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Comparative studies on Conventional -Microwave assisted synthesis of 2-azetidinone derivatives

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Abstract: *A series of 2-Azetidinone (3a-3f) were synthesized, the structure of these new derivatives were confirmed using spectral methods starting from Hydrazide derivative of Ketoprofen ethyl ester a Schiff bases were synthesized using different aromatic aldehydes in ethanol which prepared by the conventional and the microwave methods then Determination of the Microwave optimum conditions for Schiff bases synthesis, and the final compounds were obtained by cyclocondensation using chloroacetylechloride also by the conventional and the microwave method then Determination Microwave optimum conditions for the final compounds synthesis. The synthesis of the designed compounds has been successfully achieved. Purity and characterization were confirmed by determination of physical properties (melting points & R_f values), FT-IR spectroscopy and ^{1}H-NMR Sp.*

Key wards: *Microwave, Schiff base, 2-Azetidinone*

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I. Introduction

Microwave irradiation is becoming a very popular method for heating samples in the chemistry laboratories. It provides a cheap, convenient and clean heating technique which usually gives more yield and less time for the reaction [1&2]. Dielectric microwave heating result's uses the capability of some solids or liquids to convert the electromagnetically energies to heat and so initiate reactions (chemical ones). This insitu kind of power transformation has several advantages for the chemist [3]. There are different means for achieving microwave boosted reactions of organic kind either by means of home ovens or lab reactors that was usually known as microwave-induced organic reaction enhancement (MORE) chemistries [4&5]. In a high boiling point solvents such as dimethylformamide (DMF) Heating rate is high, yet maximum temperature must be selected beneath the point of boiling of the solvents to evade evaporation of the solvent. The chemist can do this in open vessels for reactions and can select a minimum quantity of solvents when aiming for the solubility at the specified temperature of the reaction [6&7]. Microwave energy is a spectrum in the same way as the visible light, UV irradiation and infrared irradiation, Microwaves occur in the region of spectrum from approximately 300–300,000 MHz, just below the quantum energy of the infrared irradiation, This means microwave energy doesn't have the quantum energy which is necessary to form or break chemical bonds [8]. There isn't even enough quantum energy in microwaves for the rotation or vibration of the chemical bonds, the energy simply causes the molecules to orient along their dipole moment of the electric field. Since the electric field oscillates billions of times in a second, the molecule is in constant motion trying to align with the field [9]. This motion causes friction, which result a heat generation or an increase in the temperature around this molecule that is rapidly dissipated in the bulk solution with the microwave energy that can be achieved, the temperatures needed to cause the chemical conversion without the conditions that will cause molecular degradation. This will allow chemistries to take place especially those who will not react or only occur minimally under normal or conventional conditions [10&11]. Three principal heating methods exist: Dipolar polarization [12], Conduction mechanisms [13] and interfacial polarization [14].

There are many differences between the Microwave heating and conventional heating. The mechanism behind this microwave synthesis is quite different from any conventional synthesis. As shown in Table (1) [15&16].

Table (1): differences between the microwaves heating from the conventional heating

entry	conventional heating	Microwave heating
A	The heating path of the reaction pass from the outer surface to the inner surface of the vessels	The heating occur directly to inside the mixture
B	The vessels should be directly contacted to the surface of the heating source of higher temperature	The direct contact with the higher temperature source when the vessel is kept in the microwave cavity
C	The heating occur through using electrical or thermal source of heat	The heating occur by electromagnetic waves
D	Conduction is the only mechanism for heating	The heating mechanisms involve dielectric polarization and conduction and interfacial polarization
E	The energy transfer from the source to the wall of the vessel to the mixture then to the reacting particles	The mixture reacting particles is heated directly while the vessel wall is the source of heat loss
F	The maximum temperature of the reaction can be achieved is limited by the boiling point of the solvent	The temperature of the reaction can be raised above the boiling point of the solvent and achieve superheating
G	All the components of the mixture is heated equally	The reaction particles each is heated specifically
H	The speed of heating is raised slowly and gradually	The speed of heating is very much faster than the conventional way

The microwave-induced organic reaction enhancement (MORE) was grew huge acceptance as a not ordinary technique of the organic rapid synthesis in the past few years and many researchers have described an accelerated reaction rates with a big number of papers that had been appeared proving the synthetic utility of MORE chemistry in the day to day organic synthesis. It can be termed as e-chemistry because it's easy, economical, effective and eco-friendly. It is believed to be a step toward achieving the green chemistry objectives [(17)]. The efficiency of M.W. flash-heating results in a dramatic reduction in reaction time and the time saved by such approach is potentially important in the conventional organic synthesis [(18)]. Azetidin-2-ones had attracted the attention of many researchers to investigate this skeleton due to its multiple potential against several activities especially because of the antibacterial characteristics of cephalosporins and penicillin [19]. In the recent years the interest was focused on the modification and synthesis of β-lactam ring to have compounds with diverse pharmacological activities like blockers of prostate specific antigens, thrombin, cholesterol absorption, human cytomegalovirus protein, human leukocyte cysteine protease and elastase [20]. As a consequence, the interest of the organic chemists in the synthesis of many new β-lactam derivatives remains high [21]. Some of these derivatives also had been found to be active moderately against several kinds of cancer [22]. New azetidinone bioactive agents have been synthesized with expected selectivity against COX-2 enzyme using naproxen and 2-azetidinone as Pharmacophores, figure (1).The Preliminary study of their anti-inflammatory activity showed that these synthesized compounds exhibited equivalent or better effect than naproxen. Also there antibacterial activity is more than Naproxen. Moreover the preliminary cytotoxic activity study of these compounds showed highly significant effect, and may represent an exploitable source of new anticancer agent more than Naproxen [23]

II. Experimental

Physical measurements:

Melting points are determined on an electro-thermal melting point apparatus (Stuart, Germany), and they are uncorrected. Completion of reaction and purity of all compounds are checked on aluminum coated TLC plates 60 F_{245} (E.Merck) using Methanol: Acetic acid: Ether: Benzene (05:15:60: 20) [24]. As the mobile phase and visualized under iodine vapor.^{1}HNMR spectra are recorded on Bruker (400 MHZ) spectrophotometer, using DMSO-d_6 as a solvent and TMS as an internal standard. The chemical shifts are reported in parts per million (ppm).FT-IR spectra were recorded as KBr discs on Shimadzu FT-IR 8400S spectrophotometer. All reactions and the purity of the synthesized compounds were monitored by using TLC (silica gel).

A- General procedure for the Schiff's bases compounds (2a-2f).

Conventional method:

To a stirred solution of compound [1] (0.01 mole, 0.5 g) in (30 ml) ethanol, various aromatic aldehydes (0.01mole) were added, after which the mixture was heated at 90-95 ^{0}C 6-8 hours until the completion of the reaction (TLC monitoring using ethyl acetate and n-hexane 3to1 ratio). The combination were chilled to normal lab temperature. A residue were poured on crushed ice, The solid crystals gained and splashed using water then recrystallization by using water and ethanol (3:7) [(25)].

Microwave method:

Mixture of compound [1] (0.01 mole, 0.5g), aromatic aldehyde (0.01 mole) and 2 drops of the few amount of acetic acid (glacial) as a catalyst was token in (2 ml) Ethanol by the microwave vesicle, after that a reaction combination were exposed to microwave radiation by using 180 W for around 6-7min; reaction progression were controlled by (TLC), after the finishing the reaction completely, the gained materials was

transferred onto cold icy water and mixed well while a separated solids had a filtration and washing with extra amounts of methanol then afterward dried out at normal lab temperature [26&27].

(Z)-2-(3-benzoylphenyl)-N-(2-(2-benzylidenehydrazinyl)-2-oxoethyl)propanamide (2a):
$C_{25}H_{23}N_3O_3$, , faint yellow powder; yield 40.33%; sticky ,R_f 0.69; IR (KBr, m, cm^{-1}): 3107.43 ν(C-H , aromatic), 2931.90, 2852.81 ν(C-H , aliphatic), 3327.32 ν(NH) , 1701.08 ν(CO), 1656.91 ν(C=N) , 1602.90 ν(C=C);^{1}H NMR (DMSO, 400 MHz) δ: 1.57 (3H, d, CH_3), 3.75 (1H, q, CH), 4.51 (2H,d ,CH_2) , 7.48- 7.88 (11H ,m, Ar-H), 8.44 (1H ,s, NH), 8.59 (1H ,s, NH attached to imine), 8.11 (1H ,s, CH=N).

(Z)-2-(3-benzoylphenyl)-N-(2-(2-(4-chlorobenzylidene)hydrazinyl)-2-oxoethyl) propanamide(2b)
$C_{25}H_{22}ClN_3O_3$, Yellow crystals; yield 52.61%; mp.193-198 ^{0}C ,R_f 0.79; IR (KBr, m, cm^{-1}): 3061.13 ν(C-H , aromatic), 2974.33 ,2931.91 ν(C-H , aliphatic), 3327.32 ν(NH) , 1693.56 ν(CO), 1654.98 ν(C=N) , 1089.82 ν(C-Cl);^{1}H NMR (DMSO, 400 MHz) δ: 1.57 (3H, d, CH_3), 3.75 (1H, q, CH), 4.51 (2H,d ,CH_2) , 7.25- 7.78 (11H ,m, Ar-H), 8.57 (1H ,s, NH), 9.23 (1H ,s, NH attached to imine), 8.11 (1H ,s, CH=N).

(Z)-2-(3-benzoylphenyl)-N-(2-(2-(4-(dimethylamino)benzylidene)hydrazinyl)-2oxoethyl) propanamide(2c):
$C_{27}H_{28}N_4O_3$,Orange crystals; yield 65.04 %; mp.170-175^{0}C , R_f 0.70; IR (KBr, m, cm^{-1}): 3059.20 ν(C-H , aromatic), 2970.84 , 2929.97 ν(C-H , aliphatic), 3298.83 ν(NH), 1683.97 ν(CO), 1656.91 ν(C=N) , 1602.91 ν(C=C) ;^{1}H NMR (DMSO, 400 MHz) δ: 1.57 (3H, d, CH_3), 3.75 (1H, q, CH), 4.51 (2H,d ,CH_2) , 7.28- 7.91 (11H ,m, Ar-H), 8.59 (1H ,s, NH), 9.01 (1H ,s, NH attached to imine), 8.11 (1H ,s, CH=N).

(Z)-2-(3-benzoylphenyl)-N-(2-(2-(4-hydroxybenzylidene)hydrazinyl)-2oxoethyl)propanamide(2d)
$C_{25}H_{23}N_3O_4$,Faint yellow crystals; yield 44.63 %; mp.99-104 ^{0}C , R_f 0.72; IR (KBr, m, cm^{-1}): 3066.92 ν(C-H , aromatic), 2976.26 , 2935.76 ν(C-H , aliphatic), 3225.09 ν(NH) , 3413.82 ν(OH) , 1678.13 ν(CO), 1653.05 ν(C=N) , 1604.83 ν(C=C) ;^{1}H NMR (DMSO, 400 MHz) δ: 1.61 (3H, d, CH_3), 3.77 (1H, q, CH) , 4.44 -4.52 (2H,d ,CH_2) , 7.28- 7.82 (12H ,m, Ar-H), 8.13 (1H ,s, NH), 8.38 (1H ,s, OH), 9.55 (1H ,s, CH=N).

(Z)-2-(3-benzoylphenyl)-N-(2-(2-(4-methoxybenzylidene)hydrazinyl)-2oxoethyl)propanamide(2e):
$C_{26}H_{25}N_3O_4$,off white crystals; yield 61.19 %; mp.146-150^{0}C , R_f 0.69; IR (KBr, m, cm^{-1}): 3068.85 ν(C-H , aromatic), 2929.97 , 2847.97 ν(C-H , aliphatic), 3325.39 ν(NH) , 1255.7 ν(OCH_3) , 1681.98 ν(CO), 1658.84 ν(C=N) , 1602.60 ν(C=C) ;^{1}H NMR (DMSO, 400 MHz) δ: 1.56 (3H, d, CH_3), 3.7 (1H, q, CH) , 3.89 (3H,s ,OCH_3) , 7.28- 7.96 (11H ,m, Ar-H), 8.28 (1H ,s, N=CH), 8.57 (1H ,s, NH), 9.61 (1H ,s, N<u>H</u>-N=CH).

(Z)-2-(3-benzoylphenyl)-N-(2-(2-(4-nitrobenzylidene)hydrazinyl)-2-oxoethyl) propanamide(2f) :
$C_{25}H_{22}N_4O_5$,Pale green crystals; yield 70.08 %; mp.110-116^{0}C , R_f 0.61; IR (KBr, m, cm^{-1}): 3045.50 ν(C-H , aromatic), 2933.83, 2854.74 ν(C-H , aliphatic), 3248.88 ν(NH) , 1537.32 ,1348.29 ν(NO_2) , 1697.41 ν(CO), 1654.98 ν(C=N) , 1602.90 ν(C=C);^{1}H NMR (DMSO, 400 MHz) δ: 1.57 (3H, d, CH_3), 3.75 (1H, q, CH), 4.51 (2H,d ,CH_2) , 7.54- 8.45, 9.50 (1H ,s, NH attached to imine), 8.11 (1H ,s, CH=N).

General procedure for the 2-Azetidinone compounds (3a-3f).
Conventional method

To a solution of [2a -2f] (0.001 mole) in (25 ml) anhydrous 1,4-dioxane chloroacetylchloride (0.0015 mole, 0.169 g) and triethylamine (TEA) (0.001 mole, 0.101 g) were added drop wise in a period of 20 min at 0–5 °C . The mixture of reaction was stirred at room temperature for 3 hours and the solid (triethylamine hydrochloride) was removed. The solution was heated under reflux for 5 hours and then the solvent were vaporized by low pressure conditions. The solid product were washed by using (10 ml) water, filtered off, dried and recrystallized from absolute ethanol [28].

Microwave method

A (0.01 mole) Schiff base mixture in (3 ml) Dimethyl formamide (DMF) was taken in a conical flask cooled to 5-10 0C and (0.01mole, 1.2 g) Chloroacetylechloride and (0.01mole, 1.011g) TEA was cooled and added drop by drop to the previous mixture in a period of 10 minutes at low temperature . The total mixture was irradiated by microwave device for 8 minutes W180 [29&30].

2-(3-benzoylphenyl)-N-(2-((3-chloro-2-oxo-4-phenylazetidin-1-yl)amino)-2-oxoethyl)propanamide (3a):
$C_{27}H_{24}ClN_3O_4$, Dark Yellow sticky matter ; yield 43.37 %;, R_f 0.74, IR (KBr, m, cm^{-1}): 1681.98 ν(C=O), 1737.92 ν(C=O), 788.91ν(C-Cl) ;^{1}H NMR (DMSO, 400 MHz) δ:4.53 (1H, d, CH-Ar of Azetidin) 5.15 (1H, d, CH-Cl of Azetidine).

2-(3-benzoylphenyl)-N-(2-((3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)amino)-2-oxoethyl) propanamide(3b):
$C_{27}H_{23}Cl_2N_3O_4$, Yellow crystals, yield 31.60 %; mp.78-82^{0}C;, R_f*0.88*IR (KBr, m, cm^{-1}): 1658.84ν(CO), 1724.59ν(C=O), 790.84ν(C-Cl) ;^{1}H NMR (DMSO, 400 MHz) δ: 4.67 (1H, d, CH-Ar ofAzetidin) 5.47 (1H, d, CH-Cl of Azetidine).

2-(3-benzoylphenyl)-N-(2-((3-chloro-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-1-yl)amino)-2-oxoethyl)propanamide (3c) :
$C_{29}H_{29}ClN_4O_4$, Dark red crystals, yield 68.41 %; mp.94-98^{0}C; $R_{f\ 0.61}$IR (KBr, m, cm^{-1}):1645.98 ν(C=O), 1732.13ν(C=O), 790.84ν(C-Cl) ;^{1}H NMR (DMSO, 400 MHz) δ: 4.82 (1H, d, CH-Ar of Azetidin) 5.27 (1H, d, CH-Cl of Azetidine).

2-(3-benzoylphenyl)-N-(2-((3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl)amino)-2-oxoethyl)propanamide (3d):
$C_{27}H_{24}ClN_3O_5$,Yellowish brown crystals, yield 35.04 %; mp.80-85^{0}C, R_f*0.76* IR (KBr, m, cm^{-1}): 1654.98ν(C=O), 1734.06 ν(C=O), 788.91ν(C-Cl) ;^{1}H NMR (DMSO, 400 MHz) δ: 4.82 (1H, d, CH-Ar of Azetidin) 5.54 (1H, d, CH-Cl of Azetidine).

2-(3-benzoylphenyl)-N-(2-((3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)amino)-2-oxoethyl)propanamide (3e) :
$C_{28}H_{26}ClN_3O_5$, Dark brown crystals, yield 36.042 %; mp.69-73^{0}C, R_f*0.91* IR (KBr, m, cm^{-1}): 1654.98ν(C=O), 1732.13ν(C=O), 788.91ν(C-Cl) ;^{1}H NMR (DMSO, 400 MHz) δ: 4.85 (1H, d, CH-Ar of Azetidin) 5.47 (1H, d, CH-Cl of Azetidine).

2-(3-benzoylphenyl)-N-(2-((3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)amino)-2-oxoethyl)propanamide (3f):
$C_{27}H_{23}Cl\ N_4O_6$, Dark green crystals yield 33.08 %; mp.88-92 ^{0}C, R_f*0.92* IR (KBr, m, cm^{-1}): 1697.41ν(CO), 1726.35ν(C=O), 786.98ν(C-Cl) ;^{1}H NMR (DMSO, 400 MHz) δ: 4.46 (1H, d, CH-Ar of Azetidin) 5.83 (1H, d, CH-Cl of Azetidine).

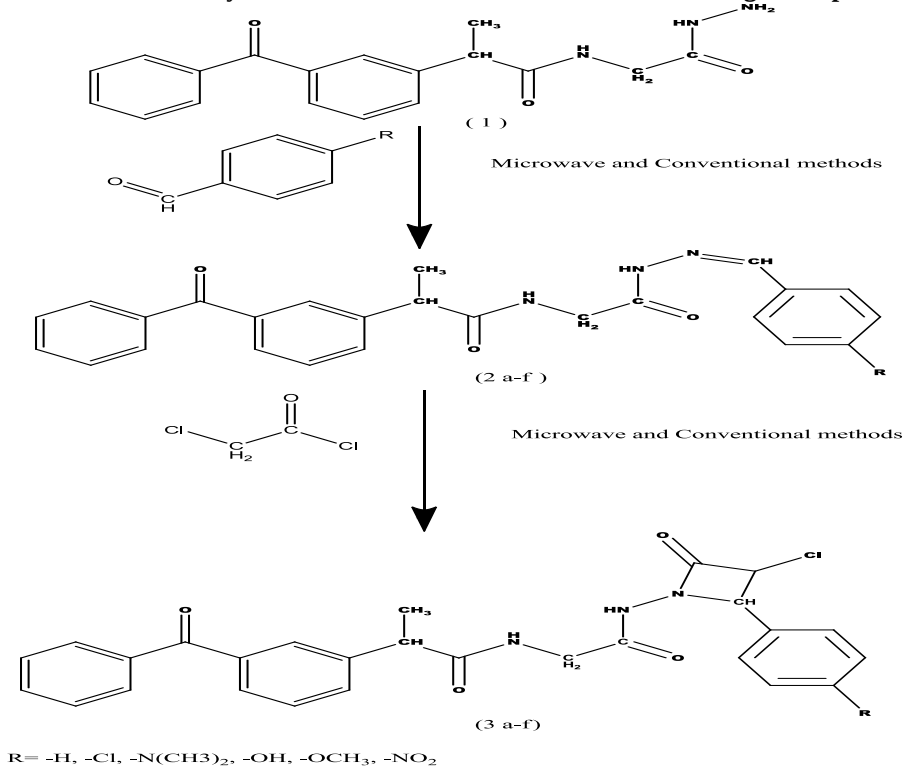
Table (2): characterization and physical properties of the intermediates and the target compounds

Com Num	R	Mol. Formula	Mol. weight	Time / Yield		Color	M.P /˚C	R_f value
				Conventional method	Microwave method			
1	-	$C_{18}H_{19}N_3O_3$	325	24 hr. /62.84%	-	Off-white	60-62	0.38
2a	H	$C_{25}H_{23}N_3O_3$	233	7.5 hr. /40.33%	6 min. /75.05%	Pale-yellow	150-152	0.69
2b	-Cl	$C_{25}H_{22}ClN_3O_3$	447.9	7 hr. /52.61%	6 min. /83.76%	Yellow	195-198	0.79
2c	$N(CH_3)_2$	$C_{27}H_{28}N_4O_3$	456	6.5 hr. /65.04%	6.5 min. /93.24%	Orange	173-175	0.70
2d	-OH	$C_{25}H_{23}N_3O_4$	429	9 hr. /44.63%	7 min. /81.17%	Pale-yellow	100-103	0.72
2e	$-OCH_3$	$C_{26}H_{25}N_3O_4$	443	7.5 hr. /61.19%	7 min. /79.88%	Off-white	147-150	0.69
2f	$-NO_2$	$C_{25}H_{22}N_4O_5$	458	9 hr. /70.08%	7 min. /92.61%	Pale-green	113-116	0.61
3a	H	$C_{27}H_{24}ClN_3O_4$	489.9	9 hr. /43.37%	8 min. /71.92%	Yellow	112-115	0.74
3b	-Cl	$C_{27}H_{23}Cl_2N_3O_4$	524	8.5 hr. /31.60%	7.5 min. /74.66%	Yellow	79-82	0.88
3c	$N(CH_3)_2$	$C_{29}H_{29}ClN_4O_4$	533	8 hr. /68.41%	7 min. /83.18%	Red	95-98	0.61
3d	-OH	$C_{27}H_{24}ClN_3O_5$	505.9	9.5 hr. /35.04%	7 min. /78.83%	Yellowish brown	83-85	0.76
3e	$-OCH_3$	$C_{28}H_{26}ClN_3O_5$	519.9	9 hr. /36.42%	7.5 min. /72.11%	Brown	70-73	0.91
3f	$-NO_2$	$C_{27}H_{23}ClN_4O_6$	534.9	10 hr. /33.08%	8 min. /81.63%	Green	90-92	0.92

III. Result and discussion

Azetidinone derivatives (4a-f) were prepared using the method summarized in scheme (1). First the 2-(3-benzoylphenyl)-N-(2-hydrazinyl-2-oxoethyl) propanamide was reacted by the condensation reaction with various aromatic aldehydes yielded Schiff's bases compounds (2 a-f). Finally, the compounds (2a-f) upon reaction with chloracetylchloride in the presence of trietylamin afforded 2-Azetidinonescompounds (3a-f).

Scheme 1: General synthetic scheme for the intermediates and target compounds



Synthesis of Compounds [2a-2f]; Formation of Schiff base.

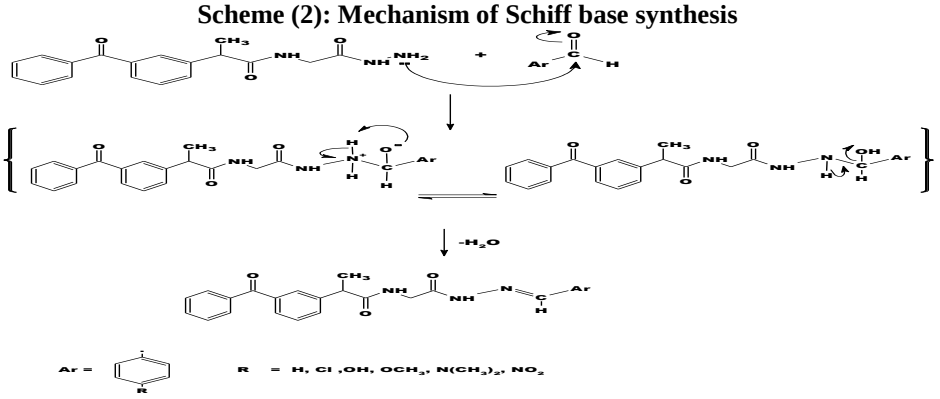
The reaction of aromatic aldehyde with acid hydrazide is the most common reactions to synthesize hydrazone compound (Schiff base or imine). Imines were made by using acid catalysis by reversible process which begins with neucleophilic addition of a primary amine to the carbonyl group, then transferring the proton to the oxygen from nitrogen to produce carbinolamine or which is neutral amino alcohol. Protonation of the carbinolamine oxygen through the use of an acid catalyst after that converts the (–OH) into a better leaving group (-OH2), and loss of water produces an iminium ion. Loss of a proton from nitrogen gives the final product and regenerates the acid catalyst as shown in Scheme (2) [(31)].

The structure of compounds [2a-2f] was identified by melting point and R_f values given in Table (2). FT-IR shows characteristic absorption bands at 3327.32-3225.09 cm^{-1} is for υ_{NH} stretching of amide , bands in region 1701.08-1678.13cm^{-1}refer to $\upsilon_{C=O}$ stretching of amidic and ketone group which combination band of $\upsilon_{C=O}$ stretching of amide and $\upsilon_{C=N}$ stretching at region 1658.84-1653.05 cm^{-1}.

^{1}H-NMR spectra of compound [2a-2f], showed the broad singlet at (8.48- ppm) integrated for NH amide proton ,The spectrum also shows signal at (9.01- ppm) integrated for one proton assigned for the proton of imine (CH=N) group.

The reaction proceeds by means of attack (nucleophilic type) of the amino-group which is located on the carbonyl carbon atom of the aldehyde group with loss of water molecule [(32)]. The mechanism may be outlined as follows in scheme (2)

Scheme (2): Mechanism of Schiff base synthesis



Determination Microwave optimum conditions for Schiff bases:

In the present study, Schiff base of Ketoprofen derivatives [2a-2f] were synthesized using both conventional and microwave-assisted methods. Detailed information on these methods is given in the Experimental section. For the microwave-assisted method, the reaction of hydrazide [1] with different Para-substituted benzaldehydes was carried out at [50W - 100W - 150W - 200W - 250W and 300W] for 2 min in the synthesis of [2c] (because it have the highest yield in the conventional method) to optimize the reaction of microwave irradiation (MWI) power. The obtained results showed that the yield of product [2c] was improved as the MWI power increased from 50 W to 200 W but as the MWI power continued to increase the yield of the products decreased as shown in table (3), which encouraged us to continue for further segmentation.

Table (3) The percent yield compression of compounds [2a-2f] with 50-300W time 2 min

Entry.	Power	Yield
1	50	45.25%
2	100	80.77%
3	150	89.21%
4	200	84.01%
5	250	60.97%
6	300	60.05%

The previous study was further segmented to study the most optimum microwave irradiation power between 150W to 200 W and follow up the yield% as illustrated in Table (4), the results obtained referred that 180W was the best power for the synthesis of Schiff base compounds [2a-2f] .

Table (4) the percent yield compression of compounds [2a-2f] with 150-200W time 2 min

Entry.	Power	Yield
1	150	88%
2	160	88%
3	170	90%
4	180	93%
5	190	89%
6	200	84%

Then we determine the optimum time for the reaction of hydrazide [1] with different para-substituted benzaldehyde which was carried out at 4 min, 8min, 12min, 16min and 20min at 180W in the synthesis of [2c] to optimize the reaction time of microwave irradiation. The gained results showed that the yield of product [2c] was improved as the temperature increased and started to decrease after 8 min as shown in table (5), which encouraged us to continue for further segmentation

Table (5) The percent yield compression of compounds [2a-2f] with 180W time range 4-20 min

Entry.	time	Yield
1	4	90%
2	8	93%
3	12	86%
4	16	83%
5	20	79%

The previous study was further segmented by ranging the time scale at 180W and study the most optimum conditions for microwave irradiation and follow up the yield% as illustrated in table (6), the results obtained referred that 180W and time 7 min are the best conditions for the synthesis of schiff bases [2a-2f].

Table (6) The percent yield compression of compounds [2a-2f] with 180W time range 4-8 min

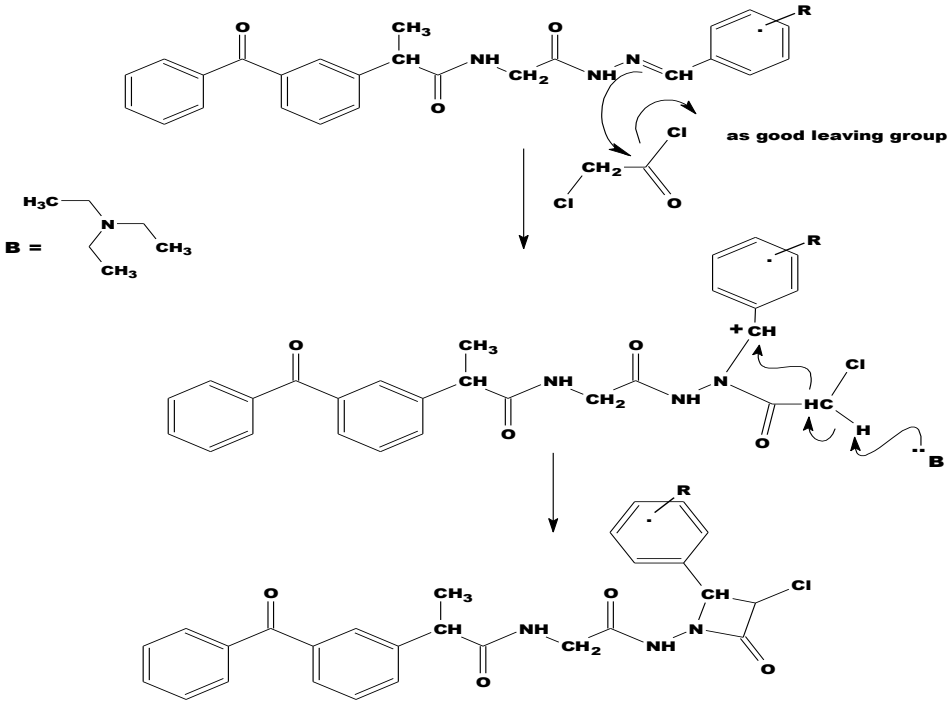
Entry.	time	Yield
1	4	90%
2	5	91%
3	6	93%
4	7	95%
5	8	93%

Synthesis of 2-azetidinones derivatives [3a-3f]

The synthesis of 2-azetidinones was achieved by the reaction different Schiff a simple and efficient method for the synthesis of 2-azetidinones by bases of [2a-2f], with chloroacetylchloride in triethylamine revealed with fairly high yields by conventional and microwave techniques using mild and low cost reagent .

These conditions enable this method to be applicable for the synthesis of 2-azetidinone based heterocyclic. The structure of compounds [3a-3f] was identified by melting point and R_f values given in Table (2). FT-IR characteristic absorption bands of compounds [3a-3f], clearly shows the disappearance of $\upsilon_{N=CH}$ (azomethine group) peak at a range of (1701.08-1678.13cm^{-1}) of compounds [1, 2a-2f] ,and the appearance of carbonyl group of the β- lactam ring as a charachterctic absorption band in the range range of (1737.92-1726.35 cm^{-1}) and υ_{C-Cl} bands in a range (1790.84-786.98cm^{-1}) which confirms that the cyclization reaction with chloracetyl chloride took place in both methods. ^{1}H-NMR spectra of compound [3a-3f], showed the doublet at (4.82-4.85-ppm) integrated for CH-Ar of Azetidinone ,The spectrum also shows doublet signal at (5.27-5.54 -ppm) integrated for CH-Cl of Azetidinone and disappearance of (7.82-8.28 -ppm) broad singlet which belong to N=CH group. The mechanism in Scheme (3) was more probable for the formation of the final compounds. Staudinger's ketene-imine reaction is the most common method for the synthesis of monocyclic 2-azetidinone. β-lactams have been prepared by means of the reaction of acid chloride and imine in the presence of a tertiary amine or a-diazoketone as ketene precursor [(33)]. β-lactam synthesis by adding of the (C=O), (C–N) constituents to make the acetyl chloride's rings with substitution, furthermore withdrawing (electron) substituent and no less than hydrogen (1-atom) on the carbon- α added to imine with a bases (amine) existence. This mechanisms occur by not concerted cyclo-addition interaction as showed via the below schemes.

Scheme (3): Mechanism of 2-azetidinones (β- lactam) synthesis



Determination Microwave optimum conditions for final compounds.

The same study done for the Schiff bases was replied for the final compounds (compound [3c] because it have the highest yield in the conventional method) the optimum power was fixed at 100W and the optimum time was fixed at 8 minutes. The only limitation in this study is the lack of high amounts of the studied compound so we had to reduce the study to be one for optimum power and one for the optimum time as shown in tables (7)&(8).

Table (7) percent yield with 50-250W at time 5 min for synthesis of compounds [3a-3f] using M.W. technique

Entry.	Power	Yield
1	50	80.03%
2	100	87.84%
3	150	81.12%
4	200	77.24%
5	250	sticky

Table (8) percent yield with 100 W at time 4-16 min for synthesis of compounds [3a-3f] using M.W. technique

Entry.	time	Yield
1	4	79.65%
2	8	83.14%
3	12	77.42%
4	16	68.02%

IV. Conclusion

The synthesis of the designed compounds has been successfully achieved. Characterization& identification of the target compounds were confirmed by determination of the physical properties, FT-IR spectroscopy and 1H-NMR spectra .Using the microwave technique provides an efficient method for better yield and time saving.

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