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Synthesis and characterization of novel β-Lactam derivative

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Abstract: In this present work β-Lactam was synthesized through a 2-((4-chlorophenyl) (piperidin-4-yloxy) methyl) pyridine, bromoethyl acetate, hydrazine hydrate, substituted aldehyde to obtain Schiff base derivatives by using glacial Acetic acid in ethanol. Further Cyclization of Shiff bases with Chloroacetyl chloride in the presence of triethyl amine give the corresponding β-lactam derivatives. All these compounds identified by (FTIR ,1H-NMR, 13C-NMR) and follow by (TLC) and melting points of them.

Keywords: 2-((4-chlorophenyl) (piperidin-4-yloxy) methyl) pyridine, Schiff base, Heterocyclic compound, β-Lactam derivative.

INTRODUCTION

Shiff bases are Compounds with an azomethine group (-CH=N-) can be prepared from react a carbonyl compound with a primary amine[1-2] Schiff bases have several applications. It is used as an intermediate compound to prepare many heterocyclic derivatives such as β-lactam.[3] β-Lactam nucleus is the core of the biological activity of a large class of antibiotics characterized by the presence of this four-membered ring and differentiated by side chains, unsaturations, heteroatoms, and, in many cases, by the presence of five-or six-membered rings.

β-lactams have been occupying the attention of organic and medicinal chemists. In addition to their well-established importance in medicinal chemistry, [4] in the last several decades β-lactams have been recognized as valuable building blocks for the synthesis of various classes of organic compounds. The use of β-lactams as intermediates in organic synthesis is known as "β-lactam synthon method", [5] and several extensive reviews have been written on this topic in the last decade.[6]

β-Lactam building blocks have been used for the synthesis of numerous biologically active and natural compounds.[7]Some of the examples include nonnatural amino acids, peptides and peptidomimetics,[8]anticancer drug paclitaxel and other taxoids,[9] and antitumor antibiotic lankacidin.[10]

The first synthesis of a β-lactam was accomplished in 1907 when Staudinger discovered that ketenes and imines could undergo [2+2] cycloadditions to yield the β-lactam ring.[11] In 1940s, β-lactam antibiotics have been used to cure bacterial infection, several of the lactam derivatives are also a chemical reaction such as cephalosporins.[12] Also noted several other biological activities like anti-cancer activity, and the activity of blood sugar, and antitubercular activity and anti-leishmaniasis activity in a compound containing β-lactam ring[13]

Due to biological activities of β-lactam they have been a target molecule for synthesis over the last few decades. So, this research involve synthesis of some new β-lactam derivatives.

RESULTS AND DISCUSSION

A new series of β-lactam was prepared using the reaction of 2-((4-chlorophenyl)(piperidin-4-yloxy)methyl)pyridine, bromoethylacetate , hydrazine hydrate, substituted aldehyde to obtain Schiff base derivatives by using glacial Acetic acid in ethanol. Further Cyclization of Shiff bases with Chloroacetyl chloride in the presence of triethyl amine give the corresponding β-lactam derivatives. **(scheme 1)**

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In order to optimize the reaction conditions and get the best catalytic activity, the reaction of Shiff bases with Chloroacetyl chloride was examined as a model reaction in the several catalysts. As indicated in **Table 1**, the model reaction was carried out using Diethylamine, KOH, Triethylamine (TEA), NaOH, Sodium carbonate, Sodium bicarbonate, Potassium carbonate. In this study, it was observed that TEA in 1,4 Dioxane under cooling 0-5°C gives better yield of the desired product **(Table 1).**

After optimizing the catalyst amount, a diversity of β-lactam derivatives was synthesized using TEA (1.5 mmol) under cooling 0-5°C **(Table 2, entries 9a–9j).** The reactions worked well with all benzaldehydes with electron-donating or electron-withdrawing substituent.

All synthesized products were characterized by FT-IR, ^{1}HNMR and ^{13}C-NMR spectra and elemental analysis.

Scheme 1. Synthesis of substituted β-lactam catalyzed by TEA.

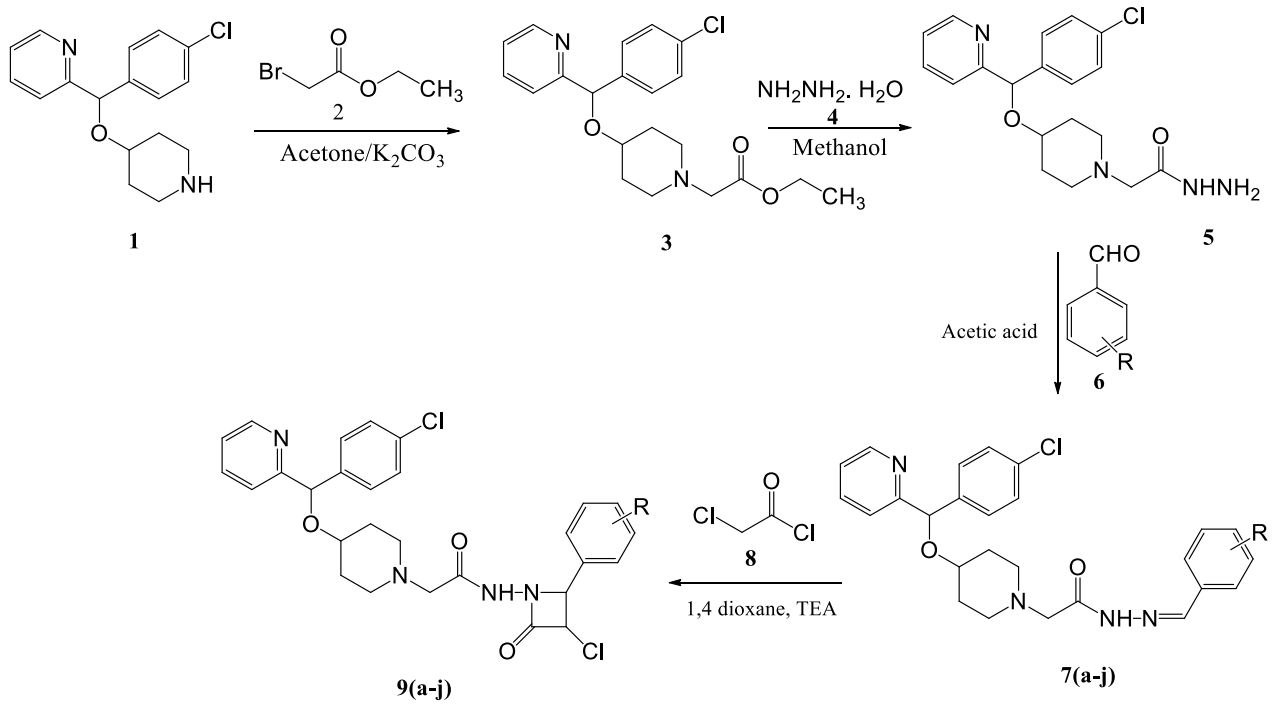

Table 1. Synthesis of 4a by different catalysts

Entry.	Catalyst	Time(hr)	Yield of product(%)
1	Diethylamine	15	88
2	KOH	12	75
3	Potassium carbonate	13	81
4	Sodium carbonate	12	86
5	Sodium bicarbonate	13	82
6	Triethylamine	**10**	**95**
7	NaOH	12	90

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Table 2. Synthesis of β-lactam derivatives 4(a-j) catalyzed by TEA[b].

Compound code	R	Time (hr)	Yield (%)	Melting point
4a	H	10	95	150-152
4b	4-Cl	13	89	160-165
4c	2-Cl	12	82	152-154
4d	4-Br	10	90	145-148
4e	3-Br	14	91	162-167
4f	4-OCH_3	15	88	140-143
4g	3-NO_2	10	92	148-150
4h	3-Cl	12	90	165-170
4i	3-OCH_3	14	85	141-146
4j	4-OH	15	82	148-153

[b]All yields refer to isolated products.

CONCLUSION

1. In this study we are reported synthesis of many novel β-Lactam derivatives via, Staudinger Reaction[2+2]cyclo addition.
2. The work included preparation of Schiff base compounds from -((4-chlorophenyl)(piperidin-4-yloxy)methyl)pyridine, bromoethylacetate , hydrazine hydrate, substituted aldehyde as the first step then cyclization process for these compounds by using chloro acety chloride in the basic medium.
3. These derivatives confirmed from spectral data analysis; FTIR, 1HNMR and 13CNMR.

Experimental section:

Unless and otherwise noted, all Chemicals used were of commercial grade and they were used without any further purification. All reactions were monitored by thin layer chromatography using aluminium sheets precoated with silica gel 60 F254 (Merck) using either UV light or iodine vapours as visualizing agents. The products were identified fully or by comparison of melting points and spectroscopic data with the previously reported ones.

General procedure for the synthesis of ethyl2-(4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidin-1-yl)acetate (3)

To a Mixture of 2-((4-chlorophenyl)(piperidin-4-yloxy)methyl)pyridine **(1) (1 mmol)**, bromoethylacetate **(2) (1 mmol)** dissolves in acetone (10 ml). To that mixture add K_2CO_3 **(2 mmol)** was added and the reaction mixture was reflux for 7 hour. The reaction was monitored on Merck pre-coated aluminum TLC plates 60F-254 and product was visualized by UV-light using n-hexane and ethyl acetate as solvent system. After completion of the reaction, the reaction mixture was filtered and concentrates the solvent to get the pure compound.

General procedure for the synthesis of 2-(4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidin-1-yl)acetohydrazide (5)

To a Mixture of **Compound (3) (1 mmol)**, Hydrazine hydrate **(4) (5 mmol)** dissolves in ethanol (10 ml). The reaction mixture was reflux for 7 hour. The reaction was monitored on Merck pre-coated aluminum TLC plates 60F-254 and

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product was visualized by UV-light using n-hexane and ethyl acetate as solvent system. After completion of the reaction the reaction mixture was poured into ice cold water the precipitate was filtered and dried.

General procedure for Synthesis of Schiff bases Derivatives 7(a-j)

To a Mixture of **Compound (5) (1 mmol)**, substituted aldehyde **(6) (1 mmol)** dissolves in ethanol (10 ml). To that mixture add drop of glacial acetic acid and the reaction mixture was 8-10 hour. The reaction was monitored on Merck pre-coated aluminum TLC plates 60F-254 and product was visualized by UV-light using n-hexane and ethyl acetate as solvent system. After completion of the reaction the reaction mixture was poured into ice cold water the precipitate was filtered and recrystallized with ethanol to give pure product.

General procedure for Synthesis of β-lactam Derivatives 9(a-j)

To a Mixture of Schiff bases Derivatives **7(a-j) (1 mmol),** triethylamine **(1.5 mmol)** dissolves in 1,4 dioxane (10 ml). The reaction mixture cool to 0-5°C then slowly add chloro acetyl chloride **(8) (1 mmol)** dropwise. The reaction mass was stir for 10-15hour at cooling. The reaction was monitored on Merck pre-coated aluminum TLC plates 60F-254 and product was visualized by UV-light using n-hexane and ethyl acetate as solvent system. After completion of the reaction the reaction mixture was poured into ice cold water then extracts the product with ethyl acetate, concentrate the solvent to get the crude solid further the solid was purified with column chromatography.

Characterization

Melting points were measured in open capillaries and are uncorrected. IR spectra was recorded on Bruker FTIR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker FTNMR (500MHz) spectrophotometer with DMSO-d6 as solvent and TMS as internal standard. Solvent peaks in ^{1}H-NMR and ^{13}C-NMR spectra have been removed in tracing. The chemical shifts in parts per million (δ) are reported downfield from TMS (0 ppm). The abbreviations s, d, t, q, m and dd refer to singlet, doublet, triplet, quartet, multiplet and doublet of doublet respectively.

N-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-(4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidin-1-yl)acetamide **(4a):**

Molecular Formula: $C_{28}H_{28}Cl_2N_4O_3$

Molecular Weight (gmol-1): 539.45

Melting Point (ºC): 150-152

IR (KBr, cm-1): 3247 (NH), 1689 and 1658(C=O), 1589 (C=N), 1272 (C-O), 725 (C-Cl).

^{1}H NMR (500 MHz, DMSO, δppm): 1.2-1.3 (m, 4H, CH4), 1.6-1.7(m, 4H, CH4), 2.17 (S, 2H, CH2), 3.0-3.1(m, 1H, CH), 3.3 (d, 1H, CH), 3.8 (d, 1H, CH-Cl), 5.4(s, 1H, CH), 7.0-8.0(m, 9H, Ar-H), 11.1 (s, 1H, NH).

^{13}C NMR (500 MHz, DMSO, δ ppm): 29.0, 29.1, 48.5, 48.5, 51.6, 51.7, 62.2, 71.9, 79.2 , 121.5, 122.6, 126.8, 127.3, 128.3, 128.4, 129.0, 134.6, 136.4, 136.6, 139.0, 149.4, 157.4, 168.2, 169.1.

N-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)-2-(4-((4-chlorophenyl) (pyridin-2-yl) methoxy) piperidin-1-yl)acetamide **(4b)**

Molecular Formula: $C_{28}H_{27}Cl_3N_4O_3$

Molecular Weight (gmol-1): 573.90

Melting Point (ºC): 160-165

IR (KBr, cm-1): 3235 (NH), 1679 and 1668(C=O), 1559 (C=N), 1232 (C-O), 785 (C-Cl).

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^{1}H NMR (500 MHz, DMSO, δ ppm): 1.3-1.4 (m, 4H, CH4), 1.7-1.8(m, 4H, CH4), 2.19 (S, 2H, CH2), 3.2-3.3(m, 1H, CH), 3.4 (d, 1H, CH), 3.9 (d, 1H, CH-Cl), 5.6(s, 1H, CH), 7.2-8.0(m, 8H, Ar-H), 11.4 (s, 1H, NH).

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^{13}C NMR (500 MHz, DMSO, δ ppm): 29.2, 29.3, 48.8, 48.9, 51.8, 51.8, 62.4, 71.8, 79.4 , 121.1, 122.4, 126.7, 127.1, 128.1, 128.2, 129.5, 134.7, 136.6, 136.7, 139.5, 149.5, 157.3, 168.1, 169.2.

N-(3-chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-yl)-2-(4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidin-1-yl)acetamide **(4c)**

Molecular Formula: $C_{28}H_{27}Cl_3N_4O_3$

Molecular Weight (gmol-1): 573.90

Melting Point (ºC): 152-154

IR (KBr, cm-1): 3335 (NH), 1579 and 1668(C=O), 1459 (C=N), 1132 (C-O), 685 (C-Cl).

^{1}H NMR (500 MHz, DMSO, δ ppm): 1.2-1.3 (m, 4H, CH4), 1.6-1.7(m, 4H, CH4), 2.09 (S, 2H, CH2), 3.1-3.2(m, 1H, CH), 3.2 (d, 1H, CH), 3.7 (d, 1H, CH-Cl), 5.1(s, 1H, CH), 7.4-8.0(m, 8H, Ar-H), 11.01 (s, 1H, NH).

^{13}C NMR (500 MHz, DMSO, δ ppm): 28.2, 28.3, 47.8, 47.9, 50.6, 50.8, 61.4, 70.8, 78.4 , 120.1, 121.4, 125.7, 126.1, 127.1, 127.2, 128.5, 133.7, 135.6, 135.7, 138.5, 148.5, 156.3, 167.1, 168.2.

N-(2-(4-bromophenyl)-3-chloro-4-oxoazetidin-1-yl)-2-(4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidin-1-yl)acetamide **(4d)**

Molecular Formula: $C_{28}H_{27}BrCl_2N_4O_3$

Molecular Weight (gmol-1): 618.35

Melting Point (ºC): 145-148

IR (KBr, cm-1): 3235 (NH), 1679 and 1768(C=O), 1559 (C=N), 1142 (C-O), 785 (C-Cl).

^{1}H NMR (500 MHz, DMSO, δ ppm): 1.2-1.3 (m, 4H, CH4), 1.5-1.6(m, 4H, CH4), 2.19 (S, 2H, CH2), 3.2-3.3(m, 1H, CH), 3.5 (d, 1H, CH), 3.8 (d, 1H, CH-Cl), 5.3(s, 1H, CH), 7.2-8.0(m, 8H, Ar-H), 11.2 (s, 1H, NH).

^{13}C NMR (500 MHz, DMSO, δ ppm): 29.2, 29.3, 48.8, 48.9, 50.5, 50.7, 60.4, 71.8, 79.4 , 121.1, 122.4, 126.7, 127.1, 128.1, 128.2, 129.5, 132.7, 134.6, 136.7, 139.5, 147.5, 157.3, 168.1, 169.2.

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