Synthesis, Characterization of Some New 2-Azetidinone Derivatives

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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 chloroacetylechloride. The synthesis of the designed compounds has been successfully achieved. Purity and characterization were confirmed by determination of physical properties (melting points & Rf values), FT-IR spectroscopy and ¹H-NMR Sp.

Keywords: Ketoprofen, Schiff base, 2-Azetidinone

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. COX-1 and COX-2 have a similar catalytic activities and structures, but COX-2 has valine instated of isoleucine at positions 523 and 434. 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, 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.

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. 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 cytomegalo-virus protein, human leukocyte cysteine protease and elastase.

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

**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 F254 (E. Merck) using Methanol: Acetic acid: Ether: Benzene (05:15:60: 20) 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-benzylophenyl) 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 0ºC for 30 min. To this solution was added dicyclohexylcarbodimide (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.

C_{20}H_{21}NO_4, White powder; yield 54.32%; mp.80-83 ºC; IR (KBr, m, cm^{-1}): 3113 v(C-H, aromatic), 2962.2895 v(C-H, aliphatic), 3284.88 v(NH amide), 1749.49v(CO, ester) 1654.89 v(CO, ketone overtone with amide), 1448.59 ν(C=C, \text{C-H}), 1312 ν(C-O, ester), 1258 ν(C-O, ether), 1035 ν(C-O, aliphatic), 725 ν(C-O, aromatic).

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.

C_{18}H_{19}N_3O_3, Off-White powder; yield 62.84%; mp.60-62 ºC ,R_f 0.38; IR (KBr, m, cm^{-1}): 3049.56 ν(C-H, aromatic), 2976.26, 2929.97 ν(C-H, aliphatic), 1664.41, 1653.05ν(CO, amide) , 1600.97 ν(C=C), \text{C-H}, 1448.59 ν(C=C), 3549.14 ν(NHNH_2), 3329.25 ν(NHNH_2), 1448.59 ν(C=C).

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 90-95ºC 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
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splashed using water then recrystallization by using water and ethanol (3:7) \[15\].

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

C_{25}H_{23}N_{3}O_{3}, , faint yellow powder; yield 40.33%; sticky ,R_f 0.69; IR (KBr, m, cm^{-1}): 3107.43 v(C-H , aromatic), 2931.90, 2852.81 v(C-H , aliphatic), 3327.32 v(NH), 1701.08 v(CO), 1656.91 v(C=N), 1602.90 v(C=C); \textsuperscript{1}H NMR (DMSO, 400 MHz) \(\delta\): 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)hydrizinyl)-2-oxoethyl)propanamide (3b):

C_{25}H_{22}ClN_{3}O_{3}, Yellow crystals; yield 52.61%; mp.193-198 °C, R_f 0.79; IR (KBr, m, cm^{-1}): 3061.13 v(C-H , aromatic), 2974.33, 2931. 91 v(C-H , aliphatic), 3327.32 v(NH), 1693.56 v(CO), 1654.98 v(C=N), 1089.82 v(C-Cl); \textsuperscript{1}H NMR (DMSO, 400 MHz) \(\delta\): 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)-2-oxoethyl) propanamide (3c):

C_{23}H_{28}N_{4}O_{3}, ,Orange crystals; yield 65.04 %; mp.170-175 °C, R_f 0.70; IR (KBr, m, cm^{-1}): 3059.20 v(C-H , aromatic), 2970.84, 2929.97 v(C-H , aliphatic), 3298.83 v(NH), 1683.97 v(CO), 1656.91 v(C=N), 1602.91 v(C=C); \textsuperscript{1}H NMR (DMSO, 400 MHz) \(\delta\): 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).

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

C_{25}H_{23}N_{3}O_{4} , Faint yellow crystals; yield 44.63 %; mp.99-104 °C, R_f 0.72; IR (KBr, m, cm^{-1}): 3066.92 v(C-H , aromatic), 2976.26, 2935.76 v(C-H , aliphatic), 3225.09 v(NH), 3413.82 v(OH), 1678.13 v(CO), 1653.05 v(C=N), 1604.83 v(C=C); \textsuperscript{1}H NMR (DMSO, 400 MHz) \(\delta\): 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)-2-oxoethyl)propanamide(3e):

C_{25}H_{25}N_{3}O_{4} ,off white crystals; yield 61.19 %; mp.146-150 °C, R_f 0.69; IR (KBr, m, cm^{-1}): 3068.85 v(C-H , aromatic), 2929.97, 2847.97 v(C-H , aliphatic), 3325.39 v(NH), 1255.7 v(OCH_{3}), 1681.98 v(CO), 1658.84 v(C=N), 1602.60 v(C=C); \textsuperscript{1}H NMR (DMSO, 400 MHz) \(\delta\): 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, NH=CH=N).

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

C_{23}H_{22}N_{4}O_{5} ,Pale green crystals; yield 70.08 %; mp.110-116 °C, R_f 0.61; IR (KBr, m, cm^{-1}): 3045.50 v(C-H , aromatic), 2933.83, 2854.74 v(C-H , aliphatic), 3248.88 v(NH), 1537.32, 1348.29 v(NO_{2}), 1697.41 v(CO), 1654.98 v(C=N), 1602.90 v(C=C); \textsuperscript{1}H NMR (DMSO, 400 MHz) \(\delta\): 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-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-benzyloxyphenyl)-N-(2-((3-chloro-2-oxo-4-phenylazetidin-1-yl)amino)-2-oxoethyl)propanamide (4a):

C_{27}H_{21}CIN_{3}O_{6}, Dark Yellow sticky matter; yield 43.37 %; R{\text{f}} 0.74, IR (KBr, m, cm{	ext{-}1}): 1681.98 ν(C=O), 1737.92 ν(C=O), 788.91ν(C-Cl);{\text{^1}}H NMR (DMSO, 400 MHz) δ: 4.53 (1H, d, CH of Azetidin) 5.15 (1H, d, CH-Cl of Azetidin).

2-(3-benzyloxyphenyl)-N-(2-((3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)amino)-2-oxoethyl)propanamide (4b):

C_{27}H_{21}CIC_{5}N_{3}O_{4}, Yellow crystals, yield 31.60 %; mp.78-82°C; R{\text{f}} 0.88IR (KBr, m, cm{	ext{-}1}): 1658.84ν(CO), 1724.59ν(C=O), 790.84ν(C-Cl);{\text{^1}}H NMR (DMSO, 400 MHz) δ: 4.67 (1H, d, CH-Ar of Azetidin) 5.47 (1H, d, CH-Cl of Azetidin).

2-(3-benzyloxyphenyl)-N-(2-((3-chloro-2-(4-dimethylamino)phenyl)-4-oxoazetidin-1-yl)amino)-2-oxoethyl)propanamide (4c):

C_{29}H_{27}CIN_{4}O_{4}, Dark red crystals, yield 68.41 %; mp.94-98°C; R{\text{f}} 0.61IR (KBr, m, cm{	ext{-}1}):1645.98 ν(C=O), 1732.13ν(C=O), 790.84ν(C-Cl);{\text{^1}}H NMR (DMSO, 400 MHz) δ: 4.82 (1H, d, CH-Ar of Azetidin) 5.27 (1H, d, CH-Cl of Azetidin).

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

C_{27}H_{24}CIN_{3}O_{5}, Yellowish brown crystals, yield 35.04 %; mp.80-85°C, R{\text{f}} 0.76 IR (KBr, m, cm{	ext{-}1}): 1654.98ν(C=O), 1734.06 ν(C=O), 788.91ν(C-Cl);{\text{^1}}H NMR (DMSO, 400 MHz) δ: 4.82 (1H, d, CH-Ar of Azetidin) 5.54 (1H, d, CH-Cl of Azetidin).

2-(3-benzyloxyphenyl)-N-(2-((3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)amino)-2-oxoethyl)propanamide (4e):

C_{29}H_{26}CIN_{3}O_{6}, Dark green crystals, yield 36.042 %; mp.69-73°C, R{\text{f}} 0.91IR (KBr, m, cm{	ext{-}1}): 1654.98ν(C=O), 1732.13ν(C=O), 788.91ν(C-Cl);{\text{^1}}H NMR (DMSO, 400 MHz) δ: 4.85 (1H, d, CH-Ar of Azetidin) 5.47 (1H, d, CH-Cl of Azetidin).

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

C_{27}H_{27}CIN_{4}O_{6}, Dark green crystals, yield 33.08 %; mp.88-92°C, R{\text{f}} 0.92IR (KBr, m, cm{	ext{-}1}): 1697.41ν(CO), 1726.35ν(C=O), 786.98ν(C-Cl);{\text{^1}}H NMR (DMSO, 400 MHz) δ: 4.46 (1H, d, CH-Ar of Azetidin) 5.83 (1H, d, CH-Cl of Azetidin).

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-benzyloxyphenyl) propanoyl] aminoacetate (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 yieldedSchiff’s bases compounds (3a-f). Finally, the compounds (3a-f) upon reaction with chloracetyl 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, $^1$H NMR) data.

In the FTIR of the azetidinone derivatives (4a-f) showed absorption bands for the carbonyl group of the β-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 $^1$H 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 $^1$H 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 5.15-5.83 ppm), respectively. The spectral data
lend strong support to the proposed structures of all the synthesized compounds.

Mechanism of the percyclic reaction between an imine group and chloroacetylchloride for preparing 2-Azetidinones 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: 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 Schiffbase derivatives (3 a-f).

**References:**


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