxylate (13p)
Colorless solid; mp 126–128 °C.

IR (neat): 2946, 1731, 1708, 1606, 1435, 1370, 1321, 1251, 1203, 1120, 1084, 1032, 982, 782, 732 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 8.7 Hz, 1 H, H-4), 7.83 (s, 1 H, H-6), 7.69 (d, *J* = 7.1 Hz, 2 H, $OCH_2C_6H_5$), 7.45–7.30 (m, 4 H), 6.97 (d, *J* = 3.0 Hz, 1 H), 6.83 (d, *J* = 3.0 Hz, 1 H), 5.54 (s, 2 H, OCH_2Ph), 3.89 (s, 3 H, CO_2CH_3), 2.80 (s, 3 H, CH_3), 2.57 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9 (C), 158.7 (C), 154.7 (C), 143.1 (C), 140.8 (C), 137.9 (C), 137.4 (C), 134.5 (CH), 133.6 (C), 128.7 (2 CH), 128.4 (C), 128.3 (2 CH), 127.9 (CH), 127.6 (CH), 127.3 (CH), 125.6 (CH), 123.8 (C), 123.5 (CH), 77.4 (CH_2), 52.3 (CH_3), 25.5 (CH_3), 15.3 (CH_3).

MS (+APCI): *m*/*z* (%) = 404 (100, $[M + H]^+$).

Anal. Calcd for $C_{24}H_{21}NO_3S \cdot H_2O$: C, 70.65; H, 5.25; N, 3.47. Found: C, 70.72; H, 5.28; N, 3.25.

Methyl 8′-(Benzyloxy)-2′-methyl-3,5′-biquinoline-7′-carboxylate (13r)
Light brown solid; 156–157 °C.

IR (neat): 3059, 1715, 1608, 1555, 1489, 1428, 1373, 1316, 1249, 1220, 1206, 1167, 1123, 1084, 1043, 969, 898, 837, 781, 751, 729, 696 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.02 (d, *J* = 2.0 Hz, 1 H, H-2′), 8.24 (d, *J* = 1.6 Hz, 1 H, H-4′), 8.21 (d. *J* = 8.5 Hz, 1 H, H-8′), 8.07 (d, *J* = 8.7 Hz, 1 H, H-4), 7.89 (d, *J* = 8.2 Hz, 1 H, H-5′), 7.86 (s, 1 H, H-6), 7.79 (t, *J* = 7.0 Hz, 1 H, H-7′), 7.72 (d, *J* = 7.0 Hz, 2 H, $OCH_2C_6H_5$), 7.63 (t, *J* = 7.0 Hz, 1 H, H-6′), 7.43 (t, *J* = 7.0 Hz, 2 H, $OCH_2C_6H_5$), 7.36 (t, *J* = 7.0 Hz, 1 H, $OCH_2C_6H_5$), 7.35 (d, *J* = 8.7 Hz, 1 H, H-3), 5.60 (s, 2 H, OCH_2Ph), 3.91 (s, 3 H, CO_2CH_3), 2.82 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9 (C), 159.0 (C), 155.3 (C), 151.9 (CH), 147.4 (C), 143.2 (C), 137.8 (C), 136.4 (CH), 133.9 (CH), 131.8 (C), 131.7 (C), 129.9 (CH), 129.4 (CH), 128.7 (2 CH), 128.3 (2 CH), 128.2 (C), 128.0 (CH), 127.9 (CH), 127.7 (C), 127.4 (CH), 127.3 (CH), 124.0 (C), 123.9 (CH), 77.4 (CH_2), 52.4 (CH_3), 25.6 (CH_3).

MS (+APCI): *m*/*z* (%) = 435 (100, $[M + H]^+$).

Anal. Calcd for $C_{28}H_{22}N_2O_3 \cdot H_2O$: C, 76.61; H, 5.17; N, 6.38. Found: C, 76.62; H, 5.06; N, 6.20.

Methyl 5-(2,1,3-Benzoxadiazol-5-yl)-8-(benzyloxy)-2-methylquinoline-7-carboxylate (13s)
Beige solid; mp 172–174 °C.

IR (neat): 1732, 1497, 1439, 1373, 1315, 1257, 1242, 1209, 1171, 1119, 1079, 1008, 961, 874, 829, 756, 739 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.7 Hz, 1 H, H-4), 7.95 (d, *J* = 9.3 Hz, 1 H, H-7′), 7.91 (s, 1 H, H-4′), 7.84 (s, 1 H, H-6), 7.69 (d, *J* = 7.0 Hz, 2 H, $OCH_2C_6H_5$), 7.53 (dd, *J* = 9.3 Hz, 1.1 Hz, 1 H, H-6′), 7.38–7.45 (m, 5 H), 5.60 (s, 2 H, OCH_2Ph), 3.91 (s, 3 H, CO_2CH_3), 2.83 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6 (C), 159.2 (C), 155.8 (C), 149.3 (C), 148.4 (C), 143.2 (C), 142.3 (C), 137.6 (C), 134.7 (CH), 133.5 (CH), 132.6 (C), 128.7 (2 CH), 128.3 (2 CH), 128.1 (CH), 127.5 (C), 126.9 (CH), 124.0 (CH), 123.8 (C), 116.5 (CH), 116.4 (CH), 77.7 (CH_2), 52.4 (CH_3), 25.5 (CH_3).

MS (+APCI): *m*/*z* (%) = 426.2 (100, $[M + H]^+$).

Anal. Calcd for $C_{25}H_{19}N_3O_4$: C, 70.58; H, 4.50; N, 9.88. Found: C, 70.50; H, 4.51; N, 9.77.

Compounds 3; General Procedure

Method A: To a suspension of **13** (0.5 mmol) in AcOH (4 mL) was added a 48% aq solution of HBr (6 mL) and the resulting mixture was heated under reflux for 18 h. After cooling to r.t., the mixture was concentrated under reduced pressure and the residue was suspended in H_2O (4 mL). Aq 3 N NaOH was added until pH 10 was reached and the mixture was then reacidified to pH 3–4 with aq 1 N HCl. The precipitate was filtered, washed thoroughly with hot H_2O, *i*-PrOH, and Et_2O, and dried in vacuo to give the title compound **3**.

Method B: To a stirred solution of **13** (0.5 mmol) in dioxane (2 mL) and MeOH (6 mL) was added 6 N aq NaOH (8 mL). The mixture was heated at reflux under N_2 for 16h. After cooling, the solvents were removed under reduced pressure and the mixture was acidified to pH 3 with aq 3 N HCl. The mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (5 mL) and dried ($MgSO_4$). After removal of the solvent, the crude acid **14** obtained was taken into a 3:1 mixture of MeOH and EtOAc (3 mL) and placed in a 10 mL pressure tube with a stir bar. Cyclohexa-1,4-diene (500 mg, 25 mmol) and 10% Pd/C (10 mg) were added, the tube was capped and heated under microwave conditions (100 °C, 20 bar) for 10 min. MeOH (20 mL) was added and the catalyst was filtered through Celite. The filtrate was concentrated under reduced pressure and the resulting solid was triturated with *i*-PrOH (5 mL), filtered, and dried in vacuo to give the title compound **3**.

8-Hydroxy-2-methyl-5-phenylquinoline-7-carboxylic Acid (3a)

Brown solid; mp 207–209 °C.

IR (neat): 3650–2300, 1693, 1656, 1596, 1567, 1514, 1449, 1423, 1395, 1365, 1302, 1263, 1096, 1030, 828, 788, 763, 746, 697 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.20 (d, *J* = 8.5 Hz, 1 H, H-4), 7.76 (s, 1 H, H-6), 7.60–7.38 (m, 6 H), 2.74 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.9 (C), 161.2 (C), 155.8 (C), 139.1 (C), 138.1 (C), 135.8 (CH), 129.7 (2 CH), 128.5 (2 CH), 127.5 (C), 127.4 (CH), 126.9 (CH), 124.5 (C), 123.9 (CH), 113.2 (C), 23.7 (CH_3).

MS (–APCI): *m*/*z* (%) = 278 (100, $[M - H]^-$).

Anal. Calcd for $C_{17}H_{13}NO_3 \cdot H_2O$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.40; H, 4.96; N, 4.67.

8-Hydroxy-2-methyl-5-*p*-tolylquinoline-7-carboxylic Acid (3b)

Orange solid; mp 220–222 °C.

IR (neat): 3700–3000, 2922, 1698, 1635, 1590, 1572, 1517, 1447, 1392, 1364, 1312, 1302, 1262, 1092, 1021, 856, 826, 816, 788, 737 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.36 (d, *J* = 8.5 Hz, 1 H, H-4), 7.76 (s, 1 H, H-6), 7.68 (d, *J* = 8.5 Hz, 1 H, H-3), 7.32 (s, 4 H), 2.82 (s, 3 H, CH_3), 2.39 (s, 3 H, PhC*H*$_3$).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.4 (C), 159.9 (C), 156.1 (C), 138.5 (CH), 136.6 (C), 135.5 (C), 135.3 (C), 129.6 (2 CH), 129.3 (2 CH), 128.3 (C), 127.4 (CH), 125.1 (CH), 125.0 (C), 112.0 (C), 22.1 (CH_3), 20.7 (CH_3).

MS (–APCI): *m*/*z* (%) = 292 (100, $[M - H]^-$).

Anal. Calcd for $C_{18}H_{15}NO_3 \cdot 1/5H_2O$: C, 72.81; H, 5.23; N, 4.72. Found: C, 73.08; H, 5.41; N, 4.54.

8-Hydroxy-2-methyl-5-naphthalen-2-ylquinoline-7-carboxylic Acid (3c)

Brown solid; mp 219–222 °C.

IR (neat): 3600–3100, 1652, 1595, 1568, 1517, 1477, 1433, 1400, 1358, 1216, 1142, 1090, 863, 829, 789, 748, 722 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.24 (d, *J* = 8.5 Hz, 1 H, H-4), 8.08–7.92 (m, 4 H), 7.87 (s, 1 H, H-6), 7.64–7.45 (m, 4 H), 2.74 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.0 (C), 161.3 (C), 156.0 (C), 138.0 (C), 136.6 (C), 136.2 (CH), 133.2 (C), 131.9 (C), 128.2 (CH), 128.1 (CH), 127.9 (3 CH), 127.7 (C), 127.5 (CH), 126.3 (CH), 126.0 (CH), 124.4 (C), 124.2 (CH), 113.4 (C), 23.2 (CH_3).

MS (–ESI): *m*/*z* (%) = 328 (100, $[M - H]^-$, 284 (8, $[M - CO_2]^-$).

Anal. Calcd for $C_{21}H_{15}NO_3 \cdot 4/3\ H_2O$: C, 71.38; H, 5.04; N, 3.96. Found: C, 71.36; H, 4.83; N, 3.67.

8-Hydroxy-5-(4-chlorophenyl)-2-methylquinoline-7-carboxylic Acid (3d)

Yellowish solid; mp 235 °C (dec.).

IR (neat): 3900–2900, 1683, 1587, 1513, 1449, 1398, 1366, 1309, 1130, 1088, 1014, 833, 785, 758 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.35 (d, *J* = 7.3 Hz, 1 H, H-4), 7.79 (s, 1 H, H-6), 7.70 (d, *J* = 7.3 Hz, 1 H, H-3), 7.58 (d, *J* = 7.2 Hz, 2 H), 7.48 (d, *J* = 7.2 Hz, 2 H), 2.83 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.5 (C), 160.7 (C), 156.1 (C), 137.3 (C), 136.4 (C), 132.0 (C), 131.5 (2 CH), 129.7 (CH), 128.6 (2 CH), 127.8 (C), 127.7 (CH), 124.9 (CH), 123.4 (C), 112.5 (C), 22.5 (CH_3).

MS (–ESI): *m*/*z* (%) = 314 (30), 312 (100, $[M - H]^-$).

Anal. Calcd for $C_{17}H_{12}ClNO_3 \cdot 3/5\ H_2O$: C, 62.91; H, 4.10; N, 4.32. Found: C, 63.16; H, 4.41; N, 3.92.

5-(4-Fluorophenyl)-8-hydroxy-2-methylquinoline-7-carboxylic Acid (3e)

Burgundy red solid; mp 156–161 °C.

IR (neat): 3600–2600, 1699, 1662, 1604, 1522, 1511, 1464, 1419, 1372, 1285, 1234, 1160, 1106, 849, 839, 818, 781, 754 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.32 (d, *J* = 7.3 Hz, 1 H, H-4), 7.76 (s, 1 H, H-6), 7.69 (d, *J* = 7.3 Hz, 1 H, H-3), 7.48 (t *J* = 6.0 Hz, 2 H, H-2′, H-6′), 7.40–7.30 (m, 2 H, H-3′, H-5′), 2.82 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.4 (C), 161.5 (d, $J_{C,F}$ = 244.0 Hz, CF, C-4′), 156.2 (C), 138.3 (CH), 135.5 (C), 134.5 (d, $J_{C,F}$ = 2.7 Hz, C, C-1′), 131.7 (d, $J_{C,F}$ = 8.2 Hz, 2 CH, C-2′, C-6′), 128.2 (C), 127.7 (CH), 125.2 (CH), 123.9 (C), 115.5 (d, $J_{C,F}$ = 21.4 Hz, 2 CH, C-3′, C-5′), 111.9 (C), 22.1 (CH_3).

^{19}F NMR (188 MHz, DMSO-d_6): δ = –113.31.

MS (–ESI): *m*/*z* (%) = 296 (100, $[M - H]^-$).

Anal. Calcd for $C_{17}H_{12}FNO_3 \cdot H_2O$: C, 67.66; H, 4.17; N, 4.64. Found: C, 67.67; H, 4.65; N, 4.30.

8-Hydroxy-5-(3-hydroxyphenyl)-2-methylquinoline-7-carboxylic Acid (3f)

Orange solid; mp 200 °C (dec.).

IR (neat): 3400–2400, 1636, 1595, 1572, 1458, 1405, 1379, 1358, 1318, 1259, 1223, 1096, 890, 867, 829, 788, 768, 737, 698 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 9.70 (br s, 1 H, OH), 8.22 (d, *J* = 8.2 Hz, 1 H, H-4), 7.74 (s, 1 H, H-6), 7.51 (d, *J* = 8.2 Hz, 1 H, H-3), 7.27 (t, *J* = 7.3 Hz, 1 H, H-5′), 6.82 (br s, 3 H, H-2′, H-4′, H-6′), 2.73 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.2 (C), 161.0 (C), 157.5 (C), 156.0 (C), 140.3 (C), 138.0 (C), 136.1 (CH), 129.5 (CH), 127.6 (C), 127.1 (CH), 124.9 (C), 124.0 (CH), 120.4 (CH), 116.6 (CH), 114.1 (CH), 113.2 (C), 23.3 (CH_3).

MS (–ESI): *m*/*z* (%) = 294 (100, $[M - H]^-$), 250 (8, $[M - H - CO_2]^-$).

Anal. Calcd for $C_{17}H_{13}NO_4 \cdot HCl \cdot H_2O$: C, 59.92; H, 4.44; N, 4.11. Found: C, 59.22; H, 4.38; N, 3.71.

8-Hydroxy-5-(4-hydroxymethylphenyl)-2-methylquinoline-7-carboxylic Acid (3g)
Red solid; mp 211–214 °C.

IR (neat): 3600–2800, 1682, 1648, 1592, 1572, 1506, 1442, 1393, 1363, 1310, 1273, 1203, 1142, 1097, 1049, 1038, 1017, 825, 804, 743, 717 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.22 (d, *J* = 7.0 Hz, 1 H, H-4), 7.76 (s, 1 H, H-6), 7.55 (d, *J* = 7.0 Hz, 1 H, H-3), 7.44 (d, *J* = 7.2 Hz, 2 H, H-3′, H-5′), 7.37 (d, *J* = 7.2 Hz, 2 H, H-2′, H-6′), 5.30 (br s, 1 H, OH), 4.58 (s, 2 H, C*H*$_2$OH), 2.75 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.0 (C), 160.7 (C), 156.0 (C), 141.4 (C), 137.4 (C), 137.2 (C), 136.6 (CH), 129.5 (2 CH), 127.8 (C), 127.4 (CH), 126.7 (2 CH), 124.9 (C), 124.3 (CH), 113.0 (C), 62.6 (CH_2), 23.0 (CH_3).

MS (–APCI): *m*/*z* (%) = 308 (100, $[M - H]^-$).

Anal. Calcd for $C_{18}H_{15}NO_4 \cdot 2/3H_2O$: C, 67.28; H, 5.12; N, 4.36. Found: C, 67.35; H, 5.32; N, 3.80.

8-Hydroxy-2-methyl-5-(3-nitrophenyl)quinoline-7-carboxylic Acid (3h)
Yellowish solid; mp 185–188 °C.

IR (neat): 3800–2500, 1688, 1647, 1630, 1596, 1526, 1441, 1345, 1307, 1263, 1093, 839, 808, 740 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.37 (d, *J* = 8.7 Hz, 1 H, H-4), 8.29 (d, *J* = 7.8 Hz, 1 H, H-4′), 8.22 (s, 1 H, H-2′), 7.94 (d, *J* = 7.8 Hz, 1 H, H-6′), 7.87 (s, 1 H, H-6), 7.81 (t, *J* = 7.8 Hz, 1 H, H-5′), 7.69 (d, *J* = 8.7 Hz, 1 H, H-3), 2.83 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.2 (C), 161.3 (C), 156.2 (C), 148.0 (C), 142.0 (C), 140.0 (C), 137.7 (CH), 136.3 (CH), 136.1 (C), 130.2 (CH), 128.4 (CH), 127.8 (C), 125.3 (CH), 124.1 (CH), 122.0 (CH), 112.5 (C), 22.2 (CH_3).

MS (–ESI): *m*/*z* (%) = 669 (59, $[2 M + Na - 2H]^-$), 323 (100, $[M - H]^-$).

Anal. Calcd for $C_{17}H_{12}N_2O_5 \cdot H_2O$: C, 61.26; H, 3.93; N, 8.41. Found: C, 61.08; H, 3.86; N, 8.08.

8-Hydroxy-2-methyl-5-(4-methoxyphenyl)quinoline-7-carboxylic Acid (3i)
Orange solid; mp 236–237 °C.

IR (neat): 3400–2500, 1712, 1626, 1610, 1538, 1515, 1484, 1462, 1423, 1371, 1307, 1293, 1250, 1184, 1037, 965, 858, 831 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.28 (d, *J* = 8.5 Hz, 1 H, H-4), 7.74 (s, 1 H, H-6), 7.61 (d, *J* = 8.5 Hz, 1 H, H-3), 7.34 (d, *J* = 7.5 Hz, 2 H, H-2′, H-6′), 7.06 (d, *J* = 7.5 Hz, 2 H, H-3′, H-5′), 3.17 (s, 3 H, OCH_3), 2.79 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.6 (C), 160.0 (C), 158.5 (C), 156.0 (C), 137.7 (CH), 136.2 (C), 130.8 (2 CH), 130.7 (C), 128.2 (C), 127.2 (CH), 124.8 (C), 124.7 (CH), 114.0 (2 CH), 112.3 (C), 55.1 (CH_3), 22.5 (CH_3).

MS (–ESI): *m*/*z* (%) = 308 (100, $[M - H]^-$).

Anal. Calcd for $C_{18}H_{15}NO_4 \cdot 2/3H_2O$: C, 67.28; H, 5.12; N, 4.36. Found: C, 67.02; H, 5.01; N, 4.32.

8-Hydroxy-2-methyl-5-(4-methylsulfanylphenyl)quinoline-7-carboxylic Acid (3j)
Orange solid; mp 220 °C (dec.).

IR (neat): 3700–3050, 2927, 2097, 1702, 1630, 1587, 1510, 1429, 1390, 1373, 1308, 1294, 1257, 1212, 1085, 1029, 1011, 969, 829, 790, 777 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.35 (d, *J* = 8.1 Hz, 1 H, H-4), 7.76 (s, 1 H, H-6), 7.67 (d, *J* = 8.1 Hz, 1 H, H-3), 7.38 (s, 4 H, H-2′, H-3′, H-5′, H-6′), 2.77 (s, 3 H, CH_3), 2.15 (s, 3 H, SCH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.3 (C), 160.1 (C), 156.1 (C), 138.3 (C), 137.3 (C), 135.6 (C), 134.6 (C), 130.1 (2 CH), 128.1 (C), 127.4 (CH), 126.0 (2 CH), 125.1 (C), 124.3 (CH), 112.0 (C), 22.1 (CH_3), 14.6 (CH_3).

MS (–ESI): *m*/*z* (%) = 671 (3, $[2 M + Na - 2 H]^-$), 324 (100, $[M - H]^-$), 280 (3, $[M - CO_2H]^-$).

Anal. Calcd for $C_{18}H_{15}NO_3S \cdot HCl \cdot 4/3H_2O$: C, 56.03; H, 4.88; N, 3.63. Found: C, 56.01; H, 4.50; N, 3.42.

5-(4-Acetylphenyl)-8-hydroxy-2-methylquinoline-7-carboxylic Acid (3l)
Ochre solid; mp 255 °C (dec.).

IR (neat): 3800–3300, 2922, 1673, 1600, 1574, 1454, 1434, 1380, 1361, 1307, 1270, 1094, 956, 835, 786, 729 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.41 (d, *J* = 7.6 Hz, 1 H, H-4), 8.10 (d, *J* = 6.7 Hz, 2 H, H-3′, H-5′), 7.85 (s, 1 H, H-6), 7.72 (d, *J* = 7.6 Hz, 1 H, H-3), 7.62 (d, *J* = 6.7 Hz, 2 H, H-2′, H-6′), 2.84 (s, 3 H, CH_3), 2.65 (s, 3 H, $COCH_3$).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 197.5 (C), 170.4 (C), 161.6 (C), 156.2 (C), 143.4 (C), 137.5 (CH), 136.4 (C), 135.3 (C), 129.9 (2 CH), 128.6 (2 CH), 128.1 (CH), 127.7 (C), 125.0 (CH), 123.4 (C), 112.7 (C), 26.7 (CH_3), 22.2 (CH_3).

MS (–ESI): *m*/*z* (%) = 663 (20, $[2 M - 2 H + Na]^-$), 320 (100, $[M - H]^-$).

5-(4-Carboxyphenyl)-8-hydroxy-2-methylquinoline-7-carboxylic Acid (3m)
Dark brown solid; mp 280 °C (dec.).

IR (neat): 3400–2300, 1722, 1679, 1604, 1535, 1507, 1462, 1415, 1375, 1302, 1231, 1186, 1107, 859, 781, 764 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 13.00 (br s, 1 H, CO_2H), 8.42 (d, *J* = 7.4 Hz, 1 H, H-4), 8.08 (d, *J* = 7.4 Hz, 2 H, H-3′, H-5′), 7.85 (s, 1 H, H-6), 7.72 (d, *J* = 7.4 Hz, 1 H, H-2′, H-6′), 7.59 (d, *J* = 7.4 Hz, 1 H, H-3), 2.84 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.2 (C), 167.1 (C), 160.8 (C), 156.2 (C), 142.7 (C), 138.6 (CH), 135.5 (C), 129.9 (2 CH), 129.7 (2 CH), 129.5 (C), 128.2 (CH), 128.0 (C), 125.4 (CH), 123.6 (C), 112.2 (C), 22.0 (CH_3).

MS (–ESI): *m*/*z* (%) = 667 (35, $[2 M - 2 H + Na]^-$), 344 (5, $[M + Na - 2 H]^-$), 322 (100, $[M - H]^-$).

Anal. Calcd for $C_{18}H_{13}NO_5 \cdot HCl \cdot H_2O$: C, 58.63; H, 4.10; N, 3.80. Found: 58.47; H, 3.81; N, 3.71.

5-(4-Formylphenyl)-8-hydroxy-2-methylquinoline-7-carboxylic Acid (3n)
Red solid; mp 164–169 °C.

IR (neat): 3800–2900, 1701, 1659, 1642, 1596, 1571, 1510, 1455, 1367, 1309, 1270, 1098, 967, 836, 786 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 10.10 (s, CHO), 8.39 (d, *J* = 8.3 Hz, 1 H, H-4), 797 (br s, 2 H), 7.85 (s, 1 H, H-6), 7.80–7.60 (m, 3 H), 2.84 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 193.2 (CH), 170.2 (C), 160.6 (C), 156.3 (C), 139.0 (C), 138.4 (CH), 136.6 (C), 135.6 (CH), 135.5 (C), 131.0 (CH), 129.6 (CH), 128.1 (CH), 128.0 (C), 127.8 (CH), 125.4 (CH), 123.4 (C), 112.1 (C), 22.0 (CH_3).

MS (–APCI): *m/z* (%) = 306 (100, [M – H]$^-$).

Anal. Calcd for $C_{18}H_{13}NO_4 \cdot H_2O$: C, 65.25; H, 4.77; N, 4.23. Found: C, 65.21; H, 4.48; N, 4.11.

5-Furan-3-yl-8-hydroxy-2-methylquinoline-7-carboxylic Acid (3o)

Orange solid; mp 230–233 °C.

IR (neat): 3600–2700, 1693, 1647, 1592, 1575, 1428, 1362, 1305, 1244, 1227, 1158, 1102, 1025, 873, 830, 805, 785 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.55 (d, *J* = 8.5 Hz, 1 H, H-4), 7.98 (s, 1 H, H-2′), 7.84 (s, 2 H, H-6, H-5′), 7.69 (d, *J* = 8.5 Hz, 1 H, H-3), 6.80 (s, 1 H, H-4′), 2.81 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.4 (C), 160.2 (C), 156.0 (C), 143.7 (CH), 140.4 (CH), 137.9 (C), 136.2 (C), 128.1 (C), 127.3 (CH), 124.9 (CH), 122.6 (C), 115.5 (C), 112.4 (C), 111.9 (CH), 22.3 (CH_3).

MS (–ESI): *m/z* (%) = 268 (100, [M – H]$^-$).

Anal. Calcd for $C_{15}H_{11}NO_4 \cdot H_2O$: C, 62.72; H, 4.56; N, 4.88. Found: C, 62.91; H, 4.61; N, 4.91.

8-Hydroxy-2-methyl-5-(5-methylthiophen-2-yl)quinoline-7-carboxylic Acid (3p)

Orange solid; mp 220 °C (dec.).

IR (neat): 3900–2900, 1648, 1592 1481, 1444, 1401, 1364, 1086, 867, 829, 787 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.31 (d, *J* = 8.6 Hz, 1 H, H-4), 7.83 (s, 1 H, H-6), 7.41 (d, *J* = 8.6 Hz, 1 H, H-3), 6.93 (d, *J* = 2.9 Hz, 1 H, H-3′), 6.87 (d, *J* = 2.9 Hz, 1 H, H-4′), 2.64 (s, 3 H, CH_3), 2.50 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.5 (C), 162.5 (C), 156.1 (C), 140.5 (C), 138.8 (C), 138.5 (C), 133.6 (CH), 128.0 (CH), 127.3 (C), 126.3 (CH), 125.9 (CH), 123.5 (CH), 117.0 (C), 114.0 (C), 24.4 (CH_3), 14.9 (CH_3).

MS (+ESI): *m/z* (%) = 298 (100, [M – H]$^-$).

Anal. Calcd for $C_{16}H_{13}NO_3S \cdot 3/2H_2O$: C, 58.88; H, 4.94; N, 4.29. Found: C, 58.34; H, 4.44; N, 4.19.

8′-Hydroxy-2′-methyl[3,5′]biquinolinyl-7′-carboxylic Acid (3r)

Olive brown solid; 270–273 °C.

IR (neat): 3800–2800, 1621, 1592, 1572, 1511, 1432, 1364, 1326, 1292, 1092, 1072, 831, 786, 729 cm^{-1}.

^{1}H NMR (300 MHz, TFA-d_1–acetone-d_6, 9:1): δ = 9.11 (s, 1 H, H-8′), 9.07 (s, 1 H, H-6′), 8.65 (d, *J* = 8.9 Hz, 1 H, H-4), 8.25 (s, 1 H, H-6), 8.16 (t, *J* = 8.7 Hz, 2 H), 8.09 (t, *J* = 8.2 Hz, 1 H), 7.90–7.83 (m, 2 H), 2.95 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, TFA-d_1–acetone-d_6, 9:1): δ = 171.2 (C), 160.9 (C), 154.3 (C), 149.5 (CH), 145.2 (CH), 144.3 (CH), 137.9 (C), 137.7 (CH), 132.3 (CH), 132.2 (CH), 131.0 (C), 130.2 (CH), 129.9 (C), 129.7 (C), 128.5 (CH), 124.2 (C), 121.0 (CH), 20.4 (CH_3), 2 C undetected.

MS (–APCI): *m/z* (%) = 329 (100, [M – H]$^-$), 285 (12, [(M – CO_2H]$^-$).

Anal. Calcd for $C_{20}H_{14}N_2O_3 \cdot$HCl: C, 65.49; H, 4.12; N, 7.64. Found: C, 66.16; H, 4.05; N, 7.32.

5-Benzo[1,2,5]oxadiazol-5-yl-8-hydroxy-2-methylquinoline-7-carboxylic Acid (3s)

Orange solid; mp 245 °C (dec.).

IR (neat): 3800–3000, 1657, 1612, 1539, 1462, 1371, 1302, 1261, 1082, 1096, 969, 878, 843, 810 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.46 (d, *J* = 8.5 Hz, 1 H, H-4), 8.15 (d, *J* = 9.2 Hz, 2 H, H-7′), 8.10 (s, 1 H, H-4′), 7.95 (s, 1 H, H-6), 7.72 (d, *J* = 8.5 Hz, 2 H, H-3, H-6′), 2.83 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.4 (C), 156.2 (C), 149.4 (C), 148.2 (C), 143.6 (C), 142.9 (C), 136.9 (CH), 136.1 (CH), 128.5 (CH), 127.6 (C), 124.8 (CH), 121.8 (C), 116.9 (C), 116.1 (CH), 114.9 (CH), 113.0 (C), 22.7 (CH_3).

MS (–ESI): *m/z* (%) = 663 (13, [2 M – 2 H + Na]$^-$), 320 (100, [M – H]$^-$).

Styrylquinolines; 2-[2-(3,4-Dihydroxyphenyl)vinyl]-8-hydroxy-5-phenylquinoline-7-carboxylic Acid (2a); Typical Procedure

To a solution of quinaldine **3a** (100 mg, 0.36 mmol) in Ac_2O (10 mL) was added 3,4-dihydroxybenzaldehyde (222 mg, 1.60 mmol). The mixture was heated under reflux for 72 h and concentrated in vacuo. The residue was taken up in pyridine–H_2O (4:1, 10 mL) and the resulting solution was heated under reflux for 3 h. After cooling, the solvents were removed under reduced pressure. The residue was triturated with MeOH (10 mL) and filtered through a sintered glass funnel. The solid was washed with EtOAc (5 mL) and Et_2O (5 mL) and dried under reduced pressure to afford styrylquinoline **2a** (59 mg, 41%); burgundy solid; mp >190 °C (dec.).

IR (neat): 3600–2930, 1635, 1583, 1497, 1448, 1387, 1289, 1125, 955, 868, 794, 738, 699 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.61 (s, 1 H, OH), 9.29 (s, 1 H, OH), 8.29 (d, *J* = 8.5 Hz, 1 H, H-4), 8.13 (d, *J* = 8.5 Hz, 1 H, H-3), 7.84 (d, *J* = 16.0 Hz, 1 H, HC=C*H*), 7.75 (s, 1 H, H-5), 7.60–7.40 (m, 6 H), 7.15 (s, 1 H, H-2′), 7.04 (d, *J* = 7.8 Hz, 1 H, H-6′), 6.84 (d, *J* = 7.8 Hz, 1 H, H-5′).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.4 (C), 160.0 (C), 152.9 (C), 148.0 (C), 145.8 (C), 139.1 (CH), 138.4 (C), 137.4 (CH), 135.9 (C), 129.8 (2 CH), 128.8 (2 CH), 128.1 (C), 127.7 (CH), 127.4 (CH), 127.3 (C), 125.5 (C), 121.0 (CH), 120.9 (CH), 120.5 (CH), 116.0 (CH), 114.3 (CH), 112.4 (C).

MS (–ESI): *m/z* (%) = 398 (100, [M – H]$^-$), 354.2 (3, [M – H – CO_2]$^-$).

2-[2-(3,4-Dihydroxyphenyl)vinyl]-8-hydroxy-5-(3-nitrophenyl)quinoline-7-carboxylic Acid (2h)

According to the typical procedure described above the styrylquinoline **2h** was obtained in 43% from quinaldine **3h**; orange solid; mp >230 °C (dec.).

IR (neat): 3700–2800, 1630, 1582, 1525, 1512, 1476, 1451, 1387, 1347, 1292, 1256, 1199, 1167, 1102, 1005, 804 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.57 (s, 1 H, OH), 9.24 (s, 1 H, OH), 8.45–8.20 (m, 2 H), 8.26 (s, 1 H, H-2′), 8.14 (m, 1 H, H-3), 7.97 (d, *J* = 6.0, H-6′), 7.89 (d, *J* = 16.0 Hz, 1 H, HC=C*H*), 7.84 (s, 1 H, H-6), 7.81), 7.52 (d, *J* = 16.0 Hz, 1 H, *H*C=CH), 7.14 (s, 1 H, H-2′), 7.05 (d, *J* = 6.7 Hz, 1 H, H-6′), 6.83 (d, *J* = 6.7 Hz, 1 H, H-5′).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.0 (C), 160.9 (C), 152.9 (C), 148.1 (C), 148.0 (C), 145.7 (C), 139.9 (C), 139.5 (CH), 137.1 (CH), 136.3 (CH), 135.9 (C), 130.3 (CH), 128.5 (CH), 127.8 (C), 127.2 (C), 124.2 (CH), 122.6 (C), 122.1 (CH), 121.3 (CH), 120.9 (CH), 120.1 (CH), 116.0 (CH), 114.2 (CH), 112.5 (C).

MS (–ESI): *m/z* (%) = 443 (100, [M – H]$^-$), 399 (2, [M – H – CO_2]$^-$).

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