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Azetidinone: Different methods of synthesis and its biological profile

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ABSTRACT

2- Azetidinone is a β- lactam cyclic amide with four atoms in a ring. This nucleus has attracted considerable attention as they are endowed with a wide range of pharmaceutical activities. This β- lactam is part of antibiotics such as penicillin's, cephalosporins, and carbapenams. These molecules interfere with the final step of bacterial cell wall biosynthesis by inhibition of the D,D-transpeptidase enzyme involved in the cross linking of peptidoglycon strands, which are also known as penicillin binding proteins. The mechanism based inhibitor prevents the construction of cell wall and eventually lead to cell lysis and death. Cyclization of Schiff bases with chloroacetylchloride in the presence of triethylamine result in the formation of 2-azetidinone. The present work is an attempt to review chemistry, synthesis, and biological activities of 2-azetidinone.

Keywords: 2-azetadinone, β-lactam, Schiff base, biological activities.

INTRODUCTION

β- Lactam antibiotics are the most commonly used antibiotics. The 2- carbonyl derivative of 4-membered heterocyclic ring with nitrogen atom is designated as 2-azetidinones. The chemistry of β-lactams has taken as important place in organic chemistry since the discovery of penicillin's by sir Alexander Fleming in 1928[1].The β-lactam heterocyclic are still most prescribed antibiotics, They are considered as an important contribution of science to humanity. The most widely used antibiotics such as penicillin's, cephalosporin's, carumonam, azetreonam, thienamycine and the nocardicins all contain β- lactam ring[2]. The development of several synthetic and semi synthetic β- lactam antibiotics by the pharmaceutical industry was due to the growing resistance of bacteria towards the β- lactam antibiotics and the need for medicines with more specific antibacterial activity. Azetidinones which are the part of the antibiotic structure are known to exhibit interesting biological activities. A large number of β- lactams posses powerful antibacterial, antimicrobial, antifungal, anti-inflammatory, anticonvulsant, anti-tubercular, enzyme inhibition and central nervous system activities[3,4,5]. The review of literature revel that 2-azetidinones shows various biological activities with different substituted heterocyclic moieties such as thiazole, pyrazole, oxazole, indole, pyridine etc.

2-Azetidinones also plays an important role in the enzyme inhibition activity. The β- lactam antibiotics are given in the form of penicillin's and cephalosporin's to treat the infection caused by bacteria. These molecules interfere with the final step of bacterial cell wall biosynthesis by inhibition of the D,D- transpeptidase enzyme involved in the cross linking of peptidoglycon strands which are also known as penicillin binding proteins. The mechanism based inhibitor prevents the construction of cell wall and eventually lead to cell lysis and death. β- Lactamases are bacterial defence enzymes that very efficiently hydrolyse the β- lactam moiety in practically all classes of β- lactam antibiotics[6].

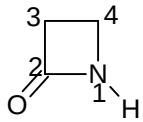
2- Azetidinones acts as cholesterol absorption inhibitor. It blocks the intestinal sources of cholesterol, has become an increasingly important choice for reducing the serum cholesterol level. It inhibits the absorption of dietary or recycled cholesterol in the intestine and can be used either alone or combination with a statins, effectively reduce the LDL-C concentrations. It also increases the high density lipoprotein cholesterol (HDL-C), and may reduce elevated triglyceride (TG) concentrations[7].

Also several recent studies of β- lactams have uncovered novel therapeutic activities such as cholesterol lowering ability and serine protease inhibition. Additionally β- lactams serves as important chiral building blocks in organic chemistry. The important and structural diversity of biologically active β- lactams antibiotics led to the development of many novel methods for the construction of appropriately substituted azetidinones with attendant control of functional group and stereochemistry[8].

Even now the research in this area is stimulated because of development of bacterial resistance to widely existing antibiotics of this class. There is a need for functionalized β- lactams or for new active principles in the β- lactam series.

Chemistry of azetidinones:

The name lactam is given to cyclic amides. In older nomenclature second carbon in an aliphatic carboxylic acids 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 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.



2- Azetidinone

SAR:

a) A β -Lactam ring is a lactam with a heteroatomic ring structure consisting of 3-carbon atom and one nitrogen atom.

b) β -Lactam antibiotics are the most commonly used antibiotics, β-lactam skeleton is essential requirement for the antimicrobial activity.

c) A Carbonyl group attached to the lactam ring is common feature.

d) Substitution of o-hydroxyphenyl group at C-4 position showed maximal insecticidal and antifungal activity and with p-methoxyphenyl groups shows antimicrobial activity.

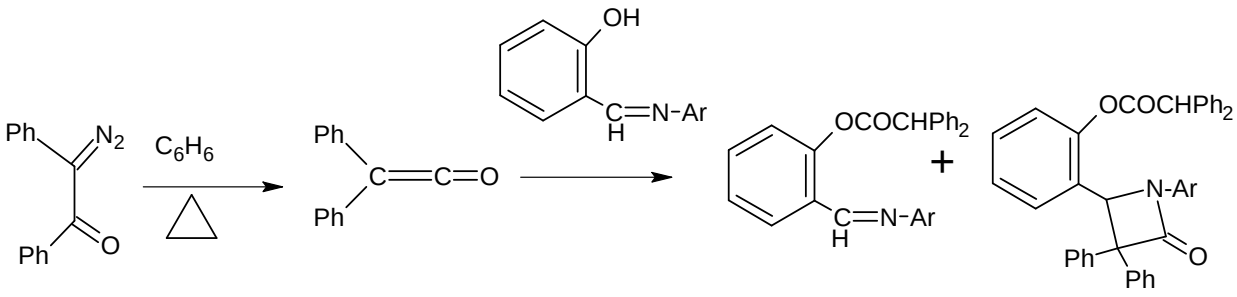
e) The presence of fluoro, bromo, chloro group at C-4 position in the moiety enhances its antimicrobial activity due to high electronegetivity and increase the solubility in lipids.

f) Bulky substitution and the highly nucleophilicity nature of the molecule favorable for antitubercular activity.

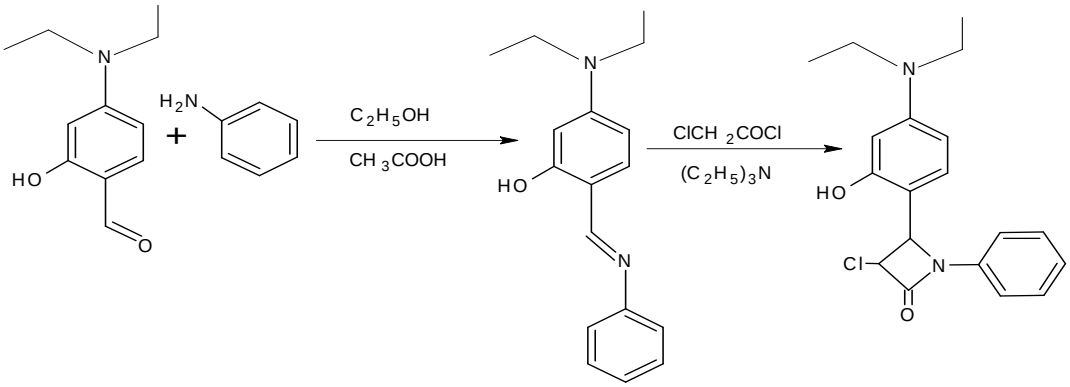
g) Substitution in the aryl part at position 1 of 2-oxo-azetidinones with groups having increased hydrophobicity or steric bulk and electropositive character result in the increase the antimicrobial activity.
h) Substitution of phenyl, 4-methoxyphenyl and 4-hydroxy phenyl at C-4 position it shows potent antimicrobial activity.
i) The incorporation of an isoniazid or an acidic substituent at the α-position of the side chain it shows increasing the activity.
j) N1-Substitution by cyclohexyl and isopropyl essential for antidiabetic activity.
k) At C4-para-methoxy phenyl substitution was more favorable for the antidiabetic activity.
l) N1-Aryl, C3-alkylaryl, p-hydroxy at C4-phenyl, Benzylic hydroxyl in C3 chain shows activity of inhibitors of cholesterol absorption inhibitors.
m) The lipid solubility influences the pharmacokinetic and antibacterial activity. In general as the lipid solubility increases the half life and antibacterial activity also increases.

Different synthetic methods of azetidinones:
During recent years there has been intense investigation on azetidinone compounds because of it possess interesting biological activities. Many methods had been reported in the literature. Some few of these methods are listed in this study.

1. ketene-imine Cycloaddition
The ketene-imine Cycloaddition was reported by Staudinger[9]. Girija S. Singh *et al*[10] reported the reaction of imines with acid chloride in the presence of tertiary base. This reaction depends, on many factors including temperature, which often needs to be optimized. The reactions of N-salicylidene amines with diarylketenes generated from thermal decomposition of the 2-diazo-1, 2-diarylethanones. The reactions of various N-salicylideneamines with 2-diazo-1, 2-diarylethanones have been carried out to afford 1-substituted -3,3-diaryl-4-[2 -(O-diarylacyl) hydroxyphenyl]-2-azetidinones.

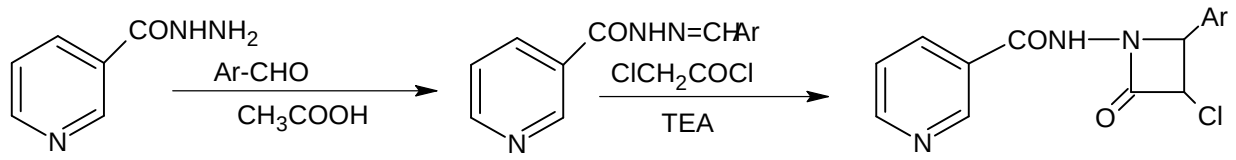


2. Synthesis of β- lactams using microwave irradiation.
Jignesh P Raval *et al*[11] reported the synthesis of azetidin-2-one by microwave reactions under solvent free conditions. The reaction of various Schiff bases with chloroacetylchloride in the presence of triethylamine to form azetidinones. Microwave irradiation has been also applied to carry out synthesis in open vessel using organic solvents such as ethanol, N, N-Dimethyl formamide (DMF), 1,2-Dichloroefhane(DCE), 1,2-Dichloro benzene etc., as energy transfer media which absorbs microwave energy efficiently through dipole rotation.

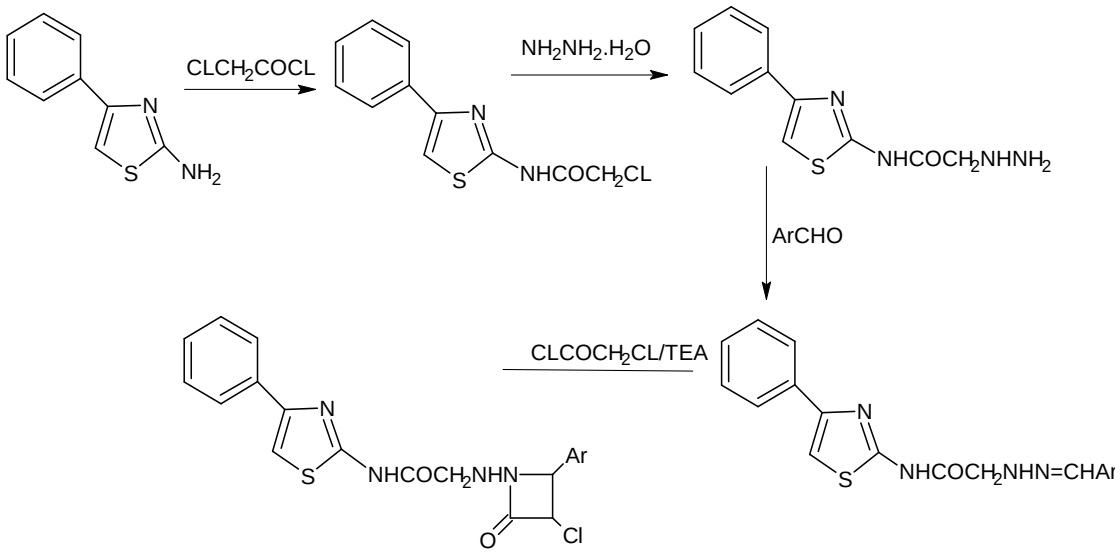


3. Synthesis of β- lactams from cyclization.

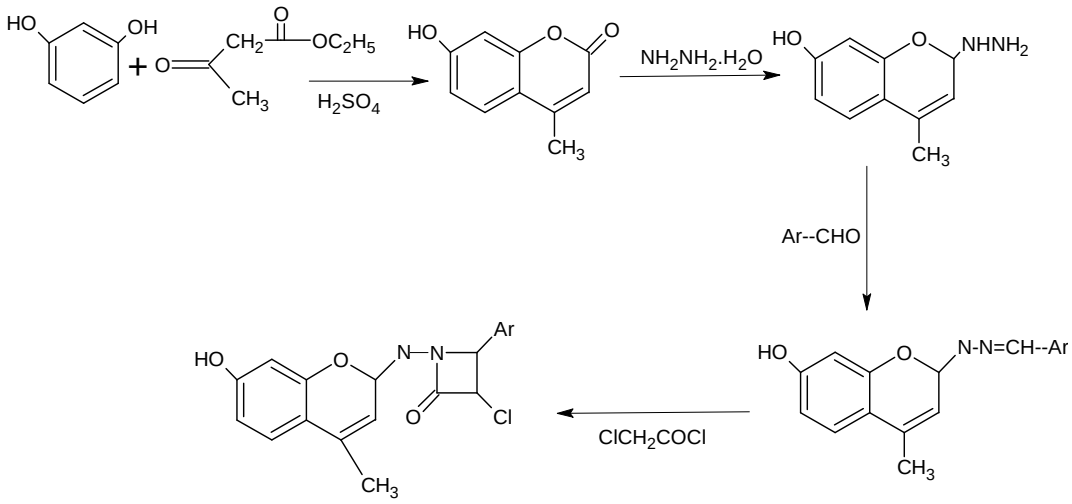
B.C Revanasiddappa *et al*[12] synthesis of some novel 2- azetidinones via reaction of hydrazide with substituted aromatic aldehydes in the presence of few drops of glacial acetic acid yielded Schiff bases. The Schiff bases up on cyclization with chloroacetylchloride in the presence of triethyl amine will form the β- lactams.



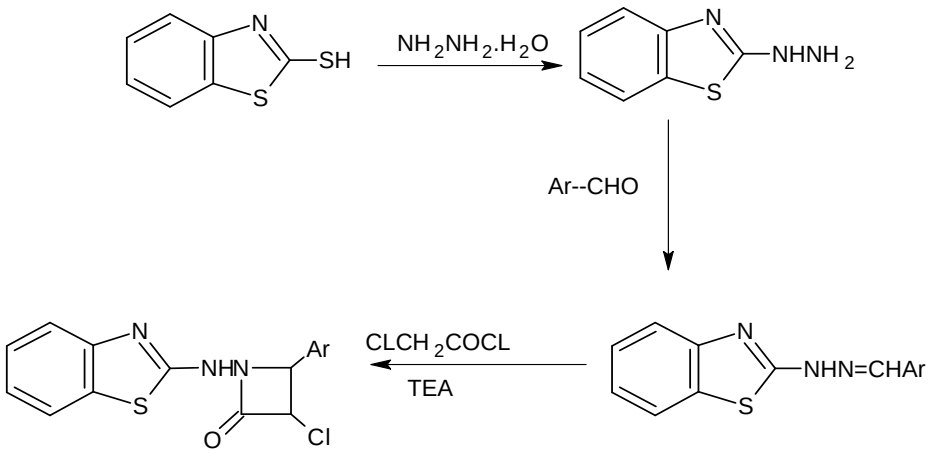
4. S.K Sonwane *et al*[13] reported the synthesis of 2-[2′-{4″-substituted aryl-3″-chloro-2″-oxo-azetidine}-acetyl-amino]-4phenyl-1,3-thiazoles by using 2-amino-4-phenyl-1,3-thiazole reaction with acid chloride, which on amination with hydrazine hydrazide afforded condensation with aldehydes to form Schiff bases and were reacted with acid chlorides to produce β- lactam.



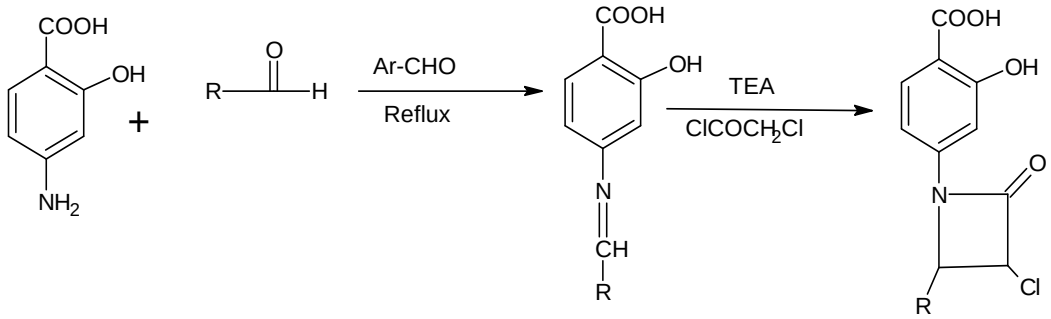
5. B.B Subudhi *et al*[14] synthesized 3-chloro(substituted)-1-(2′-imino-4′-methyl-7′-hydroxy coumarinyl) azetidin-2-one from 4-methyl-7-hydroxy coumarin reaction with hydrazine hydrate affords Schiff bases finally reaction with acid chloride and triethylamine.



6. Rajiv Dua *et al*[15] reported the synthesis of 2-(4-substituted aryl-3-chloro-2-oxo azetidine)-2-iminobenzothiazoles by the hetero cyclization of 2-substituted hydrazine benzothiazoles, with chloroacetyl chloride in the presence of tri-ethyl amine under microwave irradiation.

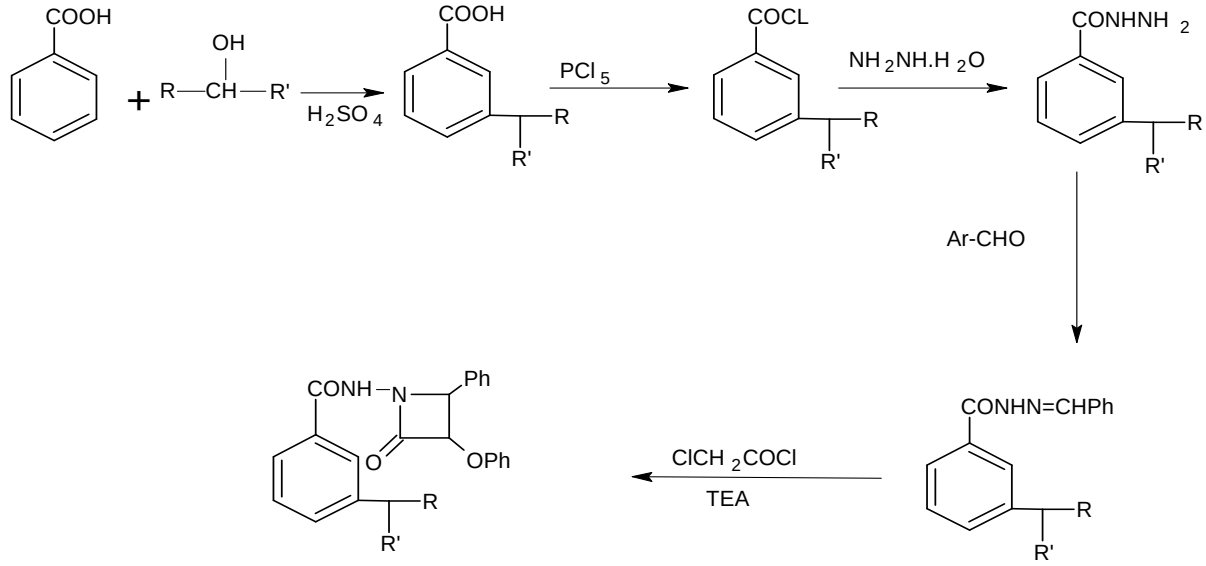


7. S.J. Wadher *et al*[16] synthesized Schiff bases, azetidinone based on computer aided drug designing, Approach was employed to understand the probable binding of para-amino salicylic acid on the active site of AMpc enzyme of HKY28 which will suggest the better insight in the designing of novel analogues of Schiff bases, azetidinone of PAS as a probable antimicrobial agent.



8. V.K Pandey *et al*[17] reported the reaction of amido/imido alcohol/2-phenyl-3-hydroxy ethyl quinazoline-4-one with benzoic acid. The acid chloride reaction with hydrazine hydrate affords

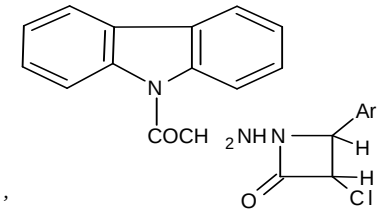
hydrazide and condensation with aldehydes in acetic acid produce hydrazones. It undergoes cyclization with phenoxy acetic acid and/or acid chloride to form β- lactam.



Biological activities of azetidiones:

Antimicrobial activity.

S K Srivastava, *et al*[18] has reported synthesis of some new N^9-[hydrazinoacetyl- (2-oxo-3-chloro-4-substituted aryl azetidinone)] - carbazole. Carbazole on treatment with chloroacetyl chloride afforded N^9-(chloroacetyl)-carbazole which on reaction with hydrazine hydrate yielded (hydrazinoacetyl) - carbazole. Condensation with various aromatic aldehydes gave N^9–(arylidene hydrazinoacetyl)- carbazole which on Cycloaddition with chloroacetyl chloride in the presence of triethyl amine yielded N^9-[hydrazinoacetyl-(2-oxo-3-chloro-4-substituted aryl azetidinone)]-carbazole. The compounds were screened for antibacterial activity at two concentration (50 and 100 ppm) against *B subtillis, E. coli, A. niger, F. oxisporium* and antifungal activity at two concentrations (100 and 500 ppm) against *A. niger, A. flavous, F. oxisporium and T. viride* by filter paper disc technique. Standard antibacterial streptomycin and antifungal griseofulvin screened under similar condition for comparison.



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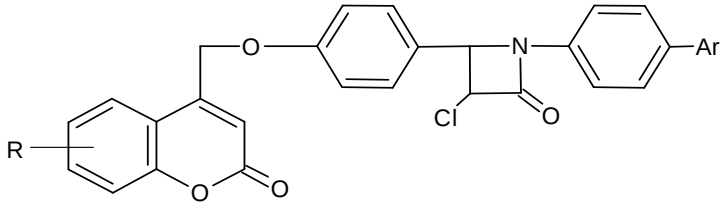
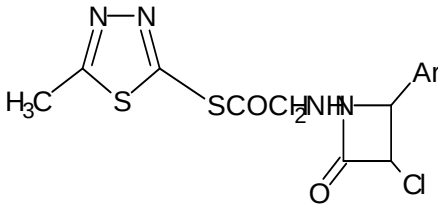
Ar = a) C_6H_5, b) p-$CH_3C_6H_4$, c) p-$CH_3OC_6H_4$, d) o-ClC_6H_4, e) p-ClC_6H_4, f) o-OHC_6H_4, g) p-OHC_6H_4, h) p-$(CH_3)_2NC_6H_4$, i) $NO_2C_6H_4$

Rangappa S. Keri *et al*[19] have synthesized 3-chloro-4-[4-(-oxo-2H-chromen-4-ylmethoxy)-1-phenyl]-1-phenyl-azetidin-2-onemfrom 4-aryloxymethyl coumarins. The compounds are screened for anti-microbial activity against *S. aureus, E. coli, A. fumigates, C. alabicans* penicillium used for the invitro study by the tube dilution technique. Ciprofloxacin and gentamycin were dissolved in DMSO initially 250 µg/ml and were serially diluted in culture medium as 125, 62.5, 31.250, 16, 8, 4, 2, and 1 µg/ml concentrations.



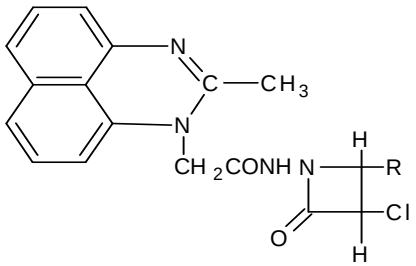
R = 6-CH_3, Ar = 4-ClC_6H_4, R = 7-CH_3, Ar = 4-ClC_6H_4,
R = 6-Cl, Ar = 4-ClC_6H_4, R = 5,6-Benzo, Ar = 4-ClC_6H_4

Rajiv Dua *et al*[20] have synthesized 2-[2-{4-substituted-aryl-3-chloro-2-oxo-azetidine}-acetyl-amino-mercapto]-5-methyl-1,3,4-thiadiazoles and evaluated for their antimicrobial activity at two concentrations (50 and 100 ppm) against *B. subtillis, E. coli, K. pneumonia, A. niger, F,* oxisporium by filter paper disc method. Standard antibacterial streptomycin and fungicide griseofulvin also screened under similar condition for comparison.



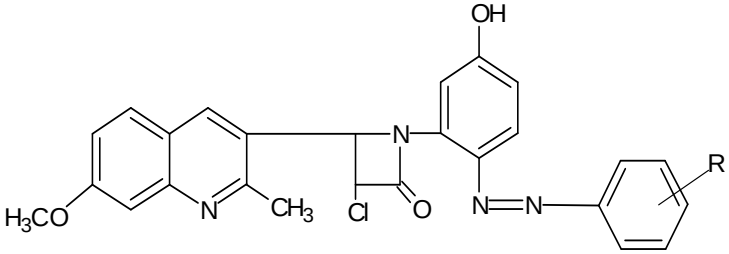
Ar = Substituted aryl groups

Dinesh R. Panchasara *et al*[21] have synthesized 3-Chloro-1-(4-perimidine methyl carbonyl amino)-4-phenyl-azetidin-2-one and evaluated for their antibacterial activity at a concentration of 50µg/ml against *B. subtillis, S.aureus, E. coli, S. typhi and K. promioe* by agar cup plate method. Standard tetracycline was also tested under similar condition for comparison.



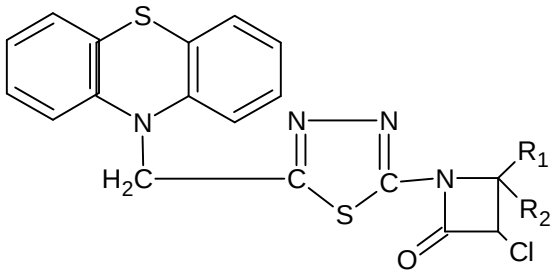
R = a) C_6H_5, b) 4-OH-C_6H_4, c) 2-OH-C_6H_4, d) 4-OCH_3-C_6H_4,
e) 4-OH-3-OCH_3- C_6H_3, f) 4-Cl-C_6H_4, g) 2-NO_2-C_6H_4, h) 5-Br-2-OH-C_6H_5

Jigish A Patel *et al*[22] have synthesized 3-chloro-4-(2-chloro-7-methoxy-3-quinolyl)-1-[3-hydroxy-6-(aryldiazenyl) phenyl] azetidin-4-one and evaluated for their antibacterial activity at 512, 256, 128, 64, 32, 16, 8, 4, 2, 1 µg/ml against *S. aureus, E. coli and P.* aeruginosa by tube dilution method.



R = a) 4-NO_2, b) 3,4,5-$(OCH_3)_3$, c) 2-OH, d) 3-OH, e) 4-OH

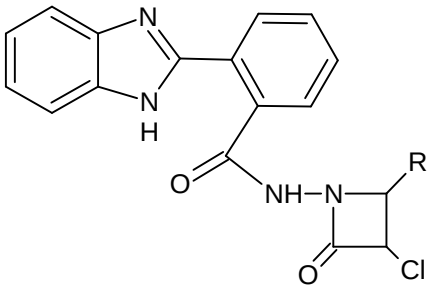
T R Rawat *et al*[23] have synthesized 1-[5'(N[10]-phenothiazinomethyl)-1',3',4'-thiadiazol-2'-yl-]-4-substituted-2-azetidin-ones and screened for antibacterial activity at concentration of 100 and 500 ppm against *B. subtillis, S.aureus, E. coli, C. alabicans, R. oryzae, C. pannical* by using Paper disc method. Standard streptomycin and griseofulvin was tested under similar condition for comparison.



R_1 = a) 2,3,4-ClC_6H_4, b) 2,3,4-BrC_6H_4, c) 2,3,4-$OCH_3C_6H_4$, d) 2,3,4-$NO_2C_6H_4$
R_2 = a) C_6H_5, b) C_6H_4OH, c) C_6H_4Cl, d) $C_6H_4OCH_3$

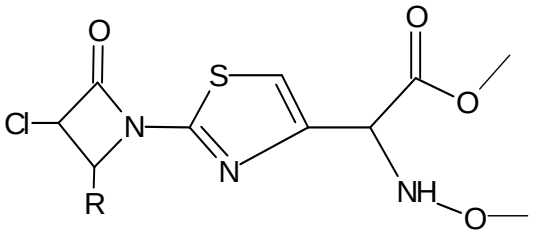
Antitubercular activity

Preethi Kaythara *et al*[24] has synthesis 4 Aryl-3-chloro-1-(benzimidazole-2yl-benzamido)-2-azetidinonel and tested in-vitro for their antitubercular activity against *$H_{37}Rv$* strain of *Mycobacterium tuberculli* using Lowenstein Jensen's egg medium by serial two fold dilution method.



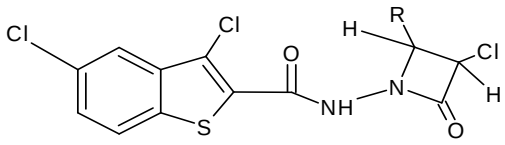
R = a) 2-OH-4CH_3Ph, b) 4-ClPh, c) 2-NO_2Ph, d)4-$(CH_3)_2$Ph

Khyathi A Parikh *et al*[25] reported synthesis of 4-aryl-1-(4'-a-methoxyimino-carbmethoxy methyl thiazol-2'-yl)-3-chloro-2-azetidinones and evaluated the compounds for their antitubercular activity against *$H_{37}Rv$* strain of *Mycobacterium tuberculosis* using Lowenstein Jensen's egg medium by serial two fold dilution method.



R = a) C_6H_5CHO, b) 4-$CH_3C_6H_5$, c) 4-ClC_6H_5, d) 4-$NO_2C_6H_5$,
e) 4-OHC_6H_5, f) 3,4-$(CH_3)_2C_6H_5$, g) 3-CH_3-4-OHC_6H_5

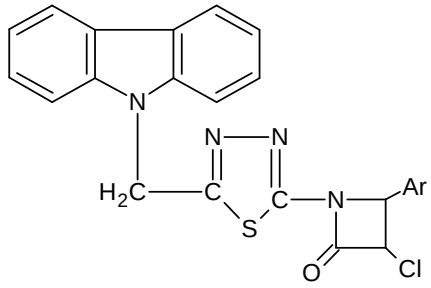
K.M Thakar *et al*[26] have synthesized 4-aryl-3-chloro-1-(3',5'-dichloro-2'-benzo (b) thio phenyl amino)-2-azetidinones and evaluated their antitubercular activity against *$H_{37}Rv$* strain of *Mycobacterium tuberculli* using Lowenstein Jensen's egg medium by serial two fold dilution method.



R_1 = a) H, b) 4-CH_3, c) 4-CN, d) 4-Cl, e) 4-F

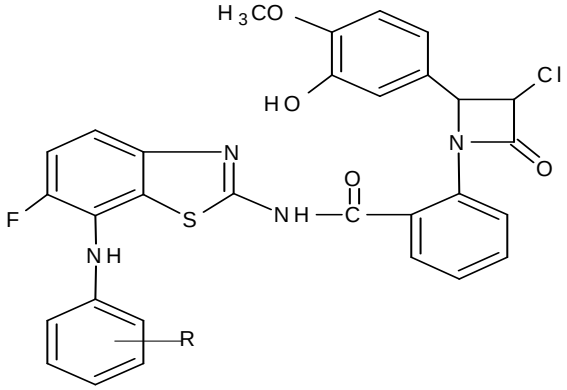
Anticonvulsant activity

S.K Srivastava *et al*[27] S. synthesized 1-[5'-(N9-Carbazolylmethyl)- 1',3',4'-thiadiazole-2-yl)]-4-substituted-3chloro-2-oxo-azetidines. The compounds were screened for their anticonvulsant activity and anti-inflammatory activity at 50 mg/kg by using carrageenan induced rat hind paw edema method.



Ar = a) 2-BrC_6H_4, b) 3-BrC_6H_4, c) 4- BrC_6H_4,
d) 2-ClC_6H_4, e) 3-ClC_6H_4, f) 4-ClC_6H_4,

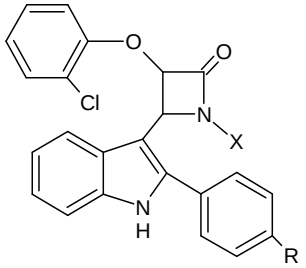
Vijay Kumar, M.M.J *et al*[28] has synthesized N-Substituted-3-chloro-2-azetidinones. The compounds were screened for their anticonvulsant and anti-inflammatory activities by using inhibition of albumin denaturation technique. The Ibuprofen was used as a standard drug[28].



R = o-NO_2, m-NO_2, p-NO_2 aniline
R = o-Cl, m-Cl, p-Cl aniline

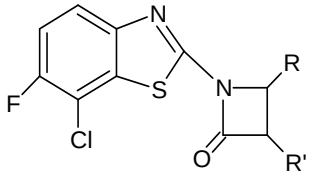
C.N.S .Activity

Rajesh Agarwal *et al*[29] have synthesized 1-substituted -2-oxo-3-chloro/3-(2-chlorophenoxy)-4-(2-arylindol-3-yl)-azetidines showed C.N.S. depressant activity.



R= H, CH_3, Cl

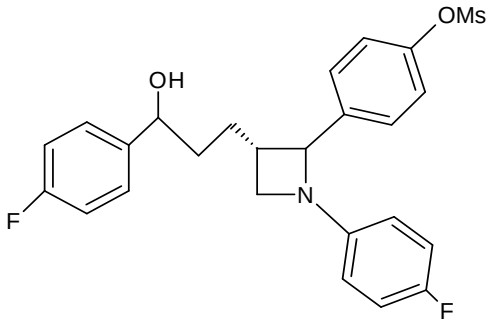
B. M. Gurupadayya *et al*[30] have synthesized 1-(7-chloro-6-flurobenzothiazol-2-yl)-3,4-substituted-arylazetidin-2-ones exhibited C.N.S. depressant activity[30].



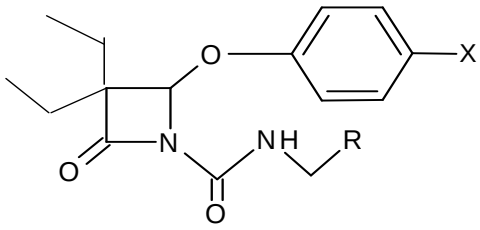
R= C_6H_5, C_6H_4-2-OH, R′= H, Cl

Enzyme inhibition activity

Xianxiu Xu *et al*[31] have reported Design, synthesis, and evaluation of cholesterol absorption inhibitors.



Allan Urbach *et al*[32] have synthesized 3-Alkenyl-2-azetidinones as fatty acid amide hydrolase inhibitors[32].



CONCLUSION

Azetidinone-2-one derivatives containing β- lactam nucleus which are used as antibiotics, it contain β –lactam ring has become an integral part of chemotherapeutic agent. The activity of famous antibiotics such as penicillin's, cephalosporins, and carbapenams are attributed to the presence of 2-azetidinone ring in them. The literature confirms that 2-azetidinone moiety have different biological activities such as antimicrobial, antiviral, anti tubercular, anticonvulsant, central nervous depressant and enzyme inhibition. Hence with a view to further asses the pharmacological profile of azetidinone, different synthetic methods are developed for the formation of 2-azetidinone. Therefore it can be concluded that 2- azetidinone derivatives are important bioactive molecule.

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