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Bis-N-aryl-β-lactams: Vilsmeier Reagent as an efficient entity for the Synthesis via Alternate Cycloaddition Reaction and In vitro Biology

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Abstract

A practical synthesis of cis bis-β-lactams has been executed using Chloromethylenedimethylammonium chloride (Vilsmeier reagent), prepared easily from N, N-dimethylformamide and Phosphorus Oxychloride in situ. It works out as a versatile acid activator reagent for the direct [2+2] ketene–imine alternate cycloaddition of aromatic acetic acid and bis-imines in one-pot synthesis under mild reaction conditions proving as a high yielding protocol for bis-β-lactam. This protocol has been proved to be high yielding, efficient and cheap for cis bis-β-lactam synthesis. Some of physic-chemical properties associated with bis-β-lactam have been discussed.

Keywords: Vilsmeier, Azetidinones, Bis-β-lactams, Cycloaddition.

INTRODUCTION

The β-Lactam nucleus is the key to the biological activity of a large class of compounds 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. The successful application of β-lactam antibiotics in the treatment of infectious diseases has been well documented for many years [1]. The potential use of some β-lactams as therapeutic agents for lowering plasma cholesterol levels [2, 3] , as inhibitors of enzymes such as thrombin [4], HLE (human leukocyte elastase) [5] and the protease, responsible for capsid assembly and viral

maturation of HCMV (human cytomegalovirus), [6] has been documented as well. The β-lactam structure is also the essential scaffold of several antagonists directed to the vasopressin V1 receptor, [7] and 2-azetidinones have been reported to show apoptosis inducing properties against human solid tumor cell lines [8]. Due to the large pharmacological potential and use of the β-lactam systems, intensive research has generated numerous methods for synthesizing this skeleton. In addition to its use in the synthesis of variety of β-lactam antibiotics, the β-lactam skeleton has been recognized as a useful building block by exploiting its strain energy associated with four member ring [9]. Efforts have been made in exploring such new aspects of β-lactam chemistry using pure β-lactams as versatile intermediates for organic syntheses [10]. Ojima et al. [11] have shown the utility of bis-β-lactams for the synthesis of peptides. The synthesis of bis-β-lactams, in general, has been reported by a step-wise construction of β-lactam rings [12]. In continuation of our work on the synthesis of β-lactams (Monobactams) [13] and bis-β-lactams, [14] we were interested in building bis-β-lactams from bisimines using the Staudinger cycloaddition reaction employing newer reagents.

Among the various methods available for the synthesis of β-lactams, the Staudinger cycloaddition reaction (ketene–imine cycloaddition reaction) is the most widely used [15] mainly because of the simplicity in reaction procedures. This method has been used for the synthesis of a large number of monocyclic, bicyclic, tricyclic and spirocyclic β-lactams [16]. The ketenes are commonly generated in situ from acyl halides in the presence of tertiary amines [17]. In addition to the utilization of acyl halides, a variety of other methods have been described to activate carboxylic acids [18]. These methods are conventionally useful when the acid halides are not commercially available, difficult to prepare or when they are unstable. Some acid activating agents include 1, 1-carbonyldi-imidazole [19], triphosgene [20], ethyl chloroformate [21], trifluoroacetic anhydride [22], p-toluenesulfonyl chloride [23], phosphorus-derived reagents [24], cyanuric chloride [25], the Mukaiyama reagent [26] and acetic anhydride [27].

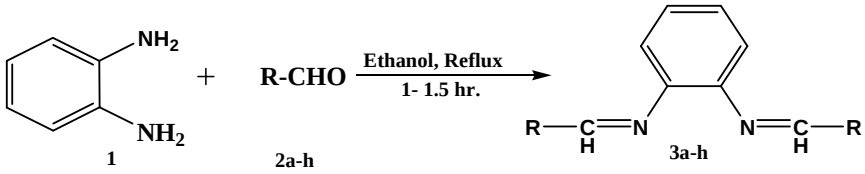
Herein this communication, we wish to report the synthesis of bis-β-lactams using Vilsmeier reagent. Chloromethylenedimethylammonium chloride (Vilsmeier reagent) has been known as a formylating agent [28]. It has also emerged as an efficient synthetic auxiliary for the synthesis of some important class of organic compounds. This white solid is easily synthesized by reaction of N, N-dimethylformamide (DMF) and chlorinating agents such as $POCl_3$ or $SOCl_2$ [29]. This reagent was reported for the synthesis of monobactams by A. Jarrahpour [31]. We have extended its applicability in the synthesis of bis β-lactams by generating it in situ. In our methodology, we have generated this reagent in situ using DMF and $POCl_3$ in dichloromethane as reported [32]. In this paper we wish to describe the versatility and utility of the Vilsmeier reagent for the activation of carboxylic acids in bis-β-lactam synthesis under simple and mild reaction conditions. It has proved to be a high yielding protocol for the synthesis of bis-β-lactams.

RESULT AND DISCUSSION

Chemistry:

We selected 1, 2-diaminobenzene for the preparation of various bisimines from different aldehydes and this imine were used for the construction of bis-β-lactams. The bisimines **3 a–h** were prepared by refluxing 1, 2-diaminobenzene with 2 mole equivalent of aldehydes (benzaldehyde, 2-hydroxybenzaldehyde, 4-hydroxybenzaldehyde, 2-nitrobenzaldehyde, 3-

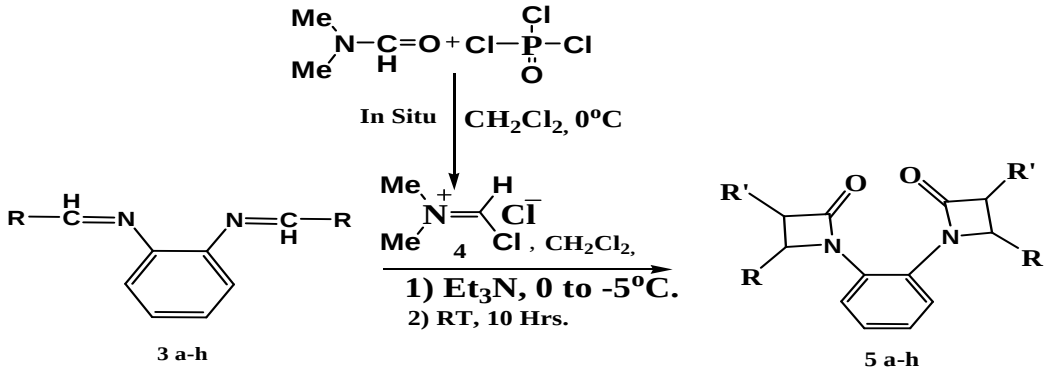
nitrobenzaldehyde, 4-methoxybenzaldehyde, 4-fluorobenzaldehyde and 4-N, N-dimethylaminobenzaldehyde in ethanol for about 1 to 1.5 hrs as shown in **Scheme 1** according to known method [24]. Crude bis-imines were recrystallized with hot methanol.



2a,3a R=C_6H_5 , 2e,3e R=3-$NO_2C_6H_4$,
2b,3b R=2-OHC_6H_4, 2f,3f R=4-N,N-$C_6H_3(CH_3)_2$
2c,3c R=4-OHC_6H_4, 2g,3g R=4-OMe-C_6H_4,
2d,3d R=2-$NO_2C_6H_4$, 2h,3h R=4-F-C_6H_4.

Scheme 1. Synthesis of bis-imines 3 a-h.

Chloromethylenedimethylammonium chloride **4** was prepared from DMF and phosphorus oxychloride in dry CH_2Cl_2 as reported [30]. We have successfully employed the Vilsmeier reagent for the one-step cycloaddition reaction of various imines **3 a-h** and phenoxyacetic acid to obtain bis-β-lactams **5 a-h** (**Scheme 2**). Solution of Chloromethylenedimethylammonium chloride **4** was added to a solution of mixture of acid, imines and triethylamine in CH_2Cl_2 between 0 to -5°C and the reaction mixture was stirred at room temperature for 10 h. The usual work-up and then crystallization from hot methanol gave pure bis-β-lactams **5 a-h** in high yields. We found that this method was very efficient, simple and clean. The DMF and triethylammonium salt are two by-products, which were removed by simple aqueous work-up. In all cases the cycloaddition afforded only *cis*, *cis* bis-β-lactams **5 a-h**.



3a,5a R=C_6H_5 , 3e, 5e R=3-$NO_2C_6H_4$,
3b,5b R=2-OHC_6H_4, 3f, 5f R=4-N,N-ph$(CH_3)_2$,
3c,5c R=4-OHC_6H_4, 3g, 5g R=4-OMe-C_6H_4,
3d,5d R=2-$NO_2C_6H_4$, 3h, 5h R=4-F-C_6H_4.

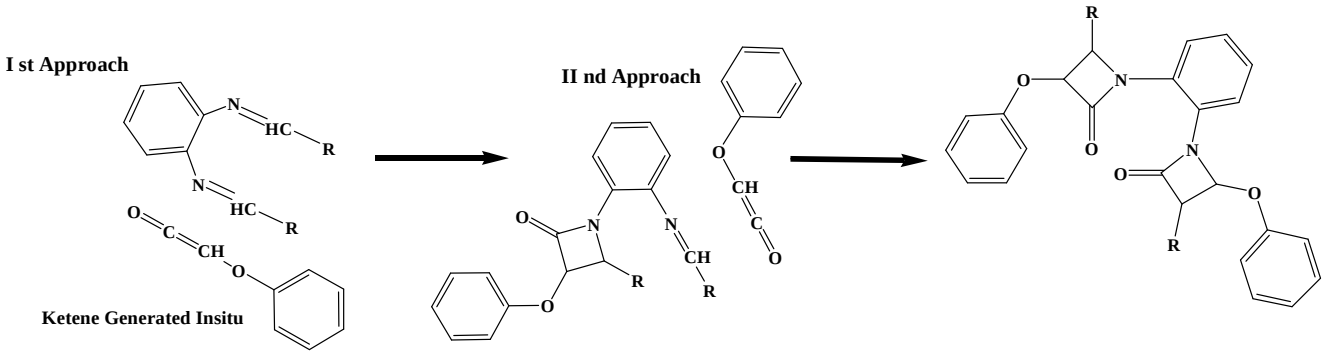
R' = —O—

Scheme 2. General synthesis of bis-β-lactam products 5 a-h.

The *cis* steriochemistry for bis-β-lactam **5 a-h** was assigned on the basis of ^{1}H NMR spectral analysis. The ^{1}H NMR spectra showed two doublets between 5.30 and 5.62 ppm for cis-β-lactam

ring protons (J=4.6 to 4.8 Hz for *cis* β-lactam protons). The absence of –CH=N protons in **5 a-h** show the azetidinone ring formation. The IR spectra of the bis-imines **3 a-h** were compared with those of the bis-β-lactams in order to draw conclusion on cycloaddition. There were some guide peaks in the spectrum of the bis-imines and bis-lactams, which were helpful in achieving this goal. The position and the intensities of these peaks are expected to change upon cycloaddition. In the spectrum of bis-imines, the characteristic absorption around 1620-1655 cm^{-1} can be assigned to (-C=N) azomethine linkage which disappears in the spectrum of the bis-β-lactams confirming the acheivment of cycloaddition. In the spectrum of bis-lactams, the characteristic absorption around 1770-1750 cm^{-1} can be assigned to (-C=0) linkage. The mass spectra of these compounds displayed a molecular ion peak at their respective m/z values which are corresponding well with the respective molecular mass. All the compounds have given the satisfactory elemental analysis.

We believe that mono-β-lactam is initially formed by the reaction of the most stable bis-imine (I^{st} approach) with ketene. The approach of the ketene in the Staudinger cycloaddition reaction is such that the steric interaction between the aryl group of the imine and phenoxy group of the ketene is minimum in



Scheme 3. Approaches in the formation of *cis, cis* bis-β-Lactam.

the transition state (**Scheme 3**) resulting in the formation of *cis*-β-lactam. However, the formation of trans-β-lactam is unfavorable due to severe steric interaction between the aryl group of imine and phenoxy group of ketene in the transition state. The mono β-lactam further undergoes cycloaddition reaction with the second molecule of ketene to give bis-β-lactam (**Scheme 3**). The approach of the second ketene towards the imine is from the opposite site of the preformed azetidinone ring to give bis-β-lactam **5a**. In this approach, the ketenes are generated not from the acid chlorides but directly from the carboxylic acid using Vilsmeier reagent. Thus, the Staudinger reaction of imines with carboxylic acids using Vilsmeier reagent **4** as an activator proceeded smoothly under milder reaction conditions. As acid chlorides are usually unstable, this approach is quite practical as starting carboxylic acid can be easily handled and stored as compared to respected acid chloride.

In vitro antimicrobial screening:

The agar cup plate method using Hi-Media agar medium was employed to study the antibacterial activity of **5 (a-h)** against *S. aureus, p. vulgaris, P. aeruginosa* and *E. coli*. Preparation of

nutrient broth, subculture, base layer medium, agar medium and peptone water was done as the standard procedure. Each test compound (50 mg) was dissolved in dimethylformamide (50 mL, 1000 µg/mL), which was used as sample solution. Sample size for all the compounds was fixed at 0.1 ml. Using a sterilized cork borer, cups were scooped out of Agar medium contained in a petri dish which was previously inoculated with the microorganisms. The test compound solution (0.1 mL) was added in the cups and the petri dishes were subsequently incubated at 37 °C for 48 h. Ampicillin and Streptomycin were used as reference drugs and dimethylformamide as a negative control. Zones of inhibition produced by each compound were measured in mm, and the results are listed in Table 1.

The prepared compounds were examined against two strains each of Gram-positive and Gram-negative bacteria. The test results, presented in Table 1, suggest that compounds **5b**, **5c, 5f** and **5h** are highly active against two strains each of Gram-positive and Gram-negative bacteria showing the broadest spectrum of antibacterial activity. The rest of the compounds were found to be moderately active, slightly active or inactive against the tested microorganisms. The results show that the prepared compounds are toxic against the bacteria.

Table 1. Antibacterial activity of compounds (5a)-(5h).

	Gram (+) bacteria		Gram (-) bacteria	
Compd.	**A**	**B**	**C**	**D**
5a	+++	++	-	-
5b	+++	+++	+++	++
5c	++	++	+	+
5d	++	-	-	+
5e	+	-	+	-
5f	+++	++	+++	++
5g	++	-	-	+
5h	+	++	+	+
AMP	+++	++	++	+++
STREP	+++	+++	+++	+++

AMP: Ampicillin; STREP: Streptomycin. A: S.aureus; B: P.vulgaris; C: E.coli; D: P.aeruginosa. Inactive = - (inhibition zone < 5 mm); slightly active = + (inhibition zone 5-10 mm); moderately active = + + (inhibition zone 10-15 mm); highly active = + + + (inhibition zone > 15 mm).

CONCLUSION

In conclusion, we have shown the application and versatility of chloromethylenedimethylammonium chloride (Vilsmeier reagent) as an acid activator for the synthesis of bis-β-lactams under mild reaction condition via ketene–imine cycloaddition reactions. The Vilsmeier reagent was easily prepared from cheap and available materials in situ. It works out as a versatile acid activator reagent for the direct [2+2] ketene–imine alternate cycloaddition of aromatic acetic acid and bis-imines in one-pot synthesis under mild reaction conditions proving as a high yielding protocol for the synthesis of bis-β-lactams. The antimicrobial screening data revealed that compounds **5b**, **5c, 5f** and **5h** are highly active against two strains each of Gram-positive and Gram-negative bacteria showing the broadest spectrum of

antibacterial activity. The rest of the compounds were found to be moderately active, slightly active or inactive against the tested microorganisms.

MATERIALS AND METHODS

The solvents and reagents used in the synthetic work were of analytical grade obtained from Qualigens India and were purified by distillation or crystallization where necessary and their boiling or melting points were compared with the available literature values. Melting points were determined in open capillaries and are uncorrected. ^{1}H-NMR spectra were recorded on a Perkin Elmer FT-NMR Cryo-magnet Spectrometer 400 MHz (Bruker) instrument using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as a solvent. Chemical shifts are given in parts per million (ppm). Infrared spectra were recorded on Schimadzu-IR Prestige 21. Mass spectra were recorded on a Waters Micromass Q-T of Micro spectrometer. The reactions were monitored and the purity of products was checked out on pre-coated TLC plates (Silica gel 60 F254, Merck), visualizing the spots under ultraviolet light and iodine chamber.

Experimental:

General procedure for the preparation of bis-imines 3 a–h:

A mixture of freshly distilled benzaldehyde (2.78 g, 26.3 mmol) and 1, 2-diaminobenzene (2.20 g, 17.5 mmol) in ethanol (30 mL) was refluxed for 1 to 1.5 hrs. The completion of the reaction was monitored by thin layer chromatography. After disappearance of the starting materials, the reaction mixture was allowed to attain the room temperature during which solid precipitated out. It was filtered out and recrystallized from hot methanol. It was obtained as a yellow crystalline solid. Following this procedure bisimines **3b–h** were prepared in excellent yield.

N, N$^{'}$-dibenzylidinebenzene-1, 2-diamine (3 a):

It was obtained as yellow solid, 87%. M.P., 120-122°C, IR (KBr): 3990, 2970, 2950, 1625, 1355 cm^{-1}. ^{1}H NMR ($CDCl_3$): 6.95-7.60 (m, 14H, Ar), 9.30 (s, 2H, -CH=N). MS: m/z: 284 (M^+, 100%), 285 (72%), 286 (28%). Anal. Calc. for $C_{20}H_{16}N_2$: C, 84.48, H, 5.67, N, 9.85, Found: C, 84.42, H, 5.71, N, 9.88.

N, N$^{'}$-bis (2-hydroxybenzylidine) benzene-1, 2-diamine (3 b):

It was obtained as Orange solid, 85%. M.P., 138-140°C, IR (KBr): 3985, 2972, 2944, 1626, 1352 cm^{-1}. ^{1}H NMR ($CDCl_3$): 12.10 (s, 2H, OH), 6.90-7.55 (m, 12H, Ar), 9.25 (s, 2H, -CH=N). MS: m/z: 316 (M^+, 100%), 317 (67%), 318 (24%). Anal. Calc. for $C_{20}H_{16}N_2O_2$: C, 75.93, H, 5.10, N, 8.86, O, 10.11. Found: C, 75.98, H, 5.15, N, 8.90, O, 10.15.

N, N$^{'}$-bis (4-hydroxybenzylidine) benzene-1, 2-diamine (3 c):

It was obtained as Dark Yellow solid, 82%. M.P., 158-160°C, IR (KBr): 3980, 2975, 2948, 1620, 1350 cm^{-1}. ^{1}H NMR ($CDCl_3$): 12.05 (s, 2H, OH), 6.90-7.50 (m, 12H, Ar), 9.30 (s, 2H, -CH=N). MS: m/z: 316 (M^+, 100%), 317 (65%), 318 (28%). Anal. Calc. for $C_{20}H_{16}N_2O_2$: C, 75.93, H, 5.10, N, 8.86, O, 10.11. Found: C, 75.95, H, 5.16, N, 8.88, O, 10.14.

N, N$^{'}$-bis (2-nitrobenzylidine) benzene-1, 2-diamine (3 d):

It was obtained as Orange solid, 88%. M.P., 122-125°C, IR (KBr): 3970, 2965, 2940, 1625, 1345 cm^{-1}. ^{1}H NMR ($CDCl_3$): 6.85-7.60 (m, 12H, Ar), 9.10 (s, 2H, -CH=N). MS: m/z: 374 (M^+,

100%), 375 (76%), 376 (27%). Anal. Calc. for $C_{20}H_{14}N_4O_4$: C, 64.17, H, 3.77, N, 14.97, O, 17.10. Found: C, 64.20, H, 3.80, N, 14.95, O, 17.13.

N, N'-bis (3-nitrobenzylidine) benzene-1, 2-diamine (3 e):
It was obtained as Orange solid, 86%. M.P., 142-145°C, IR (KBr): 3974, 2970, 2940, 1630, 1347 cm^{-1}. ^1H NMR ($CDCl_3$): 6.80-7.55 (m, 12H, Ar), 9.10 (s, 2H, -CH=N). MS: m/z: 374 (M^+, 100%), 375 (73%), 376 (28%). Anal. Calc. for $C_{20}H_{14}N_4O_4$: C, 64.17, H, 3.77, N, 14.97, O, 17.10. Found: C, 64.22, H, 3.81, N, 14.97, O, 17.14.

N, N'-bis (4-N, N-dimethylbenzylidine) benzene-1, 2-diamine (3 f):
It was obtained as Brown solid, 79%. M.P., 140-143°C, IR (KBr): 3981, 2975, 2944, 1635, 1340 cm^{-1}. ^1H NMR ($CDCl_3$): 3.44 (s, 12H, N-CH_3), 6.75-7.65 (m, 12H, Ar), 9.14 (s, 2H, -CH=N). MS: m/z: 370 (M^+, 100%), 371 (73%), 372 (30%). Anal. Calc. for $C_{24}H_{26}N_4$: C, 77.80, H, 7.07, N, 15.12. Found: C, 77.80, H, 7.07, N, 15.12.

N, N'-bis (4-methoxybenzylidine) benzene-1, 2-diamine (3 g):
It was obtained as Yellow solid, 76%. M.P., 112-115°C, IR (KBr): 3966, 2967, 2945, 1640, 1345 cm^{-1}. ^1H NMR ($CDCl_3$): 3.95 (s, 2H, O-Me), 6.77-7.60 (m, 12H, Ar), 9.15 (s, 2H, -CH=N). MS: m/z: 344 (M^+, 100%), 345 (72%), 346 (25%). Anal. Calc. for $C_{22}H_{20}N_2O_2$: C, 76.72, H, 5.85, N, 8.15, O, 9.23. Found: C, 76.76, H, 5.87, N, 8.19, O, 9.26.

N, N'-bis (4-fluorobenzylidine) benzene-1, 2-diamine (3 h):
It was obtained as Yellow solid, 86%. M.P., 102-105°C, IR (KBr): 3975, 2981, 2950, 1650, 1355 cm^{-1}. ^1H NMR ($CDCl_3$): 6.76-7.45 (m, 12H, Ar), 9.18 (s, 2H, -CH=N). MS: m/z: 316 (M^+, 100%), 317 (65%), 318 (28%). Anal. Calc. for $C_{20}H_{16}N_2O_2$: C, 74.99, H, 4.41, N, 8.75. Found: C, 75.05, H, 4.46, N, 8.78.

A typical procedure for the preparation of bis-β-lactams 5 a–h:
In a 100 ml Round bottom flask, (1.0 g, 3.52 mmol) bis-imine **3a** was charged followed by (10 ml) dichloromethane. To it (1.07 g, 7.04 mmol), Phenoxyacetic acid followed by (1.42 g, 14.08 mmol), triethylamine was charged. It was chilled to -5°C. To a separate 50 ml flask, (1.2 g, 8.04 mmol), $POCl_3$ solution in (10 ml) dichloromethane was prepared. The solution was cooled to 10°C and a solution of DMF (0.50 g, 6.7 mmol), in 5 ml dichloromethane was added over 10 minutes maintaining the temperature between 10 to 15°C. When the addition was complete, the mixture was allowed to stir at room temperature for 30 min. This Vilsmeier solution was then added gradually to the above prepared bis-imine solution over 15 min, maintaining the temperature between 0 and -5°C. After the addition was complete, the reaction mixture was allowed to warm up to room temperature and stirred for 10 h. The reaction mixture was then washed with water (2 x 20 ml), saturated sodium bicarbonate solution (20 ml) and saturated brine solution (20 ml). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated to give the crude bis-β-lactams. It was recrystallized from hot methanol to give pure bis-β-lactams. Following this procedure other β-lactams **5 b–h** were prepared**.**

1-(2-(2-oxo-3-phenoxy-4-phenylazetidin-1-yl) phenyl)-3-phenoxy-4-phenylazetidin-2-one 5(a):
This compound was obtained as white solid, 78%, m.p. 220-223°C, IR (KBr): 3120, 2965, 2970, 1760, 1365 cm^{-1}. ^1H NMR (DMSO-d_6): 5.22 (d, 1H, J=4.8 Hz), 5.55 (d, 1H, J=4.8 Hz), 4.93 (d, 1H, J=4.6 Hz), 5.67 (d, 1H, J=4.6 Hz), 6.50-8.61 (m, 22H, Ar-H). MS: m/z: 552 (M^+, 100%), 553 (71 %), 544 (52 %). Anal. Calc. for $C_{36}H_{28}N_2O_4$: C, 78.24, H, 5.11, N, 5.07, O, 11.58. Found: C, 78.28, H, 5.16, N, 5.11, O, 11.62.

4-(2-hydroxyphenyl)-1-(2-(2-(2-hydroxyphenyl)-4-oxo-3-phenoxyazetidin-1-yl)-phenyl)-3-phenoxyazetidin-2-ones 5(b):
This compound was obtained as white solid, 80%, m.p. 220–223°C, IR (KBr): 3300, 3122, 2960, 2965, 1765, 1368 cm^{-1}. ^1H NMR (DMSO-d_6): 5.25 (d, 1H, J=4.8 Hz), 5.58 (d, 1H, J=4.8 Hz), 4.98 (d, 1H, J=4.6 Hz), 5.86 (d, 1H, J=4.6 Hz), 6.45-8.45 (m, 20H, Ar-H), 11.10 (s, 2H, -OH). MS: m/z: 584 (M^+, 100), 585 (68%), 586 (30%). Anal. Calc. for $C_{36}H_{28}N_2O_6$: C, 73.96, H, 4.83, N, 4.79, O, 16.42. Found: C, 73.98, H, 4.87, N, 4.81, O, 16.47.

4-(4-hydroxyphenyl)-1-(2-(2-(4-hydroxyphenyl)-4-oxo-3-phenoxyazetidin-1-yl)-phenyl)-3-phenoxyazetidin-2-ones 5(c):
This compound was obtained as Buff white solid, 82%, m.p. 186–188°C, IR (KBr): 3300, 3120, 2962, 2964, 1758, 1366 cm^{-1}. ^1H NMR (DMSO-d_6): 5.27 (d, 1H, J=4.8 Hz), 5.57 (d, 1H, J=4.8 Hz), 4.95 (d, 1H, J=4.6 Hz), 5.88 (d, 1H, J=4.6 Hz), 6.447-8.50 (m, 20H, Ar-H), 11.12 (s, 2H, -OH). MS: m/z: 584 (M^+, 100), 585 (73%), 586 (42%). Anal. Calc. for $C_{36}H_{28}N_2O_6$: C, 73.96, H, 4.83, N, 4.79, O, 16.42. Found: C, 73.99, H, 4.89, N, 4.82, O, 16.48.

4-(2-nitrophenyl)-1-(2-(2-(2-nitrophenyl)-4-oxo-3-phenoxyazetidin-1-yl)-phenyl)-3-phenoxyazetidin-2-ones 5(d):
This compound was obtained as yellow solid, 77%, m.p. 182–184°C, IR (KBr): 3122, 2975, 2970, 1755, 1366 cm^{-1}. ^1H NMR (DMSO-d_6): 5.21 (d, 1H, J=4.8 Hz), 5.52 (d, 1H, J=4.8 Hz), 4.88 (d, 1H, J=4.6 Hz), 5.82 (d, 1H, J=4.6 Hz), 6.62-8.20 (m, 20H, Ar-H). MS: m/z: 642 (M^+, 100%), 643 (62%), 644 (26%). Anal. Calc. for $C_{36}H_{26}N_4O_8$: C, 67.29, H, 4.08, N, 8.72, O, 19.92. Found: C, 67.32, H, 4.12, N, 8.77, O, 19.98.

4-(3-nitrophenyl)-1-(2-(2-(3-nitrophenyl)-4-oxo-3-phenoxyazetidin-1-yl)-phenyl)-3-phenoxyazetidin-2-ones 5(e):
This compound was obtained as yellow solid, 72%, m.p. 205–207°C, IR (KBr): 3118, 2971, 2969, 1765, 1365 cm^{-1}. ^1H NMR (DMSO-d_6): 5.20 (d, 1H, J=4.8 Hz), 5.54 (d, 1H, J=4.8 Hz), 4.89 (d, 1H, J=4.6 Hz), 5.95 (d, 1H, J=4.6 Hz), 6.60-8.26 (m, 20H, Ar-H). MS: m/z: 642 (M^+, 100%), 644 (65%), 645 (24%). Anal. Calc. for $C_{36}H_{26}N_4O_8$: C, 67.29, H, 4.08, N, 8.72, O, 19.92. Found: C, 67.34, H, 4.11, N, 8.74, O, 19.97.

4-(4-N, N-dimethylphenyl)-1-(2-(2-(4-N, N-dimethylphenyl)-4-oxo-3-phenoxyazetidin-1-yl)-phenyl)-3-phenoxyazetidin-2-ones 5(f):
This compound was obtained as white solid, 69%, m.p. 192–194°C, IR (KBr): 3120, 2965, 2970, 1755, 1365, 1040 cm^{-1}. ^1H NMR (DMSO-d_6): 3.12 (s, 12H, N-CH_3), 5.28 (d, 1H, J=4.8 Hz), 5.59 (d, 1H, J=4.8 Hz), 4.92 (d, 1H, J=4.6 Hz), 5.98 (d, 1H, J=4.6 Hz), 6.65-8.45 (m, 20H, Ar-H).

MS: m/z: 638 (M^+, 100%), 639 (61%), 640 (23%). Anal. Calc. for $C_{40}H_{38}N_4O_4$: C, 75.21, H, 6.00, N, 8.77, O, 10.02. Found: C, 75.25, H, 6.05, N, 8.80, O, 10.06.

4-(4-methoxyphenyl)-1-(2-(2-(4-methoxyphenyl)-4-oxo-3-phenoxyazetidin-1-yl)-phenyl)-3-phenoxyazetidin-2-ones 5(g):

This compound was obtained as white solid, 71%, m.p. 178–180°C, IR (KBr): 3122, 2965, 2970, 1762 cm^{-1}. ^1H NMR (DMSO-d_6): 3.89 (s, 6H, O-CH_3), 5.25 (d, 1H, J=4.8 Hz), 5.55 (d, 1H, J=4.8 Hz), 4.78 (d, 1H, J=4.6 Hz), 5.91 (d, 1H, J=4.6 Hz), 6.62-8.40 (m, 20H, Ar-H). MS: m/z: 612 (M^+, 100%), 613 (73%), 614 (30%). Anal. Calc. for $C_{38}H_{32}N_2O_6$: C, 74.49, H, 5.26, N, 4.57, O, 15.67. Found: C, 74.49, H, 5.26, N, 4.57, O, 15.67.

4-(4-fluorophenyl)-1-(2-(2-(4-fluorophenyl)-4-oxo-3-phenoxyazetidin-1-yl)-phenyl)-3-phenoxyazetidin-2-ones 5(h):

This compound was obtained as white solid, 76%, m.p. 160–162°C, IR (KBr): 3130, 2971, 2975, 1768 cm^{-1}. ^1H NMR (DMSO-d_6): 5.25 (d, 1H, J=4.8 Hz), 5.58 (d, 1H, J=4.8 Hz), 4.85 (d, 1H, J=4.6 Hz), 5.97 (d, 1H, J=4.6 Hz), 6.52-8.32d (m, 20H, Ar-H). MS: m/z: 588 (M^+, 100%), 589 (76%), 590 (34%). Anal. Calc. for $C_{36}H_{26}F_2N_2O_4$: C, 73.46, H, 4.45, N, 4.45, O, 10.87. Found: C, 73.46, H, 4.45, N, 4.45, O, 10.87.

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REFERENCES

[1]. (a) U, Grafe. Biochemie der Antibiotika, Spectrum Akademischer: Heidelberg, **1992**, p 359, (b) Jones, R. N., Barry, A. L., Thornsberry, C. *J. Antimicrob. Chemother.* **1989**, 24, 9.
[2]. J. W. Clader, D. A. Burnett, M. A. Caplen, M. S. Domalski, H. R. Davis, *J. Med. Chem.* **1996**, 39, 3684–3693.
[3]. D. A. Burnett, M. A. Caplen, H. R. Davis, Burrier, R. E. Clader. **J. Med. Chem. 1994**, 37, 1733–1736.
[4]. R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, F. Maggioni, A. Pugliesi, *J. Org. Chem.* **2003**, 68, 2952–2955.
[5]. M. I. Konaklieva. *Med. Chem. Rev*. **2002**, 1, 133–140.
[6]. R. De´ ziel, E. Malenfant. *Bioorg. Med. Chem. Lett.* **1998**, 8, 1437–1442.
[7]. De, B., Plattner, J. J., Bush, E. N., Jae, H. S., Diaz, G., Johnson, E. S., Perun, T. J. *J. Med. Chem.* **1989**, 32, 2036–2038.
[8]. D. M. Smith, A. Kazi, L. Smith, T. E. Long, B. Heldreth, E. Turos, Q. P. Dou. Mol. *Pharmacol*. **2002**, 61, 1348–1358.
[9]. M. S. Manhas, S. G. Amin, A. K. Bose. *Heterocycles.* **1976**, 5, 669.
[10]. C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide. *Curr. Med. Chem.* **2004**, 11, 1837.
[11]. I. Ojima, N. Hatanaka, N. Yoda, R. Abe, M. Yatabe, M. Yanashita. In Peptide Chemistry, Sakakibara, S., Ed., Protein Research Foundation: Osaka, **1983**, pp 29–34.

[12]. I. Ojima, M. Zhao, T. Yamato, K. Nakahashi, M. Yamashita. R. Abe. *J. Org. Chem*. **1991**, 56, 526.
[13]. A. Parvez, M. Jyotsna, Y. Hamid, H. Taibi. Article accepted for publication in *Phosphorus, Sulphur, Silicon and related elements*. Manuscript ID (GPSS-**2009**-0124.R_1).
[14]. A. Parvez, M. Jyotsna, T. Vandana. *Journal of Heterocyclic Chemistry*. Article in Press. Manuscript ID (TGCL-**2009**- 0123).
[15]. H. Staudinger. *Liebigs Ann. Chem.* **1907**, 356, 51–123.
[16]. R. B. Morin, M. Gorman. Chemistry and Biology of β-Lactam Antibiotics, Academic: New York, NY, **1982**.
[17]. F. H. Van der Steen, G. Van Koten. *Tetrahedron*. **1991**, 47, 7503–7524,
[18]. Georg, G. I. The Organic Chemistry of β-Lactams. VCH: New York, NY, **1993**.
[19]. M. Nahmany, A. Melman. *J. Org. Chem*. **2006**, 71, 5804–5806.
[20]. A. R. Deshmukh, D. Krishnaswamy, V. V. Govande, B. M. Bhawal, V. K Gumaste. *Tetrahedron*. **2002**, 58, 2215.
[21]. A. K. Bose, Manhas, M. S., Amin, S. G., Kapur, J. C., Kreder, J., Mukkavilli, L., Ram, B., Vincent, J. E. *Tetrahedron Lett*. **1979**, 2771–2774.
[22]. A. K. Bose, J. C.Kapur, S. D. Sharma, M. S. Manhas. *Tetrahedron Lett*. **1973**, 2319–2320.
[23]. A. Jarrahpour, M. Zarei. *Molecules* **2007**, 12, 2364–2379.
[24]. A. Bhalla, P. Venugopalany, S. S. Bari. *Tetrahedron* **2006**, 62, 8291.
[25]. M. S. Manhas, A. K. Bose, M. S. Khajavi. *Synthesis* **1981**, 209.
[26]. S. Matsui, Y. Hashimoto, K. Saigo. *Synthesis* **1998**, 1161.
[27]. P. D. Croce, C. La Rosa. *Tetrahedron: Asymmetry* **1999**, 10, 1193.
[28]. E. Campaigne, W. L. Archer,. *J. Am. Chem. Soc.* **1953**, 75, 141.
[29]. H. Eilingsfeld, M. Seefelder, H. Weidenger. *Angew. Chem.* **1969**, 72, 836.
[30] U. C. Dyer, D. A. Henderson, P. D. Tiffin. *Organic Process Research & Development* **2002**, 6, 311-316.
[31] A. Jarrahpour, M. Zarei. *Tetrahedron letters*. **2007**, 48, 8712.