Buchwald-Hartwig vs. Microwave-Assisted Amination of Chloroquinoline – En Route to the Pyoverdin Chromophore

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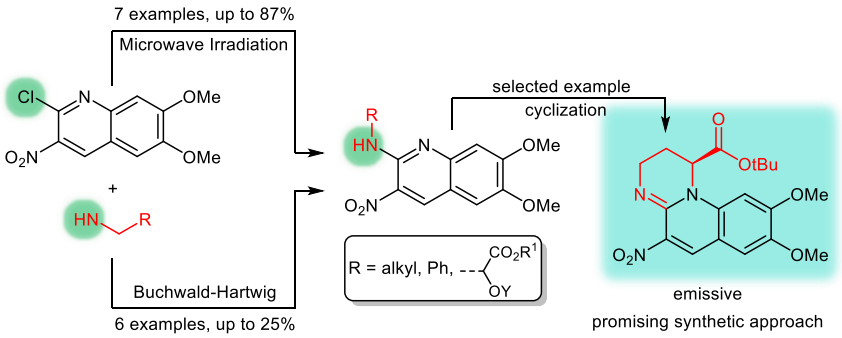
Abstract

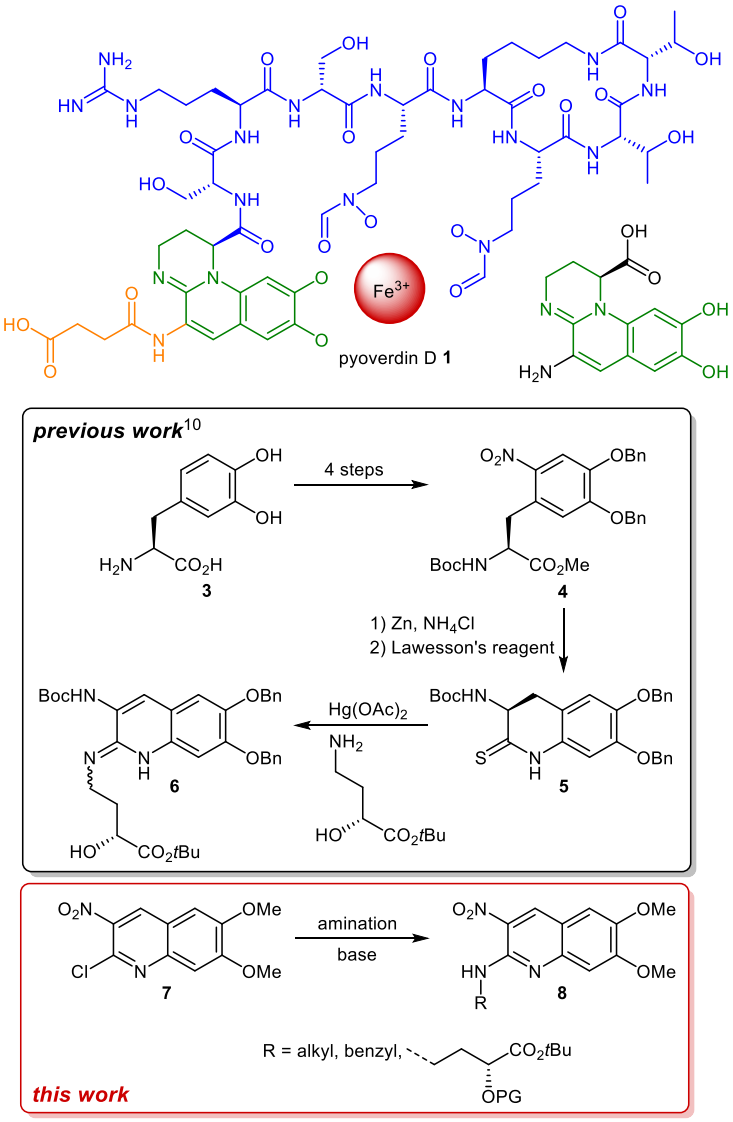


The reaction of 2-chloro-3-nitroquinoline and a series of amines and aminoalkanoates under basic microwave-mediated conditions and Buchwald-Hartwig amination conditions is reported. The microwave irradiation favored the reaction with amines, resulting in yields up to 80%, while amino acid functionalization gave yields comparable to those of Buchwald-Hartwig amination. (2*R*)-4-[(6,7-dimethoxy-3-nitroquinolinyl)amino]-2-hydroxybutanoate could be successfully cyclized to the pyoverdin chromophore, a subunit of siderophores.

Key words amination, 2-amino-3-nitroquinolines, tricyclic chromophore, pyoverdin

Siderophores are a structurally diverse class of high-affinity Fe^{3+} chelating compounds produced by microorganisms. Siderophores usually form stable, hexadentate octahedral complexes preferentially with Fe^{3+} compared to other naturally occurring abundant metal ions.[1] In addition, there is increasing evidence for non-classical functions of siderophores, e.g. Zn^{2+}, Mn^{3+}, Cu^{2+}, V^{5+}, Mo^{4+} binding, transport through bacterial membranes and cell signalling.[1b] When siderophores are covalently linked to antibiotics these hybrids can be used as Trojan horses enabling transport of the antibiotics into the bacterial cell, a strategy which is highly attractive in the fight against antibiotic resistance.[2] Pyoverdins, such as pyoverdin D **1** are siderophores produced by *Pseudomonas aeruginosa* and are essential for pathogenesis in infections due to their capacity to acquire Fe^{3+}. Pyoverdin D **1** consists of a polypeptide fragment (7–14 amino acids) and a tricyclic 5-amino-8,9-dihydroxy-1,2,3,4-tetrahydro-11λ^4-pyrimido[1,2-a]quinoline-1-carboxylic acid chromophore unit **2** (Scheme 1).[3,4]

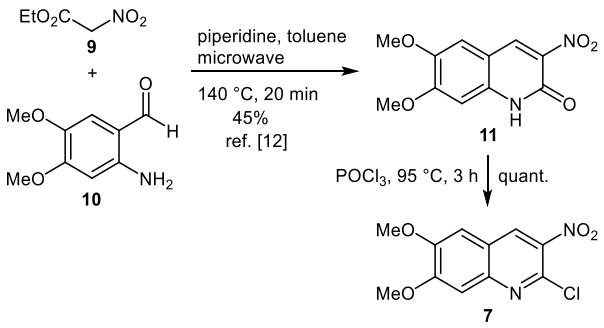
The unique structure of pyoverdins and their biological activity resulted in research efforts regarding spectroscopic properties,[5] biosynthesis,[6] isolation of novel members[7] and studies on hybrids.[8] Surprisingly, the biological role of the chromophoric unit and its contribution to the siderophore function remains virtually unexplored, despite the fact that it contains two of the six iron binding sites.[3] However, in order to be able to study the biology of this subunit, a convenient synthetic access is required. Based on the first racemic synthesis of the chromophore **2** by Miller in 1990,[9] an enantioselective total synthesis of pyoverdin D **1** was reported in 2013 by Mashiach and Meijler (Scheme 1).[10] Key steps of these syntheses were a protection and nitration of DOPA **3**, followed by reductive cyclization and conversion to the thioquinolone **5** with Lawesson's reagent and subsequent Hg^{2+}-mediated amination of the thioamide **5**. Due to the toxicity of these reagents we aimed at an alternative protocol towards 2-functionalized quinolines **6**. We here report on the microwave-assisted basic amination of 2-chloro-3-nitroquinoline **7** and preliminary results regarding the subsequent functionalization towards the pyoverdin chromophore.[11]



Scheme 1

The required 2-chloro-3-nitroquinoline **7** was prepared in two steps by condensation of ethyl 2-nitroacetate **9** and 2-amino-4,5-dimethoxybenzaldehyde **10** in the presence of piperidine in toluene under microwave irradiation as reported by Schwendt and Glasnov[12] to give the 2-nitroquinolone **11** in 45% yield (Scheme 2). Subsequent treatment with $POCl_3$ at 95 °C provided 2-chloro-3-nitroquinoline **7** quantitatively.

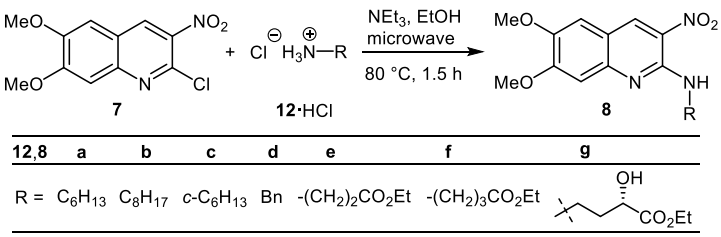
In order to test the substrate scope of the amination reaction, 2-chloro-3-nitroquinoline **7** was treated with different amine hydrochlorides **12**·HCl in the presence of NEt_3 in EtOH at 80 °C under microwave irradiation for 1.5 h (Table 1; see also Supporting Information (SI) and General Procedure A).[13]



Scheme 2 Synthesis of starting 2-chloro-3-nitroquinoline **7** following a literature procedure[12]

For example, *n*-hexylamine hydrochloride **12a**·HCl provided the corresponding *N*-hexyl-aminoquinoline **8a** in 53% after chromatography (entry 1). The higher homologue **12b**·HCl worked equally well yielding the amination product **8b** in 60% (entry 2). In contrast, cyclo-hexylamine hydrochloride **12c**·HCl gave only a crude yield of 9%, from which the desired product **8c** could not be obtained in pure form (entry 3). The highest yield was obtained for benzylamine hydrochloride **12d**·HCl providing quinoline **8d** in 87% (entry 4).

Table 1 Amination of 2-Chloro-3-nitroquinoline **7** to *N*-Alkylated 2-Amino-3-nitroquinolines **8**



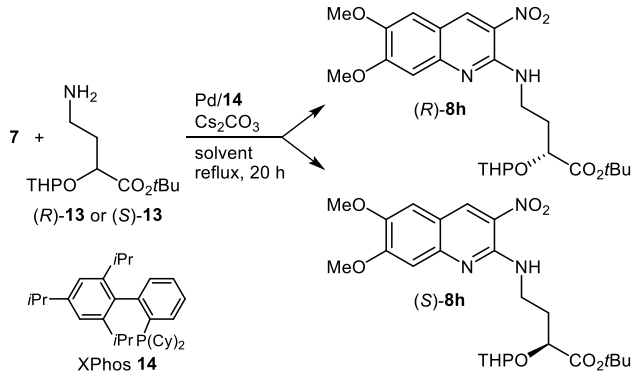
Entry	**12**·HCl	R	**8**	Yield (%)
1	**12a**·HCl	C_6H_{13}	**8a**	53
2	**12b**·HCl	C_8H_{17}	**8b**	60
3	**12c**·HCl	c-C_6H_{13}	**8c**	9[a]
4	**12d**·HCl	Bn	**8d**	87
5	**12e**·HCl	$(CH_2)_2CO_2Et$	**8e**	33
6	**12f**·HCl	$(CH_2)_3CO_2Et$	**8f**	49[b]
7	**12g**·HCl	$(CH_2)_2CH(OH)CO_2Et$	(*S*)-**8g**	17

[a] NMR yield, pure **8c** could not be obtained. [b] Inseparable (1.5:1) mixture of **7** and **8f**.

Upon use of the hydrochlorides of ethyl 3-aminopropionate **12e**·HCl and ethyl 4-aminobutanoate **12f**·HCl either the yield decreased to 33% (entry 5) or quinoline **8f** was obtained in 49% crude yield as an inseparable (1.5 : 1) mixture of starting material **7** and **8f** (entry 6). When ethyl (*S*)-4-amino-2-hydroxybutanoate hydrochloride **12g**·HCl was employed, the desired amination product ethyl (2*S*)-4-[(6,7-dimethoxy-3-nitroquinolin-2-yl)amino]-2-hydroxybutanoate (*S*)-**8g** was isolated, albeit in a yield of 17% (entry 7), which was caused by a low conversion. The major amount of starting material could be reisolated.

As an alternative approach the Buchwald-Hartwig amination[14,15] was studied (Table 2; see also SI and General Procedure B).[16]

Table 2 Buchwald-Hartwig Amination of **7** to Product **8h**[a]



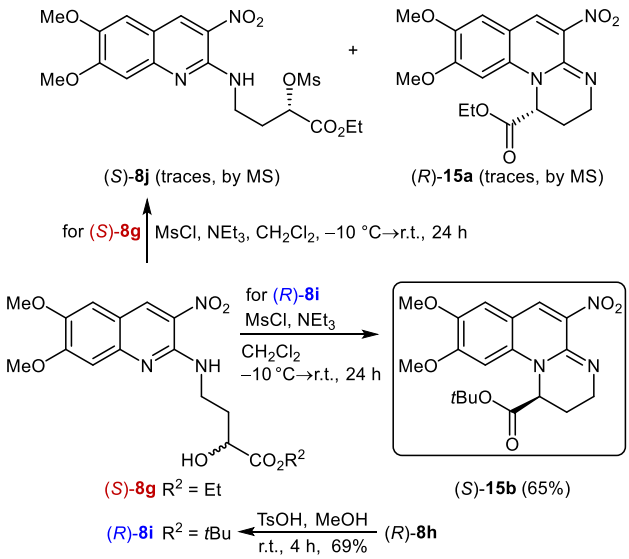
Entry	Amine	Pd/Ligand	Solvent	**8**	Yield (%)
1	(*S*)-**13**	$Pd(OAc)_2$/**14**	toluene	(*S*)-**8h**	20
2	(*R*)-**13**	$Pd(OAc)_2$/**14**	toluene	(*R*)-**8h**	25
3	(*R*)-**13**	$Pd(OAc)_2$/**14**	THF	(*R*)-**8h**	traces[b]
4	(*R*)-**13**	$Pd(OAc)_2$/**14**	toluene/H_2O	(*R*)-**8h**	20
5	(*R*)-**13**	$Pd(PPh_3)_4$	toluene	(*R*)-**8h**	25[c]
6	**12a**	$Pd(OAc)_2$/**14**	toluene	**8a**	24

[a] Pd source (4 mol%), **14** (8 mol%), base Cs_2CO_3 (4.8 equivalents); conversion determined by GC. [b] Determined by TLC and MS. [c] **8h** contained traces of $O=PPh_3$, which could not be separated by chromatography.

Treatment of 2-chloro-3-nitroquinoline **7** with *tert*-butyl (2*S*)-2-amino-2-(tetrahydro-2*H*-pyran-2-yloxy)butanoate (*S*)-**13** in the presence of $Pd(OAc)_2$, XPhos **14** and Cs_2CO_3 (4.8

equivalents) in toluene under reflux for 20 h gave the desired product (*S*)-**8h** in 20% yield (entry 1, Table 2). Similar results were obtained with the corresponding optical antipode (*R*)-**13**, yielding (*R*)-**8h** in 25% (entry 2, Table 2). Replacement of toluene by THF or toluene / H_2O did not improve the yield (entries 3, 4, Table 2). When $Pd(PPh_3)_4$ was used as a catalyst, the desired compound (*R*)-**8h** was isolated in 25% crude yield containing nearly 40% of $Ph_3P{=}O$, which could not be removed by chromatography. In an additional experiment *n*-hexylamine **12a** was reacted with **7** under the Buchwald-Hartwig conditions with $Pd(OAc)_2$ / **14** providing **8a** in a meager yield of 24% (entry 6, Table 2).

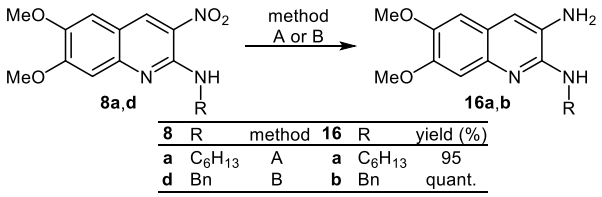
With the amination products **8** in hand, the cyclization towards the pyoverdin chromophore **2** was examined (Scheme 3). When ethyl ester (*S*)-**8g** was treated with MsCl and NEt_3 according to the protocol by Mashiach and Meijler[10] both the cyclized compound (*R*)-**15a** and mesylate **8j** were detected in traces via ESI-MS of the crude mixture. In contrast, when the corresponding *tert*-butyl ester (*R*)-**8i** was employed under similar conditions, the tricyclic chromophore (*S*)-**15b** could be isolated in 65% yield.[17]



Scheme 3 Cyclization to chromophores **15** following a literature procedure[10]

In order to access the pyoverdin chromophore, conditions for the reduction of nitroquinolines were tested. After some experimentation, model compound **8a** could be successfully re-

duced to the amine **16a** with $HSiCl_3$ and *i*Pr_2NEt in CH_2Cl_2 in 95% yield according to a method by Orlandi[18] (Scheme 4).[19] Nitroquinoline **8d** was converted quantitatively to amine **16b** by Pd-catalyzed reduction.



8	R	method	16	R	yield (%)
a	C_6H_{13}	A	**a**	C_6H_{13}	95
d	Bn	B	**b**	Bn	quant.

A: $HSiCl_3$, *i*Pr_2NEt, CH_2Cl_2, 0 °C→r.t., 18 h
B: Pd/C, H_2, MeOH, r.t., 1.5 h

Scheme 4 Reduction of nitroquinolines **8** to the corresponding amino derivatives **16**

Unfortunately, when these conditions were applied to the tricyclic nitro compound (*S*)-**15b**, only trace amounts of the desired amine could be detected, while the majority of the crude mixture contained the *N*-chlorinated amine (see SI, Scheme S5).

The tricyclic scaffold (*S*)-**15b** was examined for its chromophoric properties by UV/Vis and fluorescence spectroscopy. First concentration-dependent absorption spectra were recorded, revealing a relatively strong absorption band with a broad shoulder at 232 nm as well as weak broad bands with maxima at 299 nm, 358 nm and in the visible range at 433 nm (23095 cm^{-1}) irrespective of the concentration (Figure 1a). Thus, aggregation of the molecules can be excluded. The fluorescence emission spectrum of (*S*)-**15b** is shown in Figure 1b. The excitation wavelength λ_{exc} = 440 nm was chosen because of the location of the absorption band in the visible region. An emission band at 500 nm (19995 cm^{-1}) was observed, resulting in a Stokes shift of the visible band of 3100 cm^{-1}. For spectroscopic results of other relevant derivatives and preliminary biological studies see the Supporting Information.

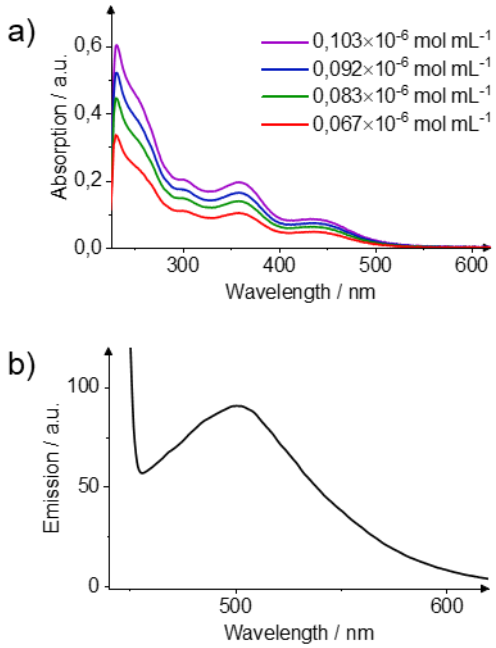


Figure 1 (a) Concentration-dependent absorption spectra and (b) fluorescence emission spectrum of (*S*)-**15b** (0.020×10^{-6} mol mL^{-1}, excitation wavelength λ_{exc} = 440 nm) measured in CH_2Cl_2

In conclusion, a novel microwave-induced basic amination of 2-chloro-3-nitroquinoline **7** was developed, whose substrate scope showed better yields for sterically less demanding alkyl or benzyl amines as compared to amino acid derivatives. Buchwald-Hartwig amination gave similar results regarding amino acid substrates. The amino acid-functionalized quinoline (*R*)-**8i** could be converted to the corresponding pyoverdin chromophore, thus demonstrating the potential of this amination / cyclization for the formation of heterocyclic target compounds with higher complexity.

Acknowledgement

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Supporting Information

Synthesis, absorption and emission spectra and preliminary biological investigation.

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(13) **General Procedure A**

To a solution of **7** (0.19 mmol) and the appropriate amine hydrochloride **12**·HCl (0.84 mmol) in abs. EtOH (3 mL) NEt_3 (0.84 mmol) was added and the reaction mixture was stirred in a microwave vial for 1.5 h at 80 °C. The reaction mixture was then poured onto H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), and the solvents were removed under reduced pressure. The residue was purified by column chromatography on SiO_2 with hexanes/EtOAc to give the respective product **8**.

***N*-Benzyl-6,7-dimethoxy-3-nitroquinolin-2-amine (8d)**

Amorphous red solid; yield: 44 mg (87%). R_f = 0.85. FT-IR (ATR): $\tilde{\nu}$ = 3800 (w), 3731 (w), 3627 (w), 3408 (w), 2928 (m), 2260 (w), 2211 (w), 2191 (w), 2172 (w), 2155 (w), 2139 (w), 2079 (w), 2044 (w), 2026 (w), 1986 (w), 1968 (w), 1611 (vs), 1569 (w), 1533 (m), 1494 (s), 1464 (m), 1417 (s), 1371 (m), 1352 (m), 1231 (vs), 1162 (m), 1009 (w), 846 (w), 734 (w), 700 (w), 616 (w), 493 (w), 469 (w), 448 (w), 424 (w) cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ = 3.98 (s, 3 H), 4.05 (s, 3 H), 4.92 (d, *J* = 5.7 Hz, 2 H), 6.95 (s, 1 H), 7.26 (s, 1 H), 7.30 (t, *J* = 7.6 Hz, 1 H), 7.37 (t, *J* = 7.5 Hz, 2 H), 7.44 (d, *J* = 7.5, 2 H), 8.28 (s, 1 H), 8.55 (s, 1 H). ^{13}C NMR (176 MHz, $CDCl_3$): δ = 45.32, 56.21, 56.47, 102.80, 106.49, 127.81, 128.11, 128.69, 129.00, 133.32, 135.29, 139.27, 148.26, 152.21, 154.66, 156.99. MS (ESI): *m/z* =362.11 $[M+Na]^+$, 340.13 $[M]^+$, 294.14 $[M-NO_2]^+$. HRMS (ESI): calcd. for $[C_{18}H_{17}N_3O_4, M+H]^+$: 340.1297; found: 340.1293 $[M+H]^+$.

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(16) **General Procedure B**

The appropriate amine (1.02 mmol), **7** (0.85 mmol), $Pd(OAc)_2$ (34 µmol), XPhos **14** (68 µmol) and Cs_2CO_3 (4.09 mmol) were dissolved under inert gas atmosphere in de-gassed abs. toluene (2 mL), and the reaction mixture was stirred for 20 h at reflux. The suspension was cooled to room temperature, filtered and rinsed with toluene (50 mL) and EtOAc (10 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by chromatography on SiO_2 with hexanes/EtOAc (2 : 1).

***tert*-Butyl (2*R*)-4-[(6,7-dimethoxy-3-nitrochinolin-2-yl)amino]-2-(tetrahydro-2*H*-pyran-2-yloxy)butanoate ((*R*)-8h)**

Red solid; yield: 104 mg, (25%); mp 76 °C. R_f = 0.64. FT-IR (ATR): $\tilde{\nu}$ = 3407 (w), 2929 (m), 2854 (w), 2253 (w), 1740 (m), 1611 (s), 1569 (w), 1535 (m), 1495 (s), 1465 (m), 1418 (s), 1369 (m), 1356 (m), 1299 (m), 1231 (vs), 1160 (s), 1124 (m), 1075 (m), 1032 (s), 1006 (m), 913 (w), 869 (w), 846 (w), 813 (w), 767 (w), 732 (w), 697 (w), 647 (w), 615 (w), 577 (w), 471 (w), 419 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.47 (d, *J* = 4.8 Hz, 9 H, *t*Bu), 1.52–1.96 (m, 6 H), 2.02–2.42 (m, 2 H), 3.39–3.63 (m, 0.5 H), 3.66–3.87 (m, 0.5 H), 3.96 (s, 3 H), 4.03–4.07 (m, 4 H), 4.40 (dd, *J* = 9.0 Hz, 4.0 Hz, 1 H), 4.63–4.77 (m, 2 H), 4.96 (m, 1 H), 6.91 (s, 1 H), 7.02 (s, 1 H), 8.21 (s, 1 H), 8.78 (s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 19.91, 25.37, 28.01, 28.11, 30.60, 32.08, 37.57, 56.09, 56.37, 63.42, 72.90, 81.63, 98.47, 99.87, 105.56, 106.25, 115.96, 134.78, 134.84, 147.48, 149.26, 149.51, 156.71, 171.81. $[\alpha]_D^{20}$ = +46.0 (c = 0.50, CH_2Cl_2). MS (ESI): *m/z* = 514.22 $[M + K]^+$, 514.22 $[M + Na]^+$, 492.23 $[M]^+$, 408.18, 352.11. HRMS (ESI): calcd. for $[C_{24}H_{33}N_3O_8, M+Na]^+$: 514.2160; found: 514.2162 $[M+Na]^+$.

(17) ***tert*-Butyl (1*S*)-8,9-dimethoxy-5-nitro-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoline-1-carboxylate ((*S*)-15b)**

Red solid; yield: 18.0 mg (65%); mp. 157 °C. R_f = 0.4 (EtOAc/hexanes 2 : 1). FT-IR (ATR): $\tilde{\nu}$ = 2929 (m), 2853 (w), 2257 (w), 1994 (w), 1732 (m), 1650 (m), 1621 (m), 1596 (m), 1563 (m), 1526 (s), 1455 (m), 1428 (m), 1393 (m), 1367 (m), 1334 (m), 1269

(s), 1251 (vs), 1220 (m), 1204 (m), 1189 (m), 1150 (vs), 1099 (m), 1060 (m), 1013 (s), 988 (m), 912 (m), 879 (m), 846 (m), 817 (m), 727 (vs), 665 (m), 645 (m), 615 (w), 579 (w), 518 (w), 477 (w), 451 (w) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 9 H), 2.03–2.20 (m, 1 H) 2.35 (m, 1 H) 3.47 (m, 1 H), 3.76–3.64 (m, 1 H), 3.89 (s, 3 H), 3.92 (s, 3 H), 4.74 (dd, *J* = 6.2, 2.3 Hz, 1 H), 6.35 (s, 1 H), 6.82 (s, 1 H), 7.60 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 22.91, 28.07, 40.61, 56.20, 56.46, 56.93, 83.41, 95.22, 109.69, 111.67, 129.40, 137.36, 141.40, 142.29, 144.96, 153.69, 169.94. $[\alpha]_D^{20}$ = –18.0 (c = 0.50, CH_2Cl_2). MS (ESI): *m/z* = 412.15 $[M + Na]^+$, 390.16 $[M]^+$, 334.10 $[M - t\text{Bu}]^+$. HRMS (ESI): calcd. for $[C_{19}H_{23}N_3O_6, M+H]^+$: 390.1660; found: 390.1642 $[M+H]^+$. UV-VIS: $\varepsilon_{232\,nm}$ = 7.55, $\varepsilon_{299\,nm}$ = 2.59, $\varepsilon_{358\,nm}$ = 2.54, $\varepsilon_{433\,nm}$ = 1.08 (in 10^6 mL/mol·cm).

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(19) ***N*²-Hexyl-6,7-dimethoxyquinoline-2,3-diamine (16a)**

Colorless to light yellow oil; yield: 13 mg (95%). FT-IR (ATR): $\tilde{\nu}$ = 3408 (w), 3246 (w), 2953 (m), 2926 (s), 2854 (m), 2160 (w), 2106 (w), 2082 (w), 2049 (w), 2027 (w), 1974 (w), 1724 (w), 1616 (m), 1509 (s), 1463 (s), 1446 (s), 1420 (vs), 1372 (m), 1254 (vs), 1216 (s), 1153 (m), 1014 (m), 882 (w), 848 (w), 804 (w), 752 (w), 731 (w), 614 (w), 453 (w), 433 (w) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 8.3 Hz, 7.6 Hz, 3 H), 1.17–1.54 (m, 6 H), 1.70 (p, *J* = 7.2 Hz, 2 H), 3.22 (bs, 2 H), 3.55 (t, *J* = 7.2 Hz, 2 H), 3.93 (s, 3 H), 3.97 (s, 3 H), 6.81 (s, 1 H), 7.05 (s, 1 H), 7.17 (s, 1 H), 8.08 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.07, 22.64, 26.94, 29.70, 31.69, 41.85, 55.91, 55.94, 104.90, 109.95, 118.08, 127.62, 129.71, 139.93, 146.49, 147.67, 149.65. MS (ESI): *m/z* = 338.16, 304.20 $[M]^+$. HRMS (ESI): calcd. for $[C_{17}H_{25}N_3O_2, M+H]^+$: 304.2020; found: 304.2019 $[M+H]^+$.