Microwave Assisted Synthesis Characterization and Study of Some Novel Chalcones Compounds Derived From Mefenamic Acid

Hanan Al-Hazam¹ Zeki A Al – Shamkhan¹, Abdulelah A Al-Mayah²and Rawaa M Hraishawi

¹Chemistry Dep., Science College, Basrah University, Basrah- Iraq.
²Clinical Laboratory Sciences, Pharmacy College, Basrah University, Basrah- Iraq.

Abstract. New chalcones compounds were synthesis by reaction mefenamyl chloride with P-aminoacetophenone to from N–(4-acetyl phenyl)-2-(2/3- dimethyl phenyl) amino benzamide(A). The chalcones produced by Claisen – Schmidt condensation of compound A with substituted benzaidehydes [(2,4-dihydroxy(1), 3-NH₂(2) and 4- OMe (3) ] in ethanolic KOH solvent by using microwave irradiation . The new compounds were characterized by M.P, TLC, CHN, FT-IR, ¹HNMNR and ¹³CNMR. The biological screening data of the synthesized compounds were also presented. The theoretical study by using AM1 semi-empirical method emphasizes these compounds exists as trans configuration.

Keyword chalcones, mefenamic acid, microwave irradiation, Anti-bacterial activity, MIC,AM1-semi-empirical method

Introduction

Chalcones, considered to be the precursor of flavonoids and isoflavonoids, are abundant in edible plants. They consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α, β-unsaturated carbonyl system. Studies revealed that compounds with a Chalone-based structure have anti-inflammatory (¹,⁵) antibacterial (⁴), antifungal (⁵), and anti-tumor activities (⁴). These activities are largely attributed due to the α, β-unsaturated ketone moiety. Introduction of various substituents into the two-aryl rings is also a subject of interest because it leads to useful structure-activity relationship. The chemistry of chalcones has generated intensive scientific studies throughout the world. Especially interest has been focused on the synthesis and biodynamic activities of chalcones. These compounds are also known as benzalacetophenone (⁶-⁸) or benzylidene acetophenone (⁹-¹¹). In chalcones, two aromatic rings are linked by an aliphatic three-carbon chain. Chalcone bears a very good synthon so that variety of novel heterocycles with good pharmaceutical profile can be designed. Chalcones are unsaturated ketone containing the reactive ketoethylenic group – CO-CH=CH-. These are colored compounds because of the presence of the chromophore -CO-CH=CH-, which depends in the presence of other auxochromes. Different methods are available for the preparation of Chalcones. The most convenient method is the Claisen-Schmidt condensation of equimolar quantities of arylmethylketone with aryl aldehyde in the presence of alcoholic alkali (¹²-¹⁶) Chalcones are used to synthesize several derivatives like cyanopyridines, pyrazolines, isoxazoles and pyrimidines having different heterocyclic ring systems. Chalcones are the compounds were aromatic substituents are introduced in to the terminal position of the system C = C-C=O. So Chalcones are...
characterized by their position of a Ar (A) –CO-CH=CH-Ar (B) this type of structure in which two aromatic rings A and B are linked by an aliphatic three carbon chain.\(^{[17,20]}\)

### Experimental part

Melting point were determined in Gallen Kamp melting point apparatus and were uncorrected, Elemental analysis (CHN) were recorded in EA300 Euro-Vector in University of Al-Albayt in Jordon. FT-IR Spectra were recorded on Shimadzu FT-IR 8400 Fourier Transform infrared as KBr disk. \(^1\)HNMR and \(^13\)CNR spectra were recorded on Brucker spectrospin ultra shield magnets 400MHz instrument using tetramethylsilane (TMS) as an internal standard and DMSO-d6 as a solvent in university of Tabriz-Iran. Thin layer chromatography were performed on pre-coated sheets with 0.25 mm layer of Slica Gel GF254 of the Merck company.

### Synthesis of compounds

**4-(acetyl phenyl) -2-(2,3- dimethyl phenyl) amino ben 3- amide [A]:**

A mixture of mfenamyl chloride (7mg, 1.00mmol) and p-amino acetonaphene (41mg, 3.00mmol) was irradiated under microwave for 5min., the mixture was cooled to room temperature and rinsed with CHCl\(_3\) (2 x10ml) and me combined extract was washed successively with a solution of 5% NaHCO\(_3\) (10ml). The organic layer was dried (MgSO\(_4\)) and evaporate to dryness. The crude product was purified by washing with pentane, dried and recrystallized from ethanol to give product [A], M.P. 122-124\(^\circ\)C.

### General procedure for the preparation chalcone derivatives

To a mixture at compound A (35mg, 1mmol) in ETOH in 20% NaOH in (40mg, 1.00mmol) and the mixture was stirred under microwave irradiation for 6 – 8min. the reaction progress was monitored by thin–layer chromatography (TLC). After completion of h – reaction, the mixture was poured onto ice – cold water and neutralized with dil. HCl. The resulting solid was filtered, dried and recrystallized from EtOH.

### 1- N-(2,4-dihydroxy phenyl ) acryloyl phenyl -2-(2,3- dimethyl phenyl amino) benzamide (1) yield 70% , M.P. 223-224\(^\circ\)C. Elemental Analysis, calculated C 73.302, H 5.485, N 5.854, Founded; C 73.121, H 5.334, N 5.698; IR spectra, KBr disk,1460 C=C-H str. ; 3344.57 N-H str. (amide NH str.) (broad) 1658,72 C=O amide, 1566,20 C=C ar. HNMR 2,12(3H,s,H\(_3\)), 3,34(3H, s,H\(_3\)), 6,7(1H d,H\(_6\)), 9,77(1H,s,NHamine),10,25 (IH, s, NH amide), 6,39(1H,d,H\(_6\)), 7,45(1H,d,H\(_6\)), 7,8 (2H,d,H\(_6\)\(_2\)), 7,87(2H,d,H\(_3\)), 7,42(2H,d,H\(_6\)) J=15), 8,33(1H,d/H\(_6\)) J=15), 11,85(1H,s,H\(_3\)), 6,21(1H,d,H\(_6\)). 7.93(1H, d, H\(_6\)). \(^{13}\)CNMR: 120.7C\(_\alpha\), 148.4C\(_\beta\), 119.2C\(_\gamma\), 127.8C\(_\delta\), 77.881, H 5.785, N 9.008; Founded

### 2- E– N-(-3-amino phenyl) acryloyl phenyl 1-2-(2,3-dimethyl amino) benzamide yield 70% , M.P. 220-221\(^\circ\)C, C 78,071, H 5,902, N 9.101, Fixed; C 77.881, H 5.785, N 9.008; IR (film) 3332.99,3224.94 N-H st. of NH2 3394,7.4 NH st. of secondary amine 1654,92 CO str.;\(^1\)HNMR: 2,12(3H,s,H\(_3\)), 2,85(3H,s,H\(_3\)), 6,4 (1H,m,H\(_6\)), 7,85(1H,m,H\(_6\)), 7,3(1H,m,H\(_6\)), 8,3(1H,d,H\(_6\)), 7,6(1H,m,H\(_6\)), 6,7(1H,m,H\(_6\)), 7,3(1H,m,H\(_6\)), 7,82(2H,m,H\(_6\), \(_2\)), 7,92(2H,m,H\(_6\), \(_2\)), 6,65(1H,m,H\(_6\)), 7,05(1H,m,H\(_6\)), 7,04(1H,m,H\(_6\)), 6,06(1H,m,H\(_6\)), 5,28(2H,m,NH\(_2\)). \(^{13}\)CNMR: 238.4C\(_\alpha\), 148C\(_\gamma\), 119.2C\(_\delta\), 119.8C\(_\zeta\), 126.5C\(_\zeta\), 127C\(_\zeta\), 120.7C\(_\zeta\), 148C\(_\zeta\), 119.2C\(_\zeta\), 133C\(_\zeta\), 118.3C\(_\zeta\), 128.4C\(_\zeta\), 138.4C\(_\zeta\), 137.7C\(_\zeta\), 119.8C\(_\zeta\), 126.5C\(_\zeta\), 127.2C\(_\zeta\), 165CONH, 142.7C\(_\zeta\), 122.1C\(_\zeta\), 131.4C\(_\zeta\), 133,5C\(_\zeta\), 189.7CO, 121.3Ca, 141.0C_p, 115.5C\(_\zeta\), 155.1C\(_\zeta\), 155.2C\(_\zeta\), 103.5C\(_\zeta\), 159.4C\(_\zeta\), 108.4C\(_\zeta\), 131.2C\(_\zeta\).

### 3- (2,3-dimethylphenyl amino) N- 2/ (3(3-methoxy phenyl) acryloyl phenyl) benzamine (3), X=3-OMe yield 70% , M.P. 199-200\(^\circ\)C; C 78,071, H 5,902, N 9.101, Fixed; C 77.958, H 5.842, N 8.998; IR(film): 1446C=C-H str. , 1338 C-N str. , 3059-NH str. , 1573 C=C st.; \(^1\)HNMR:
Theoretical Study
Theoretical study were done by using AM1 semi-empirical method in program hyper chem8.1 were utilized.

Results and Discussion
In the present work new chalcones compounds were synthesized as shown in scheme under microwave irradiation
dihydroxy-.) in the presence of 20% NaOH for 6–8 min under MWI afforded, after chromatographic, the desired chalcone derivatives in 70–80% yield. Alternatively, the analogues were prepared in 75–85% yield by refluxing of with substituted benzaldehydes in the presence of ethanolic NaOH for 4–5 h.

The structures were assigned on the basis of their (IR, 1HNMR, and 13CNMR), which showed rather similar patterns for the aromatic scaffold. The IR spectrum for new compounds dive anew absorption band near 1670 – 1580 cm\(^{-1}\) and at 1460 cm\(^{-1}\) – related to C=\(^\alpha\) aromatic and C=\(^\beta\)CH st. respectively. 1HNMR give new signal related to H\(^\alpha\) and H\(^\beta\) at 7.63 – 7.60ppm and 7.01 – 8.23ppm respectively with coupling constant J about 15 – 14.8Hz. This results fixed that proton (H\(^\alpha\), H\(^\beta\)) was trans to each other.

**Biological Activity**

The present study included antibacterial activity of above derivatives on some clinical bacterial isolates (*Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa*). Six concentrations were serial diluted from derivatives stocks (2, 5, 10, 100, 200 and 300) Mg/ml. All dilutions were have not any detectable effect on above bacterial spp. Most antibiotics used today are produced in laboratories, but they are often based on compounds have found in nature. (23) Non–steroidal Anti – inflammatory Drugs are medications widely used to relief pain, reduce inflammation and bring down a high temperature (fever). They are often used to relief symptoms of headaches, pain, cold, flu, arthritis and other causes of long-term pain. Although NSAIDs are commonly used, they are not suitable for everyone and can sometime cause trouble some side effects. The main types of NSAIDs included ibuprofen, naproxen, diclofenac acid, celecoxib, mefenamic acid, etoricoxib and indometcin (24).

Mefenamic acid a member of anthranilic acid derivatives or fenamate class of NSAIDs, it is used to treat mild to moderate pain from various conditions. It is also used to decrease pain, common side effects of mefenamic acid include nausea, vomiting, upset stomach, stomach pain, diarrhea, constipation, gas, indigestion and dizziness (25).

**Bacterial Isolates**

Clinical pathogenic bacteria were obtained from clinical Laboratory research in college of pharmacy, Department of Clinical Laboratory Sciences.

**2-1-2- Identification of Isolates**

The stock of clinical isolates were grown on nutrient agar by striking. The plats were incubated at 37°C for overnight, the colonies were picked up as smear on glass slid for microscopic examination.

**2-1-3- Antibacterial Activity**

Six serial dilution of derivatives (2, 5, 10, 100, 200, and 300) mg/ml were applied to evaluate antibacterial activity against pathogenic bacteria.

Paper discs in agar diffusion method were applied (26). All pathogenic bacteria were re cultured in nutrient broth for 2hr at 37°C, then 100µl were cultured by striking on Muller Hinton agar, paper discs were submerged in different derivatives dilution then applied on the Muller Hinton agar plate and incubated at 37°C for overnight. The inhibition zone were measured for each disc paper.

The mefenamic acid derivatives with different applied concentrations haven’t detectable effect on all clinical bacterial isolates (staphylococcus aureus, Escherichia coli and pseudomonas aeruginosa). Usually antibacterial activity depend on many mechanisms like cell wall synthesis inhibitors, DNA synthesis inhibitors, RNA synthesis inhibitors and protein synthesis inhibitors (27) hence the prepared derivatives haven’t any of above mechanisms.

Also The hydrophobicity of any compounds consider as limited factor for its activity (28,29). In addition infusibility of the compounds determined penetration of these derivatives to enter inside bacterial cell (30). Further studies should be done to explain antibacterial activity of prepared derivatives.

**Theoretical study**

There are two conformational isomer E and Z of chalcone compounds due to the free rotation a long single bond between C-carbonyl and C\(^\alpha\) as show in Fig1. The result of heat of formation table 1 by using MA1 semi-empirical method show that E isomer is more stable than Z isomer due to firstly,
the strong steric effect between carbonyl group and substituted phenyl ring, and the secondly, the field effect between C=C and C=O\(^{(31,32)}\).

| \(\Delta E\) (kJ/mole) | 4-OMe | 3-NH\(_2\) | 2,4-di-OH |
|------------------------|-------|------------|-----------|
| \(\Delta E_{\text{Z-iso}}\) | 290.66 | 256.60     | 210.2     |
| \(\Delta E_{\text{E-iso}}\) | 290.005 | 255.09     | 209.9     |

The ball and stick model of compounds, X=3- NH\(_2\), OMe and 2,4-diOH respectively.
References

[1] R. Jayapcil and N. Y. Sreedhar, Inte. J. Curr. Pharm Res. 2010, 2, (4), 60-62.
[2] N. Sreedhar, M. Rajapal, K. Sreenivoosa and P. Redly, PJPBCS, 2010, 1(4), 400-480.
[3] A. Vogel, 1665 (parchment ry. 3rd ed Jangmans, group. Yd, London 718.
[4] H. Suwito, J. Mustofa, N. Yoman, J. chemical and pharm aceutical Res., 2014, 6(5) 1076-1088.
[5] E.H. Ziman, In T. J. Chem and Natural Sciences, 2014, 2, (4), 109-115.
[6] D.A. Shrin, P. Kunjadia and P. patel. Int. J. Pharm. Science and Prng Res., 2011, 3(4). 331-337.
[7] Zeki A. Al-Shamkani H. A. Al-Hazam and Suha K.-Al-Mosawi, Chem., and Materials Res., 2015, 7, 6, 50-57.
[8] H. AL-Hazam, J. Mohamed and J. Ahmed, Int. J. Applied Chem., science Res., 2014, 2 (2), 1-20.
[9] A. F. Abbas, A. Turki and A. J. Hameed, J. Material Environ. Sci., 2012, 3(6), 1071-1078.
[10] D. Sankur and R. Namratha, Der pharma chemical, 2017, 5(1), 235-240.
[11] H. Hasam, S. Shied and M. Shaheen word J. Chem., 2011, 6(1), 01-07.
[12] A. Trived, D. Dodiya, N Raval and V. Shab, Arkicoc, 2008, (xi), 31-41.
[13] A. Al- Sabawi, Mosul, J. Chem., 2014, 35-39.
[14] R. M. Shra, I. Qomer, N. Priyanka and K. Thg, Der Pharmacia since, 2012, 3(3), 32-37.
[15] C. Patrics S. Mahajan and A. Ka Hi J. Pharma. Sci. Res. 2009, 1(3), 11-22.
[16] N. Jun, G. Hong and L. Eun, Bioorganic and Medicinal chem., 2007, 115, 2396-2402.
[17] O. Nerya, R. Musa, S. Khatib photochem., 2004, 65, 1389-1395.
[18] J. Rojas, M. Poaya, H. Doming and M. Luisa, Bioorg., and Medicine chem., Le H, 2002, 12, 195-1954.
[19] S. Sharma, S. Kanr, T. Bansal and T. Gaba, chem., Sci. Transaction 2014 3(3), 861-875.
[20] B. Reddy, Indian J. Chem., 2015, 54B, 825-828.
[21] A. K. Rathod and Cn. Bulkmmn, Pharma Tech. 2011, 3(2) 728-731.
[22] S. Naikal, J. Amanagutiand, J. Shivara, Der Pharma chemiea 2015, 7(3), 95-99.
[23] A. A. Al-Bader, fungi. Bas. J. Vet. Res., 2008, 7(2), 101-106.
[24] K.N.Dutta, S. Annduraa and K. Mezumdar, Int. Jantimicrb Agent, 2007, 30 (3), 242-249.
[25] H. Kruszewska, T. Zareba, S. Tyski, Acta pol pham, 2006, 63, 457-600.
[26] A.S. Al- Janabi, Asian J. Pharm. 2009, 3, 143-152.
[27] M. M. Kochanski, D.J. A. Dwyer, and J.J. Collins, Nat Rev microbial, 2010, 8(6), 423-435.
[28] K. ThaKur, G.Totaro, Journal of Environmental chemical Engineering, 2016, 4(2), 1743-1752.
[29] K. Yamauchi, Y. Yao, T. Ochiai, M. Sakai, Y. Kubota, and G. Yamauchi, Journal of Nanotechnology, (2011).
[30] L. Jiang, F. Wang, F. Han, W. Prinyawiwatkul, H.K. No, and B. Ge, Journal of Applied Microbiology, 2012, 114, 956-963.
[31] B. A. Koz and R. Grton, J. Parm. Sci., 2011, 36,225-242.
[32] Y. Yun and X. Gong, J. Mol. Stru. (theochem), 2009, 901, 226-231.