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Review article

Chemistry and biological activities of 2-azetidinone derivatives – A mini-review

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ABSTRACT

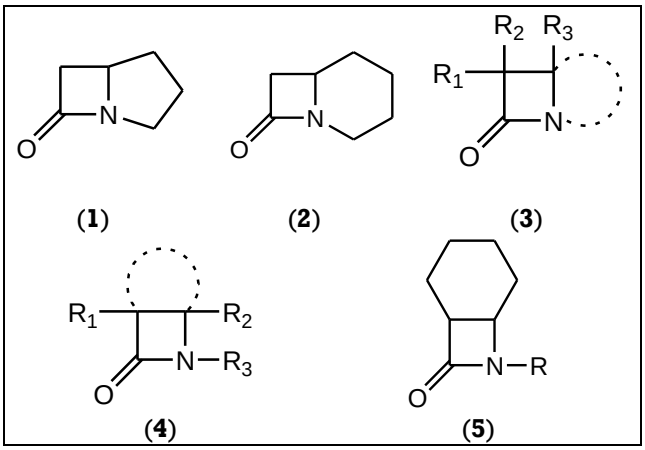
2-Azetidinone skeleton is well established as the pharmacophore of β-lactam antibiotics. β-lactam antibiotics are the most widely employed class of antibiotics. The structural diversity of biologically active β-lactam antibiotics led to the development of many novel methods for the construction of appropriately substituted azetidine with attendant control of functional group and stereochemistry. Azetidine derivatives are reported to show a variety of antimicrobial, antitubercular, anticonvulsant, anti-inflammatory and cardiovascular activities. These activities showed that the minor change in the substitution pattern activities of azetidine derivatives have enhanced dramatically.

INTRODUCTION

Azetidine is a saturated heterocyclic organic compound containing three carbon atoms and one nitrogen atom. It is a liquid at room temperature with a strong odour of ammonia and is strongly basic compared to most secondary amines. Azetidines do not occur as frequently in nature and have been studied far less than closely related chemical compounds such as pyrrolidine and β-lactam. 2-Azetidinone is a chemical compound with the molecular formula C_3H_5NO. It is the simplest β-lactam and it forms the central core structure of the β-lactam antibiotics and certain cholesterol medications. Azetidine and its derivatives are relatively rare structural motifs in natural products. They are the main component of mugineic acids and penaresidins. The most abundant azetidine containing natural product is azetidine-2-carboxylic acid, a non-proteinogenic homolog of proline. The β-lactams are 4-membered cyclic amides derived from 3-aminopropanic acids. Though the first member synthesized by Staudinger in 1907, the β-lactams as a class acquired importance since the discovery of penicillin which contains β-lactams unit as an essential structural feature of its molecule. In the late 1990s, several groups reported novel methodologies for the synthesis of azetidinones of potential biological activities by applying known methods (Hidelomo et al., 1996; Karupaiyan et al., 1997; Singh et al., 1997; Barrett et al., 1997, 1998; Anklam and Licbscher, 1998; Linder and Podiech, 1999; Rossi et al., 1999; Tomioka et al., 1999; Hosmi and Rouszeau, 1999; Croce et al., 1999; Singh, 2003; Palomo et al., 2004).

Monocyclic β-lactams are usually referred to as azetidin-2-ones or 2-oxoazetidine, based on the nomenclature of the parent heterocycle, azetidine. However, the trivial names "penam" for the fused β-lactam (**1a**) and "cepham" for the bicyclic system (**2a**) are also used. Similarly, the term *o*-penam, *o*-cepham, azepenam and azacepham were coined for the bicyclic β-laclams. This trivial system of nomenclature is inadequate, especially in the case of fused β-lactams having no bridgehead nitrogen atom, and in those having no heteroatom at position 1 or alterations in the positions of the hetero atom of the non-β-lactam ring. This discrepancy can be removed by adopting a new system in which fused β-lactams (**3**) and (**4**) may be called "Alkanam" and "isoalkanam" respectively. Thus, β-lactams containing 7, 8 and 9 atoms in the bicyclic system (**3**) may be given generic names, heptanam, octanam, nonanam and so on. The fused β-lactams of the type (**4**) may be termed as isohcptanam, isoctanam, isononanam and so on, depending on the number of atoms in the bicyclic system. The

numbering of ring atoms in this case may be the one used for azetidin-2-ones, and is shown in (**5**).

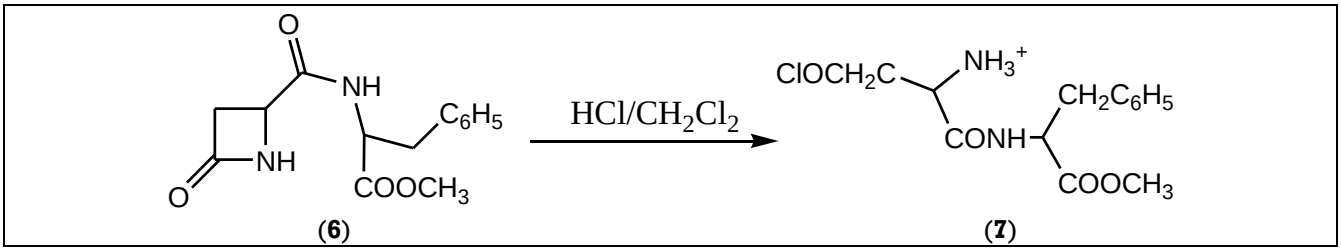


A bicyclic β-lactam containing a double bond in the ring system may be given the corresponding generic name derived from the collective name "Alkenam" or "Isoalkenam" depending on the mode of fusion of the rings. For a stereo description of the molecule, the terms α and β denoting the configuration of the substituents, which may be below or above the plane of the β-lactam ring, may be used as in case of steroids.

REACTIONS AND PROPERTIES OF β-LACTAMS

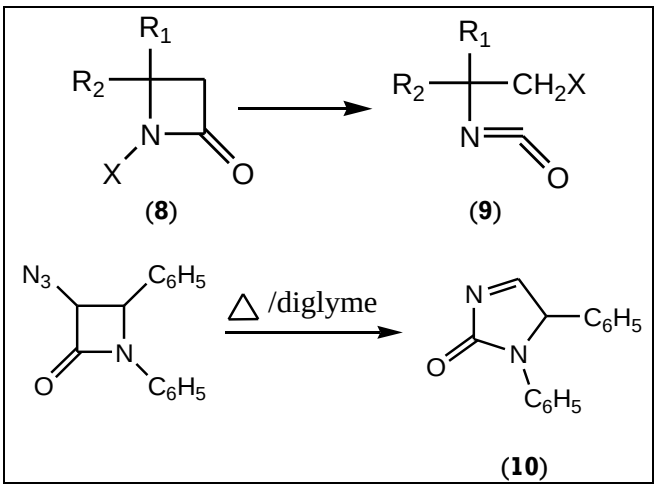
Cleavage of the β-lactam bond

The β-lactam bond undergoes rupture in the presence of an alkali, acid and β-lactamase, yielding 3-aminopropanoic acids. By selective degradation, natural β-lactams could afford useful amino acids. In the presence of dry hydrogen chloride, β-amino acid hydrochloride is generated. For example, the compound (**6**) gave (**7**) on treatment with hydrogen chloride in methylene chloride. Similarly, the β-lactam may be cleaved by imines (Pietsch, 1976).



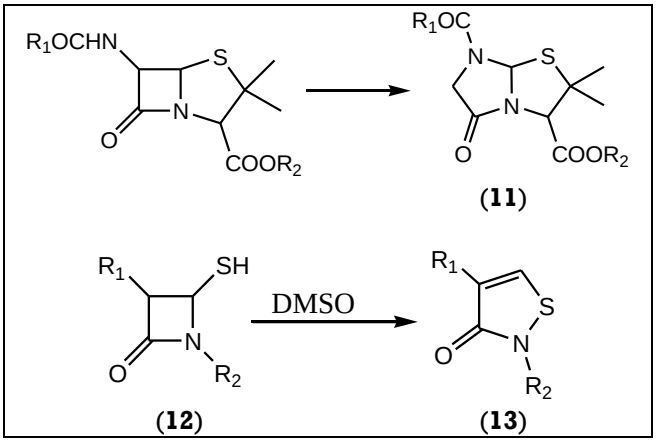
Cleavage of the 2, 3-bond in azetidin-2-ones

l-Haloazetidin-2-ones (**8**) undergo photolytic cleavage to give isocyanates (**9**) capable of undergoing secondary cyclisation under suitable conditions. Similarly, 3-azidoazetidin-2-one (**10**) on refluxing in diglyme, underwent ring expansion through 2,3-bond cleavage (Kampe, 1969).



Cleavage of 5,6-bond in penicillin

Rearrangement of penicillin of penilloic acid (**11**) involves cleavage of 5,6-bond. Similar bond cleavage was observed in penicillin-1-oxide (Clarke et al., 1949).



Cleavage of the 1,4-bond in azetidin-2-ones and collapse of the bridge in bicyclic β-lactams

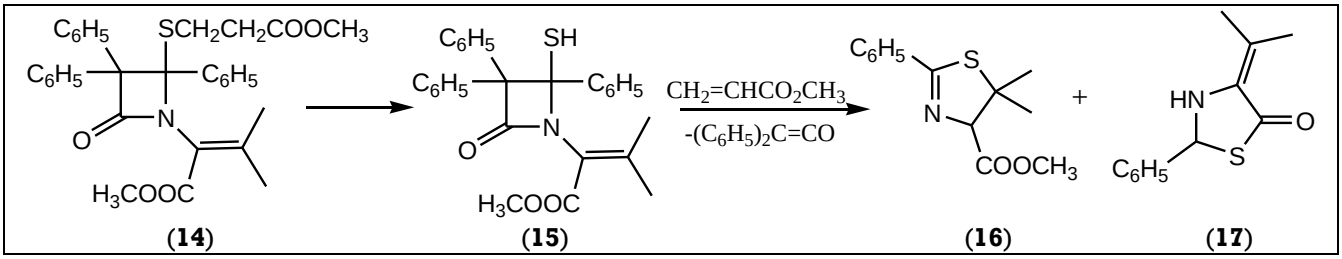
β-Lactams bearing a C-4 hetero atom are unstable and easily undergo 1,4-bond cleavage (Nakano et al., 1976). For example, the 4-mercapto azetidine-2~one (**12**) changes to isothiazolinone (**13**), on treatment with dimethylsulfoxide.

Fragmentation of β-lactams

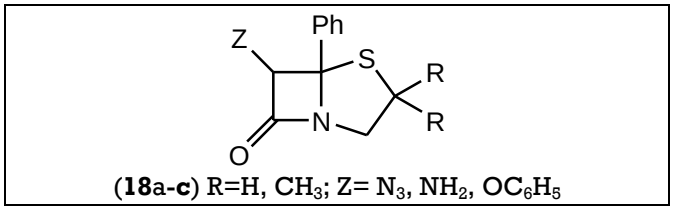
Monocyclic β-lactams on photolysis or thermolysis break up into ketones and imines or alkenes and isocyanates, depending on the substituents present in the molecule and whichever fragmentation is energetically profitable. This

process is essentially a case of retrocycloaddition. Reagent induced fragmentation leads lo diverse products, depending on the substituents and reagents used.

Fragmentation of penicillin and cephalosporin (Terao et al., 1974) occurred on treatment with trifluoroacetic acid, the fragments being amido ketenes, and Δ^2-thiazoline and Δ^2-l,3-thiazine derivatives respectively. Sometimes the fragment formed as primary products may undergo secondary reactions. For example, β-lactam (**14**) on retro Michael reaction, gave (**15**) and subsequently (**16**) and (**17**).



Enzyme catalyzed fragmentation of benzylpenicillin was reported (Manhas et al., 1973). It is noteworthy that the azido group in β-lactam (**18a**) on reduction with Adam's catalyst and subsequent acylation with phenoxyacetylchioride and triethylamine afforded the 6-phenoxy compound (**18c**). Such an unusual result may be explained only on the assumption that the 6-amino compound (**18b**) undergoes fragmentation and generates a Δ^2-thiazoline, which then reacts with phenoxyacetyl chloride and triethylamine in the usual way.



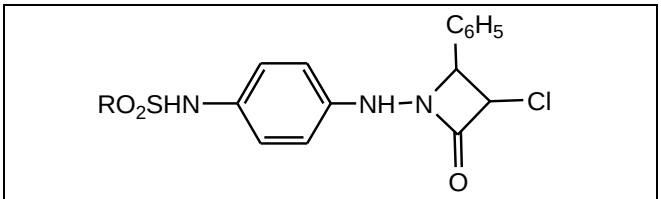
(**18a-c**) R=H, CH_3; Z= N_3, NH_2, OC_6H_5

BIOLOGICAL ACTIVITIES

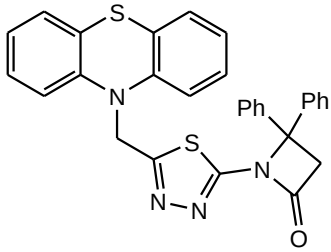
Azetidine derivatives are reported to show a variety of antimicrobial, antitubercular, anticonvulsant, anti-inflammatory and cardiovascular activities.

Antimicrobial activity

Azetidine and their derivatives have been extensively explored for their applications in the field of medicine. Likewise, azetidin-2-ones are of great importance because of β-lactam derivatives as an antibacterial agent. Incorporation of these compounds have witnessed a great upsurge in the treatment of tuberculosis and other chemotherapeutic diseases (Vashi et al., 1995). Antibacterial activity of some N-sulphonamoyl-phenylamino-3-chloro-4-phenyl-azetidin-2-ones, most of the compounds exhibited significant antibacterial activity. Compound l-[4-(5,6-dimethoxypyrimidino-sulphonamoyl) phenyl-amino]-3-chloro-4-phenylazetidin-2-oiie (**19**) has been found to be more potent than standard drug against *E. coli* (Sharma et al., 1998). A series of l-[5-(N^{10}-phenothiazinomethyl)-l,3,4-thiadiazoi-2'-yl]-4-substituted-2-azetidinones as antifungal agents have been reported. All the compounds were screened for their antifungal activity against the fungi C. *albicans, R. oryzae and C. pannical.* The fungicidal data indicated that all the compounds were moderate to highly toxic. The toxicity of compounds depends upon the nature and position of the substituents at the aryl moiety. Compound (**20**) displayed promising antifungal activity (Rawat and Srivastava, 1998).



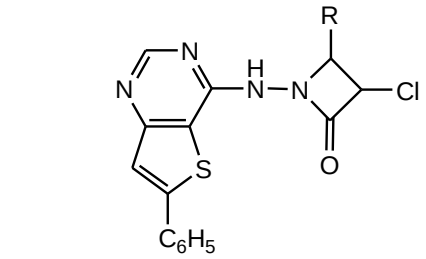
(**19**) R = 4,5-dimclhoxypyrimidyl



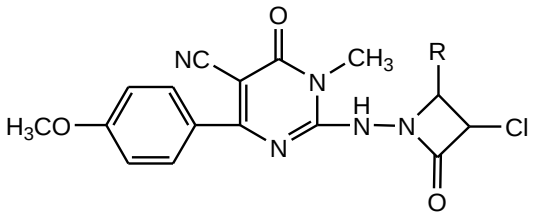
(**20**)

Synthesized azetidinones (**21**) from hydrazine thieno [3,2-d] pyrimidines as potential antimicrobial agents. All the products have been evaluated for their *in vitro* growth inhibitory activity against several microbes like *B. megatilis, B. subtilis, E. coli, A. aerogens* and *A. awamori.* Most of the compounds exhibited maximum activity in the range of 21-27 mm against *A. aerogens.* Other compounds showed either moderate or less activity against these organisms. None of the compounds was found to exhibit significant activity against, *B. siiblilis* (Shah et al., 1998). Synthesis of azetidlnones from hydrazinopyrimidine as potential antimicrobial agents, all the compounds were tested for their *in vitro* growth inhibitory activity

against several microbes like *B. megaterium, B. subtilis, E. coli, P. fluorescens* and *A. awamori* (Parmar et al., 1999). All the compounds exhibited mild to moderate antimicrobial activity against all microorganisms except (**22**) which exhibited promising activity with ampicillin and chloramphenicol against *P. fluorescens.* Antimicrobial activity of azetidin-2-ones has also been reported by various authors (Mogihiiah et al., 1999; Desai et al., 2000; Joshi et al., 1994; Mogilaiah et al., 1999).



(21) R=H, CH_3

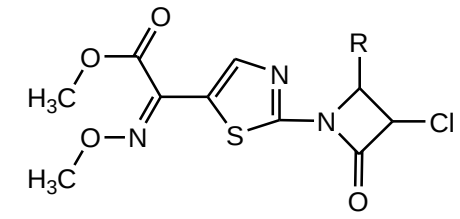


(**22**) R=aryl/substituted aryl group

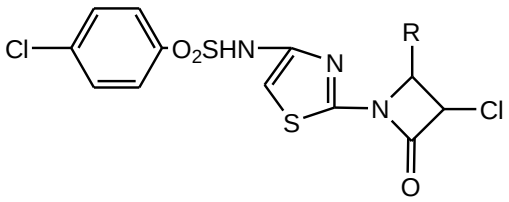
Antitubercular activity

The antitubercular activity of l,3,4-trisubstituted-azetidin-2-ones (**23**) has been reported. The representative compounds were tested *in vitro* for their antitubercular activity against *M. tuberculosis H37Rv.* The data were compared with standard drug rifampin. All the compounds showed moderate antitubercular activity against *M. tuberculosis* (Parikh et al., 2000). The antitubercular activity of 2-[4-(4-substitutedphenyl)-3-chloro-2-azetidinon-l-yl]-4-[2-(4-chloro-benzenesulphon-amido)-phenyl]thiazoles (**24**), primary screening of the compounds for antitubercular activity was conducted at 12.5 µg/ml against *M. tuberculosis* H37Rv. Compounds demonstrating at least 99% inhibition in the primary screening were tested at lower concentrations against this microorganism to determine the actual minimal inhibitory concentration (MIC). The antitubercular activity data showed that most of the azetidinone derivatives exhibited 100% inhibition in the primary screen at 12.5 µg/ml concentration (Patel et al., 1999).

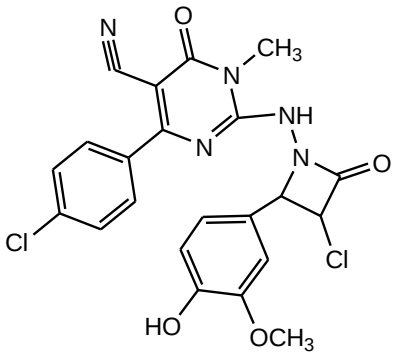
The antitubercular activity of 2-azetidinones bearing thymol moiety, the compounds displayed moderate to good tuberculostatic activity [20]. The antitubercular activity of 2-(4-aryl-3-chloro-2-azetidinon-l-yl-amino)-6-(4-chlorophenyl)-5-cyano-3-N-methyl-3,4-dihydropyrimidin-4-ones, all the products displayed mild to moderate antitubercular activity against *M. tuberculosis.* Compound (**25**) was the most active member of this series (Modha et al., 2002).



(**23**) R=Cl, F, CH_3



(**24**) R=CH_3, C_2H_5



(**25**)

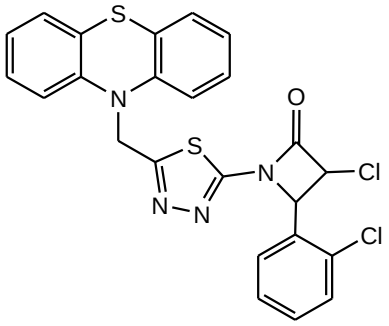
Anti-inflammatory activity

Some l-[5-(carbazolylmethyl)-l,3,4-thiadiazol-2-yl)]-4-(substituted phenyl)-3-chloro-2-oxo-azetidines have been synthesized and evaluated for their anti-inflammatory activity. All the compounds displayed mild to moderate anti-inflammatory activity except compound (**26**) that showed anti-inflammatory activity that was comparable to standard drug phenylbutazone (Srivastava et al., 1999). Many l-[5-(N^{10}-2-chloro phenothiazino methyl)-l,3,4-thiadiazol-2-yl]-4-(substituted phenyl)-3-chloro-2-oxoazetidines have been tested for their anti-inflammatory activity All the compounds tested for anti-inflammatory activity exhibited mild to moderate activity. The compound **(27)** was the most potent and active member of this series. It displayed comparable anti-inflammatory activity but lesser than the standard phenylbtitazolie (Srivastava et al., 2003).

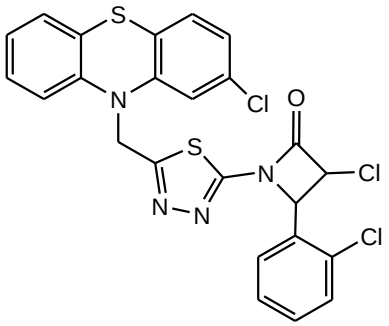
Miscellaneous activities

Use of strain therapy is a key first-line approach in preventing coronary heart disease events and stroke in people at increased risk of

developing complications. Ezetimibe the first licensed azetidinone drug is being promoted as an adjunct to strain therapy to achieve greater reduction in blood cholesterol concentrations than occur with a strain alone. Many workers have also reported azetidinones as cholesterol absorption inhibitors (Heek et al., 2003; Clader, 2004), antiviral agents (Ramtohul et al., 2002; Lall et al., 2002), and anticancer agents (Sutton et al., 2002; Spletstoser et al., 2004; Sun et al., 2004) and human tryptase inhibitors (Qian et al., 2002; Bisacchi et al., 2004).



(**26**)



(**27**)

CONCLUSIONS

The study reports the biological activities of the compounds bearing an azetidinone moiety revealed that the compounds showed moderate to good anti-inflammatory, antimicrobial, antifungal and other activities. Some of the compounds displayed promising activities and are of interest for further transformations towards more potent derivatives. Process optimization, clinical safety and dosage form development of these compounds are needed. Furthermore, the development of new azetidine derivative by this scheme is highly desirable.

CONFLICT OF INTEREST

Authors declare no conflicts of interest.

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