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Azetidinone as an important biologically active agent - A review

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***Abstract*—Azetidinone is a saturated form of nitrogen containing cyclobutane having carbonyl group. It has been considered as a versatile nucleus which possess almost all types of biological activities mainly antimicrobial and antifungal activity. This diversity in the biological response profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. The present review article explains the chemistry, synthesis and various biological activities of azetidinones.**

***Index Terms*—azetidinone, cyarbonyl, lectum ring, biological activities.**

I. INTRODUCTION

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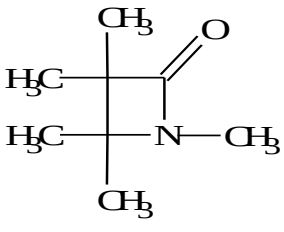
The chemistry of β-lactams has taken an important place in organic chemistry since the discovery of Penicillin by Sir Alexander Fleming in 1928 and shortly thereafter Cephalosporin which were both used as successful antibiotics. Since the advent of penicillin, the β-lactam antibiotics have been the subject of much discussion and investigation, within both the scientific and public sectors. The primary biological targets of the β-lactam antibacterial drugs are the penicillin binding proteins, a group of transpeptidases anchored within the bacterial cellular membrane, which mediate the final step of cell wall biosynthesis[1].

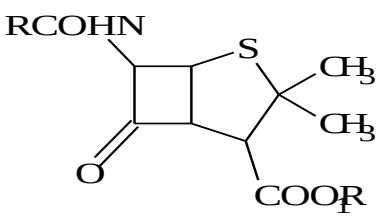
β - lactams are well - known heterocyclic compounds among the organic and medicinal chemist.[2] The most widely used antibiotic such as the penicillins, cephalosporins, carumonam, aztreonam, thienamycine and the nocardicins contain β - lactam ring[3], which are known to exhibit interesting biological activities[4]. Apart from antibiotic activity β-lactam also possess antifungal, antitubercular, antitumor etc. activities. From several recent studies of β – lactams, it has been uncovered that β – lactams also have novel therapeutic activities such as cholesterol lowering ability and serine protease inhibition[5]. Additionally, β - lactams serves as important chiral building blocks in organic chemistry (e.g. taxol semi synthesis)[6].

The extensive use of common β-lactam antibiotics such as penicillins and cephalosporins in medicine has resulted in an increasing number of resistant strains of bacteria through mutation and β-lactamase gene transfer. Additional impetus for research efforts on β-lactam chemistry has been provided by the introduction of the β-lactam synthon method, a term coined by Ojima 20 years ago, according to which 2-azetidinones can be employed as useful intermediates in organic synthesis. The cyclic 2-azetidinone skeleton has been extensively used as a template on which to build the heterocyclic structure fused to the four membered ring, using the chirality and functionalization of the β-lactam nucleus as a stereocontrolling element. As a result of the long standing interest of β - lactams in medicine, biology and chemistry, many approaches to their stereoselective synthesis have been developed[7].

The four membered 2 - azetidinone rings (I) are also known as β - lactam ring. For many years azetidinone has been of great practical significant as the centre of penicillin (II) and cephalosporins (III) reactivity. Until the beginning of 20th century no authentic β - lactams were known. The first β - lactam was prepared by staudinger[8] in 1907. Prior to 1940, the chemistry of β - lactam has received little attention and it was subject of minor interest. β - lactam as a class acquired importance only after 1943 when “Penicillin” (II) was established and it contains a β - lactam ring[9].



(I)



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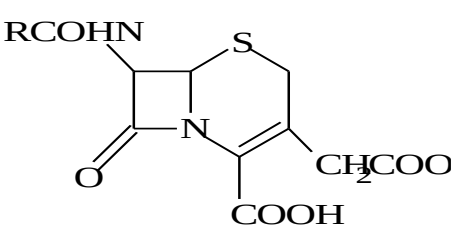


(III)

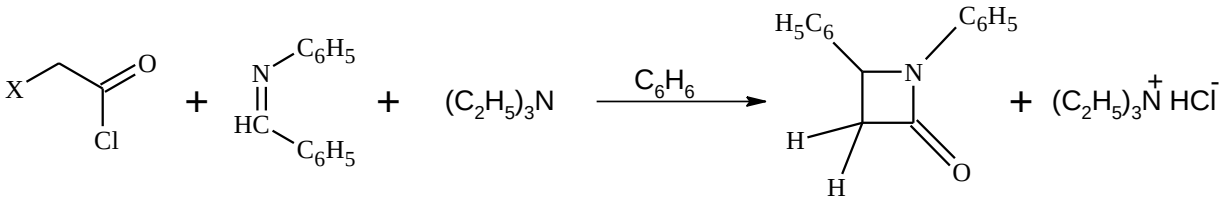
These molecules operate by forming a covalent adducts with membrane bound bacterial transpeptidases which are also known as penicillin binding proteins (PBPs) involved in the biosynthesis of cell wall[10]. These mechanism based inhibitors prevent the construction of cell wall and eventually lead to cell lysis and death. Moreover due to their β - lactamase inhibitory action 2-azetidinones based heterocycles represent an attractive target of contemporary organic synthesis[11].

II. CHEMISTRY

The name lactam is given to cyclic amides. In older nomenclature second carbon in an aliphatic carboxylic acid was designated as α, the third as β and so on. Thus a β - lactam is a cyclic amide with four atoms in its ring. The contemporary name for this ring system is azetidinone. β - lactam came to be a generic descriptor for penicillin family. The ring ultimately proved to be the main component of the pharmacophore. So the term possesses medicinal as well as chemical significance.

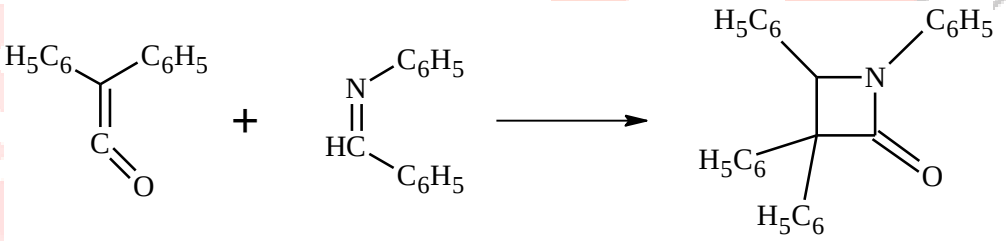
The recent and the advanced increase in both the spectrum of β – lactam antibiotics and the number of the known producing organisms is due to the development of new and more sensitive screening techniques. Further progress had been added by continuous synthetic derivatization to those monocyclic β - lactam compounds. Many methods had been reported in the literature. Some of those methods were listed in this review.

One of the most important synthetic procedure of β - lactams (VII), developed in connection with the problem of penicillin synthesis, involves the combination of an imine (V) or thiazoline and an acid chloride (IV), with loss of hydrogen chloride, in the presence of tertiary amine (VI)[12,13].



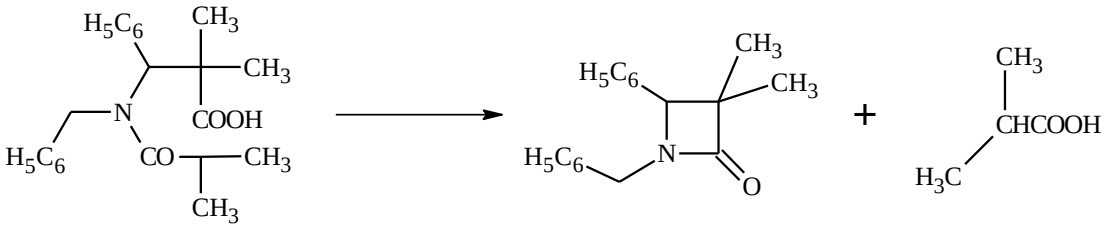
(IV) **(V)** **(VI)** **(VII)**

The direct combination of ketene in particular disubstituted or "ketoketenes" with imines has been the most commonly employed method for synthesis of β - lactam. For example, diphenyl ketene (VIII) reacts readily with benzylidene aniline (IX) at room temperature to yield the crystalline β - lactam, 1, 3, 3, 4 - tetraphenyl - 2 - azetidinone (X) in 72 % yield[14]. This was the first known β - lactam.



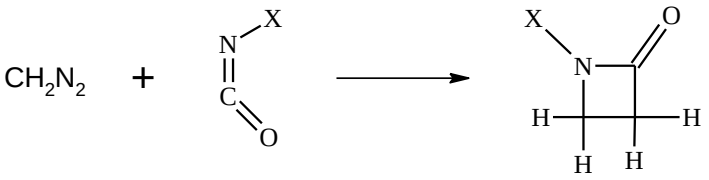
(VIII) **(IX)** **(X)**

One of the simple and direct method for closing the β - lactam ring (XII) was discovered by Staudinger[15]. When certain β - acylamino acids (XI) are heated at their melting point, ring closure is effected with the loss of carboxylic acid (XIII) which was originally present as acyl group in β - acyl amino acid.



(XI) **(XII)** **(XIII)**

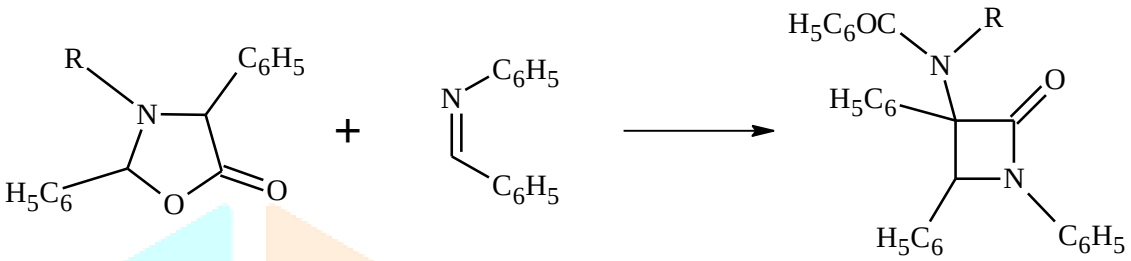
It was found that diazomethane (XIV) reacts with phenyl and 4 - bromophenyl isocynates (XV) to give the corresponding β - lactams (XVI)[16].



(XIV) (XV) (XVI)

Where, X = C_6H_5 , 4-Br C_6H_5

N - Substituted mesoionic oxazolones (XVII) have been reported to react with schiff's bases (XVIII) to afford azetidinone (XIX)[17].



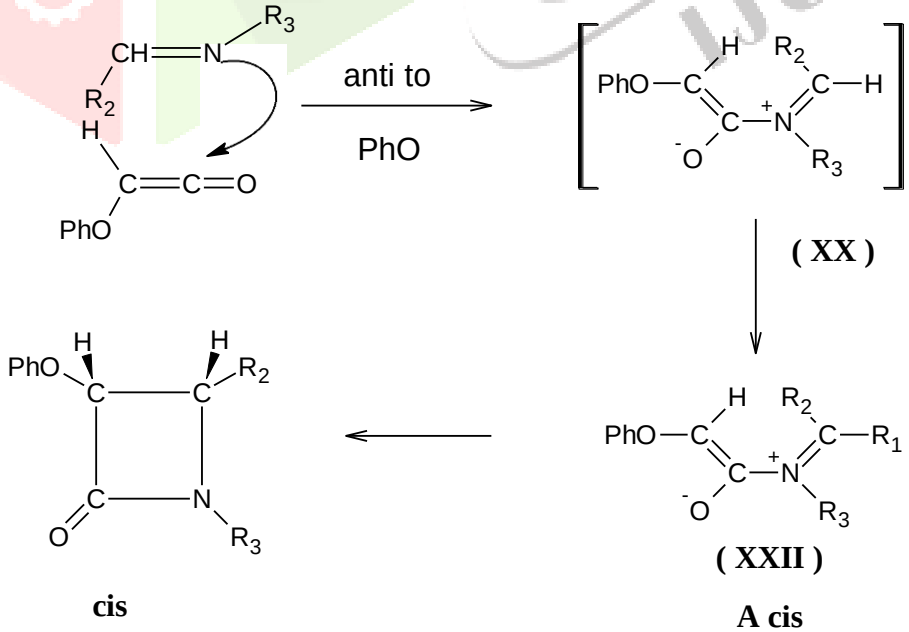
(XVII) (XVIII) (XIX)

III. MECHANISM

The formation of β - lactam have been explained by following mechanism[18, 19].

The formation of cis and trans β - lactam takes place via (2 + 2) cycloaddition involving ketene and an imine obtained from phenyl glyoxal or phenoxy ketene and phenyl ethylamine or N - methylimines. The cis and trans stereo chemistry mainly depends on the substituents attached with ketene part and imine is believed to exist in more stable E - configuration.

The nitrogen atom of azomethine has lone pair of electron. This nitrogen nucleophile of azomethine attacks on ketene possessing donor group such as alkoxy or aryloxy and acceptor group such as thioalkoxy or thioaryloxy, thereby generates intermediates such as (XX) and (XXI). They have three types of resonating structure which on cyclisation generates cis β - lactam through less stable intermediate (XXII) and also generates more stable trans β - lactam via more stable intermediate (XXIII) and (XXIV) stabilized due to sulfur atom.

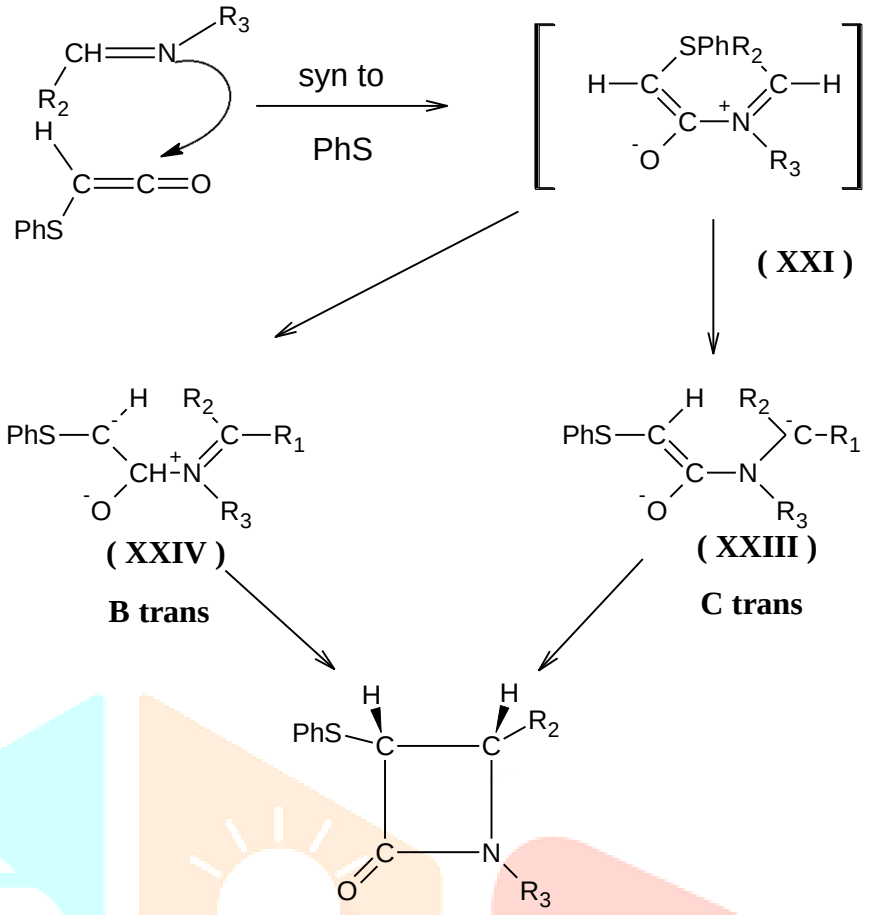


(XX)

(XXII)

A cis

cis



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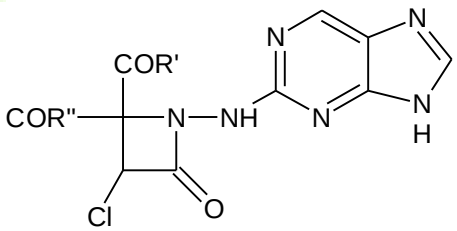
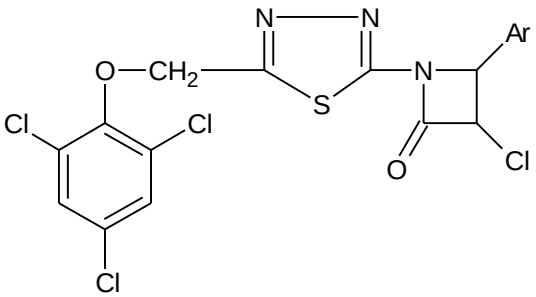
IV. Biological Importance

2-Azetidinones commonly known as β-lactams are well-known heterocyclic compounds among organic and medicinal chemists. The activity of famous antibiotics such as penicillins, cephalosporins, nocardicins and carbapenems are attributed to the presence of 2-azetidinone ring in them. Azetidinones are very important class of compounds possessing wide range of biological activities such as antimicrobial[20-36], pesticidal[36], antitumor[37], antitubercular[38], anticancer[39], cytotoxic[40-42], enzyme inhibitors[43], elastase inhibitors[44] & cholesterol absorption inhibitors[45]. Bis heterocyclic synthesis and antimicrobial studies of biologically significant 2-[N-(3'- chloro-4'-substitutedazetidinone-2)] amino-4-hydroxypurines (XXV) have been given by Sharma and her co-workers[46].



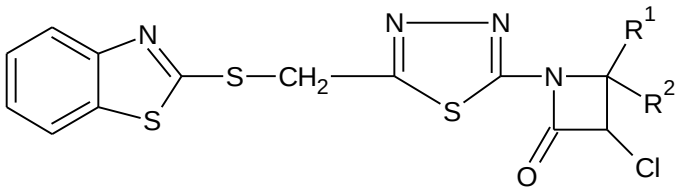
(XXV)

Desai and his co-worker synthesized 4-substitutedphenyl-1-[2-(2,4,6-trichlorophenoxymethyl)-1,3,4-thiadiazol-5-yl]-3-chloro-2-azetidinone (XXVI) as antibacterial agent[47].



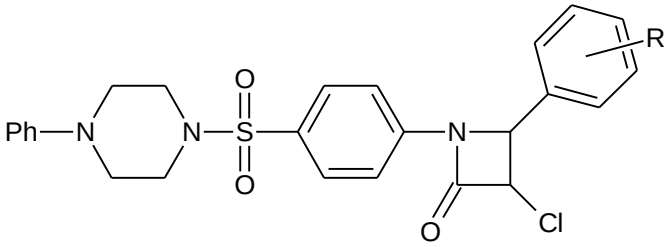
(XXVI)

Srivastava and his coworkers synthesized 1-[5'-{(2- benzothiazolylthio)methyl}-1,3,4-thiadiazol-2-yl]-4-(substitutedphenyl)-3-chloro-2-oxoazetidine (XXVII) as antimicrobial and anthelmintic agents[48].



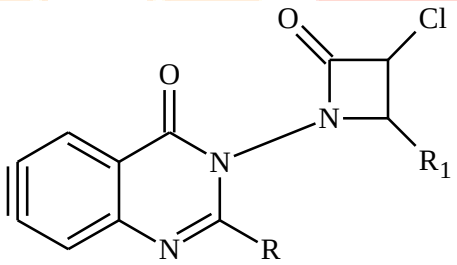
(XXVII)

Patel and Mistry have synthesized novel azetidinones (XXVIII) and studied their antibacterial activity[49].



(XXVIII)

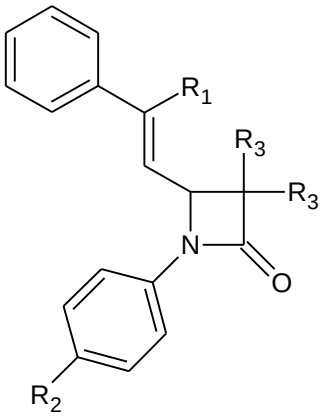
Azetidinones of general structure (XXIX) were synthesized and tested for their antiparkinson activity against tremor, rigidity, ptosis, hypokinesia and catatonia. It was also studied further for their mode of action on dopamine receptor binding using rat brain striate membrane preparation[50].



(XXIX)

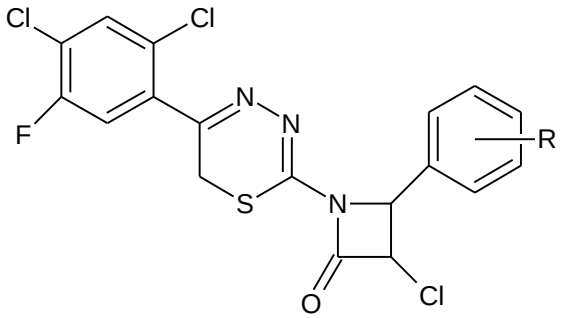
$R = CH_3$ or C_2H_5 and R_1 = Aryl

Tan and his co-workers have synthesized 1-(Substituted phenyl)-4-(substituted styryl)-2-azetidinones (XXX) and studied their antimicrobial activity[51].



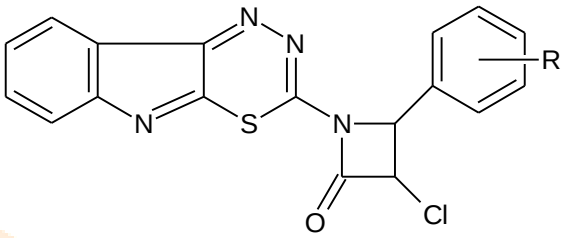
(XXX)

Synthesis and biological active compounds 1-[5'-(2,4-dichloro-5-fluorophenyl)-6-H1,3,4-thiadiazin-2-yl]-4-(substituted phenyl)-3-chloro-2-oxoazetidines (XXXI) have been given by Patel and Desai[52].



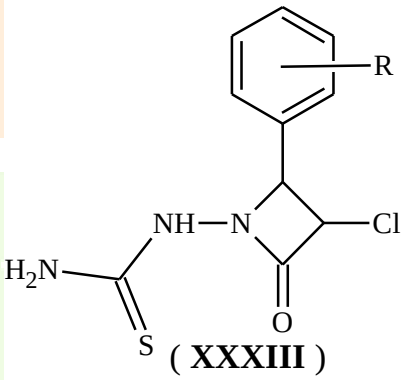
(XXXI)

Panwar et al have synthesized 2-[3-chloro-2-(substitutedphenyl)-4-azetidinon-3-yl]-1,3,4-thiadiazino[6,5-b]indole (XXXII) as prospective antimicrobial agents[53].



(XXXII)

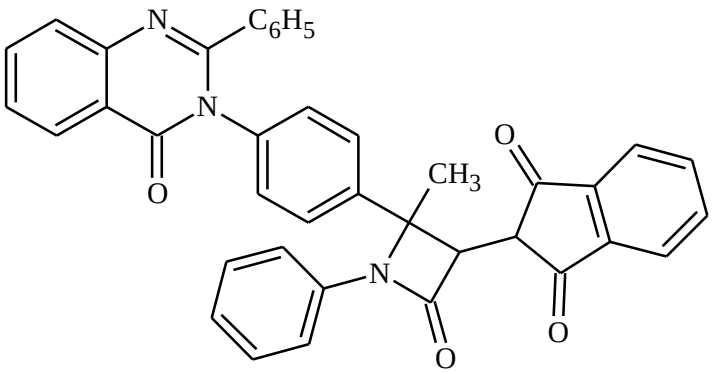
Some thiouryl azetidinone derivatives (XXXIII) have been synthesized and studied for their antiparkinsonian activity. This study showed that thiouryl azetidinone having phenyl and 4 - methoxy phenyl group at 2nd and 4th position were found most potent. Some of these compounds showed lesser toxicity[54].



(XXXIII)

R = H, 4-N-(CH_3),4-OCH_3 etc.

Padam Kant and R K Saxena[55] synthesized 2 - azetidinone derivatives (XXXIV) containing quinazoline scaffold as an antibacterial and antifungal agent.

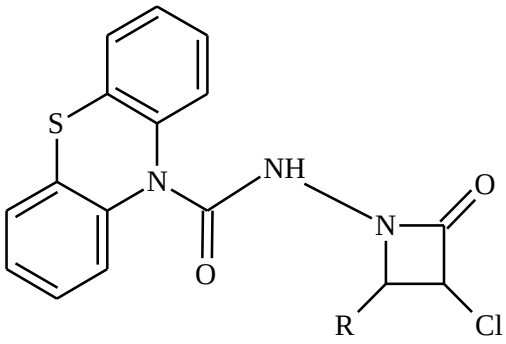


(XXXIV)

Where R= Different aryl groups

Some new N - sulfonyl phenyl amino - 3 - chloro - 4 - phenyl azetidin - 2 - one derivatives have been synthesized and found to be more potent antibacterial agent against E. coli.[56] 2 - Azetidinone derivatives containing quinoline moiety have been reported to exhibit antibacterial activity[57]. Hogale[58] reported 2 - azetidinone derivatives (XXXV) which were screened for in vitro

antibacterial activity against Bacillus substilis, Salmonella typhirium, E. coli and Klebsiella pneumoniac. This compounds were found active at concentration of 300 - 100 mg/ml. Patel et al.[59] have combined sulfone moiety with 2 - azetidinone rings (XXXVI) for their eventual antimicrobial activity.



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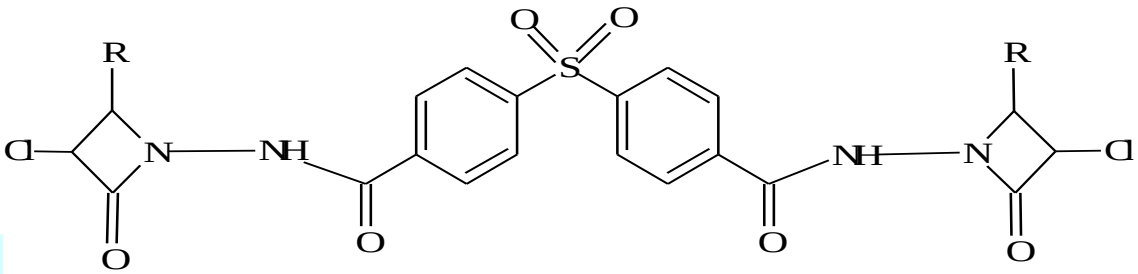
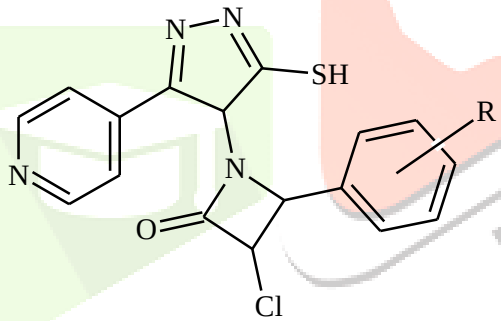


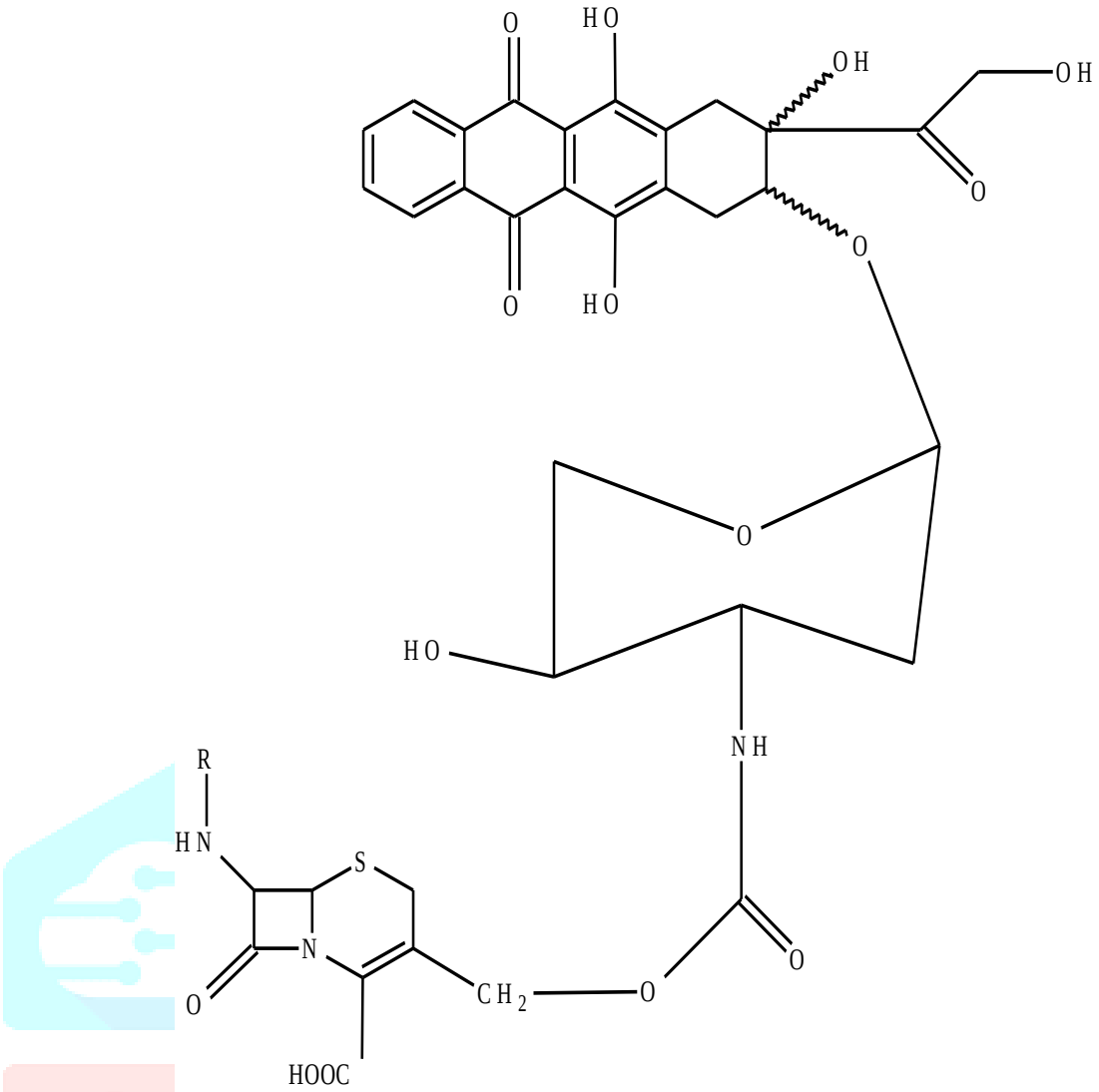
(XXXVI)

R Priyadarsini, R Vijayaraj, T K Ravi and M Prabha[60] have synthesized some azetidinones (XXXVII) for their antitubercular, antibacterial and antifungal activities.



(XXXVII)

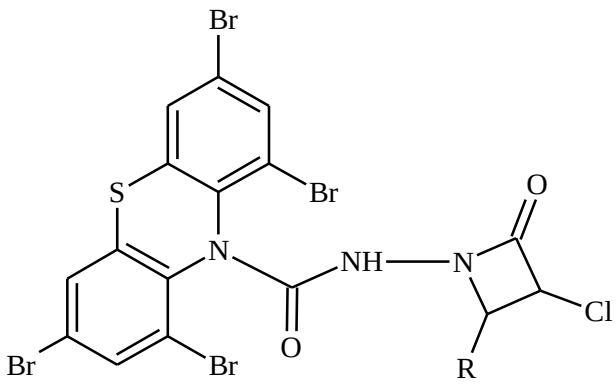
Peter et al[61] have synthesized cephalosporin derivatives of Doxorubicin (XXXIX) asprodrug for activation by monoclonal antibody β - lactamase conjugates and showed influence in the activity towards the higher side by nature substituent at 7th position.



(XXXIX)

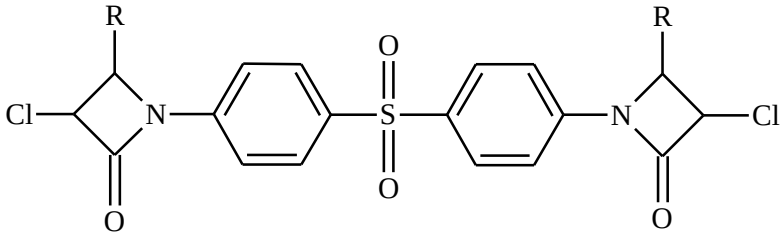
Where R = $C_6H_5CH_2CO$

Trivedi et al.[62] have synthesized 2 - azetidinone derivatives (XXXVIII) and thiazolidinones derivatives and studied their antibacterial activity against *E.coli, S.aureus* and tubercullostatic activity against $H_{37}Rv$ strain of *Mycobecterium tuberculosis.*



(XXXVIII)

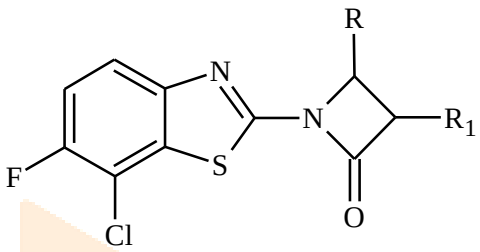
P D Mehta, N P S Sengar, E V S Subruhmanyam have synthesized 4-4'-bis(3-chloro-4-(4-methylphenyl)-2-oxo-azetidin-1-yl)diphenyl sulphone (XXXX) and studied their antimicrobial as well as tubercullostatic activities[63].



(XXXX)

Where R= Heterocyclic or aromatic aldehyde

B M Gurupadayya, M Gopal, Y N Manohara, have synthesized some azetidinones (XXXXI) for their anti-inflammatory, analgesic, CNS depressant and skeletal muscle relaxant activity[64].

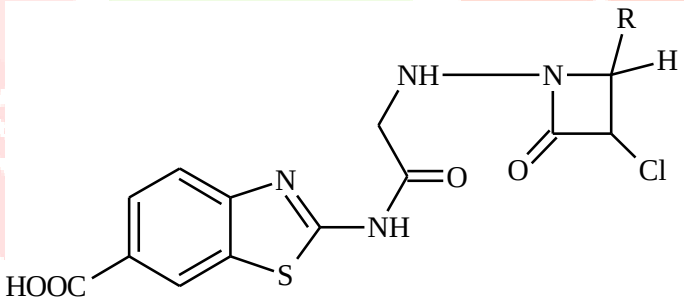


(XXXXI)

Where, R = C_6H_5, C_6H_4-4-OCH_3, C_6H_4-4-$N(OCH_3)_2$ etc.

R_1 = H, Cl and C_6H_5

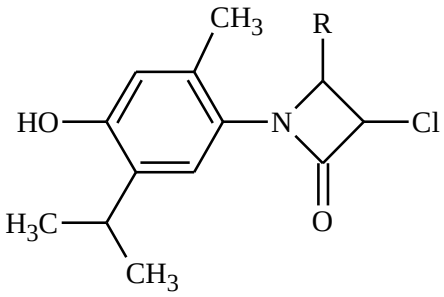
A Ameya, Chavan and Nandini R Pal[65] have synthesized 2 - { 2 - [3 - chloro - 2 - (aryl) - (4 - oxo - azetidin - 1 - yl) amino] - acetylamino } benzothiazole - 6 - carboxylic acids (XXXXII) and studied their antibacterial activity against four microorganisms: *Staphylococcus aureus, Bacillus subtilis, Psuedomonas aeruginosa* and *E.coli.*



(XXXXII)

Where, R = 4-NO_2 C_6H_4,3-Br C_6H_4, C_6H_5, 2-Cl C_6H_4 etc.

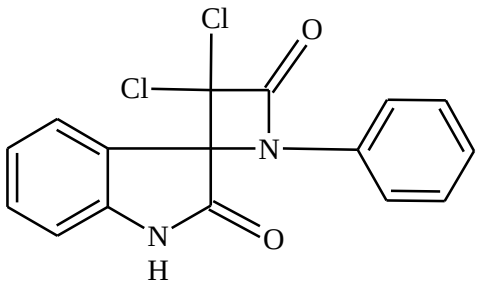
Several 4 - aryl - 3 - chloro-1- (4'- hydroxyl - 5' - isopropyl - 2' - methyl phenyl) - 2 - azetidinone (XXXXIII) have been synthesized and screened for their antimicrobial activities[66].



(XXXXIII)

R= C_6H_5 , 2-ClC_6H_5 , 3-ClC_6H_5 etc.

Spirodichloro azetidinone (XXXXIV) has been synthesized which shows good activity against bacteria[67].



(XXXXIV)

Rey *et al*., have described methods for the preparation of N - substituted - 2 - azetidinones, which are useful in the synthesis of taxol and taxol derivatives[68].

Patel et al., have carried out the synthesis of azetidinone and thiazolidinone derivatives from 2 - amino - 6 - (2 - naphthalenyl) thiazole [3,2 - d] thiadiazole[69].

Singh and co - workers have prepared some new 2 - azetidinones from N - (salicylidene) amines and 2 - diazo - 1,2 - diaryl ethanones[70].

More over, 2 - azetidinone derivatives have been reported to possess anti-inflammatory[71,72], antidegenerative[73], fungicidal[74], antibiotic[75] etc. activities.

V. CONCLUSION

The literature survey reveals that azetidinones have diverse biological potential, and the easy synthetic routes for synthesis have taken attention of the chemists, pharmacologists and researchers. Due to its unique nature 2-azetidinone nucleus is found in various antimicrobial, antifungal activity papers. By the present scenario it can be concluded that azetidinones have a great potential for further research and novel derivatives can be synthesized containing this moiety and can be explored for various biological activities.

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