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SYNTHESIS OF FLUORESCENCE PYRIPROXYFEN ANALOGUES AS JUVENILE HORMONE AGONISTS

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Abstract – Four fluorescence analogues of juvenile hormone agonist pyriproxyfen were designed and synthesized. The synthetic analogue having a dimethylamino group exhibited fluorescence, and therefore can be used for investigation of the mode of action of pyriproxyfen as a juvenile hormone analogue.

Pyriproxyfen (**1**),[1] 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine, is a widely used insecticide[2] developed by Sumitomo Chemical Co., Ltd. in the 1990s. It is a broad-spectrum insect growth regulator against public health insects such as whiteflies,[3-5] aphids,[6,7] mosquitoes,[8,9] and cockroaches.[10] It has been known that pyriproxyfen mimics the action of juvenile hormone in target insects and is an insecticide with relatively low mammalian toxicity. However, its exact mode of action in target insects is not well understood. Additionally, pyriproxyfen, a potent hormone agonist, is classified as an endocrine disruptor[11] that alters function of the endocrine system and causes adverse health effects such as birth defects,[12] sexual abnormalities,[13,14] and reproductive failures[15,16] in both wildlife and humans. For that reason, concerns about the latent toxicity of pyriproxyfen to non-target organisms have recently been raised. It is therefore necessary to determine the detailed molecular mechanism of action of pyriproxyfen.

The ultimate goal of our investigation is the elucidation of the mechanism and action of pyriproxyfen against arthropods. As a first step, the design and synthesis of fluorescence analogues, an important and useful tool in biological studies, were undertaken. Fluorescence analogue **2a** having a quinoline ring as a fluorescent group instead of the pyridine ring of pyriproxyfen (**1**) was designed (Figure 1). Analogue **2b** having a dimethylamino group as an electron-donating group at the C6 position of the quinoline ring, and

analogues **2c** and **2d** involving a methyl ester group and a carboxyl group, respectively, as electron-withdrawing groups at C6, were also designed. In this report, we describe the synthesis of our designed analogues and their fluorescence properties.

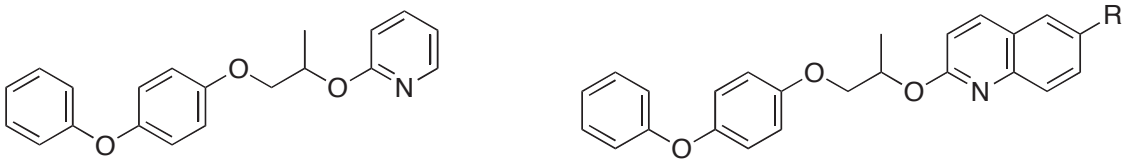
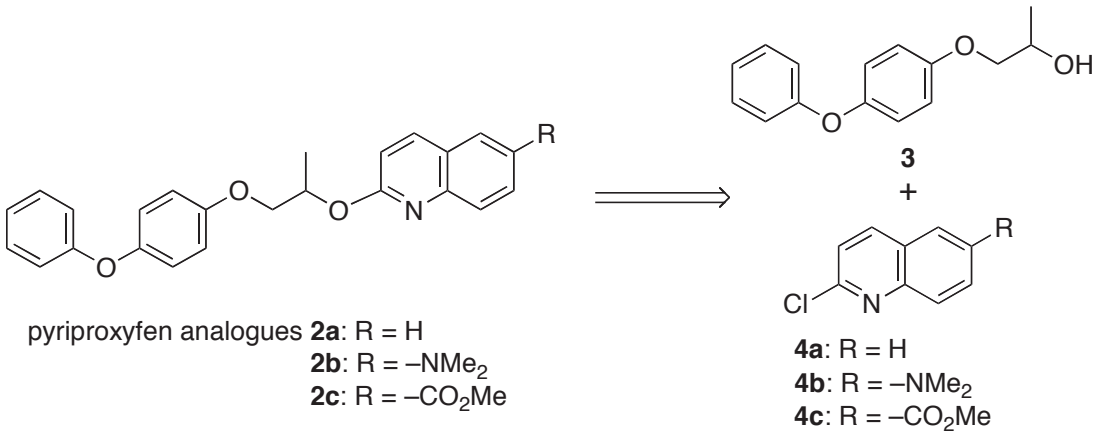


Figure 1. Structures of pyriproxyfen (**1**) and its fluorescence analogues **2a**–**2d**

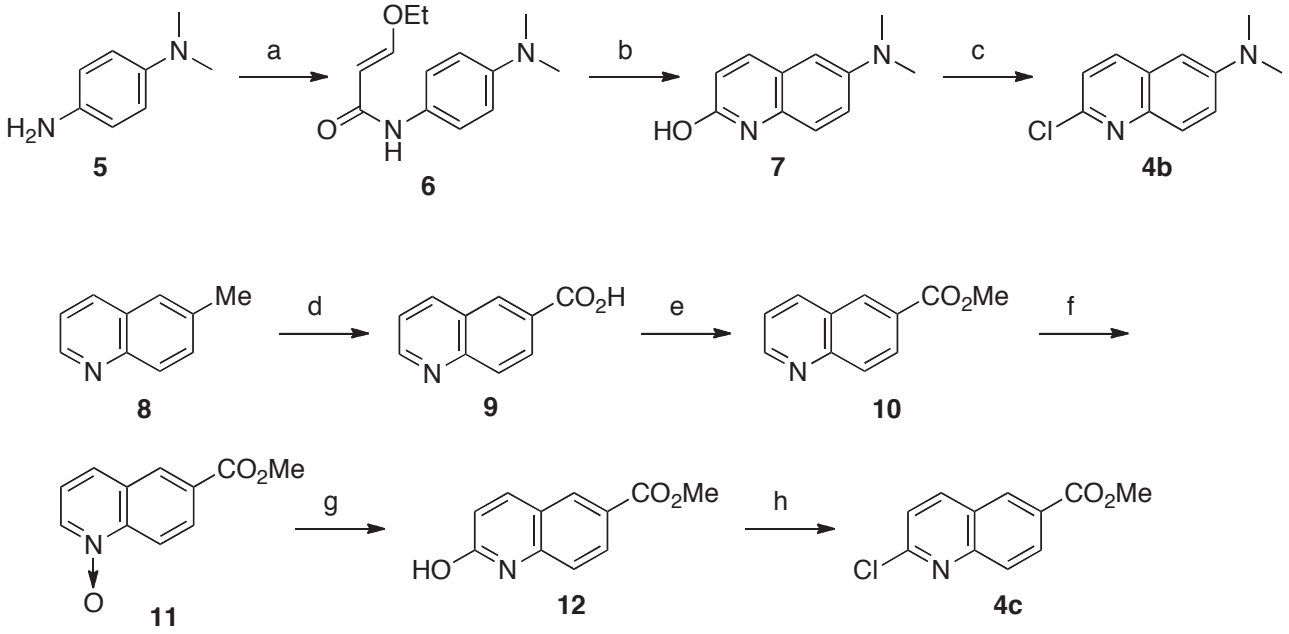
Our synthetic plan for pyriproxyfen analogues **2a**–**2c** was based on the nucleophilic aromatic substitution of 2-chloroquinoline derivatives **4a**–**4c** with a known alcohol, 1-(4-phenoxyphenoxy)propan-2-ol **3**,[17] as outlined in Scheme 1. Analogue **2d** having a carboxyl group would be easily derived by hydrolysis of the methyl ester moiety from analogue **2c**.



Scheme 1. Synthetic plan for pyriproxyfen analogues **2a**–**2c**

The syntheses of 2-chloroquinoline analogues **4b** and **4c** are shown in Scheme 2. Synthesis of 2-chloro-6-dimethylaminoquinoline (**4b**) was carried out according to Janiak's synthetic route,[18] which began with acylation of 4-dimethylaminoaniline (**5**) with 3-ethoxyacryloyl chloride[19] prepared from ethyl vinyl ether and oxalyl chloride to give the acylated aniline derivative **6** in 57% yield. Heating **6** in conc. sulfuric acid gave the cyclized product **7**. Chlorination of the resulting hydroxyl group in **7** with phosphorus oxychloride produced 2-chloro-6-dimethylaminoquinoline (**4b**) in 58% yield.

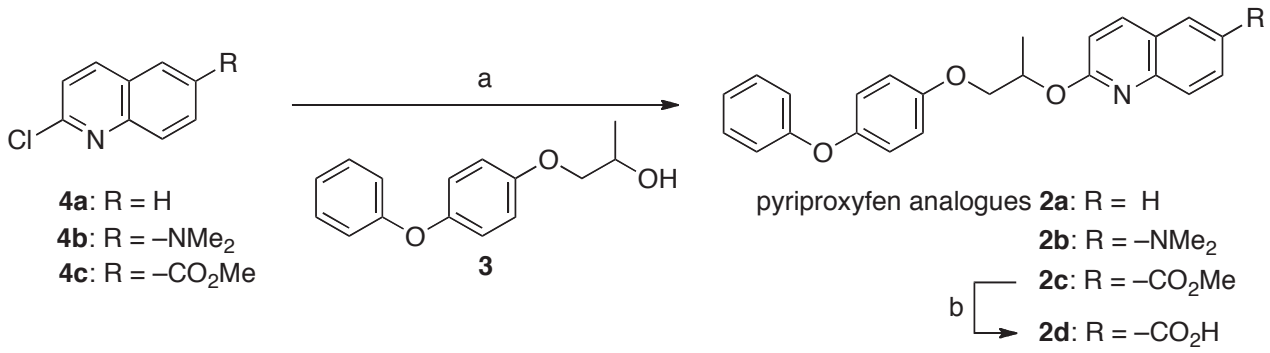
Synthesis of 2-chloro-6-methoxycarbonylquinoline (**4c**) started from commercially available 6-methylquinoline (**8**) as the starting material. Oxidation of the methyl group of **8** with chromium trioxide under acidic conditions,[20] followed by esterification of the resulting carboxylic acid **9**, gave the methyl ester **10** in 40% overall yield. Oxidation at the C2-position of the quinoline ring of **10** was accomplished by a two-step sequence to yield 2-hydroxyquinoline derivative **12**:[21] oxidation of the nitrogen atom with *m*-chloroperbenzoic acid, followed by rearrangement of the resulting *N*-oxide using acetic anhydride. Finally, chlorination of **12** gave the desired 2-chloro-6-methoxycarbonylquinoline (**4c**) in 98% yield.



Scheme 2. Syntheses of 6-substituted-2-chloroquinoline derivatives **4b** and **4c**. *Reagents and Conditions:* a) 3-ethoxypropenoylchloride, Et_3N, toluene, reflux, 2 h, 57%; b) *conc.* H_2SO_4, 50 °C, 24 h. 45%; c) $POCl_3$, reflux, 3 h, 58%; d) CrO_3, *conc.* H_2SO_4, H_2O, reflux, 24 h, 40% (based on recovered **8**); e) *p*-TsOH, MeOH, reflux, 24 h, 99%; f) *m*CPBA, $CHCl_3$, rt, 18 h, 94%; g) Ac_2O, 100 °C, then H_2O, rt, 72 h, 74%; h) $POCl_3$, reflux, 3 h, 98%.

Having the 6-substituted quinoline derivatives **4b** and **4c** in hand, nucleophilic aromatic substitution with the known alcohol **3** was investigated as shown in Scheme 3. After several attempts, the conditions for coupling the quinolines, including commercially available 2-chloroquinoline (**4a**), and secondary alcohol **3** were established as follows. Refluxing quinoline derivatives **4a** and **4b** with **3** (2 equiv) and sodium hydride (2.2 equiv) in *N*,*N*-dimethylacetamide for 16 h under argon gave the corresponding target molecules **2a** and **2b** in 81% and 46% yields, respectively. Nucleophilic aromatic substitution of **4c** and **3** in the presence of sodium hydride occurred at 0 °C to give target analogue **2c** in 67% yield. Hydrolysis of methyl ester **2c** with lithium hydroxide afforded the quinoline carboxylic acid derivative **2d**

in 70% yield.



Scheme 3. Syntheses of pyriproxyfen analogues **2a**–**2d**. *Reagents and Conditions:* a) **3**, NaH, *N,N*-Dimethylacetamide, reflux, 16 h, 81% from **4a** to **2a**; 46% from **4b** to **2b**; 0 °C, 15 min, 67% from **4c** to **2c**; b) LiOH, THF–H_2O, rt, 48 h, 70%.

Next, fluorescence properties of the synthetic analogues were analyzed. The excitation and emission wavelengths along with Stokes' shifts and quantum yields[22] of **2a**–**2d** in MeOH are displayed in Table 1. Although quantum yields of analogues **2a**, **2c**, and **2d** unfortunately were extremely low, that of analogue **2b** having a dimethylamino group exhibited a reasonable value (0.321). These spectral results indicate that analogue **2b** will be applicable for the investigation of the mode of action of pyriproxyfen.

Table 1. Fluorescence spectral data for pyriproxyfen analogues **2a**–**2d**

Analogues	Maximum wavelength (nm)		Stokes' shift (nm)	Quantum yield
	Excitation	Emission		
2a	239	343	104	0.015
2b	250	461	211	0.321
2c	247	343	96	0.005
2d	246	345	99	0.005

In conclusion, we designed four fluorescence pyriproxyfen analogues and synthesized them by using nucleophilic aromatic substitution reactions. The analogues **2a**–**2d** exhibited different fluorescence properties. It appeared that analogue **2b** would be a useful fluorescence analogue for biological investigation of pyriproxyfen. Biological studies of this synthetic analogue are now in progress.

EXPERIMENTAL

(*E*)-*N*-[4-(Dimethylamino)phenyl]-3-ethoxyacrylamide (**6**).

To a stirred solution of 4-(dimethylamino)aniline (**5**) (5.00 g, 36.7 mmol) and triethylamine (6.50 mL, 4.71 g, 46.6 mmol) in toluene (125 mL) was added dropwise a solution of 3-ethoxyacryloyl chloride[19] (4.94 g, 36 7 mmol) in toluene (25 mL) at 100 °C, and the reaction mixture was refluxed for 2 h. After the solvent was removed in vacuo, THF (100 mL) was added to the residue. The resulting suspension was filtered, and the filtrate was evaporated in vacuo. The obtained residue was recrystallized from AcOEt to give **6**[18] (4.29 g, 21.0 mmol, 57%) as pale yellow needles. m.p. 152–153 ºC (from AcOEt); IR (KBr): 3297, 3260, 1657, 1611, 1524, 1345, 1253, 1239, 1152, 811 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, *J* = 6.8 Hz, 3H), 2.93 (s, 6H), 3.80–4.08 (br m, 2H), 5.31 (d, *J* = 12.0 Hz, 1H), 6.68–6.71 (br m, 2H), 6.85–7.03 (br s, 1H), 7.26–7.52 (br m, 2H), 7.60 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 40.9 (2C), 66.9, 99.3, 113.0 (2C), 121.7 (2C), 128.5, 147.6, 160.1, 165.1; HRMS (ESI–TOF): calcd for $C_{13}H_{19}N_2O_2$ ($[M + H]^+$) 235.1447, found 235.1464.

6-(Dimethylamino)quinolin-2-ol (**7**).

To stirred conc. H_2SO_4 was added **6** (600 mg, 2.56 mol) in small portions at 0 °C, and the reaction mixture was allowed to warm to 50 °C. After stirring for 6 days at 50 °C, the mixture was made basic by addition to 5 M NaOH aqueous solution. The mixture was extracted by AcOEt (3 x 300 mL), washed with brine, and concentrated in vacuo. The residue was purified by column chromatography ($CHCl_3$–MeOH–28% NH_4OH, 360:9:1) to give **7**[18] (290 mg, 1.54 mmol, 60%) as pale yellow needles. m.p. 238–239 ºC (from $CHCl_3$); IR (KBr): 3440, 3143, 2986, 2898, 2831, 1657, 1620, 1508, 1428, 1367, 1200, 1117, 842, 816, 584 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.97 (s, 6 H), 6.67 (d, *J* = 9.5 Hz, 1H), 6.79 (d, *J* = 2.7 Hz, 1H), 7.08 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 1H), 7.72 (d, *J* = 9.5 Hz, 1H), 11.4–11.7 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.1 (2C), 108.9, 117.0, 118.5, 120.8, 121.3, 130.8, 140.6, 146.7, 164.0; HRMS (ESI–TOF): calcd for $C_{11}H_{13}N_2O$ ($[M + H]^+$) 189.1028, found 189.1020.

2-Chloro-6-(dimethylamino)quinoline (**4b**).

A suspension of **7** (257 mg, 1.27 mmol) in phosphorus oxychloride (3.75 mL) was refluxed under argon. After stirring for 3 h, excess phosphorus oxychloride was removed by distillation at atmosphere, and ice (50 mg) was added to the residue. The residue was made basic by adding 10% Na_2CO_3 aq. at pH 8–9, and the resultant **4b**[18] (165 mg, 0.798 mmol, 58%) was obtained as yellow crystals by filtration. m.p. 75–76 ºC (from $CHCl_3$); IR (KBr): 2885, 2812, 1623, 1577, 1514, 1451, 1367, 1246, 1194, 1153, 1136, 1096, 1068, 940, 846, 814, 713, 642, 543, 474 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.07 (s, 6H), 6.77 (d, *J* = 2.8 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 7.34 (dd, *J* = 9.4, 2.8 Hz, 1H), 7.86 (d, *J* = 9.4 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.4 (2C), 104.6, 119.6, 122.0, 128.2, 128.8, 136.8, 141.3, 145.7, 148.6; HRMS (ESI–TOF): calcd for $C_{11}H_{12}ClN_2$ ($[M + H]^+$) 207.0689, found 207.0680.

Quinoline-6-carboxylic acid (**9**).

To a stirred solution of 6-methylquinoline (**8**) (500 mg, 3.50 mmol) in H_2O (5 mL) was added conc. H_2SO_4 (1.3 mL) and chromium trioxide (1.35 g, 1.35 mmol), then the reaction mixture was refluxed for 24 h. After addition of H_2O (15 mL), the reaction mixture was extracted with AcOEt (9 x 100 mL), dried over $MgSO_4$, and concentrated in vacuo. The resultant solid was recrystallized from hexane–MeOH to afford **9** (119 mg, 0.687 mmol, 20%) as colorless needles. The organic layer was evaporated in vacuo and the resultant solid was recrystallized from H_2O–hexane to recover **8** (123 mg, 0,710 mmol, 20%) as colorless crystals. Compound **9**: m.p. 243–247 ºC (from hexane–MeOH); IR (KBr): 2778, 2432, 2374, 2347, 1906, 1702, 1629, 1506, 1462, 1328, 1277, 1217, 1195, 1098, 807, 789, 754, 637, 525 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.63 (dd, J = 8.3, 4.2 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 8.22 (dd, J = 8.8, 1.9 Hz, 1H), 8.57 (d, J = 8.3 Hz, 1H), 8.68 (d, J = 1.7 Hz, 1H), 9.02 (dd, J = 4.2, 1.7 Hz, 1H), 13.0–13.5 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 123.2, 128.2, 129.6, 129.7, 130.3, 131.9, 138.5, 150.3, 153.6, 167.9; HRMS (ESI–TOF): calcd for $C_{10}H_8NO_2$ ($[M + H]^+$) 174.0555, found 174.0556.

Methyl quinoline-6-carboxylate (**10**).

To a stirred solution of **9** (189 mg, 1.09 mmol) in MeOH (20 mL) was added *p*-TsOH monohydrate (415 mg, 2.18 mmol), and the mixture was refluxed for 12 h. The reaction mixture was quenched by addition of sat. $NaHCO_3$ aq. (20 mL), and the mixture was extracted with AcOEt (3 x 40 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo. The resultant residue was purified by column chromatography (hexane–AcOEt, 1:1) to afford **10** (202 mg, 1.08 mmol, 99%) as a white solid. The solid was recrystallized from AcOEt to give colorless prisms. m.p. 83–84 ºC (from AcOEt); IR (KBr): 1718, 1625, 1596, 1461, 1440, 1358, 1323, 1285, 1256, 1204, 1181, 1125, 1101, 974, 916, 847, 797, 786, 470 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.94 (s, 3H), 7.46 (dd, J = 8.3, 4.2 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.25 (dd, J = 8.3, 1.5 Hz, 1H), 8.30 (dd, J = 8.8, 1.8 Hz, 1H), 8.59 (d, J = 1.8 Hz, 1H), 9.00 (dd, J = 4.2, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.4, 121.8, 127.4, 128.1, 128.9, 129.8, 131.0, 137.3, 150.0, 152.5, 166.6; HRMS (ESI–TOF): calcd for $C_{11}H_{10}NO_2$ ($[M + H]^+$) 188.0712, found 188.0708.

Methyl quinoline-6-carboxylate *N*-oxide (**11**).

To a stirred solution of **10** (65.0 mg, 0.347 mmol) in $CHCl_3$ (4 mL) was added *m*CPBA (121 mg, 0.701 mmol), and then the reaction mixture was stirred at room temperature under Ar. After stirring for 16 h, the mixture was quenched by addition of sat. $NaHCO_3$ aq. (10 mL), and washed with H_2O. The organic layer was dried over $MgSO_4$, and the solvent was removed. The resulting residue was purified by

column chromatography (AcOEt–MeOH, 1:1) to afford **11** (66.0 mg, 0.325 mmol, 94%) as a white solid. The solid was recrystallized from $CHCl_3$ to give colorless prisms. m.p. 145–147 ºC (from $CHCl_3$); IR (KBr): 3058, 1718, 1622, 1573, 1457, 1433, 1361, 1294, 1260, 1222, 1203, 1178, 1102, 774, 578, 497 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.01 (s, 3H), 7.38 (dd, *J* = 8.5, 6.1 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 8.34 (dd, *J* = 9.1, 1.7 Hz, 1H), 8.60 (d, *J* = 6.1 Hz, 1H), 8.63 (d, *J* = 1.7 Hz, 1H), 8.80 (d, *J* = 9.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.4, 120.0, 121.7, 126.3, 129.5, 129.7, 130.1, 130.7, 136.8, 142.9, 165.4; HRMS (ESI–TOF): calcd for $C_{11}H_{10}NO_3$ ($[M + H]^+$) 204.0661, found 204.0670.

Methyl 2-hydroxyquinoline-6-carboxylate (**12**).

A solution of **11** (186 mg, 0.916 mmol) in Ac_2O (15 mL) was heated to 100 °C, and the mixture was stirred for 18 h. H_2O (15 mL) was added to the reaction mixture at room temperature, and then this mixture was stirred for 72 h at the same temperature. The mixture was extracted with $CHCl_3$ (3 x 30 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed in vacuo, and the resulting residue was purified by column chromatography ($CHCl_3$–MeOH–28% NH_4OH, 450:9:1) to afford **12** (137 mg, 0.675 mmol, 74%) as a white solid. The solid was recrystallized from $CHCl_3$ to give colorless needles. m.p. 251–253 ºC (from $CHCl_3$); IR (KBr): 3449, 3428, 1720, 1672, 1656, 1626, 1569, 1279, 1256, 1211, 545 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.96 (s, 3H), 6.74 (d, *J* = 9.5 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 7.86 (d, *J* = 9.5 Hz, 1H), 8.17 (dd, *J* = 8.6, 1.8 Hz, 1H), 8.31 (d, *J* = 1.8 Hz, 1H), 11.17–11.28 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.3, 115.9, 119.3, 122.4, 124.7, 130.3, 131.4, 141.2, 141.4, 164.3, 166.2; HRMS (ESI–TOF): calcd for $C_{11}H_{10}NO_3$ ($[M + H]^+$) 204.0661, found 204.0661.

Methyl 2-chloroquinoline-6-carboxylate (**4c**).

A suspension of **12** (109 mg, 0.537 mmol) in phosphorus oxychloride (7 mL) was refluxed under argon. After stirring for 3 h, excess phosphorus oxychloride was removed by distillation at atmosphere, and ice (100 mg) was added to the residue. The residue was made basic by adding 10% Na_2CO_3 aqueous solution at pH 8–9, and the mixture was extracted with $CHCl_3$ (3 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was recrystallized from $CHCl_3$ to afford **4c** (116 mg, 0.525 mmol, 98%) as colorless needles. m.p. 134–136 ºC (from $CHCl_3$); IR (KBr): 1727, 1584, 1454, 1310, 1279, 1196, 1187, 1140, 1103, 1091, 818, 788, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.99 (s, 3H), 7.45 (d, *J* = 8.6 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 8.19 (d, *J* = 8.6 Hz, 1H), 8.31 (dd, *J* = 8.8, 1.7 Hz, 1H), 8.56 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.5, 123.3, 126.0, 128.6, 128.9, 130.2, 130.5, 139.9, 149.7, 153.0, 166.2; HRMS (ESI–TOF): calcd for $C_{11}H_9ClNO_2$ ($[M + H]^+$) 222.0322, found 222.0311.

2-[1-(4-Phenoxyphenoxy)propan-2-yl]oxyquinoline (**2a**).

To a solution of 1-(4-phenoxyphenoxy)propan-2-ol **3**[17] (122 mg, 0.499 mmol) in *N*,*N*-dimethylacetamide (2 mL) was added NaH (24.0 mg, 55% dispersion in mineral oil, 0.549 mmol) at 0 °C, and this suspension was stirred at room temperature for 0.5 h. A solution of 2-chloroquinoline (**4a**) (41.0 mg, 0.250 mmol) in *N*,*N*-dimethylacetamide (2 mL) was added to the reaction mixture at room temperature, and then the mixture was refluxed for 16 h. The reaction mixture was quenched by addition of H_2O (10 mL), and extracted with AcOEt (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was purified by column chromatography (hexane–AcOEt, 10:1) to afford **2b** (75.6 mg, 0.204 mmol, 81%) as a colorless oil. IR (neat): 3047, 2927, 2934, 2873, 1619, 1605, 1590, 1574, 1504, 1488, 1473, 1428, 1393, 1344, 1311, 1276, 1257, 1224, 1155, 1112, 1045, 987, 870, 843, 824, 755, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.57 (d, *J* = 6.4 Hz, 3H), 4.13 (dd, *J* = 10.0, 5.2 Hz, 1H), 4.30 (dd, *J* = 10.0, 5.1 Hz, 1H), 5.87 (qdd, *J* = 6.4, 5.2, 5.1 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.94–6.97 (m, 2H), 6.98–7.01 (m, 4H), 7.02–7.07 (m, 1H), 7.28–7.33 (m, 2H), 7.38 (ddd, *J* = 7.9, 7.1, 1.2 Hz, 1H), 7.62 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H), 7.72 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 69.3, 70.9, 113.6, 115.9 (2C), 117.6 (2C), 120.8 (2C), 122.4, 124.1, 125.2, 127.3, 127.4, 129.5, 129.6 (2C), 138.9, 146.5, 150.3, 155.3, 158.6, 161.4; HRMS (ESI–TOF): calcd for $C_{24}H_{22}NO_3$ ($[M + H]^+$) 372.1600, found 372.1604.

6-Dimethylamino-2-[1-(4-phenoxyphenoxy)propan-2-yl]oxyquinoline (**2b**).

To a solution of 1-(4-phenoxyphenoxy)propan-2-ol **3** (472 mg, 1.94 mmol) in *N*,*N*-dimethylacetamide (6 mL) was added NaH (93.0 mg, 55% dispersion in mineral oil, 2.13 mmol) at 0 °C, and this suspension was stirred at room temperature. After stirring for 0.5 h at room temperature, a solution of 2-chloroquinoline **4b** (200 mg, 0.960 mmol) in *N*,*N*-dimethylacetamide (6 mL) was added to the reaction mixture at room temperature, and then the mixture was refluxed for 16 h. The reaction mixture was quenched by addition of H_2O (15 mL), and extracted with AcOEt (3 x 40 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was purified by column chromatography (hexane–AcOEt, 8:1) to afford **2b** (75.6 mg, 0.204 mmol, 81%) as a pale yellow oil. IR (neat): 1601, 1505, 1489, 1471, 1396, 1365, 1275, 1247, 1222, 1196, 1158, 1110, 1084, 1044, 991, 968, 872, 845, 820, 752, 692, 623 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.57 (d, *J* = 6.4 Hz, 3H), 3.03 (s, 6H), 4.12 (dd, *J* = 10.0, 5.4 Hz, 1H), 4.31 (dd, *J* = 10.0, 4.9 Hz, 1H), 5.75–5.88 (m, 1H), 6.82–6.90 (m, 2H), 6.94–7.10 (m, 7H), 7.27–7.36 (m, 3H), 7.74 (d, *J* = 9.2 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, CDC_3): δ 17.1, 41.2 (2C), 68.8, 70.9, 107.0, 113.4, 115.9 (2C), 117.5 (2C), 119.2, 120.8 (2C), 122.3, 126.1, 127.7, 129.6 (2C), 137.6, 139.8, 147.4, 150.1, 155.3, 158.5, 159.2;

HRMS (ESI–TOF): calcd for $C_{26}H_{27}N_2O_3$ ([M + H]$^+$) 415.2022, found 415.2011.

Methyl 2-[1-(4-phenoxyphenoxy)propan-2-yl]quinoline-6-carboxylate (**2c**).

To a solution of 1-(4-phenoxyphenoxy)propan-2-ol **3** (80.0 mg, 0.327 mmol) in *N*,*N*-dimethylacetamide (2 mL) was added NaH (15.0 mg, 55% dispersion in mineral oil, 0.344 mmol) at 0 °C, and this suspension was stirred at room temperature for 0.5 h. Next, a solution of 2-chloroquinoline **4c** (36.0 mg, 0.163 mmol) in *N*,*N*-dimethylacetamide (2 mL) was added to the reaction mixture at 0 °C, and the mixture was stirred for 15 min at 0 °C. The reaction mixture was quenched by addition of H_2O (10 mL), and extracted with AcOEt (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed. The residue was purified by column chromatography (hexane–AcOEt, 3:1) to afford **2c** (47.0 mg, 0.110 mmol, 67%) as a colorless oil. IR (neat): 1720, 1622, 1605, 1504, 1489, 1472, 1396, 1278, 1221, 1095, 691 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (d, *J* = 6.4 Hz, 3H), 3.97 (s, 3H), 4.14 (dd, *J* = 10.0, 4.9 Hz, 1H), 4.28 (dd, *J* = 10.0, 5.3 Hz, 1H), 5.80–5.94 (m, 1H), 6.91–6.99 (m, 7H), 7.00–7.07 (m, 1H), 7.27–7.34 (m, 2H), 7.83 (d, *J* = 8.7 Hz, 1H), 8.07 (d, *J* = 9.8 Hz, 1H), 8.22 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.47 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.9, 52.0, 69.8, 70.8, 114.4, 115.8 (2C), 117.6 (2C), 120.8 (2C), 122.4, 124.2, 125.7, 127.4, 129.4, 129.6 (2C), 130.4, 139.8, 149.0, 150.3, 155.1, 158.4, 162.9, 166.9; HRMS (ESI–TOF): calcd for $C_{26}H_{24}NO_5$ ([M + H]$^+$) 430.1654, found 430.1643.

2-[1-(4-Phenoxyphenoxy)propan-2-yl]quinoline-6-carboxylic acid (**2d**).

To a stirred solution of **2c** (35.0 mg, 81.6 μmol) in THF (2 mL) was added 1 M LiOH aqueous solution (1 mL) at room temperature, and this mixture was stirred at room temperature for 48 h. The reaction mixture was neutralized by addition of acetic acid at pH 6–7, extracted with AcOEt (3 x 15 mL), and dried over $MgSO_4$. The solvent was removed in vacuo, and the resulting residue was purified by column chromatography (hexane–AcOEt, 5:1) to afford **2d** (24.0 mg, 57.8 μmol, 70%) as a colorless gum. IR (neat): 2922, 1690, 1622, 1606, 1505, 1489, 1472, 1395, 1280, 1222, 822, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57 (d, *J* = 6.4 Hz, 3H), 4.15 (dd, *J* = 10.0, 4.9 Hz, 1H), 4.28 (dd, *J* = 10.0, 5.3 Hz, 1H), 5.81–5.96 (m, 1H), 6.90–7.08 (m, 8H), 7.26–7.34 (m, 2H), 7.86 (d, *J* = 8.8 Hz, 1H), 8.09 (d, *J* = 8.9 Hz, 1H), 8.29 (dd, *J* = 8.8, 1.8 Hz, 1H), 8.57 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.9, 70.0, 70.8, 114.7, 115.8 (2C), 117.6 (2C), 120.8 (2C), 122.5, 124.3, 124.7, 127.6, 129.6 (2C), 129.7, 131.4, 139.9, 149.6, 150.4, 155.1, 158.4, 163.2, 171.3; HRMS (ESI–TOF): calcd for $C_{25}H_{22}NO_5$ ([M + H]$^+$) 416.1498, found 416.1486.

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22. Quantum yields were measured on an absolute PL quantum yield measurement system (Photonic Multi-Channel Analyzer C10027, Hamamatsu Photonics K.K.).