

One-pot synthesis of 4-arylquinolines from aromatic aminoketones and vinylphosphonium salts

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Abstract The addition of acetylenic esters to aromatic amines such as 2-amino benzophenone derivatives in the presence of triphenylphosphine leads to highly functionalized phosphoranes, which undergo an intramolecular Wittig reaction following oxidation to produce quinoline derivatives.

Keywords Acetylenic esters · Triphenylphosphine · Wittig reaction · Quinoline

Introduction

Quinoline derivatives are receiving increasing importance due to their wide range of biological activities as anti-malarial, anti-bacterial, anti-asthmatic, anti-hypertensive, anti-inflammatory, anti-platelet activity and also tyrosine-kinase PDGF-RTK as inhibitor agent [1–10]. Due to such a wide range of applicability in medicine, bioorganic chemistry, industry as well as synthetic organic chemistry, there has been increasing interest in the development of efficient methodologies for the synthesis of quinolines. The structural core of quinoline has generally been synthesized by various conventional name reactions such as Skraup [12], Doebner–von Miller [11], Friedlander [12], Pfitzinger [13], Conrad–Limpach [14] and Combes [11] syntheses. These classical syntheses are well known and frequently used for the preparation of pharmaceutical agents, ligands and functional materials bearing a quinoline backbone. However, current methods for quinoline synthesis often do not allow for adequate diversity and substitution on the quinoline ring system [15]. Here we report three-component reactions of 2-amino benzophe-

none derivatives **2** and acetylenic mono or diesters **1** in the presence of PPh₃. Thus, the reaction of PPh₃ with electron deficient acetylenic esters **1** in the presence of aromatic amine such as **2** leads to functionalized quinolines **3** in good yields (Scheme 1).

When the reaction was carried out with 2-amino acetophenone only enamine derivative of 2-amino acetophenone **5** was produced in the presence of diesters, and no product was found with monoesters after 4 days of reflux in toluene (Scheme 2).

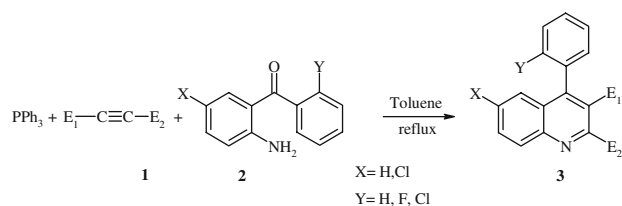
Results and discussion

On the basis of the chemistry of trivalent phosphorus nucleophiles [16, 17], it is reasonable to assume that 4-phenyl quinoline derivatives **3** result from initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the reactive 1:1 adduct by 2-amino benzophenone derivatives, followed by attack of the conjugated base of **2** on vinyl triphenylphosphonium cation **6** to generate phosphorane **7**. These phosphoranes undergo intramolecular Wittig reactions in boiling toluene to produce 1,2-dihydroquinoline derivatives **8** which on dehydrogenation afford aromatic quinoline derivatives **3** (Scheme 3).

The reaction of 2-aminoacetophenone, acetylenic ester and PPh₃ leads to stable enamine derivatives. It seems that the carbonyl group in ylide **10** withdraws the electrons of the methyl group (C_{sp3}) more efficiently and no intramolecular Wittig reaction between this carbonyl group and the carbanion of ylide is carried out, but a proton shift and PPh₃ loss take place instead producing enamine derivatives **5a–b** (Scheme 4).

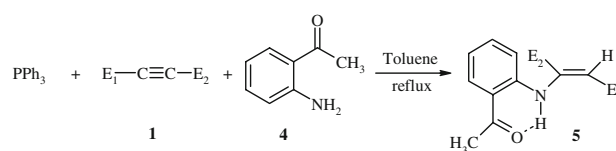
This reaction with 2-amino-5-nitrobenzophenone failed, and no product was isolated from the reaction. Here, the nitro group withdraws more efficiently the lone pair electrons of

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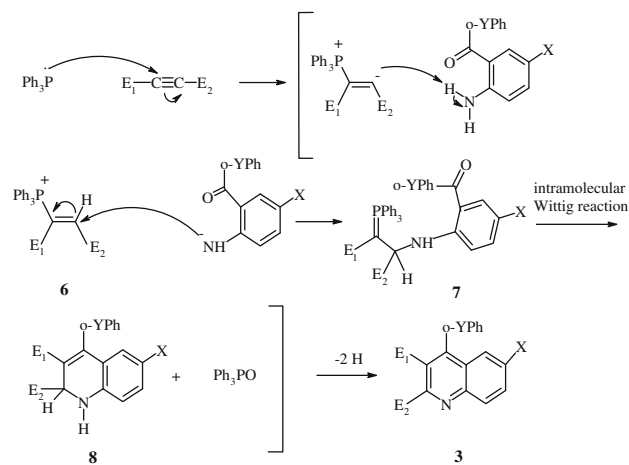
3	E ₁	E ₂	X	Y	Yield (%)
a	CO ₂ Me	CO ₂ Me	H	H	88
b	CO ₂ Et	CO ₂ Et	H	H	85
c	H	CO ₂ Me	H	H	55
d	H	CO ₂ Et	H	H	55
e	CO ₂ Me	CO ₂ Me	Cl	H	78
f	CO ₂ Et	CO ₂ Et	Cl	H	88
g	H	CO ₂ Me	Cl	H	65
h	H	CO ₂ Et	Cl	H	70
i	CO ₂ Et	CO ₂ Et	Cl	Cl	85
j	CO ₂ Me	CO ₂ Me	Cl	F	90
k	CO ₂ Et	CO ₂ Et	Cl	F	90
l	CO ₂ Me	CO ₂ Me	Cl	Cl	72

Scheme 1 Synthesis of 4-arylquinolines from aromatic aminoketones and vinylphosphonium salts



5	E ₁	E ₂	Yield %
a	CO ₂ Me	CO ₂ Me	68
b	CO ₂ Et	CO ₂ Et	75

Scheme 2 Formation of enamines from acetophenone as starting material

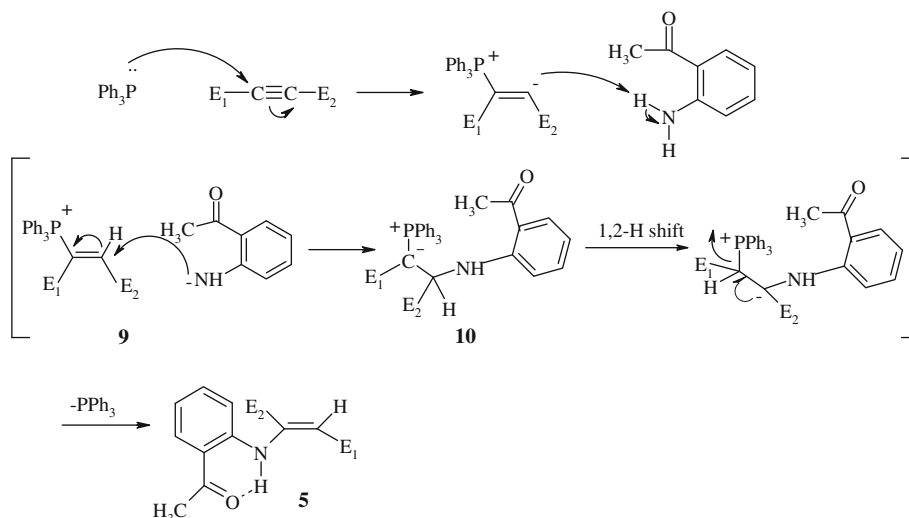


Scheme 3 Mechanism of the formation of 4-arylquinolines

the amino groups unfavouring any ylide formation. In order to confirm the proposed three-component reaction mechanism in Scheme 3, we considered the two-component reaction between acetylenic esters and aminobenzophenone. The results showed that when the reaction of aminobenzophenone

none is carried out in the presence of acetylenic diesters the product is quinoline derivative too (30% lower yield), but no products from acetylenic monoesters were produced as a result of the diminished electrophilicity of the β carbon in the acetylenic monoesters versus in acetylenic diesters.

Scheme 4 Mechanism of the formation of enamines



These foundations and the formation of triphenylphosphine oxide in the three-component reactions confirmed the proposed mechanism in Scheme 3 that is reasonable because of the higher nucleophilicity of PPh_3 than aromatic amine.

The structures of **3a–l** were deduced from their elemental analyses and their Mass, ^1H , ^{13}C NMR and IR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate m/z values and other fragmentations involved with the loss of the ester moieties.

The ^1H NMR spectra of **3a** exhibited two singlet sharp lines at δ 3.61 and 4.04 ppm for two methoxy groups and other characteristic signals with appropriate chemical shifts for the aromatic protons. The proton-decoupled ^{13}C NMR spectrum of **3a** showed 17 distinct resonances in agreement with the proposed structure. Partial assignment of these signals is given in “Materials and methods” section. The structural assignment of **3a** made on the basis of their NMR spectra was supported by their IR spectra. The strong carbonyl bond at about 1725 cm^{-1} was observed.

The ^1H and ^{13}C NMR spectra of **3c** are similar to those of **3a** except for the aromatic region, which exhibited characteristic signals with appropriate chemical shifts.

The ^1H NMR spectrum of **3e** exhibited two sharp singlet at δ 4.05 and 3.62 ppm for the methoxy groups. The other aromatic protons for **3e** appear on appropriate chemical shifts. The ^{13}C NMR of **3e** also exhibited 17 signals in agreement with the proposed structure.

The ^1H NMR spectrum of **5a** exhibited a singlet for NH proton at δ 11.9 that was not observed in the ^1H NMR spectra of **3a–l**. Also the proton-decoupled ^{13}C NMR spectrum of **5a** showed 14 distinct signals in agreement with the proposed structure. The NMR spectra of **5b** were similar to those of **5a** except for the alkoxy groups, which exhibited characteristic signal in the appropriate regions of the spectra.

In conclusion, the method presented here may be considered as a practical one-pot synthesis of functionalized quinolines using intramolecular Wittig reaction under neutral conditions that allow for adequate diversity and substitution on the quinoline ring system. The simplicity of the present procedure makes it an interesting alternative to complex multistep approaches [18–20].

Materials and methods

Elemental analyses were performed using a Heraeus CHN–O–Rapid analyzer. ^1H and ^{13}C NMR spectra were recorded on a BRUCKER DRX-300 and DRX-500 AVANCE spectrometer at 500 and 125.8, 300.13 and 75.5 MHz, respectively. Mass spectra were recorded on a Finnigan–Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. TLC was carried out on Fluka silica gel TLC-cards,

all other reagents and solvents were used as received from commercial suppliers. All of the coupling constants are given in hertz.

General procedure

A mixture of dimethyl acetylenedicarboxylate (0.285 g, 2 mmol) in toluene (3 mL) at -5°C for 10 min was added to a magnetically stirred solution of 2-amino benzophenone (0.394 g, 2 mmol) and triphenylphosphine (0.524 g, 2 mmol) in toluene (20 mL). The reaction mixture was then allowed to warm up to room temperature and then refluxed for 10 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography using hexane: ethyl acetate (80:20) as eluent. The solvent was removed under reduced pressure and the products **3a–l** and **5a–b** were obtained.

Dimethyl 4-phenyl-2,3-quinolinedicarboxylate (**3a**)

White powder; yield: 88%, mp $123\text{--}125^\circ\text{C}$; IR (KBr): $\text{C}_{\text{sp}2}\text{--H}$ 3050, $\text{C}_{\text{sp}3}\text{--H}$ 2995, C=O 1725 cm^{-1} .

^1H NMR (500.13 MHz, CDCl_3): δ 8.3 (d, $^3J_{\text{HH}}=8.5\text{ Hz}$, 1H, CH), 7.79 (ddd, $^3J_{\text{HH}}=8.5\text{ Hz}$, $^3J_{\text{HH}}=7.7\text{ Hz}$, $^4J_{\text{HH}}=1.4\text{ Hz}$, 1H, CH), 7.62 (d, $^3J_{\text{HH}}=7.7\text{ Hz}$, 1H, CH), 7.55 (t, $^3J_{\text{HH}}=7.7\text{ Hz}$, 1H, CH), 7.48 (t, $^3J_{\text{HH}}=6.4\text{ Hz}$, 1H, CH), 7.47 (d, $^3J_{\text{HH}}=2.0\text{ Hz}$, 2H, 2CH), 7.34 (dd, $^3J_{\text{HH}}=6.4\text{ Hz}$, $^3J_{\text{HH}}=2.0\text{ Hz}$, 2H, 2CH), 4.04 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3).

^{13}C NMR (125.77 MHz, CDCl_3): δ 167.5 and 165.5 (2C=O), 148.0, 147.1, 145.0, 134.5, 130.9, 130.6, 129.3, 129.1, 128.8, 128.2, 127.6, 127.1 and 126.6 (aromatic carbons), 53.3 and 52.3 (2OCH_3).

MS, m/z (%): 321 (11, M^+), 262 (21), 204 (100), 203 (44), 77 (8), 59 (81).

Anal. Calcd. for $\text{C}_{19}\text{H}_{15}\text{NO}_4$ (321.34): C 71.02, H 4.71, N 4.36%. Found: C 69.91, H 4.68, N 4.33%.

Diethyl 4-phenyl-2,3-quinolinedicarboxylate (**3b**)

White powder; yield: 85%, mp $95\text{--}97^\circ\text{C}$. IR (KBr): $\text{C}_{\text{sp}2}\text{--H}$ 3030, $\text{C}_{\text{sp}3}\text{--H}$ 2985, C=O 1728 cm^{-1} .

^1H NMR (500.13, CDCl_3): δ 8.29 (d, $^3J_{\text{HH}}=8.5\text{ Hz}$, 1H, CH), 7.76 (ddd, $^3J_{\text{HH}}=8.5\text{ Hz}$, $^3J_{\text{HH}}=7.8\text{ Hz}$, $^4J_{\text{HH}}=1.4\text{ Hz}$, 1H, CH), 7.59 (d, $^3J_{\text{HH}}=7.8\text{ Hz}$, 1H, CH), 7.53 (t, $^3J_{\text{HH}}=7.8\text{ Hz}$, 1H, CH), 7.46 (t, $^3J_{\text{HH}}=6.5\text{ Hz}$, 1H, CH), 7.45 (d, $^3J_{\text{HH}}=2.2\text{ Hz}$, 2H, 2CH), 7.33 (dd, $^3J_{\text{HH}}=6.5\text{ Hz}$, $^3J_{\text{HH}}=2.2\text{ Hz}$, 2H, 2CH), 4.50 (q, $^3J_{\text{HH}}=7.1\text{ Hz}$, 2H, OCH_2), 4.06 (q, $^3J_{\text{HH}}=7.1\text{ Hz}$, 2H, OCH_2), 1.43 (t, $^3J_{\text{HH}}=7.1\text{ Hz}$, 3H, CH_3), 0.96 (t, $^3J_{\text{HH}}=7.1\text{ Hz}$, 3H, CH_3).

^{13}C NMR (125.77 MHz, CDCl_3): δ 167.0 and 165.2 (2C=O), 147.9, 147.1, 146.0, 134.8, 130.8, 130.6, 129.9,

128.9, 128.7, 128.2, 127.5, 127.0 and 126.5 (aromatic carbons), 62.5 and 61.4 (2OCH₂), 14.1 and 13.5 (2CH₃).

MS, *m/z* (%): 349 (3, M⁺), 276 (100), 204 (100), 203 (75), 77 (14).

Anal. Calcd. for C₂₁H₁₉NO₄ (349.39): C 72.19, H 5.48, N 4.01%. Found: C 72.05, H 5.44, N 3.98%.

Methyl 4-phenyl-2-quinoline carboxylate (**3c**)

White powder; yield: 55%, mp 101–103 °C.

IR (KBr): C_{sp2}–H 3010, C_{sp3}–H 2995, C=O 1725 cm^{−1}.

¹H NMR (500.13 MHz, CDCl₃): δ_H 8.36 (d, ³J_{HH} = 8.4 Hz, 1H, CH), 8.14 (s, 1H, CH), 7.96 (d, ³J_{HH} = 8.3 Hz, 1H, CH), 7.7 (ddd, ³J_{HH} = 8.4 Hz, ³J_{HH} = 7.7 Hz, ⁴J_{HH} = 1.2 Hz, 1H, CH), 7.58 (ddd, ³J_{HH} = 8.3 Hz, ³J_{HH} = 7.7 Hz, ⁴J_{HH} = 1.1 Hz, 1H, CH), 7.49–7.54 (m, 5H, -Ph), 4.07 (s, 3H, OCH₃).

¹³C NMR (125.77 MHz, CDCl₃): δ_C 166.0 (C=O), 149.9, 148.3, 147.5, 137.5, 131.1, 130.0, 129.5, 128.7, 128.6, 128.6, 127.8, 125.7 and 121.2 (aromatic carbons), 53.1 (OCH₃).

MS, *m/z* (%): 263 (2, M⁺), 205 (49), 204 (17), 77 (40), 59 (94), 44 (100).

Anal. Calcd. for C₁₇H₁₃NO₂ (263.30): C 77.55, H 4.98, N 5.32%. Found: C 77.48, H 4.95, N 4.98%.

Ethyl 4-phenyl-2-quinolinecarboxylate (**3d**)

White powder; yield: 55%, mp 125–127 °C.

IR (KBr): C_{sp2}–H 3045, C_{sp3}–H 2985, C=O 1724 cm^{−1}.

¹H NMR (500.13 MHz, CDCl₃): δ_H 8.36 (d, ³J_{HH} = 8.4 Hz, 1H, CH), 8.11 (s, 1H, CH), 7.94 (d, ³J_{HH} = 8.4 Hz, 1H, CH), 7.76 (ddd, ³J_{HH} = 8.4 Hz, ³J_{HH} = 7.7 Hz, ⁴J_{HH} = 1.1 Hz, 1H, CH), 7.57 (ddd, ³J_{HH} = 8.4 Hz, ³J_{HH} = 7.7 Hz, ⁴J_{HH} = 1.1 Hz, 1H, CH), 7.49–7.53 (m, 5H, -Ph), 4.55 (q, ³J_{HH} = 7.1 Hz, 2H, OCH₂), 1.47 (t, ³J_{HH} = 7.1 Hz, 3H, CH₃).

¹³C NMR (125.77 MHz, CDCl₃): δ_C 165.5 (C=O), 149.8, 148.2, 147.9, 137.6, 131.2, 129.9, 129.5, 128.6, 128.6, 128.5, 127.8, 125.6 and 121.2 (aromatic carbons), 62.2 (OCH₂), 14.3 (CH₃).

MS, *m/z* (%): 277 (3, M⁺), 205 (100), 204 (26), 71 (4), 44 (9).

Anal. Calcd. for C₁₈H₁₅NO₂ (277.32): C 77.96, H 5.45, N 5.05%. Found: C 77.91, H 5.42, N 5.03%.

Dimethyl 6-chloro-4-phenyl-2,3-quinolinedicarboxylate (**3e**)

White powder; yield: 78%, mp 158–160 °C. IR (KBr): C_{sp2}–H 3074, C_{sp3}–H 2958, C=O 1732, 1729 cm^{−1}.

¹H NMR (300.13, CDCl₃): δ_H 8.24 (d, ³J_{HH} = 9 Hz, 1H, -Ph), 7.73 (dd, ³J_{HH} = 9 Hz, ⁴J_{HH} = 2.3 Hz, 1H, -Ph), 7.58 (d, ⁴J_{HH} = 2.3 Hz, 1H, -Ph), 7.50–7.53 (m, 3H,

-Ph), 7.32–7.36 (m, 2H, -Ph), 4.05 (s, 3H, OCH₃), 3.62 (s, 3H, OCH₃).

¹³C NMR (75.5 MHz, CDCl₃): δ_C 167.2 and 165.2 (2C=O), 147.2, 145.4, 144.9, 135.6, 133.7, 132.1, 131.9, 129.2, 129.1, 128.5, 128.4, 128.0 and 125.4 (aromatic carbons), 53.5, 52.6 (2OCH₃).

MS, *m/z* (%): 355 (30, M⁺), 357 (10), 326 (6), 324 (16), 298 (10), 296 (31), 241 (34), 239 (100), 204 (30), 176 (18), 77 (5).

Anal. Calcd. for C₁₉H₁₄NO₄Cl (355.76): C 64.15, H 3.96, N 3.94%. Found: C 64.12, H 3.92, N 3.92%.

Diethyl 6-chloro-4-phenyl-2,3-quinolinedicarboxylate (**3f**)

White powder; yield: 88%, mp 165–167 °C.

IR (KBr): C_{sp2}–H 3075, C_{sp3}–H 2988, C=O 1739, 1724 cm^{−1}.

¹H NMR (300.13 MHz, CDCl₃): δ_H 8.26 (d, ³J_{HH} = 8.26 Hz, 1H, -Ph), 7.74 (dd, ³J_{HH} = 9 Hz, ⁴J_{HH} = 2.1 Hz, 1H, -Ph), 7.57 (d, ⁴J_{HH} = 2.1 Hz, 1H, -Ph), 7.50–7.53 (m, 3H, -Ph), 7.33–7.36 (m, 2H, -Ph), 4.52 (q, ³J_{HH} = 7.1 Hz, 2H, OCH₂), 4.09 (q, ³J_{HH} = 7.1 Hz, 2H, OCH₂), 1.45 (t, ³J_{HH} = 7.1 Hz, 3H, CH₃), 0.98 (t, ³J_{HH} = 7.1 Hz, 3H, CH₃).

¹³C NMR (75.5 MHz, CDCl₃): δ_C 166.7, 164.9 (2C=O), 147.1, 145.9, 145.4, 135.3, 134.0, 132.2, 131.9, 129.3, 129.0, 128.4, 128.3, 127.9 and 125.3 (aromatic carbons), 62.7 (OCH₂), 61.6 (OCH₂), 14.1 (CH₃), 13.5 (CH₃).

MS, *m/z* (%): 383 (12, M⁺), 385 (4), 341 (8), 339 (24), 312 (28), 310 (83), 241 (35), 239 (100), 203 (34), 176 (13), 77 (3).

Anal. Calcd. for C₂₁H₁₈NO₄Cl (383.82): C 65.72, H 4.73, N 3.65%. Found: C 65.68, H 4.71, N 3.62%.

Methyl 6-chloro-4-phenyl-2-quinolinecarboxylate (**3g**)

White powder; yield: 65%, mp 177–179 °C.

IR (KBr): C_{sp2}–H 3054, C_{sp3}–H 2998, C=O 1719 cm^{−1}.

¹H NMR (300.13 MHz, CDCl₃): δ_H 8.30 (d, ³J_{HH} = 9.00 Hz, 1H, -Ph), 8.16 (s, 1H, H_{py}), 7.93 (d, ⁴J_{HH} = 2.6 Hz, 1H, -Ph), 7.77 (dd, ³J_{HH} = 9.04 Hz, ⁴J_{HH} = 2.60 Hz, 1H, -Ph), 7.47–7.60 (m, 5H, -Ph), 4.08 (s, 3H, OCH₃).

¹³C NMR (75.5 MHz, CDCl₃): δ_C 165.6 (C=O), 149.1, 147.6, 146.5, 136.7, 134.9, 132.6, 131.8, 129.4, 129.0, 128.9, 128.5, 124.6 and 122.0 (aromatic carbons), 53.2 (OCH₃).

MS, *m/z* (%): 297 (23, M⁺), 299 (8), 239 (100), 241 (34), 203 (35), 176 (13), 77 (3).

Anal. Calcd. for C₁₇H₁₂NO₂Cl (297.75): C 68.58, H 4.06, N 4.70%. Found: C 68.52, H 4.03, N 4.66%.

Ethyl 6-chloro-4-phenyl-2-quinolinecarboxylate (**3h**)

Yellow powder; yield: 70%, mp 172–174 °C.

IR (KBr): C_{sp2} -H 3064, C_{sp3} -H 2983, C=O 1729 cm^{-1} .

1H NMR (300.13 MHz, $CDCl_3$): 8.32 (d, $^3J_{HH} = 9$ Hz, 1H, -Ph), 8.15 (s, 1H, H_{py}), 7.93 (d, $^4J_{HH} = 2.3$ Hz, 1H, -Ph), 7.72 (dd, $^3J_{HH} = 9.00$ Hz, $^4J_{HH} = 2.3$ Hz, 1H, -Ph), 7.50–7.61 (m, 5H, -Ph), 4.57 (q, $^3J_{HH} = 7.1$ Hz, 2H, OCH_2), 1.49 (t, $^3J_{HH} = 7.1$ Hz, 3H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 165.1 (C=O), 149.1, 147.9, 146.5, 136.8, 134.8, 132.7, 131.1, 129.4, 129.0, 128.9, 128.4, 124.5 and 122.0 (aromatic carbons), 62.4 (OCH_2), 14.3 (CH_3).

MS, m/z (%): 311 (12, M^+), 313 (4), 269 (4), 267 (13), 241 (33), 239 (100), 203 (53), 176 (20), 77 (4).

Anal. Calcd. for $C_{18}H_{14}NO_2Cl$ (311.76): C 69.35, H 4.52, N 4.49%. Found: C 69.31, H 4.46, N 4.47%.

Diethyl 6-chloro-4-(2-chlorophenyl)-2,3-quinolinedicarboxylate (**3i**)

White powder; yield: 85%, mp 127–129 °C.

IR (KBr): C_{sp2} -H 3074, C_{sp3} -H 2983, C=O 1729, 1724 cm^{-1} .

1H NMR (300.13 MHz, $CDCl_3$): δ_H 8.27 (d, $^3J_{HH} = 9$ Hz, 1H, -Ph), 7.76 (d, $^3J_{HH} = 9$ Hz, 1H, -Ph), 7.56 (d, $^3J_{HH} = 9$ Hz, 1H, -Ph), 7.48 (t, $^3J_{HH} = 7.4$ Hz, 1H, -Ph), 7.41 (t, $^3J_{HH} = 7.4$ Hz, 1H, -Ph), 7.36 (s, 1H, -Ph), 7.28 (d, $^3J_{HH} = 7.6$ Hz, 1H, -Ph), 4.52 (q, $^3J_{HH} = 7.1$ Hz, 2H, OCH_2), 4.06–4.15 (m, 2H, OCH_2), 1.45 (t, $^3J_{HH} = 7.1$ Hz, 3H, CH_3), 1.00 (t, $^3J_{HH} = 7.1$ Hz, 3H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 166.0, 164.9 (2C=O), 146.8, 145.4, 144.7, 135.6, 133.6, 133.2, 132.3, 132.2, 131.1, 130.6, 129.7, 127.8, 127.6, 126.7 and 124.9 (aromatic carbons), 62.6 (OCH_2), 61.7 (OCH_2), 14.1 (CH_3), 13.5 (CH_3).

MS, m/z (%): 418 (35, M^+), 382 (100), 308 (53), 273 (21), 201 (21).

Anal. Calcd. for $C_{21}H_{17}NO_4Cl_2$ (418.27): C 60.30, H 4.09, N 3.35%. Found: C 60.27, H 4.10, N 3.34%.

Dimethyl 6-chloro-4-(2-fluorophenyl)-2,3-quinolinedicarboxylate (**3j**)

White powder; yield: 90%, mp 210–212 °C.

IR (KBr): C_{sp2} -H 3079, C_{sp3} -H 2953, C=O 1729, 1718 cm^{-1} .

1H NMR (300.13 MHz, $CDCl_3$): 8.27 (d, $^3J_{HH} = 9$ Hz, 1H, -Ph), 7.71 (dd, $^3J_{HH} = 9$ Hz, $^4J_{HH} = 2.1$ Hz, 1H), 7.52–7.55 (m, 1H, -Ph), 7.49 (s, 1H, -Ph), 7.24–7.33 (m, 3H, -Ph), 4.06 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 166.7 and 165.2 (2C=O), 159.5 (d, $^1J_{FC} = 249.3$ Hz), 145.7, 145.3, 141.8, 135.9, 132.4, 132.2, 131.6 (d, $^3J_{FC} = 8.1$ Hz), 131.1 (d, $^3J_{FC} = 2.4$ Hz), 128.4, 128.2, 124.9, 124.3 (d, $^2J_{FC} = 3.5$ Hz), 121.5 (d, $^2J_{FC} = 16.8$ Hz), 115.9 (d, $^2J_{FC} = 21.1$ Hz), and (aromatic carbons), 53.5 (OCH_3), 52.6 (OCH_3).

MS, m/z (%): 374 (97, M^+), 314 (39), 257 (100), 222 (39), 59 (25).

Anal. Calcd. for $C_{19}H_{13}NO_4ClF$ (373.77): C 61.05, H 3.50, N 3.75%. Found: C 61.08, H 3.56, N 3.79%.

Diethyl 6-chloro-4-(2-fluorophenyl)-2,3-quinolinedicarboxylate (**3k**)

White powder; yield: 90%, mp 135–137 °C.

IR (KBr): C_{sp2} -H 3084, C_{sp3} -H 2983, C=O 1729, 1719 cm^{-1} .

1H NMR (300.13 MHz, $CDCl_3$): δ_H 8.25 (d, $^3J_{HH} = 9$ Hz, 1H, -Ph), 7.74 (dd, $^3J_{HH} = 9$ Hz, $^4J_{HH} = 2.3$ Hz, 1H, Ph), 7.50–7.53 (m, 2H, -Ph), 7.49 (s, 1H, -Ph), 7.22–7.29 (m, 3H, -Ph), 4.51 (q, $^3J_{HH} = 7.1$ Hz, 2H, OCH_2), 4.08–4.13 (m, 2H, OCH_2), 1.44 (t, $^3J_{HH} = 7.1$ Hz, 3H, CH_3), 1.01 (t, $^3J_{HH} = 7.1$ Hz, 3H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 166.2, 164.9 (2C=O), 159.6 (d, $^1J_{FC} = 248.8$ Hz), 146.6, 145.3, 141.6, 135.6, 131.4 (d, $^3J_{FC} = 7.8$ Hz), 131.2 (d, $^3J_{FC} = 2.5$ Hz), 132.2, 132.1, 128.3, 128.1, 124.9, 124.2 (d, $^3J_{FC} = 3.4$ Hz), 121.8 (d, $^2J_{FC} = 16.9$ Hz) and 115.9 (d, $^2J_{FC} = 21.2$ Hz) (aromatic carbons), 62.6 (OCH_2), 61.7 (OCH_2), 14.1 (CH_3), 13.5 (CH_3).

MS, m/z (%): 402 (97, M^+), 357 (46), 328 (67), 257 (100), 221 (32).

Anal. Calcd. for $C_{21}H_{17}NO_4ClF$ (401.81): C 62.77, H 4.26, N 3.49%. Found: C 62.70, H 4.2, N 3.52%.

Dimethyl 6-chloro-4-(2-chlorophenyl)-2,3-quinolinedicarboxylate (**3l**)

Yellow powder; yield: 72%, mp 190–192 °C.

IR (KBr): C_{sp2} -H 3070, C_{sp3} -H 2985, C=O 1729, 1720 cm^{-1} .

1H NMR (500.13 MHz, $CDCl_3$): δ_H 8.27 (d, $^3J_{HH} = 9$ Hz, 1H, -Ph), 7.77 (dd, $^3J_{HH} = 9$ Hz, $^4J_{HH} = 2.1$ Hz, 1H, -Ph), 7.57 (d, $^3J_{HH} = 8$ Hz, 1H, -Ph), 7.48 (t, $^3J_{HH} = 7.5$ Hz, 1H, -Ph), 7.42 (t, $^3J_{HH} = 7.5$ Hz, 1H, -Ph), 7.36 (d, $^4J_{HH} = 2$ Hz, 1H, -Ph), 7.28 (d, $^3J_{HH} = 7.4$ Hz, 1H, -Ph), 4.06 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3).

^{13}C NMR (125.77 MHz, $CDCl_3$): δ_C 166.6, 165.3 (2C=O), 145.9, 145.4, 144.9, 135.9, 133.5, 132.9, 132.4, 132.2, 130.9, 130.7, 129.8, 127.9, 127.7, 126.8 and 124.9 (aromatic carbons), 53.5 (OCH_3), 52.6 (OCH_3).

MS, m/z (%): 390 (24, M^+), 392 (15), 354 (100), 356 (84), 330 (13), 273 (14), 201 (25), 59 (18).

Anal. Calcd. for $C_{19}H_{13}NO_4Cl_2$ (390.20): C 58.48, H 3.35, N 3.58%. Found: C 58.42, H 3.38, N 3.55%.

Dimethyl (Z)-2-(2-acetylanilino)-2-butenedioate (**5a**)

Yellow powder; yield 68%, mp 96–98 °C.

IR (KBr): C_{sp2} -H 3028, C_{sp3} -H 2953, C=O 1739, 1679, 1669 cm^{-1} .

^1H NMR (300.13 MHz, CDCl_3): 11.9 (s, 1H, NH), 7.83 (dd, 1H, CH), 7.36 (td, $^3J_{\text{HH}} = 8.2 \text{ Hz}$, $^4J_{\text{HH}} = 1.4 \text{ Hz}$, 1H, CH), 7.01 (t, $^3J_{\text{HH}} = 8.2 \text{ Hz}$, 1H, CH), 6.65 (d, $^3J_{\text{HH}} = 8.2 \text{ Hz}$, 1H, CH), 5.62 (s, 1H, CH), 3.8 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 2.65 (s, 3H, CH_3).

^{13}C NMR (75.5 MHz, CDCl_3): δ_{C} 200.4, 167.8 and 165.4 (3C=O), 144.1 (N-C=C), 141.9, 133.2, 131.5, 123.8, 121.1 and 118.5 (aromatic carbons), 100.2 (N-C=C), 52.8 (OCH_3), 51.5 (OCH_3), 28.2 (CH_3).

MS, m/z (%): 277 (41, M^+), 218 (26), 186 (100), 159 (21), 143 ($\text{M}^+ - 22$), 77 (8), 43 (8).

Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{NO}_5$ (277.27): C 60.64, H 5.45, N 5.05%. Found: C 60.61, H 5.41, N 5.01%.

Diethyl (Z)-2-(2-acetylanilino)-2-butenedioate (**5b**)

Yellow powder; yield 75%, mp 70–72 °C.

IR (KBr): C_{sp2} -H 3071, C_{sp3} -H 2983, C=O 1739, 1689, 1669 cm^{-1} .

^1H NMR (300.13 MHz, CDCl_3): 11.89 (s, 1H, NH), 7.82 (dd, $^3J_{\text{HH}} = 7.9 \text{ Hz}$, $^4J_{\text{HH}} = 1.4 \text{ Hz}$, 1H, CH), 7.34 (td, $^3J_{\text{HH}} = 7.8 \text{ Hz}$, $^4J_{\text{HH}} = 1.4 \text{ Hz}$, 1H, CH), 7.00 (t, $^3J_{\text{HH}} = 7.6 \text{ Hz}$, 1H, CH), 6.69 (d, $^3J_{\text{HH}} = 8.2 \text{ Hz}$, 1H, CH), 5.62 (s, 1H, CH), 4.26 (q, $^3J_{\text{HH}} = 7.1 \text{ Hz}$, 2H, OCH_2), 4.22 (q, $^3J_{\text{HH}} = 7.1 \text{ Hz}$, 2H, OCH_2), 2.64 (s, 3H, CH_3CO), 1.30 (t, $^3J_{\text{HH}} = 7.1 \text{ Hz}$, 3H, CH_3), 1.18 (t, $^3J_{\text{HH}} = 7.1 \text{ Hz}$, 3H, CH_3).

^{13}C NMR (75.5 MHz, CDCl_3): δ_{C} 200.4, 167.4 and 164.8 (C=O), 144.4 (N-C=C), 142.0, 133.0, 131.4, 124.0, 121.1 and 119.0 (aromatic carbons), 100.5 (N-C=C), 62.1 (OCH_2), 60.2 (OCH_2), 28.1 (CH_3CO), 14.3 (CH_3), 13.7 (CH_3).

MS, m/z (%): 305 (29, M^+), 243 (35), 230 (25), 214 (100), 186 (65), 171 (15), 143 (100), 77 (8), 43 (13).

Anal. Calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}_5$ (305.32): C 62.94, H 6.27, N 4.58%. Found: C 62.92, H 6.23, N 4.53%.

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