Synthesis of 2-(4-Isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-ol; A Quinoline Building Block for Simeprevir Synthesis

Stanislav Rádl,*[a,b] Hana Rezková,[b] Iva Obadalová,[a] Jan Srbek,[a] Jiří Břicháč,[a] Tomáš Pekárek[a]

[a] Zentiva – A Sanofi Company, U kabelovny 130, 102 37 Prague, Czech Republic
Fax +420(2)67243741; E-mail: stanislav.radl@zentiva.cz

[b] Institute of Chemical Technology, Technická 5, 166 28 Prague, Czech Republic

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Dedicated to my friend and admirable human being Dr. Alfred Bader on the occasion of his 90th birthday (S.R.).

Abstract: Two synthetic approaches to the achiral quinoline fragment of simeprevir are described. Both approaches are based on the synthesis of methyl 4-hydroxy-7-methoxy-8-methylquinoline-2-carboxylate, protection of its 4-hydroxyl group, and construction of the thiazole ring from the ester group at the 2-position. The last step is acid deprotection of the 4-hydroxyl protecting group.

Key words: antiviral agents, building block, quinolones, thionation, thiazoles

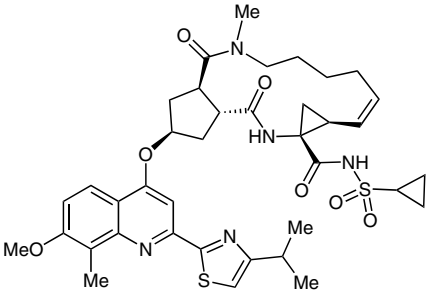
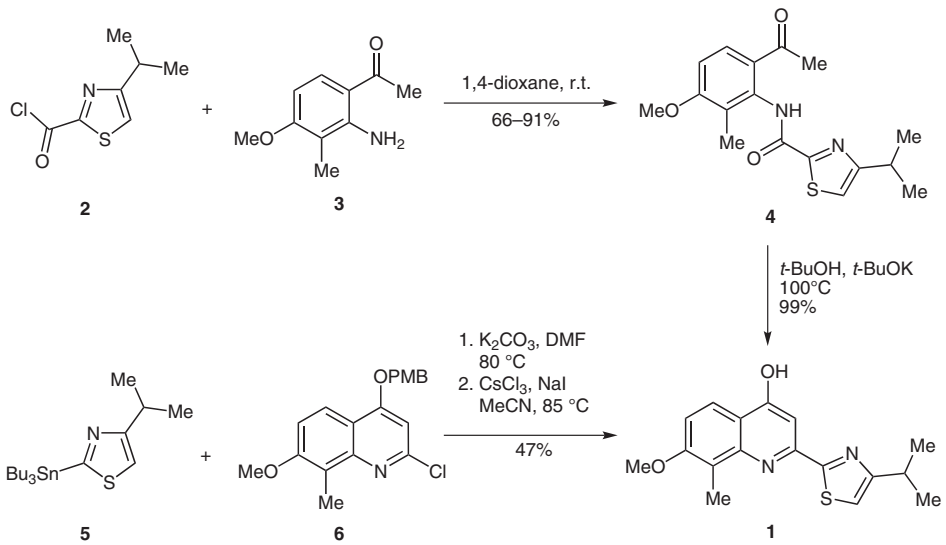


Figure 1 Structure of simeprevir

Simeprevir (Figure 1) is a potent once-daily experimental drug candidate for the treatment of hepatitis C virus (HCV) acting as a specific HCV protease inhibitor. Due to positive clinical results, the U.S. Food and Drug Administration has granted Priority Review to the New Drug Application of this drug.[1]

Although the most difficult part of the synthesis of simeprevir and similar compounds is an intramolecular ring-closing-metathesis macrocyclization, the synthesis of 2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-ol (**1**) is likewise challenging. Furthermore, the same structural fragment is also present in several other drug candidates.[2]

There are several papers[1,2] and patents[3] describing the synthesis of quinoline building block **1**. Most of these[1,2,3a–c] are based on a rather tedious synthesis of 4-isopropylthiazole-2-carboxylic acid chloride (**2**) and its reaction with 1-(2-amino-4-methoxy-3-methyl-phenyl)ethanone (**3**) leading to *N*-(6-acetyl-3-methoxy-2-methylphenyl)-4-isopropylthiazole-2-carboxamide (**4**), which is then cyclized



Scheme 1 Published methods for the synthesis of 2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-ol (**1**)

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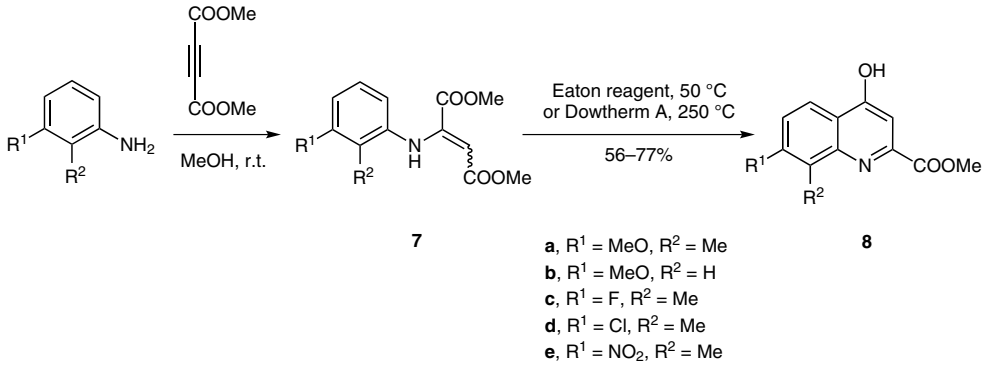
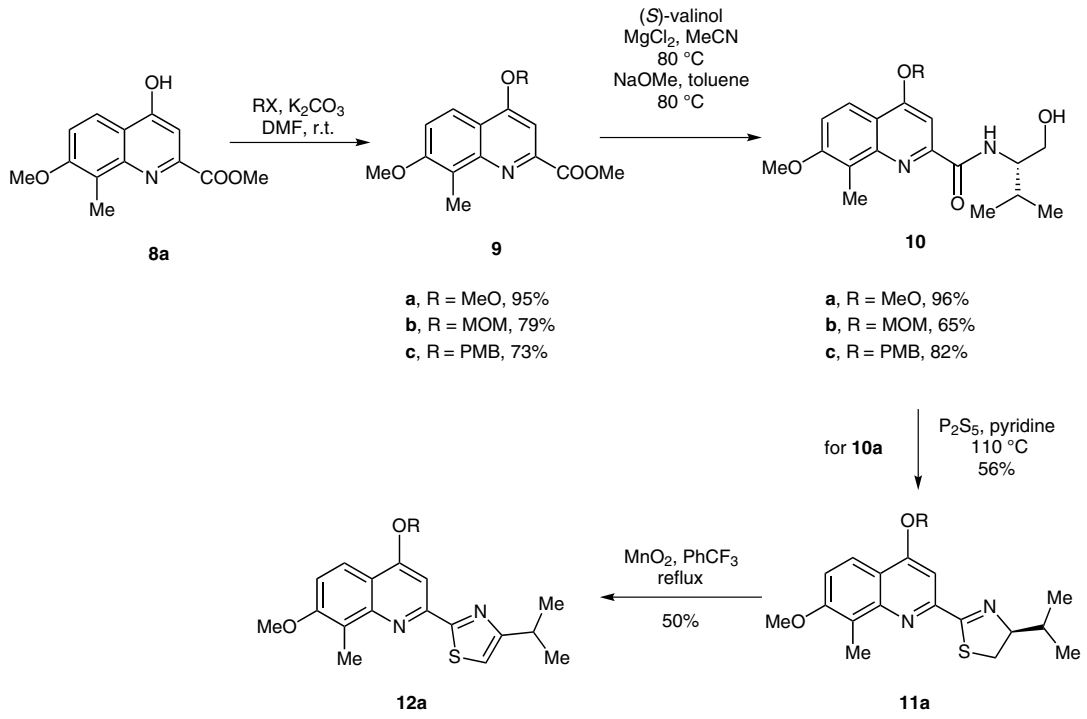


Scheme 2 Synthesis of 2-carbomethoxy-4-hydroxyquinolines **8**

to **1** (Scheme 1). The total yield of this six-step process starting from 3-methoxy-2-methylaniline was reported to be 9.1–12.5%.[1,2,3a–c] Surprisingly, a slight modification of the process provided 38.7% yield.[3d] However, upon trying to reproduce this modified synthesis, we failed to achieve comparable results. A different strategy based on the coupling of 2-(tributylstannyl)-4-isopropylthiazole (**5**) and 4-(4-methoxybenzyloxy)-2-chloro-7-methoxy-8-methylquinoline (**6**) is also described in the patent literature (Scheme 1). This procedure has six reaction steps with total yield of 7.5%.[3e]

This paper describes work leading to an improved synthesis of **1**. The process is based the facile construction of 2-carbomethoxy 4-hydroxyquinolines from the corresponding anilines according to a reported procedure.[4] We have modified the described conditions by using, in most cases, Eaton's reagent instead of thermal cyclization to obtain compounds **8a–d** (Scheme 2). Whereas the described thermal cyclization of compounds **7a** and **7b** provided only low yields of the respective products **8** (33% for **8a** and 44% for **8b** from the corresponding anilines), our conditions proved to be more efficient (76 and 56%, respectively).

Our initial study started from methyl 4-hydroxy-7-methoxy-8-methylquinoline-2-carboxylate (**8a**). Its protection using methyl iodide, methoxymethyl chloride or 4-methoxybenzyl chloride in *N*,*N*-dimethylformamide (DMF) with potassium carbonate provided the respective protected compounds **9**. Compounds **9a–c**, when treated with (*S*)-valinol under several conditions, did not react. Since we had previously succeeded in the amidation of methyl or ethyl esters catalyzed by weak Lewis acids,[5] we also explored conditions using $MgCl_2$ or $MgBr_2$. Heating compound **9a** with each of these reagents in acetonitrile



Scheme 3 Synthesis of 2-(4-isopropylthiazol-2-yl)-4,7-dimethoxy-8-methylquinoline (**12a**)

provided good yields of **10a**. Under these and even milder conditions, deprotection of the protecting groups occurred with compounds **9b** and **9c**. In these cases, basic catalysis with sodium methoxide was found to be useful. Transformation of **10a** into the thiazoline compound **11a** was achieved by using P_2S_5 in pyridine. More impurities were present using Lawesson's reagent, and no product was obtained by using P_2S_5–pyridine complex.[6] On the other hand, compounds **10b** and **10c**, when treated either with P_2S_5 in pyridine or with Lawesson's reagent, provided complex mixtures. Final dehydrogenation of **11a** into **12a** was done with MnO_2. We screened MnO_2 from several sources using a range of solvents and found that for all batches of the oxidant, the best results were obtained by using trifluoromethylbenzene as solvent. However, the dehydrogenation step was not robust since it required highly activated reagent for full conversion (Scheme 3).

For the reasons discussed above as well as because of the high price of valinol, we decided to explore other possibilities for the synthesis of **1**. Having access to 4-hydroxyl-protected esters **9a–c**, we tried an approach based on the preparation of thioamides **14** and their alkylation with 1-bromo-3-methylbutan-2-one, as shown in Scheme 4. The thionation of all three amides **13** was achieved with Lawesson's reagent at room temperature, although long reaction times were necessary for **13b** and **13c** and a complex mixture was obtained after prolonged reaction time. When P_2S_5 in pyridine was used for thionation of **13a**, mainly the corresponding nitrile **15** was detected by LC-MS.

Reaction of thioamide **14a** with 1-bromo-3-methylbutan-2-one under various conditions was evaluated, and good yields of the required product **12a** were obtained when the reaction was performed in methanol at 50 °C. However, even higher yields and greater purity was achieved by prolonged stirring at room temperature (Scheme 4).

When the reaction was performed under similar conditions in the presence of potassium carbonate, the reaction was fast, leading to a compound showing the HRMS of $C_{18}H_{23}N_2O_3S$ $[M+H]^+$. From two possible isomers **16** or **17** (Figure 2), the latter was suggested for the product based on the ^{13}C NMR and IR spectra. Its prolonged heating in isopropanol led to compound **12a**.

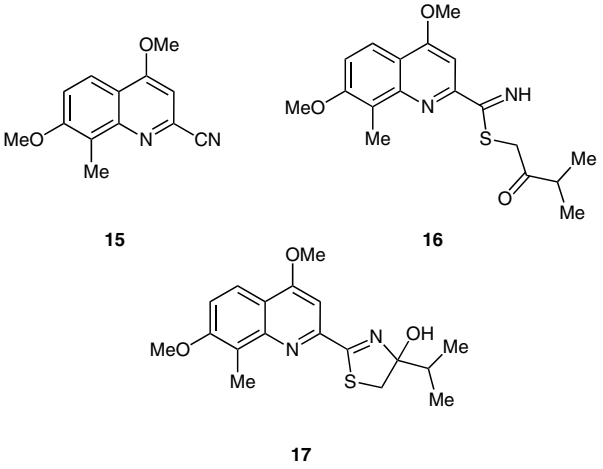
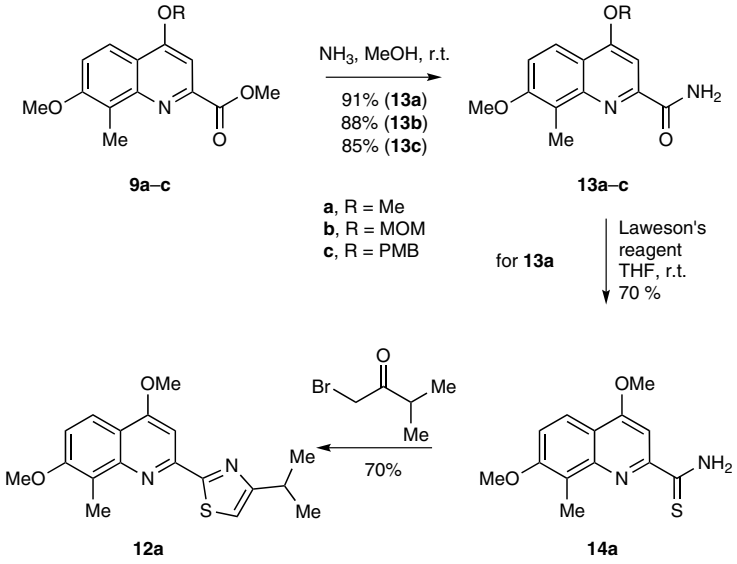


Figure 2 Nitrile **15** and possible structures of a compound with formula $C_{18}H_{23}N_2O_3S$ $[M+H]^+$

Since the thionation of **13b** and **13c** with Lawesson's reagent to higher conversion was accompanied by the formation of extensive side products, the reaction was stopped after five hours (about 50% conversion), the mixture was worked-up and then treated with 1-bromo-3-methylbutan-2-one. A low yield of **12c** (about 12%) was obtained by centrifugally accelerated axial chromatography of the crude reaction mixture. However, we failed to obtain **12b** by a similar procedure.



Scheme 4 Synthesis of 2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolines **12**

Final deprotection of **12a** leading to the desired quinoline building block **1** was accomplished by heating to reflux with aqueous 5–10% HCl. Interestingly, essentially no reaction was detected at room temperature after 24 hours. On the other hand, heating with concentrated HCl led to tar products formation.

Since the price of starting 3-methoxy-2-methylaniline is rather high, we also considered some alternatives. Starting with inexpensive anilines, compounds **8b**–**e** were prepared via the corresponding intermediates **7**. With the exception of the nitro-derivative **7e**, all the cyclizations were again performed with Eaton's reagent.

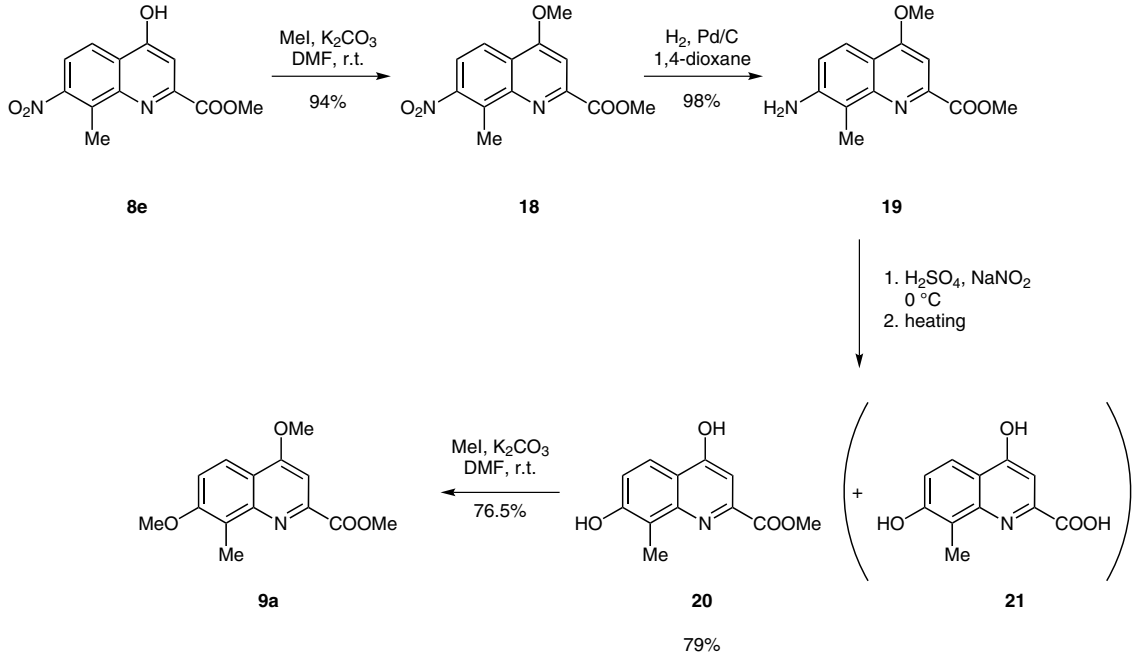
For compound **8b**, we attempted to develop conditions for selective generation of the C-8 carbanion, which, after dimethylation, can provide compound **9a** directly. However, all the experiments failed, giving mostly complex mixtures. Similar results were obtained by methylation of methyl 4,7-dimethoxyquinoline-2-carboxylate.

With compounds **8c**–**e**, we attempted to develop reaction conditions that were suitable for nucleophilic substitution of the C-7 substituent with methoxide anion. However, this chemistry also failed.

The last approach studied started from compound **8e**. Attempts to reduce the nitro moiety into an amino group were complicated by very low solubility in suitable solvents. Therefore the compound was transformed into 4-methoxy derivative **18** and a methanolic solution of this intermediate was smoothly hydrogenated on Pd to give **19**, which was transformed into **20** by diazotation followed by acid hydrolysis. During this treatment, the 4-methoxy group was demethylated and also partial ester hydrolysis to the acid **21** was observed. However, under optimized conditions, less than 3% (NMR) yield of **21** was observed. Compound **20** was then methylated with iodomethane to provide good yield of the required intermediate **9a** (Scheme 5).

In conclusion, we have described two methods of synthesis of **1**, which is a building block of simeprevir. For both methods, protection of the 4-OH group in the form of the 4-methoxy group was found to be superior to the other tested possibilities (*O*-MOM, *O*-PMB), which were not stable in at least one of the reaction steps. The first method, which consists of seven steps from 3-methoxy-2-methylaniline, based on the formation of dihydrothiazole **11a** and its dehydrogenation, provides **1** in an overall yield of 15.5%. Although the yield was better than most of the published yields, the price of valinol disfavored the process. The second method, based on the preparation of thioamide **14a** and its reaction with 1-bromo-3-methylbutan-2-one, provided **1** in seven steps in an overall yield of 28%, based on the respective aniline. The method provides high purity compound without the need for chromatographic purification in any step, which makes it superior to the existing synthetic methodologies.

All solvents and reagents were purchased from commercial sources and used without additional purification. Melting points were measured with a Kofler block and are uncorrected. NMR experiments were carried out with a Bruker Avance 250 spectrometer at 250.13 MHz (^{1}H) and 62.59 MHz (^{13}C); $CDCl_3$ was used as reference [δ = 7.26 (^{1}H) and 77.0 (^{13}C) ppm]. IR spectra were measured with an FTIR Nicolet Nexus (Thermo, USA) spectrometer using ZnSe ATR crystal technique by accumulation of 64 scans with 4 cm^{-1} resolution. UV spectra were recorded in MeOH with a Lambda 25 spectrophotometer (Perkin–Elmer, USA) in the range 200–700 nm. Mass spectra [MS/MS; ionization mode APCI(+)] were measured with an API 3000 PE machine (Sciex Instruments, Applied Biosystems). The purity of the prepared substances was evaluated by TLC



Scheme 5 An alternative method of synthesis of methyl 4,7-dimethoxy-8-methylqinoline-2-carboxylate (**9a**)

on silica gel (FP KG F 254, Merck) and with a HP Agilent 1050 HPLC system [Phenomenex Luna 5 μm C18(2); 0.25 m × 4.6 mm] with UV detection (240 nm) and gradient elution with mobile phase A [phosphate buffer (1.2 g NaH_2PO_4 diluted in 1000 mL of H_2O), pH adjusted to 3.0 with 50% phosphoric acid] and mobile phase B (MeOH). The results are given as LCAP (liquid chromatography area percent). Flash chromatography was performed on silica gel Merck, particle size 0.04–0.063 mm. Centrifugally accelerated axial chromatography was performed with a Cyclograph instrument (Analtech) with silica gel pre-scraped rotors.

With the exception of compounds **1**[1–3], **8a**,[4b] and **8b**,[4b,7] which were characterized only by NMR and/or MS data, the synthesized compounds were not previously described.

Dimethyl 2-(3-Methoxy-2-methylphenylamino)-2-butenedioate (7a)

A solution of dimethyl acetylenedicarboxylate (17 g, 0.12 mol) in MeOH (20 mL) was added dropwise over 1 h to a solution of 3-methoxy-2-methylaniline (13.7 g, 0.1 mol) in MeOH (80 mL) stirred at r.t., and the mixture was stirred at r.t. for an additional 4 h. Evaporation of MeOH provided **7a** (29.7 g; quantitative yield corresponds to 27.9 g) of yellowish oil (HPLC purity 93.5%), which was used for the following step without further purification.

Dimethyl 2-(2-Methyl-3-nitrophenylamino)-2-butenedioate (7e)

A solution of dimethyl acetylenedicarboxylate (6.8 g, 47.9 mmol) in MeOH (20 mL) was added dropwise over 1 h to a solution of 2-methyl-3-nitroaniline (6.0 g, 39.4 mol) in MeOH (80 mL) stirred at r.t., and the mixture was mechanically stirred at r.t. for an additional 2 h. The very thick suspension formed was allowed to stand overnight in a fridge, then the insoluble portion was filtered off, washed with MeOH, and dried.

Yield: 10.2 g (88%); yellow crystals; HPLC purity 96.5%; mp 101–104 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.58 (s, 1 H, CH), 7.58 (d, *J* = 7.5 Hz, 1 H, H-4), 7.60 (m, 1 H, H-5), 6.96 (d, *J* = 7.5 Hz, 1 H, H-6), 5.60 (s, 1 H, NH), 3.77 (s, 3 H, COOMe), 3.69 (s, 3 H, COOMe), 2.48 (s, 3 H, Me).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 169.93, 163.99, 147.59, 141.27, 126.37, 125.48, 120.20, 96.10, 52.70, 51.48, 13.73.

HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{15}N_2O_6$: 295.0930; found: 295.0927.

Methyl 4-Hydroxy-7-methoxy-8-methylquinoline-2-carboxylate (8a)

Eaton's reagent (100 mL) was added to crude **7a** (29.7 g) and the mixture was stirred at 50 °C for 1 h. The mixture was poured on ice (250 g) and the mixture was neutralized with 20% NaOH. The formed precipitate was filtered off, washed with H_2O, and dried. Recrystallization (MeOH) gave **8a**.

Yield: 18.7 g (76% based on 3-methoxy-2-methylaniline); white crystals; HPLC purity 99.2%; mp 198–203 °C.

IR: 3399 (O-H), 1718 (C=O), 1614 [$(C=C)_{Ar}$+$(C=N)_{Ar}$], 1265 (C-O), 1184 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.82 (br s, 1 H, OH), 8.26 (d, *J* = 10.0 Hz, 1 H, H-5), 7.06 (d, *J* = 10.0 Hz, 1 H, H-6), 6.93 (s, 1 H, H-3), 4.06 (s, 3 H, MeO), 3.99 (s, 3 H, MeO), 2.42 (s, 3 H, Me).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 179.56, 163.76, 160.22, 138.92, 135.92, 125.56, 120.80, 111.11, 110.69, 109.06, 56.09, 53.79, 8.52.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{14}NO_4$: 248.0923; found: 248.0907.

UV: λ_{max} (log ε) = 224 (4.71), 249 (4.52) nm.

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.22; H, 5.21; N, 5.73.

Compounds **8b–d** were obtained from the corresponding aniline derivative by using the same procedure.

Methyl 4-Hydroxy-7-methoxyquinoline-2-carboxylate (8b)

Yield: 56% (two steps); HPLC purity 99.5%; mp 246–250 °C.

IR: 3075 [(O-H)+(C-H)], 2948, 1725 (C=O), 1615 [$(C=C)_{Ar}$+$(C=N)_{Ar}$], 1256 (C-O), 1135 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 11.63 (br s, 1 H, OH), 8.00 (d, *J* = 7.5 Hz, 1 H, H-5), 7.31 (s, 1 H, H-8), 6.84 (d, *J* = 7.5 Hz, 1 H, H-6), 6.66 (s, 1 H, H-3), 3.94 (s, 3 H, MeO), 3.82 (s, 3 H, MeO).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 162.87, 158.77, 142.16, 136.96, 126.72, 120.81, 114.60, 111.08, 99.91, 55.38, 53.23.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{12}NO_4$: 234.0766; found: 234.0764.

UV: λ_{max} (log ε) = 243 (4.51), 333 (4.11) nm.

Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.93; H, 5.06; N, 5.87.

Methyl 7-Fluoro-4-hydroxy-8-methylquinoline-2-carboxylate (8c)

Yield: 77% (two steps); HPLC purity 96.7%; mp 171–174 °C.

IR: 3375 (O-H), 1723 (C=O), 1593 [$(C=C)_{Ar}$+$(C=N)_{Ar}$], 1269 (C-O), 1137 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.80 (br s, 1 H, OH), 8.26 (m, 1 H, H-5), 7.12 (m, 1 H, H-6), 6.98 (s, 1 H, H-3), 4.08 (s, 3 H, MeO), 2.46 (s, 3 H, Me).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 178.91, 165.13, 163.32, 161.14, 139.42, 139.28, 136.38, 126.26, 126.08, 122.79, 122.76, 113.63, 113.23, 111.71, 111.22, 110.90, 54.00, 39.46.

UV: λ_{max} (log ε) = 240 (4.14), 341 (3.83) nm.

Anal. Calcd for $C_{12}H_{10}FNO_3$: C, 61.28; H, 4.29; N, 5.95. Found: C, 61.43; H, 4.17; N, 6.03.

Methyl 7-Chloro-4-hydroxy-8-methylquinoline-2-carboxylate (8d)

Yield: 68% (two steps); HPLC purity 97.5%; mp 205–208 °C.

IR: 3382 (O-H), 1721 (C=O), 1592 [$(C=C)_{Ar}$+$(C=N)_{Ar}$], 1270 (C-O), 1149 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.90 (br s, 1 H, OH), 8.17 (d, *J* = 7.5 Hz, 1 H, H-5), 7.39 (d, *J* = 7.5 Hz, 1 H, H-6), 6.99 (s, 1 H, H-3), 4.08 (s, 3 H, MeO), 2.62 (s, 3 H, Me).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 179.29, 163.42, 139.01, 138.46, 136.03, 125.59, 125.04, 124.86, 122.97, 111.93, 54.00, 13.34.

UV: λ_{max} (log ε) = 240 (4.46), 343 (4.04) nm.

Anal. Calcd for $C_{12}H_{10}ClNO_3$: C, 57.27; H, 4.01; N, 5.57. Found: C, 57.41; H, 3.94; N, 5.62.

Methyl 4-Hydroxy-8-methyl-7-nitroquinoline-2-carboxylate (8e)

Compound **7e** (9.6 g, 32.6 mmol) was added portionwise during 10 min into Dowtherm A (100 mL) stirred at 250 °C and the mixture was stirred at this temperature for 30 min. The mixture was stirred overnight at r.t., then hexane (100 mL) was added and the insoluble portion was filtered off, washed with hexane, and dried to provide **8e** (HPLC purity 95.2%). A sample was crystallized from MeOH to achieve HPLC purity 97.8%.

Yield: 6.5 g (76%); mp 195–201 °C.

IR: 3371 (O-H), 1723 (C=O), 1599 [$(C=C)_{Ar}$+$(C=N)_{Ar}$], 1535 (N=O), 1358, 1281 (C-O), 1141 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.05 (br s, 1 H, OH), 8.33 (d, *J* = 7.5 Hz, 1 H, H-5), 7.68 (d, *J* = 7.5 Hz, 1 H, H-6), 7.02 (s, 1 H, H-3), 4.08 (s, 3 H, MeO), 2.66 (s, 3 H, Me).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 178.75, 163.10, 152.54, 138.34, 137.01, 127.51, 125.86, 120.36, 118.84, 112.60, 54.26, 12.31.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}N_2O_5$: 263.0668; found: 263.0662.

UV: λ_{max} (log ε) = 349 (3.98) nm.

Anal. Calcd for $C_{12}H_{10}N_2O_5$: C, 54.97; H, 3.84; N, 10.68. Found: C, 55.12; H, 3.75; N, 10.81.

Methyl 4,7-Dimethoxy-8-methylquinoline-2-carboxylate (9a)
Iodomethane (16.6 mL) was added via septum to a stirred mixture of **8a** (16.6 g, 67.1 mmol), K_2CO_3 (15 g), and anhydrous DMF (160 mL), and the mixture was stirred at r.t. for 5 h. The mixture was poured into H_2O (500 mL), and the formed precipitate was filtered off, washed with H_2O and dried to give **9a**.

Yield: 16.7 g (95%); white powder; HPLC purity 99.1%; mp 178–181 °C.

IR: 3008 (C-H), 2943, 1729 (C=O), 1611 [$(C=C)_{Ar}$+$(C=N)_{Ar}$], 1220 (C-O), 1141 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 7.5 Hz, 1 H, H-5), 7.47 (s, 1 H, H-3), 7.36 (d, *J* = 7.5 Hz, 1 H, H-6), 4.12 (s, 3 H, MeO), 4.08 (s, 3 H, MeO), 4.02 (s, 3 H, MeO), 2.76 (s, 3 H, Me).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 166.72, 163.52, 158.20, 148.71, 148.34, 123.13, 119.95, 117.03, 113.87, 98.00, 56.24, 55.96, 53.04, 10.16.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}NO_4$: 262.1079; found: 262.1074.

UV: λ_{max} (log ε) = 247 (4.86), 293 (4.00) nm.

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.44; H, 5.37; N, 5.45.

Methyl 7-Methoxy-4-(methoxymethoxy)-8-methyl-quinoline-2-carboxylate (9b)
Prepared from **8a** (2.5 g, 10 mmol) and methoxymethyl chloride (1.1 g, 13.7 mmol).

Yield: 2.3 g (79%); creamy powder; HPLC purity 99.7%; mp 104–105 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 10.0 Hz, 1 H, H-5), 7.61 (s, 1 H, H-3), 7.35 (d, *J* = 10.0 Hz, 1 H, H-6), 5.48 (s, 2 H, CH_2), 4.03 (s, 3 H, MeO), 3.99 (s, 3 H, MeO), 3.55 (s, 3 H, MeO), 2.73 (s, 3 H, Me).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 166.42, 160.84, 158.14, 148.58, 148.55, 123.22, 119.89, 117.10, 114.05, 100.61, 94.37, 56.79, 56.22, 52.95, 10.09.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{18}NO_5$: 292.1185; found: 292.1174.

UV: λ_{max} (log ε) = 232 (4.43), 339 (3.93) nm.

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.9. Found: C, 62.16; H, 5.51; N, 5.12.

Methyl 7-Methoxy-4-(4-methoxybenzyloxy)-8-methylquinoline-2-carboxylate (9c)
Prepared from **8a** (2.5 g, 10 mmol) and 4-methoxybenzyl chloride (1.75 g, 11.2 mmol).

Yield: 2.7 g (73%); creamy powder; HPLC purity 97.5%; mp 157–161 °C.

IR: 2952 (C-H), 2837, 1713 (C=O), 1609 [$(C=C)_{Ar}$+$(C=N)_{Ar}$], 1243 (C-O), 1166 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.5 Hz, 1 H, H-5), 7.54 (s, 1 H, H-3), 7.45 (d, *J* = 10.0 Hz, 2 H, H-2′, H-6′), 7.30 (d, *J* = 7.5 Hz, 1 H, H-6), 6.96 (d, *J* = 10.0 Hz, 2 H, H-3′, H-5′), 5.25 (s, 2 H, CH_2), 4.05 (s, 3 H, MeO), 3.97 (s, 3 H, MeO), 3.84 (s, 3 H, MeO), 2.73 (s, 3 H, Me).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 166.71, 162.62, 159.80, 158.23, 148.65, 148.45, 129.56, 127.71, 123.08, 120.23, 117.14, 114.14, 113.82, 98.97, 70.41, 56.24, 55.35, 53.08, 10.19.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}NO_5$: 368.1498; found: 368.1491.

UV: λ_{max} (log ε) = 248 (4.74), 292 (4.06) nm.

Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.88; H, 5.56; N, 3.95.

***N*-(*R*)-(1-Hydroxy-3-methylbutan-2-yl)-4,7-dimethoxy-8-methylquinoline-2-carboxamide (10a)**
A mixture of **9a** (2.6 g, 10 mmol), anhydrous $MgCl_2$ (7 g), anhydrous MeCN (50 mL), and L-valinol (3.1 g, 30 mmol) was stirred at 80 °C for 20 h. The residue after evaporation was triturated with cold water and the insoluble portion was filtered off, washed with H_2O, and dried to give **10a**.

Yield: 3.2 g (96%); white crystals; HPLC purity 99.4%; mp 135–140 °C.

IR: 3431 [(N-H)+(O-H)], 3350, 2958 (C-H), 2869, 1665 (C=O), 1613 [$(C=C)_{Ar}$+$(C=N)_{Ar}$], 1505 δ(N-H), 1266 (C-O) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.67 (br d, 1 H, NH), 8.08 (d, *J* = 7.5 Hz, 1 H, H-5), 7.55 (s, 1 H, H-3), 7.31 (d, *J* = 7.5 Hz, 1 H, H-6), 4.10 (s, 3 H, MeO), 4.00 (s, 3 H, MeO), 3.95 (m, 1 H, NCH), 3.85 (m, 2 H, CH_2O), 2.65 (s, 3 H, Me), 2.18 (m, 1 H, CH), 1.64 (br s, 1 H, OH), 1.10 (s, 3 H, *i*-Pr), 1.07 (s, 3 H, *i*-Pr).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 166.30, 164.04, 158.13, 150.35, 121.71, 120.28, 116.91, 113.38, 95.65, 64.93, 58.10, 56.30, 56.08, 29.37, 19.81, 18.36, 9.95.

HRMS: *m*/*z* [M + H]$^+$ for $C_{18}H_{25}N_2O_4$: 333.1814; found: 333.1807.

UV: λ_{max} (log ε) = 214 (4.48), 246 (4.77), 295 (3.95), 306 (3.91), 344 (3.68) nm.

Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 64.87; H, 7.13; N, 8.57.

***N*-(*R*)-(1-Hydroxy-3-methylbutan-2-yl)-7-methoxy-4-(methoxymethoxy)-8-methylquinoline-2-carboxamide (10b)**
A mixture of **9b** (2.9 g, 10 mmol), MeONa (0.54 g, 10 mmol), toluene (50 mL) and L-valinol (1.5 g, 15 mmol) was stirred at 80 °C for 1 h. The residue after evaporation was triturated with cold H_2O, acidified with acetic acid and the insoluble portion was filtered off, washed with H_2O and dried to give **10b**.

Yield: 2.4 g (66%); white crystals; HPLC purity 98.2%.

IR: 3456 [(N-H)+(O-H)], 3366, 2860 (C-H), 1661 (C=O), 1613 [$(C=C)_{Ar}$+$(C=N)_{Ar}$], 1509 δ(N-H), 1269 (C-O) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.63 (br d, 1 H, NH), 8.10 (d, *J* = 5.0 Hz, 1 H, H-5), 7.70 (s, 1 H, H-3), 7.31 (d, *J* = 5.0 Hz, 1 H, H-6), 5.48 (s, 2 H, CH_2), 3.97 (s, 3 H, MeO), 3.94 (m, 1 H, NCH), 3.83 (m, 2 H, CH_2O), 3.54 (s, 3 H, MeO), 3.28 (br s, 1 H, OH), 2.64 (s, 3 H, Me), 2.12 (m, 1 H, CH), 1.09 (s, 3 H, *i*-Pr), 1.07 (s, 3 H, *i*-Pr).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 166.03, 161.30, 158.07, 150.22, 147.42, 121.79, 120.21, 117.00, 113.55, 98.17, 94.44, 64.73, 57.98, 56.30, 56.78, 56.28, 29.29, 19.77, 18.29, 9.86.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{27}N_2O_5$: 363.1920; found: 363.1912.

UV: λ_{max} (log ε) = 214 (4.42), 246 (4.71), 294 (3.85), 305 (3.85), 346 (3.64) nm.

Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73. Found: C, 62.73; H, 7.01; N, 7.93.

***N*-(*R*)-(1-Hydroxy-3-methylbutan-2-yl)-7-methoxy-4-(4-methoxybenzyloxy)-8-methylquinoline-2-carboxamide (10c)**
Obtained analogously to **10b** from 1.84 g (5 mmol) of **9c**.

Yield: 1.8 g (82%); HPLC purity 97.9%.

IR: 3364 [(N-H)+(O-H)], 2961 (C-H), 1676 (C=O), 1613 [(C=C)$_{Ar}$+(C=N)$_{Ar}$], 1507 δ(N-H), 1252 (C-O) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.65 (br d, 1 H, NH), 8.07 (d, *J* = 5.0 Hz, 1 H, H-5), 7.61 (s, 1 H, H-3), 7.42 (d, *J* = 5.0 Hz, 2 H, H-2′, 6′), 7.25 (d, *J* = 5.0 Hz, 1 H, H-6), 6.94 (d, *J* = 5.0 Hz, 2 H, H-3′,5′), 5.23 (q, *J* = 5.0 Hz, 2 H, CH_2O), 3.97 (s, 3 H, MeO), 3.94 (m, 1 H, NCH), 3.85 (m, 2 H, CH_2O), 3.81 (s, 3 H, MeO), 2.63 (s, 3 H, Me), 2.12 (m, 1 H, CH), 1.09 (s, 3 H, *i*-Pr), 1.07 (s, 3 H, *i*-Pr).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 166.13, 163.01, 159.70, 158.05, 150.26, 147.28, 129.43, 127.79, 121.61, 120.43, 116.94, 114.06, 113.22, 96.50, 70.33, 64.66, 57.92, 56.21, 55.28, 29.34, 19.76, 18.30, 9.89.

HRMS: [M + H]$^+$ calcd for $C_{25}H_{31}N_2O_5$: 439.2233; found: 439.2239.

UV: λ_{max} (log ε) = 238 (4.82), 246 (4.84), 295 (3.98), 305 (3.93), 346 (3.72) nm.

Anal. Calcd for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39. Found: C, 68.44; H, 6.78; N, 6.51.

2-(4,7-Dimethoxy-8-methylquinoline-2-yl)-4-isopropyl-4,5-dihydrothiazole (11a)

A mixture of **10a** (6.7 g, 20 mmol), P_2S_5 (6.7 g) and pyridine (100 mL) was stirred at 110 °C under nitrogen for 10 h. The residue after evaporation was triturated with CH_2Cl_2 (250 mL) and the insoluble portion was filtered off and washed with hot CH_2Cl_2 (4 × 50 mL). The combined extracts were evaporated (6.9 g) and purified by flash chromatography (silica; hexane–acetone, 9:1). Evaporation of the combined fractions provided **11a**. A sample crystallized from MeOH provided yellow crystals.

Yield: 3.7 g (56%); yellowish solid; HPLC purity 99.0%; mp 89–94 °C.

IR: 2960 (C-H), 2917, 2849, 1613 [(C=C)$_{Ar}$+(C=N)$_{Ar}$], 1260 (C-O) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 7.5 Hz, 1 H, H-5), 7.42 (s, 1 H, H-3), 7.27 (d, *J* = 7.5 Hz, 1 H, H-6), 4.58 (m, 1 H, =NCH), 4.09 (s, 3 H, MeO), 3.98 (s, 3 H, MeO), 3.36 (m, 1 H, CH_2S), 3.10 (m, 1 H, CH_2S), 2.69 (s, 3 H, Me), 2.18 (m, 1 H, CH), 1.16 (s, 3 H, *i*-Pr), 1.06 (s, 3 H, *i*-Pr).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 170.90, 162.76, 157.96, 151.76, 148.16, 122.57, 119.92, 116.70, 112.94, 95.23, 84.81, 56.22, 55.88, 33.67, 33.42, 19.84, 18.84, 9.94.

HRMS: *m*/*z* [M + H]$^+$ for $C_{18}H_{23}N_2O_2S$: 331.1480; found: 331.1477.

UV: λ_{max} (log ε) = 253 (4.61), 305 (3.90), 292 (3.98) nm.

Anal. Calcd for $C_{18}H_{22}N_2O_2S$: C, 65.42; H, 6.71; N, 8.48. Found: C, 65.38; H, 6.65; N, 8.62.

2-(4,7-Dimethoxy-8-methylquinoline-2-yl)-4-isopropylthiazole (12a); Method A

A mixture of **11a** (1 g, 3 mmol), trifluoromethylbenzene (10 mL) and activated MnO_2 (Alfa Aesar, Lot USLF005538; 2.5 g) was heated at reflux for 24 h. The mixture was filtered through Celite, the cake was washed with hot trifluoromethylbenzene (4 × 5 mL), the combined filtrates were evaporated and the residue was crystallized from MeOH to give **12a**.

Yield: 0.5 g (50%); white crystals; HPLC purity 95.7%; mp 104–106 °C.

IR: 2959 (C-H), 2931, 2868, 1608 [(C=C)$_{Ar}$+(C=N)$_{Ar}$], 1265 (C-O) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.5 Hz, 1 H, H-5), 7.56 (s, 1 H, H-3), 7.22 (d, *J* = 7.5 Hz, 1 H, H-6), 7.02 (s, 1 H, H-5′), 4.14 (s, 3 H, MeO), 3.98 (s, 3 H, MeO), 3.20 (m, 1 H, CH), 2.70 (s, 3 H, Me), 1.40 (s, 3 H, *i*-Pr), 1.38 (s, 3 H, *i*-Pr).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 169.70, 164.54, 162.76, 157.65, 151.65, 148.10, 121.55, 119.65, 116.10, 113.76, 111.86, 94.00, 55.84, 55.56, 30.73, 22.10, 9.51.

HRMS: *m*/*z* [M + H]$^+$ for $C_{18}H_{21}N_2O_2S$: 329.1324; found: 329.1319.

UV: λ_{max} (log ε) = 223 (4.51), 237 (4.51), 331 (4.26) nm.

Anal. Calcd for $C_{18}H_{20}N_2O_2S$: C, 65.83; H, 6.14; N, 8.53. Found: C, 65.66; H, 6.21; N, 8.71.

4,7-Dimethoxy-8-methylquinoline-2-carboxamide (13a)

A mixture of **9a** (2.6 g, 10 mmol) and sat. ammonia in MeOH (25 mL) was stirred at r.t. in a pressure flask for 24 h (when commercial 7 M solution was used, prolonged time of about 3–4 days was necessary for full conversion). The flask was placed in a refrigerator overnight, then the insoluble portion was filtered off and dried to give **13a**.

Yield: 2.25 g (91%); white crystals; HPLC purity 99.7%; mp 187–191 °C.

IR: 3427 (N-H), 3191, 2934 (C-H), 2836, 1694 (C=O), 1611 [(C=C)$_{Ar}$+(C=N)$_{Ar}$], 1257 (C-O), 1138 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.21 (br s, 1 H, NH_2), 8.05 (d, *J* = 7.5 Hz, 1 H, H-5), 7.73 (br s, 1 H, NH_2), 7.50 (d, *J* = 7.5 Hz, 1 H, H-6), 7.46 (s, 1 H, H-3), 4.08 (s, 3 H, MeO), 3.95 (s, 3 H, MeO), 2.61 (s, 3 H, Me).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 166.52, 163.26, 157.83, 151.44, 146.90, 121.04, 119.90, 115.96, 113.77, 95.65, 56.18, 56.77, 10.12.

HRMS: *m*/*z* [M + H]$^+$ for $C_{13}H_{15}N_2O_3$: 247.1083; found: 247.1080.

UV: λ_{max} (log ε) = 214 (4.43), 246 (4.70), 292 (3.85), 303 (3.82), 346 (3.55) nm.

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.52; H, 5.55; N, 11.52.

7-Methoxy-4-(methoxymethoxy)-8-methylquinoline-2-carboxamide (13b)

Prepared from 1.45 g (5 mmol) of **9b**.

Yield: 1.2 g (88%); white crystals; HPLC purity 99.1%; mp 192–197 °C.

IR: 3403 (N-H), 3150, 2921 (C-H), 2835, 1685 (C=O), 1611 [(C=C)$_{Ar}$+(C=N)$_{Ar}$], 1254 (C-O), 1140 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.19 (br s, 1 H, NH_2), 8.08 (d, *J* = 7.5 Hz, 1 H, H-5), 7.73 (br s, 1 H, NH_2), 7.60 (s, 1 H, H-3), 7.51 (d, *J* = 7.5 Hz, 1 H, H-6), 5.56 (s, 2 H, CH_2), 3.98 (s, 3 H, MeO), 3.49 (s, 3 H, MeO), 2.63 (s, 3 H, Me).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 166.35, 160.58, 157.74, 151.00, 147.04, 121.03, 119.86, 116.13, 113.82, 98.00, 94.18, 56.28, 56.06, 9.94.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}N_2O_4$: 277.1188; found: 277.1196.

UV: λ_{max} (log ε) = 225 (4.46), 246 (4.72), 292 (3.82), 303 (3.78), 347 (3.60) nm.

Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 61.03; H, 5.77; N, 10.21.

7-Methoxy-4-(4-methoxybenzyloxy)-8-methylquinoline-2-carboxamide (13c)

Prepared from 1.8 g (5 mmol) of **9c**.

Yield: 1.5 g (85%); white crystals; HPLC purity 99.8%; mp 178–180 °C.

IR: 3422 (N-H), 3138, 2994 (C-H), 2918, 1704 (C=O), 1611 [(C=C)$_{Ar}$+(C=N)$_{Ar}$], 1255 (C-O), 1175 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.23 (br s, 1 H, NH_2), 8.03 (d, *J* = 10 Hz, 1 H, H-5), 7.73 (br s, 1 H, NH_2), 7.58 (s, 1 H, H-3), 7.47–

7.52 (m, 3 H, H-6 + ArH), 6.97 (d, J = 7.5 Hz, 2 H, ArH), 5.37 (s, 2 H, CH_2), 3.96 (s, 3 H, MeO), 3.78 (s, 3 H, MeO), 2.62 (s, 3 H, Me).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 166.44, 162.19, 159.21, 157.79, 151.30, 146.93, 129.51, 127.97, 120.98, 119.97, 116.08, 113.95, 113.75, 96.70, 69.76, 56.11, 55.10, 10.04.

HRMS: m/z [M + H]$^+$ calcd for $C_{20}H_{21}N_2O_4$: 353.1501; found: 353.1493.

UV: λ_{max} (log ε) = 231 (4.70), 247 (4.75), 280 (3.93), 293 (3.88), 347 (3.71) nm.

Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.32; H, 5.55; N, 8.01.

4,7-Dimethoxy-8-methylquinoline-2-carboxthioamide (14a)
Lawesson's reagent (2.8 g, 6.9 mmol) was added to a stirred suspension of **13a** (2.8 g, 11.4 mmol) in THF (80 mL) and the mixture was stirred under nitrogen for 5 h. The formed dark-reddish-brown mixture was poured into H_2O (70 mL) and extracted with EtOAc (100 mL, 4 × 25 mL). The combined extracts were dried ($MgSO_4$) and evaporated to give an orange residue (5.1 g; HPLC 52.2%). Crystallization from MeOH provided **14a**.

Yield: 2.1 g (70%); yellow crystals; HPLC purity 99.8%; mp 184–186 °C.

IR: 3368 (N-H), 3235, 2916 (C-H), 1584 δ(N-H), 1252 (C=S) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.89 (br s, 1 H, NH_2), 8.12 (s, 1 H, H-3), 8.09 (d, J = 7.5 Hz, 1 H, H-5), 7.69 (br s, 1 H, NH_2), 7.32 (d, J = 7.5 Hz, 1 H, H-6), 4.14 (s, 3 H, MeO), 4.00 (s, 3 H, MeO), 2.64 (s, 3 H, Me).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 197.01, 163.18, 158.26, 150.60, 146.49, 120.09, 120.23, 116.76, 113.73, 98.07, 56.28, 56.07, 10.06.

HRMS: m/z [M + H]$^+$ calcd for $C_{13}H_{15}N_2O_2S$: 263.0854; found: 263.0848.

UV: λ_{max} (log ε) = 212 (4.63), 224 (4.59), 257 (4.63), 315 (4.29) nm.

Anal. Calcd for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68. Found: C, 59.36; H, 5.31; N, 10.83.

4,7-Dimethoxy-8-methylquinoline-2-carbonitrile (15)
A mixture of **13a** (0.25 g, 1 mmol), P_2S_5 (0.2 g) and pyridine (7.5 mL) was stirred at 100 °C for 4 h (TLC showed full conversion). The mixture was evaporated, the residue was triturated with CH_2Cl_2 (5 mL) and 5% aqueous HCl (2 mL) and then extracted with CH_2Cl_2 (2 × 5 mL). The organic phase was washed with brine and dried with $MgSO_4$, and the residue after evaporation was crystallized from MeOH to provide **15**.

Yield: 0.15 g (66%); off-white crystals; mp 182–186 °C.

IR: 3091 (C-H), 2922, 2838, 2237 (C≡N), 1609 [(C=C)$_{Ar}$+(C=N)$_{Ar}$], 1588, 1264 (C-O) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.09 (d, J = 7.5 Hz, 1 H, H-5), 7.36 (d, J = 7.5 Hz, 1 H, H-6), 7.26 (s, 1 H, H-3), 4.07 (s, 3 H, MeO), 4.00 (s, 3 H, MeO), 2.64 (s, 3 H, Me).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 163.20, 158.66, 134.05, 122.88, 120.15, 118.21, 116.54, 114.45, 100.72, 56.24, 56.16, 9.97.

HRM: m/z [M + H]$^+$ calcd for $C_{13}H_{13}N_2O_2$: 229.0977; found: 229.0989.

UV: λ_{max} (log ε) = 209 (5.06), 247 (4.64), 268 (4.02), 293 (3.74), 304 (3.64), 352 (3.44) nm.

Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.54; H, 5.22; N, 12.41.

2-(4,7-Dimethoxy-8-methylquinoline-2-yl)-4-isopropylthiazole (12a); Method B
1-Bromo-3-methylbutan-2-one (1 g, 6 mmol) was added via septum to a solution of **14a** (1.31 g, 5 mmol) in MeOH (35 mL) and the mixture was stirred at r.t. for two days. The mixture was evaporated, the residue was triturated with 10% solution of $NaHCO_3$ (10 mL), and the insoluble portion was filtered off, washed with H_2O and dried. Recrystallization from MeOH provided **12a**.

Yield: 1.25 g (76%); creamy crystals; HPLC purity 99.3%; mp 112–115 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.03 (d, J = 7.5 Hz, 1 H, H-5), 7.56 (s, 1 H, H-3), 7.22 (d, J = 7.5 Hz, 1 H, H-6), 7.02 (s, 1 H, H-5′), 4.14 (s, 3 H, MeO), 3.98 (s, 3 H, MeO), 3.20 (m, 1 H, CH), 2.70 (s, 3 H, Me), 1.40 (s, 3 H, *i*-Pr), 1.38 (s, 3 H, *i*-Pr).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 169.70, 164.54, 162.76, 157.65, 151.65, 148.10, 121.55, 119.65, 116.10, 113.76, 111.86, 94.00, 55.84, 55.56, 30.73, 22.10, 9.51.

HRMS: m/z [M + H]$^+$ calcd for $C_{18}H_{21}N_2O_2S$: 329.1324; found: 329.1319.

4,5-Dihydro-4-isopropyl-2-(4,7-dimethoxy-8-methylquinolin-2-yl)thiazol-4-ol (17)
A mixture of **14a** (0.13 g, 0.5 mmol), MeOH (3 mL), K_2CO_3 (0.1 g) and 1-bromo-3-methylbutan-2-one (0.1 g, 0.6 mmol) was stirred at 50 °C for 24 h. The mixture was evaporated, H_2O was added, and the insoluble portion was dried and crystallized from MeOH to give **17**.

Yield: 0.08 g (46%); yellowish crystals; HPLC purity 94.5%; mp 168–184 °C (dec.).

IR: 3150 (O-H), 2950 (C-H), 1614 [(C=C)$_{Ar}$+(C=N)$_{Ar}$], 1587, 1267 (C-O) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.05 (d, J = 5.0 Hz, 1 H, H-5), 7.46 (s, 1 H, H-3), 7.28 (d, J = 5.0 Hz, 1 H, H-6), 4.10 (s, 3 H, MeO), 3.99 (s, 3 H, MeO), 3.46 (d, J = 7.5 Hz, 1 H, CH_2), 3.24 (d, J = 7.5 Hz, 1 H, CH_2), 2.65 (s, 3 H, Me), 2.32 (m, 1 H, CH), 1.15 (d, J = 2.5 Hz, 3 H, Me), 1.03 (d, J = 2.5 Hz, 3 H, Me).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 173.51, 162.95, 158.02, 151.25, 148.12, 122.58, 120.03, 116.89, 113.22, 112.72, 95.52, 56.23, 56.18, 38.30, 38.26, 17.60, 16.99, 9.94.

HRMS: m/z [M + H]$^+$ calcd for $C_{18}H_{23}N_2O_3S$: 347.1429; found: 347.1427.

UV: λ_{max} (log ε) = 209 (5.28), 254 (4.88), 293 (4.15), 304 (4.10) nm.

Anal. Calcd for $C_{18}H_{22}N_2O_3S$: C, 62.40; H, 6.40; N, 8.09. Found: C, 62.12; H, 6.27; N, 7.88.

2-(4,7-Dimethoxy-8-methylquinolin-2-yl)-4-isopropylthiazole (12a); Method C
A solution of compound **17** (50 mg) in 2-propanol (0.5 mL) was heated in a vial at 100 °C for 24 h. HPLC analysis showed full conversion of **17** into **12** (HPLC purity 93.2%).

2-(4-Isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-ol (1)
A mixture of **12a** (0.33 g, 1 mmol) and 10% HCl (7 mL) was heated at reflux under nitrogen for 14 h. The cold mixture was poured into cold H_2O (25 mL), and the insoluble portion was filtered off, washed with H_2O, and dried to give **1**.

Yield: 0.25 g (80%); beige crystals; HPLC purity 96.4%; mp 169–173 °C.

IR: 3301 (O-H), 2964 (C-H), 2173 (C≡N), 1621 [(C=C)$_{Ar}$+(C=N)$_{Ar}$], 1593, 1270 (C-O) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.40 (d, J = 7.5 Hz, 1 H, H-5), 8.38 (s, 1 H, H-5′), 7.40 (d, J = 7.5 Hz, 1 H, H-6), 7.39 (s, 1 H, H-3), 4.10

(s, 3 H, MeO), 3.25 (m, 1 H, CH), 2.57 (s, 3 H, Me), 1.41 (s, 3 H, *i*-Pr), 1.42 (s, 3 H, *i*-Pr).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 173.67, 166.35, 162.25, 156.91, 143.42, 138.47, 125.21, 118.85, 115.38, 113.03, 111.26, 102.16, 56.68, 30.89, 22.37, 8.46.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{19}N_2O_2S$: 315.1167; found: 315.1162.

UV: λ_{max} (log ε) = 228 (4.54), 278 (4.37), 334 (4.36) nm.

Methyl 4-Methoxy-8-methyl-7-nitroquinoline-2-carboxylate (18)

Iodomethane (0.75 mL) was added via septum to a stirred mixture of **8e** (1.3 g, 5 mmol), K_2CO_3 (1.5 g) and anhydrous DMF (25 mL), and the mixture was stirred at r.t. for 6 h. The mixture was poured into H_2O (100 mL), and the formed precipitate was filtered off, washed with H_2O and dried to give **18**. A small sample for elemental analysis was crystallized from 1,4-dioxane.

Yield: 1.3 g (94%); off-white powder; HPLC purity 98.7%; mp 178–180 °C.

IR: 3023 (C-H), 1756 (C=O), 1595 $[(C=C)_{Ar}+(C=N)_{Ar}]$, 1524 (N=O), 1347, 1264 (C-O), 1174 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.21 (m, 1 H, H-5 or H-6), 8.08 (m, 1 H, H-5 or H-6), 7.69 (s, 1 H, H-3), 4.17 (s, 3 H, MeO), 4.00 (s, 3 H, MeO), 2.91 (s, 3 H, Me).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 165.58, 163.57, 150.54, 150.40, 146.85, 133.12, 123.63, 122.26, 121.33, 102.82, 57.45, 53.43, 13.71.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{13}N_2O_5$: 277.0824; found: 277.0819.

UV: λ_{max} (log ε) = 230 (4.38), 265 (4.26), 305 (3.73) nm.

Anal. Calcd for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.33; H, 4.11; N, 10.22.

Methyl 7-Amino-4-methoxy-8-methylquinoline-2-carboxylate (19)

A solution of **18** (0.55 g, 2 mmol) in 1,4-dioxane (10 mL) was hydrogenated over Pd/C (10%, 25 mg) using a balloon overnight. The catalyst was filtered off through Celite, and the residue after evaporation was crystallized from MeOH to give **19**.

Yield: 0.48 g (98%); yellow crystals; HPLC purity 98.2%; mp 152–156 °C.

IR: 3391 (N-H), 3366, 2929 (C-H), 2845, 1704 (C=O), 1631 $[(C=C)_{Ar}+(C=N)_{Ar}]$, 1591, 1253 (C-O), 1183 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.5 Hz, 1 H, H-5), 7.41 (s, 1 H, H-3), 7.07 (d, *J* = 7.5 Hz, 1 H, H-6), 4.09 (s, 3 H, MeO), 4.07 (s, 3 H, MeO), 2.68 (s, 3 H, Me).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 166.81, 163.39, 148.57, 148.21, 145.73, 119.82, 118.86, 115.95, 115.67, 97.44, 55.81, 52.92, 10.60.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{15}N_2O_3$: 247.1083; found: 247.1071.

UV: λ_{max} (log ε) = 211 (5.16), 261 (4.80), 268 (4.73), 376 (3.47) nm.

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.17; H, 5.55; N, 11.52.

Methyl 4,7-Dihydroxy-8-methylquinoline-2-carboxylate (20)

To a cold solution of **19** (0.47 g, 1.9 mmol) in a mixture of concentrated sulfuric acid (1 mL) and H_2O (2 mL) placed in an ice bath, a solution of sodium nitrite (0.18 g) in H_2O (1 mL) was added dropwise. After 30 min stirring in the ice bath, the flask was placed into a bath heated to 80 °C and stirred for 1 h. After cooling, the solution was washed with CH_2Cl_2 (2 × 20 mL), the aqueous layer was neutralized with sat. aq Na_2CO_3, and the insoluble portion was filtered off, washed with H_2O, and dried to give **20**.

Yield: 0.35 g (79%); yellow crystals; HPLC purity 98.9%; mp 213–217 °C.

IR: 3550 (O-H), 3307, 1591 (C=O), 1482 $[(C=C)_{Ar}+(C=N)_{Ar}]$, 1287 (C-O), 1266, 1168 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.03 (s, 1 H, OH), 7.91 (d, *J* = 10.0 Hz, 1 H, H-5), 7.39 (s, 1 H, H-3), 7.30 (d, *J* = 10.0 Hz, 1 H, H-6), 4.08 (s, 3 H, MeO), 2.55 (s, 3 H, Me).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 166.62, 169.99, 156.44, 148.84, 148.08, 119.37, 119.00, 118.49, 115.26, 97.38, 56.09, 10.03.

HRMS: *m*/*z* $[M + H]^+$ calcd $C_{12}H_{12}NO_4$: 234.0766; found: 234.0783.

Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.59; H, 4.54; N, 6.13.

UV: λ_{max} (log ε) = 245 (4.56), 300 (3.90), 317 (3.90) nm.

Methyl 4,7-Dimethoxy-8-methylqinoline-2-carboxylate (9a)

Iodomethane (0.3 mL) was added via septum to a stirred mixture of **20** (0.23 g, 1 mmol), K_2CO_3 (0.7 g) and anhydrous DMF (7 mL) and the mixture was stirred at r.t. for 15 h. The mixture was poured into H_2O (25 mL) and the formed precipitate was filtered off, washed with H_2O and dried to give **9a**.

Yield: 0.18 g (76.5%); white powder; HPLC purity 97.2%.

Data identical to those of **9a** obtained from **7a**.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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