IJPSR (2015), Vol. 6, Issue 3 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 03 July, 2014; received in revised form, 25 September, 2014; accepted, 16 November, 2014; published 01 March, 2015

β-LACTAMS: A MINI REVIEW OF THEIR BIOLOGICAL ACTIVITY

Apoorva Gupta* and A. K. Halve

School of Studies in Chemistry, Jiwaji University, Gwalior (M. P.), 474011, India

Keywords:

β -lactam, Antimicrobial, Anti tubercular, Anticancer, Antidiabetic

Correspondence to Author:
Apoorva Gupta

Research Scholar
School of Studies in Chemistry,
Jiwaji University,
Gwalior (M.P.), India

E-mail: apoorva.phd12@gmail.com

ABSTRACT: Synthesis of heterocylic compound has always drawn the attention of chemist over the years mainly because of their important biological properties. Particularly, the role of β–lactam which are endowed with unique structure and potent biological activity. The β-lactam heterocycles are considered as an important contribution of science to humanity since they have been constituents of living organisms, natural products, drugs and many more substances useful to mankind and society in all walks of life. Their synthesis and evaluation has always drawn the attention of biologists over the years. β-lactam, a four member heterocyclic compound involved in research aimed to evaluate new products that possess interesting biological activities. Natural and synthetic β-lactam derivatives occupy a central place among medicinally important compounds due to their diverse and interesting antibiotic activities and are still the most prescribed antibiotics used in medicine. The present review article focuses on the pharmacological profile of β-lactam with their potential activities. The ring system exhibits a wide range of activities like antimicrobial, antitubercular, anticancer, antidiabetic, tryptase and chymase inhibitory activity etc. attracting the attention of researchers. The biological profile of β–lactam reported by organic chemist is reviewed here comprehensively with examples under eleven different activities.

INTRODUCTION: Nitrogen heterocycles comprise the vast majority of medicinal on the market today. The four membered β-lactam ring system has for many years been of great practical significance as the centre of reactivity and because of their important biological properties [1]. Recent years have seen a resurgence of interest in the development of stereo- and enantioselective methodologies. The utility of β –lactam as synthons for various biologically active compounds [2]. Since then a plethora of work has appeared in the literature. It would therefore be useful to review the work done in this area more frequently [3]. The purpose of this review is to assemble the literature dealing with the biological activity of β -lactam.

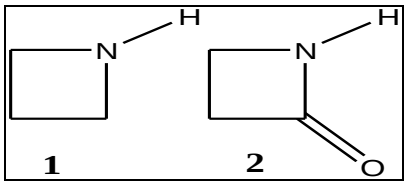
QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(3).978-87

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(3).978-87

Azetidine **1** and its derivatives constitute an important class, four membered heterocyclic compounds possessing diverse biological activities. The 2-Carbonyl derivatives of azetidines are called 2-azetidinones **2** or more commonly named as β-lactams.



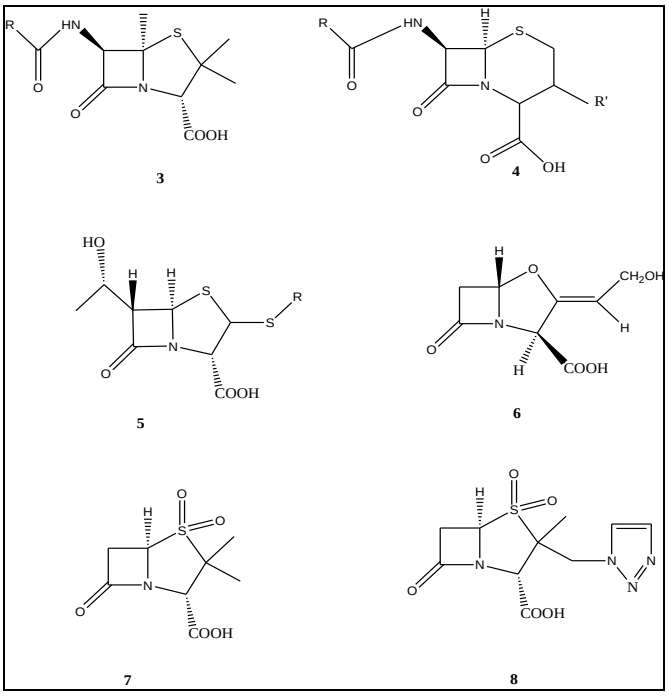
1 **2**

Since the discovery of penicillins [4] and cephalosporins as the most successful antibiotics, β-lactam have been the subject of regular discussion and investigation The β-lactam ring system is the common structural feature of a number of broad spectrum β-lactam antibiotics, including penicillins **3**, cephalosporins **4**, carbapenems **5**, clavulanic acid **6**, sulbactams **7** and tazobactams **8**, which have been widely used as

chemotherapeutic agents to treat bacterial infections and microbial diseases.

These molecules operate by forming a covalent adduct with membrane bound bacterial transpeptidases which are also known as penicillin binding proteins (PBPs) and prevent the biosynthesis of cell wall [5]. The biological activity of the β-lactam skeleton is generally believed to be associated with the chemical reactivity of the β-lactam ring as well as the substituents especially at the nitrogen of the β-lactam ring. The substituents at the N-1, C-3 and C-4 position may be varied. The continuous increase in the activity spectrum of the β-lactam antibiotics and also the discovery of more types of microorganisms producing them can be attributed to the development of more sensitive screening techniques.

This has given impetus to increased interest in synthesis and evaluation of more and more derivatives of β-lactam. Furthermore, the β-lactam ring also serves as a synthon or versatile intermediates for the synthesis of aromatic amino acid derivatives, peptides, polyamines, polyamino alcohols, amino sugars and polyamino ethers, as well as, for many biologically important classes of organic compounds [6-17]. Due to this, the investigation into the chemistry of these compounds continues to appeal the synthetic and medicinal organic chemists world over.



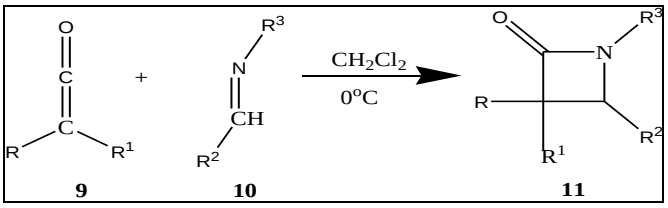
SYNTHESIS:

Many synthetic methods have been developed for the formation of the β-lactam. Staudinger's keteneeimine reaction is the most common method for the synthesis β-lactam ring.

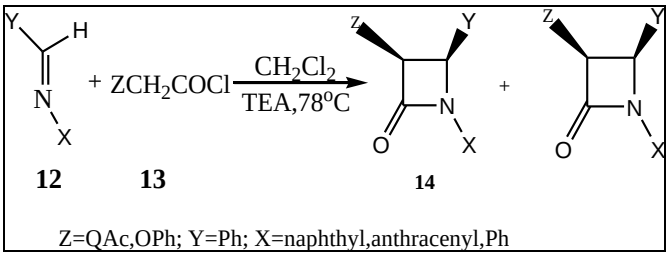
Staüdinger reaction:

Keteneeimine cycloaddition:

Keteneeimine cycloaddition was reported by Staüdinger [18] in 1907 and it has been applied to the synthesis of a wide variety of β-lactam structures. This reaction is still now-a-days one of the majorly used synthesis of β-lactam derivatives. The formal [2 þ 2]-cycloaddition of ketenes **9** to imines **10** to forms β-lactam **11**.



Banik and Becker [19] have reported for the first time the reaction of the polycyclic aromatic imines **12** with acid chlorides **13** under normal Staüdinger conditions, leading to the formation of the trans-azetidinones **14.**



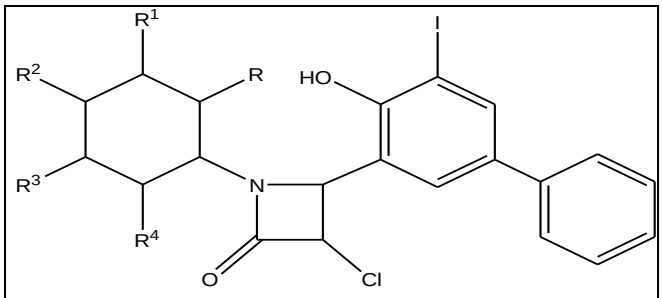
Biological profile:

Anti microbial:

β-lactam and their derivatives are still the most widely used antibiotics and have shown a broad spectrum of activity against various pathogens. Since the discovery of penicillins, many antibiotic compounds containing β-lactam moiety have been isolated from natural sources or synthesized chemically, or are semi synthetic derivatives of the natural scaffolds produced by microorganisms.

Junne *et al.* [20] studied the effect of more bulky aryl substituents at the 4-position of the azetidin-2-one moiety. They have prepared a series of 3-chloro-4-

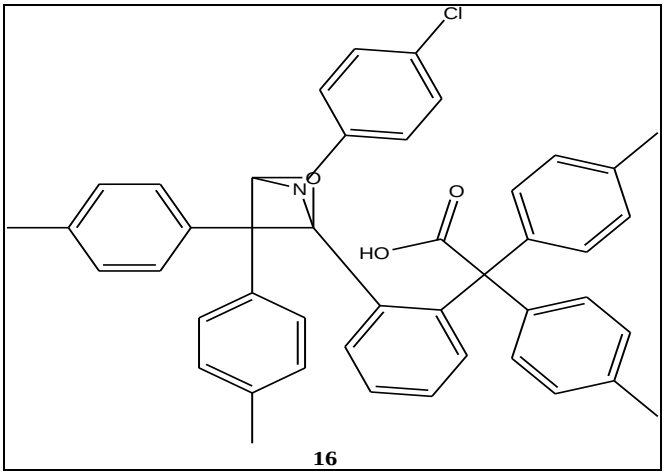
(4 - hydroxy - 5 - iodobiphenyl - 3 - yl) -1 (substitutedphenyl) azetidin-2-one **15** derivatives and screened for antibacterial activity against *Xanthomonas citri, E. coli, Erwinia carotovora* and *B. subtilis* using penicillin G as standard antibiotic for comparison.



R,R^1,R^2,R^3,R^4= H,H,NO_2 ,H,I;H,H,I,H,NO_2;
H,H,I,H,Cl;H,H,Cl,H,I;Cl,H,I,H,Cl
I,H,Me,H,I;I,H,NO_2,H,I;
Me,I,H,NO_2,H;H,H,COOH,H,I;
I,H,COOH,H,I;I,H,H,NO_2,H;
H,H,H,Cl,I;H,H,I,H,COOH;

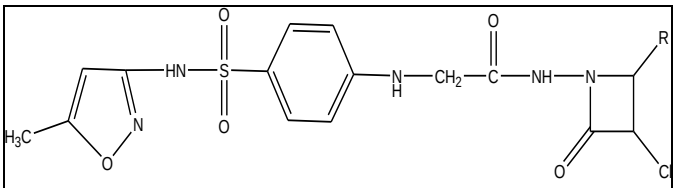
15

Some of the compounds were found to be nearly equal or more active against all the bacteria tested, except *B. subtilis* as compared to the standard. On similar lines Singh *et al.* [21], have synthesized a series of some novel 2-azetidinone derivatives through the reactions of N-salicylideneamines with diarylketenes generated from thermal decomposition of the 2-diazo-1, 2- diarylethanones **16**. The products were screened for their antibacterial and antifungal activity against *S. aureus, E. coli, P. aeruginosa, B. subtilis, Candida mycoderma* and *Saccharomyces cerevisiae*. The compounds exhibited moderate to good activity.



16

I.K. Bhat *et al.* [22], have prepared a series of N-[3-chloro-4-(4-substitutedphenyl)-2-oxoazetin-1-yl]-2-(N'-5-methyl-3-isoxazolyl) sulphonamides **17** using sulfadiazine and sulfamethoxazole as starting materials, respectively. The compounds were tested for their antibacterial and antifungal activities against four different bacterial cultures, viz., *S. aureus, E. coli, P. aeruginosa and B. subtilis* and one fungal culture; *C. albicans*. Sulfadiazine, ampicillin and griseofulvin were used as standards for antibacterial and antifungal activities. Some of the synthesized compounds showed remarkable antibacterial and antifungal activities as comparable to the standard drugs.



R=2-OHPh,4-OMeh,4-NMe_2Ph

17

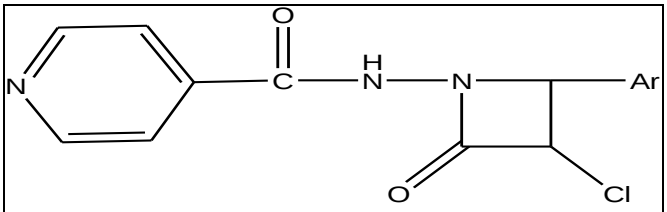
Anti tubercular activity:

Tuberculosis (TB) caused usually by Mycobacterium tuberculosis remains the major cause of death all over the world. In 2011, there were approx. 8.7million cases of TB of which 1.4 million deaths were of TB amongst HIV-negative people and 0.43 million deaths of people having HIV-associated TB.

Multidrug-Resistant Tuberculosis (MDRTB) refers to M. tuberculosis strains with resistance to the two most effective antituberculosis drugs, isoniazid (INH) and rifampin (RFP). MDRTB has become a major barrier to achieving successful control of TB, as alternate therapy is less effective, associated with more adverse events and is more costly to treat as compared to the standard first line therapy. Therefore, now a days there is a growing demand for a new class of antitubercular agents, preferably acting through a new mode of action.

S. Hussain et al.[23], have synthesized a series of N-[3-chloro-4-(aryl)-2-oxoazetidin-1-y]-pyridine-4-carboxamides **18** and screened for antimycobacterial activity, against standard strain

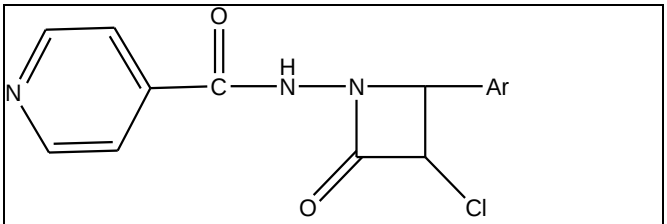
H37Rv and two other human strains [Human strain-I and Human strain-II] isolated from patients suffering from pulmonary tuberculosis. Isoniazid was used as standard drug. The compounds showed significant antimycobacterial activity.



Ar=4-OHPh,4-MePh,
4-OMePh,4-NMe_2Ph

18

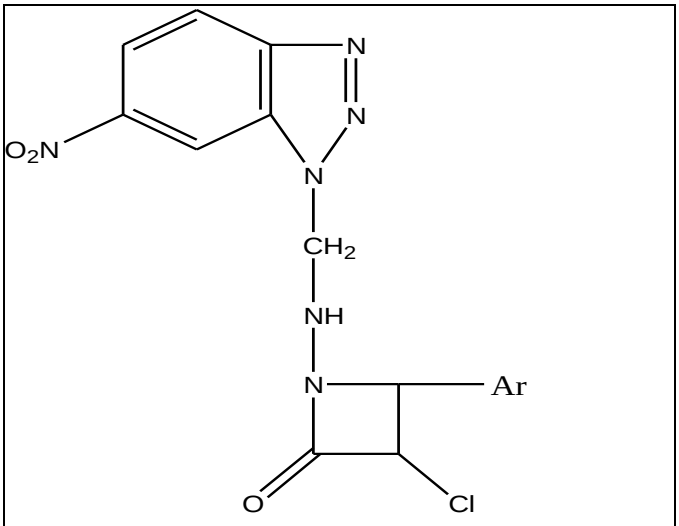
Nikalje et al. [24], have reported the synthesis and QSAR study of novel N-(3-chloro-2-oxo-4-substitutedazetidin-1-yl) isonicotinamide **19** derivatives as antimycobacterial agents against M. tuberculosis H_{37}Rv. Isoniazid and rifampicin were used as reference standards. Comparative study of the substitution pattern of the aryl and heteryl group at C-4 toward antimycobacterial activity has shown that electron donating groups impart better activity while electron withdrawing groups cause less activity. The QSAR model indicated the thermodynamic descriptors (molar refractivity), electronic descriptors (dipole moment), principal moment inertia etc, play to important roles in the antimycobacterial activities of these compounds.



Ar=4-ClPh,4-NO_2Ph,2-OHPh,4-OHPh,
4-OH-3-OMePh,4-OMePh,4-NMe_2Ph,
Ph,Furfuryl,etc

19

A novel series of 3-chloro-1-{[2-(6-nitro-1H-indazol-1-yl) ethyl] amino}-4-(substituted-phenyl)-2-azetidinones **20** were synthesized in four steps from 6-nitro-1H-indazole by Samadhiya et al. [25]
For the evaluation of antitubercular activity against M. tuberculosis (H_{37}Rv strain), isoniazid and rifampicin were taken as standards (MIC range 1.25-2.50 mg/ml). Results revealed that the nitro group containing compounds showed higher activity than chloro or bromo containing compounds. The sequence of the activity was found as NO2 > Cl > Br > H.



Ar= Ph,4-ClPh,3-ClPh,2-ClPh,4-BrPh,3-BrPh,
2-BrPh,4-NO_2Ph,3-NO_2Ph

20

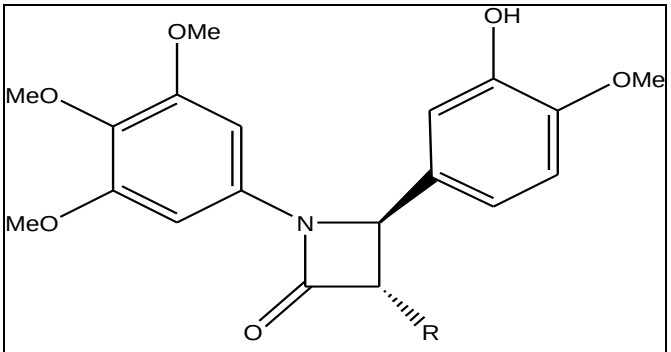
Anticancer:

Cancer can be defined as a disease in which a group of abnormal cells grow uncontrollably by disregarding the normal rules of cell division. In fact, almost 90% of cancer-related deaths are due to tumor spreading process call metastatis. Cancer is caused by both internal factors (such as inherited mutations, hormones, and immune conditions) and acquired factors (such as tobacco, diet, radiation, and infectious organisms). Anticancer drug discovery is a major area of research, worldwide.

O'Boyle *et al.* [26], have also synthesized a series of azetidin-2-ones substituted at positions 1, 3 and 4 of the azetidinone ring scaffold via the Staüdinger reaction and evaluated for antiproliferative, cytotoxic and tubulin-binding activity. In these compounds, the cis double bond of the vascular

targeting agent combretastatin A-4 is replaced with the azetidinone ring in an attempt to enhance the antiproliferative effects displayed by combretastatin A-4 and prevent the cis/trans isomerization that is associated with inactivation of combretastatin A-4. Of a diverse range of heterocyclic derivatives the 3-(2-thienyl) analog I and 3-(3-thienyl) analog II **21** displayed the highest potency in human MCF-7 breast cancer cells with IC50 values of 7 nM and 10 nM, respectively, comparable to combretastatin A-4. Compounds from this series also exhibited potent activity in MDA-MB- 231 breast cancer cells and in the NCI60 cell line panel. No significant toxicitywas observed in normal murine breast epithelial cells. The presence of larger, bulkier groups at the 3-position, e.g., 3-naphthyl derivative and 3-benzothienyl derivative, resulted in relatively lower antiproliferative activity in the micromolar range.

Tubulin-binding studies of I (IC50 ¼ 1.37 mM) confirmed that the molecular target of this series of compounds is tubulin. These novel 3-(thienyl) β-lactam antiproliferative agents are useful scaffolds for.the development of tubulin-targeting drugs.



21

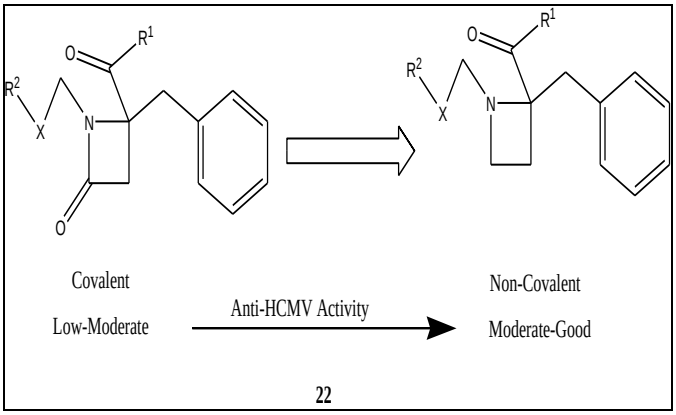
R= 2-thienyl(I),3-thienyl(II)

D. Human cytomegalovirus protease activity:

Human cytomegalovirus (HCMV) is a ubiquitous member of the herpes virus family. Although most infections are asymptomatic, severe manifestations of HCMV can be seen in individuals whose immune system has been weakened by a disease, such as late-stage cancers and AIDS, or by immunosuppressive therapy following organ transplantation. What makes this protease unique is that, the HCMV serine protease active site is composed of a His-His-Sertriad, instead of the usual Asp-His-Ser catalytic triad, which is found in most trypsin-like proteases. Due to its critical role in capsid assembly and viral maturation, HCMV serine protease has become an attractive target for the development of anti-HMCV drugs Starting from the structure of known β–lactam covalent HCMV protease inhibitors and the knowledge of the residues implicated in the active site of this enzyme, G.G.Navarro et al. [27] designed a series of phenylalanine-derived β –lactam bearing a 4-carboxylate moiety that could be apt for additional interactions with the guanidine group of the Arg165/Arg166 residues of the viral protease.

Some compounds within this series showed anti-HCMV activity at 10-50 mM, but rather high toxicity. The presence of aromatic 1-acyl groups and a certain hydrophobic character in the region of the 4-carboxylate were stringent requirements for anti- HCMV activity. To go a step ahead into the search for effective.

HCMV medicines, a series of non covalent inhibitors by simple deletion of the carbonyl group in the β -lactam derivatives to provide the corresponding azetidines was developed **[**Conversion of β -lactam derivatives to corresponding azetidines] **22**. This led to low micromolar inhibitors of HCMV replication, particularly promising lead compounds for further investigation, although their toxicity still needs to be lowered.



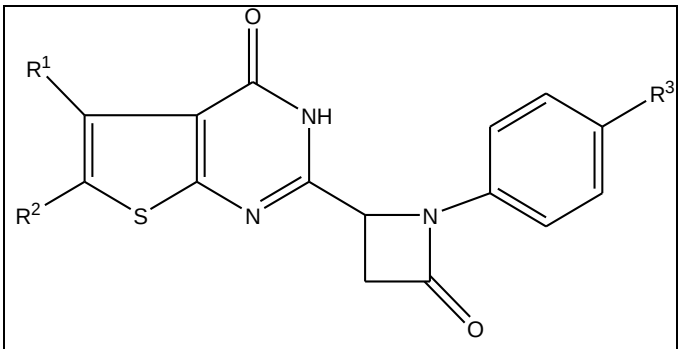
22

Cholesterol absorption inhibitory activity:

Elevated lipid levels, one of the main risk factors of atherosclerosis and related cardiovascular diseases and stroke (and is directly connected to mortality and morbidity). Lipid lowering is one of the major

approaches employed to prevent coronary heart diseases and stroke. Therefore, designing, synthesizing and evaluating a variety of new molecules for antihyperlipidemic activity is a major area of research.

Jain *et al*. [28], have synthesized a series of novel 2-[1-(substitutedphenyl) - 4-oxo-azetidin-2-yl]-5, 6-disubstitutedthieno [2, 3-d] pyrimidin-4(3H)-ones **23**. The compounds are thienopyrimidine derivatives of the β –lactam designed to combine the structural features of azetidin-2-one moiety with the potentially antihyperlipidemic, 2-substitutedthieno [2, 3-d]-pyrimidin-4-ones. The compounds were evaluated for their lipid lowering activity in Wistar albino rats. Some of them showed significant lipid lowering effects.



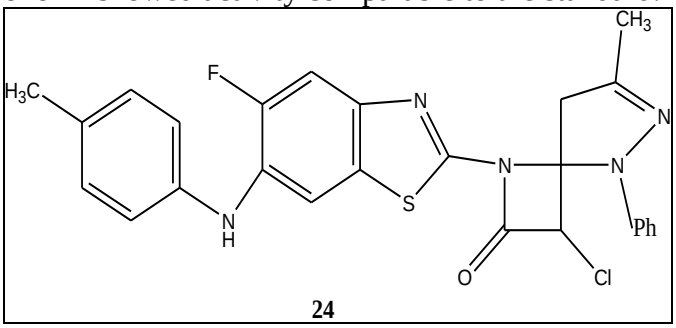
R^1,R^2= aryl,cycloalkyl,H etc;R^3= alkyl,halo etc.

23

Anti-diabetic activity:

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. Insulin deficiency in turn leads to chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism.

Reddy *et. al.* [29] series of N1-benzothiazolyl-3-chloro-1,5,6-triazaspiro[3.4] oct – 6 – en – 2 - ones prepared through the stepwise condensation of 3-methyl - 1 - phenyl -5 - pyrazolone with the aminobenzothiazole to form the Schiff base, followed by its cyclization with ClCOCH2Cl to form the β –lactam which were finally condensed with different primary and secondary amines. This was screened for anti-diabetic activity by using a-amylase inhibition activity based on colorimetric method and acarbose was used as control for comparison. Among these the compound; 3-chloro-1-(6-fluoro-7- p-tolylaminobenzothiazol-2-yl)-7-methyl-5-phenyl-1,5,6- triazaspiro[3.4]-oct-6-en-2-one **24** showed activity comparable to the standard.

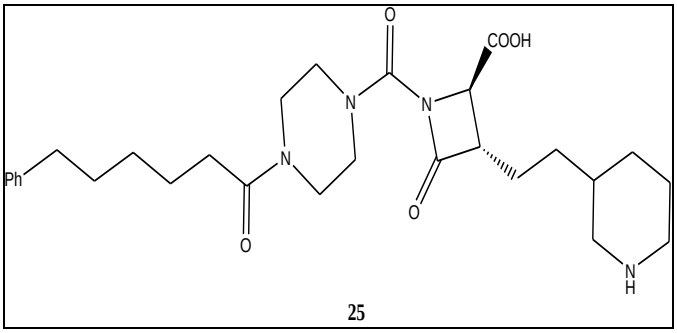


24

Tryptase and chymase inhibitory activity:

Tryptase and chymase are serine proteases that are almost exclusively located to the secretory granules of mast cells. They are the most abundant protein products in mast cell granules, which consist of approximately 50% total protein in the granules. Upon degranulation, tryptase and chymase are released from mast cells along with histamine, heparin, and other mast cell granule products.Large quantities of active form tryptase and chymase (up to 40 pg, per mast cell) in mast cells implicate that these mast cell unique mediators are likely to play a role in mast cell related diseases.

Bisacchi *et al*. [30], carried out the synthesis of a number of potent β –lactam tryptase inhibitors in which the guanidine moiety at the ring C-3 position of BMS-363131 and BMS- 363130 was replaced with primary or secondary amine or aminopyridine functionality and found that one of the compound BMS-354326 **25** having an IC50 for tryptase of 1.8 nM, displayed excellent selectivity against trypsin and most other related serine proteases.



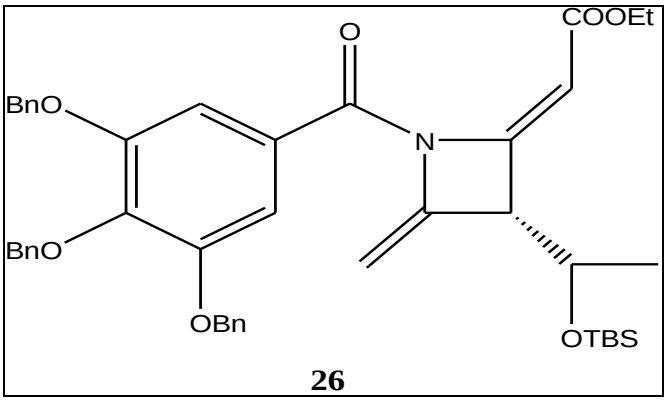
25

Human leukocyte elastase inhibitory activity:

Human leukocyte elastase (HLE) is a serine protease found in the azurophilic granules of the neutrophil. It is also known as human neutrophil elastase. They have the ability to degrade elastin

and other connective tissue components. The imbalance between HLE and its endogenous inhibitors and the subsequent excessive elastin proteolysis has been implicated in acute and chronic inflammatory diseases of the lungs. Thus, specific inhibitors of HLE capable of restoring the protease/antiprotease imbalance might be beneficial in such pathologies.

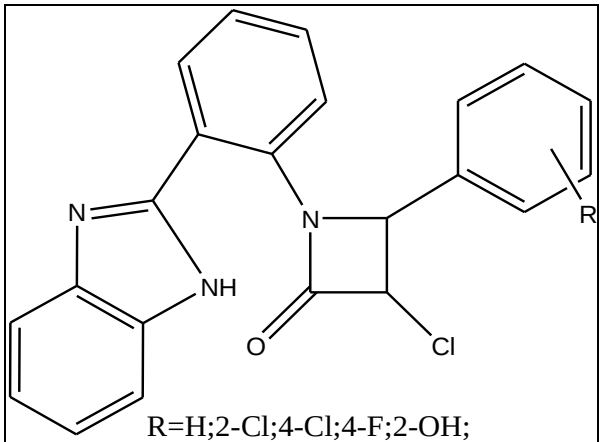
A series of compounds combining the β-lactam and polyphenol scaffold were prepared and evaluated for inhibition of human leukocyte elastase and matrix metallo-proteases MMP-2 and MMP- 9 by Cainelli et al. [31]. The compounds were designed based on the 'overlapping-type' strategy where two pharmacophores are linked in a single molecule. The most powerful compound against elastase was an N-galloyl-4-alkyliden β–lactam[3-[1-(tertbutyldimethylsilanyloxy)ethyl]-2-oxo-1-(3,4,5-tris-benzyloxybenzoyl azetidin-4-ylidene]-aceticacidethylester **26**, with an IC50 of 0.5 mM; while the most powerful against MMP-2 was a 4-alkyliden b-lactam arylated on the C-3 hydroxy side chain (3, 5-bisbenzyloxy – 4 - hydroxy benzoicacid-1-(2-ethoxycarbonylmethylene-2-oxo-azetidin-3-yl)ethyl-ester) with an IC50 of 4 mM. Of the total 35 compounds tested, high levels of inhibition of elastase and of MMPs were separately exerted by distinct molecules.



26

Analgesic and anti-inflammatory activities:

β –lactam are the important pharmacodynamic heterocyclic nuclei and have been combined with various heterocyclic templates to give hybrid structures.A series of 1-(2-(1H-benzimidazol-2-yl) phenyl) – 3 – chloro – 4 - (un/substituted -phenyl) azetidin-2-ones **27** have been synthesized and screened them for analgesic and anti-inflammatory activities on acetic acid induced writhing in mice and carrageenan induced pawedema in rats by Chhajed *et al.* [32]. One of the compound (R ¼ Cl) exhibited better analgesic and anti-inflammatory potential as compared to the standard drug nimesulide. To check binding modes and binding affinity of synthesized compounds were docked into the active sites of enzyme COX-II. A good correlation is found between in silico docking analysis and biological screening.



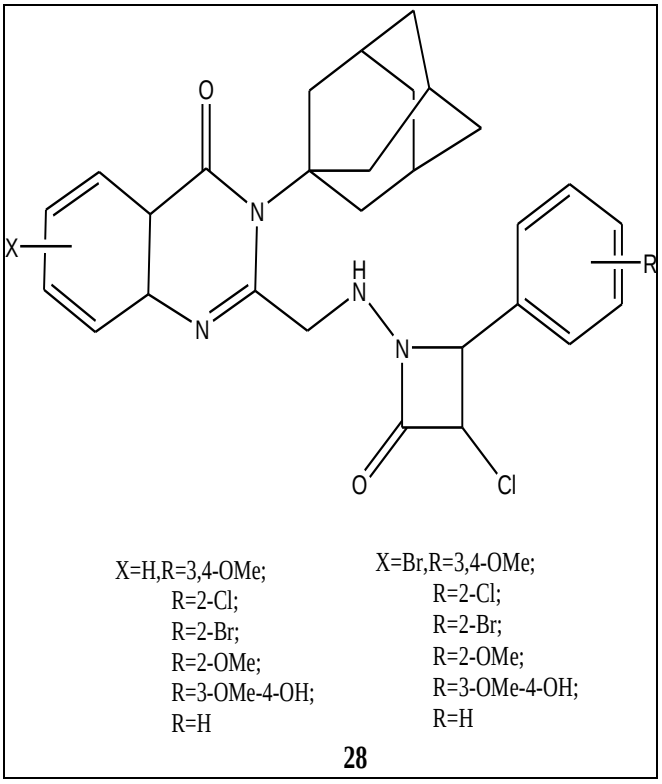
27

Antiparkinsonian activity:

Parkinson's disease is one of the most common progressive neurological degenerative disorders. It is characterized by motor dysfunction including resting tremor, slowness of movements (bradykinesia), difficulty in initiating movements (akinesia), rigidity, gait disturbance and postural instability as well as the more recently emphasized non-motor dysfunctions. The pathological hallmark of Parkinson's disease is progressive dopamine neuronal loss within the *substantia nigra* and other brain structures combined with the appearance of intracytoplasmic inclusions composed of a-synuclein aggregates known as Lewy bodies. The cerebellum is also a potential target for some parkinsonian symptoms.

S. Kumar *et al.* [33] quinazolinone derivatives as antiparkinsonian agentshave synthesized and screened a series of 3-amantadinyl-2-[(4-(substituted-phenyl) - 3 - chloro - 2 - oxoazetidin – 1 -yl) methylamino] quinazolin-4(3H)-ones **28** for antiparkinsonian activity. These compounds exhibited almost equipotent antitremor activity as L-dopa. The newly synthesized compounds were

also tested for approximate lethal dose LD_{50} and were found to exhibit a higher value, LD_{50} i.e., more than 1000 mg/kg.



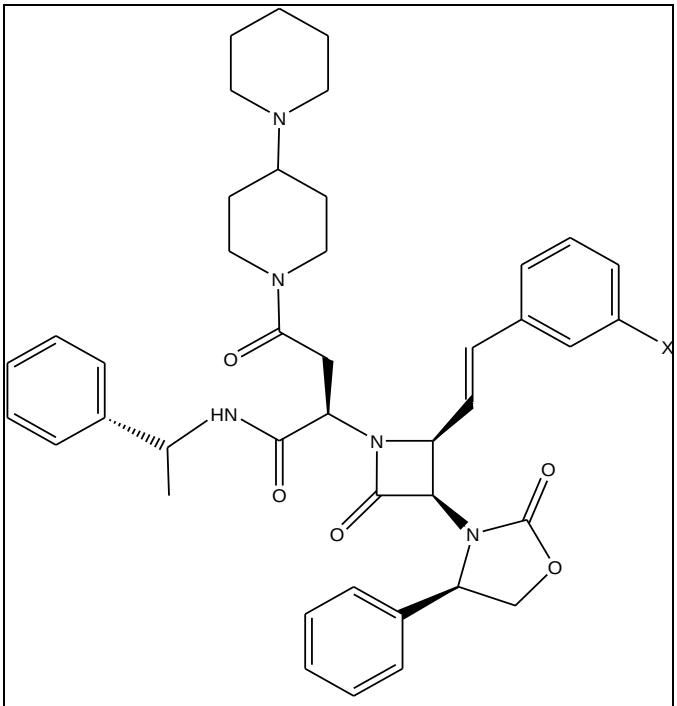
28

Vasopressin via antagonist:

Arginine vasopressin (AVP) is a cyclic non apeptide synthesized exclusively by neurosecretory cells of the central nervous system (CNS). Three distinct AVP receptor subtypes; V1a, V1b, and V2 have been identified, of which, V1a is predominantly found in the brain, especially high levels are found in the cerebral cortex, limbic system, hypothalamus and brainstem. K.

Fabio *et al.* [34] have developed a reliable method to prepare a versatile precursor that should allow access to both PET (18F, 11C) and SPECT (123I) derivatives of SRX246 {(R)-4-([1,4-Bipiperidin]-10-yl)-2-((2R,3S)-2-((E)-3-substitutedstyryl) - 4 - oxo-3-((S)-2-oxo-4-phenyloxazoli din – 3 - yl) azetidin-1-yl) - 4 - oxo - N - ((R) – 1 - phenylethyl) Butanamides}**29**, a highly selective and potent hV1a antagonist.

Other compounds bearing F, I, and Mewere also synthesized and have shown that they exhibit strong hV1a receptor affinity, do not bind to V1b and V2 receptors, and have a high likelihood of brain penetration based on PAMPA-BBB results. For each compound, the potential utility of corresponding radiolabeled analogs for PET and SPECT imaging is discussed. These findings offer the potential to begin a broader investigation into the role of the human vasopressin V1a receptor in various CNS functions using relevant imaging tracers.



29

CONCLUSION: β-lactam is a versatile biologically important scaffold, as well as, synthon for various biologically important compounds thus, making it an appealing target for medicinal chemists all over the world. An attempt has been made to review biological profiles of various β-lactam derivatives.

ACKNOWLEGEMENT: We are thankful to the Head, School of studies in Chemistry and Central Library of Jiwaji University, Gwalior, India for providing necessary facility and support of this work.

REFERENCES:

1. Balaban AT, Oniciu DC and Katritzky AR: Aromaticity as a cornerstone of heterocyclic chemistry. Chem. Rev, 2004; 104:2777-2812.

2. Morin RB and Gorman M: Chemistry and Biology of b-lactam Antibiotics, sixth ed. Academic Press, New York, 1982.
3. Brandi A, Cicchi S and Cordero FM: Novel syntheses of azetidines and azetidinones. Chem. Rev, 2008; 10:3988-4035.
4. Fleming A: On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenzae. Br. J. Exp. Pathol, 1929; 10:226-236.
5. Knowles JR: Penicillin resistance- the chemistry of .beta.-lactamase inhibition .Acc. Chem. Res, 1985; 18:97-104.
6. Zarei M, Mohamadzadeh M: 3-Thiolated 2-azetidinones: synthesis and in vitro antibacterial and antifungal activities. Tetrahedron, 2011; 67: 5832-5840.
7. Noolvi M, Agrawal S, Patel H, Badiger A, Gaba M, Zambre A: Synthesis, antimicrobial and cytotoxic activity of novel azetidine-2-one derivatives of 1H-benzimidazole. Arabian Journal of Chemistry, 2011; doi: 10.1016 /j.arabjc. 2011.02.011.
8. Kaura A, Sharma L, Dharb VJ: Synthesis, spectral and antimicrobial study of some novel schiff bases and beta-lactam Derivatives. Int. J. Chem. Sci, 2011; 9:2009-2015.
9. Dubey A, Srivastava SK, Srivastava SD: Conventional and microwave assisted synthesis of 2-oxo-4-substituted aryl-azetidine derivatives of benzotriazole: A new class of biological compounds. Bioorganic & Medicinal Chemistry Letters, 2011; 21: 569–573.
10. Sharma R, Samadhiya P, Srivastava SD, Srivastava SK: Synthesis and pharmaceutical importance of 2-azetidinone derivatives of phenothiazine. J. Chem. Sci, 2012; 124: 633–637.
11. Saundane AR, Yarlakatti M, Walmik Pand Katkar VK: Synthesis, antioxidant and antimicrobial evaluation of thiazolidinone, azetidinone encompassing indolylthienopyrimidines. J. Chem. Sci, 2012; 124: 469–481.
12. Pathak RB, Chovatia PT, Parekh HH:Synthesis, antitubercular and antimicrobial evaluation of 3-(4-chlorophenyl)-4-substituted pyrazole derivatives. Bioorganic & Medicinal Chemistry Letters, 2012; http://dx.doi.org/10.1016/j.bmcl.2012.05.063.
13. Chopde HN, Meshram JS, Pagadala R: Synthesis, characterization and antibacterial evaluation of some azetidinone derivatives of 3-methyl-1H-pyrazol-5(4H)-one. Archives of Applied Science Research, 2012; 4 (3):1442-1446.
14. Mashelkar UC, Jha MS, Mashelkar BU: Synthesis of 2-azetidinones substituted coumarin derivatives. J. Serb. Chem. Soc, 2012; 77:1339–1344.
15. Singh P, Raj R, Kumar V, Mahajan MP, Bedi PMS, Kaur T, Saxena AK: 1, 2, 3-Triazole tethered b-lactam-Chalcone bifunctional hybrids: Synthesis and anticancer evaluation. European Journal of Medicinal Chemistry 2012; 47:594-600.
16. Kayarmar R, Nagaraja GK, Naik P, Manjunatha H, Revanasiddappa BC, Arulmoli T: Synthesis and characterization of novel imidazoquinoline based 2-azetidinones as potent antimicrobial and anticancer agents. Journal of Saudi Chemical Society, 2014; http: //dx.doi.org/10.1016/j. jscs.2014. S07. 003.
17. Galletti P, Soldati R, Pori M, Durso M, Tolomelli A, Gentilucci L, Dattoli SD, Baiula M, Spampinato S, Giacomini D: Targeting integrins avb3 and a5b1 with new b-lactam derivatives. European Journal of Medicinal Chemistry, 2014; 83:284-293.
18. Staüdinger H: "Zur Kenntniss der Ketene: Diphenylketen". JustusLiebigs. Ann.Chem. 1907; 356: 51–123.
19. Banik BK and Becker FF: Heterocycles. Tetrahedron Lett. 2000; 4:6551-6554.
20. Junne SB, Kadam AB, Zangade SB, Shinde SL and Vibhute YB: Synthesis of benzthiazole derivatives grouping with substituted azetidinone ring and its functional behavior. Int. Multidiscip. Res. J, 2012; 2:44-47.
21. Singh GS, Mbukwa E and Pheko T: Synthesis and antimicrobial activity of new 2-azetidinones from *N*-(salicylidene) amines and 2-diazo-1, 2-diarylethanones.ARKIVOC 2007; IX: 80-90.
22. Bhat IK, Mishra SK, James JP and Shastry CS: Antimicrobial studies of synthesized azetidinone derivatives from sulfamethoxazole moiety. J. Chem. Pharm Res, 2011; 3:114-118.
23. Hussain S, Jadhav S, Rai M and Farooqui M: Synthesis, Characterization and Biological Evaluation of N [3-Chloro-2 (aryl)-4-oxoazitidin-1-y] pyridine-4-carboxamide.Int. J. Drug Des. Discov, 2011; 2:527-532**.**
24. Nikalje APG, Pathana M, Narute AS, Ghodke MS and Rajani D: Synthesis and QSAR Study of Novel N-(3-chloro-2-oxo-4-substituted azetidin-1-yl) isonicotinamide derivatives as Anti mycobacterial Agents. Der Pharm.Sin, 2012; 3:229-238.
25. Samadhiya P, Sharma R, Srivastava SK and Srivastava SD: Synthesis of 2-azetidinone derivatives of 6-nitro-1*h*-indazole and their biological importance. Quim. Nova, 2012; 35: 914-919.
26. O'Boyle NM, Greene LM, Bergin O, Fichet JB, McCabe T, Lloyd DG, Zisterer DM and Meegan MJ :Synthesis, evaluation and structural studies of antiproliferative tubulin-targeting azetidin-2-ones. Bioorg. Med. Chem. 2011; 19:2306-2325**.**
27. Navarro GG, DeVega MJP, López MTG, Andrei G, Snoeck R, Clercq ED, Balzarini J and Muñiz RG: From 1-AScyl-â-lactam Human Cytomegalovirus Protease Inhibitors to1-Benzyloxycarbonylazetidines with Improved Antiviral Activity- A Straightforward Approach To Convert Covalent to Noncovalent Inhibitors. J. Med. Chem, 2005; 48:2612-2621.
28. Arya N, Munde MK, Dwivedi, Jagdale AY and Jain KS: Design, synthesis, and antihyperlipidemic evaluation of novel 2-[1-(substitutedphenyl)-4-oxo-azetidin-2-yl]-5, 6-disubstitutedthieno [2, 3-d]

pyrimidin-4(3H)-ones. Arch. Pharm. Chem. Life Sci, 2013; 346:588-595.
29. Reddy DR and Namratha RJ: Synthesis and biological evaluation of 6-fluoro benzothiazole substitutedpyrazolo azetidinones. Der Pharma Chem, 2013; 5: 235-240.
30. Bisacchi GS, Slusarchyk WA, Bolton SA, Hartl KS, Jacobs G, Mathur A, Meng W, Ogletree ML, Pi Z, Sutton JC, Treuner U, Zahler R, Zhao G and Seiler SM: Synthesis of potent and highly selective nonguanidine azetidinone inhibitors of human tryptase. Bioorg. Med. Chem. Lett, 2004; 14:2227-2231.
31. Cainelli G, Galletti P, Garbisa S, Giacomini D, Sartorb L and Quintavalla A: 4-Alkyliden-*b*-lactams conjugated to polyphenols Synthesis and inhibitory activity. Bioorg. Med. Chem, 2005; 13: 6120-6132.
32. Chhajed SS and Upasani CD: Synthesis and molecular modeling studies of 3-chloro-4-substituted-1-(8-hydroxy-quinolin-5-yl)-azetidin-2-ones as novel anti-filarial agents. Arab. J. Chem, 2012; in press, http://dx.doi.org/10.1016/j.arabjc.2012.04.038.
33. Kumar S, Kaur H and Kumar A: Synthesis of new azetidinonyl/thiazolidinonyl. Arab. J. Chem, 2012; 5:475-484.
34. Fabio K, Guillon C, Lacey CJ, Lu S, Heindel ND, Ferris CF, Placzek M, Jones G, Brownstein MJ and Sim NG: Synthesis and evaluation of potent and selective human V1a receptor antagonists as potential ligands for PET or SPECT imaging. Bioorg. Med. Chem, 2012; 20:1337-1345.

How to cite this article:
Gupta A and Halve AK: β-Lactams: A Mini Review 0f Their Biological Activity. Int J Pharm Sci Res 2015; 6(3): 978-87.doi: 10.13040/IJPSR.0975-8232.6 (3).978-87.