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A REVIEW ON SYNTHETIC APPROCHES AND BIOLOGICAL ACTIVITIES OF AZETIDIN-2-ONE LINKED HETEROCYCLIC DERIVATIVES

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ABSTRACT

Heterocyclic chemistry is regarded as a multifaceted area that investigates the synthesis, characterisation and various applications. The overview of recent approaches for the synthesis of azetidine-2-one derivatives was made as a result of prestigious position that chemistry of β-lactam has acquired in organic and medicinal chemistry and it is a lead molecule for the development of possible bioactive substances, additionally diverse synthetic information. Many of the heterocyclic structures fused to the four-membered ring, the cyclic azetidin-2-one has served as a template. The antibacterial characteristics of penicillin and cephalosporins have drawn particular attention to azetidin-2-ones. These are a special class of compounds that have been linked to a variety of biological activities such as antibacterial, anti-tubercular, anticancer, anti-inflammatory, CNS activity, antihyperglycemic, antitumor, antimicrobial and enzyme inhibitors etc. This present article briefly discusses about the conventional synthesis along with certain green synthetic methods and biological activities of azetidine-2-ones to facilitate and improve potential future research on new medications that can be introduced to the market quickly, effectively and sustainably.

KEYWORDS: Azetidin-2-one, β-lactam, Synthetic methods, Biological activities, Antimicrobial.

1. INTRODUCTION

Heterocyclic compounds are primary interest of medicinal chemistry. Heterocyclic chemistry is typically one of the most complicated subfields of chemistry. It is equally intriguing in terms of its practical and physiological implications, the variety of its synthetic process, and its theoretical implications. In addition to having a significant impact on every aspect of human life, synthetic heterocyclic chemistry has also found applications in a wide range of fields including medical, agriculture, polymer, and numerous industries. The most of synthetic heterocyclic compounds are employed in medicine as antibiotics, anticonvulsants, hypnotics, antineoplastics, antiseptics, antihistaminic, antiviral, anti-fungal agents and etc. Numerous heterocyclic medications are added to pharmacopeia's each year.[1] Medicines and heterocycles have lately been linked. The heterocyclic nucleus is present in the majority of life-saving contemporary medications. The pharmaceutical, biotechnological, and electrical sectors are particularly interested in heterocycles because of their biological characteristics in general. The main method for creating chemical compounds with practical applications is through organic synthesis.[2]

Azetidin-2-ones are 2-Azetidinones, also referred to as "β-lactams," have a four-membered cyclic amide ring. It carries that name, because in relation to the carbonyl, the nitrogen atom is connected to the β-carbon. Azetidin-2- one also known as β- propiolactam, 2-azetidinone, azacyclobutanone.[3]

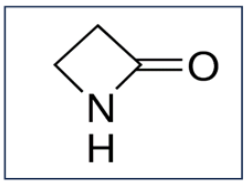


Fig.1: Azetidin-2-one.

Hermann Staudinger created the first synthetic β-lactam in 1907 by reacting the Schiff base of aniline and benzaldehyde with [2+2] cycloaddition of diphenylketene.[4]

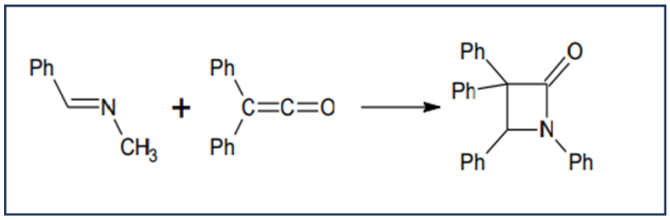


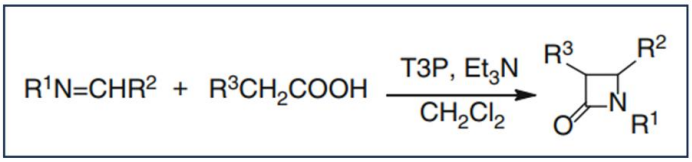
Fig. 2: Synthesis of First synthetic β-lactam antibiotic.[3]

The first antibiotic was discovered by Alexander Fleming in 1928, and shortly thereafter, Cephalosporin was discovered. Since then, β-lactams and the chemistry of derivatives β-lactams have become more significant and have been effectively used as antibiotics.[5] Numerous broad-spectrum antibiotics and compounds, such as penicillin I, cephalosporins II, carbapenams III, Nocardicin A IV and monobactams include the azetidin-2-one ring as their nucleus.[6] All of them have been widely used as a chemotherapeutic agent in the treatment of a variety of bacterial infections and microbial illnesses.[7] Due to their intimate association with numerous sorts of biological activity, azetidine-2-ones have received a great deal of attention from organic chemists.[8] Azetidine-2-ones are also highly significant since β -lactam derivatives are used as antibacterial agents.[9] Recent reports indicate that molecules with a 2-azetidinone ring have some additional biological activity beyond their antibacterial properties. These biological activities include antimicrobial, antitubercular, anti-cancer, anti-inflammatory, local anaesthetic, hypoglycaemia and anticonvulsant activities.[10]

2. METHODS FOR SYNTHESIS OF AZETIDIN-2-ONE DERIVATIVES

2.1 Method of Green Synthesis of Azetidin-2-ones by [2+2] ketene- imine cycloaddition

Maaroof Z. had been researched and reported the series of derivatives of Azetidin-2-ones (Scheme I). They used [2+2] ketene-imine cycloaddition as their strategy for the synthesis of β-lactam analogues. They have utilized Acetic acids and imines in their substituted forms, where propyl phosphonic anhydride had been used as an acid activator. They discovered outstanding yields by their strategy. The found products were known to be 3-electron withdrawing and the β-lactam analogues were spirocyclic, monocyclic.[11]

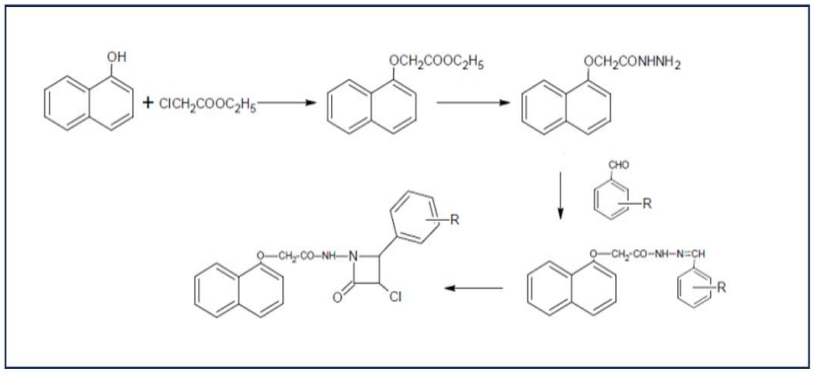


Scheme I: Synthesis of β-lactams by [2+2] ketene-imine cycloaddition.

2.2. Method of synthesis N-[3-Chloro-2-oxo-4-(4-substituted phenyl)-azetidin-1-yl]-2-(napthalen-1-yloxy) acetamides:

Kumar and his coworkers reported the method for systematic synthesis of N-[3-Chloro-2-oxo-4-(4-substituted phenyl)-azetidin-1-yl]-2-(napthalen-1-yloxy) acetamides by using α-Naphthol as a starting material. They have utilized this procedure, where they combined bismuth chloride with Ethyl acetoacetate to procure the desired product. The obtained product

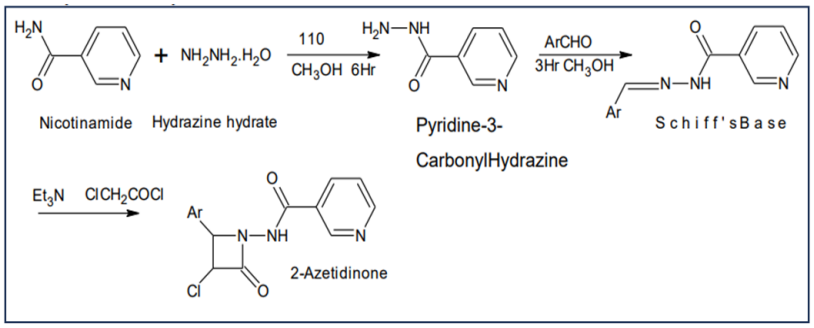
was oxidized, subsequent to that is 2-oxo-2*H*-benzochromene-4-carbaldehyde. That was allowed for condensation with aromatic primary amines to acquire Schiff bases. The obtained Schiff bases were permitted to react with acid chlorides in the presence of base in toluene to produce 1,3,4-substitited azetidine-2-ones (Scheme II).[12]



Scheme II: Synthesis of Azetidin-2-one derivatives.[13]

2.3. Method of synthesis of N-(3-chloro-2-oxo-4-phenylazetidin-1-yl) pyridine-3-carboxamide

Preethi and coworkers prepared a series of analogues of 2-azetidinones (Scheme III) by refluxing Schiff bases with Chloroacetyl chloride and triethyl amine. Schiff bases were prepared by refluxing Nicotinamide with Hydrazine hydrate for 6 hrs at 110˚ C in the presence of methanol as a solvent. The produced substances were verified by ^{1}H-NMR, IR, Mass spectrometry, and elemental analysis.[14]

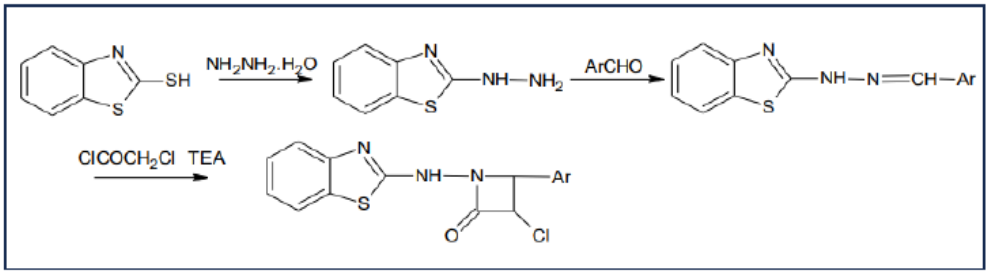


Scheme III: synthesis of N-(3-chloro-2-oxo-4-phenylazetidin-1-yl) pyridine-3-carboxamide.[3]

2.4. Method of Microwave synthesis of 2-(4-substituted aryl-3-chloro-2-oxo-azetidine)-2 imino˚ benzothiazoles

Dua and coworkers reported the microwave synthesis by heterocyclizing 2-substituted arylidene hydrazinobenzothiazoles with chloroacetyl chloride, 2-(4-substituted aryl-3-chloro-

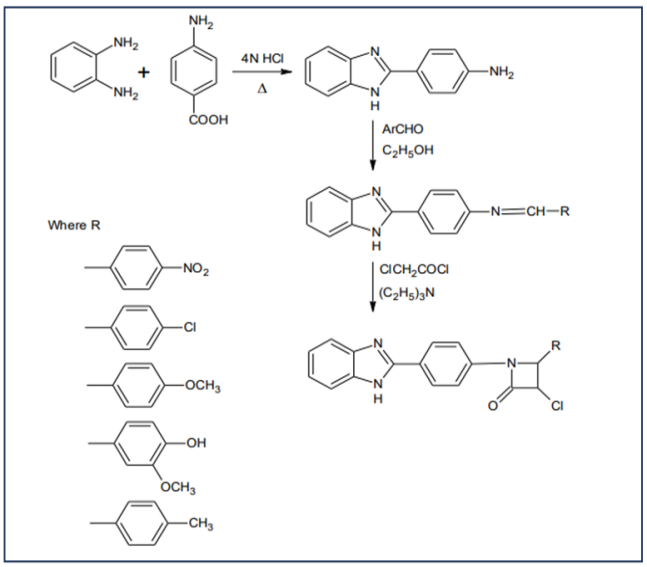
2 -oxo-azetidine)-2-imino benzothiazoles (Scheme IV) are produced in the presence of triethylamine under microwave irradiation. The percentage yield and reaction rate are improved substantially under microwave irradiation in comparison to conventional methodologies.[15]



Scheme IV: Microwave synthesis of Azetidin-2-one derivatives.[3]

2.5 Method of Synthesis of 1-(4-(1*H*-benzo[d] imidazole-2-yl) phenyl)-3-chloro-4-(4-substituted phenyl) azetidin-2-one

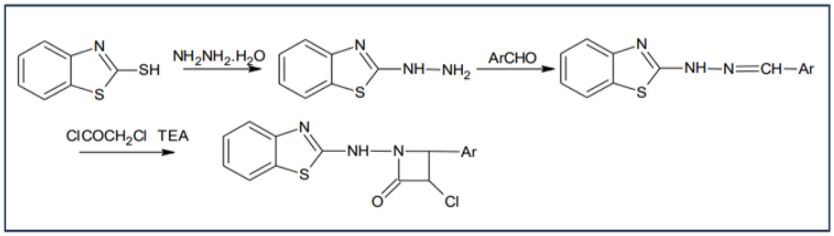
Selvam and his coworkers reported that, equimolar quantities of o-phenylenediamine and p-amino benzoic acid in 4N HCl was refluxed for 30 min. to synthesize the azetidine-2-one derivatives. A mixture of equimolar portions of aromatic aldehyde and 4-(1*H*-benzo[d]imidazole-2-yl) benzamine was refluxed for around 20 minutes in 20ml of Ethanol to produce N-(4-substituted benzylidene)-4-(1*H*-benzo[d]imidazol-2-yl) benzamine is the Schiff base. A mixture of obtained Schiff base, chloro acetyl chloride, triethylamine and 1,4-Dioxan was stirred to acquire the 1-(4-(1*H* benzo[d] imidazole-2-yl) phenyl)-3-chloro-4-(4-substituted phenyl) azetidine-2-one (Scheme V).[16]



Scheme V: Synthesis of Benzimidazole substituted azetidn-2-ones.[3]

2.6 Method of synthesis of 4-aryl-3-chloro-1-nicotinamide-azetidin-2-one:

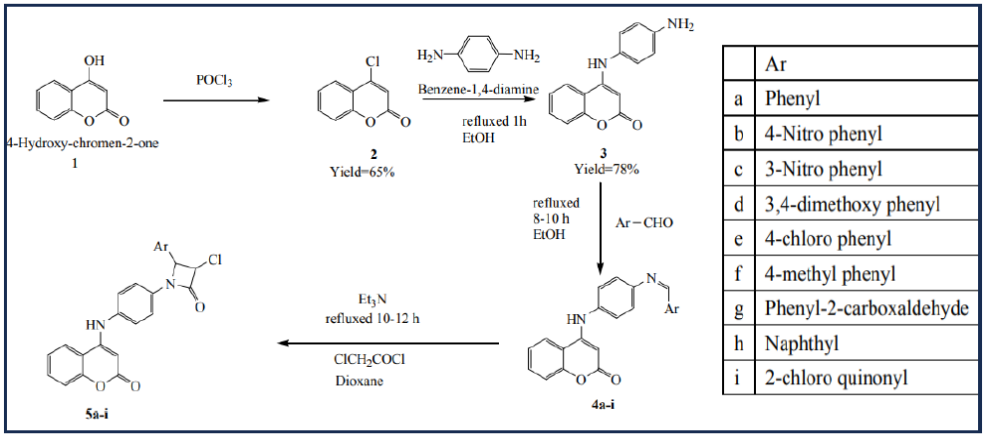
Ramalakshmi and her coworkers have been reported the series of 4-aryl-3-chloro-1-nicotinamide-2-azetidin-2-one. Nicotinic acid was treated with PCl_5 at 100˚ C gives pyridine-3-carbonyl chloride, which upon treating with Hydrazine hydrate gives pyridine-3-carbohydrazide. The obtained pyridine-3-carbohydrazide was treated with various aromatic aldehydes using ethanol as a solvent produces Schiff bases. The Schiff base, chloro acetyl chloride, triethylamine and 1,4-dioxane were stirred to yield corresponding 4-aryl-3-chloro-1-nicotinamide-azetidn-2-one derivatives (Scheme VI).[17]



Scheme VI: Synthesis of Pyridine substituted azetidin-2-ones.[3]

2.7. Method of synthesis of 3-chloro-1-[4-[(2-oxochromen-4-yl) amino]-4-phenylazetidin-2-one:

Patel and coworkers have been reported the synthesis of analogues of novel azetidine-2-ones (Scheme VII) by cyclocondensation of different coumarin Schiff bases with chloroacetyl chloride and triethylamine. The synthesis involves reaction of 4-hydroxy coumarin with $POCl_3$ resulted in chloro coumarin. The obtained chloro coumarin was used to react with p-phenylenediamine to form 4-[(4-aminophenyl) amino]-2*H*-chromen-2-one. Numerous coumarin Schiff bases were produced by condensing 4-[(4-aminophenyl) amino] with various aromatic aldehydes.[18]

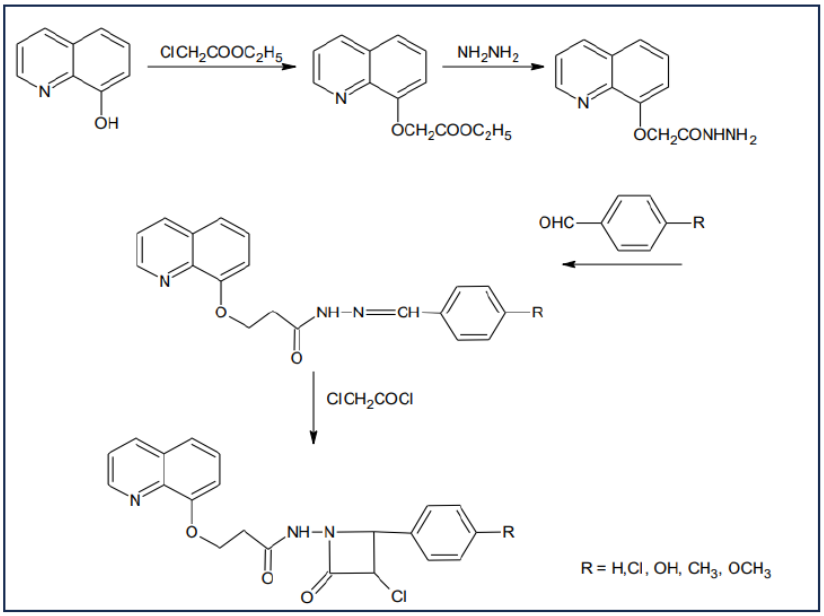


	Ar
a	Phenyl
b	4-Nitro phenyl
c	3-Nitro phenyl
d	3,4-dimethoxy phenyl
e	4-chloro phenyl
f	4-methyl phenyl
g	Phenyl-2-carboxaldehyde
h	Naphthyl
i	2-chloro quinonyl

Scheme VII: Synthesis of coumarin substituted azetidine-2-ones.

2.8. Method of synthesis of Quinolinyloxy methyl azetidine-2-ones

Sangu and coworkers reported the synthesis of new series of azetidine-2-ones (Scheme VIII) through quinoline. The oxymethylcarbamide at 8th position of quinoline ring was determined that the ring regulated the biological processes of the molecules with these newer quinolinyloxy methyl azetidine-2-ones were formed from 8-hydroxy quinoline via an intermediate of quinoline-8-yloxy acetyl hydrazide. The synthesized derivatives of azetidine-2-ones were confirmed by IR, mass, ^{1}H NMR spectroscopic techniques and have been assessed for antimicrobial activity.[19]



Scheme VIII: synthesis of Quinoline substituted azetidn-2-one derivatives.[3]

3. BIOLOGICAL ACTIVITIES OF AZETIDIN-2-ONES

3.1. ANTIMICROBIAL ACTIVITY

3.1.1. Patel R and his coworker have reported a novel series of Azetidin-2-ones, in which they have synthesized various analogues of N-(4,4- disubstituted-3-chloro-2-oxo-azetidine-1-yl) isonicitinamide (Fig 3). They have provided the antimicrobial screening data of synthesized compounds, showed good to moderate activity against bacterial, fungal and mycobacterium strain when compared with the respective standard drugs. The compound with phenyl substitutions at R and R' position of azetidine ring showed good activity against *E. coli* while showed moderate activity against *C. Albicans, S. aureus* and *mycobacterium tuberculosis.* Some compounds showed moderate to good activity against all strains. Few other compounds showed excellent antibacterial, antifungal and anti-tuberculotic activity against tested strains. The antimicrobial activity of novel azetidine-2-ones was due to the

presence of therapeutically active β-lactam ring and also showed that the activity was elevated by the introduction of phenyl / heterocyclic moiety substitution at 4 position of β-lactam ring. The analogue with indole substitution at 4 position of β-lactam ring shown highest activity against mycobacterium tuberculosis when compared with other synthesized compounds.[20]

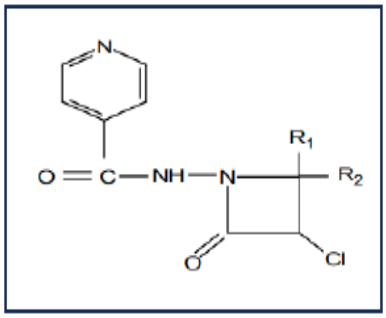


Fig 3: Azetidin-2-one derivative: N-(4,4- disubstituted-3-chloro-2-oxo-azetidn-1-yl) isonicotinamide.

3.1.2 Junneet and coworkers have reported synthesis of Azetidin-2-ones derivatives, and yielded 3-chloro-4-(4-hydroxy-5-iodobiphenyl-3-yl)-1(substitutedphenyl)azetidine-2-one (Fig 4). They have researched their analogues to verify the antibacterial effectiveness against a variety of bacterial strains such as *E. Coli*, *B. Subtlis, Xanthomonascitri*, *Erwiniacarotovara* etc. It has been discovered that their analogues possess outstanding and roughly equivalent biological activities and in some other cases showed more activity against the bacteria are used for confirming the activities, with the exception of *B. subtilis* which has not been discovered to be accurate as per the standard expectations.[21]

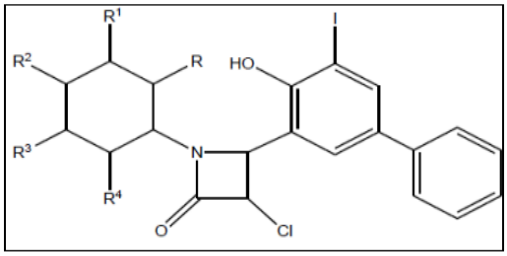


Fig.4: Azetidin-2-one derivative:3-chloro-4-(4-hydroxy-5-iodobiphenyl-3-yl)-1(substituted-phenyl) azetidine-2-one.[13]

3.1.3. Subudhi B. B. and coworkers have reported the synthesis of series of 3-chloro-4-(substituted)-1-(2'-imino-4'-methyl-7'-hydroxy coumarinyl) azetidine-2-one derivatives (Fig 5). The synthesized derivatives were tested in vitro to evaluate their antibacterial efficacy

against particular pathogens that cause urinary tract infections, such as gram-positive bacteria *E. faecalis* and *S. aureus* and gram-negative bacteria *E. coli, P. aeruginosa, K. pneumoniae* and *P. mirabilis*. Through the examination of zone of inhibition, they have concluded that, the relative potency of the all the derivatives were tested against reference drug Nitrofurantoin was found to be comparative and, in some cases, more active shown against the above-mentioned strains. Compounds with substitution on phenyl ring of azetidine-2-one with chlorine showed substantially more activity against *S. aureus*.[22]

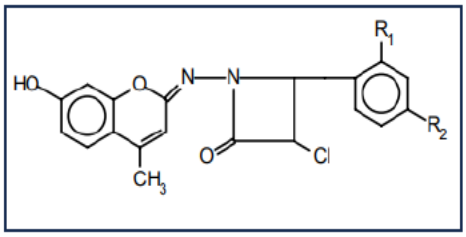


Fig 5: Azetidin-2-one derivative: 3-chloro-4-(substituted)-1-(2'-imino-4'-methyl-7'-hydroxy coumarinyl) azetidine-2-one.

3.1.4 Entesar and coworkers have been reported the synthesis of novel azetidine-2-ones (Fig 6) through the Amoxicillin. The synthesized compounds were evaluated for antibacterial activity against several bacterial organisms with gram-positive strains such as *S. aureus* and *Bacillus* and gram-negative bacterial strains such as *E. coli* and *P. aeruginosa* using DMSO solvent to obtain necessary concentration (400µg/ml) and the reference was amoxicillin. The analogues showed antibacterial activity against all bacterial strains more than the standard drug amoxicillin.[23]

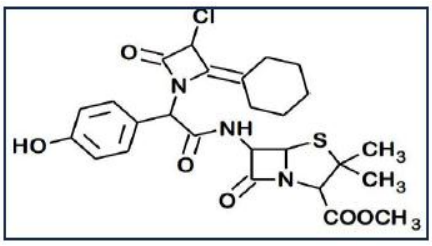


Fig 6: Azetidin-2-one derivative: methyl 6-(2-(3-chloro-2-cyclohexylidene-4-oxoazetidin-1-yl)-2-(4-hydroxyphenyl) acetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicylo [3.2.0] heptane-2-carboxylate.

3.2 ANTITUBERCULAR ACTIVITY

3.2.1 Hussain. S and coworkers carried out research with a number of azetidine-2-one compounds. They also discovered derivatives of N-[3-chloro 4-(aryl)-2-oxoazetidin-1yl]-

pyridine-4-carboxamides (Fig. 7) as new series of analogues were discovered to fit the criteria. These analogues underwent several methods of screening of antimicrobial effectiveness. A majority of these analogues were discovered to display exceptionally good antitubercular activities.[24]

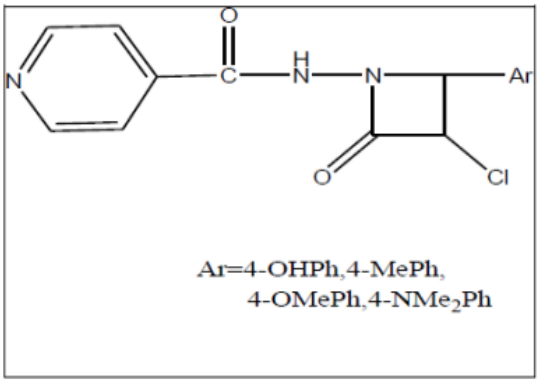


Fig.7: Azetidin-2-one derivative: N-[3-chloro-4-(aryl)-2-oxoazetidin-1-yl]-pyridne-4-carboxamides.[13]

3.2.2 Kumbar and coworkers have reported design and synthesis of the novel series of coumarin-azetidinones (Fig 8). The synthesized compounds underwent invitro evaluation of antimicrobial and antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain and cytotoxicity studies against *Vero* cells. Some compounds showed substantial action towards both bacterial and fungal species according to antimicrobial research. Considering the finding of antitubercular evaluations, the compounds showed MIC 0.2 g/mL against *Mycobacterium tuberculosis* when compared with first line standard such as Isoniazid. The docking study results revealed the potential value of coumarino-azetidin-2-ones as antibacterial and antitubercular drugs.[25]

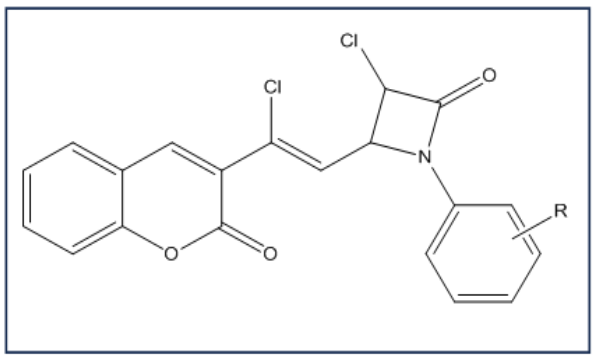


Fig. 8: Azetidin-2-one derivative: (Z)-3-chlro-4-(2-chloro-2-[2-oxo-2*H*-chromen-3-yl] vinyl)-1-phenylazetidin-2-one.

3.3 ANTICANCER ACTIVITY

3.3.1 Neha Sharma and coworkers reported the synthesis of novel series of thiazole conjugate 2 azetidinones (Fig.9). All the synthesized compounds were evaluated for Hela cancer cell lines and antimicrobial activity. In comparison to their anticancer activity, the produced compounds shown stronger antibacterial activity. They discovered that one of the compounds was the most effective antibacterial agent with 3-nitro benzaldehyde substitution on phenyl on azetidine-2-one ring. The compound with 4-nitro benzaldehyde substitution on phenyl moiety on azetidine-2-one ring has been demonstrated to be the most effective anticancer drug (IC_{50}= 58.86 µM) in terms of anticancer activity.[26]

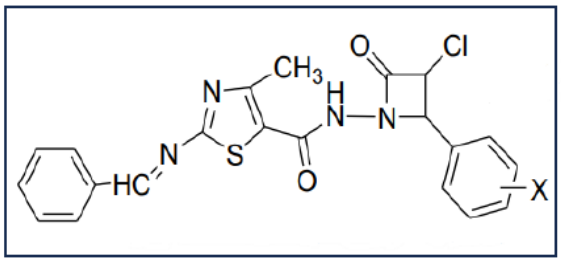


Fig. 9: Azetidin-2-one derivative: (E)-2-(benzylidene-amino)-N-(3-chloro-2-oxo-4-phenyl) azetidin-1-yl)-4-methyl-thiazole-5- carboxamide.

3.3.2 O'Boyle and coworkers have been reported the sequence of synthesis in which they substituted the molecule at positions 1,3, and 4 each time (Fig 10). Several compounds were prepared in this series were discovered to have substantial activity in especially for cancer treatment, they were discovered to powerful against the MDA-MB-231 breast cancer cells and they also function well with the NCL60 line panel.[27]

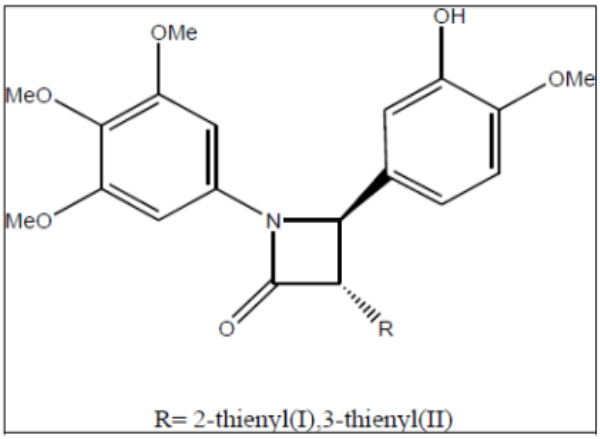


Fig. 10: Azetidin-2-one derivative: a series of azetidine-2-ones with substitution at 1,3,4 positions.[13]

3.4 ANTIDIABETIC ACTIVITY

Reddy and coworkers have been reported the series of analogues of N-1-benzothiazolyl-3-chloro-1,5,6-triazaspiro [3.4]-oct-6-en-2-ones. By sequentially condensing 3-methyl-1-phenyl-5-pyrazolone and amino benzothiazole, they created Schiff bases. They have synthesized several compounds, whereas 3-chloro-1-(6-flouro-7-ptolylaminobenzothiazol-2-yl)-7-methyl-5-phenyl-1,5,6-triazaspiro [3.4]-oct-6-en-2-one (Fig 11) has been discovered to be following the anticipated traits and its activity was comparable with reference drug.[28]

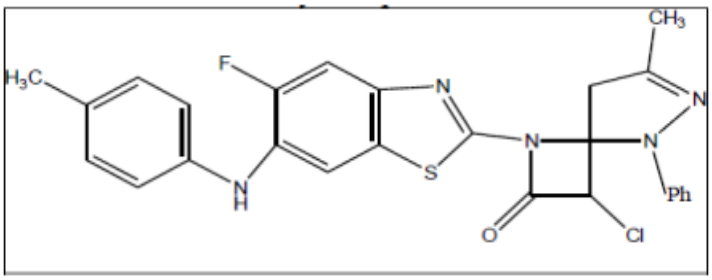


Fig. 11: Azetidin-2-one derivative: 3-chloro-1-(6-flouro-7-ptolylaminobenzothiazol-2-yl)-7-methyl-5-phenyl-1,5,6-triazaspiro [3.4]-oct-6-en-2-one.[13]

Researchers have identified other unique series in addition to these, and the azetidine-2-one derivatives has also been discovered to display inhibitory activity of chymase and tryptase,[29] inhibitory activity of human leukocyte,[30] antiparkinsonian activity,[31] anti-inflammatory activity and analgesic activities.[32]

CONCLUSION

Azetidin-2-ones have emerged as one of the most significant heterocycles in recent chemistry research because of its most significant pharmaceutical applications in biological science and medicinal chemistry. Different azetidine-2-one derivatives showed different activity against many microorganisms. These research investigations may act as an overall basis for the chemical transformations with the aim of creating a new class of derivatives azetidine-2-one. The review on their synthesis and biological activities in single spot may provide a convenient way to gather extensive information and to be a initiative to encourage this evergreen concept for researchers and medicinal chemists to collaborate with the more and more to support future development.

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