Synthesis of Some New 3-Pyrrolidinylquinoline Derivatives via 1,3-Dipolar Cycloaddition of Stabilized Azomethine Ylides to Quinolinyl α,β-Unsaturated Ketones

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Abstract: N-Metallated azomethine ylide generated from methyl (*E*)-*N*-benzylideneglycinate, LiBr and triethylamine underwent cycloaddition to quinolyl α,β-unsaturated ketones with excellent diastereoselectivity to afford new functionalised 3-pyrrolidinylquinoline derivatives.

Keywords: 1,3-dipolar cycloaddition, quinoline, pyrrolidine synthesis, azomethine ylides.

INTRODUCTION

Quinolines derivatives have attracted considerable interest for many years due to their presence in the skeleton of a large number of bioactive compounds and natural products [1]. For example, quinoline alkaloids, such as quinine, chloroquine, mefloquine and amodiaquine, are used as efficient drugs for the treatment of malaria [2].

On the other hand 1,3-dipolar cycloaddition reactions of azomethine ylides with olefinic dipolarophiles had resulted in a number of novel heterocyclic scaffolds which are particularly useful for the creation of diverse chemical libraries of drug-like molecules for biological screening [3]. Functionalized pyrrolidine containing compounds are also of significant importance because of their biological activities and widespread employment in catalysis [4].

The coupling of this chemical entity with quinoline unit might as well be envisioned to bring with some biological activities. In this context, some limited investigations have been carried out which involved the combination of the quinolyl moiety and the pyrrolidine unit.

As a part of our program related to the preparation and biological evaluation of quinolyl derivatives [5], we have recently described a practical and an efficient synthesis of some 3-pyrrolidinylquinoline derivatives from quinolinyl α,β-unsaturated esters as starting materials via 1,3-dipolar cycloaddition [6]. In a continuation of our efforts in this area, we report here an efficient procedure for the preparation of new pyrrolidine derivatives bearing a quinoline ring at C-3, aroyl or acetyl group at C-4, and a phenyl substituent at C-5 via an 1,3-dipolar cycloaddition reaction of a stabilized metallo-azomethine ylide to quinolinyl α,β-unsaturated ketones [7].

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RESULTS AND DISCUSSION

Starting from the corresponding 2-chloro-3-formylquinoline derivatives **1**, chalcones **2a-2h** were synthesized by Claisen-Schmidt condensation reactions of appropriately substituted acetophenone in ethanol in the presence of 10% of aqueous NaOH [8]. The methylketone derivatives **2i-2j** were prepared from the aldehydes **1** via a Wittig reaction using methyl(triphenylphosphoranylidene) acetate and were obtained in good yields (Scheme **1**).

The *E*-configurated dipolarophiles (**2a-2j**) reacted with azomethine ylide, generated from methyl (*E*)-*N*-benzylideneglycinate in the presence of LiBr and triethylamine at room temperature, employing dry THF as the solvent (Scheme **2**).

In accordance with literature reports [9, 10], this 1,3-dipolar cycloaddition reaction of the *in situ* generated metallo-azomethine ylide, exhibited high regio and stereoselectivity leading to the expected *syn-endo* cycloadduct (**3a-3j**).

All results reported below shown that pyrrolidines were obtained with conservation of the stereochemistry of starting alkenes [11], giving only one diastereoisomer with no evidence of any other isomers in the ^{1}H NMR spectra of the crude products (Table **1**).

The structure of compounds 3a-3j has been established by analogy and by comparison of their ^{1}H NMR with those reported [12]. The shielding of the protons of the methyl connected to the aroyl group attached at C-4 by the adjacent 5-phenyl ring (δ=1.83 ppm) confirms the regiochemistry and demonstrated the 4,5-*cis* configuration relationship [6, 13].

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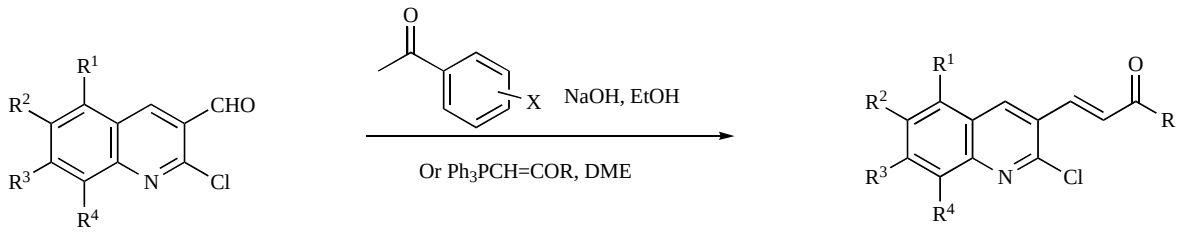
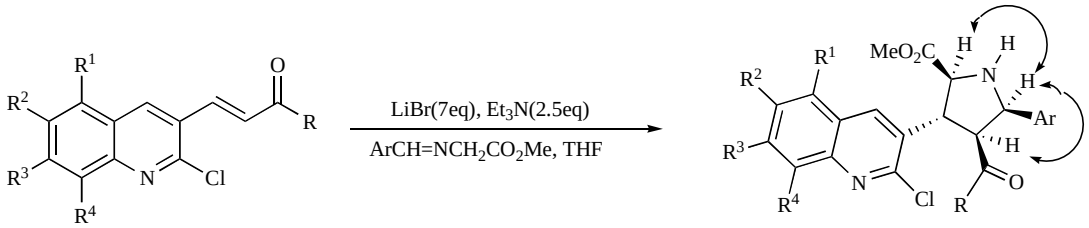


1a-1e **2a-2j**

Scheme 1. Synthesis of chalcone and methyl(vinylquinoline) ketone derivatives.



2a-2j **3a-3j**

Scheme 2. Synthesis of quinolylpyrrolidine N-H derivatives (**3a-3j**).

Table 1. Synthesis of 3-pyrrolidinylquinolines 3

Compound	R^1	R^2	R^3	R^4	R	Yield (%)
3a	H	H	H	Me	2-MeC_6H_4	70
3b	H	H	H	H	2-MeC_6H_4	58
3c	OMe	H	H	OMe	2-MeC_6H_4	71
3d	H	Me	H	H	2-MeC_6H_4	62
3e	H	H	H	Me	4-$OMeC_6H_4$	60
3f	H	OMe	H	H	4-$OMeC_6H_4$	65
3g	H	H	H	Me	3,4-di$MeOC_6H_3$	53
3h	H	H	H	Me	3,4,5-tri$MeOC_6H_2$	54
3i	H	Me	H	H	Me	67
3j	H	H	H	H	Me	59

The structure of compound **3a**, as representative example, was elucidated by detailed NMR studies (Table **2**). The ^1H and ^{13}C NMR assignments were made on the basis of high-field one and two-dimensional methods (HSQC, COSY, and NOESY H, H). The '2,4,5-*cis*' configuration of these pyrrolidines was confirmed by the observed NOE enhancement between the two pairs (H-2 and H-5) and (H-2 and H-4) (Table **2**).

X-ray crystallography of **3e** (Fig. **1**) showed an asymmetric unit which contains two independent molecules and the analysis demonstrate that the two stereoisomers have for each one, the absolute stereochemistry (2*S*,3*R*,4*S*,5*R*) and

Table 2. Significant ^1H, ^{13}C NMR Data, Selected H-H Coupling NOE for 3a

	$\delta\ ^{13}C$	$\delta\ ^1H$ (m, J)	$^1H\{^1H\}$n.O.e[a]	$^1H,^1H$ cosy
H-2	66.5	4.40 (d, 7.9)	H-5, H-4 Qui, 2-CO_2Me	4.69
H-5	66.4	4.96 (d, 8.1)	H-2, H-6 Ar, H-2 Ar	4.77
H-4	60.8	4.77 (t, 8.0)	H-2, H-4 Qui	4.69, 4.96
H-3	50.5	4.69 (t, 8.0)	H-4 Qui	4.40, 4.77

[a]Obtained by 2D-NOESY spectroscopy.

(2*R*,3*S*,4*R*,5*S*) of the new stereocenters created in the cycloaddition reactions [14].

Fig. (1). ORTEP of asymmetric unit of compound **3e** which contains two independent molecules projection down (010).

CONCLUSIONS

In conclusion, we report herein an efficient approach to 3-pyrrolidinylquinoline derivatives that exploits [3+2] cycloaddition reactions of azomethine ylides. This approach allows a diverse range of compounds to be generated in good yield and the pharmacological actions of the new pyrrolidine derivatives will be inspected afterwards.

EXPERIMENTAL SECTION

General Information

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 DME from NaH. EtOH was distilled from magnesium. Melting points were determined on an Electrothermal Digital Melting Points Apparatus IA 9200 and are uncorrected. I.R 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 Brüker Avance DMX300 spectrometer. Chemical shifts (δ) are given in ppm and J values in Hertz (Hz). 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). X-Ray crystallographic analysis was performed with an Enraf–Nonius KAPPA CCD at 293 K using Mo Kα radiation (λ = 0.71073 Å).

Substituted 2-chloroquinolyl-3-carbaldehydes have been synthesized according to reported methods [15]. Methyl benzylidene aminoacetate is obtained by treatment of benzaldehyde with methyl glycinate hydrochloride in basic medium [16].

General Method for the Synthesis of Chalcone Derivatives (2a-2h)

To a solution of 10% NaOH (520 mg, 13 mmol) in 95% ethanol (20 mL) was added 500 mg (2.61 mmol) of 2-chloro-3-formylquinoline and the acetophenone derivative (1.0 eq., 2.61 mmol). The mixture was stirred at 25 °C for 24 h. The contents were then cooled and poured into cold water then neutralized with dilute HCl. The solid obtained was filtered, washed, and dried on air to afford the crude chalcone.

(E)-3-(2-Chloro-8-methylquinolin-3-yl)-1-o-tolylprop-2-en-1-one (2a)

Yd 94%. R_f (CH_2Cl_2): 0.60. Mp 165-167 °C. IR ν_{max} (KBr) 1645 cm^{-1} (C=O, ketone). ^1H NMR (250 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.00 (d, *J*=16.1, 1H), 7.75 (d, *J*=8.9, 1H), 7.52 (dd, *J*=9.1, *J*=2.4, 1H), 7.50-7.43 (m, 3H), 7.40 (ddd, *J*=8.9, *J*=8.1, *J*=2.3, 1H), 7.38 (dd, *J*=9.4, *J*=1.2, 1H), 7.25 (d, *J*=16.1, 1H), 2.75 (s, 3H), 2.50 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 195.2 (C=O), 149.1 (C), 147.1 (C), 140.5 (CH), 138.2 (C), 137.4 (C), 136.7 (CH), 136.4 (CH), 131.7 (C), 131.5 (CH), 130.9 (CH), 130.2 (C), 128.4 (CH), 127.4 (CH), 127.3 (C), 127.0 (CH), 125.8 (CH), 125.5 (CH), 20.4 (CH_3), 17.7 (CH_3). HRMS (EI): m/z [M^+] Calcd. for $C_{20}H_{16}NO^{35}Cl$: 321.09204, found 321.0928.

(E)-3-(2-Chloroquinolin-3-yl)-1-o-tolylprop-2-en-1-one (2b)

Yd 88%. R_f (CH_2Cl_2): 0.65. Mp 120-124 °C. IR ν_{max} (KBr) 1685 cm^{-1} (C=O, ketone). ^1H NMR (250 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.95 (d, *J*=15.9, 1H), 7.79 (dd, *J*=8.7, *J*=8.4, 1H), 7.52 (dd, *J*=8.9, *J*=2.4, 1H), 7.50-7.32 (4H, m), 7.37 (dd, *J*=8.4, *J*=1.2, 1H), 7.29 (d, *J*=15.9, 1H), 6.82 (td, *J*=9.1, *J*=2.1, 1H), 2.50 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 195.2 (C=O), 150.2 (C), 147.8 (C), 140.1 (CH), 138.1 (C), 137.5 (C), 137.3 (CH), 136.1 (CH), 133.4(CH), 132.0 (CH), 131.6 (CH), 131.4 (CH), 131.3 (C), 130.6 (CH), 129.9 (CH), 127.2 (C), 125.5 (CH), 124.8 (CH), 20.4 (CH_3). HRMS (EI): m/z [M^+] Calcd. for $C_{19}H_{14}NO^{35}Cl$: 307.07639, found 307.0769.

(E)-3-(2-Chloro-5,8-dimethoxyquinolin-3-yl)-1-o-tolylprop-2-en-1-one (2c)

Yd 87%. R_f (CH_2Cl_2): 0.62. Mp 169-170 °C. IR ν_{max} (KBr) 1672 cm^{-1} (C=O, ketone). ^1H NMR (300 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.97 (d, *J*=16.0, 1H), 7.60 (d, *J*=7.5, 1H), 7.49 (d, *J*=7.4, 1H), 7.19-7.42 (m, 3H), 7.05 (d, *J*=16.0, 1H), 6.89 (d, *J*=8.6, 1H), 4.04 (s, 3H), 4.00 (s, 3H), 2.51 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ197.5 (C=O), 151.3 (C), 148.9 (C), 148.4 (C), 140.6 (CH), 138.7 (C), 135.6 (CH), 132.1 (C), 131.5 (C), 131.5 (CH), 130.9 (CH), 130.4 (C), 128.4 (CH), 127.9 (CH), 125.5 (CH), 121.8 (C), 109.8 (CH), 104.8 (CH), 56.2 (OCH_3), 55.8 (OCH_3), 20.4 (CH_3). HRMS (EI): m/z [M^+] Calcd. for $C_{21}H_{18}NO_3{}^{35}Cl$: 367.09752, found 367.0961.

(E)-3-(2-Chloro-6-methylquinolin-3-yl)-1-o-tolylprop-2-en-1-one (2d)

Yield 91%. R_f (CH_2Cl_2): 0.59. Mp 143-145 °C. IR ν_{max} (KBr) 1654 cm^{-1} (C=O, ketone). ^1H NMR (250 MHz, $CDCl_3$) δ 8,41 (s, 1H), 7.90 (d, *J*=16.0, 1H), 7.85 (d, *J*=8.3, 1H), 7.60-7.55 (m, 5H), 7.32 (d, *J*=16.0, 1H), 7.00 (dd, *J*=8.4, *J*=2.2, 1H), 2.43 (s, 3H), 2.66 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.8 (C=O), 150.1 (C), 146.6 (C), 140.5

(CH), 138.2 (C), 136.0 (C), 136.5 (CH), 135.4 (CH), 131.7 (C), 131.5 (CH), 130.9 (CH), 130.2 (C), 128.4 (CH), 128.1 (CH), 127.4 (C), 127.0 (CH), 125.6 (CH), 125.2 (CH), 20.4 (CH_3), 18.1 (CH_3). HRMS (EI): m/z [M^+] Calcd. for $C_{20}H_{16}NO^{35}Cl$: 321.09204, found 321.0928.

(E)-3-(2-Chloro-8-methylquinolin-3-yl)-1-(4-methoxyphenyl) prop-2-en-1-one (2e)

Yield 97%. R_f (CH_2Cl_2): 0.55. Mp 131-134 °C. IR ν_{max}(KBr) 1662 cm^{-1} (C=O, ketone). ^1H NMR (250 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.15 (d, *J*=15.7, 1H), 8.14 (d, *J*=8.8, 2H), 7.77-7.67 (m, 3H), 7.60 (d, *J*=15.7, 1H), 7.00 (d, *J*=8.8, 2H), 3.96 (s, 3H), 2.75 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 187.7 (C=O), 163.6 (C), 149.7 (C), 149.3 (C), 147.0 (C), 138.7 (CH), 136.6 (CH), 136.3 (C), 131.5 (CH), 131.0 (CH), 130.5 (C), 130.3 (CH), 127.7 (2×CH), 127.3 (CH), 127.0 (C), 113.9 (2×CH), 55.5 (OCH_3), 17.7 (CH_3). HRMS (EI): m/z [M^+] Calcd. for $C_{20}H_{16}NO_2{}^{35}Cl$: 337.08696, found 337.0869.

(E)-3-(2-Chloro-6-methoxyquinolin-3-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (2f)

Yield 90%. R_f (CH_2Cl_2): 0.65. Mp 142-145 °C. IR ν_{max}(KBr) 1653 cm^{-1} (C=O, ketone). ^1H NMR (250 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.21 (d, *J*=15.9, 1H), 7.57 (d, *J*=8.1, 1H), 7.55 (d, *J*=8.7, 2H**),** 7.22 (d, *J*=8.9, 1H), 7.15 (d, *J*=15.9, 1H), 7.12 (s, 1H) 6.75 (d, *J*=8.6, 2H), 4.00 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 195.8 (C=O), 162.5 (C), 155.4 (C), 142.7 (C), 142.5 (C), 137.9 (C), 134.4 (CH), 132.6 (C), 131.5 (CH), 131.8 (CH), 127.0 (CH), 126.2 (C), 125.9 (2xCH), 121.6 (CH), 113.1 (2xCH), 108.6 (CH), 55.5 (OCH_3), 54.4 (OCH_3). HRMS (EI): m/z [M^+] Calcd. for $C_{20}H_{16}NO_3{}^{35}Cl$: 353.08187, found 353.0825.

(E)-3-(2-Chloro-8-methylquinolin-3-yl)-1-(3,4-dimethoxyphenyl)prop-2-en-1-one (2g)

Yield 90%. R_f (CH_2Cl_2): 0.64. Mp 183-184 °C. IR ν_{max} (KBr) 1658 cm^{-1} (C=O, ketone). ^1H NMR (250 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.25 (d, *J*=15.7, 1H), 7.75-7.67 (m, 4H), 7.52 (d, *J*=15.7, 1H), 7.50 (s, 1H), 7.00 (d, *J*=8.4, 1H), 4.00 (s, 3H), 3.96 (s, 3H), 2.78 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 195.5 (C=O), 153.5 (C), 150.0 (C), 149.2 (C), 146.9 (C), 145.7 (CH), 138.7 (CH), 136.6 (C), 136.4 (CH), 136.3 (CH), 131.5 (C), 130.8 (CH), 128.6 (C), 127.7 (CH), 127.3 (C), 124.9 (CH), 110.7 (CH), 109.8 (CH), 56.2 (OCH_3), 56.1 (OCH_3), 17.7 (CH_3). HRMS (EI): m/z [M^+] Calcd. for $C_{21}H_{18}NO_3{}^{35}Cl$: 367.09752, found 367.0997.

(E)-3-(2-Chloro-8-methylquinolin-3-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (2h)

Yield 72 %. R_f (CH_2Cl_2): 0.65. Mp 122-124 °C. IR ν_{max}(KBr) 1656 cm^{-1} (C=O, ketone). ^1H NMR (250 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.20 (d, *J*=15.5, 1H), 7.89 (d, *J*=7.1, 1H), 7.40 (d, *J*=7.4, 1H), 7.34 (d, *J*=7.1, 1H), 7.09 (d, *J*=15.5, 1H), 6.89 (s, 2H), 3.97 (s, 3H), 3.93 (s, 3H), 3.83 (s, 6H), 2.65 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 195.0 (C=O), 151.7 (C), 148.9 (C), 144.3 (C), 143.5 (C) , 136.3 (C), 136.2 (CH), 136.0 (C), 132.4 (C), 131.3 (CH), 130.4 (C), 128.9 (CH), 128.1 (CH), 127.4 (CH), 127.3 (C), 125.4 (CH), 105.6 (2×CH), 59.9 (OCH_3), 55.9 (OCH_3), 54.9 (OCH_3), 17.8 (CH_3). HRMS (EI): m/z [M^+] Calcd. for $C_{22}H_{20}NO_4{}^{35}Cl$: 367.09752, found 367.0997.

General Procedure for the Preparation of Methyl(vinylquinoline) Ketone Derivatives

A suspension of the ylide Ph_3P=CHCOMe (313 mg, 1.1 mmol) and the 2-chloro-3-formylquinoline (191.5 mg, 1.0 mmol) in DME (10 mL) was refluxing for three hours. After cooling to room temperature, the mixture was filtered and the filtrate was condensed under reduced pressure. The residue was then purified by column chromatography over silica gel (CH_2Cl_2) to give the olefinic product.

(E)-4-(2-Chloro-6-methylquinolin-3-yl)but-3-en-2-one (2i)

Yield 56%. R_f (CH_2Cl_2): 0.75. Mp 73-74 °C. IR ν_{max}(KBr) 1645 cm^{-1} (C=O, ketone). ^1H NMR (250 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.90 (d, *J*=16.3, 1H), 7.73 (s, 1H), 7.57-7.54 (m, 2H), 6.75 (d, *J*=16.3, 1H), 2.52 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.8 (C=O), 149.1 (C), 146.5 (C), 138.1 (CH), 137.9 (C), 135.4 (CH), 134.0 (CH), 130.8 (CH), 128.0 (CH), 127.1 (C), 127.0 (C), 126.8 (CH), 27.3 (CH_3), 21.6 (CH_3). HRMS (EI): m/z [M^+] Calcd. for $C_{14}H_{12}NO^{35}Cl$: 245.06074, found 245.0607.

(E)-4-(2-Chloroquinolin-3-yl)but-3-en-2-one (2j)

Yield 70%. R_f (CH_2Cl_2): 0.72. Mp 175-177 °C. IR ν_{max}(KBr) 1651 cm^{-1} (C=O, ketone). ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.04 (d, 8.4,, 1H), 7.98(d, *J*=16.3, 1H), 7.88 (d, *J*=8.2, 1H), 7.80 (t, *J*=7.9, 1H), 7.62 (t, *J*=7.3, 1H), 6.82 (d, *J*=16.3, 1H), 2.48 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 197.6 (C), 148.5 (C), 138.0 (CH), 136.1 (CH), 133.4 (C), 131.9 (C), 131.7 (CH), 131.0 (C), 128.4 (CH), 128.0 (CH), 127.7 (C), 126.4 (CH), 30.9 (CH_3). HRMS (EI): m/z [M^+] Calcd. for $C_{13}H_{10}NO^{35}Cl$: 231.04509, found 231.0452.

General Procedure for the Preparation of Quinolylpyrrolidine N-H Derivatives

To 1.5 eq. of lithium bromide dissolved in dry THF (e.g 0.5 g in 40 mL) was added, under magnetic stirring and at room temperature, 1 eq. of benzylidene glycine imine, 1 eq. of substituted quinolyl α,β-unsaturated ketone derivative and 1.2 eq. of dry Et_3N. The reaction mixture was kept under stirring, at room temperature and the progress of the reaction was monitored by TLC still disappearance of starting product. The mixture was diluted with ether (15 mL) and work up by treatment with saturated aqueous ammonium chloride (10 mL). The organic layers were separated and dried over anhydrous $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography on silica gel using $CHCl_3$ as eluent to afford pure product.

Methyl 4-(2-methylbenzoyl)-3-(2-chloro-8-methylquinolin-3-yl)-5-phenylpyrrolidine-2-carboxylate (3a)

Yield 70%. R_f ($CHCl_3$): 0.34. Mp 74-76 °C. IR (ATR) ν 3332, 2953, 1737, 1678, 1574, 1479, 1455, 1372, 1335, 1239, 753 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.69 (d, *J*=8.1, 1H), 7.57 (d, *J*=6.9, 1H), 7.46 (m, 2H), 7.27 (td, *J*=7.5, *J*=1.3, 1H), 7.16-7.02 (m, 6H), 6.99 (d, J=7.5, 1H), 4.96 (d, *J*=8.1, 1H), 4.77 (t, *J*=8.0, 1H), 4.69 (t, *J*=8.0, 1H), 4.40 (d, *J*=7.9, 1H),3.80 (s, 3H), 3.00 (brs, 1H), 2.80 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 202.0 (C=O), 173.3 (C=O), 150.0 (C), 146.3 (C), 139.8 (C), 139.0 (C), 137.9 (C), 137.8 (CH), 136.9 (C), 132.4 (C), 132.2

(CH), 131.8 (CH), 130.9 (CH), 129.0 (CH), 128.7 (2×CH), 128.1 (CH), 127.8 (C), 127.7 (2×CH), 127.5 (CH), 125.7 (CH), 125.6 (CH), 66.5 (CH, C-2), 66.4 (CH, C-5), 60.8 (CH, C-4), 52.9 (OCH_3), 50.5 (CH, C-3), 21.0 (CH_3), 18.1 (CH_3). MS (ESI): m/z 499.1 (MH^+, 100), 439 (10), 394 (3), 322 (30), 178 (77), 119 (21), 91 (5), 60 (5).

Methyl 4-(2-methylbenzoyl)-3-(2-chloroquinolin-3-yl)-5-phenylpyrrolidine-2-carboxylate (3b)

Yield 58%. R_f ($CHCl_3$): 0.34. Mp 79-81 °C. IR (ATR) ν 3347, 2926, 1735, 1676, 1567, 1488, 1454, 1331, 1202, 1133, 731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.04 (d, *J*=8.5, 1H), 8.86 (d, *J*=8.1, 1H), 7.72 (td, *J*=7.7, *J*=1.1, 1H), 7.59 (t, *J*=7.4, 1H), 7.46 (d, *J*=7.7, 1H), 7.24 (t, *J*=7.6, 1H), 7.17-7.11 (m, 6H), 6.99 (d, *J*=7.5, 1H), 4.96 (d, *J*=8.2, 1H), 4.81 (t, *J*=8.1, 1H), 4.70 (t, *J*=8.1, 1H), 4.37 (d, *J*=8.3, 1H), 3.79 (s, 3H), 2.88 (brs, 1H), 1.83 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 201.7 (C=O), 173.2 (C=O), 151.3 (C), 147.1 (C), 139.9 (C), 139.0 (C), 138.4 (C), 137.8 (C),137.5 (CH), 132.8 (C), 132.2 (CH), 131.9 (CH), 130.9 (CH), 129.0 (CH), 128.7 (2xCH), 128.6 (CH), 128.6 (CH), 128.1 (CH), 127.7 (2xCH), 127.7 (CH), 125.8 (CH), 66.6 (CH, C-2), 66.3 (CH, C-5), 61.0 (CH, C-4), 53.0 (OCH_3), 50.2 (CH, C-3), 21.0 (CH_3). MS (ESI): m/z 485.2 (MH^+, 100), 425 (8), 380 (5), 308 (28), 178 (75), 146 (7), 119 (56), 91 (8), 60(7). HRMS (ESI): m/z [MH^+] Calcd. for $C_{29}H_{26}N_2O_3{}^{35}Cl$: 485.16320, found 485.1628.

Methyl 4-(2-methylbenzoyl)-3-(2-chloro-5,8-dimethoxyquinolin-3-yl)-5-phenylpyrrolidine -2-carboxylate (3c)

Yield 71%. R_f ($CHCl_3$): 0.34. Mp 153-154 °C. IR (ATR) ν 3339, 2953, 1733, 1674, 1617, 1592, 1481, 1330, 1263, 1014, 725 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.39 (d, *J*=7.7, 1H), 7.24 (td, *J*= 7.4, *J*=1.2, 1H), 7.15-7.11 (m, 6H), 6.98 (m, 2H), 6.78 (d, *J*=8.5, 1H), 4.96 (d, *J*=8.1, 1H), 4.73 (t, *J*=7.9, 1H), 4.72 (t, *J*=8.0, 1H), 4.35 (d, *J*=8.2, 1H), 4.03 (s, 3H), 3.98 (s, 3H), 3.77 (s, 3H), 3.23 (brs, 1H), 1.80 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 202.14 (C=O), 173.2 (C=O), 151.3 (C), 148.9 (C), 148.6 (C), 139.7 (C), 139.1 (C), 139.0 (C), 138.0 (C), 132.7 (C), 132.1 (CH), 131.8 (CH), 128.9 (CH), 128.7 (2xCH), 128.0 (CH), 127.7 (2xCH), 127.4 (CH), 125.7 (CH), 121.1 (C), 108.6 (CH), 104.9 (CH), 67.1 (CH, C-2), 66.5 (CH, C-5), 61.0 (CH, C-4), 56.5 (OCH_3), 56.1 (OCH_3), 52.9 (OCH_3), 51.0 (CH, C-3), 20.9 (CH_3). MS (ESI): m/z 545.1 (MH^+, 100), 509 (10), 485 (5), 368 (38), 332 (3), 178 (38), 119 (15), 91 (1), 60 (1). HRMS (ESI): m/z [MH^+] Calcd. for $C_{31}H_{30}N_2O_5{}^{35}Cl$: 545.18432, found 545.1839.

Methyl 4-(2-methylbenzoyl)-3-(2-chloro-6-methylquinolin-3-yl)-5-phenylpyrrolidine-2-carboxylate (3d)

Yield 62%. R_f ($CHCl_3$): 0.29. Mp 83-85 °C. IR (ATR) ν 3336, 2952, 1736, 1677, 1597, 1494, 1338, 1215, 1129, 1044, 731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.93 (d, *J*=8.6, 1H), 7.62 (s, 1H), 7.57 (dd, *J*=8.7, *J*=1.7, 1H), 7.43 (d, *J*=7.7, 1H), 7.26 (td, *J*= 7.4, *J*=1.2, 1H), 7.17-7.14 (m, 6H), 6.99 (d, *J*=7.5, 1H), 4.95 (d, *J*=8.0, 1H) 4.78 (t, *J*=8.0, 1H), 4.67 (t, *J*=8.1, 1H), 4.37 (d, *J*=7.9, 1H), 3.79 (s, 3H), 2.78 (brs, 1H), 2.55 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 201.8 (C=O), 173.3 (C=O), 150.3 (C), 145.7 (C), 139.8 (C), 139.0 (C), 137.8 (C), 137.8 (C), 136.9 (CH), 133.1 (CH), 132.6 (C), 132.2 (CH), 131.9 (CH), 129.0 (CH), 128.7 (2xCH), 128.3 (CH), 128.1 (CH), 127.8 (C), 127.7 (2xCH), 126.6 (CH), 125.7 (CH), 66.4 (CH, C-2), 66.3 (CH, C-5), 61.0 (CH, C-4), 52.9 (OCH_3), 50.2 (CH, C-3), 22.0 (CH_3), 21.0 (CH_3). HRMS (ESI): m/z [MH^+] Calcd. for $C_{30}H_{28}N_2O_3{}^{35}Cl$: 499.17885, found 499.1793.

Methyl 4-(4-methoxybenzoyl)-3-(2-chloro-8-methylquinoline-3-yl)-5-phenylpyrrolidine-2-carboxylate (3e)

Yield 60%. R_f ($CHCl_3$): 0.32. Mp 108 °C. IR (ATR) ν 3342, 2924, 1740, 1656, 1595, 1512, 1433, 1374, 1227, 1024, 749, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.69 (d, *J*=8.1, 1H), 7.57-7.50 (m, 3H), 7.48 (t, *J*=7.7, 1H), 7.18-7.08 (m, 5H), 6.72 (d, *J* =8.8, 2H), 4.98 (d, *J*=8.1, 1H), 4.72 (t, *J*=7.9, 1H), 4.56 (t, *J*=7.9, 1H), 4.43 (d, *J*=8.0, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.22 (brs, 1H), 2.78 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 197.6 (C=O), 173.6 (C=O), 163.6 (C), 150.3 (C), 146.3 (C), 138.6 (C), 137.4 (CH), 136.8 (C), 132.9 (C), 130.8 (2xCH), 130.6 (C), 129,5 (CH), 128.6 (2xCH), 128.1 (CH), 127.7 (C),127.6 (2xCH), 127.5 (CH), 125.7 (CH), 113.7 (2xCH), 66.8 (CH, C-2), 66.0 (CH, C-5), 58.8 (CH, C-4), 55.7 (OCH_3), 53.0 (OCH_3), 50.4 (CH, C-3), 18.14 (CH_3). MS (ESI): m/z 515.3 (MH^+, 85), 455 (10), 410 (8), 338 (24), 178 (100), 135 (21), 118 (10), 91 (3), 60 (3). Calcd for $C_{30}H_{27}N_2O_4Cl$: C, 69.97; H, 5.28; N. 5.44, Found C, 69.33; H, 5.36; N, 5.39.

Methyl 4-(4-methoxybenzoyl)-3-(2-chloro-6-methoxyquinolin-3-yl)-5-phenylpyrrolidine-2-carboxylate (3f)

Yield 65%. R_f ($CHCl_3$): 0.28. Mp 100-103 °C. IR (ATR) ν 3354, 2952, 1734, 1655, 1596, 1494, 1353, 1223, 1170, 907, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.91 (d, *J*=9.0, 1H), 7.55 (d, *J*=8.8, 2H), 7.36 (dd, *J*=9.1, *J*=2.6, 1H), 7.18-7.05 (m, 6H), 6.70 (d, *J*=8.8, 2H), 4.97 (d, *J*=8.1, 1H), 4.68 (t, *J*=8.0, 1H), 4.40 (t, *J*=8.0, 1H), 4.39 (d, *J*=7.9, 1H), 3.93 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.10 (brs, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 197.6 (C=O), 175.6 (C=O), 163.6 (C), 158.7 (C), 148.6 (C), 143.1 (C), 138.5 (C), 136.0 (CH), 133.4 (C), 130.8 (2xCH), 130.6 (C), 129.9 (CH), 128.8 (C), 128.6 (2xCH), 128.2 (CH), 127.6 (2xCH), 123.5 (CH), 113.7 (2xCH), 105.3 (CH), 66.7 (CH, C-2), 66.0 (CH, C-5), 58.6 (CH, C-4), 56.0 (OCH_3), 55.7 (OCH_3), 53.0 (OCH_3), 50.3 (CH, C-3). MS (ESI): m/z 531.3 (MH^+, 73), 471 (7), 426 (7), 366 (5), 354 (28), 178 (100), 135 (24), 118 (17), 91 (8), 60 (7). HRMS (ESI): m/z [MH^+] Calcd. for $C_{30}H_{28}N_2O_5{}^{35}Cl$: 531.16868, found 531.1680.

Methyl 4-(3,4-dimethoxybenzoyl)-3-(2-chloro-8-methylquinolin-3-yl)-5-phenyl pyrrolidine -2-carboxylate (3g)

Yield 53%. R_f ($CHCl_3$): 0.30. Mp 115-116 °C. IR (ATR) ν 3350, 1758, 1653, 1586, 1492, 1850, 709 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.64-7.00 (m, 10H), 6.71 (d, *J*=8.0, 1H), 5.00 (d, *J*=8.0, 1H), 4.78 (t, *J*=8.0, 1H), 4.60 (t, *J*=8.2 , 1H), 4.53 (d, *J*=8.0, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.76 (s, 3H), 2.78 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 197.2 (C=O), 173.2 (C=O), 153.0 (C), 150.0 (C), 148.6 (C), 145.8 (C), 137.9 (CH), 36.9 (C), 136.4 (C), 133.4 (C), 130.4 (CH), 129.6 (C), 128.2 (2xCH), 127.8 (CH), 127.3 (C), 127.2 (2xCH), 127.1 (CH), 125.3 (CH), 122.9 (CH), 110.0 (CH), 109.5 (CH), 66.2 (CH), 65.4 (CH), 58.4 (CH), 55.9 (OCH_3), 55.7 (OCH_3), 52.6 (OCH_3), 49.1 (CH), 17.7 (CH_3). HRMS (ESI): m/z [MH^+] Calcd. for $C_{31}H_{30}N_2O_5{}^{35}Cl$: 545.18433, found 545.1843.

Methyl 4-(3,4,5-trimethoxybenzoyl)-3-(2-chloro-8-methylquinolin-3-yl)-5-phenyl pyrrolid-ine-2-carboxylate (3h)

Yield 54%. R_f ($CHCl_3$): 0.38. Mp 209-210 °C. IR (ATR) ν 3354, 2949, 1732, 1648, 1494, 1250, 1185, 915, 708 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, s), 7.71 (d, *J*=7.9, 1H), 7.59 (d, *J*=7.9, 1H), 7.48 (t, *J*=7.9, 1H), 7.16-7.10 (m, 5H), 6.77 (s, 2H), 4.95 (d, *J*=8.1, 1H**)**, 4.71 (t, *J*=8.0, 1H), 4.42-4.44 (m, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.76 (s, 6H), 3.30 (s, 3H), 2.78 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 198.0 (C=O), 173.4 (C=O), 152.5 (C), 149.8 (C), 145.9 (C), 142.4 (C) , 137.9 (C), 136.8 (CH), 136.4 (C), 132.4 (C), 132.2 (C), 130.5 (CH), 128.3 (2×CH), 128.0 (CH), 127.3 (2×CH), 127.2 (C), 127.2 (CH), 125.3 (CH), 105.8 (2×CH), 66.4 (CH), 65.3 (CH), 60.8 (OCH_3), 58.8 (CH), 56.2 (OCH_3), 52.7 (OCH_3), 50.0 (CH), 17.7 (CH_3). HRMS (ESI): m/z [MH^+] Calcd. for $C_{32}H_{32}N_2O_6{}^{35}Cl$: 575.19489, found 575.1917.

Methyl 4-(methylketone)-3-(2-chloro-6-methylquinolin-3-yl)-5-phenylpyrrolidine-2-carboxylate (3i)

Yellow oil. Yield 67%. R_f ($CHCl_3$): 0.54. IR (ATR) ν 3350, 2957, 1732, 1657, 1285, 1226, 1085, 910, 695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.94 (d, *J*=8.5, 1H), 7.68 (s, 1H), 7.60 (dd, *J*=8.5, *J*=1.6, 1H), 7.37-7.25 (m, 5H), 4.87 (d, *J*=8.0, 1H), 4.53 (t, *J*=8.1, 1H), 4.35 (d, *J*=7.9, 1H), 3.82 (s, 3H), 3.60 (dd, *J*=7.9, *J*=4.8, 1H), 2.55 (s, 3H), 1.50 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 208.0 (C=O), 172.6 (C=O), 149.6 (C), 145.0 (C), 137.4 (C), 136.8 (CH), 135.9 (C), 132.8 (CH), 132.2 (C), 128.8 (2×CH), 128.4 (CH), 127.5 (CH), 127.3 (C), 126.9 (2×CH), 126.4 (CH), 64.8 (CH), 64.3 (CH), 63.9 (CH), 52.7 (OCH_3), 49.0 (CH), 28.3 (OCH_3), 21.4 (CH_3). HRMS (EI): m/z [M^+] Calcd. for $C_{24}H_{22}N_2O_3{}^{35}Cl$: 421.13190, found 421.1329.

Methyl 4-(methylketone)-3-(2-chloroquinolin-3-yl)-5-phenyl-pyrrolidine-2-carboxylate (3j)

Yellow oil. Yield 59%. R_f ($CHCl_3$): 0.45. IR (ATR) ν 3367, 1739, 1651, 1342, 1237, 1110 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.08 (d, *J*=8.4, 1H), 7,90 (d, *J*=8.1, 1H), 7.73 (t, *J*=7.0, 1H), 7.61 (t, *J*=7.1, 1H), 7.30-7.45 (m, 5H), 4.85 (d, *J*=8.0, 1H), 4.51(t, *J*=8.0, 1H), 4.32 (d, *J*=7.9, 1H), 3.83 (s, 3H), 3.61 (dd, *J*=8.0, *J*=4.8, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 207.8 (C=O), 172.8 (C=O), 150.6 (C), 146.6 (C), 139.2 (C), 137.3 (CH), 136.7 (CH), 132.7 (C), 130.6 (CH), 128.9 (2xCH), 128.4 (CH), 128.1 (CH), 127.5 (CH), 127.3 (C), 127.0 (2xCH), 65.2 (CH) ,65.1 (CH), 52.7 (OCH_3), 49.2 (CH), 31.2 (CH), 28.3 (CH_3). HRMS (EI): m/z [M^+] Calcd. for $C_{23}H_{21}N_2O_3{}^{35}Cl$: 408.12407, found 408.1221.

ACKNOWLEDGEMENTS

ANDRS (Agence Nationale pour le Développement de la Recherche en Santé) and MESRES (Ministère de l'Enseignement Supérieur et de la Recherche Scientifique) are gratefully acknowledged for their financial support. AB thanks l'Agence Universitaire de la Francophonie (AUF) for financial support.

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[14] The single-crystal growth was carried out in $CHCl_3$ at room temperature. X-ray diffraction data have been collected with an Enraf–Nonius KAPPA CCD at 293 K using Mo Kα radiation (λ = 0.71073 Å). The crystal **3e** belong to the triclinic space group P_{-1}, with unit-cell parameters *a* = 12.4982(2)Å, *b* = 13.6473(4)Å, *c* 18.3062(2)Å, α = 110.709(3)°, β= 105.647(4)° and γ= 89.9690(10)°. The asymmetric unit contains two molecules. Bond angles, bond distances and other crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary Publication No. CCDC-662754 for compound **3e**. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK.

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Received: December 14, 2009 Revised: February 27, 2010 Accepted: March 12, 2010