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THE CHEMISTRY AND PHARMACOLOGICAL POTENTIAL OF 2-AZETIDINONES INCORPORATED WITH HALOGEN ATOMS AND CYANO GROUPS: A REVIEW

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ABSTRACT

2-Azetidinones nitrogen containing four-membered heterocyclics with a unique ring system present in living organisms, natural products, drugs and in many other substances represent interesting chemistry and great biological potential and are useful to mankind and society in all walks of life. Besides antibiotic activity, the ring system exhibits a wide range of pharmacological activities which is attracting the attention of researchers. In recent years, renewed interest has been focused on the synthesis and modification of β-lactam ring to obtain new compounds by applying known or new methods for diverse pharmacological activities. The present review gives a brief account on the chemistry, reactivity and methods of synthesis focusing on the detailed and extensive update on biological and pharmacological profiles of azetidin-2-ones specially incorporated with halogen and cyano groups.

KEYWORDS: β-Lactam ring, 2-azetidinones, pharmacological activity, cyanoethylation, halogen and cyano groups.

INTRODUCTION

2-Azetidinones (nitrogen containing four-membered heterocyclics) are one of the most significant areas of research in the field of medicinal chemistry and are considered as an important contribution of science to humanity. Azetidinone is an important nucleus has gained wide acceptance across the world but bacteria continue to challenge the society and scientific community with their mortality. The serious threat of superbugs and the emergence

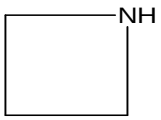
of clinically isolated antibiotic resistant species of common pathogens were reported in the world. [1]

The synthesis of 2-azetidinones has always attracted the attention of chemists due to their important biological properties over the years. [2] 2-azetidinones are useful in organic chemistry for the preparation of bioactive compounds by the incorporation of halogen and cyano groups in the different positions of the ring. Since the discovery of penicillins [3,4] and cephalosporins: the most successful antibiotics, 2-azetidinones have been the subject of regular discussion and investigation for the organic chemists. The aim of the present study is concentrated much on the concise works reported in the synthesis of pharmacologically potent 2-azetidinones incorporated with halogen and cyano groups.

A plethora of work has appeared in the literature on their biological as well as synthetic potential. The discovery of penicillins triggered the therapeutic field of chemistry to a remarkable extent with a number of antibiotics. Discovery of penicillins, cephalosporins, and other antibiotics such as nocardincins and monobactams has led to sustained interest in the synthesis of many β-lactam synthons. [5] The chemists are engaged in investigating different routes for the synthesis of β-lactams of medicinal values. The ester-imine condensation route of β-lactams has been highly developed over the past decades. [6] Solvent less synthesis methods were also found suitable for the synthesis of N-containing heterocyclic ring compounds and revolutionizing the field of synthesis. [7] The imines are the most important and essential starting materials for the synthesis of the β-lactams. Bose *et al.* prepared successfully 3-chlorocarbonyl 2-azetidinones from imines, thioimidates and substituted malonylchlorides. [8] Tellis and co-workers reported phenyl aspartic acid derivatives to form β-lactams. [9] The structure modification and biological activity assay has been the theme of research for preparing better molacules of considerable therapeutic values. Antibacterial activity of cephalosporins against Gram "-" ve pathogens were observed better when a potential leaving group present at the 3' position. [10-12] The kinetic studies on the β-lactams revealed the importance of substituents in actual therateutic molecules and the effect of leaving group in the ring opening mechanism of cephalosporins reported; cephalosporins with direct 3-position side chains like methyl can exhibit excellent activity depending on the nature of 7-acylamino side chain.

CHEMISTRY OF 2-AZETIDINONES

Azetidinones are a part of antibiotic structure, which possesses interesting biological activities.[13-15] A large number of 3-chloromonocyclic 2-azetidinone rings [16-18] having substitution at position -1 and -4 exhibited powerful antibacterial [19-23] antifungal, [24-26] pharmaceutical, [27] anti-inflammatory, [28,29] herbicidal, [30] hypocholesterolemic, [31] anticonvulsant, [32,33] antitubercular, [34,35] anticancer [36,37] and antibiotic [38] activities. They also function as enzyme inhibitors and are effective against the CNS (central nervous system) .[39-41] These are carbonyl derivatives of azetidines **(1)** containing carbonyl group at position-2. They are also known as 2-azetidinones **(2)** or more commonly β-lactams.



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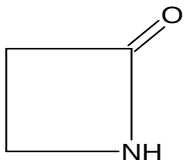
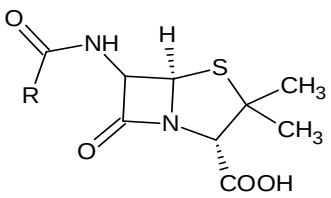


(2)

The first 2-azetidinone was synthesized by H. Staudinger [42] in 1907 about four decades before the invention of penicillin via [2+2] cycloaddition reaction of ketene and imine which is termed as the Staudinger reaction [43-45] but 2-azetidinone class of compounds became attractive only after it was established that penicillin contained a 2-azetidinone structural nucleous. [46] The phenomenal success of penicillins, cephalosporins and other 2-azetidinone antibiotics has focused an extensive β-lactam research in many industrial and academic laboratories. [47] Among the naturally occurring bicyclic antibiotics, penicillin **(3)** and cephalosporin **(4)** are the most important. These compounds were found to be somewhat effective against typhoid fever. Until recently, interest in newly generated β-lactams tended to focus solely on their ability to induce bacterial cell death due to their historically successful application in this role.



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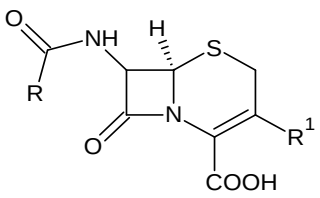


(4)

The name penicillin was coined by Alexander Fleming, who in 1928 observed bacteriolysis in a nutrient broth at St. Mary's Hospital in London. [48,49] Although the discovery was

attributed to Fleming, there are indications that the same observation was made earlier by others. [50] However, several years passed until the clinical value of the substance was recognised and demonstrated. Due in particular to the work of scientists at Oxford, including Florey, Chain and Abraham, the drug was isolated and entered into clinical trials by 1941. It was used successfully to treat battle casualties at the end of World War IInd and was soon hailed as the true medical miracle of the century.

Penicillin is chemically characterised by the presence of a 2-azetidinone ring, fused to a five-membered thiazolidine ring, as was demonstrated by Dorothy Hodgkin. [51] Penicillin exerts its antibiotic action on DD-transpeptidases (penicillin-binding proteins) enzymes involved in the biosynthesis of the bacterial cell wall. [52] 2-azetidinone drugs act as pseudo substrates and acylate the active sites of these enzymes, thereby inhibiting their action. Giuseppe Brotzu discovered and analysed cephalosporin from cultures of *Cephalosporium acremonium* isolated from a sewer in *Sardinia*, [53] subsequently isolated and further analysed. [54]

Due to the effectiveness and lack of toxicity, 2-azetidinone compounds are amongst the most successful and widely used antibiotics in history. However, the emergence of multi-drug resistant bacterial strains such as *Staphylococcus aureus* is threatening the effectiveness of 2-azetidinone antibiotics. [55] The common resistance mechanism in Gram "-"ve bacteria is the cellular expression of β-lactamases (or penicillinase), which hydrolyze the 2-azetidinone ring and thus inactivate antibiotics.[56-59]

Another shortcoming to the effectiveness of β-lactamase antibiotics is the bacterial outer membrane, which is a formidable barrier in Gram "-"ve organisms. In addition, the bacterial membrane could acquire efflux pumps that facilitate active elimination of drug from the bacterial cytosol. [60,61] One of the most fruitful 2-azetidinone SAR studies has been the modification of the N-acyl groups. These studies have led to the discovery of 2-azetidinone analogues with superior antibacterial activity. [62-64]

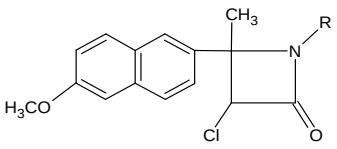
Besides their importance as the key structural component of 2-azetidinone antibiotics, they have been attracting considerable interest in organic synthesis as versatile synthetic intermediates and chiral synthons. [65-68] In addition, the 2-azetidinone scaffold has found new pharmaceutical applications other than its use as antibiotics, such as LHRH (luteinizing hormone-releasing hormone) antagonists, [69] cholesterol absorption inhibitors [70] and anticancer agents. [71-74] The ring strain of the 2-azetidinone skeleton facilitates ring-opening

reactions [75,76] and this unique property has been exploited for the synthesis of a variety of medicinally active compounds. For the last couple of decades, a large number of 2-azetidinone based synthetic methods collectively termed as "2-azetidinone synthon method" has been developed.

2-Azetidinone showed a broad-spectrum of activity on various pathogens and a considerable research has been done on the synthesis of new potent antibacterial and antifungal 2-azetidinones. [77,78]

Most of the researches up to early 90's have been focused on synthesis and study of antibacterial property of 2-azetidinones. In recent decades, renewed interest has been focused on the synthesis and modification of 2-azetidinone ring to obtain compounds with diverse pharmacological activities. 1-aryl-3-chloro-4-(6'methoxy-β-naphthyl)-4-methyl-azetidin-2-one **(5)** has been synthesized and screened for antibacterial and antifungal activity, [79] against Gram "+"ve and Gram "-"ve bacteria. Shah *et al*. observed that when R-4-methoxy phenyl, the zone of inhibition was 22 mm against *E. coli*, 19 mm against *B. subtilis* as compared to standard drug ampicillin. Literature survey reveals that 4-aryl-3-chloro-1-(2-trifluoromethyl-1,8-naphthyridine-3-carbonylamino)-2-azetidinones **(6)** exhibits good antibacterial activity[80] against *E. coli*.

In addition, 2-azetidinone derivatives also display a board range of enzyme inhibitory activity[81-84] and have attracted considerable attention due to wide range of pharmaceutical activities.[85,86]



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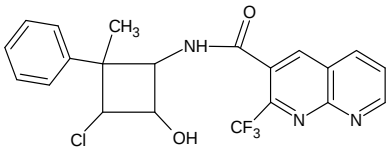

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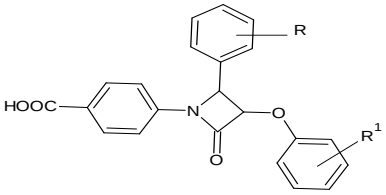
Some new biologically active 2-azetidinone derivatives **(7)** and **(8)** have been recently obtained via incorporation of 2-aminopyridine moiety by Kumbhar [87] *et al.*



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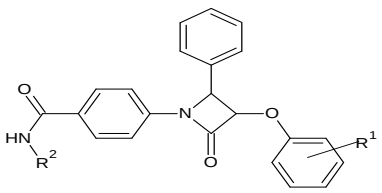
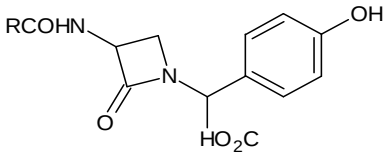


(8)

A large number of 3-chloro monocyclic β-lactams possess powerful antibacterial, anti-inflammatory, anticonvulsant and anti-tubercular activity. [88-90] An interesting group of β-lactams are molecules that do not contain another ring fused to the 2-azetidinone one is the monocyclic β-lactams. The discovery of the nocardicins **(9)** and monobactam **(10)**, demonstrated for the first time that β-lactams do not require a conformationally constrained bicyclic structure to have antibacterial properties, [91] suggesting that the biological activity was strictly correlated to the presence of a suitably functionalized 2-azetidinone ring. [92,93]



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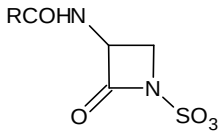
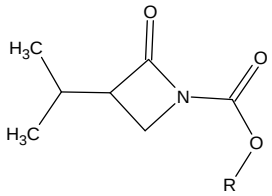


(10)

Squibb and Takeda disclosed new horizons for the clinical application of 2-azetidinone antibiotics, since some of them like aztreonam and carumonam possess a specific activity against Gram "-"ve bacteria. Monocyclic β-lactams served as versatile synthetic precursors for β-amino acid derivatives. N-acyl-3-alkylidenyl and 3-alkyl azetidin-2-ones as a new class of monocyclic 2-azetidinone antibacterial agents reported by Brickner *et al.* A series of N-acyl-3-isopropyldienyl **(11)** and 3-isopropyl-2-azetidinones **(12)** having potent *in-vitro* antibacterial activity especially against anaerobic bacteria was synthesized. [94]



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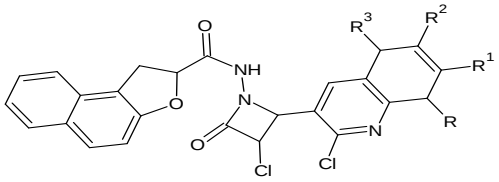


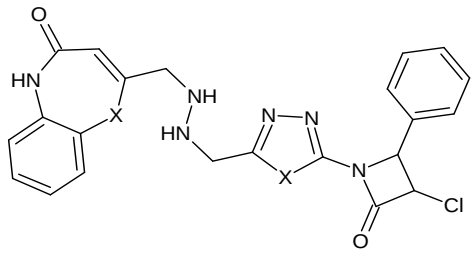
(12)

Sulfadrug moiety containing new azetidinone derivatives owing good antimicrobial activity: Ishwar K. Bhat reported formation of some azetidinone derivatives having activity against some microbes. [95] 4-[3-Chloro-2-(5-nitro-furan-2-yl)-4-oxo-azetidin-1-yl]-N-pyrimidin-2-yl-benzenesulfonamide were prepared by Salman [96] *et al*. via cyclocondensation of the azomethines, derived from sulfa drugs with chloroacetylchloride in the presence of triethylamine.

2-Azetdinone derivatives containing aryl sulfonate moiety reported with anti-inflammatory and antimicrobial activity. Bausare [97] *et al.* reported the synthesis of novel azetidin-2-one

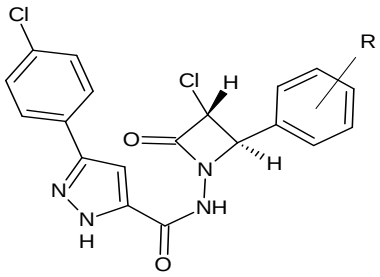
derivatives containing aryl sulfonate moiety in good to moderate yield, few of them showed good anti-inflammatory activity.

4-Carbamoyl and 4-alkoxycarbonyl β-lactams were found to be inhibitors of HIV-1 protease[98] or human leukocyte elastase and porcine pancreatic elastase. [99] On the other hand, 4-cyano and 4-carbamoyl-β-lactams have been used as precursors of thienamycin and isopenam. [100] Over the past decades, many synthetic methods [101,102] such as Kinugasa reaction of alkynes with nitrones, [103] Ugi three component/four-centre condensation of β-amino acids with aldehydes and isonitriles, [104,105] cyclization reactions of β-amino acids [106] and reactions of chromium carbene complexes with imines [107] have been developed for the construction of the 2-azetidinone skeleton. However, the Staudinger reaction [108,109] still remains the most efficient route to β-lactams. The reaction of 2-azetidinone carbenes with alkyl isonitriles was investigated. Two different types of products, 4-cyano- or 4-carbamoyl-β-lactams, were isolated, depending upon the nature of the alkyl group of the isonitriles. [110] Ashok Kumar [111] *et al.* have synthesized new substituted benzoxazepine and benzothiazepine derivatives **(15)**, and evaluated for antipsychotic as well as anticonvulsant activity.



(15)

2-Azetidinones bearing a pyrazole scaffold exhibited potent biological activities because pyrazoles and their derivatives are important on account of use in therapy in different diseases [112-115] such as antibacterial, [116] fungicidal, [117] anti-diuretic, [118] anticancer, [119] anti-HIV, [120] anti-tumour [121] *etc.* Pathak [122] *et al.* have synthesized such 3-(4-chlorophe nyl)-4-substitutedpyrazole-azetidinone derivatives **(16)** and evaluated as good to excellent antimicrobial and anti-tubercular activity. Recently a new series of 3-chloro-4-{4-[2-{5-(4-chlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydro-pyrazol-1-yl}-2-oxoethoxy]pheny- l}-1-(substituted-phenyl)azetidin-2-one derivatives **(17)** has been synthesized and subjected to evaluate their antimicrobial activity by Patel [123] *et al.*



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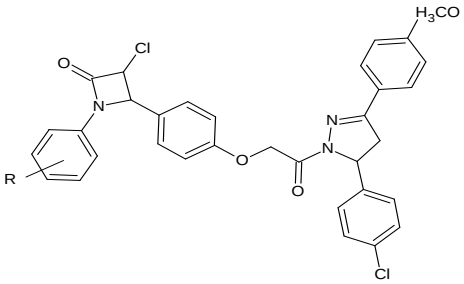
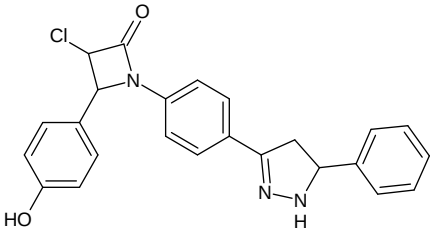


(17)

A new series of 3-chloro-1-{4-[5-(Substituted-phenyl)-4,5-dihydro-pyrazol- 3-yl]phenyl}-4-(4-hydroxyphenyl)azetidin-2-one **(18)** have been synthesized by reacting 3-chloro-1-{4-[3-(Substituted-phenyl)prop-2-enoyl]phenyl}-4-(4-hydroxyphenyl)azetidin- 2-one with hydrazine hydrate and were evaluated for their antibacterial and antifungal activities. [124]

Kumar and co-workers have synthesized bioactive azetidinones **(19)** and thiazolidinones of 3-methyl-1-phenyl-1H-pyarazol-5-ol [125] and screened them for biological activities against bacterial strains.



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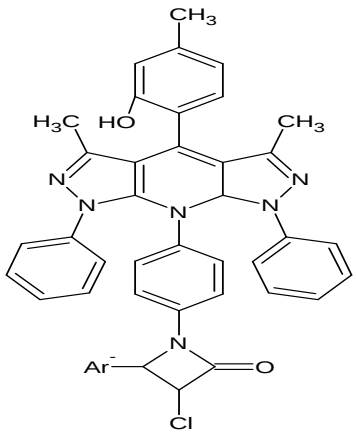
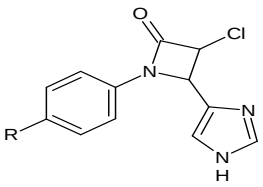


(19)

The biological activity of the 2-azetidinone skeleton is generally believed to be associated with the chemical reactivity of their 2-azetidinone ring and on the substituents especially at nitrogen of the 2-azetidinone ring. The oxo group is at 2nd position *ie.* 2-azetidi- none substituents at the N-1, C-3 and C-4 position may be varied. Synthesis and antimicrobial susceptibility of derivatives of 3-chloro-4-(1H-imidazol-4-yl)-1-(4-substituted phenyl)azetidin-2-one **(20)** and 3-chloro-4-(1-(morpholinomethyl)-1H-imidazol-4-yl)-1-phe-nylazetidin-2-one **(21)** reported recently by Esther [126] and co-workers.



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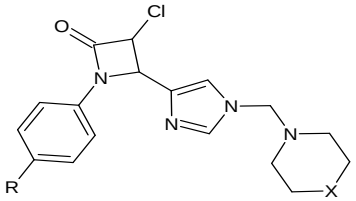

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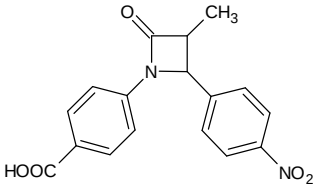
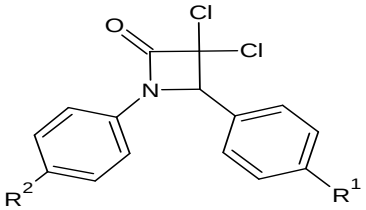
Sugumaran *et al.* have reported 2-azetidinone **(22)** and 4-thiazolidinone derivatives exhibiting promising antimicrobial activity against a set of micro-organisms. [127]



(22)

Since the discovery of penicillin's many antibiotic compounds containing 2-azetidinone moiety have been isolated from natural sources or synthesized chemically, or are semi synthetic derivatives of the natural scaffolds produced by micro-organisms. Effect of more bulky aryl substituents at the 4-position of the azetidin-2-one **(23)** moiety has been studied by Junne [128] *et al*. A new series of 3-chloro-1-{[2-(6-nitro-1H-indazol- 1-yl)ethyl]amino}-4-(substituted phenyl)-2-azetidinones **(24)** have been synthesized and screened *in-vitro* for their antibacterial, antifungal and anti-tubercular activities against some selected micro-organism for their anti-inflammatory activity *in-vivo* by Samadhiya [129]*et al.*



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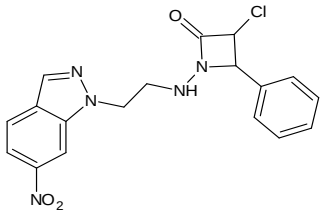

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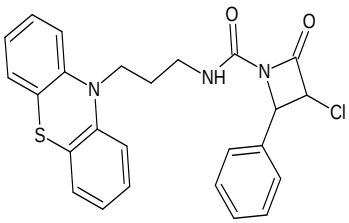
Samadhiya *et al.* also have synthesized 2-azetidinone (N-(3-(10H-phenothiazin-10-yl) propyl)-3-chloro-2-oxo-4-substitutedphenylazetidine-1-carboxamide) derivatives **(25)** of phenolthiazine [130] and evaluated as antimicrobial and anti-tubercular. Patel *et al.* have synthesized some 5H-dibenzo azepine-5-carboxamido-4'-aryl-3'-aryl-piperazine-2'-azetidinone derivatives. [131] **(26)**



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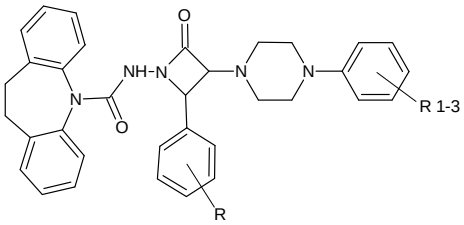
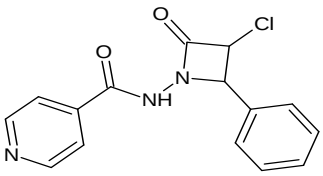


(26)

Nikalje *et al.* have synthesized novel N-(3-chloro-2-oxo-4-substituted azetidin-1-yl) isonicotinamide derivatives **(27)** as antimycobacterial agents [132]. Preethi *et al.* have synthesized novel 4-thiazolidinone and 2-azetidinone derivatives **(28)** and evaluated them for different activities [133] *viz.* anti-tubercular, anticonvulsant antibacterial and antifungal.



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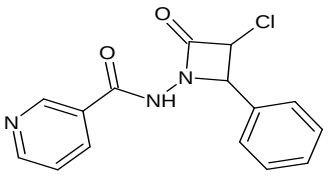
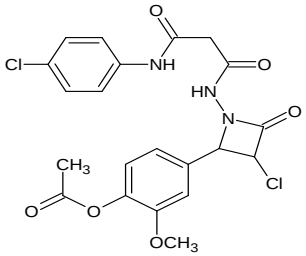


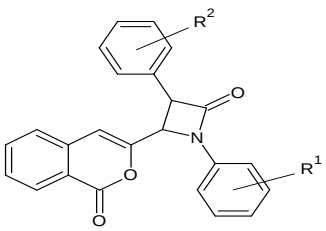
(28)

A series of 3-chloro-1-(aryl)-4-(2-(2-chloro-6-methylquinolin-3-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)-4-ethyl-azetidin-2-ones, have been synthesized and were screened for their antibacterial activity by Dodiya [134] *et al*. A series of 3-chloro-4-(3-methoxy-4-acetyl oxyphenyl)-1-[3-oxo-3-(phen-ylamino)propanamido]azetidin-2-ones **(29)** and 3-chloro-4-[2-hydroxy-5-(nitro-substituted-phenylazo)phenyl]-1-phenylazetidin-2-ones [135] have been synthesized and assayed *in-vitro* for their growth inhibitory activity against pathogenic micro-organisms.

The results of antimicrobial screening indicated that the nature of substituents and their position on 2-azetidinone nucleus affected the *in-vitro* activity significantly. Mashelkar *et al.* have synthesized 1, 3, 4-substituted-(4-(1-oxo-1H-isochromen-3-yl)-1-aryl-3-phenyl azetidin-2-ones)-2-azetidinones. [136] **(30)**

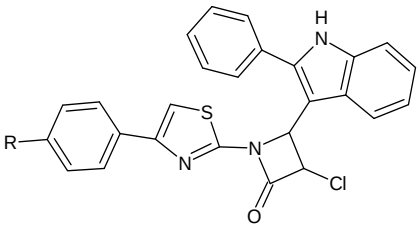


(29)

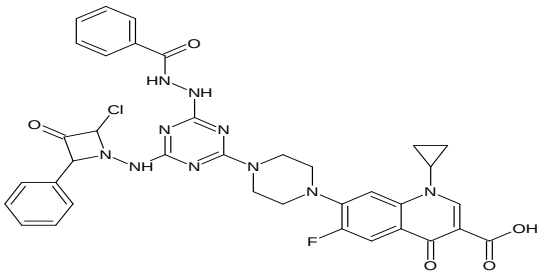


(30)

The 2-azetidinone structure has been found to have very low toxicity in most cases and this characteristic makes them an excellent candidate for further development. Strides have been made towards achieving this goal, with an increasing number of publications revealing promising results in this area. In 2002 for the first time the ability of β-lactams to induce cell death in cancerous cells was reported. [137] Stereoselective synthesis of racemic and optically active novel β-lactams using Staudinger cycloaddition reaction with imines and ketenes and identification of a few β-lactams demonstrating anticancer activity has been achieved by Banik. [138] Saundane *et al*. synthesized azetidinone and thiazolidinone moieties linked to indole. [139] 2-N-(2-phenyl-1H-indol-3-yl)imino-4-arylthiazoles were used as key synthons for the preparation of (4-aryl thiazol-2-yl)-4-(2-phenyl-1H-indol-3-yl)azetidin-2-one and 3-(4-arylthiazol-2-yl)-2-(2-phe nyl-1H-indol-3-yl)thiazolidin-4-ones **(31)**. Desai *et al.* have synthesized azitidinone derivatives 7-(4-(4-(2-benzoylhydrazinyl)-6-(2-chloro-3-oxo-4-substitutedbenzaldehyde-azetidin-1-ylamino)-1,3,5-triazin-2-yl)piperazin-1-yl)-1-cyclopro pyl-6-fluoro-4-oxo-1,4-di-hydro quinoline-3-carboxylic acid **(32)** and evaluated biologically for antimicrobial activity. [140] Singh [141] *et al.* described the reactions of *N*-salicylidene amines with diarylketenes generated from thermal decomposition of the 2-diazo-1,2-diarylethanones.

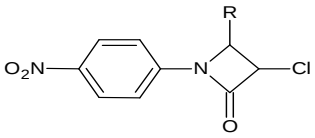


(31)



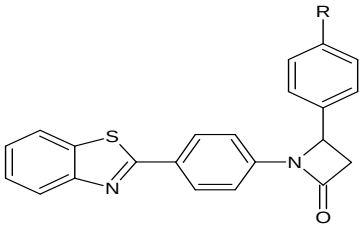
(32)

Presence of electron withdrawing functional groups: nitro (-NO_2) and chloro (-Cl) at *p*-positions, show better activities, revealed by the recently synthesized new derivatives of 3-chloro-1-(4-nitrophenyl)-4-phenylazetidin-2-one **(33)** and their antimicrobial activity against both strains of Gram "+"ve and Gram "-"ve strains by Sarangi [142] *et al*. Recently, a series of coumarin based azetidine-2-one(3-Chloro-1-[4-(2-oxo-2H-chromen-4-ylamino)-phenyl}-4-phenyl-azetidin-2-one derivatives have been successfully synthesized by Joshi [143] and were tested for their *in-vitro* antimicrobial activity displaying that most of the compounds were active against E. *coli*, *S. aureus* and B. *subtilis*.



(33)

A simple and convenient synthesis in good yield with a wide variety of functional groups benzothiazole appended 2-azetidinone **(34)** was described by Reddy [144] *et al.* via a methodology involving [2+2] cycloaddition of benzothiazole substituted imines with chloroacetylchloride in the presence of triethylamine.



(34)

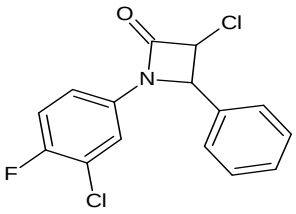
A method described by Rey *et al*. for the preparation of *N*-substituted-2-azetidinones is useful in the synthesis of taxol and its derivatives. [145] Patel *et al*. have carried out the synthesis of azetidinone and thiazolidinone derivatives from 2-amino-6-(2-naphthal enyl)thiazolo[3,2-d]thiadiazole. [146] Singh and co-workers have prepared some new 2-azetidi nones from *N*-(salicylidene) amines and 2-diazo-1,2-diarylethanones. [147] Recently, synthesis and characterization of some new derivatives of 2-azetidinones have been reported by Prabhakar [148] *et al*. A new series of antibacterial, antifungal and anti-tubercular activities, *N*-[2-(1*H*-1,2,3-benzotriazol-1-yl)ethyl]-4-(substitutedphenyl)-3-chloro-2-oxo-1-imino-azetidi nes were synthesized by Samadhiya [149] *et al*. Some new 2-azetidinone derivatives displaying moderate to good antimicrobial activity possessing benzimidazole nucleus were synthesized and screened by Joshi [150] using cup plate method.

SYNTHESIS AND PHARMACOLOGICAL PROFILE OF 2-AZETIDINONES INCORPORATED WITH HALOGENS

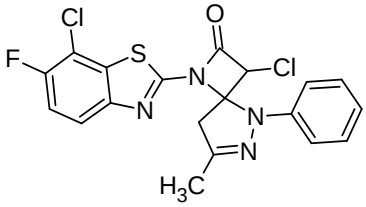
Now a day's vast number of compounds with fluorobenzene moiety features in diverse areas like antibacterial, antifungal, anti-inflammatory, psychoactive agents, pesticides and herbicides [151] *etc*. The new generation antibiotics incorporated with fluorobenzene moiety proved their efficacy as potent bioactive molecules [152]. Some authors were interested in synthesizing azetidinone derivatives with different substituent specially halogens, which are

known for their activity. Hence Dinnimath *et al.* have synthesized chloro, fluoro and phenyl substituted azetidin-2-ones **(35)** by microwave technique with good yield in short span of time and eco-friendly method and further screened for antimicrobial activities. [153] These derivatives have shown displaying promising activities as antibacterial, antifungal and anti-tubercular agents.

In a work done by Reddy [154] *et al.*, 3-chloro-1-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl-7-methyl-5-phenyl-1,5-triazaspiro[3,4]oct-6-en-2-one)2-azetidinone **(36)** which were further condensed with different primary and secondary amines and were screened further for anti-inflammatory, antidiabetic, antioxidant and antimicrobial activities.



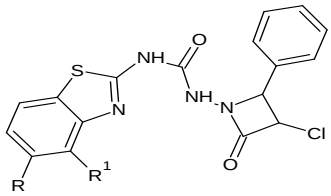
(35)



(36)

A novel series of azetidinone 1-(3-chloro-2-oxo-4-(o-tolyl)azetidin-1-yl)-3-(4-chloro-5-fluorobenzo[d]thiazol-2-yl)urea derivatives **(37)** with antibacterial activity have been prepared by Sarkar [155] *et al.* from the building blocks of 2,3,4(trisubstituted-benzaldehyde)-*N*-(6,7-substituted-1,3-benzothiazol-2-yl)semicarbazone.

Fluoro and chloro substituted 2-azetidinone derivatives *ie.* *N*-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl)-2-[(3-chloro-2-oxo-4-phenylazetidin-1-yl)amino]acetamide **(38)** have been synthesized from benzothiazole and screened *in-vitro* as well as *in-vivo* for their antimicrobial, anti-inflammatory, anticonvulsant and anthelmintic activity by Shivakumar [156] *et al.*



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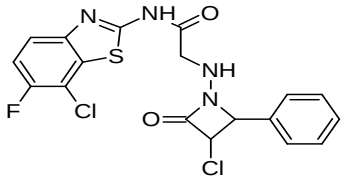
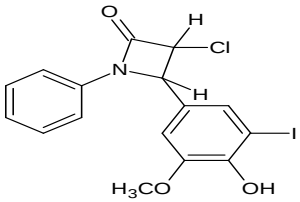


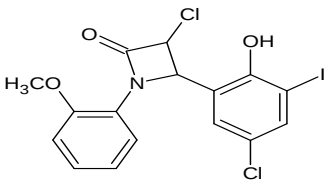
(38)

Some azetidinones **(39)** containing methoxy group are endowed with antibacterial activity[157], it has been found recently, that 1-(4-methoxyphenyl)-3-chloro-4-(2'-hydroxy3-

iodo-5-chlorophenyl)-2-azetidinones **(40)** exhibits good antibacterial activity against E. *coli* and B. *subtilis* [158].

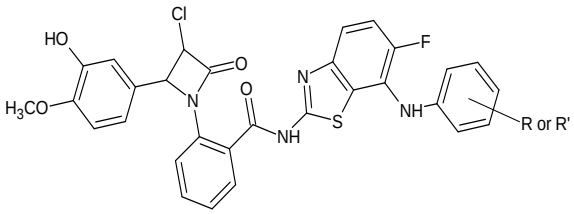


(39)



(40)

Various substituted-4-(*m*-hydroxy-*p*-methoxyphenyl)-1[(6'-fluoro-7'-substitu- ted-1,3-benzothiazol-2'-yl)amido-2-phenyl]3-chloroazetidin-2-one**(41)** containing different functional groups have been synthesized and were tested for significant anticonvulsant activity. [159] Biologically significant 4-substituted-phenyl-1-[2-(2,4,6-trichlorophenolxy methyl)-1,3,4-thia diazol-5-yl]3-chloro-2-azetidinone**(42)** were reported as antibacterial agents.[160]



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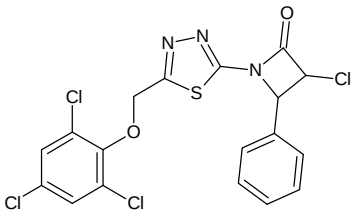

(42)

1-(substituted-phenyl)-spiro[5-bromoindole-3,4-3-chloroazetidin]-2,2-1H-dione has been reported by Al-Majidi [161] *et al.* as antimicrobial active compound. Various substitute-3-(4-fluorophenylimino)indolin-2-one and 5-chloro-3-(4-fluorophenyl imino)indolin-2-one derivatives were synthesized by Nanda [162] *et al*. and screened them for antimicrobial as well as β-lactamase activity. Fluorine substitution, which does not introduce a large steric hindrance, is particularly interesting for a possible biological effect and possible stability towards β-lactamase. β-Bromopropionamide derivatives were prepared, by Wasserman's procedure using sodium hydride to give the N-(3-carboxy-6-methylphenyl)3-difluoro-2-azetidinone. [163]

The reactivity of β-lactams is dominated by the effect of electron withdrawing groups as in α-alkylidene-2-azetidinone, which is 4-unsubstituted, is less reactive. [164]

SYNTHESIS AND PHARMACOLOGICAL PROFILE OF 2-AZETIDINONES INCORPORATED WITH CYANO GROUP

In the last few decades, organic cyano compounds have been found extensive utilization in the synthesis of heterocyclic. The cyano β-lactams were derived by a N-to-C 1,3-rearrangement of the keten-imine intermediates, while the carbamoyl-β-lactams were the hydrolysis products of the intermediates. The chemistry of cyano compounds is very rapidly developing [165] and enormous number of reports, reviews and monographs [166-168] has been written to cover the developments in this area. Benzothiazoles with a cyanomethyl group have been the subject of extensive study in the recent past. Numerous reports highlight their utilization in chemistry. However, heterocyclics containing cyano acetyl group are relatively unexplored. [169] The pyridine skeleton containing CN group is also of great importance to chemists as well as to biologists because it is found in a large variety of naturally occurring compounds and also in clinically useful molecules having diverse biological activities. [170-173]

Cyano group is the structural basis of the ricinine, 3-cyanopyridin-2-one nucleus which is the first the known alkaloid. 4, 6-bis[2′-amino-3′-cyano-4′-(substituted phenyl)-6′-pyridyl] has been found to possess antifeedant activity[174]. A series of cyanovinylpyrrole containing aroylhydrazones, derived from ethyl 2-cyano-3-(5-formyl-1H-pyrrol-2-yl)-acrylate. [175]

Antibacterial agents containing 2-azetidinone has become an integral part of the chemotherapeutic arsenal available to today's medical practitioners. Although the number of existing agents are quite extensive, but the search for better and more effective drug is still going on. Many compounds containing cyanoethyl group have shown significant anticancer activity. [176,177] Derivatives of 2-cyano-3-(2'-furyl) propenoic acid with a markedly polarized double bond inhibit the growth of microbes. [178] Pharmacological effect of the N-(β-cyanoethyl) moiety is dependent on the opioid on which it is substituted. It caused a large increase in antinociceptive potency. [179] Konkova *et al.* reported the formation of 2-aryl-3-cyano ethyltetrahydro-1,3-oxazines and 2-aryl-3-cyanoethyl-1,3-oxazolidines. [180,181]

CONCLUSION

The present work is concentrated much on a precise study in the synthesis and pharmacological potential of 2-azetidinones incorporated with halogen and cyano groups due to the effectiveness and lack of toxicity. The therapeutically active halogen and cyano groups had been exploited in the recent years for the synthesis of various pharmacologically active compounds. By the present scenario it can be concluded that 2-azetidinones have a great

potential for further research and novel derivatives can be synthesized and explored for various biological activities.

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