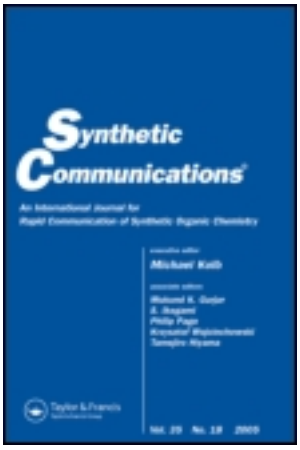

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Efficient Synthesis of 3-Pyrrolylquinolines via an 1,3-Dipolar Cycloaddition/ Oxidation Sequence

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Efficient Synthesis of 3-Pyrrolylquinolines via an 1,3-Dipolar Cycloaddition/Oxidation Sequence

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Abstract: The synthesis of some new functionalized quinolyl derivatives relies on the 1,3-dipolar cycloaddition of an azomethine ylide, generated from sarcosine and paraformaldehyde, to quinolyl α,β-unsaturated esters, followed by oxidation of the pyrrolidinyl moiety to pyrrole with activated MnO_2.

Keywords: Dipolar cycloaddition, oxidation, pyrroles, quinolines, Wittig reaction

3-Substituted 2-chloroquinolines and their derivatives, 2-aminoquinolines, 2-alkoxyquinolines, and quinolin-2-(1*H*)-ones, have attracted considerable interest because of their important biological activities.[1] This has stimulated the search for more potent and specific derivatives, and a great variety of

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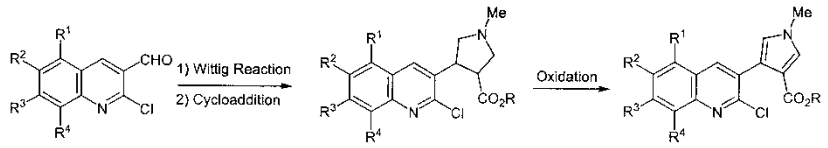
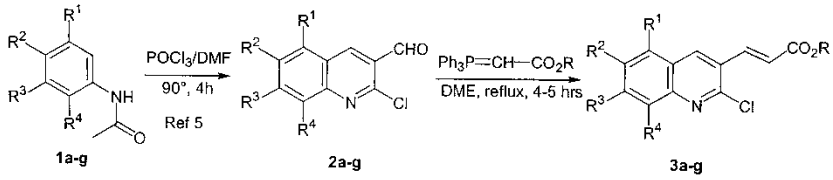


Scheme 1.

compounds have been synthesized that incorporated new functional groups into these structural cores, heterocycles for example.[2] To the best of our knowledge, pyrrolidines and pyrroles, which are present in many biologically active molecules,[3] have never been combined with quinoline subunits. In the course of our ongoing program related to the synthesis and the biological evaluation of quinolyl derivatives,[4] we have elaborated an efficient and straightforward route for the synthesis of 3-pyrrolidinyl- and 3-pyrrolylquinolines using a 1,3-dipolar cycloaddition/oxidation key sequence (Scheme 1).

Starting quinolylcarbaldehyde derivatives **1a**–**1g** were obtained by subjecting the suitable N-phenylacetamide to Vilsmeier reagent ($POCl_3$/DMF in a 7/3 ratio) as previously reported. [4,5] Condensation with stabilized phosphonium ylides $Ph_3P = CHCO_2R$, (R = Me or Et) in refluxing 1,2-dimethoxyethane gave the corresponding (*E*)-quinolyl α,β-unsaturated esters (coupling constant between the two ethylenic protons, $J = 16$ Hz) with high stereoselectivity and good yields (Scheme 2, Table 1)

Having in hand the starting activated alkenes **3**, we then turned our attention to the synthesis of the cycloadducts **4**. 1,3-Dipolar cycloaddition reaction of azomethine ylides is one of the most efficient methods for the construction of five-membered heterocycles in a convergent and stereocontrolled manner.[6] Among the various routes available to prepare these dipoles, we chose an in situ generatcon from *N*-substituted glycine and paraformaldehyde, which was reported to give excellent results with electron-deficient alkenes.[7] The reaction was conducted in refluxing dry toluene and afforded new pyrrolidines **4a**–**4g** in good yields as single diastereoisomers with no evidence of any others in the ^{1}H NMR or TLC of the crude products. These pyrrolidine derivatives were easily converted into the corresponding pyrroles **5** in moderate to good yields (59–77%) by oxidation with a fivefold excess of activated manganese dioxide in refluxing THF during 5 h (Scheme 3,



Scheme 2.

Table 1. Synthesis of quinolyl α,β-unsaturated esters **3**

Compound	R^1	R^2	R^3	R^4	R	Yield (%)[a]
3a	H	H	H	H	Me	66
3b	Me	H	Me	H	Me	70
3c	Me	H	H	Me	Et	63
3d	H	H	OMe	H	Me	63
3e	H	H	Me	H	Me	70
3f	H	Me	Me	H	Me	73
3g	H	OCH_2O		H	Et	64

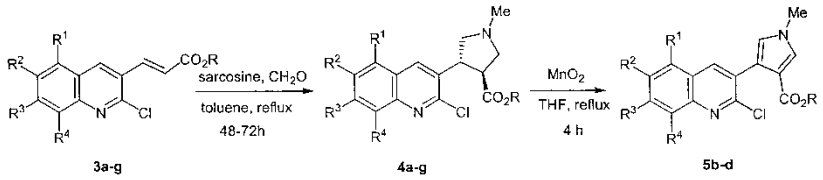
[a]Yields of isolated pure products.

Table 2). ^1H and ^{13}C NMR data were in full agreement with the proposed structures of compounds **4** and **5**.

In summary, we have prepared some new 3-pyrrolidinylquinolines by 1,3-dipolar cycloaddition of a symmetrical, unstabilized azomethine ylide to the corresponding α,β-unsaturated esters. Oxidative dehydrogenation of these cycloadducts with activated MnO_2 under mild conditions provided the corresponding pyrroles. Efforts to extend this methodology to other substituted azomethine ylides and to exploit the presence of versatile ester functionality are in progress in our laboratory.

EXPERIMENTAL

THF and toluene were freshly distilled from sodium/benzophenone, and $POCl_3$ and $CHCl_3$ from P_2O_5 DMF was kept for few hours over $CaCl_2$ and distilled from CaO, and DME from NaH. Melting points were determined on a electrothermal capillary fine-control apparatus and are uncorrected. All IR spectra were performed on Shimadzu FT-IR-8201 PC spectrophotometer and only significant absorption-band frequency is cited. ^1H NMR and ^{13}C NMR spectra were recorded in deuterochloroform on a Brüker Avance DPX 250 spectrometer at 250 MHz for proton and at 62.9 MHz for ^{13}C. Chemical shifts are given in ppm and *J* values in Hertz (Hz). High-resolution mass spectra were obtained on a Varian MAT 311 (electron impact) or



Scheme 3.

Table 2. Synthesis of 3-pyrrohdinyl- and 3-pyrrolylquinolines **4** and **5**

R^1	R^2	R^3	R^4	R	Compound	Yield (%)[a]	Compound	Yield (%)[a]
H	H	H	H	Me	**4a**	71	**5a**	71
Me	H	Me	H	Me	**4b**	62	**5b**	59
Me	H	H	Me	Et	**4c**	86	**5c**	77
H	H	OMe	H	Me	**4d**	75	**5d**	65
H	Me	Me	H	Me	**4e**	88	**5e**	74
H	H	Me	H	Me	**4f**	68	—	—
H	OCH_2O		H	Et	**4g**	77	—	—

[a]Yields of isolated pure product.

Micromass ZABSpec TOF [LSIMS or electrospray (CH_3CN, H_2O)], spectrometers by the "Centre Régional de Mesures Physiques," Université de Rennes 1, France. Flash column chromatography was performed on Merck silica gel (60, particle size 0.063–0.2 mm) using $CHCl_3$ as eluent. Thin-layer chromatography (TLC) was carried out on precoated Merck silica-gel aluminium sheets 60 F_{254}.

Substituted 2-chloroquinolyl-3-carbaldehydes **2a–2f** have been synthesized in accordance with established methods.[4] Spectroscopic results and physical properties are in agreement with literature reports.[4,5]

Preparation of Substituted Quinolyl α,β-Unsaturated Esters 3a–3g

Substituted 2-chloroquinolyl-3-carbaldehyde derivative **2** (10 mmol) was added, under magnetic stirring, to 1.1 eq. (11 mmol) of stabilized phosphonium ylide dissolved in an appropriate quantity of dry DME (50 ml–2.10^{-1} M solution). The reaction mixture was refluxed for 4–5 h (the progress of the reaction was monitored by TLC until disappearance of starting materials). The oil bath was then removed, and the contents were allowed to cool to room temperature. The solvent was evaporated in vacuum and the residue was washed with a mixture of pentan6/ether (50/50). The precipitate ($OPPh_3$) was filtered off, and the filtrate was concentrated under reduced pressure to give a residue, which was subjected to flash column chromatography (silica gel, eluent: $CHCl_3$) to afford pure crystalline product.

Methyl (*2E*)-3-(2-chloroquinolin-3-yl)acrylate **3a**:[8] $R_f = 0.5$, mp 162–163°C. IR (ν_{max}, KBr) = 1711 (C═O, ester). ^{1}H NMR (δ ppm, *J* Hz): 8.30 (s, 1H), 8.05 (d, $J = 15.9$, 1H), 7.90 (dd, $J = 8.4$, 2.4 1H), 7.78 (dd, $J = 8.4$, 2.4, 1H), 7.70 (dd, $J = 8.6$, 2.4, 1H), 7.54 (d, $J = 8.6$, 2.4, 1H), 6.50 (d, $J = 15.9$, 1H), 3.80 (s, 3H). ^{13}C NMR (δ ppm): 165.3 (CO), 148.9

(C), 146.9 (C), 138.5 (CH), 135.0 (CH), 130.5 (CH), 127.4 (C), 126.9 (CH), 126.6 (CH), 126.3 (CH), 125.9 (C), 121.2 (CH), 52.2 (CH_3).

Methyl (*2E*)-3-(2-chloro-5,7-dimethylquinolin-3-yl)]acrylate **3b**: $R_f = 0.75$, mp 167–168°C. IR(ν_{max}, KBr) = 1716 (C═O, ester). ^{1}H NMR (δ PPm, *J* Hz): 8.46 (s, 1H), 8.14 (d, $J = 15.9$, 1H), 7.64 (s, 1H), 7.28 (s, 1H), 6.58 (d, $J = 15.9$, 1H), 3.88 (s, 3H), 2.66 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (δ ppm): 167.0 (CO), 149.5 (C), 148.3 (C), 142.5 (C), 140.0 (CH), 138.0 (C), 135.4 (CH), 132.9 (CH), 130.1 (C), 126.3 (CH), 125.1 (CH), 121.9 (C), 52.0 (CH_3), 22.0 (CH_3), 18.6 (CH_3). HRMS (E.I) $[M]^{+\cdot}$ calcd for $C_{15}H_{14}ClNO_2 = 275.0713$; found 275.0738.

Ethyl (*2E*)-3-(2-chloro-5,8-dimethylquinolin-3-y1)]acrylate **3c**: $R_f = 0.77$, mp 120–121°C. IR (ν_{max}, KBr) = 1705 (C═O, ester). ^{1}H NMR (δ ppm, *J* Hz): 8.48 (s, 1H), 8.15 (d, $J = 16.0$, 1H), 7.48 (d, $J = 7.2$, 1H), 7.29 (d, $J = 7.2$, 1H), 6.53 (d, $J = 16.0$, 1H), 4.35 (q, $J = 7.1$, 2H), 2.72 (s, 3H), 2.67 (s, 3H), 1.40 (t, $J = 7.1$, 3H) ^{13}C NMR (δ ppm): 166.7 (CO), 149.7 (C), 147.5 (C), 140.1 (CH), 135.3 (CH), 133.1 (C), 132.5 (C), 130.7 (CH), 127.1 (C), 125.8 (CH), 122.5 (C), 121.7 (CH), 60.9 (CH_2), 18.5 (CH_3), 14.3 (CH_3).

Methyl (*2E*)-3-(-2-chloro-7-methoxyquinolin-3-yl)]acrylate **3d**: $R_f = 0.80$, mp 142–145°C. IR (ν_{max}, KBr) = 1712 (C═O, ester). ^{1}H NMR (δ ppm, *J* Hz): 8.26 (s, 1H), 8.09 (d, $J = 15.9$, 1H), 7.70 (d, $J = 8.9$, 1H), 7.50 (d, $J = 8.9$, 2.4, 1H), 7.29 (d, $J = 2.4$, 1H), 6.50 (d, $J = 15.9$, 1H), 3.94 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (δ ppm): 169.8 (CO), 161.1 (C), 151.8 (C), 149.2 (C), 141.3 (CH), 136.8 (CH), 133.6 (CH), 129.4 (C), 125.4 (CH), 123.1 (C), 121.0 (CH), 106.6 (CH), 56.0 (CH_3), 51.5 (CH_3). HRMS (E.I) $[M]^{+\cdot}$ calcd. for $C_{14}H_{12}ClNO_3 = 227.05057$; found 227.0511.

Methyl (*2E*)-3-(2-chloro-7-methylquinolin-3-yl)acrylate **3e**: $R_f = 0.50$, mp 142°C. IR (ν_{max}, KBr) = 1713 (C═O, ester). ^{1}H NMR (δ ppm, *J* Hz): 8.60 (s, 1H), 8.24 (d, $J = 15.9$, 1H), 7.80 (d, $J = 8.8$, 1H), 7.80 (s, 1H), 7.42 (d, $J = 8.8$, 1H), 6.58 (d, $J = 15.9$, 1H), 3.88 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (δ ppm): 162.7 (CO), 148.5 (C), 146.7 (C), 138.0 (CH), 134.8 (CH), 130.6 (CH), 127.2 (C), 126.7 (CH), 126.3 (CH), 121.3 (C), 120.3 (CH), 116.3 (C), 52.0 (CH_3), 23.0 (CH_3). HRMS (E.I) $[M\text{-}Cl^{\cdot}]^+$ calcd. for $C_{14}H_{12}C1NO_2 = 226.08680$; found 226.0873.

Methyl (*2E*)-3-(2-chloro-6,7-dimethylquinolin$_a$3-yl) acrylate **3f**: $R_f = 0.53$, mp 153°C. IR (ν_{max}, KBr) = 1716 (C═O, ester). ^{1}H NMR (δ ppm, *J* Hz): 8.15 (s, 1H), 8.11 (d, $J = 16.0$, 1H), 7.78 (s, 1H), 7.57 (s, 1H), 6.53 (d, $J = 6.0$, 1H), 3.87 (s, 3H), 2.66 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (δ ppm): 166.5 (CO), 149.0 (C), 146.5 (C), 143.8 (C), 140.0 (CH), 138.3 (C), 135.4 (CH), 127.8 (CH), 127.3 (C), 126.2 (CH), 125.4 (CH), 121.3 (C), 52.0 (CH_3), 20.7 (CH_3), 20.6 (CH_3).

Ethyl (*2E*)-3-(2-chloro-6,7-deoxymethylquinolin-3-yl)acrylate **3g**: $R_f = 0.8$, mp 168–170°C. IR (ν_{max}, KBr) = 1709 (C=O, ester). ^{1}H NMR (δ ppm, *J* Hz): 8.01 (s, 1H), 7.94 (d, $J = 16.0$, 1H), 7.14 (s, 1H), 6.92 (s, 1H), 6.38 (d, $J = 16.0$, 1H), 6.06 (s, 2H), 4.21 (q, $J = 2$H), 1.28 (t, $J = 7.1$, 3H). ^{13}C NMR (δ ppm): 165.0 (CO), 151.4 (C), 147.6 (C), 146.9 (C), 145.5 (C), 138.2 (CH), 133.4 (CH), 124.0 (C), 123.0 (C), 120.4 (CH), 104.0 (CH), 101.6 (CH), 101.3 (CH_2), 59.8 (CH_2), 13.2 (CH_3).

Synthesis of Quinolyl Pyrrolidine Derivatives 4a–4g

To a mixture of a substituted quinolyl α,β-unsaturated ester derivative (10 mmol) and sarcosine (2 eq., 20 mmol) dissolved in dry toluene (4.10^{-2} M) was added, under magnetic stirring, CH_2O (5 eq., 50 mmol), portion by portion, of over 2 hours. The reaction mixture was refluxed for 48–72 h and water was removed by means of a Dean Stark trap (the progress of the reaction was monitored by TLC). The oil bath was removed, and the mixture was then allowed to cool to room temperature. The precipitate was filtered off, and the filtrate was concentrated under, reduced pressure. The residue was subjected to column chromatography (silica gel, eluent: $CHCl_3$) to afford pure product.

Methyl 4-(2-chloroquinolin-3-yl)-l-methylpyrrolidine-3-carboxylate **4a**: $R_f =$ 0.40. IR (ν_{max}, KBr) = 1736 (C=O, ester). ^{1}H NMR (δ ppm, *J* Hz): 8.30 (s, 1H), 7.95 (d, $J = 8.4$, 1H), 7.80 (dd, $J = 8.4$, 1H), 7.68 (td, $J = 8.4$, 1.0, 1H), 7.60 (td, $J = 8.4$, 1.1 H), 4.24 (td, $J = 8.1$, 5.1, 1H), 3.70 (s, 3H), 3.33–3.24 (m, 2H), 3.02 (dd, $J = 8.5$, 8.1, 1H), 2.90 (dd, $J = 9.5$, 8.1, 1H), 2.84–2.73 (m, 1H), 2.50 (s, 3H). ^{13}C NMR (δ ppm): 173.6 (CO), 150.7 (C), 146.4 (C), 136.4 (CH), 134.9 (CH), 130.2 (CH), 128.0 (C), 127.4 (CH), 127.1 (CH), 126.7 (C), 62.5 (CH_2), 59.3 (CH_2), 52.0 (CH_3), 50.5 (CH), 43.9 (CH), 41.7 (CH_3). HRMS (E.I) $[M]^{+\cdot}$ calcd. for $C_{17}H_{19}C1N_2O_2 = 318.11351$; found 318.1147.

Methyl 4-(2-chloro-5,7-dimethylquinolin-3-yl)-1-methylpyrrolidine-3-carboxylate **4b**: $R_f = 0.35$, mp. 77–78°C. IR(ν_{max}, KBr) = 1736 (C=O, ester). ^{1}H NMR (δ ppm, *J* Hz): 8.27 (s, 1H), 7.52 (s, 1H), 7.10 (s, 1H), 4.17 (dt, $J = 8.1$, 5.1, 1H), 3.64 (s, 3H), 3.26–3.11 (m, 2H), 3.02 (dd, $J = 9.4$, 8.3, 1H), 2.87–2.78 (m, 2H), 2.57 (s, 3H), 2.40 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (δ ppm): 173.9 (CO), 150.3 (C), 147.0 (C), 140.2 (C), 133.9 (C), 133.5 (C), 132.7 (CH), 129.8 (CH), 125.1 (CH), 124.8 (C), 62.8 (CH_2), 59.4 (CH_2), 52.1 (CH_3), 50.6 (CH), 44.2 (CH), 41.7 (CH_3), 21.7 (CH_3), 18.5 (CH_3). HRMS (E.I) $[M]^{+\cdot}$ calcd. for $C_{18}H_{21}C1N_2O_2 = 332.12916$; found 332.1286.

Ethyl 4-(2-chloro-5,8-dimethylquinolin-3-yl) -1-methylpyrrolidine-3-carboxylate **4c**: $R_f = 0.38$, oil. IR (ν_{max}, KBr) = 1730 (C=O, ester). ^{1}H NMR (δ ppm, *J* Hz): 8.37 (s, 1H), 7.39 (d, $J = 7.2$, 1H), 7.22 (d, $J = 7.2$, 1H),

4.27 (dt, $J = 8.2, 5.8$, 1H), 4.23–4.18 (m, 2H), 3.29 (dd, $J = 8.1, 6.4$, 1H), 3.22 (dd, $J = 8.1, 7.3$, 1H), 3.12 (dd, $J = 8.2, 7.2$, 1H), 2.94–2.86 (m, 2H), 2.69 (s, 3H), 2.64 (s, 3H), 2.46 (s, 3H), 1.25 (t, $J = 7.2$, 3H). ^{13}C NMR (δ ppm): 173.6 (CO), 149.4 (C), 146.0 (C), 134.3 (C), 134.0 (C), 133.1 (CH), 131.9 (C), 129.8 (CH), 127.2 (CH), 126.8 (C), 62.9 (CH_2), 61.0 (CH_2), 59.5 (CH_2), 50.8 (CH), 44.3 (CH), 41.8 (CH_3), 18.6 (CH_3), 17.7 (CH_3), 14.2 (CH_3).

Methyl 4-(2-chloro-7-methoxyquinolin-3-yl)-1-methylpyrrolidine-3-carboxylate **4d**: $R_f = 0.6$, oil. IR (ν_{max}, KBr) = 1735 (C═O, ester). ^{1}H NMR (δ ppm, J Hz): 8.14 (s, 1H), 7.63 (d, $J = 8.8$, 1H), 7.24 (d, $J = 2.5$, 1H), 7.12 (dd, $J = 8.8, 2.5$, 1H), 4.20 (dd, $J = 8.1, 5.2$, 1H), 3.86 (s, 3H), 3.66 (s, 3H), 3.22–3.14 (m, 2H), 2.99 (dd, $J = 9.5, 8.2$, 1H), 2.85 (dd, $J = 9.7, 5.1$, 1H), 2.81–2.73 (m, 1H), 2.40 (s, 3H). ^{13}C NMR (δ ppm): 174.0 (CO), 161.1 (C), 151.0 (C), 148.1 (C), 135.9 (CH), 132.8 (CH), 128.3 (C), 122.6 (C), 120.1 (CH), 106.1 (CH), 62.8 (CH_2), 59.5 (CH_2), 55.4 (CH_3), 52.1 (CO_2CH_3), 50.7 (CH), 43.8 (CH), 41.7 (CH_3). HRMS (E.I) $[M]^{+\cdot}$ calcd. for $C_{17}H_{19}C1N_2O_3 = 334.10842$; found 334.1070.

Methyl 4-(2-chloro-7-methylquinolin-3-yl)-1-methylpyrrolidine-3-carboxylate **4e**: $R_f = 0.35$, mp 65–66°C. IR (ν_{max}, KBr) = 1719 (C═O, ester). ^{1}H NMR (δ ppm, J Hz): 8.25 (s, 1H), 7.75 (d, $J = 8.4$, 1H), 7.48 (s, 1H), 7.40 (d, $J = 8.4$, 1H), 4.23 (dd, $J = 8.1, 5.0$, 1H), 3.71 (s, 3H), 3.26–3.18 (m, 2H), 3.03 (dd, $J = 9.5, 8.1$, 1H), 2.89 (dd, $J = 9.5, 5.0$, 1H), 2.83–2.75 (m, H), 2.54 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (δ ppm): 173.9 (CO), 150.7 (C), 146.5 (C), 140.6 (CH), 134.2 (CH), 131.9 (CH), 128.6 (CH), 127.0 (C), 125.5 (C), 124.8 (C), 62.7 (CH_2), 59.4 (CH_2), 52.2 (CH_3), 50.6 (CH), 43.9 (CH), 41.8 (CH_3), 21.9 (CH_3). HRMS (E.I) $[M]^{+\cdot}$ cacld. for $C_{16}H_{17}C1N_2O_2 = 304.09786$; found 304.0975.

Methyl 4-(2-chloro-6,7-dimethylquinolin-3-yl)-1-methylpyrrolidine-3-carboxylate **4f**: $R_f = 0.40$, oil. IR (ν_{max}, KBr) = 1742 (C═O, ester). ^{1}H NMR (δ ppm, J Hz): 8.20 (s, 1H), 7.73 (s, 1H), 7.56 (s, 1H), 4.24 (dd, $J = 8.2, 5.5$ 1H), 3.70 (s, 3H), 3.34–3.24 (m, 2H), 3.11 (d, $J = 9.6$, 8.3, 1H), 3.01 (d, $J = 9.5, 5.4$, 1H), 2.97–2.85 (m, 2H), 2.51 (s, 3H), 2.44 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (δ ppm): 173.9 (CO), 149.7 (C), 145.5 (C), 140.5 (C), 137.0 (C), 135.2 (C), 134.0 (CH), 127.3 (C), 126.5 (CH), 126.0 (CH), 62.6 (CH_2), 59.4 (CH_2), 52.1 (CH_3), 50.6 (CH), 43.9 (CH), 41.7 (CH_3), 20.4 (CH_3), 19.9 (CH_3).

Ethyl 4-(2-chloro-6,7-deoxymethylquinolin-3-yl)-1-methylpyrrolidine-3-carboxylate **4g**: $R_f = 0.62$, yellow crystals, mp 224–225°C. IR (ν_{max}, KBr) = 1735 (C═O, ester). ^{1}H NMR (δ ppm, J Hz): 8.35 (s, 1H), 7.28 (s, 1H), 7.13 (s, 1H), 6.14 (s, 2H), 4.35–4.14 (m, 3H), 3.57–3.31 (m, 2H), 3.25 (dd, $J = 9.4, 8.2$, 1H), 2.97 (dd, $J = 9.4, 5.1$, 1H), 2.84–2.75 (m, 1H), 2.52 (s, 3H). 1.35 (t, $J = 7.1$, 3H). ^{13}C NMR (δ ppm): 172.4 (CO), 151.4 (C), 148.3 (C), 148.1 (C), 144.9 (C), 134.4 (CH), 131.7 (C), 124.9 (C),

104.9 (CH), 102.6 (CH), 102.0 (CH_2), 62.0 (CH_2), 61.4 (CH_2), 58.9 (CH_2), 51.7 (CH), 43.3 (CH), 41.7 (CH_3), 14.0 (CH_3). HRMS (E.I) $[M]^{+\cdot}$ calcd. for $C_{18}H_{19}C1N_2O_4 = 362.10334$; found 362.1032.

Synthesis of Quinolyl Pyrrole Derivatives 5

To a 0.1 M solution of **4** (1.5 mmol, in 15 ml of dry THF) was added, at one time, 2.5 equiv of activated MnO_2. The mixture was refluxed for 2.5 h. The same portion of activated MnO_2 was then added, and the reflux was continued for an additional 2.5 h. After cooling, the mixture was diluted with THF (5 ml) and filtered through celite. Celite was washed with THF (5 × 5 ml), and the filtrate was concentrated under reduced pressure, diluted with CH_2Cl_2, and washed with aqueous 1 N hydrochloric acid (2 × 5 m1). The organic layers were separated and dried over anhydrous $MgSO_4$. The filtrate was concentrated and the residue purified by flash chromatography on silica gel using $CHCl_3$ as eluent to afford pure corresponding pyrrole derivatives.

Methyl 4-(2-chloroquinolin-3-yl)-l-methyl-*1H*-pyrrole-3-carboxylate **5a**: $R_f = 0.77$, mp = 115–116°C. IR(ν_{max}, KBr) = 1712 (C═O, ester) ^{1}H NMR (δ ppm, *J* Hz): 8.11 (s, 1H), 8.05 (dd, $J = 8.4$, 1H), 7.80 (dd, $J = 8.4$, 1H) 7.70 (td, $J = 8.4$, 1.1 1H), 7.52 (td, $J = 8.4$, 1.1 1H), 7.41 (d, $J = 2.4$, 1H), 6.72 (d, $J = 2.4$, 1H), 3.78 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (δ ppm): 164.6 (C), 151.5 (C), 146.6 (C), 138.7 (CH), 129.9 (CH), 128.8 (C), 128.3 (CH), 127.9 (CH), 127.3 (C), 127.0 (CH), 126.8 (C), 123.2 (CH), 121.8 (CH), 115.0 (C), 50.9 (CH_3), 36.8 (CH_3). HRMS (E.I) $[M]^{+\cdot}$ calcd. for $C_{16}H_{13}C1N_2O_2 = 300.06656$; found 300.0661.

Methyl 4-(2-chloro-5,7-dimethylquinolin-3-yl)-1-methyl-*1H*-pyrrole-3-carboxylate **5b**: $R_f = 0.8$, IR (KBr): ν (cm^{-1}) = 1712 (C═O, ester). ^{1}H NMR (δ ppm, *J* Hz): 8.20 (s, 1H), 7.73 (s, 1H), 7.40 (d, $J = 2.4$, 1H), 7.23 (s, 1H), 6.72 (d, $J = 2.4$, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 2.63 (s, 3H), 2.53 (s, 3H). ^{13}C NMR (δ ppm): 166.9 (CO), 150.9 (C), 146.4 (C), 139.4 (C), 136.2 (CH), 133.5 (C), 129.4 (C), 127.8 (C), 127.0 (C), 125.7 (CH), 124.1 (CH), 122.9 (CH), 121.7 (CH), 110.7 (C), 51.6 (CH_3), 41.7 (CH_3), 21.7 (CH_3), 18.5 (CH_3). HRMS (E.I) $[M]^{+\cdot}$ cacld. for $C_{18}H_{17}C1N_2O_2 = 328.09786$; found 328.0985.

Ethyl 4-(2-chloro-5,8-dimethylquinolin-3-yl)-1-methyl-*1H*-pyrrole-3-carboxylate **5c**: Yd = 65%. $R_f = 0.7$. IR (KBr): ν(cm^{-1}) = 1708 (C═O, ester). ^{1}H NMR (δ ppm, *J* Hz): 8.18 (s, 1H), 7.45 (d, $J = 7.2$, 1H), 7.40 (d, $J = 2.4$, 1H), 7.26 (d, $J = 7.2$, 1H), 6.72 (d, $J = 2.4$ 1H), 4.14 (q, $J = 7.1$, 2H), 3.78 (s, 3H), 2.76 (s, 3H), 2.68 (s, 3H), 1.09 (t, $J = 7.1$, 3H). ^{13}C NMR (δ ppm): 167.6 (C), 150.7 (C), 146.7 (C), 139.8 (C), 134.2 (CH), 133.8 (C), 129.7 (CH), 128.8 (C), 128.2 (C), 125.8 (CH), 124.7 (CH), 123.1 (C), 115.4 (C), 61.0 (CH_2) 41.8 (CH_3) 18.6 (CH_3) 17.7 (CH_3), 14.2 (CH_3).

Methyl 4-(2-chloro-7-methoxyquinolin-3-yl)-1 methyl-*1H*-pyrrole-3-carboxylate **5d**: $R_f = 0.75$, mp = 115–117 °C. IR(ν_{max}, KBr) = 1710 (C═O, ester). ^{1}H NMR (δ ppm, *J* Hz): 8.13 (s, 1H), 7.71 (d, $J = 8.9$, 1H), 7.34–7.36 (m, 2H), 7.17 (dd, $J = 8.9$, 2.2, 1H), 6.70 (d, $J = 2.4$, 1H), 3.96 (s, 3H), 3.75 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (δ ppm): 167.1 (C), 161.3 (C), 151.1 (C), 148.9 (C), 135.9 (CH), 131.1 (CH), 128.7 (C), 125.6 (C), 124.2 (CH), 123.0 (C), 122.7 (C), 121.0 (CH), 115.1 (C), 106.6 (CH), 56.1 (CH_3), 51.6 (CH_3), 41.7 (CH_3). HRMS (E.I) $[M]^{+\cdot}$ calcd. for $C_{17}H_{15}C1N_2O_3 = 330.07712$; found 330.0781.

Methyl 4-(2-chloro-7-methylquinolin-3-yl)-1-methyl-*1H*-pyrrole-3-carboxylate **5e**: $R_f = 0.7$, mp = 177–178 °C. IR(ν_{max}, KBr) = 1716 (C═O, ester). ^{1}H NMR (δ ppm, *J* Hz): 8.04 (s, 1H), 7.84 (d, $J = 2.2$, 1H), 7.74 (d, $J = 8.2$, 1H), 7.40 (d, $J = 2.4$, 1H), 7.39 ($J = 2.4$, 1H), 6.73 (d, $J = 2.4$, 1H), 3.77 (s, 3H), 3.65 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (δ ppm): 169.2 (C), 146.9 (C), 140.3 (C), 138.4 (CH), 130.8 (CH), 129.0 (CH), 128.7 (CH), 127.8 (C), 127.3 (C), 126.9 (C), 125.8 (C), 123.2 (CH), 121.7 (CH), 115.2 (C), 51.2 (CH_3), 36.7 (CH_3), 21.8 (CH_3). HRMS (E.I) $[M]^{+\cdot}$ calcd. for $C_{17}H_{15}C1N_2O_2 = 314.08221$; found 314.0816.

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