Molbank **2015**, M868; doi:10.3390/M868

OPEN ACCESS

molbank

ISSN 1422-8599

www.mdpi.com/journal/molbank

Short Note

1,1′-{1,4-Phenylene bis[3-(6-chloro-2-methyl-4-phenylquinolin-3-yl)-4,5-dihydro-1*H*-pyrazole-5,1-diyl]}dibutan-1-one

Allaoua Kedjadja [1,2,*], Elhadj Kolli [1], Abdelmalek Bouraiou [3], Rachid Merdes [1] and Naoufel Haddour [4]

[1] Laboratoire de chimie Appliquée, Faculté des Mathématiques et de l'Informatique et des Sciences de la Matière, Université de Guelma, Guelma 24000, Algeria;
E-Mails: kollielhadj@gmail.com (E.K.); merdesra@yahoo.fr (R.M.)

[2] Département de Tronc Commun, Faculté des Science de la Nature et de la Vie, Université Abderrahmane Mira Bejaia, Bejaia 6000, Algeria

[3] Unité de Recherche de Chimie de l'Environnement et Moléculaire Structurale, Université des Frères Mentouri, Route de Ain El Bey, Constantine 25000, Algeria; E-Mail: bouraiou.abdelmalek@yahoo.fr

[4] Laboratoire Ampère, UMR CNRS 5005, Ecole Centrale de Lyon, Université Claude Bernard Lyon 1, Ecully 69130, France; E-Mail: naoufel.haddour@ec-lyon.fr

* Author to whom correspondence should be addressed; E-Mail: kedjadjaalla@yahoo.fr or allaoua.kedjadja@univ-bejaia.dz; Tel.: +213-07-73012507; Fax: +213-031818816.

Academic Editor: Norbert Haider

Received: 14 July 2015 / Accepted: 22 September 2015 / Published: 5 October 2015

Abstract: A new polycyclic compound, 1,1′-{1,4-phenylene bis[3-(6-chloro-2-methyl-4-phenylquinolin-3-yl)-4,5-dihydro-1*H*-pyrazole-5,1-diyl]}dibutan-1-one (**3**) has been synthesized by cyclocondensation of (2*E*,2′*E*)-1,1′-bis(6-chloro-2-methyl-4-phenylquinolin-3-yl)-3,3′-(1,4-phenylene)diprop-2-en-1-one (**2**) and hydrazine hydrate in butanoic acid. The structure of this compound was established by elemental analysis, ^{1}H-NMR, ^{13}C-NMR, mass and IR spectroscopy.

Keywords: quinoline; pyrazoline; cyclocondensation; terephthalaldehyde

---

1. Introduction

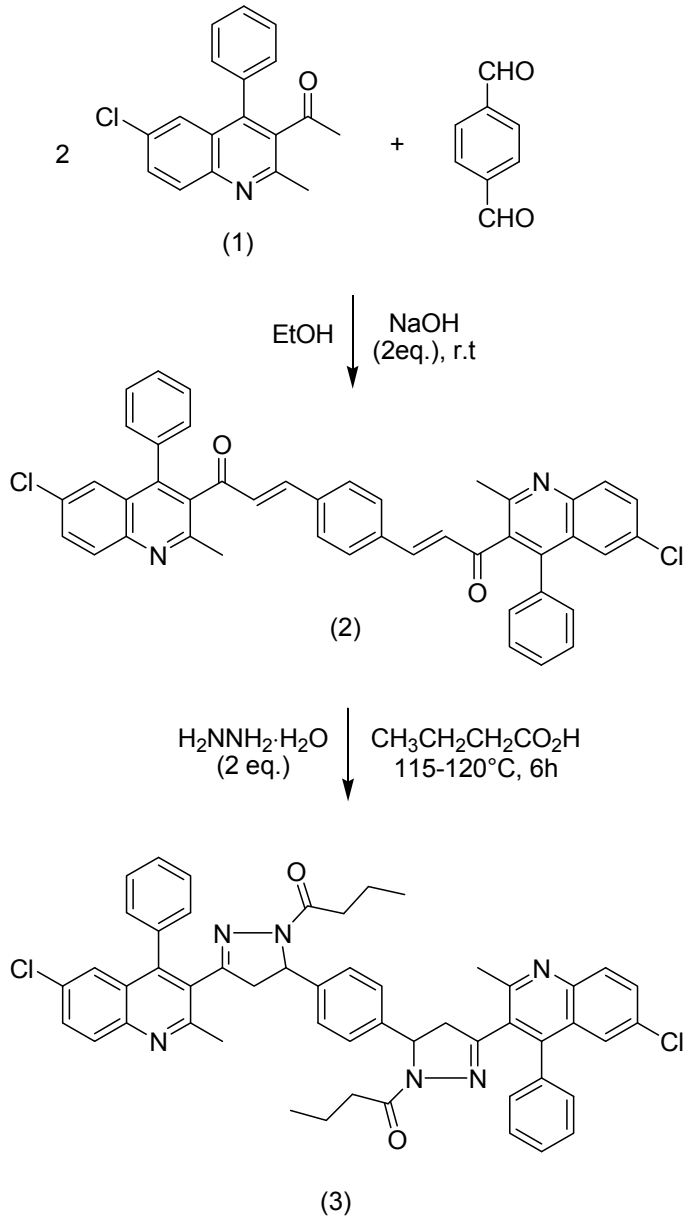
Quinoline nucleus is an important pharmacophore found in a large number of natural products and synthetic compounds with a wide range of applications. Indeed quinoline derivatives are some of the oldest compounds which have been utilized for the treatment of a variety of diseases; the bark of Cinchona plants containing quinine has been utilized to treat palpitations [1]. Compounds containing quinoline motif are most widely used as antimalarials [2], antibacterials [3], antifungals [4] and anticancer agents [5]. On the other hand, the pyrazoline moiety is an important nitrogen-containing 5-membered heterocyclic compound and various synthetic methods for their preparation have been reported [6]. Numerous pyrazoline derivatives have been found to possess considerable biological activities, which has stimulated the research activity in this field. They have several prominent effects, such as antimicrobial [7], antimycobacterial [8], anti-inflammatory, analgesic [9] and antiamoebic activity [10]. 2-Pyrazolines seem to be the most frequently studied pyrazoline type compounds. As a result, a large number of 2-pyrazolines using different synthetic methods for their preparation have been described in the chemistry literature. An especially popular procedure is based on the reaction of *α*,*β*-unsaturated ketones with hydrazines [11–13]. The coupling of this chemical entity with a quinoline unit might be considered to have some biological activities. Here we are reporting a novel bis[3-(quinol-3-yl)pyrazoline] prepared by cyclocondensation of the known (2*E*,2′*E*)-1,1′-bis(6-chloro-2-methyl-4-phenylquinolin-3-yl)-3,3′-(1,4-phenylene)diprop-2-en-1-one (**2**) in presence of hydrazine hydrate (Scheme 1).

2. Experimental Section

2.1. General Methods

The starting materials were generally used as received (Acros, Fontenay-sous-Bois, France) without any further purification. Melting points were determined on an electrothermal capillary fine-control apparatus and are uncorrected. All IR spectra were performed on Shimadzu FT-IR-8201 PC spectrophotometer (Constantine, Algeria) and only significant absorption-band frequency is cited. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in deuterated chloroform on a Brüker Avance DPX 250 spectrometer (Constantine, Algeria) 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). The mass spectrum was scanned on a Shimadzu GCMS-QP2010 and the elemental analysis was obtained using a LECO CHNS-900 elemental analyzer (Lyon, France) and the values are within ±0.4% of the theoretical values.

3-Acetyl-6-chloro-2-methyl-4-phenylquinoline (**1**) has been synthesized in accordance with established methods [14]. Spectroscopic results and physical properties are in agreement with literature reports [15,16].



Scheme 1. The synthesis of 1,1′-{1,4-phenylene bis[3-(6-chloro-2-methyl-4-phenylquinolin-3-yl)-4,5-dihydro-1*H*-pyrazole-5,1-diyl]}dibutan-1-one.

2.2. Synthesis of 1,1'-{1,4-phenylene bis[3-(6-chloro-2-methyl-4-phenylquinolin-3-yl)-4,5-dihydro-1H-pyrazole-5,1-diyl]}dibutan-1-one (**3**)

A solution of 3-acetyl-6-chloro-2-methyl-4-phenylquinoline (2.00 g, 6.7682 mmol, 2 eq.) and terephthalaldehyde (0.4568 g, 3.3841 mmol, 1 eq.) in an ethanolic solution of NaOH 10% (1.0 g in 10 mL of ethanol) was stirred for 8 h at room temperature. The solution was poured into ice cold water and solution was adjusted to pH ~ 2 by HCl (1 N). The solid was separated off and then dissolved in CH_2Cl_2. The organic layer was washed with a saturated solution of $NaHCO_3$ and the solvent was evaporated to dryness. The residue was recrystallized from ethyl acetate/petroleum ether (1/1) solution to give the intermediate compound (**2**), m.p.: >300 °C, yield: 75%. Compound **2** is known in literature [17] and its structure has been confirmed by spectroscopic methods. Next, the title compound (**3**) was prepared by heating (2*E*,2′*E*)-1,1′-Bis(6-chloro-2-methyl-4-phenylquinolin-3-yl)-3,3′-(1,4-

phenylene)diprop-2-en-1-one **2** (1.0 g, 0.0014 mol) and hydrazine hydrate (0.1451 g, 0.0029 mol) in butanoic acid (20 mL) at 115–120 °C for 6 h. After completion, the solution was cooled, and then poured onto ice. The resulting solid was filtered, washed with water, dried, and then recrystallized from chloroform/ethyl acetate mixture (1:1).

White powder; (50% EtOAc in CH_3Cl, $R_f = 0.46$); Yield: 86%; m.p. > 300 °C.

HRMS (ESI): $[M + H]^+$ calculated for $C_{52}H_{47}Cl_2N_6O_2$ = 857.3138; found 857.3126.

IR (KBr) ν_{max} cm^{-1}: 1639.4 (C=O ketone), 1566.1 (C=N pyrazoline).

^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.66 (d, *J* = 8.4 Hz, 2H, H-8 quinoline), 8.28 (dd, *J* = 8.4 Hz, *J* = 1.7 Hz, 2H, H-7 quinoline), 8.07-7.91 (m, 10H, H-Ar), 7.87–7.79 (m, 4H, H-Ar), 7.21 (s, 4H, phenylene), 5.86 (dd, *J* = 12.0 Hz, *J* = 5.0 Hz, 2H, H-5 pyrazoline), 3.64 (dd, *J* = 18.4 Hz, *J* = 12.0 Hz, 2H, H-4 pyrazoline), 3.36 (s, 6H, $2CH_3$), 3.33-3.16 (m, 4H, $2CH_2$), 2.98 (dd, *J* = 18.4 Hz, *J* = 5.0 Hz, 2H, H-4′ pyrazoline), 2.12–2.35 (m, 4H, $2CH_2$), 1.52 (t, *J* = 7.5 Hz, 6H, $2CH_3$).

^{13}C-NMR (62.9 MHz, $CDCl_3$) δ: 171.82 (2CO), 156.55 (2C, C2 quinoline), 154.07(2C, C3 pyrazoline), 148.43, 147.52, 140.72, 135.67, 130.48, 130.02, 129.60, 128.87, 128.76, 128.65, 126.64, 126.48, 126.04, 125.80, 124.68 (C, CH phenyl and quinoline, 34C), 59.28 (2CH, C5 pyrazoline), 46.30 ($2CH_2$, C4 pyrazoline), 36.42 ($2CH_2$), 24.87 ($2CH_2$), 18.77 ($2CH_3$), 14.10 ($2CH_3$).

Anal. calcd. For $C_{52}H_{46}Cl_2N_6O_2$: C, 72.80; H, 5.40; N, 9.80; Found C, 72.82; H, 5.39; N, 9.83.

Copies of these spectra should be provided in the Supplementary Materials.

Acknowledgments

We thank ANDRS (Agence Nationale pour le Développement de la Recherche en Santé) and MESRS (Ministère de 1'Enseignement Supérieur et de la Recherche Scientifique) for partial financial support.

Author Contributions

Kedjadja Allaoua and Merdes Rachid have contributed to the experimental part of this work. Experimental characterization was made by Kolli Elhadj. Bouraiou Abdelmalek and Haddour Naoufel analyzed the NMR and have contributed to the preparation of the manuscript. All authors read and approve the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Levy, S.; Azoulay, S. Stories About the Origin of Quinquina and Quinidine. *J. Cardiovas. Electrophysiol*. **1994**, *5*, 635–636.
2. Roma, G.; Braccio, M.D.; Grossi, G.; Mattioli, F.; Ghia, H. 1,8-Naphthyridines IV. 9-Substituted *N*,*N*-dialkyl-5-(alkylamino or cycloalkylamino) [1,2,4]triazolo[4,3-*a*][1,8]naphthyridine-6-carboxamides, new compounds with anti-aggressive and potent anti-inflammatory activities. *Eur. J. Med. Chem*. **2000**, *35*, 1021–1035.
3. Phan, L.T.; Jian, T.; Chen, Z.; Qiu, Y.L.; Wang, Z.; Beach, T.; Polemeropoulos, A.; Or, Y.S. Synthesis and Antibacterial Activity of a Novel Class of 4′-Substituted 16-Membered Ring Macrolides Derived from Tylosin. *J. Med. Chem*. **2004**, *47*, 2965–2968.
4. Vargas, L.Y.; Castelli, M.V.; Kouznetsov, V.V.; Urbina, J.M.; Lopez, S.N.; Sortino, M.; Enriz, R.D.; Ribas, J.C.; Zacchino, S. *In vitro* antifungal activity of new series of homoallylamines and related compounds with inhibitory properties of the synthesis of fungal cell wall polymers. *Bioorg. Med. Chem*. **2003**, *11*, 1531–1550.
5. Dassonneville, L.; Lansiaux, A.; Wattelet, A.; Wattez, N.; Mahieu, C.; Van Miert, S.; Pieters, L.; Bailly, C. Cytotoxicity and cell cycle effects of the plant alkaloids cryptolepine and neocryptolepine: Relation to drug-induced apoptosis. *Eur. J. Pharmacol*. **2000**, *409*, 9–18.
6. Levai, A. Synthesis of pyrazolines by the reactions of *α*,*β*-enones with diazomethane and hydrazines. *Chem. Heterocycl. Compd.* **1997**, *33*, 647–659.
7. Özdemir, A.; Zitouni, T.G.; Kaplancıklı, Z.A.; Revial, G.; Güven, K. Synthesis and antimicrobial activity of 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives. *Eur. J. Med. Chem.* **2007**, *42*, 403–409.
8. Shaharyar, M.; Siddiqui, A.A.; Ali, M.A.; Sriram, D.; Yogeeswari, P. Synthesis and *in vitro* antimycobacterial activity of N^1-nicotinoyl-3-(4′-hydroxy-3′-methyl phenyl)-5-[(sub)phenyl]-2-pyrazolines. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3947–3949.
9. Manna, F.; Chimenti, F.; Bolasco, A.; Cenicola, M.L.; D'Amico, M.; Parrillo, C.; Rossi, F.; Marmo, E. Anti-inflammatory, analgesic and antipyretic N-acetyl-Δ^2-pyrazolines and dihydrothienocoumarines. *Eur. J. Med. Chem.* **1992**, *27*, 633–639.
10. Bhat, A.R.; Athar, F.; Azam, A. Bis-pyrazolines: Synthesis, characterization and antiamoebic activity as inhibitors of growth of *Entamoeba histolytica*. *Eur. J. Med. Chem*. **2009**, *44*, 426–431.
11. Manna, F.; Chimenti, F.; Bolasco, A.; Secci, D.; Bizzarri, B.; Befani, O.; Turini, P.; Mondovi, B.; Alcaro, S.; Tafi, A. Inhibition of amine oxidases activity by 1-acetyl-3,5-diphenyl-4,5-dihydro-(1H)-pyrazole derivatives. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3629–3633.
12. Levai, A.; Patonay, T.; Silva, A.M.S.; Pinto, D.C.G.A.; Cavaleiro, J.A.S. Synthesis of 3-aryl-5-styryl-2-pyrazolines by the reaction of (*E,E*)-cinnamylideneacetophenones with hydrazines and their oxidation into pyrazoles. *J. Heterocycl. Chem.* **2002**, *39*, 751–758.
13. Kedjadja. A.; Kolli, E.; Bouraiou, A.; Merdes, R. 1-[3-(2-Methyl-4-phenylquinolin-3-yl)-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl]-propane-1-one. *Molbank* **2015**, *2015*, M863.
14. Wang, G.W.; Jia, C.S.; Dong, Y.W. Benign and highly efficient synthesis of quinolines from 2-aminoarylketone or 2-aminoarylaldehyde and carbonyl compounds mediated by hydrochloric acid in water. *Tetrahedron Lett.* **2006**, *47*, 1059–1063.

15. Kotra, V.; Ganapaty, S.; Adapa, S.R. Synthesis of new series of quinolinylchalcones as anticancer and anti-inflammatory agents. *Indian J. Chem. Sec. B* **2010**, *49*, 1109–1116.
16. Fun, H.K.; Loh, W.S.; Sarveswari, S.; Vijayakumar. V.; Reddy, B.P. 1-(6-Chloro-2-methyl-4-phenyl-3-quinolyl)ethanone. *Acta Crystallogr.* **2009**, *E65*, o2688–o2689.
17. Kedjadja, A.; Merdes, R.; Bouacida, S.; Roisnel, T.; Belfaitah, A. (2*E*,2′*E*)-1,1′-Bis(6-chloro-2-methyl-4-phenylquinolin-3-yl)-3,3′-(1,4-phenylene)diprop-2-en-1-one ethyl acetate disolvate. *Acta Crystallogr.* **2013**, *E69*, o37–o38.