Heterocyclic Letters
Vol. 11| No.3|453-456| May-July|2021
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

ULTRASOUND MEDIATED SYNTHESIS, ANTIBACTERIAL ACTIVITY OF MORPHOLINYL-QUINOLINE BASED CHALCONE DERIVATIVES

GUGULOTH RAVI* [1] , K.BHASKAR 2 , SRINIVAS GALI [2] , BAVU RAJKUMAR [2]

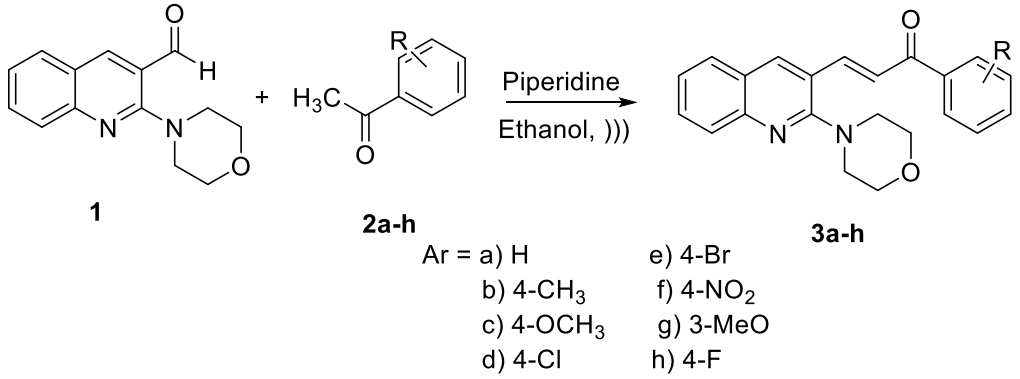
***[1] UGC-POST DOCTORAL FELLOW, DEPARTMENT OF CHEMISTRY, OSMANIA UNIVERSITY, HYDERABAD-007, TELANGANA, INDIA.**
[2] DEPARTMENT OF CHEMISTRY, SRR GOVERNMENT ARTS AND SCIENCE COLLEGE, KARIMNAGAR-001, TELANGANA, INDIA.

Abstract: A series morpholinyl-quinoline based chalcone derivatives were prepared by the condensation of morpholine-substituted-quinoline aldehyde with various acetophenones using piperidine as base in ultrasound irradiation. The compounds were characterized by using ^{1}H NMR, ^{13}C NMR and mass spectrometry.

Keywords: Ultrasound irradiation, Chalcone, Quinoline, morpholine, Antimicrobial activity

Introduction: Chalcone and their derivative are pharmacologically active compounds with wide variety of biological activities such as antimicrobial[i], anticancer[ii], anti-inflammatory[iii] and antidiabetic[iv] activities. The chalcone derivatives are generally prepared by the condensation of aldehyde with acetophenone in the presence of base or acids. However, the methods suffer from low yields with higher reaction times and gives undesired products[v]. On the other hand, Quinoline and their derivative is important core in medicinal chemistry due to their wide variety of biological activities including anticancer[vi], anti-HIV[vii], antimicrobial[viii], antituberculosis[ix], antiviral[x], antimalarial[xi], antioxidant[xii], anti-inflammatory[xiii], anti-protozoal[xiv] activities. In addition, morpholine scaffold is also responsible for different biological activities such as antimicrobial[xv] and anti-inflammatory[xvi] activities. In green chemistry concern, ultrasound assisted synthesis have become popular as novel and promising method for synthesis of various chemical molecules. Thus, we prompted us to synthesis morpholinyl-quinoline based chalcone derivatives were prepared by the condensation of morpholine-substituted-quinoline aldehyde with various acetophenones using piperidine as base in ultrasound irradiation. The method has proved to be an easy, efficient high yields with short routine, and being more environmentally-friendly.

Scheme-1: Synthesis of morpholine-substituted-quinoline aldehydes



Experimental: The IR spectra were recorded on a Perkin-Elmer FT-IR-8400s, using samples in KBr disks. The purity of the compounds was checked by TLC using precoated silica gel plates 60_{254}(Merck). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II 400 MHz spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer. Elemental analysis was performed on a Perkin Elmer CHN-2400 analyzer.

General procedure for synthesis of compound 3a-h: To a solution of 2-morpholinoquinoline-3-carbaldehyde **(1)** (1 mmol), acetophenone **(2a-h)** (1 mmol), piperidine (3 mmol) and ethanol (10 ml) was stirred under ultrasound at ethanol reflux temperature for 20-30 min. Progress of the reaction monitored by TLC, after completion of the reaction. The reaction mixture poured into ice cold water, slowly the solid separates out, it filtered, washed with water, dried and purified by using column chromatography using n-hexane:ethyl acetate (9:1) to afford corresponding pure morpholinyl-quinoline based chalcone derivatives **3a-h**.

3a. (E)-3-(2-morpholinoquinolin-3-yl)-1-phenylprop-2-en-1-one: IR (KBr): 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 3.35-3.39 (t, 4H, NCH_2), 3.82-3.86 (t, 4H, OCH_2), 7.33-7.99 (m, 11H, Ar-H), 8.25 (s, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$): 51.2, 66.7, 122.2, 123.2, 124.3, 124.9, 127.5, 127.5, 128.4, 128.2, 128.7, 130.4, 133.0, 137.1, 137.7, 141.9, 147.5, 159.3, 189.8; MS: *m/z* = 345 $(M+H)^+$.

3b. (E)-3-(2-morpholinoquinolin-3-yl)-1-(*p*-tolyl)prop-2-en-1-one: IR (KBr): 1662 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.45 (s, 3H, CH_3), 3.36-3.40 (t, 4H, NCH_2), 3.84-3.90 (t, 4H, OCH_2), 7.33-7.97 (m, 10H, Ar-H), 8.26 (s, 1H, Ar-H), ^{13}C-NMR ($CDCl_3$): 21.5, 51.1, 66.7, 122.5, 123.3, 124.2, 124.7, 124.7, 125.9, 127.6, 127.8, 128.7, 129.5, 130.8, 137.7, 138.5, 139.2, 141.4, 144.3, 147.6, 159.4, 189.2; MS: *m/z* = 359 $(M+H)^+$.

3c. (E)-1-(4-methoxyphenyl)-3-(2-morpholinoquinolin-3-yl)prop-2-en-1-one: IR (KBr): 1665 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 3.34-3.38 (t, 4H, NCH_2), 3.85-3.91 (t, 4H, OCH_2), 7.00-7.95 (m, 10H, Ar-H), 8.24 (s, 1H, Ar-H), ^{13}C-NMR ($CDCl_3$): 50.7, 55.4, 66.7, 114.0, 122.8, 122.5, 124.7, 124.8, 127.6, 130.1, 130.6, 130.8, 130.9, 137.8, 141.0, 147.6, 159.6, 163.6, 188.0; MS: *m/z* = 375 $(M+H)^+$.

3d. (E)-1-(4-Chlorophenyl)-3-(2-morpholinoquinolin-3-yl)prop-2-en-1-one: IR (KBr): 1658 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 3.34-3.38 (t, 4H, NCH_2), 3.84-3.90 (t, 4H, OCH_2), 7.38-7.99 (m, 10H, Ar-H), 8.25 (s, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$): 50.6, 66.6, 122.2, 122.8, 123.2, 124.8, 124.9, 127.5, 127.8, 129.0, 129.5, 130.7, 136.2, 137.3, 139.8, 142.3, 147.9, 159.4, 188.9; MS: *m/z* = 379 $(M+H)^+$.

3e. (E)-1-(4-bromophenyl)-3-(2-morpholinoquinolin-3-yl)prop-2-en-1-one: IR (KBr): 1659 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 3.36-3.39 (t, 4H, NCH_2), 3.86-3.92 (t, 4H, OCH_2), 7.39-8.01 (m, 10H, Ar-H), 8.26 (s, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$): 51.0, 66.8, 122.3, 122.5, 124.8, 124.9, 127.6, 127.8, 128.2, 130.0, 130.8, 132.0, 136.5, 137.4, 142.1, 159.3, 189.5; MS: *m/z* = 423 $(M+H)^+$, 425 $(M+2H)^+$.

3f. (E)-3-(2-morpholinoquinolin-3-yl)-1-(4-nitrophenyl)prop-2-en-1-one: IR (KBr): 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 3.35-3.38 (t, 4H, NCH_2), 3.85-3.90 (t, 4H, OCH_2), 7.38-8.22 (m, 8H, Ar-H), 8.29 (s, 1H, Ar-H), 8.35-8.37 (d, 2H, Ar-H); ^{13}C-NMR ($CDCl_3$): 51.1, 67.0, 123.8, 124.1, 124.5, 124.8, 127.5, 127.9, 128.3, 128.7, 129.3, 130.1, 133.5, 135.2, 136.7, 144.3, 149.6, 162.5, 190.5; MS: *m/z* = 390 $(M+H)^+$.

3g. (E)-1-(3-methoxyphenyl)-3-(2-morpholinoquinolin-3-yl)prop-2-en-1-one: IR (KBr): 1662 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 3.35-3.38 (t, 4H, NCH_2), 3.85-3.91 (t, 4H, OCH_2), 7.18-8.00 (m, 10H, Ar-H), 8.27 (s, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$): 51.2, 55.6, 66.8, 113.2, 113.5, 122.0, 123.2, 124.2, 124.5, 127.1, 127.4, 127.9, 130.2, 130.8, 131.2, 136.8, 141.5, 147.5, 160.1, 163.0, 188.9; MS: *m/z* = 375 $(M+H)^+$.

3h. (E)-1-(4-fluorophenyl)-3-(2-morpholinoquinolin-3-yl)prop-2-en-1-one: IR (KBr): 1658 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 3.34-3.39 (t, 4H, NCH_2), 3.84-3.89 (t, 4H, OCH_2), 7.19-8.02 (m, 10H, Ar-H), 8.26 (s, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$): 51.2, 66.7, 121.5, 122.6, 124.0, 124.5, 127.3, 127.5, 129.0, 129.9, 130.5, 136.4, 137.0, 139.3, 143.0, 147.5, 160.5, 189.3; MS: *m/z* = 379 $(M+H)^+$.

Result and discussion:

The title morpholinyl-quinoline based chalcone derivatives were prepared by the condensation of 2-morpholinoquinoline-3-carbaldehyde (**1**) with different acetophenones using piperidine as base in ethanol medium at reflux condition for 3-4 hrs to get corresponding chalcones in good yield. The synthesized compounds were well characterized by different spectral data showed in spectral data. The key starting material 2-morpholinoquinoline-3-carbaldehyde was prepared as per previously reported experimental procedure.

Biological activity:

Antibacterial activity: The synthesized compounds **(3a-h)** were evaluated for *in vitro* antibacterial activity against four bacterial strains such as Staphylococcus *aureus*, *Bacillus subtilis, Pseudomonas aeruginosa* and *Escherichia coli.* The screening result evident that the compounds **3b, 3f, 3g** and **3h** were showed good antibacterial activity against all the bacterial stains and reaming compounds showed moderated to low activity. The antibacterial screening study was done by paper disc method and Norfloxacin used as the standard drug by measuring the zone of inhibition in mm. The compounds were screened at the concentrations of 100µg/ml in DMSO.

Conclusion:

We have successfully synthesised various morpholinyl-quinoline based chalcone derivatives under ultrasound assisted method using piperidine as base. The method proved to be an easy, simple, economic and high yielding with short reaction time. Antibacerial study of the title compound evident that the compounds **3b, 3f, 3g** and **3h** were showed good antibacterial activity against all the bacterial stains.

References:

i. Dragana D. B.; Marina M.; Branka I. and Ivana C.; Antibacterial activity of three newly-synthesized chalcones & synergism with antibiotics against clinical isolates of methicillin-resistant Staphylococcus aureus; Indian J. Med. Res.; 2014, **140(1)**, 130.

ii. Karthikeyan, C.; Moorthy, N.S.; Ramasamy, S.; Vanam, U.; Manivannan, E.; Karunagaran, D.; Trivedi, P.; Advances in chalcones with anticancer activities; Recent Pat. Anticancer Drug Discov.; 2015, **10(1)**, 97.

iii. Hsieh, H.K.; Tsao, L.T.; Wang J.P. and Lin, C.N.; Synthesis and anti-inflammatory effect of chalcones; J. Pharm Pharmacol.; 2000, **52(2)**, 163.

iv. Hsieh, C.T.; Hsieh, T.J.; El-Shazly, M.; Chuang, D.W.; Tsai, Y.H.; Yen, C.T.; Wu, S.F.; Wu Y.C. and Chang, F.R.; Synthesis of chalcone derivatives as potential anti-diabetic agents; Bioorg Med. Chem. Lett.; 2012, **22(12)**, 3912.

v. Hathaway, B.A.; An Aldol Condensation Experiment Using a Number of Aldehydes and Ketones; J. Chem. Educ.; 1987, **64**, 367.

vi. Yeh-Long Ch.; Hsien-Ming H.; Chih-Ming L.; Kuang-Chieh L.; Cherng-Chyi T.; Synthesis and anti-inflammatory evaluation of 4-anilinofuro[2,3- b]quinoline and 4-phenoxyfuro[2,3- b]quinoline derivatives. Part 3.; Bioorg. Med. Chem., 2004, **12(24)**, 6539.

vii. Zai-gang, L.; Cheng-chu, Z.; Fang, W.; Hong-qiu, H.; Cun-xin, W.; Hong-guang D., and Li-ming, H.; Synthesis and Biological Activities of Quinoline Derivatives as HIV-1 Integrase Inhibitors; Chem. Res. Chinese Universities; 2009, **25(6)**, 841.

viii. Desai, N. C.; Patel B.Y. and Dave, B.P.; Synthesis and antimicrobial activity of novel quinoline derivatives bearing pyrazoline and pyridine analogues; Med. Chem. Res., 2017, 26, 109.

ix. Keri R.S. and Patil, S. A.; Quinoline: a promising antitubercular target; Biomed Pharmacother., 2014, **68(8)**, 1161.

x. Carolina de Guardia, David E. Stephens, Hang T. Dang, Mario Quijada, Oleg V. Larionov, and Ricardo Lleonart, Antiviral Activity of Novel Quinoline Derivatives against Dengue Virus Serotype 2Molecules, 23(3), 672 (2018).

xi. Foley M. and Tilley, L.; Pharmacol T.; Quinoline antimalarials: mechanisms of action and resistance and prospects for new agents; 1998, **79(1)**, 55.

xii. Orhan Püsküllü, M.; Tekiner B. and Suzen, S.; Recent studies of antioxidant quinoline derivatives; Mini Rev. Med. Chem., 2013, **13(3)**, 365.

xiii. Mukherjee S. and Pal, M.; Medicinal chemistry of quinolines as emerging anti-inflammatory agents: an overview. Curr. Med. Chem.; 2013, **20(35)**, 4386.

xiv. García, E.; Coa, J.C.; Otero, E.; Synthesis and antiprotozoal activity of furanchalcone-quinoline, furanchalcone–chromone and furanchalcone–imida-zole hybrids; Med. Chem. Res., 2018, **27**, 497.

xv. Bektas, H.; Ceylan, S.; Demirbaş, N.; Alpay-Karaoğlu S.; and Sokman, B.B.; Antimicrobial and antiurease activities of newly synthesized morpholine derivatives containing an azole nucleus; Med. Chem. Res., 2013, **22(8)**, 3629.

xvi. Ahmadi, A.; Khalili, M.; Hajikhani, R.; New morpholine analogues of phencyclidine: Chemical synthesis and pain perception in rats; Med. Chem. Res., 2012, **21**, 3532.

Received on May 21, 2021.