Indian Journal of Chemistry
Vol. 62, August 2023, pp. 879-883
DOI: 10.56042/ijc.v62i8.4795

Design and synthesis of new tricyclic quinoline derivatives from intramolecular cyclization of benzylidene malonic derivatives

Adéyolé Timotou[a,b], Tchambaga Etienne Camara[b], Kouassi Yves Guillaume Molou*[b,c], Souleymane Coulibaly*[b], Doumadé Zon[a,b], Ahmont Landry Claude Kablan[a,b], Aka Joseph N'Gouan[d], Siomenan Coulibali[b] & Ané Adjou[b]

[a] Département de Mathématiques-Physique-Chimie, UFR des Sciences Biologiques, Université Peleforo Gon Coulibaly, Korhogo, Côte d'Ivoire
[b] Laboratoire de Constitution et Réaction de la Matière, UFR Sciences des Structures de la Matière et Technologie,
Université Félix Houphouët-Boigny de Cocody, 22 BP 582 Abidjan 22, Côte d'Ivoire
[c] Département Sciences et Technologie, Section Physique-Chimie, Ecole Normale Supérieure d'Abidjan Côte d'Ivoire,
08 BP 10 Abidjan 08, Côte d'Ivoire
[d] Laboratoire de Cristallographie et Physique Moléculaire, UFR Sciences des Structures de la Matière et Technologie,
Université Félix Houphouët Boigny de Cocody, 22 BP 582 Abidjan 22, Côte d'ivoire
E-mail: souleydestras@yahoo.fr, moloukouassi@yahoo.fr

Received 23 December 2022; accepted (revised) 12 July 2023

Quinolines are very important compounds due to their numerous biological and pharmacological applications. This article describes the synthesis of new tricyclic quinoline derivatives *via* intramolecular cyclization of malonic benzylidene derivatives. The malonic benzylidene derivatives **2a-c** have been obtained by condensation of N-substituted aldehydes **1a-c** with malononitrile or ethyl cyanoacetate. These latter have been cyclized by reflux in DMF to give the compounds **3a-f**. The structures of the compounds have been determined by ^{1}H and ^{13}C NMR spectroscopy, and High-Resolution Mass Spectrometry (HRMS) analysis. Two of the synthesized compounds have been identified and confirmed by X-ray crystallography.

Keywords: Tricyclic quinoline, Malonic benzylidene, Intramolecular cyclization, Malononitrile, Ethyl cyanoacetate, X-ray crystallography

Quinoline derivatives have always been of interest to chemists due to their diverse biological and pharmacological properties. Indeed, these compounds have shown various activities including antimalarial[1-4], antibacterial[5-8], antifungal[9-11], anticancer[12-15], anti-inflammatory[16-19] and analgesic[19]. Therefore, the quinoline scaffold is present in various natural products, especially in alkaloids, and is widely used in the design of many compounds with diverse pharmacological properties. Many natural products containing the quinoline ring are used as pharmaceuticals or as building blocks for the development of newly high potent compounds. For example, quinine, isolated from cinchona bark, is used for the treatment of malaria. Structure determination and structure-activity studies have led to the discovery of new antimalarial drugs such as chloroquine, primaquine and mefloquine (even if this least is less used actually due to multiresistance of plasmodium). A number of protocols for the synthesis of the quinoline ring have been reported, which can be modified to produce various substituted quinolines. Common used methods are the classical syntheses such as the Skraup, Doebner-Von Miller, Pfitzinger, Friedlander, Conrad-Limpach and Combes synthesis[20]. In this work, we present the synthesis of new tricyclic quinoline derivatives by intramolecular cyclization of malonic benzylidene derivatives.

Experimental Section

All chemicals were purchased from Aldrich Chemical, Fischer Scientific (France), and were used without further purification unless otherwise stated. The reactions were followed by TLC on pre-coated Merck 60 F254 silica gel plates and revealed using a UV lamp (6 W, 254 nm, and/or 365 nm). The purification of the products was carried out on a Merck G60 silica gel column. Melting points (m.p., °C) were determined using a temperature gradient (40-265°C) Kofler bench. For all compounds, the Nuclear Magnetic Resonance (NMR) spectra of proton ^{1}H and carbon ^{13}C were recorded on a Brucker 300 advance device. Tetramethylsilane (TMS) was used as a reference for chemical displacements expressed in δ (ppm). The NMR spectra description uses the following symbols: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quadruplet), m (multiplet). The mass spectra were recorded on a JEOL JMS DX300 spectrometer in ESI mode (electrospray/quadripolar ionization or ESI mass).

General procedure for the synthesis of malonic aryldene derivatives, 2a-c

To compounds N-substituted aldehydes **1a-c** (1 eq, 10 mmol) dissolved in 25 mL of distilled ethanol was added either malononitrile or ethyl cyanoacetate (1.2 eq, 12 mmol). The mixture was kept under magnetic stirring at room temperature (rt) and then 4 mL of triethylamine were added drop-wise. The mixture was heated under reflux for 2 to 5 h, then cooled to rt. After that, the precipitate obtained was filtered, washed several times and purified by recrystallization from ethanol.

2-[5-Nitro-2-(pyrrolidin-1-yl)benzylidene]malononitrile, 2a: Red crystals. Yield 74%. m.p.228-230°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) : 8.79 (d, 1H, H_{Ar}, J = 3 Hz), 8.36 (dd, 1H, H_{Ar}, J = 3 Hz, J = 9 Hz), 8.00 (s, 1H, HC=CY), 7.68 (d, 1H, H_{Ar}, J = 9 Hz), 3.43-3.42 (m, 4H, 2×CH_2), 1.96 (m, 4H, 2×CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) : 154.85, 119.12, 153.27, 139.30, 128.78, 125.54, 120.18, 117.61, 102.00, 52.77, 25.14; HRMS (ESI): Calcd for $C_{14}H_{13}N_4O_2$ (M+H+): *m/z* 269.096. Found: 269.098.

2-[5-Nitro-2-(piperidin-1-yl)benzylidene]malonomitrile, 2b: Yellow crystals. Yield 66%. m.p.158-160°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) : 8.82 (d, 1H, H_{Ar}, J = 3 Hz), 8.32 (dd, 1H, H_{Ar}, J = 3 Hz, J = 9 Hz), 7.85 (s, 1H, HC=CY), 7.14 (d, 1H, H_{Ar}, J = 9 Hz), 3.17-3.20 (m, 4H, 2×CH_2), 1.64-1.82 (m, 6H, 3×CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 159.18, 156.21, 138.15, 128.48, 127.10, 119.40, 112.29, 111.87, 104.14, 54.63, 26.02, 23.13; HRMS (ESI): Calcd for $C_{15}H_{15}N_4O_2$ (M+H+): *m/z* 283.112. Found: 283.114.

2-[5-Nitro-2-(morpholin-1-yl) benzylidene]malon-onitrile, 2c: Green crystals. Yield 67%. m.p.194-196°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) : 8.79 (d, 1H, H_{Ar}, J = 3 Hz), 8.33 (dd, 1H, H_{Ar}, J = 3 Hz, J_{H4H3} = 9 Hz), 7.87 (s, 1H, HC=CY), 7.13 (d, 1H, H_{Ar}, J = 9 Hz), 3.87-3.84 (m, 4H, 2×NCH_2), 3.07-3.17 (m, 4H, 2×OCH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 157.00, 155.35, 143.02, 127.10, 123.76, 122.04, 113.04, 111.49, 102.00, 63.08, 53.09; HRMS (ESI): Calcd for $C_{14}H_{13}N_4O_3$ (M+H+): *m/z* 285.091. Found: 285.094.

(E)-Ethyl 2-cyano-3-[5-nitro-2-(pyrrolidin-1-yl)phenyl]acrylate, 2d: Yellow crystals. Yield 77%. m.p.184-186°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.49 (d, 1H, H_{Ar}, J = 2.4 Hz), 8.43 (s, 1H, HC=CY), 7.95 (dd, 1H, H_{Ar}, J = 2.4 Hz, J = 9.3 Hz), 6.68 (d, 1H, H_{Ar}, J = 9.6 Hz), 4.30 (q, 2H, OCH_2, J = 7.2 Hz), 3.43-3.40 (m, 4H, 2×CH_2), 1,95-1.98 (m, 4H, 2×CH_2), 1.35 (t, 3H, CH_3, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) : 162.43, 154.85, 150.27, 137.00, 127.78, 127.54, 119.20, 116.19, 114.61, 102.00, 62.80, 52.77, 26.02, 14.21; HRMS (ESI): Calcd for $C_{16}H_{18}N_3O_4$ (M+H+): *m/z* 316.122. Found: 316.124.

(E)-Ethyl 2-cyano-3-[5-nitro-2-(piperidin-1-yl)phenyl]acrylate, 2e: Yellow crystals. Yield 92%. m.p.174-176°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.86 (d, 1H, H_{Ar}, J = 2.4 Hz), 8.32 (s,1H, HC=CY), 8.28 (dd, 1H, H_{Ar}, J = 2.4 Hz, J = 9.3 Hz), 7.08 (d, 1H, H_{Ar}, J = 9.3 Hz), 4.40 (q, 2H, CH_2, J = 7.2 Hz), 3.13-3.16 (m, 4H, 2×NCH_2), 1,67-1,79 (m, 6H, 3×CH_2), 1.40 (t, 3H, CH_3, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) : 162.23, 153.72, 152.18, 136.20, 127.68, 126.50, 118.79, 118.35, 114.72, 104.01, 62.88, 54.29, 26.06, 23.74, 14.20; HRMS (ESI): Calcd for $C_{17}H_{20}N_3O_4$ (M+H+): *m/z* 330.138. Found: 330.140.

(E)-Ethyl 2-cyano-3-[5-nitro-2-(morpholin-1-yl)phenyl]acrylate, 2f: Yellow crystals. Yield 75%. m.p.198-200°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.68 (d, 1H, H_{Ar}, J = 2.7 Hz), 8.41 (s, 1H, HC=CY), 8.34 (dd, 1H, H_{Ar}, J = 2.7 Hz, J = 9 Hz), 7.14 (d, 1H, H_{Ar}, J = 9 Hz), 4.44 (q, 2H, CH_2, J = 7,2 Hz), 3.90-3.93 (m, 4H, 2×NCH_2), 3.17-3.13 (m, 4H, 2×OCH_2), 1.43 (t, 3H, CH_3, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.94, 158.00, 153.27, 142.07, 128.24, 125.77, 124.09, 118.47, 114.36, 102.00, 63.66, 63.08, 53.09, 14.17; HRMS (ESI): Calcd for $C_{16}H_{18}N_3O_5$ (M+H+): *m/z* 331.117. Found: 331.115.

General procedure for the synthesis of tricyclic quinoline derivatives, 3a-f

To 10 mL of DMF was dissolved malonic benzylidene **2a-f** (1 eq, 6 mmol). The mixture was heated under reflux for 24 h. After cooling, 20 mL of water was added and the organic layer was extracted with ethyl acetate (2×100 mL), then washed with water (2×20 mL), dried over anhydrous sodium sulfate (anhyd. Na_2SO_4) and the solvent was removed by evaporation under reduced pressure. The residue obtained was purified by chromatography over silica gel. Eluent: (hexane / ethyl acetate: 80/20).

7-Nitro-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4,4(5*H*)-dicarbonitrile, 3a: Yellow crystals. Yield 75%. m.p.248-250°C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 7.98 (dd, 1H, H$_{Ar}$, J = 9,2 Hz, J = 3 Hz), 7.91 (d, 1H, H$_{Ar}$, J = 3 Hz), 6.66 (d, 1H, H$_{Ar}$, J = 9.2 Hz), 3.68-2.50 (m, 5H, 2 CH$_2$, CH), 1.73-2.01 (m, 4H, 2 CH$_2$); ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 153.27, 147.60, 128.80, 125.10, 124.89, 117.30, 110.15, 61.46, 52.70, 47.68, 35.50, 28.76, 22.44; HRMS (ESI): Calcd for $C_{14}H_{13}N_4O_2$ (M+H+): *m/z* 269.096. Found: 269.098.

8-Nitro-2,3,4,4a-tetrahydro-1*H*-pyrido[1,2-a]quinoline-5,5(6*H*)-dicarbonitrile, 3b: Yellow crystals. Yield 73%. m.p.180-182°C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 8.08 (dd, 1H, H$_{Ar}$, J = 9 Hz, J = 2.1 Hz), 7.96 (d, 1H, H$_{Ar}$, J = 2.1 Hz), 6.93 (d, 1H, H$_{Ar}$, J = 9 Hz), 4.18-3.54 (m, 5H, 2 CH$_2$, CH), 3.06-1.64 (m, 6H, 3 CH$_2$); ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 148.85, 139.02, 137.60, 125.63, 122.55, 115.13, 111.20, 60.70, 59.88, 48.41, 36.24, 35.80, 23.43, 23.25; HRMS (ESI): Calcd for $C_{15}H_{15}N_4O_2$ (M+H+): *m/z* 283.112. Found: 283.115.

8-Nitro-1,2,4,4a-tetrahydro-[1,4]oxazino[4,3-a]quinoline-5,5(6*H*)-dicarbonitrile, 3c: Yellow crystals. Yield 61%. m.p.217-219°C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.99 (dd, 1H, H$_{Ar}$, J = 9 Hz, J = 2.1 Hz), 7.76 (d, 1H, H$_{Ar}$, J = 2.1 Hz), 6.78 (d, 1H, H$_{Ar}$, J = 9 Hz), 3.89-3.01 (m, 9H, 4 CH$_2$, CH); ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 157.17, 147.19, 137.68, 133.09, 123.49, 122.09, 119.20, 66.19, 66.42, 50.93, 50.40, 43.58, 43.39; HRMS (ESI): Calcd for $C_{14}H_{13}N_4O_3$ (M+H+): *m/z* 285.091. Found: 285.089.

Ethyl 4-cyano-7-nitro-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline-4-carboxylate, 3d: Yellow crystals. Yield 62%. m.p.124-126°C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 7.98 (dd, 1H, H$_{Ar}$, J = 9 Hz, J = 2.1 Hz), 7.63 (d, 1H, H$_{Ar}$, J = 2.1 Hz), 6.62 (d, 1H, H$_{Ar}$, J = 9 Hz), 4.37 (q, 2H, CH$_2$, J = 7.2 Hz), 3.35-2.50 (m, 5H, 2 CH$_2$), 2.01-1.73 (m, 4H, 2 CH$_2$), 1.36 (t, 3H, CH$_3$, J = 7.2 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz) δ(ppm): 166.78, 153.27, 147.60, 128.24, 125.10, 124.09, 118.47, 115.36, 63.69, 61.46, 52.60, 47.68, 35.54, 28.80, 22.46, 13.87; HRMS (ESI): Calcd for $C_{16}H_{18}N_3O_4$ (M+H+): *m/z* 316.122. Found: 316.125.

Ethyl 5-cyano-8-nitro-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-a]quinoline-5-carboxylate, 3e: Yellow crystals. Yield 58%. m.p.150-152°C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.04 (dd, 1H, H$_{Ar}$, J = 9 Hz, J = 2.1 Hz), 7.94 (d, 1H, H$_{Ar}$, J = 2.1 Hz), 6.86 (d, 1H, H$_{Ar}$, J = 9 Hz), 4.13 (q, 2H, CH$_2$, J = 7.2 Hz), 3.23-3.05(m, 5H, 2 CH$_2$), 2.02-1.62 (m, 6H, 3 CH$_2$), 1.59 (t, 3H, CH$_3$, J = 7.2 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 166.78, 152.27, 137.60, 125.12, 123.09, 122.09, 118.20, 115.36, 63.69, 60.99, 47.72, 44.98, 42.39, 26.37, 23.43, 23.25, 13.97; HRMS (ESI): Calcd for $C_{17}H_{20}N_3O_4$ (M+H+): *m/z* 330.138. Found: 330.136.

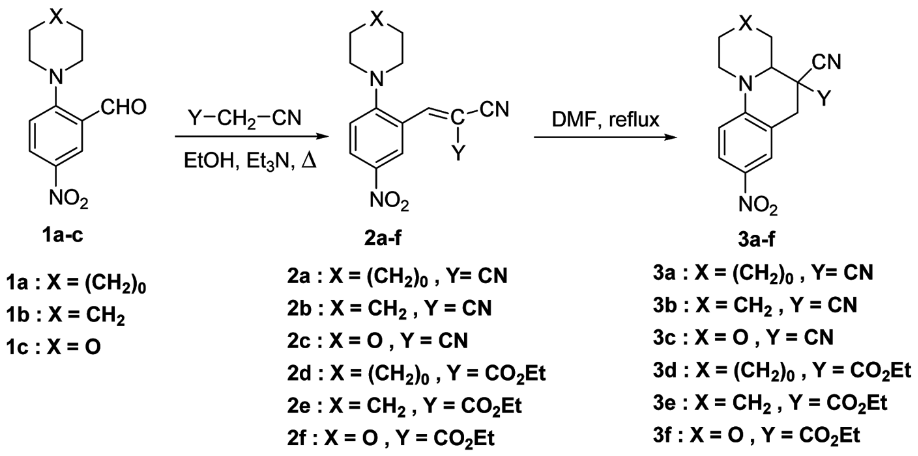
Ethyl 5-cyano-8-nitro-1,2,4,4a,5,6-hexahydro-[1,4]oxazino[4,3-a]quinoline-5-carboxylate, 3f: Yellow crystals. Yield 52%. m.p.188-190°C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 8.06 (dd, 1H, H$_{Ar}$, J = 9 Hz, J = 2.1 Hz), 7.97 (d, 1H, H$_{Ar}$, J = 2.1 Hz), 6.89 (d, 1H, H$_{Ar}$, J = 9 Hz), 4.40 (q, 2H, CH$_2$, J = 7.2 Hz), 4.14-3.15 (m, 9H, 4 CH$_2$, CH), 1.43 (t, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 166.78, 148.95, 137.29, 127.78, 123.09, 122.09, 118.20, 111.49, 67.68, 66.19, 64.12, 57.72, 56.52, 45.82, 45.65, 14.02; HRMS (ESI): Calcd for $C_{16}H_{18}N_3O_5$ (M+H+): *m/z* 331.117. Found: 331.119.

Results and Discussion

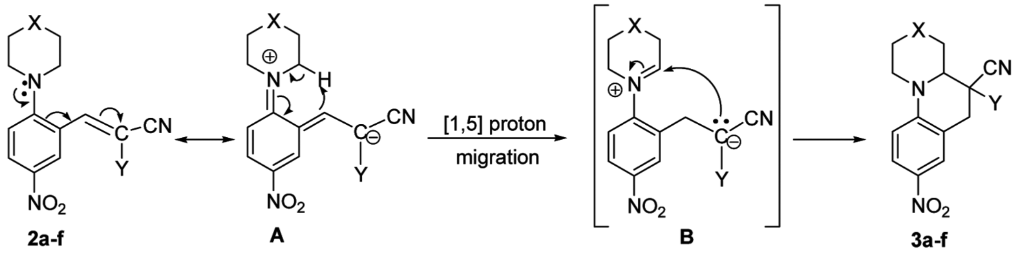
New quinolines **3a-f** were synthetized by intramolecular cyclization of malonic benzylidene **2a-f**. The precursors of these compounds, N-substituted aldehydes **1a-c**, were synthesized in previous work[21]. Therefore, their condensation with malononitrile or ethyl cyanoacetate under refluxing ethanol in the presence of a catalytic amount of triethylamine gave malonic benzylidene **2a-f** in 66-92% yields. Heating these compounds **2a-f** under reflux in DMF afforded quinolines **3a-f** in 52-75% yields (Scheme 1).

We proposed the following mechanism to explain the formation of quinolines. Compounds **2a-f** were first transform into mesomeric form A after displacement of the nitrogen atom of the heterocyclic amine. Then, an α-hydrogen from the nitrogen [1,5] sigmatropic migration leads to the bipolar intermediate B formation. This latter cyclizes to give quinolines **3a-f** (Scheme 2). The whole process was favoured by the energy input thanks to the DMF reflux.

The structures of the various compounds were confirmed by ^{1}H, ^{13}C NMR spectroscopy, and HRMS analyses. Compounds **2a-f** were characterized by the presence in ^{1}H NMR spectroscopy for all six compounds of the ethylenic proton which appears as a singlet between 7.8 and 8.4 ppm. For compounds **2d-**



Scheme 1 — Synthesis of quinolines



Scheme 2 — Plausible mechanism of quinoline formation

f, two isomers of E and Z configurations are expected which were not observed in ^{1}H and ^{13}C NMR, and no peak splitting was observed. This result was confirmed by X-ray structural analysis of compound **2d.** Here, the ORTEP diagram showed that the molecular structure of the compound was in the E conformation, considering the position of the substituents on the C=C double bond[22]. Furthermore, the pyrrolidine ring has a chair conformation and is not coplanar with the aromatic ring (Fig. 1).

The cyclization of compounds **2a-f** was characterized by the disappearance of the ethylenic proton singlet and the appearance of a singlet around 3.5 ppm corresponding to the two methylenic protons in the ^{1}H NMR spectra of the compounds. Two of the synthesized quinolines **3d** and **3e** have been the subject of crystallographic studies in some previous studies[23,24]. These studies confirmed that cyclization occurred and agreed with the structures of the compounds. The crystal structure of compound **3d** revealed that the pyrrolidine ring adopted two orientations (Fig. 2). Indeed, the C2 carbon was either above or below the axis (or plane) formed by the remaining four atoms.

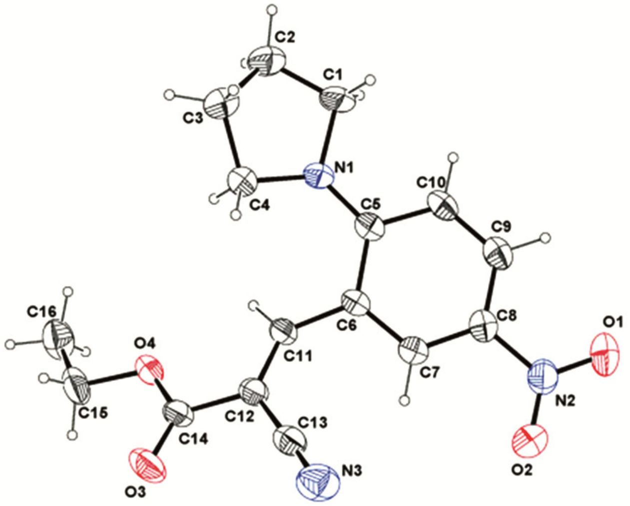


Fig. 1 — ORTEP diagram of compound 2d

In the structure of compound **3e**, the C8 carbon atom was deviated by -0.4074Å from the plane of the quinoline ring, proving that the quinoline ring is not truly plane. The piperidine ring was not coplanar with the quinoline ring and adopted a chair conformation (Fig. 3).

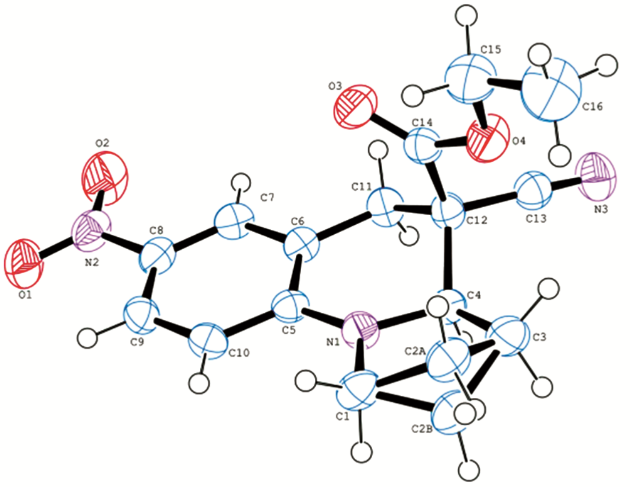


Fig. 2 — ORTEP diagram of compound 3d

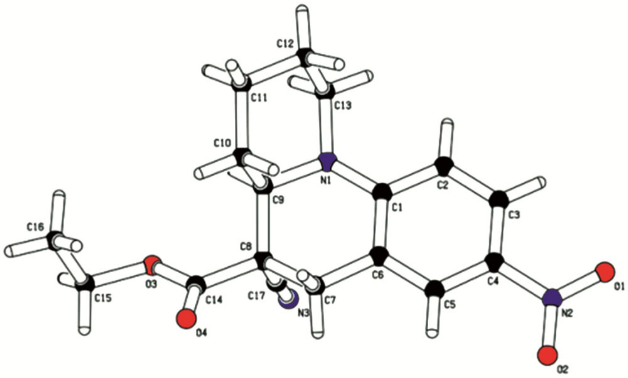


Fig. 3 — ORTEP diagram of compound 3e

Conclusion

In this work, tricyclic quinoline derivatives were synthetized by intramolecular cyclization of malonic benzylidene. All compounds were obtained in above 50% yields and their structures were confirmed by ^{1}H, ^{13}C NMR and mass spectroscopy analyses. Two compounds (**3d** and **3e**) were the subjected to X-ray structural analysis, which allowed us to highlight the spatial configuration and confirm that cyclization had indeed occurred.

Acknowledgement

The authors wish to thank the CEISAM Laboratory University of Nantes for the spectroscopic analyses.

Conflicts of interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

1 McNulty J, Vemula R, Bordón C, Yolken R & Jones-Brando L, *Org Biomol Chem*, 12 (2014) 255.
2 Bhat H R, Singh U P, Gahtori P, Ghosh S K, Gogoi K, Prakash A & Singh R K, *RSC Advances*, 3 (2013) 2942.
3 Singh B, Chetia D, Puri S K, Srivastava K & Prakash A, *Med Chem Res*, 20 (2010) 1523.
4 Shiraki H, Kozar M P, Melendez V, Hudson T H, Ohrt C, Magill A J & Lin A J, *J Med Chem*, 54 (2011) 131.
5 Bhat H R, Gupta S K & Singh U P, *RSC Advances*, 2 (2012) 12690.
6 De-Souza M V N, Pais K C, Kaiser C R, Peralta M A, Ferreira M D L & Lourenço M C S, *Bioorg Med Chem*, 17 (2009) 1474.
7 Upadhayaya R S, Vandavasi J K, Vasireddy N R, Sharma V, Dixit S S & Chattopadhyaya J, *Bioorg Med Chem*, 17 (2009) 2830.
8 Lilienkampf A, Mao J, Wan B, Wang Y, Franzblau S G & Kozikowski A P, *J Med Chem*, 52 (2009) 2109.
9 Kumar S, Bawa S, Drabu S & Panda B P, *Med Chem Res*, 20 (2010) 1340.
10 Kharkar P S, Deodhar M N & Kulkarni V M, *Med Chem Res*, 18 (2008) 421.
11 Gholap A R, Toti K S, Shirazi F, Kumari R, Bhat M K, Deshpande M V & Srinivasan K V, *Bioorg Med Chem*, 15 (2007) 6705.
12 Li Y, Shi X, Xie N, Zhao Y & Li S, *Med Chem Comm*, 4 (2013) 367.
13 Marganakop S B, Kamble R R, Taj T & Kariduraganvar M Y, *Med Chem Res*, 21 (2010) 185.
14 Miller L M, Mayer S C, Berger D M, Boschelli D H, Boschelli F, Di L & Xu W, *Bioorg & Med Chem Lett*, 19 (2009) 62.
15 Mai A, Rotili D, Tarantino D, Nebbioso A, Castellano S, Sbardella G, Tini M & Altucci L, *Bioorg & Med Chem Lett*, 19 (2009) 1132.
16 Gilbert A M, Bursavich M G, Lombardi S, Georgiadis K E, Reifenberg E, Flannery C R & Morris E A, *Bioorg & Med Chem Lett*, 18 (2008) 6454.
17 Bekhit A A, El-Sayed O A, Aboulmagd E & Park J Y, *Eur J Med Chem*, 39 (2004) 249.
18 Ko T C, Hour M J, Lien J C, Teng C M, Lee K H, Kuo S C & Huang L J, *Bioorg Med Chem Lett*, 11 (2001) 279.
19 Abadi A H, Hegazy G H & El-Zaher A A, *Bioorg Med Chem*, 13 (2005) 5759.
20 Elderfield R C, *Heterocyclic compounds* (John-Wiley and Sons, New York) (1960).
21 Timotou A, Molou K Y G, Zoakouma P S, Camara T E, Coulibaly S, Zon D, Kablan A L C, N'Gouan A J, Coulibali S & Adjou A, *Pharma Chem J*, 9 (2022) 36.
22 Yapo Y M, Abou B C, Adjou A, Yao R K G & Tenon J A, *Acta Cryst*, E66 (2010) o2497. (https://doi.org/10.1107/S1600536810033374).
23 Bibila M B Y, Adeyolé T, Adjou A, Kakou-Yao R &Tenon A, J, *Acta Cryst*, E68 (2012) o550. (https://doi.org/10.1107/S1600536812003480).
24 24 Yapo Y M, Konan K M, Adjou A, Timotou & Tenon J A, *Acta Cryst*, E66 (2010) o1735. (https://doi.org/10.1107/S160053681002283X).