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SYNTHESIS OF AMINO ACID DERIVATIVES OF 6-AMINOQUINOLINE ANTIMALARIAL AGENTS†

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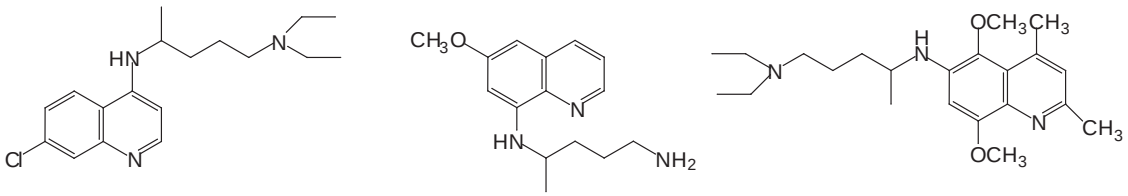
Abstract- Six new 6-aminoquinoline derivatives with amino acid in basic side chain were synthesized in order to modify their biological activities.

INTRODUCTION

Malaria remains a major prevalent infectious disease of tropical and subtropical areas of the world represents a crucial problem in public health care. The emergence of chloroquine-resistant strains of malaria parasite due to *Plasmodium falciparum* has underlined the requIRement for alternative antimalarial agents. Structure-activity relationship studies have shown that it is not only 4-aminoquinoline such as chloroquine **(1)** and 8-aminoquinoline such as primaquine **(2)** that posses antimalarial activity, but also 6-aminoquinoline derivative **(3)** have a broad spectrum of activity for antimalarial agents as well. Unfortunately, it has a highly toxic effect.[1] Introduction of 4-methyl and 5-trifluoromethylphenoxy group in **2** modified its antimalarial activity and considerably less toxic than parent compound[2,3] Moreover, **1** analogs with shortened side chains retained activity against chloroquine-resistant isolates of *P. falciparum*.[4]



1 **2** **3**

Figure 1

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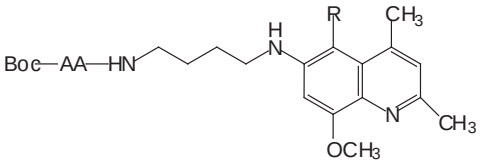
†This paper is dedicated to Professor J. P. Kutney of his 70 th birthday.

The cause of chloroquine resistance remains unknown, but it is clearly associated with alterations in membrane-associated transport processes resulting in a poor accumulation of drug in the infected erythrocytes.[5] Modification of metabolic transportation of malaria-infected erythrocytes would provide new rationales for therapeutic intervention.[6] The growth of asexual erythrocytic stage parasite utilized almost amino acids for parasite protein synthesis through degradation of ingested hemoglobin, but it requires seven exogenously supplied amino acids (Ile, Met, Cys, Gln, Glu, Pro and Tyr).[7] Interestingly, peptide derivatives of **2** showed both reduced toxicity and enhanced its therapeutic effects.[8,9] In this study, we proposed that the introduction of amino acid into basic side chain of 6-aminoquinoline derivatives **(4a-c** and **5a-c)** would be selective to malarial infected erythrocytes and modified its biological activity.

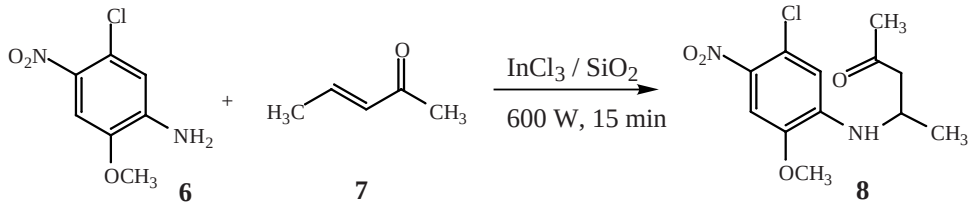


4a-c; R = Cl
5a-c; R = *m*-CF_3-phenoxy
a; AA = Ala, b; AA = Pro, c; AA = Ile

Figure 2

RESULTS AND DISCUSSION

The synthesis of nitroquinoline intermediate (**9**), firstly, was performed with a simple microwave-irradiated procedure on the indium(III) chloride impregnated silica gel according to a procedure of Ranu.[10] Condensation of 5-chloro-2-methoxy-4-nitroaniline **(6)** with 3-penten-2-one **(7)**[11] in domestic microwave oven at 600 W for 15 min resulted in Michael adduct compound (**8**) (Scheme 1).

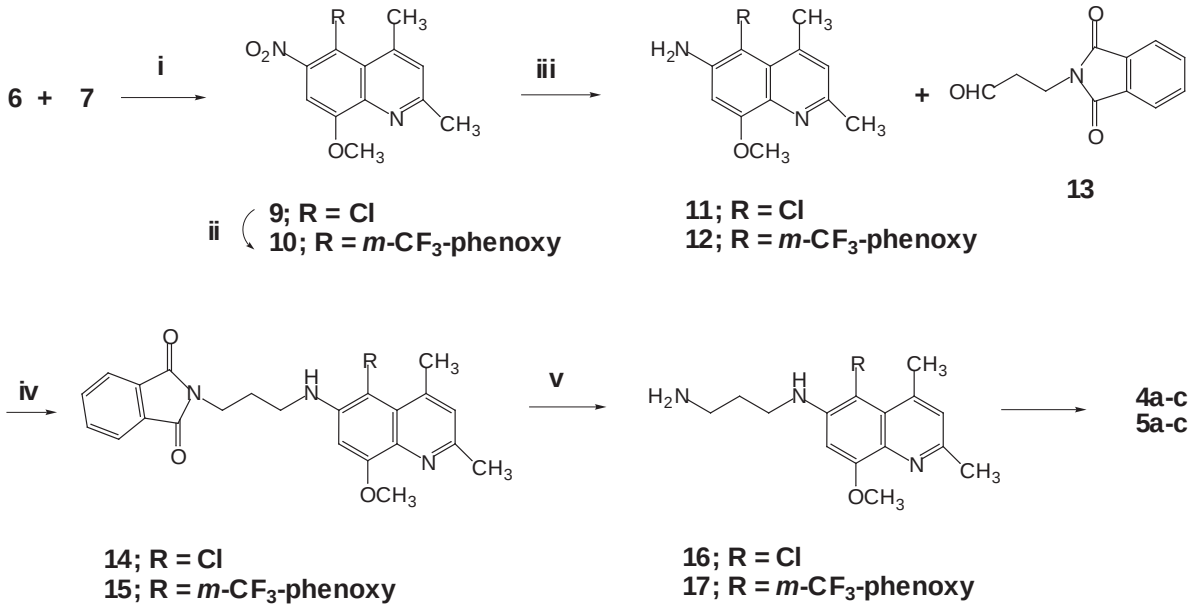


Scheme 1

Thus, Skraup reaction was employed by a procedure of Nickel[12] to produce nitroquinoline (**9**) (Scheme 2). Modification of **9** with nucleophilic aromatic substitution by the potassium salt of 3-trifluoromethyl phenol in the presence of a 18-crown-6-ether produced **10** in 58.6 % yield. The reduction process was carried out simply using titanium(III) chloride as a reducing reagent. Treatment of **9** and**10** in 50% acetic acid with excess (8 mol eq) aqueous $TiCl_3$ solution (20%) at room temperature afforded the corresponding amines (**11**) and (**12**) in 76.3% or 80.4% yields, respectively, without the reduction of quinoline ring to 1,4-dihydroquinoline noted by Somei.[13]

Subsequently, reductive amination of **11** and **12** with *N*-protected aminopropanal (**13**) in a mild condition using sodium cyanoborohydride was carried out to yield **14** (34.1%) and **15** (94.9%), respectively. A low yield of **14** would be attributed to a weak nucleophilicity of the amino group due to a withdrawing

effect of chlorine. The removal of phthaloyl protecting group with hydrazine hydrate produced the primary amines (**16**) (79.6%) and (**17**) (81.9%), respectively. Finally, the amines (**16** and **17**) were coupled with *N*-Boc amino acids (Ala, Pro and Ile) using *N*,*N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride (BOP-Cl) as a coupling reagent to produce six new amino acid derivatives of 6-aminoquinoline compounds (**4** and **5**) (Table 1).



Scheme 2

(i) As_2O_3/conc HCl,70˚C/3 h (ii) *m*-trifluoromethylphenol/18-crown-6-ether/EtOH-dioxane-DMF (1:1:1 v/v),105˚C/12 h (iii) 20%$TiCl_3$ (8 equiv)/50% AcOH/6 or 12 h (iv) $NaBH_3CN$/AcOH/MeOH, rt, overnight (v)hydrazine monohydrate/EtOH,90˚C/6 h (vi) Boc-AA/BOP-Cl/Et_3N/DCM

Table 1. Coupling reaction of basic side chain of 6-aminoquinoline derivatives with Boc-amino acids.

Product	R	Boc-AA	Yield(%)
4a	Cl	Boc-Ala	56.7
4b	Cl	Boc-Pro	78.2
4c	Cl	Boc-Ile	59.0
5a	*m*-CF_3-phenoxy	Boc-Ala	52.3
5b	*m*-CF_3-phenoxy	Boc-Pro	74.9
5c	*m*-CF_3-phenoxy	Boc-Ile	55.3

In summary, a simple and efficient method of reductive amination would be utilized for alkylation of other aminoquinoline compound.

EXPERIMENTAL

Melting points were determined by Yanaco micro melting point apparatus and are uncorrected. IR spectra were obtained in the range 4000-500 cm^{-1} on a Perkin-Elmer 1600 Series FTIR

spectrophotometer. ^{1}H NMR spectra were recorded at 500 MHz on a Varian-Unity-500 instrument with $CHCl_3$ (7.26 ppm) as an internal standard. ^{13}C NMR spectra were recorded on a Varian-Unity-500 instrument with $CDCl_3$ (77.2 ppm) as an internal standard. MS and HRMS spectra were measured on a JEOL JMS AX-505 HAD spectrometer. Optical rotations were recorded on a JASCO DIP-140 instrument. Microanalyses were performed by Microanalysis Center of Toyama Medical & Pharmaceutical University. Chromatography was performed on a silica gel column (Merck 60-No.9385 or No.7734). The extracts were dried over Na_2SO_4.

5-Chloro-2,4-dimethyl-8-methoxy-6-nitroquinoline (9). A stirred mixture of 5-chloro-2-methoxy-4-nitroaniline **(6)** (8.104 g, 0.040 mol), diarsenic trioxide (10.288 g, 0.052 mol), 50 mL of concentrated hydrochloric acid and 12 mL of water in two necked flask was warmed in oil bath at 60 ˚C. 3-Penten-2-one **(7)** (4.7 mL, 0.048 mol) was added dropwise into reaction mixture within 20 min and refluxed at 70 ˚C for 3 h. The mixture was allowed to cool down and poured into 400 mL water. The yellow suspension was partially neutralized with 24 mL of ammonia solution (28%) to pH 3, treated with 1.75 g of activated charcoal and filtered. The orange filtrate was adjusted to pH 6 by 24 mL of ammonia solution (28%) and filtered to collect yellow precipitate, which was. recrystallized from ethanol-acetone to yield **9** (4.110 g, 38.5%), mp 248-250 ˚C (lit.,[2] mp 240-242 ˚C) ; IR (KBr) 3031.3, 2973.7, 2937.6, 2846.0, 1597.7, 1530.1, 1504.1, 1334.5, 889.6 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (1H, s, H-7), 7.18 (1H, s, H-3), 4.10 (3H, s, OCH_3), 3.05 (3H, s, CH_3), 2.76 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 160.68, 155.15, 147.90, 147.94, 128.69, 125.44, 114.60, 102.59, 56.98, 25.66, 25.33; MS *m/z* (rel int) 267 ($[M]^+$, 29), 265 ($[M-2]^+$, 93).

2,4-Dimethyl-8-methoxy-6-nitro-5-(3-trifluoromethylphenoxy)quinoline (10). To a solution of 3-(trifluoromethyl)phenol (2.2 mL, 0.018 mol) in dried solvent mixtures of ethanol-dioxane-dimethylformamide (1:1:1, v/v, 36 mL) containing potassium hydroxide (1.683 g, 0.030 mol) and 18-crown-6-ether (0.793 g, 0.003 mol) was added nitroquinoline (**9**) (4.000 g, 0.015 mol). The mixture was refluxed at 100-105 ˚C for 12 h and allowed to stand overnight at rt. The solid was filtered, washed with cold ethanol and dried in vacuum. The orange solid was dissolved in 50 mL of chloroform and the solution was washed with water (50 mL x 3), and dried. The solvent was evaporated to give **10** (3.449 g, 58.6%). An analytical sample was prepared *via* recrystallization from acetone-water as yellow solid, mp 227 ˚C ; IR (KBr) 3021.1, 2927.7, 2827.6, 1600.7, 1499.4, 1448.9, 1328.2, 1132.6, 888.4 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.54 (1H, s, H-7), 7.37 (1H, t, H-5', J = 8.1 Hz), 7.30 (1H, d, H-4', J = 7.7 Hz), 7.23 (1H, s, H-3), 7.01 (1H, s, H-2'), 6.85 (1H, dd, H-6', J = 8.0, 2.1 Hz), 4.16 (3H, s, OCH_3), 2.77 (3H, s, CH_3), 2.66 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 162.10, 158.62, 153.56, 146.47, 143.29, 139.37, 138.62, 132.83, 130.80, 127.88, 122.92, 119.83, 119.80, 118.13, 112.37, 102.73, 57.01, 25.65, 23.66; MS *m/z* (rel int) 392 (M^+, 94); *Anal*. *Calcd* for $C_{19}H_{15}N_2O_4F_3$: C, 58.17; H, 3.85; N, 7.14 *Found*: C, 58.71; H, 3.50; N, 7.22.

6-Amino-5-chloro-2,4-dimethyl-8-methoxyquinoline (11). To a mixture of 6-nitroquinoline (**9**) (2.000 g, 0.0075 mol) and 50% acetic acid (240 mL) was added 20% titanium(III) chloride hydrochloric solution (27.2 mL, 0.060 mol) in one portion. The solution was stirred at rt for 6 h and 6N NaOH (200 mL) was added under ice cooling. The mixture was filtered and the precipitate was extracted with boiling

chloroform (80 mL x 10). The combined extracts were condensed to 200 mL and washed with water (100 mL x 3), brine (100 mL x 3), dried and evaporated to give crude product. The crude product was recrystallized from toluene to yield **11** (1.355 g, 76.3%), mp 213-215 ˚C; IR (KBr) 3448.0, 3418.0, 3357.4, 3327.0, 3208.2, 2932.1, 1624.3, 1500.6, 1219.2 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.04 (1H, s, H-3), 6.54 (1H, s, H-7), 4.34 (2H, br s, Ar-NH_2), 3.97 (3H, s, OCH_3), 2.95 (3H, s, CH_3), 2.63 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 154.85, 154.03, 142.99, 141.25, 136.43, 127.26, 126.39, 102.75, 99.62, 56.24, 25.51, 24.78; MS *m/z* (rel int) 237 ([M-H]$^+$+2, 46), 235 ([M-H]$^+$, 100); *Anal*. *Calcd* for $C_{12}H_{13}N_2OCl$: C, 60.89; H, 5.54; N, 11.84. *Found*: C, 61.19; H, 5.20; N, 11.72.

6-Amino-2,4-dimethyl-8-methoxy-5-(3-trifluoromethylphenoxy)quinoline (12). To a mixture of **10** (2.000 g, 0.005 mol) and 50% acetic acid (240 mL) was added 20% titanium(III) chloride hydrochloric solution (18.5 mL, 0.041 mol) in one portion. The solution was stirred at rt for 12 h and 6N NaOH (400 mL) was added under ice cooling. The mixture was filtered and the precipitate was extracted with boiling chloroform (50 mL x 5). The combined extracts were condensed to 100 mL and washed with water (100 mL x 3) and brine (100 mL x 3). The washed solvent was dried and evaporated to give crude product. The crude product was recrystallized from toluene to yield **12** (1.486 g, 80.4%), mp 215-218 ˚C; IR (KBr) 3403.0, 3306.0, 3189.9, 2932.8, 1624.3, 1482.3, 1124.5 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (1H, t, H-5', *J* = 8.1 Hz), 7.24 (1H, d, H-4', *J* = 7.6 Hz), 7.09 (1H, s, H-2'), 6.96 (1H, s, H-3), 6.88 (1H, d, H-6', *J* = 7.7 Hz), 6.58 (1H, s, H-7), 4.01 (3H, s, OCH_3), 3.83 (2H, br s, Ar-NH_2), 2.63 (3H, s, CH_3), 2.52 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 162.10, 158.62, 153.56, 146.47, 143.29, 139.37, 138.62, 132.83, 130.80, 127.88, 122.92, 119.83, 119.80, 118.13, 112.37, 102.73, 57.01, 25.65, 23.66; MS *m/z* (rel int) 362 (M$^+$, 41); *Anal.Calcd* for $C_{19}H_{17}N_2O_2F_3$: C, 62.98; H, 4.73; N, 7.73 *Found*: C, 63.08; H, 4.28; N, 8.03.

3-(1,3-Dioxoisoindolin-2-yl)propanal (13). A mixture of 2-buten-1-ol (6.0 mL, 0.698 mol) and *p*-toluenesulfonyl chloride (15.597 g, 0.837 mol) in dichloromethane (60 mL) was cooled in ice bath. Triethylamine (14.5 mL, 1.046 mol) was added and the mixture was continued stirring for overnight. The reaction mixture was extracted with dichloromethane (30 mL x 3) and the extract was washed with satu. K_2SO_4, water, satd $NaHCO_3$, and brine. The solvent was dried and evaporated giving tosylate (13.648 g, 86.5%). The mixture of the tosylate (13.648 g, 0.603 mol) and potassium phthalimide (13.895 g, 0.844 mol) in dimethylformamide (80 mL) was heated at 100 ˚C for 6 h. After being cooled to rt, the mixture was diluted with water (65 mL) and extracted with ether (80 mL x 3). The combined extract was washed with satd K_2SO_4, water, satd $NaHCO_3$, and brine. The solvent was dried and evaporated to give 1-phthalimido-3-butene (10.847 g, 89.4%) as a light yellow solid, ^1H NMR ($CDCl_3$) δ 7.69-7.86 (4H, m, Ar-H/Phth), 5.77 (1H, m, C<u>H</u>=CH_2), 4.99-5.07 (2H, m, CH=C<u>H</u>$_2$), 3.76 (2H, t, Phth-N-C<u>H</u>$_2$, *J* = 6.8 Hz), 2.43 (2H, dt, CH_2C<u>H</u>$_2$CH, *J* = 10.3, 6.8 Hz). To a stirred solution of 1-phthalimido-3-butene (1.610 g, 8 mmol) in aq. dioxane (1:1 v/v, 64 mL) was added by potassium osmate dihydrate (0.059 g, 0.16 mmol). Sodium periodate (1.711 g, 8 mmol) was added to the stirred solution by two portions after 15 min and 1 h. After being stirred for 2 h, the reaction was quenched by 10% $Na_2S_2O_3$ in satd $NaHCO_3$ (80 mL) and extracted with dichloromethane (50 mL x 3). The extracts were dried and evaporated to give a white solid of **13**, mp 116-118 ˚C; ^1H NMR ($CDCl_3$) δ 9.81 (1H, t, CHO, *J* = 1.0 Hz), 7.71-7.85 (4H, m,

Ar-H/Phth), 4.03 (2H, t, Phth-N-C$\underline{H}_2$, *J* = 7.3 Hz), 2.87 (2H, dt, C$\underline{H}_2$CHO, *J* = 7.0, 1.3 Hz). Without further purification, **13** was used in a next reaction.

5-Chloro-2,4-dimethyl-8-methoxy-6-(4-phthalimidopropylamino)quinoline (14). A solution of sodium cyanoborohydride (0.377 g, 6 mmol) in dried methanol (10 mL) was added to a solution of 6-aminoquinoline (**11**) (0.947 g, 4 mmol), **13** (1.626 g, 8 mmol), and acetic acid (3.603 g, 60 mmol) in dried methanol (20 mL). After the resulting mixture was stirred at rt for overnight, dichloromethane (30 mL) was added and the mixture was evaporated to remove solvent and acetic acid. The orange-yellow residue was redissolved in dichloromethane (80 mL), and the solution was washed with satd $NaHCO_3$ (60 mL x 3), and water (60 mL x 3). The solvent was dried and evaporated to give oily residue. This residue was mixed with aldehyde (**13**) (1.626 g, 8 mmol), acetic acid (3.603 g, 60 mmol) and dried methanol (20 mL). A solution of sodium cyanoborohydride (0.377 g, 6 mmol) in dried methanol (10 mL) was added and the mixture was stirred for overnight. Dichloromethane (30 mL) was added and the mixture was evaporated to leave the oily residue, which was chromatographed using silica gel (50 g) with dichloromethane-ethyl acetate (1:5) as eluting solvent to yield **14** (0.578 g, 34.1%) as a yellow solid, mp 207-209 ˚C (toluene); IR (neat) 3397.5, 2948.9, 1708.8, 1614.2, 1501.7, 1371.1, 1218.1 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68-7.84 (4H, m, Ar-H/Phth), 7.02 (1H, s, H-3), 6.58 (1H, s, H-7), 5.10 (1H, t, Ar-NH), 4.03 (3H, s, OCH_3), 3.86 (2H, t, Phth-N-C$\underline{H}_2$, *J* = 6.4 Hz), 3.40 (2H, m, $CH_2C\underline{H}_2NH$), 2.93 (3H, s, CH_3), 2.63 (3H, s, CH_3), 2.06 (2H, m, $CH_2C\underline{H}_2CH_2$); ^{13}C NMR ($CDCl_3$) δ 168.74, 155.11, 153.48, 142.08, 134.22, 132.14, 127.30, 126.47, 123.46, 102.55, 95.93, 56.25, 41.18, 35.51, 28.54, 25.77, 24.78; MS *m/z* (rel int) 424 ($[M-H]^+$+2, 6), 422 ($[M-H]^+$, 21); *Anal*. *Calcd* for $C_{23}H_{22}N_3O_3Cl$: C, 65.17; H, 5.23; N, 9.91 *Found*: C, 65.29; H, 5.18; N, 9.49.

2,4-Dimethyl-8-methoxy-6-(4-phthalimidopropylamino)-5-(3-trifluoromethylphenoxy)-quinoline (15). A solution of sodium cyanoborohydride (1.005 g, 16 mmol) in dried methanol (12 mL) was added to a solution of 6-aminoquinoline (**12**) (1.449 g, 4 mmol), aldehyde (**13**) (3.252 g, 16 mmol), and acetic acid (3.603 g, 60 mmol) in dried methanol (20 mL). The mixture was stirred at rt for overnight and evaporated to remove solvent and acetic acid. The orange-yellow residue was redissolved with dichloromethane (80 mL), washed with satd $NaHCO_3$ (60 mL x 3), water (60 mL x 3), dried and evaporated to give oily residue. The residue was chromatographed using silica gel (100 g) with dichloromethane-ethyl acetate (1:5) as eluting solvent to yield **15** (2.086 g, 94.9%) as yellow solid, mp 190-194 ˚C (toluene), IR (neat) 3417.5, 3018.5, 2961.5, 1710.1, 1496.0, 1218.7, 1128.4 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68-7.81 (4H, m, Ar-H/Phth), 7.32 (1H, t, H-4', *J* = 8.1 Hz), 7.22 (1H, d, H-5', *J* =7.7 Hz), 7.15 (1H, s, H-2'), 6.94 (1H, s, H-3), 6.90 (1H, d, H-6', *J* = 6.4 Hz), 6.66 (1H, s, H-7), 4.52 (1H, br t, Ar-NH, *J* = 6.4 Hz), 4.07 (3H, s, OCH_3), 3.61 (2H, t, Phth-N-C$\underline{H}_2$, *J* = 6.4 Hz), 3.26 (2H, q, $CH_2C\underline{H}_2NH$, *J* = 6.4 Hz), 2.64 (3H, s, CH_3), 2.52 (3H, s, CH_3), 1.88 (2H, m, $CH_2C\underline{H}_2CH_2$); ^{13}C NMR ($CDCl_3$) δ 168.53, 158.74, 154.15, 153.91, 140.81, 137.62, 134.13, 134.00, 132.17, 132.03, 130.50, 126.14, 123.35, 123.22, 118.82, 118.79, 118.10, 112.60, 96.15, 56.23, 40.37, 34.96, 28.45, 25.00, 22.95; MS *m/z* (rel int) 549 (M^+, 100); *Anal*. *Calcd* for $C_{30}H_{26}N_3O_4F_3$: C, 65.57; H, 4.77; N, 7.65. *Found*: C, 65.63; H, 4.96; N, 7.43

6-(4-Aminopropylamino)-5-chloro-2,4-dimethyl-8-methoxyquinoline (16). The title compound (**16**) was prepared by hydrazinolysis of **14** according to the procedure of O'Neill.[14] The mixture of **14** (0.510 g, 1.2 mmol) and ethanol (10 mL) was heated in oil bath at 80 ˚C. Hydrazine monohydrate (100%) (0.181 g, 3.6 mmol) was added and the resulting mixture was refluxed at 90 ˚C with vigorously sirring for 6 h. The mixture was allowed to cool down and filtered. The precipitate was treated with 30% potassium hydroxide (5 mL). This resulting yellow suspension was extracted with dichloromethane (10 mL x 3). The extract was washed with water, dried and evaporated to yield the solid, which was recrystallized from n-hexane-$CHCl_3$ to give **16** (0.282 g, 79.6%), mp 122-124 ˚C; IR (neat) 3421.7, 3284.3, 2937.3, 2860.3, 1614.7, 1501.1, 1217.1 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00 (1H, s, H-3), 6.62 (1H, s, H-7), 5.02 (1H, br s, Ar-NH), 4.03 (3H, s, OCH_3), 3.38 (2H, t, Ar-NHC$\underline{H}_2$, *J* = 6.4 Hz), 2.93 (3H, s, CH_3), 2.89 (2H, t, $CH_2C\underline{H}_2NH_2$, *J* = 6.4 Hz), 2.61 (3H, s, CH_3), 1.84 (2H, m, $CH_2C\underline{H}_2CH_2$), 1.26 (2H, br s, NH_2); ^{13}C NMR ($CDCl_3$) δ 155.12, 153.67, 142.71, 142.53, 134.96, 127.29, 126.42, 102.14, 96.00, 56.25, 42.31, 40.20, 33.10, 25.79, 24.79; MS *m/z* (rel int) 294 ($[M-H]^+$+2, 37), 292 ($[M-H]^+$, 96); HRMS *m/z* 293.1119, ($C_{15}H_{20}N_3OCl$ requires 293.1295).

6-(4-Aminopropylamino)-2,4-dimethyl-8-methoxy-5-(3-trifluoromethylphenoxy)quinoline (17). By a procedure similar to that for the preparation of **16**, 15 (0.659 g, 1.2 mmol) was converted with hydrazine monohydrate (100%) (0.181 g, 3.6 mmol) to **17** (0.412 g, 81.9%), mp 123-124 ˚C (n-hexane-$CHCl_3$); IR (neat) 3381.2, 3287.7, 2960.8, 2863.2, 1619.2, 1495.8, 1218.1, 1129.2 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (1H, t, H-4', *J* = 8.1 Hz), 7.23 (1H, d, H-5', *J* =7.7 Hz), 7.06 (1H, s, H-2'), 6.94 (1H, s, H-3), 6.86 (1H, d, H-6', *J* = 9.0 Hz), 6.70 (1H, s, H-7), 4.54 (1H, br s, Ar-NH), 4.08 (3H, s, OCH_3), 3.30 (2H, t, Ar-NHC$\underline{H}_2$, *J* = 6.4 Hz), 2.69 (2H, t, $CH_2C\underline{H}_2NH_2$, *J* = 6.4 Hz), 2.63 (3H, s, CH_3), 2.52 (3H, s, CH_3), 1.65 (2H, m, $CH_2C\underline{H}_2CH_2$), 1.16 (2H, br s, NH_2); ^{13}C NMR ($CDCl_3$) δ 158.66, 154.09, 153.71, 140.68, 138.43, 133.80, 132.12, 130.47, 126.06, 123.00, 122.74, 118.67, 118.64, 118.05, 112.24, 96.18, 56.17, 42.24, 40.16, 32.69, 24.94, 22.99; MS *m/z* (rel int) 418($[M-H]^+$, 76); HRMS *m/z* 419.1846, ($C_{22}H_{24}N_3O_2F_3$ requires 419.1821).

3'-*N*-(*N*$^{\varepsilon}$-Boc-alanyl)-6-(4-aminopropylamino)-5-chloro-2,4-dimethyl-8-methoxyquinoline (4a). A mixture of **16** (0.102 g, 0.34 mmol), Boc-Ala (0.099 g, 0.52 mmol), triethylamine (0.088 g, 0.87 mmol) and dichloromethane (3 mL) was cooled in ice bath for 10 min and then BOP-Cl (0.132 g, 0.52 mmol) was added. After being stirred for 1 h at 0-5 ˚C and 6 h at rt, the mixture was washed with water (10 mL x 3), dried and evaporated to give syrupy residue. The residue was chromatographed using silica gel and 1% methanol in chloroform as eluting solvent to yield **4a** as an oil (0.091 g, 56.7%); $[\alpha]^{26.0}_D$ -13.37 ˚ (*c* 1.255, $CHCl_3$); IR (neat) 3430.0, 3018.1, 2979.4, 1672.5, 1615.8, 1500.5, 1215.7 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.03 (1H, s, H-3), 6.60 (1H, s, H-7), 6.53 (1H, br s, NH-Boc), 5.02 (1H, br s, Ar-NH), 4.96 (1H, t, CO(C$\underline{H}$)CH_3, *J* = 5.6 Hz), 4.14 (1H, br t, $CH_2N\underline{H}CO$, *J* = 6.8 Hz), 4.04 (3H, s, OCH_3), 3.42 (2H, m, Ala-NHC$\underline{H}_2$), 3.67 (2H, m, Ar-NHC$\underline{H}_2$), 2.95 (3H, s, CH_3), 2.63 (3H, s, CH_3), 1.88 (2H, m, $CH_2C\underline{H}_2CH_2$), 1.41 (9H, s, *t*-Bu), 1.36 (3H, d, CO(CH)C$\underline{H}_3$, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 173.31, 155.77, 155.04, 153.40, 142.70, 142.28, 134.88, 127.29, 126.42, 102.44, 96.00, 56.22, 50.36, 41.22, 37.04, 29.71, 28.41, 25.74, 24.67, 18.46; MS *m/z* (rel int) 465 ($[M-H]^+$+2, 32), 463 ($[M-H]^+$, 86); HRMS *m/z* 464.2175, ($C_{23}H_{33}N_4O_4Cl$ requires 464.2190).

3'-*N*-(*N*$^{\varepsilon}$-Boc-prolyl)-6-(4-aminopropylamino)-5-chloro-2,4-dimethyl-8-methoxyquinoline (4b). By means of a procedure similar to that for the preparation of **4a**, **16** (0.100 g, 0.34 mmol)was converted with a mixture of Boc-Pro (0.114 g, 0.53 mmol), BOP-Cl (0.112 g, 0.44 mmol), and triethylamine (0.098 g, 0.97 mmol) in dichloromethane (3 mL) to **4b** (0.130 g, 78.2%) as an oil; $[\alpha]^{25.2}_{D}$ -39.90 ˚ (*c* 0.915, $CHCl_3$); IR (neat) 3423.9, 3333.5, 2977.5, 1679.2, 1615.4, 1507.2, 1217.1 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00 (1H, s, H-3), 6.58 (1H, s, H-7), 4.92 (1H, br s, Ar-NH), 4.24 (1H, br s, CO(C<u>H</u>)N/Pro), 4.01 (3H, s, OCH3), 3.56 (2H, br s, C<u>H</u>$_2$N(CH)/Pro), 3.32-3.35 (4H, m, C<u>H</u>$_2$CH$_2$C<u>H</u>$_2$), 2.92 (3H, s, CH_3), 2.60 (3H, d, CH_3, *J* = 1.7 Hz), 2.31 (2H, br s, (CH)C<u>H</u>$_2$CH$_2$/Pro), 2.14 (2H, br s, CH$_2$C<u>H</u>$_2$CH$_2$/Pro), 1.86 (2H, m, CH$_2$C<u>H</u>$_2$CH$_2$), 1.42 (9H, s, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 155.05, 153.37, 142.56, 142.28, 134.97, 127.24, 126.34, 95.96, 80.62, 61.38, 60.14, 56.21, 47.29, 41.23, 36.86, 29.74, 28.48, 25.70, 24.70; MS *m/z* (rel int) 491 ([M-H]$^+$+2, 10), 489 ([M-H]$^+$, 24); HRMS *m/z* 490.2338, ($C_{25}H_{35}N_4O_4Cl$ requires 490.2347).

3'-*N*-(*N*$^{\varepsilon}$-Boc-isoleucyl)-6-(4-aminopropylamino)-5-chloro-2,4-dimethyl-8-methoxyquinoline (4c). By means of a procedure similar to that for the preparation of **4a**, **16** (0.125 g, 0.42 mmol) was converted with a mixture of Boc-Ile (0.153 g, 0.63 mmol), and BOP-Cl (0.162 g, 0.63 mmol) , and triethylamine (0.107 g, 1.06 mmol) in dichloromethane (3 mL) to **4c** (0.127 g, 59.0%) as an oil; $[\alpha]^{26.2}_{D}$ -6.64 ˚ (*c* 0.765, $CHCl_3$); Ir (neat) 3431.4, 3336.2, 3031.1. 2971.3, 1661.8, 1616.0, 1503.0, 1216.6 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00 (1H, s, H-3), 6.57 (1H, s, H-7), 6.51 (1H, br t, NH-Boc, *J* = 5.6 Hz), 5.12 (1H, br d, Ar-NH, *J* = 8.5 Hz), 4.91 (1H, t, CO(C<u>H</u>)CH$_2$, *J* = 5.5 Hz), 4.01 (3H, s, OCH$_3$), 3.89 (1H, dd, CH$_3$(C<u>H</u>)CH$_2$, *J* = 8.5, 6.8 Hz), 3.40 (2H, q, Ile-NHC<u>H</u>$_2$, *J* = 6.4 Hz), 3.34 (2H, q, Ar-NHC<u>H</u>$_2$, *J* = 6.4 Hz), 2.92 (3H, s, CH_3), 2.60 (3H, s, CH_3), 1.86 (2H, m, CH$_2$C<u>H</u>$_2$CH$_2$), 1.40 (9H, s, *t*-Bu), 1.08 (2H, qd, (CH)C<u>H</u>$_2$CH$_3$, *J* = 7.7, 3.9 Hz), 0.90 (3H, d, C<u>H</u>$_3$(CH)CH$_2$, *J* = 6.9 Hz), 0.86 (3H, t, (CH)CH$_2$C<u>H</u>$_3$, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 172.33, 156.08, 155.11, 153.47, 142.57, 142.22, 135.05, 127.28, 126.41, 102.49, 95.94, 59.68, 56.22, 41.35, 37.08, 37.04, 29.75, 28.42, 25.72, 24.90, 24.75, 15.78, 11.46; MS *m/z* (rel int) 507 ([M-H]$^+$+2, 9), 505 ([M-H]$^+$, 25); HRMS *m/z* 506.2669, ($C_{26}H_{39}N_4O_4Cl$ requires 506.2660).

3'-*N*-(*N*$^{\varepsilon}$-Boc-alanyl)-6-(4-aminopropylamino)-2,4-dimethyl-8-methoxy-5-(3-trifluoromethyl-phenoxy)quinoline (5a). By means of a procedure similar to that for the preparation of **4a**, **17** (0.210 g, 0.50 mmol) was converted with a mixture of Boc-Ala (0.142 g, 0.75 mmol), BOP-Cl (0.191 g, 0.75 mmol), and triethylamine (0.126 g, 1.25 mmol) in dichloromethane (4 mL) to gave **5a** (0.154 g, 52.3%) as an oil; $[\alpha]^{25.3}_{D}$ -10.17 ˚ (*c* 0.950, $CHCl_3$); IR (neat) 3427.6, 3334.7, 2977.4, 1701.3, 1664.6, 1619.2, 1498.2, 1219.9, 1129.6 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31 (1H, t, H-4', *J* = 8.1 Hz), 7.22 (1H, d, H-5', *J* = 7.7 Hz), 7.08 (1H, s, H-2'), 6.93 (1H, s, H-3), 6.86 (1H, d, H-6', *J* = 7.3 Hz), 6.66 (1H, s, H-7), 6.50 (1H, br s, NH-Boc), 5.03 (1H, br s, Ar-NH), 4.40 (1H, s, CO(C<u>H</u>)CH$_3$), 4.05 (3H, d, OCH$_3$, *J* =1.7 Hz), 4.03 (1H, br s, CH$_2$N<u>H</u>CO), 3.22 (2H, q, Ala-NHC<u>H</u>$_2$, *J* = 6.4 Hz), 3.16 (2H, q, Ar-NHC<u>H</u>$_2$, *J* = 6.4 Hz), 2.63 (3H, d, CH_3, *J* = 1.7 Hz), 2.50 (3H, s, CH_3), 1.67 (2H, m, CH$_2$C<u>H</u>$_2$CH$_2$), 1.36 (9H, d, *t*-Bu, *J* = 1.7 Hz), 1.27 (3H, d, CO(CH)C<u>H</u>$_3$, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 173.15, 158.70, 155.71, 154.00, 153.83, 141.19, 138.10, 133.60, 132.18, 130.53, 125.76, 123.19, 122.78, 118.84, 118.81, 118.13, 112.43, 96.40, 56.25, 50.22, 40.61, 36.63, 29.75, 28.34, 24.79, 23.02, 18.33; MS *m/z* (rel int) 589 ([M-H]$^+$, 17); HRMS *m/z* 590.2682, ($C_{30}H_{37}N_4O_5F_3$ requires 590.2716).

3'-*N*-(*N*$^{\varepsilon}$-Boc-prolyl)-6-(4-aminopropylamino)-2,4-dimethyl-8-methoxy-5-(3-trifluoromethyl-phenoxy)quinoline (5b). By means of a procedure similar to that for the preparation of **4a**, **17** (0.192 g, 0.46 mmol) was converted with a mixture of Boc-Pro (0.148 g, 0.69 mmol), BOP-Cl (0.175 g, 0.69 mmol), and triethylamine (0.116 g, 1.14 mmol) in dichloromethane (4 mL) to **5b** (0.211 g, 74.9%) as an oil; $[\alpha]^{25.1}_{D}$ -29.74 ˚ (*c* 1.380, $CHCl_3$); IR (neat) 3426.2, 3332.9, 2977.7, 1679.0, 1619.4, 1496.0, 1218.4, 1128.1 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (1H, t, H-4', *J* = 8.1 Hz), 7.22 (1H, d, H-5', *J* = 7.7 Hz), 7.09 (1H, s, H2'), 6.94 (1H, s, H-3), 6.88 (1H, s, H-6'), 6.67 (1H, s, H-7), 4.38 (1H, br t, Ar-NH, *J* = 6.0 Hz), 4.16 (1H, br s, CO(C<u>H</u>)N/Pro), 4.08 (3H, s, OCH_3), 3.35 (2H, br s, C<u>H</u>$_2$N(CH)/Pro), 3.18-3.25 (4H, m, C<u>H</u>$_2$CH$_2$C<u>H</u>$_2$), 2.63 (3H, s, CH_3), 2.51 (3H, s, CH_3), 1.83 (2H, br s, CH$_2$C<u>H</u>$_2$CH$_2$/Pro), 1.68 (2H, m, CH$_2$C<u>H</u>$_2$CH$_2$), 1.39 (9H, s, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 158.69, 154.04, 153.78, 140.97, 138.01, 133.73, 132.12, 130.49, 125.70, 123.15, 122.77, 118.76, 118.73, 118.12, 112.39, 96.29, 80.48, 59.98, 56.24, 47.22, 40.54, 36.46, 29.66, 28.40, 24.87, 22.98; MS *m/z* (rel int) 615 ([M-H]$^+$, 19); HRMS *m/z* 616.2881, ($C_{32}H_{39}N_4O_5F_3$ requires 616.2873).

3'-*N*-(*N*$^{\varepsilon}$-Boc-isoleucyl)-6-(4-aminopropylamino)-2,4-dimethyl-8-methoxy-5-(3-trifluoromethyl-phenoxy)quinoline (5c). By means of a procedure similar to that for the preparation of **4a**, **17** (0.210 g, 0.50 mmol) was converted with a mixture of Boc-Ile (0.180 g, 0.75 mmol), BOP-Cl (0.191 g, 0.75 mmol), and triethylamine (0.127 g, 1.25 mmol) in dichloromethane (4 mL) to **5c** (0.175 g, 55.3%) as an oil; $[\alpha]^{25.2}_{D}$ -8.54 ˚ (*c* 0.955, $CHCl_3$); IR (neat) 3433.2, 3333.6, 2969.5, 2876.6, 1696.9, 1661.0, 1499.4, 1219.7, 1129.9 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (1H, t, H-4', *J* = 8.1 Hz), 7.21 (1H, d, H-5', *J* = 8.1 Hz), 7.08 (1H, s, H-2'), 6.92 (1H, d, H-3, *J* = 2.6 Hz), 6.86 (1H, d, H-6', *J* = 6.0 Hz), 6.65 (1H, d, H-7, *J* = 2.1 Hz), 6.30 (1H, br d, NH-Boc, *J* = 5.5 Hz), 5.01 (1H, br s, Ar-NH), 4.38 (1H, t, CO(C<u>H</u>)CH$_2$, *J* = 6.4 Hz), 4.05 (3H, d, OCH_3, *J* = 3.0 Hz), 4.00 (1H, br s, CH$_2$N<u>H</u>CO), 3.80 (1H, t, CH$_3$(C<u>H</u>)CH$_2$, *J* = 8.6 Hz), 3.15-3.21 (4H, m, C<u>H</u>$_2$CH$_2$C<u>H</u>$_2$), 2.61 (3H, d, CH_3, *J* = 3.0 Hz), 2.50 (3H, d, CH_3, *J* = 2.6 Hz), 1.66 (2H, t, CH$_2$C<u>H</u>$_2$CH$_2$, *J* = 6.4 Hz), 1.36-1.40 (9H, m, *t*-Bu), 1.04 (2H, m, (CH)C<u>H</u>$_2$CH$_3$), 0.82-0.87 (6H, t, C<u>H</u>$_3$(CH)CH$_2$C<u>H</u>$_3$ *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 172.17, 158.74, 156.02, 154.13, 153.90, 140.86, 137.96, 133.94, 132.15, 130.49, 125.79, 123.17, 122.78, 118.78, 118.75, 118.12, 112.43, 96.26, 59.55, 56.22, 40.60, 36.98, 36.55, 29.77, 28.34, 24.94, 24.83, 22.98, 15.65, 11.41; MS *m/z* (rel int) 632 ([M-H]$^+$, 65); HRMS *m/z* 632.3162, ($C_{32}H_{39}N_4O_5F_3$ requires 632.3186).

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