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Microwave Assisted Synthesis, Characterization and Antibacterial Study of Some Novel Schiff's Bases, Thaizolidinone and Chalcone Compounds Derived from Mefenamic Acid

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Abstract
This work involves synthesis of some new heterocyclic compounds including thaizolidinone compounds. The new Schiff bases derived from mefenamic acid, which was synthesized by microwave irradiation of mefenamic acid with hydrazine hydrate in absolute ethanol and this amino compound condensation with different aromatic aldehydes in absolute ethanol. Thaizolidinone compounds were synthesized by cycloaddition reaction of mercapto acetic acid to imine group of Schiff bases in dry benzene. The new chalcone derivatives synthesized by the reaction aldehyde with their compounds. M.P., TLC, CHN, UV, FTIR and NMR spectroscopy has characterized all the synthesized compounds. The biological screening data of the synthesized compounds were also studied.
Keywords: Schiff bases, thaizolidinone, chalcone, antibacterial.

Introduction

Microwave dielectric heating uses the ability of some liquids and solids to transform electromagnetic radiation into heat to drive chemical reactions. The entry of microwave ovens possible to carry out many transformations with greater efficiency and ease of workup [Hoz et al, 2005, Gedye et al,1998, Nuchter et al,2000] the use of microwave has becomes very attractive in the field of medical sciences [Chattree et al, 2013].

Molecules designed on anthranilic acid scaffold as drug candidates have attracted great interest in modern medical chemistry during recent years. It had been observed that best known non-steroidal anti-inflammatory drugs (NSAIDs) are acidic in nature. N-phenylantranilic acid derivatives like mefenamic acid and meclofenamates had been used in therapy as potent analgesic and anti-inflammatory agents in the treatment of osteoarthritis, rheumatoid arthritis and other painful musculosketal illnesses [Martindale, 1996, Aboul-Fadl et al, 2011]. Recent literature showed that substitutions at 2-position of anthranilic acid by different aryl or heteroaryl moieties markedly modulated the anti-inflammatory effect [Tiwari et al, 2011]. Nphenylanthranilic acid hydrazides were also reported to be effective as analgesic agents and showed more analgesic activity in comparison to mefenamic acid and diclofenac sodium [Almasirad et al, 2006].

The chemistry of Schiff base plays a vital role in the progress of chemistry science [Yang et al, 2002, Patil et al, 2012], synthesis of Schiff base through classical condensation of aldehydes (or ketone) and imines were pursued [Celik et al 2009, Salih, 2005] Schiff base are characterized by the N=CH- (imine) group which is important in elucidating the mechanism of transformation in biological systems. Due to great flexibility and diverse structural aspects, wide range of Schiff bases have been synthesized and their complexion behavior was studied [Yang et al, 2002. Furthermore, Schiff base are reported to show a variety of interesting biological activities, including antibacterial [Kumar et al, 2013], antifungal [Jabar, 2009], anticancer [Shukla et al, 2008, Desai et al, 2001] and herbicidal activities [Khal et al 1997]. The wide range of biological activities exhibited by thiozolidinones [Khadim et al, 2011, Gadaginamath et al, 1999] derivatives, the aim of this study is to prepare thaizolidinones containing mefenamic acid in the molecule and to explore the pharmacological activity of this combination product. Thaizolidinone is a heterocyclic compound of five-membered unsaturated ring structure composed of three carbon atoms, nitrogen and sulfur atoms at nonadjacent positions. The chemistry of thiazolidinones compounds have been of much interest due to the presence of such heterocycles in a large variety of biologically important molecules [Singh et al, 1981].

Chalcones were prepared by condensation of aromatic ketones with aromatic aldehydes in presence of suitable condensing agent [Hasan et al, 2007, Kalirajan et al, 2009]. They undergo a variety of chemical reactions that leads to many heterocyclic compounds [Elarft et al, 2012, Al-Mosawi, 2014]. Chalcones have been used as intermediates for the preparation of compounds having therapeutic value [Raj1 et al, 2012, Bhat et al, 2005]. Many reviews reveal that chalcone derivatives exhibit diverse pharmacological activities, such as potential cytotoxic agents, antimicrobial agents, antiviral, anti-inflammatory, anesthetic, etc. [Prasad et al,2008, Won et al, 2005]. In the view of the varied biological and pharmacological applications, we have planned to synthesize some heterocyclic derivatives of chalcone and test their antibacterial activity.

Chalcones having α and β unsaturated carbonyl group are one of important biocides and versatile

synthons for various chemical transformation. Chalcones are also key precursors in the synthesis of many biological important heterocyclic [Karajan et al, 2007].

Experimental Work

Melting point were determined in Buchi thermal point apparatus and were uncorrected, Elemental analysis (CHN) were recorded in EA300 Euro-Vector in University of Al-albyat in Jordon. FT-IR Spectra were recorded on Shimadzu FT-IR 8400 Fourier Transformer infrared as KBr disk in the range 40-4000cm^{-1}. Ultraviolet spectra were recorded in spectro scan 80 in the wavelength 200-800 nm. ^{1}HNMR and ^{13}CNMR spectra were recorded on Brucker spctrospin ultra shield magnets 400MHz instrument using tetramethyl silane (TMS) as an internal standard and DMSO-d6 as a solvent in university of university of Exeter (UK). The compounds were synthesized by microwave type Newal microwave instrument (China) NWL101, compact 20L, power1200 Watt and frequency 2450 MHz, by using turntable system with different powers between 90-300W. Thin layer chromatography were performed on pre-coated sheets with 0.25 mm layer of Silica Gel GF254 of the Merck Company.

Synthesis of Compounds

1) Preparation of Hydrazide Derivative (I)

An equimolar mixture of mefenamic acid (0.01M) and hydrazine hydrate (0.01M, 99%) in 30 ml ethanol was placed in small conical flask at room temperature then the mixture exposed to microwave irradiation at 300w for 3min., the solid separated on cooling was filtered, washed several times with water, dried and recrystallized from alcohol (M.P: 103-104^{o}C). FT-IR spectra νmax 3288, 3200, 3030, 2988, 1691, 1452, 1202, 712cm^{-1}.

2) Synthesis Schiff base (II) $_{a-d}$

A mixture of mefenamic hydrazide (1mmole) and aldehyde (1mmole) were dissolved in ethanol (40ml). Drops of acetic acid was added and was placed in small conical flask at room temperature then the mixture exposed to microwave irradiation at 270w for 4min, This reaction was monitored by TLC. The resultant solution was cooled and poured in cold water. The separated solid was filtered, crystallized from ethanol to give crystalline yellow.

(II)a yield 67%, Melting point 180-182^{o}C, CHN analysis that formula $C_{22}H_{21}N_3O$ calculated C, 76.943 H, 6.160 N, 12.247; Found C, 76.765 H, 6.062 N, 12.014. Ultraviolet spectra λmax 240, 255, and 330. FT-IR spectra νmax 3325, 3200, 3050, 2964, 1691 1620, 1454, 1217, 752cm^{-1}.^{1}HNMR spectra δppm, (7.3,5H), and (8.1,1H)s.^{13}CNMR spectra δppm, , 107, 110, 113, 113, 114, 115,125, 127, 142, 145, 151, 164.

(II)b yield 75%, Melting point 177-179^{o}C, CHN analysis that formula $C_{23}H_{23}N_3O$ calculated C, 77.287 H, 6.490 N, 11.767; Found C, 77.112 H, 6.233 N, 11.565. Ultraviolet spectra λmax 242, 260, and 325. FT-IR spectra νmax 3330, 3250, 3010, 1694, 1618, 1466, 1210, 790cm^{-1}.^{1}HNMR spectra δppm, (7.3,5H), and (8.1,1H)s.^{13}CNMR spectra δppm, , 107, 110, 113, 113, 114, 115,125, 127, 142, 145, 151, 164.

(II)c yield 91%, Melting point 145-147^{o}C, CHN analysis that formula $C_{22}H_{20}N_3ClO$ calculated C, 69.933 H, 5.332 N, 11.12; Found C, 69.885 H, 5.212 N, 10.994. Ultraviolet spectra λmax 230, 242, and 300. FT-IR spectra νmax 3380, 3210, 3100. 2988, 1688, 1612, 1375, 1220, 810cm^{-1}.^{1}HNMR spectra δppm, (7.3,5H), and (8.1,1H)s.^{13}CNMR spectra δppm, 107, 110, 113, 113, 114, 115,125, 127, 142, 145, 151, 164.

(II)d yield 85%, Melting point 215-217^{o}C, CHN analysis that formula $C_{22}H_{20}N_4O_3$ calculated C, 68.033 H, 5.198 N, 14.424; Found C, 67.885 H, 5.063 N, 14.215. Ultraviolet spectra λmax 230, 250, and 320. FT-IR spectra νmax 3350, 3180, 3050, 1693, 1600, 1384, 1200, 851cm^{-1}.^{1}HNMR spectra δppm, (7.3,5H), and (8.1,1H)s.^{13}CNMR spectra δppm, , 107, 110, 113, 113, 114, 115,125, 127, 142, 145, 151, 164.

3) Synthesis of Thaizolidinone (III) a-d

A mixture of (1mmole) Schiff base and mercaptoacetic acid (15ml) in 40ml dry benzene, 2g of zinc chloride was added and placed in small conical flask at room temperature then the mixture exposed to microwave irradiation at 180w for 3min, This reaction was monitored by TLC. The resultant solution was cooled and poured in cold water. The separated solid was filtered, crystallized from ethanol to give crystalline yellow.

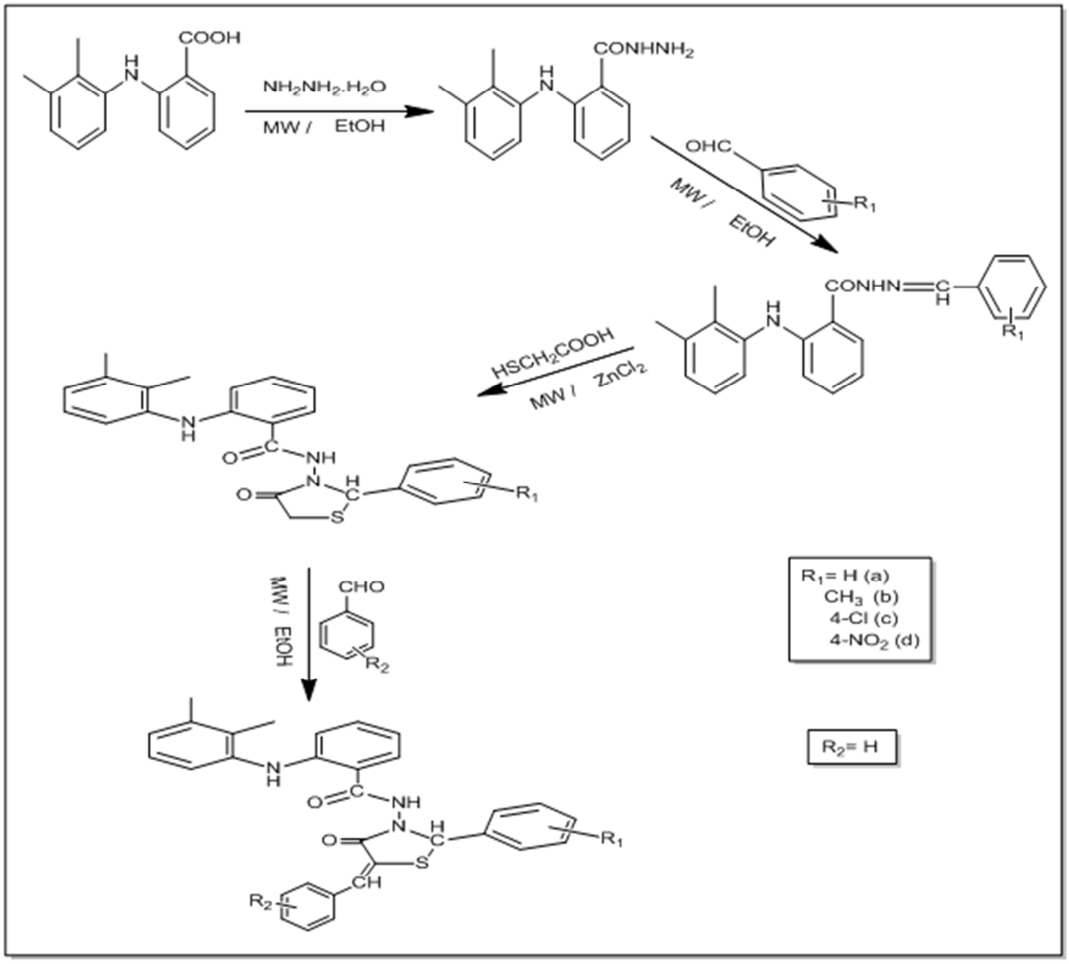
(III)a yield 77%, Melting point 200-201^{o}C, CHN analysis that formula $C_{24}H_{23}N_3O_2S$ calculated C, 69.042 H, 5.553 N, 10.067 S, 7.683 ; Found C, 68.965 H, 5.382 N, 9.894 S, 7.254. Ultraviolet spectra λmax 218, 245,285 and 325 nm. FT-IR spectra νmax 3335, 3250, 3113, 1750, 1690, 1620, 1533, 1190, 768cm^{-1}. ^{1}HNMR spectra δppm, (2,3H)s, (2,3H)s, (4,1H)s, (6.8,3H)t , (7.3,5H)d ,(7.5,3H)d and (8.4,1H)s .^{13}CNMR spectra δppm, 52, 55, 92, 114, 118, 120, 121, 123, 129, 130, 158, 158, 163, 163, 170.

(III)b yield 86%, Melting point 195-196^{o}C, CHN analysis that formula $C_{25}H_{25}N_3O_2S$ calculated C, 69.853 H, 5.842 N, 9.747 S, 7.433; Found C, 69.574 H, 5.554 N, 9.457 S, 7.211. Ultraviolet spectra λmax 230, 245, 277 and 340 nm. FT-IR spectra νmax 3330, 3220, 3010, 1730, 1692, 1620, 1500, 1175, 961cm^{-1}. ^{1}HNMR spectra δppm, (2,3H)s, (2,3H)s, (2,3H)s (4,1H)s, (6.3,3H)t , (7.2,5H)d ,(7.7,3H)d and (8.1,1H)s .^{13}CNMR spectra δppm, 50, 55, 91, 116, 118, 120, 121, 125, 129, 130,,133, 158, 159, 163, 168, 181.

(III)c yield 75%, Melting point 176-178^{o}C, CHN analysis that formula $C_{24}H_{22}N_3O_2ClS$ calculated C, 63.783 H, 4.911 N, 9.304 S, 7.094; Found C, 63.745 H, 4.662 N, 9.015 S, 6.881. Ultraviolet spectra λmax 240, 255, 288 and 330 nm. FT-IR spectra νmax 3300, 3212, 3050, 1730, 1693, 1612, 1512, 1180, 775cm^{-1}. ^{1}HNMR spectra δppm, (2.2,3H)s, , (2.4,3H)s (4.2,1H)s, (6.8,3H)t , (7.5,5H)d ,(7.9,3H)d and (8.3,1H)s .^{13}CNMR spectra δppm, 44, 51, 89, 116, 119, 121, 125, 129, 130, 133, 152, 159, 163, 170, 181.
(III)d yield 91%, Melting point 222-224oC, CHN analysis that formula $C_{24}H_{22}N_4O_4S$ calculated C, 62.325 H, 4.792 N, 12.117 S, 6.933; Found C, 62.114 H, 4.456 N, 11.914 S, 6.710. Ultraviolet spectra λmax 230, 245, 275 and 320 nm. FT-IR spectra νmax 3380, 3222, 3080, 1730, 1691, 1598, 1499, 1118, 886cm^{-1}. ^{1}HNMR spectra δppm, (2.1,3H)s, (2.4,3H)s (4.1,1H)s, (6.2,3H)t , (7.0,5H)d ,(7.5,3H)d and (8.0,1H)s .^{13}CNMR spectra δppm, 42, 49, 87, 115, 118, 123, 127, 128, 129, 135,,138, 158, 161, 167, 170, 183.

4) Synthesis of Chalcone (VI) a-d
A mixture of (1mmole, 1.57gm) from thaizolidinone(III) compounds and 10ml of benzaldehyde in 40ml ethanol and (25ml) of 10% potassium hydroxide, then the mixture exposed to microwave irradiation at 180w for 3min., this reaction was monitored by TLC. The mixture was cooled in ice to participate the solid white crystal, the participate solid was filtered and recrystallized from ethanol.
(VI)a yield 72%. Melting point 212-214^{o}C, CHN analysis that formula $C_{31}H_{27}N_3O_2S$ calculated C, 73.644 H, 5.384 N, 8.315 S, 6.342; Found C, 73.505 H, 5.114 N, 8.098. Ultraviolet spectra λmax 232,245, 290, and 310nm. FT-IR spectra νmax 3340, 3224, 3013, 1755, 1690, 1618, 1440, 1155, 960 cm^{-1}. ^{1}HNMR spectra δppm, (2.1,3H)s, (2.4,3H)s (4.1,1H)s, (6.8,3H)t , (7.2,5H)d, (7.3,4H)d, (7.5,3H)d and (8.3,1H)s .^{13}CNMR spectra δppm, 42, 45, 49, 87, 115, 118, 123, 127,128, 128, 129,133,134, 135, 138,155, 158, 161, 167, 170,177, 183.
(VI)b yield 86%. Melting point 188-190^{o}C, CHN analysis that formula $C_{32}H_{29}N_3O_2S$ calculated C, 73.961 H, 5.624 N, 8.091 S, 6.173; Found C, 73.757 H, 5.356 N, 7.898. Ultraviolet spectra λmax 230,255, 285, and 330nm. FT-IR spectra νmax 3350, 3244, 3010, 1730, 1693, 1600, 1450.1122, 880cm^{-1}. ^{1}HNMR spectra δppm, (2.0,3H)s, (2.1,3H)s (2.4,3H)s , (4.1,1H)s, (6.8,3H)t ,(7.0,4H)d, (7.2,5H)d ,(7.5,3H)d and (8.3,1H)s .^{13}CNMR spectra δppm, 42, 44, 48, 55, 86, 118, 119, 125, 127, 128, 133, 135, 138,140,144,149,155, 158, 164, 167, 172,177, 180.
(VI)c yield 81%. Melting point 167-169^{o}C, CHN analysis that formula $C_{31}H_{26}N_3ClO_2S$ calculated C, 68.945 H, 4.854 N, 7.784 S, 5.945; Found C, 68.778 H, 4.656 N, 7.521 S, 5.888. Ultraviolet spectra λmax 228,260, 295, and 330nm. FT-IR spectra νmax 3325, 3212, 3050, 1725, 1692, 1615, 1400, 1105, 977cm^{-1}. ^{1}HNMR spectra δppm, (2.1,3H)s, (2.4,3H)s (4.2,1H)s, (6.4,3H)t ,(7.2,4H)d (7.4,5H)d ,(7.9,3H)d and (8.1,1H)s .^{13}CNMR spectra δppm, 40, 45, 53, 87, 117, 118,120, 123, 127, 128, 129, 135, 138,141,144, 148, 158, 161, 171, 174,177, 181.
(VI)d yield 81%. Melting point 167-169^{o}C, CHN analysis that formula $C_{31}H_{26}N_4O_4S$ calculated C, 67.625 H, 4.765 N, 10.184 S, 8.823; Found C, 67.505 H, 4.327 N, 9.991 S, 8.658. Ultraviolet spectra λmax 231,258, 292, and 315nm.FT-IR spectra νmax 3400, 3280, 3100, 1735, 1691, 1599, 1410, 1130, 812 cm^{-1}. ^{1}HNMR spectra δppm, (2.0,3H)s, (2.3,3H)s (4.0,1H)s, (6.6,3H)t (6.9,4H), (7.1,5H)d ,(7.5,3H)d and (8.1,1H)s .^{13}CNMR spectra δppm, 49, 52, 55, 90, 118, 121, 123, 127, 130, 133, 135, 138, 140,144, 149,155,158, 166, 169, 171,175, 179.

RESULT AND DISCUSSION:
Mefenamic acid derivatives form a group of generally less investigated compounds. However, recently growing efforts are made to synthesize and characterized these compounds. Many mefenamic acid derivatives possess very promising properties regarding biological activities as shown in literature survey. In the present research, project the conventional methods to prepare some mefenamic acid compounds with expected biological activity.



Scheme 1

The objective of this work is the synthesis of new heterocyclic compound by using percyclic reaction between new imine with mercapto acetic acid [Vazzanaa et al, 2004, Elkanzi, 2013] in benzene; these compounds may have biological effects besides being prepare for this time.

The reaction carry out by microwave oven, the first step included replacement hydroxyl group of acid by hydrazine, then the aromatic aldehyde were condensate with the acyl hydrazide compound to give Schiff base according to well-known procedure [Ummathur et al, 2009, Qin et al, 2013] was reacted with mercapto acetic acid to produce five membered heterocyclic compound of thaizolidinone and then condensate with benzaldehyde to give chalcone compounds, it show in scheme (1).

The electron withdrawing groups in the aldehyde led to decreasing the electron density at the carbon atom of carbonyl, so the electrophilic properties were enhance, therefore increase positive charge of the carbon of carbonyl and make easy to attack by the nucleophilic, whereas, these factors increased the yields of products.

The structures of the synthesized compounds (II-VI)a-d were confirmed by their elemental analysis, UV, IR, and NMR. CHN were situated within the range which confirmed the validity of the suggested structure of the prepared compounds. The purification compounds were tested by thin layer chromatography (TLC) using different eluents. The best separation was obtained in mixture of (benzene: methanol) (3:7) respectively as eluent. Then, the compounds were purified by using ethanol.

UV spectrum [Al-Jumali, 2006] for Schiff bases (II) showing the three band at (220-330) nm were due to transition (π-π^*) aromatic ring. While the compound thaizolidinones (III) and chlcones (VI) which showing four band at (218-340)nm were due to interferences transition (π-π^*) aromatic heterocyclic ring with aromatic benzene ring addition to (n-π^*) for carbonyl group come back to thaizolidinone compound (III) and transition (π-π^*) for double bond come back to chalcone compound (VI) .

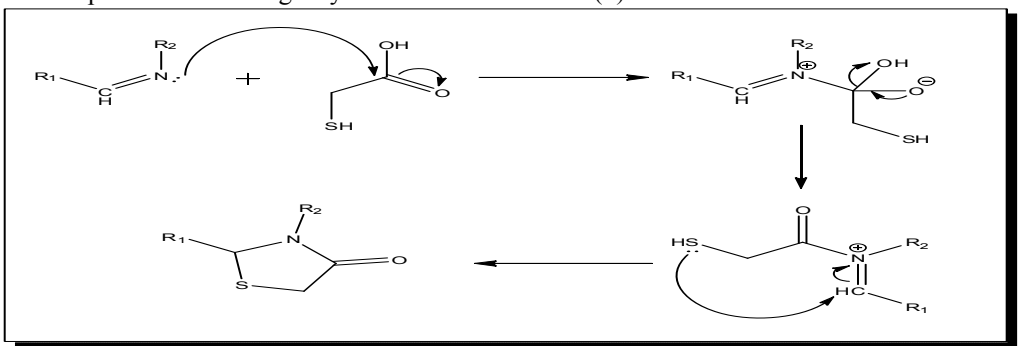
The structures of synthesized compounds were determined on the basis of their FTIR [Al-Juburi, 2012], The intense band at (1600-1620) cm^{-1} in compounds $(II)_{a-d}$ confirmed to the stretching vibrations for the C=N group. Cyclisation with mercaptoacetic acid gave compound $(III)_{a-d}$, these were characterized as the carbonyl group and C-S-C linkage vibrations, hence confirming the process of cyclisation. This compound showed the appearance of new vibration mode at (1720-1750) cm^{-1}, which was characterized as the peak for carbonyl group,

and (1118-1190) cm^{-1} for C-S. The formation of compound $(VI)_{a-d}$ was confirmed by appearance of new vibration modes at (1400-1440) cm^{-1} and (1105-1150) cm^{-1} which were characterized as the peaks for C=C and C-S. The IR spectra of these compounds showed a strong infrared absorption band in the region between (3224-3430) cm^{-1} due to NH stretching and a strong band in the region between (1680-1693) cm^{-1} due to carbonyl group of amide .

^{1}HNMR [Rudrapal et al, 2013, Al-Hazam, 2014] appears several signals for compounds $(II-VI)_{a-d}$ showed at the region (6.3-8.3)ppm for the aromatic benzene rings addition to signal of proton azomethine, The CH_2 group of the thaizolidinone nucleus in (III) appears signal at δ (2.0-2.3)ppm, in addition to signals for the CH_3 at (2.0-2.4)ppm, which exist in skeleton of mefenamic acid.

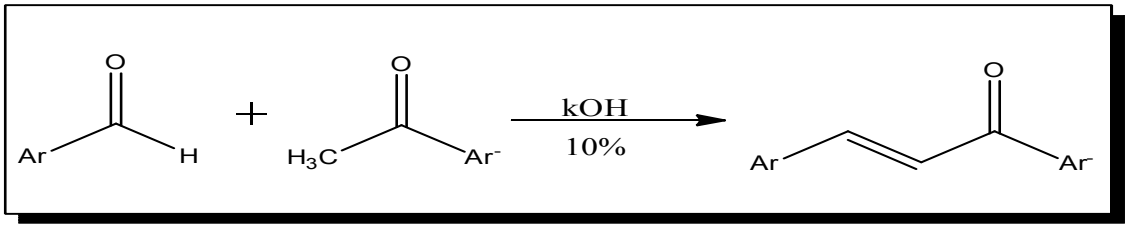
^{13}CNMR signals [Elarft et al, 2012, Al-Mosawi, 2014] appears 12 line according to 12 carbon atom exist in the structure of Schiff bases except the equivalents, thaizolidinone compounds were appears 15 line according to 15 carbon atom exist in the structure and appears 19 line according to 19 carbon atom come back to chalcone compounds.

Mechanism of the percyclic reaction between an imine group and mercaptoacetic acid for preparing thaizolidinone ring systematically investigated. The breaking and formation of bonds occur simultaneously and thus the reaction proceeds via a single cyclic as show in scheme (2).



Scheme 2

The synthesis of chalcone was accomplished according to the Claisen-Schmidt condensation [Elarft et al, 2012] of ketones with aromatic aldehydes under heating reaction as indicate to scheme (3).



Scheme 3

Several strategies for the synthesis of the system based on the formation of carbon-carbon bond have been reported. Among them the direct aldol condensation and Claisen-Schmidt condensation still occur prominent position. The main method for the synthesis of Chalcones is the classical Claisen-Schmidt condensation in presence of aqueous alkali [Al-Mosawi, 2014] however of this methods suffered from harsh reaction conditions, toxic, reagents, strong acid or base condition, prolonged reaction time, poor yield and low selectivity. Although, several modification have been made to counter these problems. There is a still a need for the development of selective and better strategies for the synthesis of α and β unsaturated carbonyl compounds.

BIOLOGICAL ACTIVITIES

The antibacterial [Al-Shamkhani and Al-Hazam, 2015] activities of the series [II-VI] have been carried out against some strain of bacteria. The result [Table 1] showed that prepared compounds are toxic against the bacteria. The compounds (III)a-d were found more active against the above microbes. The comparison of the antibacterial activity of these compounds with Streptomycin shows that these compounds have almost similar activity.

The bacterial cultures for S. aurous, and E. coli were obtained from Department of biology University of Basrah. Iraq. The bacterial cultures were incubated at 30^{o}C for 24 hours by inoculation into nutrient agar. Schiff bases and azetidinone were stored dry at room temperature and dissolved 20mg/ml in dimethyl sulfoxide [DMSO]. Antibacterial activities of each compound were evaluated by the agar disc-diffusion method. Mueller Hinton Agar Media [15 cm^3] kept at 45^{o}C was poured in the petridishes and allowed to solidify. Poured Petri

plates [9 cm] were incubated with 50µL of normal saline solution of above culture media [105-106 bacteria per ml]. Discs injected with prepared Schiff bases and azetidinone [50µL] were applied on the solid agar medium by pressing tightly. The Petri plates were placed at 37°C for 24 hours. At the end of period, the inhibition zones formed on media were measured with a zone reader in millimetres.

Table 1: The antibacterial activities of the compounds [II-VI] Antibacterial data in MIC[µg/ml]

Compound	E. Coli [gram –ve]	Staphylococcus aurous[gram +ve]
IIa	6	10
IIb	7	X
IIc	12	10
IId	10	12
IIIa	13	11
IIIb	14	15
IIIc	X	3
IIId	13	14
VIa	8	X
VIb	7	9
VIc	5	X
VId	X	6
Streptomycin standard	12	9

X=zero activity

CONCLUSION

From the above-mentioned results it is concluded that microwave assisted synthesis has proved to be fast and highly efficient method for the synthesis of Schiff's base, thaizolidinone and chalcone compounds. It has resulted in better yields of the desired products when compared with yield obtained under conventional conditions**.**

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