

Synthesis, Characterization of Some New 2-Azetidinone Derivatives

Monther Faisal Mahdi *, Rafah Fadhel Al-Smaism * and Ammar Ihsan Mahmood**

*Department of pharmaceutical Chemistry, Collage of Pharmacy, Al-Mustansriyah University

**Department of pharmaceutical Chemistry, Collage of Pharmacy, Baghdad College

E-mail: dr.monther.f71@yahoo.com

Abstract:

New series of 2-Azetidinone (4a-4f) were synthesized, the structure of these new derivatives were confirmed using spectral methods starting from Ketoprofen we prepared an amide ester by using DCC and TEA in DCM, then converted to hydrazide by using hydrazine hydrate, then a Schiff bases were synthesized using different aromatic aldehydes in ethanol, and the final compounds were obtained by cyclocondensation using chloroacetyl chloride.

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 $^1\text{H-NMR}$ Sp.

Keywords: Ketoprofen, Schiff base, 2-Azetidinone

تصنيع وتشخيص بعض مشتقات 2-ازيتيدون الجديدة

منذر فيصل مهدي*, رفاه فاضل ال-سميسم* و عمار احسان محمود**

* فرع الكيمياء الصيدلانية، كلية الصيدلة، الجامعة المستنصرية

** فرع الكيمياء الصيدلانية، كلية بغداد للصيدلة

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جديد 2-ازيتيدون تم تصنيعها من الكيتوبروفين حيث تم تصنيع مركبات مايدية (1)

على استر في تركيبها باستخدام Dichloromethane triethyl amine dicyclohexylcarbodiimide معاملةتها مع الـ Hydrazin في الايثانول المطلق لينتج مشتق الهيدرازيد (2) ثم عن طريقها تم تحضير قواعد شف باستخدام مركبات الديهيدية اروماتيه في الايثانول (3 a-f) والمركبات النهائية تم الحصول عليها بواسط Chloroacetyl chloride لاننتاج المشتقات النهائي (4 a-f).

جميع المركبات المحضرة في هذا البحث شخصت من خلال قياس درجات الانصهار طيف طيف الرنين النووي المغناطيسي وكذلك دقت المركبات من خلال الكروماتوگرافيا الرقيقة الفيزيائية الكيميائية.

الكلمات المفتاحية: كيتوبروفين، قاعدة شف، 2-ازيتيدون.

Introduction:

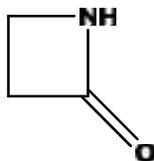
Pain, fever and inflammation have been associated with the mankind since the beginning; non-steroidal anti-inflammatory drugs (NSAIDs) are the first choice of drugs in the treatment of pain in the degenerative inflammatory joint disease^[1].

NSAIDs usually block the action of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). It was believed

that blocking (COX-2) will lead to the antipyretic analgesic and anti-inflammatory results^[2]. Despite the efficiency in defeating pain and inflammation NSAIDs including ibuprofen have some limitations such as dyspepsia, symptomatic, complicated gastric and duodenal ulcers due to blocking (COX1) activity^[3]. Mostly common NSAIDs differ in their relative inhibitory potency against both isoforms of COX: COX-1 and COX-2.

The maximum extent of damage is usually caused by NSAIDs that are favored COX-1 inhibitors and having a free carboxylic group such as Ibuprofen, Ketoprofen^[4]. COX-1 and COX-2 have a similar catalytic activities and structures, but COX-2 has valine instead of isoleucine at positions 523 and 434^[5]. Valine is smaller than isoleucine by methyl group. These substitutions cause a larger and more flexible substrate channel and a secondary internal pocket of the blocker binding site of COX-2 which isn't observed in COX-1. COX-2 selective blockers have structures which occupy the additional pocket^[6], so providing NSAIDs with larger pockets will provide more selectivity towards COX-2 enzyme and masking the COOH group will provide less local damage on the mucosa of stomach^[4&6].

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^[7]. 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^[8].



azetidin-2-one

As a consequence, the interest of the organic chemists in the synthesis of many new β -lactam derivatives remains high^[9]. Some of these derivatives also had been found to be active moderately against several kinds of cancer^[10].

Date of acceptance: 10-6-2015

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^[13].

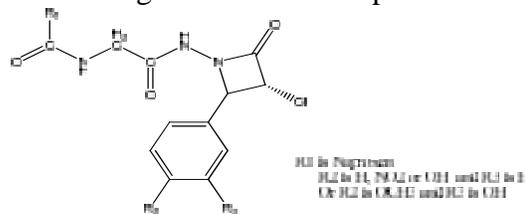


Figure-1: Series of naproxen derivatives containing 2-Azetidinone pharmacophore.

Therefore, new derivatives of ketoprofen containing azetidinone pharmacophore has been synthesized with expected activity against COX-2& may have additional actions like the antibacterial effects.

Materials and Methods:

Materials and 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 F₂₄₅ (E. Merck) using Methanol: Acetic acid: Ether: Benzene (05:15:60: 20)^[12], as the mobile phase and visualized under iodine vapor.¹HNMR spectra are recorded on Bruker (400 MHZ) spectrophotometer, using DMSO-d₆ 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).

Synthetic methods and physical data of synthesized compounds

A - The synthesis of ethyl {[2-(3-benzoylphenyl) propanoyl] amino} acetate (1)

Glycine ethyl ester hydrochloride (0.01 mole, 3.39g), (1ml) triethylamine and ketoprofen (0.01 mole, 2.54g) was dissolved in (20ml) of methylene chloride. The reaction mixture was stirred at 0°C for 30 min. To this solution was added dicyclohexylcarbodiimide (DCC) (0.01 mole, 2.06g) in (10ml) of methylene chloride slowly in a drop wise manner. Reaction mixture was stirred for 4 days. Precipitated DCU had been filtered off and the solvent was evaporated under reduced pressure. Product thus obtained was again dissolved in (15ml) of ethyl acetate and filter. Filtrate was washed with ten percent of aqueous solution of sodium bicarbonate and distilled water in order to remove unreacted ketoprofen, triethylamine-HCl and small amounts of alkali was existed. The ethyl acetate portion was dried out by using magnesium sulphate (anhydrous) and filters to obtain a clear solution of product in ethyl acetate. Solvent was evaporated under low pressure and the crude product was recrystallized by the mean of dissolving it in ethyl alcohol then adding of water until further precipitation stopped. Product was filtered, dried and stored in tightly closed container in cold condition ^[13].

$C_{20}H_{21}NO_4$, White powder; yield 54.32%; mp.80-83 °C; IR (KBr, m, cm^{-1}): 3113 (C-H, aromatic), 2962,2895 (C-H, aliphatic), 3284.88 (NH amide),

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1749.49 (CO, ester) 1654.89 (CO, ketone overtone with amide), 1448.59 (C=C), ;¹H NMR (DMSO, 400 MHz) 1.2 (3H, t, CH₃), 1.5 (3H, d, CH₃), 3.6 (1H,m ,CH) ,3.9-4.1(2H,m ,CH₂) ,4.2 (2H,d ,CH₂)7.28- 7.78 (9H ,m,Ar-H), 8.05 (1H ,s, NH).

B - The synthesis of 2-(3-benzoylphenyl)-N-(2-hydrazino-2-oxoethyl) propanamide (2)

To the solution of compound 1 (0.003 mole, 1.017 g) in (15ml) ethanol, (0.0035 mole, 0.175g) of hydrazine hydrate (80%) was added. The reaction mixture was stirred at room temperature overnight. On the next day, the white precipitate was filtered with suction filtration and washed with cold (5ml) ethanol, the solvent was removed under vacuum and the crude product was washed with ether under stirring ^[14].

$C_{18}H_{19}N_3O_3$, , Off- White powder; yield 62.84%; mp.60-62 °C , R_f 0.38; IR (KBr, m, cm^{-1}): 3049.56 (C-H , aromatic), 2976.26, 2929.97 (C-H, aliphatic), 3549.14 ,3329.25 (NHNH₂), 1664.41, 1653.05 (CO, amide) , 1600.97 (C=C), ;¹H NMR (DMSO, 400 MHz) : 1.57 (3H, d, CH₃), 3.48-3.50 (1H, q, CH), 3.69-3.74 (2H,d ,CH₂), 4.11 (2H,s ,NH₂), 7.28- 7.78 (9H ,m, Ar-H), 8.11 (1H ,s, NH), 8.92 (1H,s, NH),

C - General procedure for the Schiff's bases compounds (3a-f).

To a stirred solution of compound 2 (0.01mole, 0.5g) in (30ml) ethanol, various aromatic aldehydes (0.01mole) were added, after which the mixture was heated at 90-95°C for 6-8 hours until the completion of the reaction (TLC monitoring using ethyl acetate and n-hexane 3:1 ratio). The combination was 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) ^[15].

(Z)-2-(3-benzoylphenyl)-N-(2-(2-benzylidenehydrazinyl)-2-oxoethyl)propanamide (3a):

C₂₅H₂₃N₃O₃, faint yellow powder; yield 40.33%; sticky, R_f 0.69; IR (KBr, m, cm⁻¹): 3107.43 (C-H, aromatic), 2931.90, 2852.81 (C-H, aliphatic), 3327.32 (NH), 1701.08 (CO), 1656.91 (C=N), 1602.90 (C=C); ¹H NMR (DMSO, 400 MHz) : 1.57 (3H, d, CH₃), 3.75 (1H, q, CH), 4.51 (2H, d, CH₂), 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(3b):

C₂₅H₂₂ClN₃O₃, Yellow crystals; yield 52.61%; mp.193-198 °C, R_f 0.79; IR (KBr, m, cm⁻¹): 3061.13 (C-H, aromatic), 2974.33, 2931.91 (C-H, aliphatic), 3327.32 (NH), 1693.56 (CO), 1654.98 (C=N), 1089.82 (C-Cl); ¹H NMR (DMSO, 400 MHz) : 1.57 (3H, d, CH₃), 3.75 (1H, q, CH), 4.51 (2H, d, CH₂), 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)-2-oxoethyl) propanamide(3c):

C₂₇H₂₈N₄O₃, Orange crystals; yield 65.04 %; mp.170-175 °C, R_f 0.70; IR (KBr, m, cm⁻¹): 3059.20 (C-H, aromatic), 2970.84, 2929.97 (C-H, aliphatic), 3298.83 (NH), 1683.97 (CO), 1656.91 (C=N), 1602.91 (C=C); ¹H NMR (DMSO, 400 MHz) : 1.57 (3H, d, CH₃), 3.75 (1H, q, CH), 4.51 (2H, d, CH₂), 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).

Date of acceptance: 10-6-2015

(Z)-2-(3-benzoylphenyl)-N-(2-(2-(4-hydroxybenzylidene) hydrazinyl)-2-oxoethyl)propanamide(3d):

C₂₅H₂₃N₃O₄, Faint yellow crystals; yield 44.63 %; mp.99-104 °C, R_f 0.72; IR (KBr, m, cm⁻¹): 3066.92 (C-H, aromatic), 2976.26, 2935.76 (C-H, aliphatic), 3225.09 (NH), 3413.82 (OH), 1678.13 (CO), 1653.05 (C=N), 1604.83 (C=C); ¹H NMR (DMSO, 400 MHz) : 1.61 (3H, d, CH₃), 3.77 (1H, q, CH), 4.44 - 4.52 (2H, d, CH₂), 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)-2-oxoethyl)propanamide(3e):

C₂₆H₂₅N₃O₄, off white crystals; yield 61.19 %; mp.146-150 °C, R_f 0.69; IR (KBr, m, cm⁻¹): 3068.85 (C-H, aromatic), 2929.97, 2847.97 (C-H, aliphatic), 3325.39 (NH), 1255.7 (OCH₃), 1681.98 (CO), 1658.84 (C=N), 1602.60 (C=C); ¹H NMR (DMSO, 400 MHz) : 1.56 (3H, d, CH₃), 3.7 (1H, q, CH), 3.89 (3H, s, OCH₃), 7.28- 7.96 (11H, m, Ar-H), 8.28 (1H, s, N=CH), 8.57 (1H, s, NH), 9.61 (1H, s, NH-N=CH).

(Z)-2-(3-benzoylphenyl)-N-(2-(2-(4-nitrobenzylidene)hydrazinyl)-2-oxoethyl) propanamide(3f):

C₂₅H₂₂N₄O₅, Pale green crystals; yield 70.08 %; mp.110-116 °C, R_f 0.61; IR (KBr, m, cm⁻¹): 3045.50 (C-H, aromatic), 2933.83, 2854.74 (C-H, aliphatic), 3248.88 (NH), 1537.32, 1348.29 (NO₂), 1697.41 (CO), 1654.98 (C=N), 1602.90 (C=C); ¹H NMR (DMSO, 400 MHz) : 1.57 (3H, d, CH₃), 3.75 (1H, q, CH), 4.51 (2H, d, CH₂), 7.54- 8.45, 9.50 (1H, s, NH attached to imine), 8.11 (1H, s, CH=N).

General procedure for the 2-Azetidinones compounds (4a-f).

To a solution of 3a-f (0.001 mole) in (25ml) anhydrous 1,4-dioxane, chloroacetylchloride (0.0015 mole, 0.169g) and triethylamine (TEA) (0.001 mole, 0.101g) 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 (10ml) water, filtered off, dried and recrystallized from absolute ethanol [16].

2-(3-benzoylphenyl)-N-(2-((3-chloro-2-oxo-4-phenylazetidin-1-yl)amino)-2-oxoethyl)propanamide (4a):

$C_{27}H_{24}ClN_3O_4$, Dark Yellow sticky matter; yield 43.37 %; R_f 0.74, IR (KBr, m, cm^{-1}): 1681.98 (C=O), 1737.92 (C=O), 788.91 (C-Cl); 1H NMR (DMSO, 400 MHz) : 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(4b):

$C_{27}H_{23}Cl_2N_3O_4$, Yellow crystals, yield 31.60 %; mp.78-82 $^{\circ}C$; R_f 0.88 IR (KBr, m, cm^{-1}): 1658.84 (CO), 1724.59 (C=O), 790.84 (C-Cl) ; 1H NMR (DMSO, 400 MHz) : 4.67 (1H, d, CH-Ar of Azetidin) 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 (4c) :

$C_{29}H_{29}ClN_4O_4$, Dark red crystals, yield 68.41 %; mp.94-98 $^{\circ}C$; R_f 0.61 IR (KBr, m, cm^{-1}): 1645.98 (C=O), 1732.13 (C=O), 790.84 (C-Cl); 1H NMR (DMSO, 400 MHz) : 4.82 (1H, d, CH-Ar of Azetidin) 5.27 (1H, d, CH-Cl of Azetidine).

Date of acceptance: 10-6-2015

2-(3-benzoylphenyl)-N-(2-((3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl)amino)-2-oxoethyl)propanamide (4d):

$C_{27}H_{24}ClN_3O_5$, Yellowish brown crystals, yield 35.04 %; mp.80-85 $^{\circ}C$, R_f 0.76 IR (KBr, m, cm^{-1}): 1654.98 (C=O), 1734.06 (C=O), 788.91 (C-Cl); 1H NMR (DMSO, 400 MHz) : 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 (4e) :

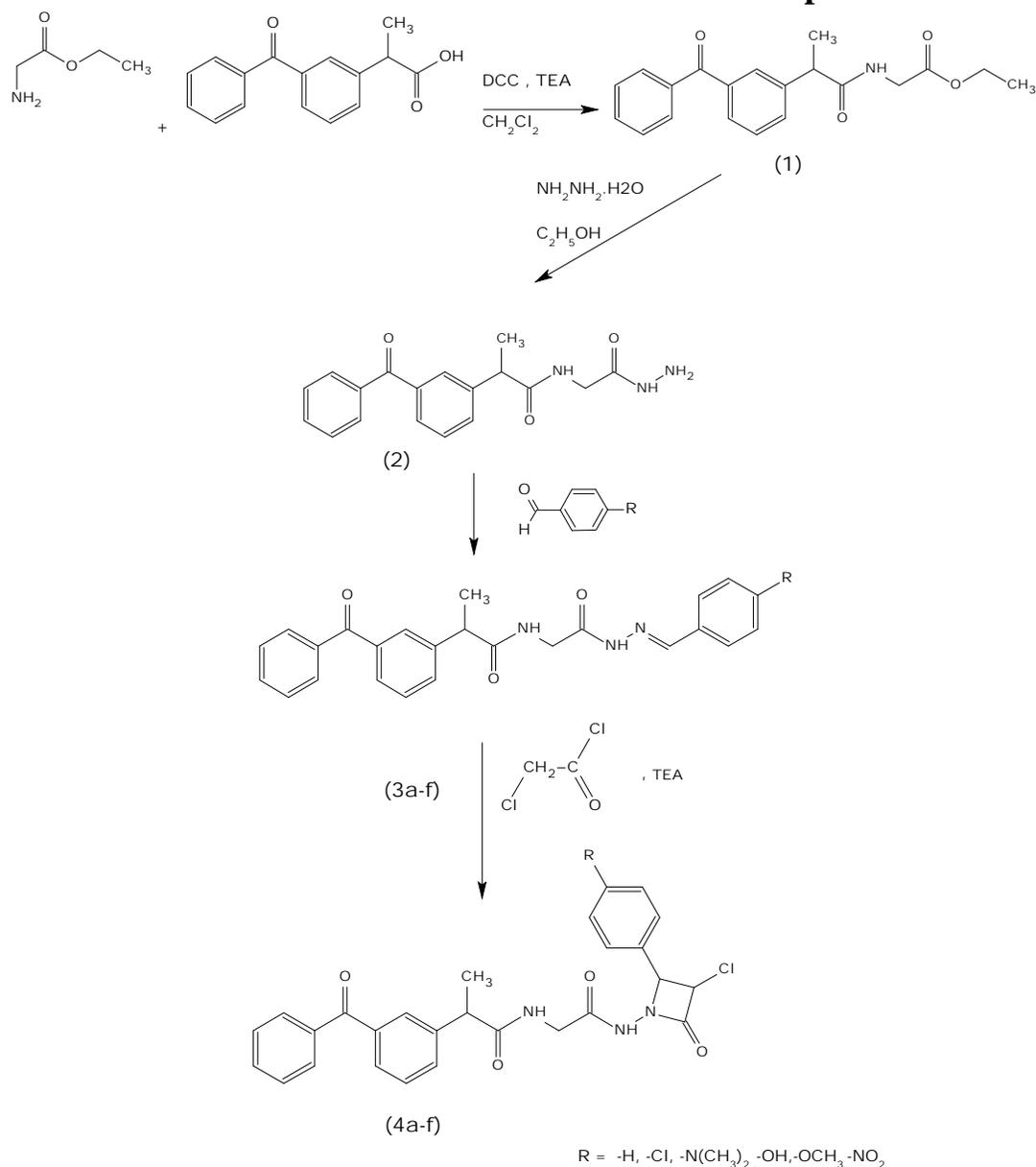
$C_{28}H_{26}ClN_3O_5$, Dark brown crystals, yield 36.042 %; mp.69-73 $^{\circ}C$, R_f 0.91 IR (KBr, m, cm^{-1}): 1654.98 (C=O), 1732.13 (C=O), 788.91 (C-Cl); 1H NMR (DMSO, 400 MHz) : 4.85 (1H, d, CH-Ar of Azetidin) 5.47 (1H, d, CH-Cl of Azetidine).

2-(3-benzoylphenyl)-N-(2-((3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)amino)-2-oxoethyl)propanamide (4f):

$C_{27}H_{23}ClN_4O_6$, Dark green crystals yield 33.08 %; mp.88-92 $^{\circ}C$, R_f 0.92 IR (KBr, m, cm^{-1}): 1697.41 (CO), 1726.35 (C=O), 786.98 (C-Cl) ; 1H NMR (DMSO, 400 MHz) : 4.46 (1H, d, CH-Ar of Azetidin) 5.83 (1H, d, CH-Cl of Azetidine).

Result and discussion:

Azetidinone derivatives (4a-f) were prepared using the method summarized in scheme 1. First, Glycine ethyl ester hydrochloride was reacted with triethylamine and ketoprofen whereby the corresponding ethyl{[2-(3-benzoylphenyl) propanoyl] amino}acetate (1) was obtained. Compound (1) on amination with hydrazine hydrate in absolute ethanol afforded compound (2).the condensation reaction of compound (2) with various aromatic aldehydes yielded Schiff's bases compounds (3a-f). Finally, the compounds (3a-f) upon reaction with chloroacetyl chloride in the presence of triethylamine afforded 2-Azetidinones compounds(4a-f) (Scheme-1).



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

The structure of the compounds was assigned on the basis of spectral (FTIR, ¹H NMR) data.

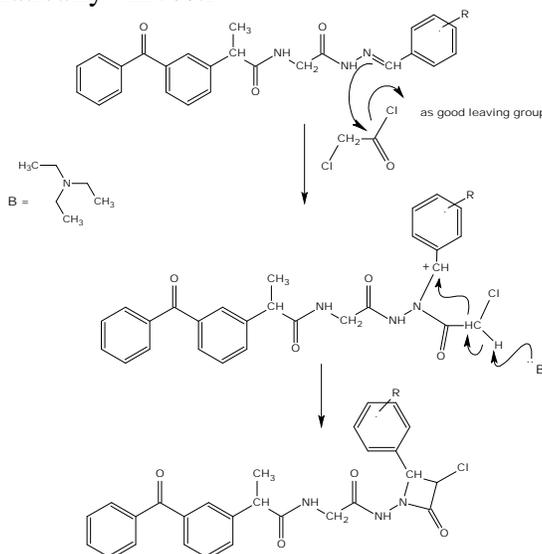
In the FTIR of the azetidinone derivatives (4a-f) showed absorption bands for the carbonyl group of the lactam ring as a characteristic absorption bands of (C=Cl) and (C=O) in the range of (786.98-790.84 and 1724.59-1737.92 cm⁻¹), respectively. The FTIR and ¹H NMR signals

characteristic of the azomethine group range (1653.05-1658.84 cm⁻¹) disappeared from the spectra of the azetidinone derivatives, which confirm that the cyclization reaction with chloroacetyl chloride took place. The ¹H NMR spectra of the final compounds showed two doublets, which are characteristic for N-CH and CH-Cl that appear in the range of (8.15-9.45 and 5.15-5.83ppm), respectively. The spectral data

lend strong support to the proposed structures of all the synthesized compounds.

Mechanism of the pericyclic reaction between an imine group and chloroacetylchloride for preparing 2-Azetidinones ring systematically investi-

gated. The breaking and formation of bonds occur simultaneously and thus the reaction proceeds via a single cyclic as show in scheme-2.



Scheme-2: Mechanism of action of cyclocondensation of the target compounds

Conclusion:

The 2-Azetidinone continue to be one of the most researched areas in medicinal chemistry, synthesis of some new substituents of 2-azetidinone has been described using conventional method by cyclo-condensation of chloroacetyl chloride with Schiff base derivatives (3 a-f).

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