1,3-Dipolar cycloaddition of stabilized azomethine ylides to alkenyl quinolines: An efficient route to polyfunctionalized 3-pyrrolidinylquinoline derivatives

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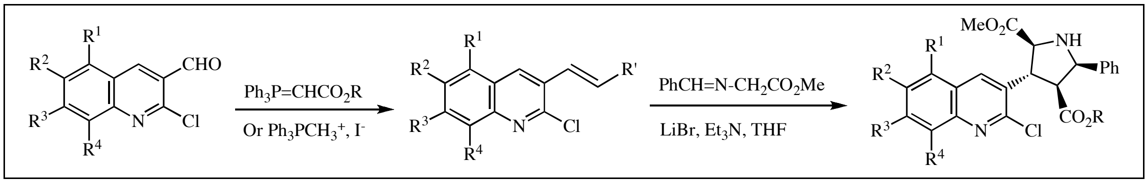

Some new polysubstituted 3-pyrrolidinylquinolinyl derivatives were prepared by 1,3 dipolar cycloadditions of an azomethine ylide, generated *in situ* from benzylideneimine of methylglycinate and triethylamine in the presence of LiBr, to quinolyl α,β–unsaturated esters

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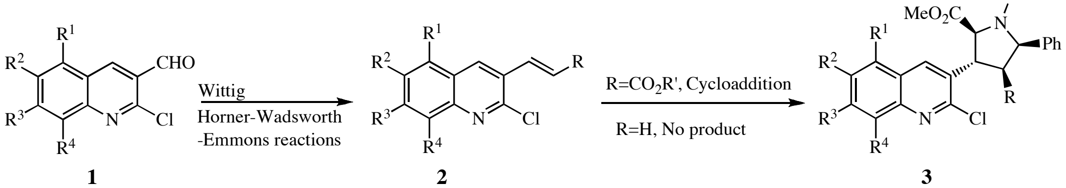
INTRODUCTION

Quinolines are an important group of heterocyclic compounds, in which 2-chloro-3-formylquinolines occupy a prominent position as key intermediates for further annelation and various functional group interconversion [1]. In recent years, significant advances were made in this area, mainly in relation with the biological activities of quinoline derivatives as antibiotic [2], anti-inflammatory [3], analgesic [4] and antitumoral [5]. On the other hand, 1,3-dipolar cycloaddition is one of the simplest approaches for the construction of five-membered rings [6]. The ease of generation of these 1,3-dipoles, coupled with a high regio and stereoselectivity, led to a number of syntheses which utilize such a reaction as the key step. In particular, the *in situ* generated N-metallated azomethine ylides are high reactive species, which react with suitably activated dipolarophiles to afford the corresponding polysubstituted N-H pyrrolidine derivatives [7]. Asymmetric versions of these [3+2] cycloadditions have been also recently reported [8]. In recent years, we have developed a program devoted to the synthesis and biological evaluation of quinolinyl derivative [9]. In a continuation of our efforts in this area, we report here an efficient and straightforward procedure for the preparation of polysubstituted 3-pyrrolidinylquinolines *via* a 1,3-dipolar cycloaddition of stabilized N-metallated azomethine ylides to the corresponding quinolyl α,β-unsaturated esters (Scheme 1) [10].

RESULTS AND DISCUSSION

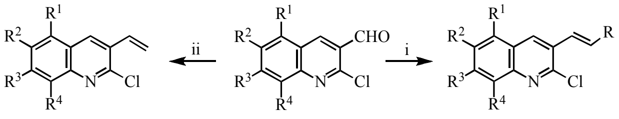
The syntheses of the starting *(E)*-quinolinyl α,β-unsaturated ester derivatives **2a**-**2h** were carried out from the aldehydes **1** *via* a Horner-Wadsworth-Emmons reaction using trialkylphosphonoacetates. Higher yields and purities were obtained compared with those previously reported with stabilized phosphonium ylides (Scheme 2) [10,11]. The rapid entry and the high stereoselectivity of this method demonstrate the utility of this variant, which has the additional advantage of producing a water-soluble phosphate salt $PO(OR)_2ONa$ as by-product, easily removed *via* aqueous extraction [12]. Compounds **2i**-**2j** were obtained from triphenylmethylene phosphorane by a modification of the previously reported procedure [13].

Scheme 1



Synthesis of 3-pyrrolidinylquinolines derivatives

Scheme 2



2i-2j **1a-g** **2a-2k**

Reagents and conditions: (i) $(EtO)_2POCH_2R$, NaH, Dimethoxyethane, 1.5h, reflux; (ii) $Ph_3PCH_3^+I^-$, *tert*-BuOK, THF, rt.

Table 1

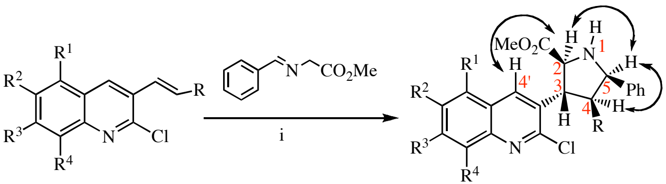
Synthesis of alkenyl quinolines derivatives

Entry	Compound	R^1	R^2	R^3	R^4	R	Yield (%)^a
1	**2a**	H	H	Me	H	CO_2Me	70
2	**2b**	H	H	H	H	CO_2Me	66
3	**2c**	H	H	OMe	H	CO_2Me	74
4	**2d**	H	OCH_2O		H	CO_2Et	69
5	**2e**	H	H	H	Me	CO_2Et	54
6	**2f**	Me	H	H	Me	CO_2Me	93
7	**2g**	H	Me	H	H	CO_2Me	87
8	**2h**	H	H	H	H	CO_2Et	70
9	**2i**	H	H	H	H	H	74
10	**2j**	H	Me	H	H	H	68

^{a} Yields of isolated products.

Having in hand the starting alkenes **2**, we then turned our attention to the synthesis of the cycloadducts. Among the various routes available to prepare N-metalled azomethine ylides, we choose an *in situ* generation from benzylidene-imine of methyl glycinate [14], lithium bromide as catalyst and triethylamine as a base (Scheme 3) [15]. The reaction was conducted at room temperature in dry THF and afforded new pyrrolidines **3a–3g** in good yields as single diastereoisomer, with no evidence in the crude products of any others by ^1H NMR spectroscopy or by T.L.C. The presence of the ester group is essential, since no adducts were detected with the monosubstituted alkene **2h–2i** (Table 2).

Scheme 3



2a-2j **3a-3h** syn-endo

Reagents and conditions: (i) LiBr, Et_3N, THF, rt.

The structure of compound **3a** was elucidated by detailed NMR studies. The ^1H and ^{13}C NMR assignments were made on the basis of high-field one and two-dimensional methods (HMBC, HSQC, COSY, and NOESY H, H). The shielding of the protons of the C-4-CO_2Me (δ= 3.17 ppm) by the adjacent phenyl group confirms the regiochemistry (2, 4-dicarboxylate structure) and demonstrated the 4, 5-cis configuration relationship. The relative configurations of the other carbon atoms were established by $^1H^1H$-COSY and NOESY experiments. The intensive NOESY cross-peaks proved the 2, 4, 5 *cis* configuration of the pyrrolidinyl ring protons (Scheme 3). The stereochemical course of this cycloaddition is therefore in agreement with an *endo* cycloadduct of the *syn* form of N-lithiated azomethine ylide [15, 16].

Table 2

Synthesis of 3-pyrrolidinylquinolines derivatives

Entry	Pyrrolidine	R^1	R^2	R^3	R^4	R	Yield (%)^a
1	**3a**	H	H	Me	H	CO_2Me	74
2	**3b**	H	H	H	H	CO_2Et	70
3	**3c**	H	H	OMe	H	CO_2Me	82
4	**3d**	H	OCH_2O		H	CO_2Et	71
5	**3e**	H	H	H	Me	CO_2Et	61
6	**3f**	Me	H	H	Me	CO_2Me	50
7	**3g**	H	Me	H	H	CO_2Me	79
8	**3h**	H	H	H	H	H	0
9	**3i**	H	Me	H	H	H	0

^{a} Yields of isolated products.

The configurations of the other quinolyl derivatives **3b-3g** were established by analogy and by comparison of their ^1H NMR spectra with those of **3a**.

In summary, we have reported a practical and efficient synthesis of 3-pyrrolidinylquinoline derivatives in good yields. Careful structural analysis confirms an *endo* approach during the cycloaddition step. The presence of the versatile ester and iminochloride functionalities would be of great help for further annelation processes. Work is currently being undertaken in our laboratory to explore the scope and limitation of this route for the construction of new enantioenriched pyrrolidinylquinolines and derivatives.

Table 3

Significant ^1H,^{13}C NMR chemical shifts, selected H-H coupling NOE and HMBC connectivities for **3a**.

	δ ^1H (m,J)	$\delta^{13}C$	$^1H\{^1H\}$ n.O.e^a	^1H,^1H COSY	^1H,^{13}C HMBC
H-2	4.23 (d,8.3)	66.7	H-5, H-4', 2-CO_2Me	4.51	2-CO_2, C-3', C-4, C-3
H-5	4.89 (d,8.5)	65.5	H-2, H-6 Ar, H-2Ar	3.65	4-CO_2, C-1Ar, C-4, C-3
H-4	3.65 (t, .8)	58.0	H-2, H-4'	4.51, 4.89	4-CO_2, C-1Ar, C-3', C-2, C-5, C-3
H-3	4.51 (t,7.7)	49.6	H-4'	4.23, 3.65	2-CO_2, 4-CO_2, C-2', C-4', C-3', C-2, C-5, C-4

$^{a:}$ Obtained by 2D-NOESY spectroscopy.

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EXPERIMENTAL

THF was freshly distilled from sodium/benzophenone, $POCl_3$ and CH_2Cl_2 from P_2O_5, DMF was kept for few hours over $CaCl_2$ and distilled from CaO and dimethoxyethane from NaH. Melting points were determined on a Electrothermal Digital Melting Points Apparatus IA 9200 and are uncorrected. IR spectra were performed on Shimadzu FT IR-8201 PC spectrophotometer and Perkin Elmer Spectrum One (FT-IR) spectrophotometer with a universal ATR sampling accessory. NMR spectra were recorded in $CDCl_3$ on a Brüker Avance DPX250 or Bruker Avance DMX300 spectrometer. Chemical shifts (δ) are given in ppm and J values in Hertz (Hz). Flash column chromatography was performed on Merck silica gel (60, particle size 0.063-0.2 mm) using $CHCl_3$ or CH_2Cl_2 as eluent. Thin layer chromatography (TLC) was carried out on precoated Merck silica gel aluminium sheets 60 F_{254}. HRMS data were obtained on spectrometer MAT 311 (Centre Régional de Mesures Physiques de l'Ouest). Low resolution mass spectra were recorded on a Finnigan PolarisQ ion trap mass spectrometer using electron impact (EI) ionization mode at 70 eV and a Finnigan LCQ ion trap mass spectrometer (ESI).

Substituted 2-chloroquinolyl-3-carbaldehydes **1a-1g** have been synthesized according to reported methods [9].

Preparation of quinolinyl α,β-unsaturated esters 2a-2h via Horner-Wadsworth-Emmons reactions. To a suspension of 50 % sodium hydride dispersion in mineral oil (26 mg, 1.1 mmol) placed in 20 mL of 1, 2-dimethoxyethane, was added, at 0°C through the pressure-equalizing dropping funnel and over a 20 minutes period, (231 mg, 1.1 mmol) of methyldiethylphosphonoacetate. The ice bath was then removed, and the contents were allowed to cool to room temperature. The reaction mixture was kept, under stirring at room temperature, for 30 minutes and (192 mg, 1 mmol) of 2-chloro-3-formylquinoline **1a** was added in one portion. The mixture was refluxed for 1.5 hours. After cooling, water was added and the residue was extracted threefold with CH_2Cl_2 (40 mL). The organic layers were separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford the desired α,β-unsaturated ester derivative.

Spectroscopic results and physical properties of **2a-2e** and **2g-2h** are in full agreement with those previously described [9, 10].

Methyl (*E*)-3-(2-chloro-5, 8-dimethylquinolin-3-yl)acrylate (2f). 150 mg (0.54 mmol) of compound **2f** was prepared according to the general procedure and obtained as white solid; mp 122°C; ir (KBr): 1710 cm^{-1} (C=O, ester); ^1H nmr (250 MHz, $CDCl_3$): δ 8.51 (1H, s, Ar), 8.19 (1H, d, *J* = 16.0, β-H), 7.52 (1H, d, *J* = 8.9, Ar), 7.30 (1H, d, *J* = 8.5, Ar), 6.62 (1H, d, *J* = 16.0, □-H), 3.96 (3H, s, OCH_3), 2.75 (3H, s, CH_3), 2.72 (3H, s, CH_3); ^{13}C nmr (75.4 MHz, $CDCl_3$): δ 166.4 (CO), 148.4 (C), 147.5 (C), 140.1 (CH), 136.6 (C), 134.5 (C), 132.9 (CH), 132.7 (C), 131.4 (CH), 127.8 (CH), 121.7 (CH), 126.2 (C), 52.0 (CH_3), 18.5 (CH_3), 17.6 (CH_3). HRMS (EI): m/z [M^+] Calcd. for $C_{15}H_{14}NO_2{}^{35}Cl$: 275.0713; found: 275.0711. MS m/z (EI) (rel. intensity %) 275 (M+, 15), 244 (5), 241 (16), 240 (100), 225 (12), 224 (6), 212 (13), 197 (7), 180 (10), 154 (5), 153 (9), 152 (13), 151 (6), 127 (7), 115 (6), 101 (6), 90 (13), 89 (11), 77 (12), 76 (15), 75 (6), 63 (6). Calcd for $C_{15}H_{14}NO_2Cl$: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.08; H, 5.51; N, 4.80.

General procedure for preparation of vinylquinolines 2i-2j. To a suspension of methyltriphenylphosphonium iodide (1.010 g, 2.5 mmol) in dry THF (5 mL) was added (561 mg, 5 mmol) of potassium *tert*-butoxide. After 5 minutes, a solution of 2-chloroquinolyl-3-carbaldehyde **1a** (192 mg, 1 mmol) in THF (2ml) was added dropwise. The resulting mixture was stirred at room temperature for 10 minutes, then diluted with water (10 mL) and extracted with CH_2Cl_2 (20 mL). The organic layer was washed twice with water (5 mL), brine (5 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* to give a residue which was purified by flash chromatography on silica gel using CH_2Cl_2 as eluent.

2-Chloro-3-vinylquinoline (2i). mp 60°C; IR (KBr): 1616, 1566, 918, 987 cm^{-1}; ^1H nmr (250 MHz, $CDCl_3$) δ 8.25 (1H, s, Ar), 8.02 (1H, d, *J* = 8.4, Ar), 7.80 (1H, d, *J* = 7.2, Ar), 7.69 (1H, ddd, *J* = 8.4, 7.2, 1.5, Ar), 7.58 (1H, ddd, *J* = 8.5, 7.2, 1.5, Ar), 7.18 (1H, dd, *J* = 17.6, 11, CH=), 5.80 (1H, d, *J* = 17.3, =CH), 5.50 (1H, d, *J* = 11.2, =CH); ^{13}C nmr (62.5 MHz, $CDCl_3$): δ 149.8 (C), 146.9 (C), 138.8 (CH), 134.2 (CH), 132.3 (CH), 128.1 (C), 127.5 (CH), 127.3 (CH), 127.1 (CH), 122.3 (C), 118.6 (CH_2). HRMS (EI): m/z [M^+] Calcd. for $C_{12}H_{10}N^{35}Cl$: 189.0345; found: 189.0342; MS: m/z (EI) (rel. intensity %) = 191 (32), 190 (12), 189 (100), 155 (10), 154 (88), 153 (25), 152 (10), 128 (13), 127 (52), 126 (21), 101 (12), 99 (5), 95 (5), 77 (29), 76 (19), 75 (15), 64 (13), 63 (25), 51 (17), 50 (11). Calcd for $C_{11}H_8NCl$: C, 69.67; H, 4.25; N, 7.39. Found: C, 69.72; H, 4.68; N, 7.03.

2-Chloro-6-methyl-3-vinylquinoline (2j). mp 120°C °C; IR (KBr): 1724, 1694, 1654, 1691, 1521, 1173, 783 cm^{-1}; ^1H nmr (250 MHz, $CDCl_3$ δ 8.20 (1H, s, Ar), 7.80 (1H, d, *J* = 8.4, Ar), 7.60-7.50 (2H, m, Ar), 7.20 (1H, dd, *J* = 17.6, 11.1, HC=), 5.83 (1H, d, *J* = 17.1, =CH), 5.50 (1H, d, *J* = 11.2, =CH), 2.55 (3H, s, CH_3); ^{13}C nmr (62.5 MHz, $CDCl_3$): δ 148.9 (C), 145.6 (C), 137.1 (CH), 133.6 (C), 132.5 (CH), 132.4 (C), 130.3 (CH), 127.8 (CH), 127.4 (CH), 126.3 (C), 118.2 (CH_2), 21.5 (CH_3). Calcd for $C_{12}H_{10}NCl$: C, 70.77; H, 4.95; N, 6.88. Found: C, 71.28; H, 5.22; N, 6.71.

Synthesis of quinolinyl pyrrolidine derivatives 3a-3h. To lithium bromide (130 mg, 1.5 mmol) dissolved in dry THF (20 mL) were added, under stirring at room temperature, benzylideneimine of methyl glycinate (177 mg, 1 mmol) [14], freshly distilled Et_3N (101 mg, 1.2 mmol) and alkenylquinoline **2** (1 mmol). The reaction mixture was kept, under stirring at room temperature, for 48 hours (the progress of the reaction was monitored by TLC). Ether (15 mL) was added followed by 10 mL of saturated aqueous solution of NH_4Cl. The organic layer was separated and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using $CHCl_3$ as eluent.

Dimethyl (2*S,3*R**,4*S**,5*R**) 3-(2-chloro-7-methylquinolin-3-yl)-5-phenylpyrrolidine-2,4-dicarboxylate (3a).** mp 159 °C; IR (ATR): 1718, 1710, 1627, 1494, 1433, 1251, 1194, 1038, 734 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 8.16 (1H, s, Ar), 7.79 (1H, s, Ar), 7.72 (1H, d, *J* = 8.5, Ar), 7.28-7.42 (6H, m, Ar), 4.89 (1H, d, *J* = 8.5, 5-H), 4.51 (1H, t, *J* = 7.7, 3-H), 4.23 (1H, d, *J* = 8.3, 2-H), 3.75 (3H, s, OCH_3), 3.65 (1H, t, *J* = 7.8, 4-H), 3.17 (3H, s, OCH_3), 3.17 (1H, br s, NH), 2.65 (3H, s, CH_3); ^{13}C nmr (75.4 MHz, $CDCl_3$): δ 173.1 (C, 2-CO_2), 172.2 (C, 4-CO_2), 151.1 (C, C-2'), 147.3 (C, C-9'), 141.5 (C, C-7'), 139.2 (C, C-1Ar), 137.0 (CH, C-4'), 131.2 (C, C-3'), 130.0 (CH, C-6'), 128.7 (2xCH, C-3 Ar, C-5 Ar), 128.5 (CH, C-4 Ar), 128.3 (CH, C-8'), 127.6 (CH, C-5'), 127.3 (2xCH, C-2 Ar, C-6 Ar), 125.7 (C, C-10'), 66.7 (CH, C-2), 65.5 (CH, C-5), 58.0 (CH, C-4), 52.9 (2-OCH_3), 51.9 (4-OCH_3), 49.6 (CH, C-3), 22.3 (CH_3); HRMS (EI): m/z [M^+]

Calcd. for $C_{24}H_{23}N_2O_4{}^{35}Cl$: 438.1346; found: 438.1358. MS (ESI): m/z 439.1 (MH$^+$, 100), 407 (31), 379 (64), 347 (17), 319 (43), 283 (8), 230 (5), 178 (4), 121 (46). Calcd for $C_{24}H_{23}N_2O_4Cl$: C, 65.68; H, 5.28; N, 6.38. Found: C, 65.41; H, 5.44; N, 6.05.

4-Ethyl-2-methyl (2*S,3*R**,4*S**,5*R**) 3-(2-chloroquinolin-3-yl)-5-phenylpyrrolidine -2,4-dicarboxylate (3b).** mp 95°C; IR (ATR): 1740, 1712, 1563, 1489, 1364, 1172, 1028, 746 cm^{-1}; ^{1}H nmr (300 MHz, CDCl$_3$): δ 8.23 (1H, s, Ar), 8.03 (1H, d, *J* = 8.1, Ar), 7.85 (1H, d, *J* = 7.3, Ar), 7.74 (1H, td, *J* = 7.7, 1.5, Ar), 7.59 (1H, td, *J* =7.7, 1.1, Ar), 7.28-7.44 (5H, m, Ar), 4.91 (1H, d, *J* = 8.5, 5-H), 4.55 (1H, t, *J* = 7.9, 3-H), 4.24 (1H, d, *J* = 8.3, 2-H), 3.76 (3H, s, OCH$_3$), 3.61-3.67 (3H, m, -CH$_2$-, 4-H), 3.10 (1H, br s, NH), 0.78 (3H, t, *J* = 7.1, CH$_3$); ^{13}C nmr (75.4 MHz, CDCl$_3$): δ 173.0 (C=O), 171.6 (C=O), 151.3 (C), 147.1 (C), 139.2 (C), 137.3 (CH), 132.4 (C), 130.9 (CH), 128.7 (2xCH), 128.3 (CH), 127.8 (2xCH), 127.7 (C),127.5 (CH), 127.4 (2xCH), 66.7 (CH, C-2), 65.5 (CH, C-5), 61.1 (CH$_2$), 58.1 (CH, C-4), 52.9 (OCH$_3$), 51.9 (CH$_3$), 49.6 (CH, C-3), 13.9 (CH$_3$). Calcd for $C_{24}H_{23}N_2O_4Cl$: C, 65.68; H, 5.28; N, 6.38. Found: C, 65.36; H, 5.35; N, 6.25.

Dimethyl (2*S,3*R**,4*S**,5*R**) 3-(2-chloro-7-methoxyquinolin-3-yl)-5-phenylpyrrolidine-2,4-dicarboxylate (3c).** mp 124-125°C; IR (ATR): 3413 (NH), 1739 and 1717 (CO, esters) cm^{-1}; ^{1}H nmr (300 MHz, CDCl$_3$): δ 8.40 (1H, s, Ar), 7.72 (1H, d, *J* = 8.9, Ar), 7.60 (1H, d, *J* = 2.5, Ar), 7.48-7.23 (5H, m, Ar), 7.20 (1H, dd, *J* = 8.9, 2.5, Ar), 5.00 (1H, d, *J* = 8.4, 5-H), 4,50 (1H, m, 3-H), 4.36 (1H, d, *J* = 8.2, 2-H), 3,94 (1H, br s, NH), 3.94 (3H, s, OCH$_3$) 3.75 (3H, s, OCH$_3$), 3,80 (1H, m, 4-H), 3.25 (3H, s, OCH$_3$); ^{13}C nmr (75.4 MHz, CDCl$_3$): δ 173.2 (C=O), 171.0 (C=O), 151.2 (C), 148.9 (C), 146.7 (C), 141.4 (C), 136.7 (CH), 131.9 (CH), 130.1 (C), 129.7 (C), 128.6 (2xCH), 128.4 (CH), 127.2 (2xCH), 125.2 (CH), 106.2 (CH), 65.5 (CH), 64.4 (CH), 56.7 (CH), 55.5 (OCH$_3$), 52.7 (OCH$_3$), 51.8 (OCH$_3$), 48.4 (CH); HRMS (EI): m/z [M$^+$] Calcd. for $C_{24}H_{23}N_2O_5{}^{35}Cl$: 454.1295; found: 454.1305. Calcd for $C_{24}H_{23}N_2O_5Cl$: C, 63.37; H, 5.10; N, 6.16. Found: C, 63.02; H, 5.58; N, 5.85.

4-Ethyl 2-methyl-(2*S,3*R**,4*S**,5*R**)-3-(6-chloro[1,3]dioxolo-[4,5-*g*]quinolin-7-yl)-5-phenylpyrrolidine-2,4-dicarbox-ylate (3d).** mp 134-136°C; IR (ATR): 1739, 1714, 1457, 1172, 1040, 952, 745, 696 cm^{-1}; ^{1}H nmr (300 MHz, CDCl$_3$) δ 7.99 (1H, s, Ar), 7.28-7.35 (6H, m, Ar), 7.06 (1H, s, Ar), 6.13 (2H, s, O-CH$_2$-O), 4.89 (1H, d, *J* = 8.5, 5-H), 4.46 (1H, t, *J* = 7.9, 3-H), 4.20 (1H, d, *J* = 8.5, 2-H), 3.75 (3H, s, OCH$_3$), 3.60-3.66 (3H, m, O-CH$_2$-, 4-H), 2.85 (1H, br s, NH), 0.77 (3H, t, *J* = 7.1, CH$_3$); ^{13}C nmr (75.4 MHz, CDCl$_3$) : δ 173.1 (C=O), 171.7 (C=O), 151.9 (C), 148.9 (C), 145.4 (C), 139.3 (C), 136.1 (C), 130.1 (C), 128.7 (2xCH), 128.3 (CH), 127.5 (2xCH), 124.8 (C), 105.3 (CH), 102.7 (CH), 102.4 (CH), 101.2 (CH$_2$), 66.6 (CH, C-2), 65.8 (CH, C-5), 61.1 (CH$_2$), 57.9 (CH, C-4), 52.9 (OCH$_3$), 49.6 (CH, C-3), 13.9 (CH$_3$).Calcd for $C_{25}H_{23}N_2O_6Cl$: C, 62.18; H, 4.80; N, 5.80. Found: C, 62.38; H, 4.92; N, 5.65.

4-Ethyl-2-methyl-(2*S,3*R**,4*S**,5*R**)-3-(2-chloro-8-methylquinolin-3-yl)-5-phenyl pyrrolidine-2,4-dicarboxylate (3e).** mp 163°C; IR (ATR): 1738, 1715, 1458, 1356, 1175, 1058, 722, 654 cm^{-1}; ^{1}H nmr (300 MHz, CDCl$_3$): δ 8.20 (1H, s, Ar),7.68 (1H, d, *J* = 7.7, Ar), 7.58 (1H, d, *J* = 6.9, Ar), 7.28-7.50 (6H, m, Ar), 4.93 (1H, d, *J* = 8.4, 5-H), 4.55 (1H, t, *J* = 7.8, 3-H), 4.28 (1H, d, *J* = 8.5, 2-H), 3.77 (3H, s, OCH$_3$), 3.55- 3.77 (3H, m, O-CH$_2$-, 4-H), 3.43 (1H, br s, NH), 2.78 (3H, s, CH$_3$), 0.79 (3H, t, *J* = 7.1, CH$_3$); ^{13}C nmr (75.4 MHz, CDCl$_3$): δ 173.1 (C=O), 171.6 (C=O), 150.2 (C), 146.3 (C), 139.1 (C), 137.5 (CH), 136.9 (C), 131.9 (C), 130.9 (CH), 128.8 (2xCH), 128.3 (CH), 127.7 (C), 127.5 (2xCH), 127.5 (CH), 125.6 (CH), 66.6 (CH, C-2), 65.5 (CH, C-5), 61.1 (CH$_2$), 58.1 (CH, C-4), 53.0 (OCH$_3$), 49.6 (CH, C-3), 18.1 (CH$_3$), 13.9 (CH$_3$); HRMS (EI): m/z [M$^+$] Calcd. for $C_{25}H_{25}N_2O_4{}^{35}Cl$: 452.1502; found: 452.1514. MS (ESI): m/z 453.4 (MH$^+$, 100%), 407 (41), 393 (39), 379 (15), 347 (18), 319(39), 283 (6), 230 (3), 178 (3), 121 (44), 91 (1). Calcd for $C_{25}H_{25}N_2O_4Cl$: C, 66.30; H, 5.56; N, 6.18. Found: C, 66.36; H, 5.70; N, 6.36.

Dimethyl-(2*S,3*R**,4*S**,5*R**)-3-(2-chloro-5,8-dimethylquinolin-3-yl)-5-phenylpyrrolidine-2,4-dicarboxylate (3f).** mp 126°C; IR (ATR): 1741, 1713, 1584, 1431, 1378, 1169, 1093, 828, 757, 701 cm^{-1}; ^{1}H nmr (300MHz, CDCl$_3$): δ 8.31 (1H, s, Ar), 7.28-7.45 (7H, m, Ar), 4.95 (1H, d, *J* = 8.5, 5-H), 4.54 (1H, t, *J* = 8.1, 3-H), 4.32 (1H, d, *J* = 8.6, 2-H), 3.77 (3H, s, OCH$_3$), 3.76 (1H, t, *J* = 8.1, 4-H), 3.19 (3H, s, OCH$_3$), 3.15 (1H, br s, NH), 2.74 (3H, s, CH$_3$), 2.68 (3H, s, CH$_3$); ^{13}C nmr (75.4 MHz, CDCl$_3$): δ 173.1 (C=O), 172.1 (C=O), 149.6 (C), 146.7 (C), 139.3 (C), 134.7 (C), 132.3 (C), 131.0 (C), 130.7 (CH), 128.8 (2xCH), 128.4 (CH), 128.0 (CH), 127.6 (CH), 127.4 (2xCH), 127.1 (C), 66.7 (CH, C-2), 65.5 (CH, C-5), 58.1 (CH, C-4), 52.9 (OCH$_3$), 51.9 (OCH$_3$), 49.9 (CH, C-3), 19.0 (CH$_3$), 18.1 (CH$_3$); HRMS (EI): m/z [M$^+$] Calcd. for $C_{25}H_{25}N_2O_4{}^{35}Cl$: 452.1502; found: 452.1514. MS (ESI): m/z 453.3 (MH+, 100%), 421 (39), 393 (62), 361 (20), 333 (34), 297(7), 244(3), 178(2), 121 (43), 91 (1). $C_{25}H_{25}N_2O_4Cl$: C, 66.30; H, 5.56; N, 6.18. Found: C, 66.17; H, 5.71; N, 6.03.

Dimethyl-(2*S,3*R**,4*S**,5*R**)-3-(2-chloro-6-methylquinolin-3-yl)-5-phenylpyrrolid-ine-2,4-dicarboxylate (3g).** mp 50°C; IR (ATR): 1740, 1727, 1592, 1434, 1166, 1042, 823, 760, 694 cm^{-1}; ^{1}H nmr (300 MHz, CDCl$_3$): δ 8.13 (1H, s, Ar), 7.92 (1H, d, *J* = 8.5, Ar), 7.58 (2H, m, Ar), 7.35 (5H, m, Ar), 4.90 (1H, d, *J* = 8.5, 5-H), 4.52 (1H, t, *J* = 7.3, 3-H), 4.25 (1H, d, *J* = 8.3, 2-H), 3.76 (3H, s, OCH$_3$), 3.66 (1H, dd, *J* = 8.4, 7.1, 4-H), 3.18 (3H, s, OCH$_3$), 2.98 (1H, br s, NH), 2.55 (3H, s, CH$_3$); ^{13}C nmr (75.4 MHz, CDCl$_3$) δ 173.1 (C=O), 172.1 (C=O), 150.2 (C), 145.7 (C), 139.2 (C), 137.8 (C), 136.7 (CH), 133.2 (CH), 132.1 (C), 128.8 (2xCH), 128.4 (CH), 128.3 (CH), 127.7 (C), 127.3 (2xCH), 126.6 (CH), 66.6 (CH, C-2), 65.5 (CH, C-5), 58.0 (CH, C-4), 52.9 (OCH$_3$), 51.9 (OCH$_3$), 49.6 (CH, C-3), 22.0 (CH$_3$). Calcd for $C_{24}H_{23}N_2O_4Cl$: C, 65.68; H, 5.28; N, 6.38. Found: C, 66.05; H, 5.58; N, 6.13.

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