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Synthesis of new lavendamycin analogues

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Abstract

Friedländer reaction between methyl acetoacetate and 2,4-diaminobenzaldehyde provided quinoline **11**. Subsequent tosylation, reduction, silylation, and then oxidation led to aldehyde **15**. The latter was subjected to a Pictet–Spengler reaction with tryptophan methyl ester that yielded product **16**, and then desilylation gave the lavendamycin analogue **17**. This compound was oxidized by Dess–Martin periodinane, and the cyclized derivative **18** was obtained via a hemiaminal intermediate. The same sequence from 2,4-diamino-5-methoxybenzaldehyde or from (2,4-diaminophenyl)propan-3-one led to compounds **30** and **31**, or **40** and **41**, respectively.

Keywords: Lavendamycin; Pictet–Spengler reaction; Cyclization; Topoisomerase

1. Introduction

Lavendamycin **1** (Scheme 1) a natural product from *Streptomyces lavendulae*,[1] showed cytotoxic properties[2] and a significant activity against topoisomerases I.[3] These interesting results gave rise to much work in this area. Several syntheses of this compound and of ester derivatives were carried out.[4] Various analogues were also synthesized.[5] Structure–activity relationships have been discussed.

A limitation to the possibility of exploiting the biological interest of lavendamycin is its toxicity that may be partly due to the presence of the quinone moiety of cycle A. We showed, several years ago,[5h] that compounds **I** with a modified cycle A, without the methyl group on cycle C and with various substituents R^1–R^7, maintained a part of the biological properties of the parent molecule. In a more recent work,[5o] we obtained a simplified analogue **5**, substituted with a hydroxymethyl group on cycle B. Our objective was to test the possibility of using this substituent to carry out an intramolecular cyclization to obtain conformationally restricted derivatives such as **3** and **4**. As numerous known inhibitors of topoisomerases I such as camptothecin itself **2**[6] and analogues, and others,[3,7] have a rigid structure, this cyclization might induce an increased activity. After numerous difficulties we found a suitable way. Compound **5** was obtained via a Pictet–Spengler reaction. Its oxidation with Dess–Martin periodinane (DMP) led to a hemiaminal intermediate and then to compound **4**. The latter was reduced to another cyclized product **3**. The objective was thus achieved but we encountered another difficulty. Compounds **3**, **4**, and **5** have a very low solubility. This made difficult, and probably poorly significant, the biological evaluation. However, it appeared that one of the cyclized products, **3**, had a stronger activity than compound **5**.

Our hypothesis was then partly validated but it was indispensable to check it with related compounds. We then planned to use the same strategy to prepare substituted derivatives. These substituents might increase the solubility and also the biological activity.

Afterward we envisioned to synthesize compounds **II**, **III**, and **IV** bearing one or several substituents, which are present in related compounds with interesting biological activities (Fig. 1). As an amino group is present on cycle A of lavendamycin, and also of streptonigrin **8**, an inhibitor of topoisomerase II,[8] we chose

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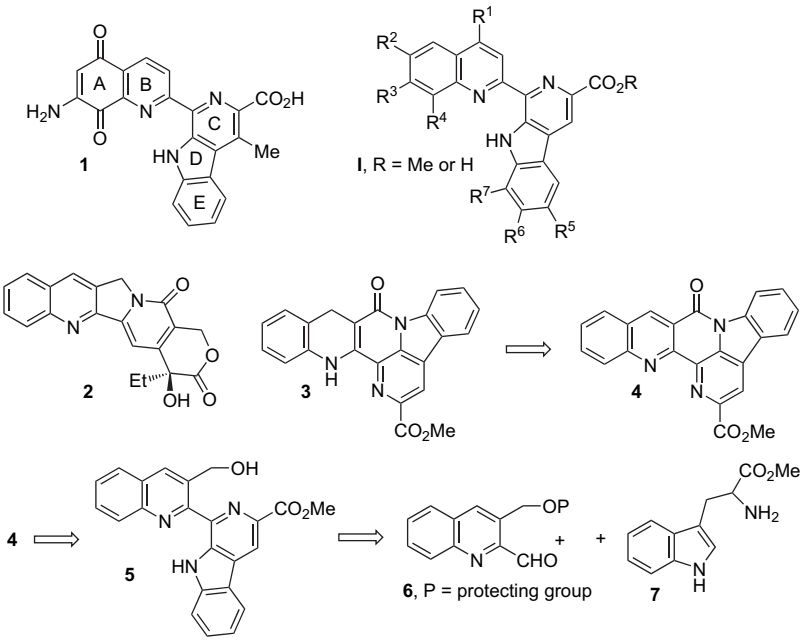


Scheme 1.

to prepare compounds with such a group, either free or protected, at the same position. We also planned to prepare compounds with another substituent, and especially a methoxy group, *ortho* to the latter, as in streptonigrin. Another possibility was to add an ethyl group on cycle B as in irinotecan (campto™) **9**, an inhibitor of topoisomerase I especially used in treatment of colon cancer.[9]

2. Results and discussion

To attain one of our objectives, preparation of compounds **II** and **III** with only a free or protected amino group, we used a similar way to the one used for preparation of compound **4**.[5o] Several attempts of Friedländer reaction between diaminoaldehyde **10** and methyl acetoacetate were carried out with and without protection of one of both amino groups, with various ratios of the reagents and different reaction times. Using of an excess of methyl acetoacetate (3.1 equiv) and of a long reaction time (5 days) led to a satisfying yield and to a lowering of the amount of byproduct resulting from a reversible attack of the 4-amino group of diaminoaldehyde **10** to methyl acetoacetate. Subsequent tosylation provided quinoline **12** (Scheme 2). After several attempts to reduce compound **12**, and related products with various protecting groups or with a free amino group, the best result was obtained using compound **12** itself, and with diisobutylaluminium hydride as the reducing agent. Silylation and then oxidation with selenium dioxide provided compound **15**. A Pictet–Spengler reaction with tryptophan methyl ester followed by desilylation yielded one of the target molecules **17**. The latter was subjected to oxidation with Dess–Martin periodinane (DMP) in *N*-methylpyrrolidone (NMP). As in the case of synthesis of compound **4**,[5o] oxidation of the CH_2OH group into CHO, cyclization into a hemiaminal and then oxidation of the latter into the desired molecule **18** occurred in one pot. Attempt of detosylation only led to an insoluble product. Therefore we decided to submit the protected products to the biological tests (see below).

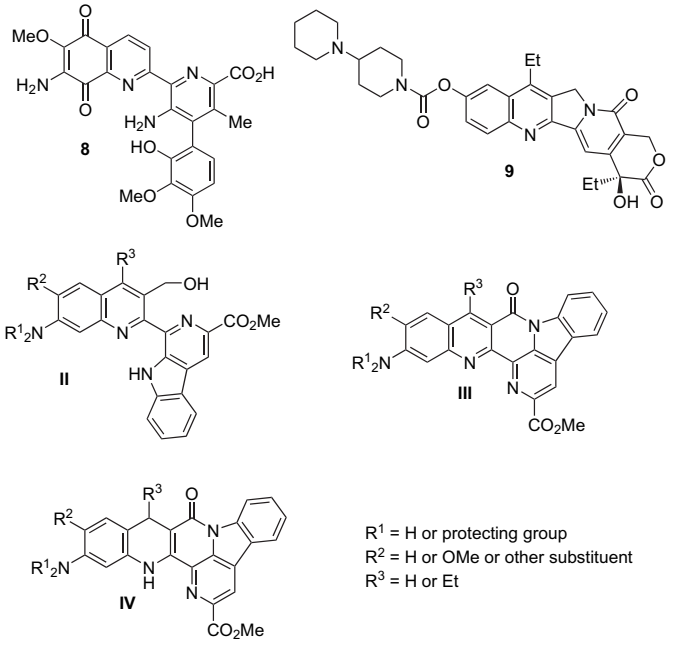
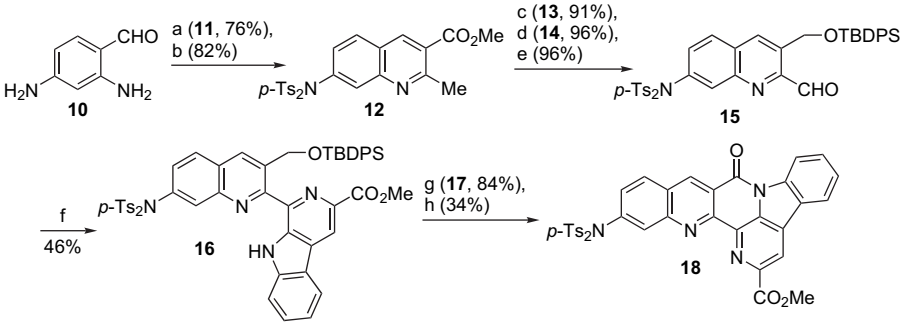


Figure 1.

As the previous way was successful, we envisioned to use the same reaction sequence for obtaining compounds **30** and **31** (Scheme 3). Dinitration of 3-methoxybenzaldehyde[10] provided a mixture of the three expected products (**20**–**22**). Separation of a **20**+**21** mixture and then reduction[11] yielded the starting diaminoaldehyde **23**, which was used to prepare these both desired products **30** and **31**.

We then tested several possibilities to prepare the starting diamino compound **33** for the synthesis of analogue **40** and then of



Scheme 2. (a) Me–CO–CH_2–CO_2Me, MeOH, piperidine; (b) NaH, THF, *p*-Ts_2O; (c) DIBAL-H, CH_2Cl_2, −78 °C; (d) *t*-$BuPh_2SiCl$, DMF, imidazole; (e) SeO_2, dioxane; (f) tryptophan methyl ester, *p*-xylene; (g) *n*-Bu_4NF, THF; (h) DMP, NMP, pyridine.

the cyclized derivative **41** (Scheme 4). Two attempts involving reaction of ethylmagnesium bromide with 2,5-dinitrobenzaldehyde or Friedel–Crafts reaction with *N*-(3-acetylaminophenyl)-acetamide gave bad results. Fortunately Sugasawa reaction[12] from diaminobenzene yielded the desired product in moderate yield but in one step. The subsequent reactions gave the expected compounds **40** and then **41**.

Biological tests in cell culture with 60 different tumor cells were carried out by the National Cancer Institute for compounds **18**, **30**, **31**, **40**, and **41**. The cyclized products **31** and **41** were more active than the parent compounds **30** and **40**. Therefore, these results confirm the interest of preparing such cyclized derivatives. The better GI50 were in the range of 10^{-6} M and most of the LC50 were higher than 10^{-4} M.

3. Conclusion

These results show that the synthetic way including a Friedländer reaction and a Pictet–Spengler reaction as the two key steps is efficient to prepare several lavendamycin analogues. The subsequent cyclizations via hemiaminal intermediates led to the conformationally restricted derivatives, more interesting on the biological point of view.

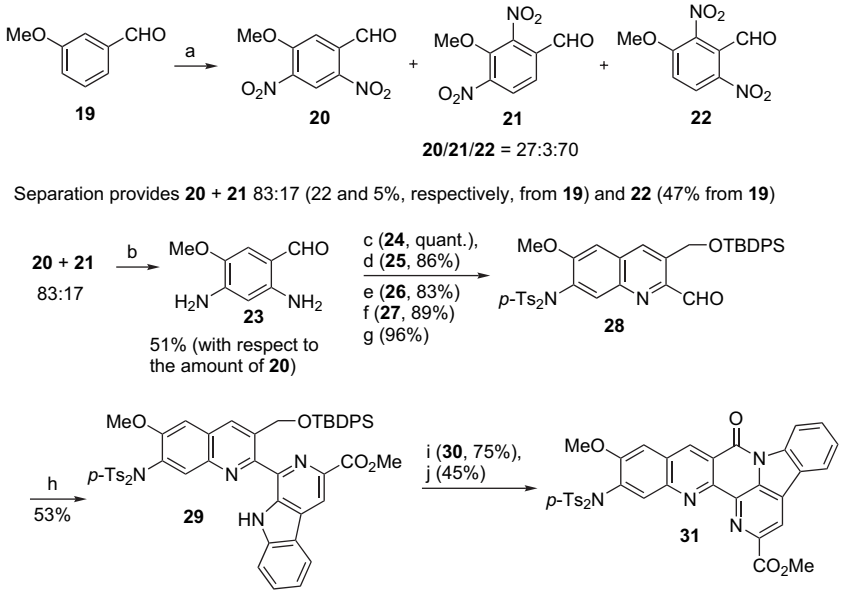
4. Experimental

4.1. General

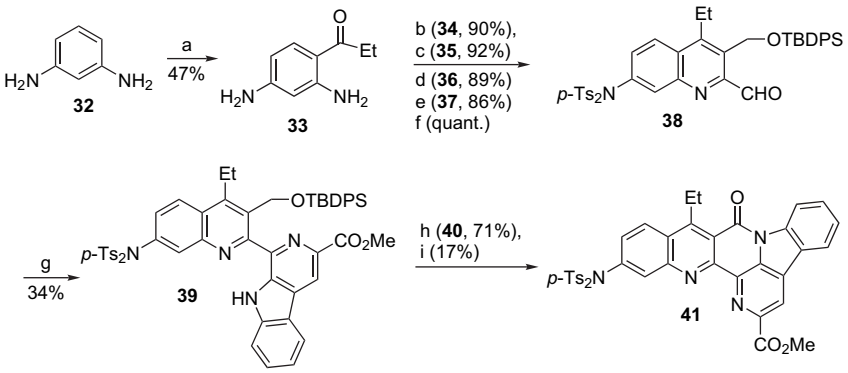
NMR spectra were recorded on a Bruker Avance 400 spectrometer. All melting points are uncorrected. Elemental analyses were performed by the service of microanalyses, CNRS, ICSN, Gif sur Yvette. High resolution mass spectra were recorded on Varian Matt 311 (CRMPO, Rennes), or on Waters-Micromass GCT Premier spectrometers. Infrared spectra were measured with a Nicolet AVATAR 370 DTGS spectrometer.

4.2. 7-Amino-2-methylquinoline-3-carboxylic acid methyl ester *11*

Methyl acetoacetate (4.64 g, 39.99 mmol) and then piperidine (0.7 mL, 7.08 mmol) were added to a stirred solution of 2,4-diaminobenzaldehyde (1.755 g, 12.9 mmol) in anhydrous methanol (60 mL). Heating at reflux for 120 h, cooling,



Scheme 3. (a) HNO_3, H_2SO_4; (b) Fe, HCl, EtOH; (c) Me–CO–CH_2–CO_2Me, MeOH, piperidine; (d) NaH, THF, Ts_2O; (e) DIBAL-H, CH_2Cl_2, −78 °C; (f) *t*-$BuPh_2SiCl$, DMF, imidazole; (g) SeO_2, dioxane; (h) tryptophan methyl ester, *p*-xylene; (i) *n*-Bu_4NF, THF; (j) DMP, NMP, pyridine.



Scheme 4. (a) EtCN, BCl_3, $AlCl_3$, $C_2H_4Cl_2$; (b) Me–CO–CH_2–CO_2Me, MeOH, H_2SO_4; (c) NaH, THF, Ts_2O; (d) DIBAL-H, CH_2Cl_2, −78 °C; (e) *t*-$BuPh_2SiCl$, DMF, imidazole; (f) SeO_2, dioxane; (g) tryptophan methyl ester, *p*-xylene; (h) *n*-Bu_4NF, THF; (i) DMP, NMP, pyridine.

evaporation, and then column chromatography on silica gel (cyclohexane/EtOAc 2:1) provided compound **11** (2.124 g, 76%) as a yellow solid. R_f=0.22 (cyclohexane/EtOAc 1:3). Mp 151.5–153.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (1H, s), 7.62 (1H, d, J=8.7 Hz), 7.10 (1H, d, J=2.1 Hz), 6.93 (1H, dd, J=2.1, 8.7 Hz), 4.31 (2H, br s, NH_2), 3.93 (3H, s), 2.93 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 159.3, 150.7, 150.0, 139.8, 130.0, 119.5, 119.4, 118.3, 108.0, 52.0, 25.8. IR (ATR) (cm^{-1}): 3397, 3166, 1701, 1593, 1499, 1438, 1389, 1273, 1212, 1182, 1070. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.39; H, 5.64; N, 12.94.

4.3. 7-Di-p-tosylamino-2-methylquinoline-3-carboxylic acid methyl ester ***12***

Sodium hydride (1.96 g of a 60% suspension in oil, 48.85 mmol) was added under nitrogen and with stirring to a cooled solution (0 °C) of compound **11** (2.113 g, 9.77 mmol) in anhydrous THF (95 mL). After 10 min, *p*-toluenesulfonic anhydride (15.9 g, 48.85 mmol) was added and then the reaction mixture was stirred at room temperature for 2 days. Methanol (30 mL) was added dropwise and the reaction mixture was evaporated. Addition of CH_2Cl_2 (20 mL) to the residue, washing of the resulting solution with water (5 mL), drying ($MgSO_4$), evaporation, and then column chromatography on silica gel (cyclohexane/EtOAc 3:1→0:1) provided compound **12** (4.193, 82%) as a white solid. R_f=0.44 (cyclohexane/EtOAc 1:1). Mp 197.3–198.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (1H, s), 7.83–7.81 (6H, m), 7.34 (4H, d, J=8.4 Hz), 7.19 (1H, dd, J=2.1, 8.6 Hz), 3.99 (3H, s), 2.98 (3H, s), 2.47 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 159.5, 148.3, 145.2, 139.4, 137.0, 136.4, 132.0, 129.7 (4C), 129.3, 129.1, 128.6 (4C), 126.2, 124.8, 52.5, 25.6, 21.7 (2C). IR (ATR) (cm^{-1}): 1730, 1593, 1370, 1283, 1185, 1160, 1066, 929, 809, 666. HRMS calcd for $C_{19}H_{17}N_2O_4S$ $(M-Ts)^+$: 369.0909, found: 369.0877.

4.4. 7-Di-p-tosylamino-3-hydroxymethyl-2-methylquinoline ***13***

DIBAL-H (28.0 mL of a 1 M solution in toluene, 28.0 mmol) was added under nitrogen and with stirring to a cooled solution (−78 °C) of compound **12** (4.193 g, 7.99 mmol) in anhydrous CH_2Cl_2 (66 mL). After 2.5 h of stirring at the same temperature, methanol (30 mL) was added dropwise and the mixture was allowed to warm up to room temperature. Addition of a 30% solution of potassium and sodium tartrate (60 mL), stirring for 30 min, decantation, extraction of the aqueous phase with CH_2Cl_2 (3×80 mL), washing of the combined organic phases with a saturated solution of $NaHCO_3$ (40 mL), and then with brine (40 mL), drying ($MgSO_4$), evaporation, and then column chromatography on silica gel (CH_2Cl_2/MeOH 1:0→99:1) provided compound **13** (3.621, 91%) as a white solid. R_f=0.41 (CH_2Cl_2/MeOH 9:1). Mp 207–208 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (1H, s), 8.00 (1H, d, J=8.7 Hz), 7.73 (4H, d, J=8.3 Hz), 7.51–7.49 (5H, m), 7.10 (1H, dd, J=2.1, 8.7 Hz), 5.54 (1H, t, J=5.3 Hz, OH), 4.71 (2H, d, J=5.3 Hz), 2.60 (3H, s), 2.46 (6H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.7, 145.5, 136.3 (2C), 135.6, 133.3, 131.7, 130.7, 130.0 (4C), 128.7, 128.0 (4C), 127.8, 127.4, 60.1, 22.1, 21.1 (2C). IR (ATR) (cm^{-1}): 3153, 1597, 1496, 1370, 1344, 1167, 1086, 928, 811, 670, 658, 546. HRMS calcd for $C_{18}H_{17}N_2O_3S$ $(M-Ts)^+$: 341.0960, found: 341.0930.

4.5. 7-Di-p-tosylamino-3-tert-butyldiphenylsilanoxymethyl-2-methylquinoline ***14***

Imidazole (1.22 g, 18 mmol) and *tert*-butyldiphenylsilyl chloride (2.8 mL, 10.8 mmol) were added to a solution of compound **13** (3.574 g, 7.20 mmol) in anhydrous DMF (35 mL). The reaction mixture was stirred for 15 h and then a saturated solution of $NaHCO_3$ (30 mL) was added. Extraction with CH_2Cl_2 (3×10 mL), washing of the combined organic phases with brine, drying ($MgSO_4$), and then column chromatography on silica gel (cyclohexane/EtOAc 9:1) provided compound **14** (5.097 g, 96%) as a white solid. R_f=0.37 (cyclohexane/EtOAc 2:1). Mp 169.5–170.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (1H, s), 7.84 (4H, d, J=8.3 Hz), 7.80 (1H, s), 7.75 (1H, d, J=8.6 Hz), 7.72–7.70 (4H, m), 7.47–7.38 (6H, m), 7.33 (4H, d, J=8.3 Hz), 7.13 (1H, d, J=8.6 Hz), 4.87 (2H, s), 2.56 (3H, s), 2.47 (6H, s), 1.14 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 146.5, 145.0, 136.6, 135.4 (4C), 134.5, 134.3, 132.9, 132.5, 131.8, 130.0, 129.6 (4C), 128.6 (4C), 128.5, 128.3, 127.9 (4C), 127.7, 63.1, 26.8 (3C), 22.5, 21.7 (2C), 19.3. IR (ATR) (cm^{-1}): 2930, 2856, 1596, 1492, 1378, 1359, 1169,

1111, 1046, 934, 809, 703, 660, 544. Anal. Calcd for $C_{41}H_{42}N_2O_5S_2Si$: C, 67.00; H, 5.76; N, 3.81. Found: C, 66.89; H, 5.68; N, 3.64.

4.6. 7-Di-p-tosylamino-3-tert-butyldiphenylsilanoxymethyl-quinoline-2-carbaldehyde **15**

Freshly sublimed SeO_2 (966 mg, 8.71 mmol) was added under nitrogen and with stirring to a solution of compound **14** (4.919 g, 6.70 mmol) in anhydrous dioxane (63 mL). The reaction mixture was refluxed for 2.5 h. Cooling, filtration, evaporation of the filtrate, and then column chromatography on silica gel (cyclohexane/EtOAc 5:1) provided compound **15** (4.842 g, 96%) as a pale yellow solid. R_f=0.33 (cyclohexane/EtOAc 4:1). Mp 92.1–94.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (1H, s), 8.80 (1H, s), 8.00 (1H, s), 7.92 (1H, d, J=8.7 Hz), 7.85 (4H, d, J=8.7 Hz), 7.71–7.70 (4H, m), 7.46–7.31 (11H, m), 5.38 (2H, s), 2.49 (6H, s), 1.19 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 149.7, 146.2, 145.3, 136.7, 136.4, 135.5, 135.4 (4C), 133.9, 133.3, 133.0, 131.9, 129.9 (2C), 129.8 (4C), 128.6 (5C), 127.9 (4C), 62.3, 27.0 (3C), 21.8 (2C), 19.5. IR (ATR) (cm^{-1}): 2929, 2856, 1710, 1596, 1427, 1379, 1168, 1112, 1084, 930, 812, 660, 545. Anal. Calcd for $C_{41}H_{40}N_2O_6S_2Si$: C, 65.75; H, 5.38; N, 3.74. Found: C, 65.51; H, 5.18; N, 3.50.

4.7. 1-[(7-Di-p-tosylamino-3-tert-butyldiphenylsilanoxymethyl)-quinolin-2-yl]-9H-β-carboline-3-carboxylic acid methyl ester **16**

Compound **15** (1.000 g, 1.34 mmol) was added under nitrogen and with stirring to a solution of tryptophan methyl ester (439 mg, 2.01 mmol) in anhydrous *p*-xylene (22 mL). The reaction mixture was refluxed for 17 h. Cooling, evaporation, and then column chromatography on silica gel (cyclohexane/EtOAc 6:1) provided compound **16** (577 mg, 46%) as a white solid. R_f=0.70 (cyclohexane/EtOAc 1:1). Mp 225–226 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.41 (1H, br s, NH), 9.07 (1H, s), 8.88 (1H, s), 8.22 (1H, d, J=7.9 Hz), 8.04 (1H, s), 7.96 (1H, d, J=8.6 Hz), 7.92 (4H, d, J=8.4 Hz), 7.79–7.77 (4H, m), 7.72 (1H, d, J=8.2 Hz), 7.68–7.66 (1H, m), 7.42–7.34 (11H, m), 7.26–7.23 (1H, m), 5.95 (2H, s), 3.53 (3H, s), 2.49 (6H, s), 1.21 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 155.3, 145.3, 145.2, 140.5, 138.6, 138.0, 136.9, 136.5, 136.0, 135.4 (4C), 135.0, 134.4, 133.6, 131.8, 130.6, 129.7 (5C), 129.5, 129.0, 128.9, 128.8 (4C), 128.2, 127.8 (4C), 121.8, 121.7, 121.0, 118.0, 112.3, 64.6, 52.0, 27.0 (3C), 21.8 (2C), 19.5. IR (ATR) (cm^{-1}): 3371, 2949, 2856, 1712, 1593, 1491, 1429, 1385, 1169, 1107, 1061, 923, 702, 656, 545. Anal. Calcd for $C_{54}H_{50}N_4O_8S_2Si$: C, 67.35; H, 5.12; N, 5.93. Found: C, 67.18; H, 5.01; N, 5.76.

4.8. 1-[(7-Di-p-tosylamino-3-hydroxymethyl)-quinolin-2-yl]-9H-β-carboline-3-carboxylic acid methyl ester **17**

Glacial acetic acid (120 μL) and TBAF (0.95 mL of a 1 M solution in THF, 0.951 mmol) were added under nitrogen and with stirring to a solution of compound **16** (300 mg, 0.317 mmol) in anhydrous THF (2.5 mL). After 1 day of stirring at room temperature and then evaporation, a mixture of petroleum ether/EtOAc 1:4 (7 mL) was added. Stirring and heating of the mixture, filtration with heating, and recuperation of the solid provided compound **17** (188 mg, 84%) as a pale yellow solid. Mp 231–232 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.37 (1H, br s, NH), 8.93 (1H, s), 8.34 (1H, s), 8.25 (1H, d, J=8.0 Hz), 8.04 (1H, d, J=2.0 Hz), 7.89 (4H, d, J=8.3 Hz), 7.85 (1H, d, J=8.6 Hz), 7.75–7.68 (2H, m), 7.45–7.42 (1H, m), 7.38 (4H, d, J=8.0 Hz), 7.23 (1H, dd, J=2.0, 8.6 Hz), 6.83 (1H, t, J=8.1 Hz, OH), 4.98 (2H, d, J=8.1 Hz), 4.08 (3H, s), 2.48 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 157.8, 145.9, 145.4, 140.8, 139.4, 138.2, 137.0, 136.4, 136.1, 135.7, 135.6, 132.0, 131.1, 130.0, 129.7 (4C), 129.4, 128.7 (4C), 128.5, 128.1, 121.9, 121.5, 121.3, 118.2, 112.5, 64.5, 52.7, 21.8 (2C). IR (ATR) (cm^{-1}): 3338, 1719, 1492, 1431, 1374, 1358, 1253, 1234, 1169, 1027, 927, 659, 545. HRMS calcd for $C_{37}H_{30}N_4O_7NaS_2$ $(M+Na)^+$: 729.1454, found: 729.1453.

4.9. 13-Di-p-tosylamino-9-oxo-9H-indolo[3,2,1-ij]quino-[3,2,c]-1,5-naphthyiridine-2-carboxylic acid methyl ester **18**

Anhydrous pyridine (215 μL, 2.55 mmol) and DMP (163 mg, 0.383 mmol) were added under nitrogen and with stirring to a solution of compound **17** (180 mg, 0.255 mmol) in anhydrous NMP (1.75 mL). After 2 days of stirring at room temperature, CH_2Cl_2 (15 mL) was added and the suspension was successively washed with a 1:1 mixture of a 5% solution of $Na_2S_2O_3$ and of a saturated solution of $NaHCO_3$ (8 mL), a saturated solution of $NaHCO_3$ (5 mL), 1 M HCl (5 mL), and then brine (5 mL). This suspension was evaporated without drying and then column chromatography on silica gel (CH_2Cl_2/EtOAc 99:1→9:1) provided compound **18** (61 mg, 34%) as a pale yellow solid. R_f=0.59 (CH_2Cl_2/EtOAc 9:1). Mp 286–287 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (1H, s), 9.03 (1H, s), 8.85 (1H, d, J=8.3 Hz), 8.44 (1H, s), 8.28 (1H, d, J=7.6 Hz), 8.12 (1H, d, J=8.7 Hz), 7.89–7.84 (5H, m), 7.68–7.65 (1H, m), 7.40–7.38 (5H, m), 4.17 (3H, s), 2.51 (6H, s). ^{13}C NMR (100 MHz, $C_2D_2Cl_4$, 340 K) δ 165.9, 158.7, 150.2, 149.6, 145.6, 144.9, 140.0, 139.3, 138.7, 136.6, 135.7, 134.7, 133.7, 132.1, 131.6, 131.3, 129.9, 128.6, 127.7, 126.3, 124.7, 124.6, 122.8, 118.7, 117.6, 53.1, 21.7 (2C). IR (ATR) (cm^{-1}): 2921, 1713, 1693, 1594, 1488, 1433, 1356, 1278, 1233, 1165, 940, 809, 739. HRMS calcd for $C_{37}H_{26}N_4O_7NaS_2$ $(M+Na)^+$: 725.1141, found: 725.1156.

4.10. 5-Methoxy-2,4-dinitrobenzaldehyde **20**, 3-methoxy-2,4-dinitrobenzaldehyde **21**, and 3-methoxy-2,6-dinitrobenzaldehyde **22**

3-Methoxybenzaldehyde (500 mg, 3.67 mmol) was added dropwise at −10 °C to a stirred solution of a mixture of fuming nitric acid (0.8 mL) and of concentrated H_2SO_4 (0.8 mL). The stirring was then kept for 1 h at the same temperature and then for 1 h at room temperature. The reaction mixture was

poured into ice (3 g). The precipitate was filtered and rinsed with a small amount of cooled water. Recuperation of the solid, evaporation, and then ^{1}H NMR analysis showed the presence of compounds **20**, **21**, and **22** in the 27:3:70 ratios, respectively. Column chromatography on silica gel (cyclohexane/EtOAc 4:1) provided compound **22** (394 mg, 47%) and a non-separable mixture of compounds **20** and **21** (224 mg) in an 83:17 ratio, respectively. Data for **20**: yellow solid. R_f=0.51 (cyclohexane/EtOAc 1:1). Mp 121.5–124.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (1H, s), 8.70 (1H, s), 7.56 (1H, s), 4.15 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.7, 156.6, 140.7, 140.3, 136.1, 123.2, 114.0, 57.9. IR (ATR) (cm^{-1}): 3113, 3067, 1698, 1589, 1518, 1489, 1384, 1333, 1281, 1251, 1159, 1046, 922, 872, 736. Anal. Calcd for $C_8H_6N_2O_6$: C, 42.49; H, 2.67; N, 12.39. Found: C, 42.47; H, 2.72; N, 12.40. Data for **21**: yellow solid. R_f=0.51 (cyclohexane/EtOAc 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (1H, s), 8.13 (1H, d, J=8.5 Hz), 7.84 (1H, d, J=8.5 Hz), 4.07 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.8, 146.5, 130.5, 127.3, 125.4, 65.3. Data for **22**: yellow solid. R_f=0.24 (cyclohexane/EtOAc 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (1H, s), 8.40 (1H, d, J=9.3 Hz), 7.31 (1H, d, J=9.3 Hz), 4.08 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.8, 155.9, 139.5 (2C), 129.7, 128.5, 114.7, 57.7.

*4.11. 2,4-Diamino-5-methoxybenzaldehyde **23***

Iron powder (19.5 g, 348 mmol), water (32 mL), and 10 M HCl (0.75 mL, 7.5 mmol) were added to a solution of a mixture of compounds **20** and **21** (83:17, 3.673 g of **20**, 16.2 mmol) in EtOH (127 mL). The reaction mixture was mechanically stirred at 95 °C for 1.5 h. Cooling, filtration, washing of the solid with EtOH (25 mL), evaporation, and then column chromatography on silica gel (cyclohexane/EtOAc/Et_3N 40:55:5) provided compound **23** (1.14 g, 51%) as an orange solid. R_f=0.33 (cyclohexane/EtOAc 1:3). Mp 174.9–176.0 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 9.49 (1H, s), 6.83 (1H, s), 6.51 (2H, br s, NH_2); 6.01 (1H, s), 5.32 (2H, br s, NH_2), 3.78 (3H, s). ^{13}C NMR (100 MHz, acetone-d_6) δ 191.0, 150.6, 147.9, 140.7, 116.5, 111.2, 99.5, 57.2. IR (ATR) (cm^{-1}): 3453, 3330, 2837, 2760, 2522, 2493, 1601, 1583, 1515, 1410, 1314, 1157, 1022, 854, 743. Anal. Calcd for $C_8H_{10}N_2O_2\cdot 0.15H_2O$: C, 56.90; H, 6.15; N, 16.59. Found: C, 56.91; H, 6.08; N, 16.34.

*4.12. 7-Amino-6-methoxy-2-methylquinoline 3-carboxylic acid methyl ester **24***

Reaction of compound **23** (1.14 g, 6.86 mmol) with the same experimental conditions as that for the preparation of compound **11**, but with cyclohexane/EtOAc 1:1→1:3 as the eluent for the column chromatography provided compound **24** (1.691 g, quant.) as a white solid. R_f=0.26 (cyclohexane/EtOAc 1:3). Mp 216–217 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (1H, s), 7.12 (1H, s), 6.97 (1H, s), 4.51 (2H, br s, NH_2), 3.98 (3H, s), 3.93 (3H, s), 2.91 (3H, s). ^{13}C NMR (100 MHz, CD_3OD) δ 168.6, 157.3, 150.1, 147.9, 146.6, 139.9, 120.9, 119.7, 105.9, 105.3, 56.4, 52.5, 24.7. IR (ATR) (cm^{-1}): 2593, 2374, 1690, 1618, 1591, 1498, 1436, 1229, 1176, 1033, 1004. Anal. Calcd for $C_{13}H_{14}N_2O_3\cdot 0.1H_2O$: C, 62.94; H, 5.77; N, 11.29. Found: C, 62.76; H, 5.78; N, 11.21.

*4.13. 7-Di-p-tosylamino-6-methoxy-2-methylquinoline 3-carboxylic acid methyl ester **25***

Reaction of compound **24** (221 mg, 0.897 mmol) with the same experimental conditions as that for the preparation of compound **12**, but with cyclohexane/EtOAc 4:1 as the eluent for the column chromatography provided compound **25** (429 mg, 86%) as a white solid. R_f=0.66 (cyclohexane/EtOAc 1:3). Mp 207–208 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (1H, s), 7.89 (1H, s), 7.84 (4H, d, J=8.3 Hz), 7.32 (4H, d, J=8.3 Hz), 7.05 (1H, s), 3.98 (3H, s), 3.53 (3H, s), 2.94 (3H, s), 2.48 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 156.8, 155.2, 144.9, 143.8, 138.2, 137.0, 133.6, 129.3 (5C), 128.8 (4C), 127.8, 124.9, 106.5, 55.5, 52.5, 25.3, 21.7 (2C). IR (ATR) (cm^{-1}): 2923, 2852, 1724, 1597, 1488, 1372, 1165, 1084, 928, 812, 667. Anal. Calcd for $C_{27}H_{26}N_2O_7S_2$: C, 58.47; H, 4.72; N, 5.05. Found: C, 58.36; H, 4.86; N, 4.92.

*4.14. 7-Di-p-tosylamino-3-hydroxymethyl-6-methoxy-2-methylquinoline **26***

Reaction of compound **25** (2.723 g, 4.91 mmol) with the same experimental conditions as that for the preparation of compound **13** provided compound **25** (2.142 g, 83%) as a white solid. R_f=0.34 (CH_2Cl_2/MeOH 9:1). Mp 228–229 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (1H, s), 7.70 (4H, d, J=8.3 Hz), 7.56 (1H, s), 7.47 (4H, d, J=8.3 Hz), 7.41 (1H, s), 5.49 (1H, t, J=5.2 Hz, OH), 4.68 (2H, d, J=5.2 Hz), 3.47 (3H, s), 2.55 (3H, s), 2.45 (6H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.7, 154.0, 145.1, 140.6, 136.3, 136.0, 132.2, 130.7, 129.5 (4C), 129.0, 128.2 (4C), 125.1, 106.7, 60.2, 55.4, 21.8, 21.1 (2C). IR (ATR) (cm^{-1}): 1597, 1493, 1373, 1348, 1166, 943, 670, 548. HRMS calcd for $C_{19}H_{19}N_2O_4S$ $(M-Ts)^+$: 371.1066, found: 371.1083.

*4.15. 7-Di-p-tosylamino-3-tert-butyldiphenylsilanoxymethyl-6-methoxy-2-methylquinoline **27***

Reaction of compound **26** (2.142 g, 4.07 mmol) with the same experimental conditions as that for the preparation of compound **14** provided compound **27** (2.768 g, 89%) as a white solid. R_f=0.43 (cyclohexane/EtOAc 2:1). Mp 191.7–192.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (1H, s), 7.89 (1H, s), 7.87 (4H, d, J=8.2 Hz), 7.73–7.71 (4H, m), 7.49–7.39 (6H, m), 7.32 (4H, d, J=8.2 Hz), 7.01 (1H, s), 4.86 (2H, s), 3.55 (3H, s), 2.52 (3H, s), 2.47 (6H, s), 1.15 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 154.8, 144.6, 141.7, 137.2, 135.4 (4C), 134.5, 133.4, 132.9, 131.3, 130.0 (2C), 129.2 (4C), 128.9 (4C), 127.9 (4C), 126.6, 106.1, 63.2, 55.4, 26.8 (3C), 22.2, 21.7 (2C), 19.4. IR (ATR) (cm^{-1}): 2929, 2856, 1596, 1490, 1375, 1354, 1166, 930, 702, 547. Anal. Calcd

for $C_{42}H_{44}N_2O_6S_2Si$: C, 65.94; H, 5.80; N, 3.66. Found: C, 65.86; H, 5.60; N, 3.42.

4.16. 7-Di-p-tosylamino-3-tert-butyldiphenylsilanoxymethyl-6-methoxyquinoline-2-carbaldehyde **28**

Reaction of compound **27** (163 mg, 0.213 mmol) with the same experimental conditions as that for the preparation of compound **15** provided compound **28** (160 mg, 96%) as a white solid. R_f=0.38 (cyclohexane/EtOAc 4:1). Mp 146.1–147.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (1H, s), 8.64 (1H, s), 8.06 (1H, s), 7.87 (4H, d, J=8.3 Hz), 7.72–7.70 (4H, m), 7.46–7.34 (10H, m), 7.10 (1H, s), 5.38 (2H, s), 3.62 (3H, s), 2.48 (6H, s), 1.19 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 157.5, 147.7, 145.0, 141.7, 137.1, 137.0, 135.4 (4C), 135.1, 133.1, 132.0, 129.9 (2C), 129.4 (4C), 128.9 (4C), 128.3, 127.9 (4C), 105.8, 62.4, 55.7, 27.0 (3C), 21.7 (2C), 19.5. IR (ATR) (cm^{-1}): 2926, 2853, 1705, 1619, 1596, 1489, 1380, 1221, 1169, 1083, 928, 659, 545. HRMS calcd for $C_{42}H_{42}N_2O_7SiS_2$ $(M+Na)^+$: 801.2100, found: 801.2111.

4.17. 1-[(7-Di-p-tosylamino-3-tert-butyldiphenylsilanoxymethyl-6-methoxy)-quinolin-2-yl]-9H-β-carboline-3-carboxylic acid methyl ester **29**

Reaction of compound **28** (159 mg, 0.204 mmol) with the same experimental conditions as that for the preparation of compound **16** provided compound **29** (106 mg, 53%) as a white solid. R_f=0.53 (cyclohexane/EtOAc 1:1). Mp 250–251 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (1H, br s, NH), 8.91 (1H, s), 8.87 (1H, s), 8.23 (1H, d, J=7.9 Hz), 8.09 (1H, s), 7.94 (4H, d, J=8.3 Hz), 7.79–7.73 (5H, m), 7.68–7.65 (1H, m), 7.43–7.35 (11H, m), 7.16 (1H, s), 5.94 (2H, s), 3.64 (3H, s), 3.53 (3H, s), 2.49 (6H, s), 1.21 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 155.7, 152.9, 144.9, 140.5, 140.4, 139.0, 138.1, 137.0, 136.7, 135.8, 135.4 (4C), 133.7 (2C), 132.9, 130.4, 130.0, 129.7, 129.3 (4C), 129.1 (4C), 128.9, 127.8 (4C), 127.2, 121.8, 121.7, 120.9, 117.7, 112.4, 106.3, 64.7, 55.5, 51.9, 27.1 (3C), 21.7 (2C), 19.5. IR (ATR) (cm^{-1}): 3360, 2927, 2851, 1702, 1492, 1432, 1376, 1361, 1261, 1244, 1168, 1071, 659, 549. Anal. Calcd for $C_{54}H_{50}N_4O_8S_2Si$: C, 66.51; H, 5.17; N, 5.75. Found: C, 66.54; H, 5.21; N, 5.40.

4.18. 1-[(7-Di-p-tosylamino-3-hydroxymethyl-6-methoxy)-quinolin-2-yl]-9H-β-carboline-3-carboxylic acid methyl ester **30**

Reaction of compound **29** (620 mg, 0.636 mmol) with the same experimental conditions as that for the preparation of compound **17** provided compound **30** (351 mg, 75%) as a pale pink solid. Mp 242–243 °C. ^{1}H NMR (400 MHz, $C_2D_2Cl_4$, 340 K) δ 11.29 (1H, br s, NH), 8.84 (1H, s), 8.18 (1H, d, J=7.8 Hz), 8.14 (1H, s), 8.01 (1H, s), 7.78 (4H, d, J=8.0 Hz), 7.66–7.57 (2H, m), 7.36–7.31 (1H, m), 7.26 (4H, d, J=8.0 Hz), 7.02 (1H, s), 6.37 (1H, br s, OH), 4.90 (2H, s), 3.99 (3H, s), 3.50 (3H, s), 2.38 (6H, s). ^{13}C NMR (100 MHz, $C_2D_2Cl_3$, 340 K) δ 166.0, 156.3, 155.3, 145.2 (2C), 141.3, 141.0, 138.8, 137.9, 137.1 (4C), 136.7, 136.1, 134.0, 131.1, 130.0, 129.4, 129.3, 129.1 (4C), 128.1, 121.9, 121.7, 121.4, 117.9, 112.6, 106.2, 64.5, 55.6, 52.6, 21.6 (2C). IR (ATR) (cm^{-1}): 3371, 1718, 1491, 1377, 1250, 1170, 1012, 926, 868, 660. Anal. Calcd for $C_{38}H_{32}N_4O_8S_2\cdot 0.25H_2O$: C, 61.57; H, 4.42; N, 7.56. Found: C, 61.33; H, 4.47; N, 7.53.

4.19. 13-Di-p-tosylamino-12-methoxy-9-oxo-9H-indolo[3,2,1-ij]quino[3,2,c]-1,5-naphthyiridine-2-carboxylic acid methyl ester **31**

Reaction of compound **30** (180 mg, 0.244 mmol) with the same experimental conditions as that for the preparation of compound **18**, but with CH_2Cl_2/EtOAc 98:2→9:1 as the eluent for the column chromatography provided compound **31** (80 mg, 45%) as a pale yellow solid. R_f=0.66 (CH_2Cl_2/EtOAc 9:1). Mp 289–290 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (1H, s), 8.96 (1H, s), 8.79 (1H, d, J=8.2 Hz), 8.52 (1H, s), 8.22 (1H, d, J=8.0 Hz), 7.91 (4H, d, J=8.3 Hz), 7.80 (1H, dd, J=1.1, 8.4 Hz), 7.61 (1H, dd, J=0.8, 7.8 Hz), 7.39 (4H, d, J=8.3 Hz), 7.26 (1H, s), 4.16 (3H, s), 3.58 (3H, s), 2.51 (6H, s). ^{13}C NMR (100 MHz, $C_2D_2Cl_4$, 340 K) δ 165.8, 158.8, 156.9, 147.4, 145.9, 145.1, 144.8, 139.3, 138.0, 137.2, 136.0, 135.5, 134.2, 132.0, 131.7, 131.4, 129.7, 129.5, 128.9, 126.2, 124.8, 122.8, 118.3, 117.6, 106.9, 55.8, 53.0, 21.7 (2C). IR (ATR) (cm^{-1}): 2953, 1716, 1687, 1590, 1482, 1379, 1346, 1249, 1166, 1084, 1017, 927, 660, 547. HRMS calcd for $C_{38}H_{28}N_4O_8NaS_2$ $(M+Na)^+$: 755.1246, found: 755.1223.

4.20. (2,4-Diaminophenyl)propan-3-one **33**[13]

Propionitrile (611 mg, 11.1 mmol) was added to a solution of 1,3-diaminobenzene (1.00 g, 9.25 mmol) in $C_2H_4Cl_2$ (19 mL). The mixture was cooled to 0 °C and then BCl_3 (10.2 mL of a 1 M solution in hexane, 10.2 mmol) and $AlCl_3$ (1.36 g, 10.18 mmol) were progressively added with stirring at this temperature. The reaction mixture was allowed to warm up to room temperature and then it was heated at reflux for 3 h. Cooling, adding of 2 M HCl (30 mL), heating at reflux for 30 min, cooling, adding of a 10% solution of NaOH until pH>10, extraction of the aqueous phase with CH_2Cl_2 (4×80 mL), washing of the combined organic phases with brine (30 mL), drying ($MgSO_4$), and then column chromatography on silica gel (cyclohexane/EtOAc 4:1→3:1) provided compound **33** (709 mg, 47%) as a white solid. R_f=0.49 (EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 (1H, d, J=8.8 Hz) 7.07 (2H, br s, NH_2), 5.84 (1H, dd, J=2.1, 8.8 Hz), 5.76 (1H, d, J=2.1 Hz), 5.70 (2H, br s, NH_2), 2.73 (2H, q, J=7.4 Hz), 1.03 (3H, t, J=7.4 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.8, 153.7, 153.4, 132.9, 108.0, 103.7, 97.0, 30.7, 9.4.

4.21. 7-Amino-4-ethyl-2-methylquinoline-3-carboxylic acid methyl ester **34**

Methyl acetoacetate (1.41 g, 12.18 mmol) and then concentrated sulfuric acid (0.35 mL) were added to a solution of

compound **33** (1.00 g, 6.09 mmol) in anhydrous MeOH (27 mL). Heating at reflux for 16 h, cooling, evaporation, adding of CH_2Cl_2 (15 mL), washing of the solution with a saturated solution of $NaHCO_3$ (5 mL), and then with brine (5 mL), drying ($MgSO_4$), and then column chromatography on silica gel (cyclohexane/EtOAc 1:1) provided compound **34** (1.338, 90%) as a pale yellow solid. R_f=0.20 (cyclohexane/EtOAc 1:3). Mp 170.2–171.5 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 7.82 (1H, d, J=9.0 Hz), 7.05 (1H, dd, J=2.3, 9.0 Hz), 7.02 (1H, d, J=2.3 Hz), 3.95 (3H, s), 2.93 (2H, q, J=7.6 Hz), 2.53 (3H, s), 1.27 (3H, t, J=7.6 Hz). ^{13}C NMR (100 MHz, CD_3OD) δ 171.3, 155.6, 152.4, 150.7, 149.8, 126.3, 124.4, 120.0, 118.6, 107.6, 52.9, 24.2, 23.1, 15.8. IR (ATR) (cm^{-1}): 3127, 2322, 1716, 1617, 1579, 1506, 1430, 1283, 1219, 1176, 855, 822. Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.52; H, 6.46; N, 11.46.

4.22. 7-Di-p-tosylamino-4-ethyl-2-methylquinoline-3-carboxylic acid methyl ester ***35***

Reaction of compound **34** (1.283 g, 5.25 mmol) with the same experimental conditions as that for the preparation of compound **12**, but with cyclohexane/EtOAc 5:1 as the eluent for the column chromatography provided compound **27** (2.656 g, 92%) as a white solid. R_f=0.45 (cyclohexane/EtOAc 1:1). Mp 164.5–165.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (1H, d, J=8.9 Hz), 7.82 (4H, d, J=8.2 Hz), 7.77 (1H, d, J=2.2 Hz), 7.33 (4H, d, J=8.2 Hz), 7.22 (1H, dd, J=2.2, 8.9 Hz), 4.01 (3H, s), 3.01 (2H, q, J=7.6 Hz), 2.67 (3H, s), 2.48 (6H, s), 1.35 (3H, t, J=7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 155.8, 147.6, 147.1, 145.2, 136.4, 135.5, 132.8, 129.7 (4C), 129.0, 128.6 (4C), 128.3, 125.4, 124.9, 52.6, 23.8, 23.6, 21.8 (2C), 15.2. IR (ATR) (cm^{-1}): 2927, 1731, 1587, 1495, 1437, 1373, 1357, 1270, 1165, 1080, 923, 868, 814, 660, 549. Anal. Calcd for $C_{28}H_{28}N_2O_6S_2$: C, 60.85; H, 5.11; N, 5.07. Found: C, 60.62; H, 5.22; N, 4.95.

4.23. 7-Di-p-tosylamino-4-ethyl-3-hydroxymethyl-2-methylquinoline ***36***

Reaction of compound **35** (2.602 g, 7.99 mmol) with the same experimental conditions as that for the preparation of compound **13**, but with cyclohexane/EtOAc 1:0→98:2 as the eluent for the column chromatography provided compound **36** (2.194 g, 89%) as a white solid. R_f=0.42 (CH_2Cl_2/MeOH 9:1). Mp 197.5–198.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (1H, d, J=9.0 Hz), 7.73 (4H, d, J=8.4 Hz), 7.50 (4H, d, J=8.4 Hz), 7.45 (1H, d, J=2.2 Hz), 7.16 (1H, dd, J=2.2, 9.0 Hz), 5.18 (1H, t, J=4.9 Hz, OH), 4.71 (2H, d, J=4.9 Hz), 3.17 (2H, q, J=7.5 Hz), 2.74 (3H, s), 2.45 (6H, s), 1.23 (3H, t, J=7.5 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 147.6, 146.1, 145.5, 135.6, 133.4, 131.9, 131.4, 130.0 (4C), 128.0 (4C), 127.7, 126.3, 125.6, 56.7, 23.5, 21.1 (2C), 20.6, 15.5. IR (ATR) (cm^{-1}): 1587, 1492, 1374, 1359, 1166, 927, 872, 811, 658, 607, 548. Anal. Calcd for $C_{27}H_{28}N_2O_5S_2\cdot 0.2H_2O$: C, 61.39; H, 5.42; N, 5.30. Found: C, 61.39; H, 5.35; N, 5.12.

4.24. 7-Di-p-tosylamino-3-tert-butyldiphenylsilanoxymethyl-4-ethyl-2-methylquinoline ***37***

Reaction of compound **36** (2.134 g, 4.07 mmol) with the same experimental conditions as that for the preparation of compound **14**, but with cyclohexane/EtOAc 9:1 as the eluent for the column chromatography provided compound **37** (2.656 g, 86%) as a white solid. R_f=0.55 (cyclohexane/EtOAc 2:1). Mp 169.1–170.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, d, J=9.0 Hz), 7.84 (4H, d, J=8.3 Hz), 7.76 (1H, d, J=2.2 Hz), 7.72–7.71 (4H, m), 7.49–7.39 (6H, m), 7.34 (4H, d, J=8.3 Hz), 7.14 (1H, dd, J=2.2, 9.0 Hz), 4.85 (2H, s), 2.91 (2H, q, J=7.6 Hz), 2.71 (3H, s), 2.48 (6H, s), 1.13 (3H, t, J=7.6 Hz), 1.07 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 148.3, 147.1, 145.0, 136.6, 135.7 (4C), 134.4, 133.0, 132.6, 130.3, 130.0, 129.7 (4C), 128.6 (4C), 128.1, 127.8 (4C), 126.7, 125.0, 59.8, 26.9 (3C), 23.9, 21.7 (2C), 21.2, 19.3, 15.5. IR (ATR) (cm^{-1}): 1589, 1492, 1379, 1358, 1171, 1086, 1021, 926, 812, 686, 600, 544. Anal. Calcd for $C_{43}H_{46}N_2O_5S_2Si$: C, 67.68; H, 6.08; N, 3.67. Found: C, 67.61; H, 6.08; N, 3.79.

4.25. 7-Di-p-tosylamino-3-tert-butyldiphenylsilanoxymethyl-4-ethylquinoline-2-carbaldehyde ***38***

Reaction of compound **37** (2.620 g, 3.43 mmol) with the same experimental conditions as that for the preparation of compound **15**, but with cyclohexane/EtOAc 6:1 as the eluent for the column chromatography provided compound **38** (2.670 g, quant.) as a pale pink solid. R_f=0.27 (cyclohexane/EtOAc 4:1). Mp 202–203 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (1H, s), 8.02 (4H, d, J=9.1 Hz), 7.96 (1H, d, J=2.2 Hz), 7.85 (4H, d, J=8.4 Hz), 7.70–7.67 (4H, m), 7.47–7.31 (11H, m), 5.30 (2H, s), 3.04 (2H, q, J=7.6 Hz), 2.49 (6H, s), 1.15 (3H, t, J=7.6 Hz), 1.04 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 152.2, 151.3, 146.9, 145.3, 136.5, 135.8 (4C), 135.5, 134.2, 133.1, 131.2, 131.0, 129.9 (2C), 129.8 (4C), 128.6 (4C), 127.7 (4C), 125.1, 57.1, 26.8 (3C), 21.8 (2C), 21.1, 19.3, 15.3. IR (ATR) (cm^{-1}): 2958, 2858, 1704, 1594, 1443, 1365, 1349, 1174, 1083, 1045, 937, 811, 706, 545. Anal. Calcd for $C_{43}H_{44}N_2O_6S_2Si$: C, 66.47; H, 5.71; N, 3.61. Found: C, 66.31; H, 5.67; N, 3.54.

4.26. 1-[(7-Di-p-tosylamino-3-tert-butyldiphenylsilanoxymethyl-6-methoxy)-4-ethylquinolin-2-yl]-9H-β-carboline-3-carboxylic acid methyl ester ***39***

Reaction of compound **38** (423 g, 1.94 mmol) with the same experimental conditions as that for the preparation of compound **15**, except that reflux time was reduced to 5 h, and CH_2Cl_2 was used as the eluent for the column chromatography provided compound **39** (427 mg, 34%) as a pale yellow solid. R_f=0.71 (CH_2Cl_2/EtOAc 9:1). Mp 126.5–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (1H, br s NH), 8.85 (1H, s), 8.24 (1H, d, J=8.6 Hz), 8.13 (1H, d, J=7.9 Hz), 7.88 (1H, d, J=2.2 Hz), 7.86 (4H, d, J=8.3 Hz), 7.66–7.58 (2H, m), 7.40 (1H, ddd, J=1.0, 6.9, 7.9 Hz), 7.36–7.33 (5H, m),

7.24–7.20 (6H, m), 7.08–7.05 (4H, m), 5.63 (2H, s), 3.95 (3H, s), 3.26 (2H, q, J=7.6 Hz), 2.45 (6H, s), 1.33 (3H, t, J=7.6 Hz), 0.69 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 157.0, 151.8, 146.4, 145.3, 140.9, 140.8, 136.5, 136.4, 136.3, 135.2 (4C), 135.0, 133.1, 133.0, 132.7, 130.4, 129.7 (4C), 129.4 (2C), 129.0, 128.6 (4C), 127.6, 127.3 (4C), 125.3, 121.9, 121.8, 120.9, 117.8, 112.2, 59.0, 52.4, 26.4 (3C), 21.8, 21.7 (2C), 18.8, 15.2. IR (ATR) (cm^{-1}): 2930, 2359, 1712, 1595, 1493, 1428, 1378, 1356, 1258, 1168, 925, 811, 701, 659, 546. HRMS calcd for $C_{55}H_{52}N_4O_7S_2Si$: 972.3047, found: 972.3033.

*4.27. 1-[(7-Di-p-tosylamino-3-hydroxymethyl-6-methoxy)-7-ethylquinolin-2-yl]-9H-β-carboline-3-carboxylic acid methyl ester **40***

Reaction of compound **39** (345 mg, 0.354 mmol) was carried out with the same experimental conditions as that for the preparation of compound **17**. After 15 h at room temperature, evaporation, addition of EtOAc to the residue (20 mL), washing of the organic phase with water (5 mL), and then with brine (5 mL), evaporation, and then column chromatography on silica gel (cyclohexane/EtOAc 3:1→2:1) provided compound **40** (185 mg, 71%) as a pale yellow solid. R_f=0.20 (cyclohexane/EtOAc 1:1). Mp 226–228 °C. ^{1}H NMR (400 MHz, $C_2D_2Cl_4$) δ 10.83 (1H, br s, NH), 8.91 (1H, s), 8.22 (1H, d, J=7.8 Hz), 8.10 (1H, d, J=9.0 Hz), 7.95 (1H, s), 7.77 (4H, d, J=8.3 Hz), 7.70–7.61 (2H, m), 7.40–7.36 (1H, m), 7.32 (4H, d, J=8.3 Hz), 7.18 (1H, dd, J=2.1, 8.9 Hz), 6.45 (1H, t, J=7.8 Hz, OH), 4.79 (2H, d, J=7.8 Hz), 4.01 (3H, s), 3.38 (2H, q, J=7.4 Hz), 2.41 (6H, s), 1.39 (3H, t, J=7.4 Hz). ^{13}C NMR (100 MHz, $C_2D_2Cl_4$) δ 166.0, 158.1, 151.8, 146.1, 145.9, 140.9, 139.3, 137.0, 136.1, 135.7, 135.1, 133.0, 132.9, 131.1, 129.9 (4C), 129.6, 129.5, 128.7 (4C), 127.6, 125.6, 122.1, 121.5 (2C), 118.2, 112.6, 58.3, 53.9, 53.0, 21.8 (2C), 15.6. IR (ATR) (cm^{-1}): 3369, 1713, 1375, 1355, 1261, 1170, 927, 735, 659, 547. HRMS calcd for $C_{39}H_{34}N_4O_7S_2$: 734.1869, found: 734.1881.

*4.28. 13-Di-p-tosylamino-10-ethyl-9-oxo-9H-indolo[3,2,1-ij]quino[3,2,c]-1,5-naphthyiridine-2-carboxylic acid methyl ester **41***

Reaction of compound **40** (60 mg, 0.0817 mmol) with the same experimental conditions as that for the preparation of compound **18**, but with cyclohexane/CH_2Cl_2 8:2→0:1 and then CH_2Cl_2/EtOAc 98:2 as the eluents for the column chromatography provided compound **41** (10 mg, 17%) as a pale yellow solid. R_f=0.66 (CH_2Cl_2/EtOAc 9:1). Mp 209–211 °C. ^{1}H NMR (400 MHz, $C_2D_2Cl_4$) δ 8.87 (1H, s), 8.80 (1H, d, J=8.2 Hz), 8.37 (1H, d, J=2.0 Hz), 8.34 (1H, d, J=9.2 Hz), 8.20 (1H, d, J=7.8 Hz), 7.80–7.75 (5H, m), 7.60–7.56 (1H, m), 7.34 (4H, d, J=8.1 Hz), 7.29 (1H, dd, J=2.0, 9.2 Hz), 4.10 (3H, s), 4.00 (2H, q, J=7.1 Hz), 2.44 (6H, s), 1.55 (3H, t, J=7.1 Hz). ^{13}C NMR (100 MHz, $C_2D_2Cl_4$) δ 165.9, 160.4, 159.4, 150.2, 149.1, 145.9, 144.2, 139.7, 137.7, 136.1, 135.4, 134.1, 134.0, 131.6, 131.5, 130.8, 130.1 (4C), 128.6 (4C), 128.1, 126.3, 126.2, 124.4, 123.0, 121.5, 118.9, 117.8, 53.4, 23.4, 22.0 (2C), 15.4. IR (ATR) (cm^{-1}): 2923, 1719, 1682, 1553, 1376, 1355, 1293, 1277, 1260, 1231, 1167, 925, 798. HRMS calcd for $C_{39}H_{31}N_4O_7S_2$ $(M+H)^+$: 731.1634, found: 731.1645.

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