BIOACTIVE AZETIDINONE: A REVIEW

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Abstract -The chemistry of β-lactams has taken an prestigious place in organic and medicinal chemistry so the review on recent methods in the synthesis of 2-Azetidinone derivatives rendered as a lead molecule for designing potential bioactive agents and it accompanying additional various synthetic information and its orientations would encompass great deal of help to researchers, chemists and pharmacologists to make it the best, most productive, economical and medicinal important compounds which will be expected to show potent pharmacological activities. In future it would be useful to design different new drugs to bring in the market by using rapid, operationally simple, efficient and green procedure. This has led to the discovery of a wide variety of compounds that are of high interest from the point of view antibacterial, anti-inflammatory, antihyperlipidemic, CNS activity, anticancer, antimicrobial, pesticidal, cytotoxic, antidiabetic, antitumor, antifungal, antitubercular activities.

IndexTerms β-Lactam. Azetidinones. Bioactive.

I. INTRODUCTION

Discovery of penicillin by Alexander Fleming in 1929 is considered as beginning of the antibiotic era. The widely cited definition of an antibiotic as a substance produced by microorganisms, which has the capacity of inhibiting the growth and destroying other microorganisms was proposed by Waksman in 1942.

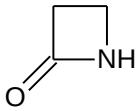
Azetidinones are heterocyclic compounds containing the carbonyl group at position 2, also called 2-azetidinone (Azetidin-2- ones) and commonly known as β-lactams. Though the ring system was known since 1907 the investigation of their chemistry began from 1947 onwards.These are currently used for chemotherapy of bacterial infections. The selective inhibition during cell wall synthesis of bacteria is responsible for its unique and lethal antibacterial action[1].

β-lactams are well-known among the medicinal compounds because their diverse pharmacological activities mainly antimicrobial potency[2]. Today Azetidinone is part of the core structure of several antibiotics, the principal ones being the pencillins, cephalosporins, carbapenems, and monobactams. The effective use of β-lactam drugs exert pressure on bacteria and do not permit the proliferation of resistant organisms by inhibiting bacterial cell wall biosynthesis. This has a lethal effect on bacteria[2]. Bacteria however contain within their population, in smaller quantities, that are resistant against beta–lactam antibiotics. They achieve this resistance by expressing beta-lactamase genes. More than 1000 different β-lactamase enzymes have been documented in various species of bacteria.

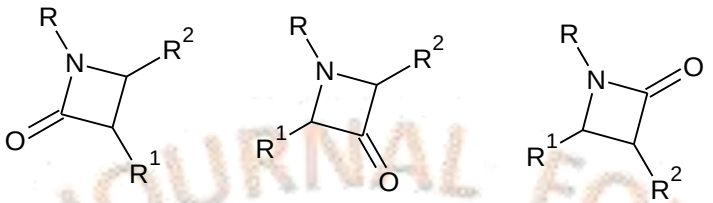
These enzymes vary widely in their chemical structure and catalytic efficiencies. When bacterial populations have these resistant subgroups, treatment with beta-lactam drug can result in the resistant strain becoming more prevalent and therefore more virulent. A comparative study of current antibiotics with those from previous decades shows an alarming increase in bacterial resistance to β-lactam drugs, and this has led to the development of several semi-synthetic and synthetic β-lactam antibiotics by the pharmaceutical industry and there is a growing need for medicines with a more specific and effective antibacterial activity today. The report says that a large number of 3-chloro monocyclic β-lactams possess powerful activities, including antibacterial, antifungal, anti-inflammatory, anticonvulsant, anti-HIV, anti-parkinsonian, antidiabetic and antitubercular activities[3]. Various Penicillins and Cephalosporins based on azetidinone nucleus have been synthesized and used for various diseases for decades. They also function as enzyme inhibitors and are effective on the central nervous system[3]. Reports suggest that 2-azetidinones have highlighted a potent mechanism-based inhibitor of several enzymes like human tryptase, chymase, thrombin, leukocyte elastase, human cytomegalovirus protease, and serine protease enzyme[3].

Chemistry of Azetidinones:

Parent heterocyclic ring of azetidinones is azetidine. Azetidine is a 4-member heterocyclic ring system with nitrogen as hetero atom. 2-Azetidinones are also known as β-lactams and it is one of the most common heterocyclic rings found in antibiotics. 2-Azetidinones consist of a carbonyl group on the second position[4].



Chemical Structure of Azetidine-2-one



Azetidine-2-one Azetidine-3-one Azetidine-4-one

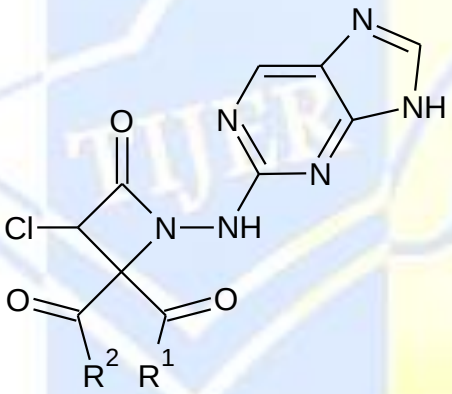
Different Possible Azetidinone Ring Structures

Biological Importance:

2-Azetidinones commonly known as β-lactams are well-known heterocyclic compounds among organic and medicinal chemists. The activity of famous antibiotics such as penicillins, cephalosporins, and carbapenems are attributed to the presence of 2-azetidinone ring in them. Azetidinones are very important class of compounds possessing wide range of biological activities such as antimicrobial[5-21], pesticidal[21], antitumor[22], antitubercular[23], anticancer[24], cytotoxic[25-27], enzyme inhibitors[28], elastase inhibitors[29]& cholesterol absorption inhibitors[30].

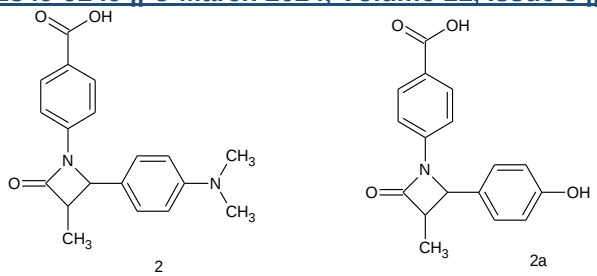
Antimicrobial Activity

Sharma and her co-workers[31] synthesised 2-[N-(3'- chloro-4'-substituted azetidinone-2)] amino-4-hydroxypurines (1) as antimicrobial agents.

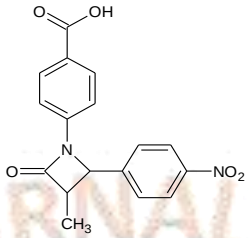


1

Sugumaran M et.al[32] Synthesized 2-Azetidinone and 4-Thiazolidinone derivatives from 4-Aminobenzoic acid as a starting material. They synthesized 6 derivatives using substituted aldehydes, chloro Acetyl chloride and triethylamine and gone for antimicrobial activity. It was evident that the 2-Azetidinones was more active against the bacterial strains and 4-Thiazolidinones were more active against the fungal strains. Among the synthesized derivatives (2, 2a and 2b) shows more potent activity against the microbials. Compound(2), 4-[3-chloro-2-[4-dimethylamino phenyl]-4-oxoazetidi-1-yl] benzoic acid was found to be more active against *Staphylococcus aureus*(gram+ve bacteria). The Compound(2a),4-[3-chloro-2-(4-hydroxyphenyl)-4-ozoazetidin-1-yl] benzoic acid was found to be more potent against *Eschericha coli* (gram–ve bacteria). The Compound(2b), 4-[2-[4-nitrophenyl]-4-oxo-1,3-thiazolidin-3-yl] benzoic acid was found to be active against *Candida albicans*.

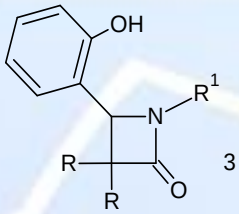


2 2a



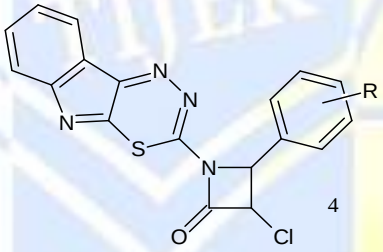
2b

Singh GS, Pheko T, reported the formation and antimicrobial activity of 2-azetidinones from selective ester cleavage in 1,3,3-trisubstituted 4-[2'-(o-diarylacyl)hydroxyphenyl]-2-azetidinones. Treatment of the 1,3,3-trisubstituted 4-[2'-(o-diarylacyl)hydroxyphenyl]-2-azetidinones with sodium hydroxide in ethanol at room temperature lead to selective cleavage of the ester linkage in the substrates forming new (3) 1,3,3-trisubstituted 4-(2'-hydroxyphenyl)-2-azetidinones, which have been characterized on the basis of analytical and spectral (IR, ^{1}H and ^{13}C NMR, MS) data. The structure elucidation also involved application of the HMQC and HMBC studies using 2-D NMR (^{1}H-^{13}C COSY) spectra[33].



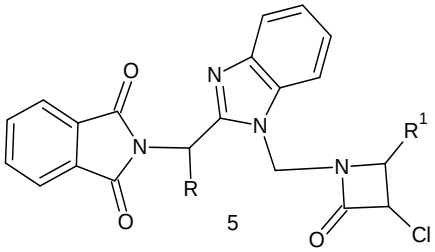
3

Panwar et al have synthesized 2-[3-chloro-2-(substitutedphenyl)-4-azetidinon-3-yl]-1,3,4-thiadiazino[6,5-b]indole (4) as prospective antimicrobial agents[34].



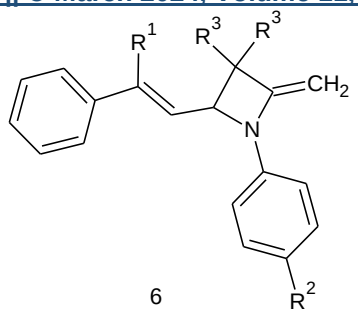
4

Snehal Lokhandwala and Dinesh Patel conducted *In-vitro* microbial studies of some newly synthesized azetidinones derivatives. Various substituted 3-chloro-4-(substitutedphenyl)-1-{4-[7-chloro-2-(3-chloropropyl)-4-oxoquinazolin-3(4H)-yl}azetidin-2-ones containing different functional groups have been synthesized by treating 7-chloro-2-(3-chloropropyl)-3-{4-[(substituted benzylidene)amino]phenyl}quinazolin-4-(3H)-ones with chloroacetyl chloride in presence of triethyl amine at reflux temperature. The lead compounds were characterized by melting point, TLC, calculated elemental analysis, IR and ^{1}H NMR spectral studies. The compounds were tested for antimicrobial studies and showed significant activity at low and high concentration as compared to standard[35].



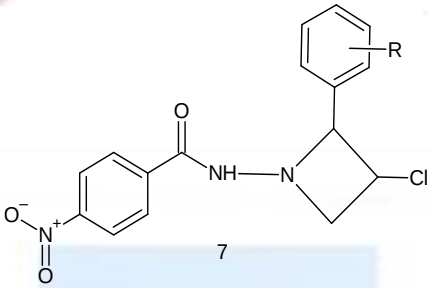
5

Tan and his co-workers have synthesized 1-(Substituted phenyl)-4-(substituted styryl)-2-azetidinones (6) and studied their antimicrobial activity[36]



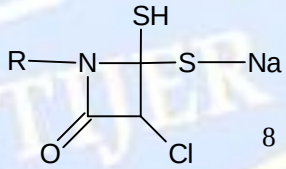
6

S.K.Gawande et al[37],Synthesized some 2-azetidinone derivatives from 4-Nitroethyl benzoate by microwave method. They synthesized five derivatives, are evaluated for antimicrobial activity. From the microbial study, they concluded that compounds bearing chloro, methoxy groups are more potent than remaining substituted compounds against gram (+) and gram (-) bacteria's. This method using microwave irradiation to synthesis 2-azetidinone derivatives offers significant improvement over existing procedures. This reproducible technique affords various azetidin-2-one derivatives with short reaction times and excellent yield and without formation of undesirable products.



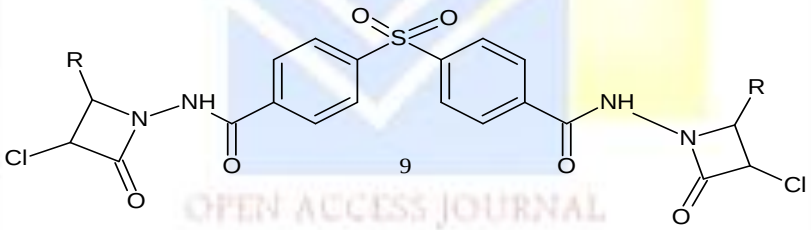
7

Kumar A, Sharma P, Mohan P reported the synthesis and antimicrobial screening of N-substituted-3- chloro-4-dithiocarbamato azetidin-2-ones. All the synthesized compounds have been evaluated for their in-vitro growth inhibitory activity against P. diminuta, B. subtilis, E. coli, S. Aureus, R. rhodochrous. All the compounds show significant antibacterial activity. N-[4'-(N'-4,6-Dimethyl pyrimidinyl)sulphonamoyl amino phenyl]-3-chloro-4-dithiocarbamato azetidin-2-one has been found to be more potent antimicrobial agent against B. subtilis[38].



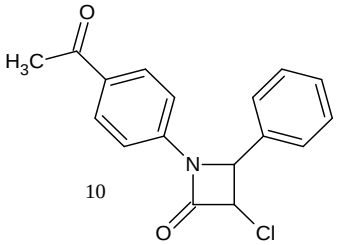
8

Patel et al[39] have combined sulfone moiety with 2 - azetidinone rings (9) for their eventual antimicrobial activity.



9

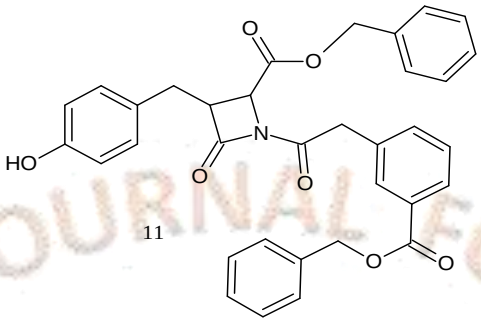
S. Jubie reported the synthesis and antimicrobial evaluation of some 2-azetidinone derivatives. P-anisidine was condensed with different substituted aromatic aldehydes to form schiff's bases, which was then cyclized with chlorocetylchloridine triethylamine to form corresponding 2-azetidinone derivative. The compounds were evaluated for their anti-microbial activity against S.faecalis, S.aureus, P.aeruginosa and E.coli. Among the derivatives 2,4 dimethyl amino phenyl at 2nd position showed good activity against all species. The activity were attributed to C=O, C-N linkages of 2-azetidinone[40] .



10

Anticancer Activity

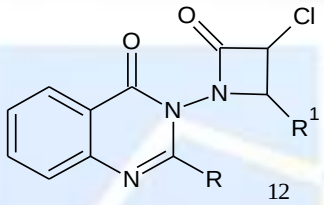
Robert M. Adlington, Jack E. Baldwin, Gerald W. Becker, Beining Chen, Leifeng Cheng, Stephen L. Cooper, Robert B. Hermann, Trevor J. Howe, William McCoull, Ann M. McNulty, Blake L. Neubauer, and Gareth J. Pritchard synthesized and studied prostate specific antigen inhibiting activity of 2-azetidinones. A homology derived molecular model of prostate specific antigen (PSA) was created and refined. The active site region was investigated for specific interacting functionality and a binding model postulated for the novel 2-azetidinone acyl enzyme inhibitor (IC(50) = 8.98 +/- 0.90 µm) which was used as a lead compound in this study[41].



11

AntiparkinsonActivity

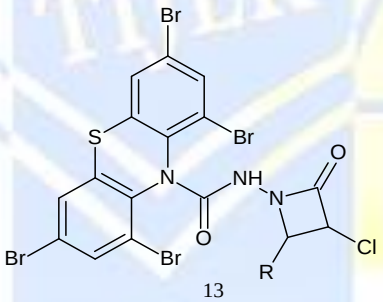
Azetidinones of general structure (12) were synthesized and tested for their antiparkinson activity against tremor, rigidity, ptosis, hypokinesia and catatonia. It was also studied further for their mode of action on dopamine receptor binding using rat brain striate membrane preparation[42].



12

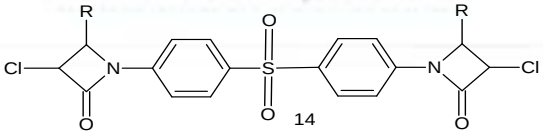
R=CH_3 or C_2H_5 and R^1=Aryl

Trivedi et al[43] have synthesized 2-azetidinone derivatives (13) and thiazolidinones derivatives and studied their antibacterial activity against E.coli, S.aureus and tubercullostatic activity against H37 Rv strain of Mycobecterium tuberculosis.



13

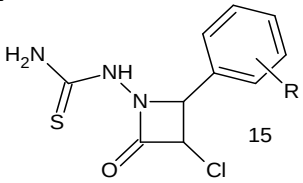
P D Mehta, N P S Sengar, E V S Subruhmanyam have synthesized 4-4'-bis(3-chloro-4-(4-methylphenyl)-2-oxo-azetidin-1- yl)diphenyl sulphone (14) and studied their tubercullostatic activities[44].



14

Where R= Heterocyclic or aromatic aldehyde

Some thiourylazetidinone derivatives (15) have been synthesized and studied for their antiparkinsonian activity. This study showed that thiourylazetidinone having phenyl and 4- methoxy phenyl group at 2nd and 4th position were found most potent. Some of these compounds showed lesser toxicity[45].

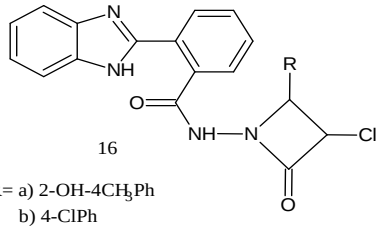


15

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

Anti tubercular activity

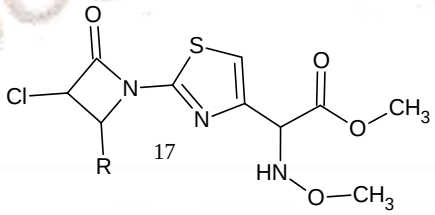
Preethi Kaythara et al[46] has synthesis 4 Aryl-3-chloro-1-(benzimidazole-2yl-benzamido)-2- azetidinonel and tested in-vitro for their antitubercular activity against H37Rv strain of Mycobacterium tuberculli using Lowenstein Jensen's egg medium by serial two fold dilution method.



16

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

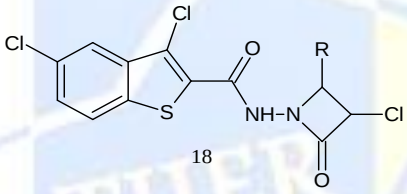
Khyathi A Parikh et al[47] reported synthesis of 4-aryl-1-(4' -a-methoxyimino-carbmethoxy methyl thiazol-2'-yl)-3-chloro-2-azetidinones and evaluated the compounds for their antitubercular activity against H_{37}Rv strain of Mycobacterium tuberculosis using Lowenstein Jensen's egg medium by serial two-fold dilution method.



17

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

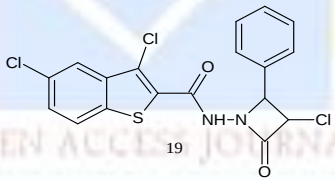
K.M Thakar et al[48] have synthesized 4-aryl-3-chloro-1-(3' ,5'-dichloro-2'-benzo (b) thio phenyl amino)-2-azetidinones and evaluated their antitubercular activity against H_{37}Rv strain of Mycobacterium tuberculli using Lowenstein Jensen's egg medium by serial two fold dilution method.



18

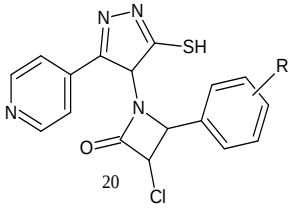
R= a)H, b) 4-CH_3, c) 4-CN, d) 4-Cl, e) 4- F

Narute AS, Khedekar PB, Bhusari KP reported a QSAR studies on 4-thiazolidindiones and 2-azetidinones bearing benzothiophene as potential anti-tubercular agents. Several significant equations with good coefficient of correlation (>0.860) were obtained. The two models are selected using internal predictive power discerned by cross-validated coefficient q^2. Both models highlight some common important feature, i.e., bulky substitution and the high nucleophilicity nature of the molecules, favorable for anti-tubercular activity[49].



19

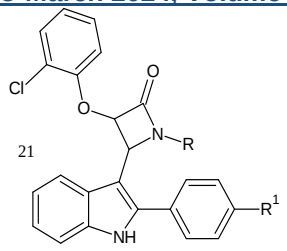
R Priyadarsini, R Vijayaraj, T K Ravi and M Prabha[50] have synthesized some azetidinones (20) for their antitubercular activities.



20

Central Nervous System Activity

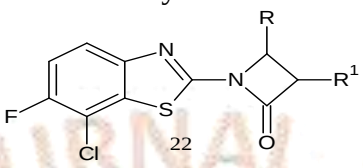
Rajesh Agarwal et al[51] have synthesized 1-substituted -2-oxo-3-chloro/3-(2-chlorophenoxy)-4- (2-arylindol-3-yl)-azetidines showed C.N.S. depressant activity.



21

R= H, CH_3, Cl

B. M. Gurupadayya et al[52] have synthesized 1-(7-chloro-6-flurobenzothiazol-2-yl)-3,4-substituted-arylazetidin-2-ones exhibited C.N.S. depressant activity.

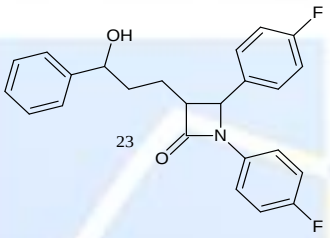


22

R= C_6H_5, C_6H_4-2-OH, R= H, Cl

Antihyperlipidemic Activity

Basak A, Rudra KR, Bdour HMM, reported the use of nitrones in the synthesis of potential antihypercholesterolemic mono and tricyclic β-lactams. The hydroxyethyl group at C-3 of a number of monocyclic β-lactams is elaborated by a series of reactions to the appropriate side chain meant for acting as cholesterol absorption inhibitor without perturbing the sensitive β-lactam moiety. In addition, a novel tricyclic β-lactam has also been synthesized using the nitrone cycloaddition approach[53].



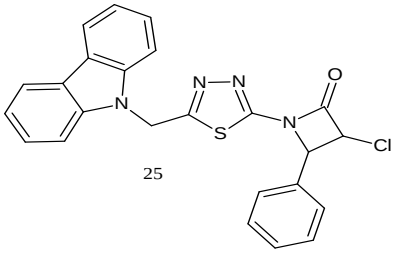
23

K.P. Bhusari reported the design and synthesis of azetidinone derivatives with hydrazine substitutions on nitrogen and their ability to inhibit cholesterol absorption and antibacterial activity was evaluated. Nine new derivatives of 2-azetdinone derivatives as cholesterol absorption inhibitors were synthesized. Most of them showed comparable effects in lowering the levels of total cholesterol in the of serum cholesterol-fed hamsters and anti-bacterial screening reveal that all the compounds showed moderate to good anti-bacterial activity against S. aureus[54].

24

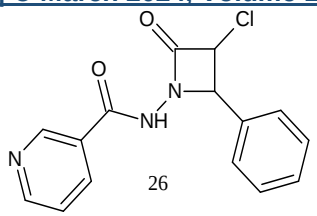
Anticonvulsant Activity

Srivastava SK, Srivastava S, Srivastava SD reported the synthesis of new carbazolyl-thiadiazol-2-oxo-azetidines. Several 2-arylidenylamino-5- (carbazolylmethyl)-1,3,4-thiadiazoles and 1-[5'- (carbazolylmethyl)-1', 3', 4'-thiadiazol-2'-yl)]-4- (substituted phenyl)-3-chloro-2-oxo-azetidines were synthesized and evaluated for their antimicrobial, anticonvulsant and anti-inflammatory activity[55].



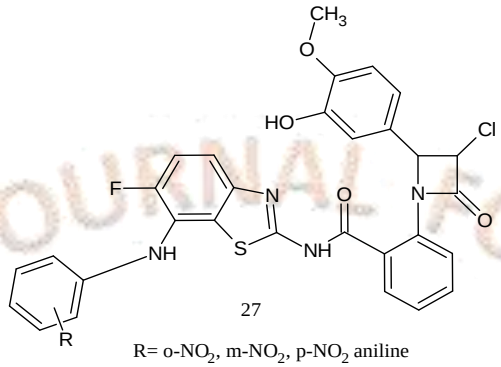
25

Preethi et al have synthesized novel 4-thiazolidinone and 2-azetidinone derivatives(26) and evaluated them for anticonvulsantactivity[56].



26

Vijay Kumar, M.M.J et al has synthesized N-Substituted-3-chloro-2-azetidinones. The compounds were screened for their anticonvulsant activity by using inhibition of albumin denaturation technique. The Ibuprofen was used as a standard drug[57].



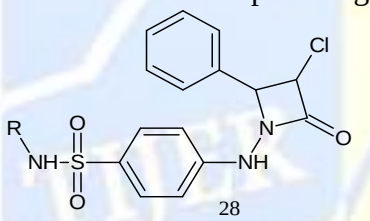
27

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

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

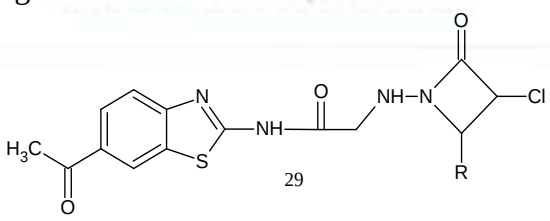
Antibacterial Activity

Sharma P, Indapurkar P, Mandloi A reported the synthesis and antibacterial screening of N-sulphonamoylphenylamino-3-chloro-4- phenylazetidin-2-ones. The derivatives were synthesized and their structures were established on the basis of consistent elemental, IR, spectral data. Anti-bacterial activity has been performed using agar diffusion technique involving paper disc method against E.coli, Pseudomonas diminuta and Bacillus subtilus. It was observed that N-(4'- nitro)phenylamino-3-chloro-4-(4'-dimethylamino)phenyl azetidine-2-one was found to be more potent against the E.coli bacteria[58].



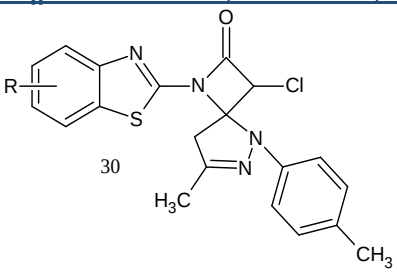
28

Ameya A. Chavan, and Nandini R. Pai reported synthesis of 2-{2-[3-chloro-2-(aryl)-4-oxoazetidin-1-ylamino]-acetylamino}benzothiazole-6-carboxylicacid,2-aminobenzothiazole-6-carboxylic acid on condensation with chloroacetyl chloride gave 2-(2-chloroacetylamino) benzothiazole-6-carboxylic acid which on further amination with hydrazine hydrate gave 2-(2-hydrazinoacetyl amino)benzothiazole-6-carboxylic acid 2-(2-hydrazinoacetyl amino) benzothiazole-6-carboxylic acid. The Schiff's bases thus obtained were treated with various aromatic aldehydes in presence of glacial acetic acid and further dehydrative annulation was carried out with chloroacetyl chloride and triethylamine to yield 2-{2-[3-chloro-2-(aryl)-4-oxoazetidin-1-ylamino] acetylamino} benzothiazole-6-carboxylic acid. It was then screened for its anti-bacterial activity against S.aureus, B.subtilus, P. aeruginosa and E.coli[59].



29

Mistry K, Desai KR, reported the synthesis of pyrazole imines and azetidinone compounds using conventional and microwave technique and studies of their antibacterial activity was conducted. A series of compounds 4-[spiro-{4"-methylphenyl)-3'-methyl}- pyrazole]-3-chloro-1-(substituted benzothiazole)-2- azetidinone was synthesized by reaction of 1-(4'- methylphenyl)-3-methyl-5-(2"- iminosubstitutedbenzothiazole) pyrazole with chloroacetyl chloride in presence of triethylamine. The synthesized compounds were screened for their anti-bacterial activity against S.aureus, B.subtilus, S.typhi and E.coli[60].



II. CONCLUSIONS

These literature reveals the various diverse biological activities such as anti-microbial, anti-bacterial, anticancer, anti-convulsant, anti-hyperlipidemic, antitubercular and antiparkinson properties of 2- azetidinone derivatives. Mechanisms for its synthesis have also been reported along with its chemistry. A variety of drugs in market today possess the β lactam moiety and many ongoing research is focused on developing newer antibiotics in which azetidinones play a crucial role. Hence it can be concluded that derivatives of 2-azetidinones have a great potential as bioactive molecules.

III. REFERENCES

1. Zachariah SM, Mridula R, George N and Ashif MS: Azetidinones: An Overview. *Int J Pharm Sci Rev Res* 2015; 30: 211-18
2. Salunkhe DS and Piste PB: A brief review on recent synthesis of 2-Azetidinone derivatives. *IJPSR* 2014; 5: 666-89.
3. Kumbhar SP, Mayur YC, Poul BN and Waghmare PV: Synthesis of some new azetidinones derived from heterocyclics and their antimicrobial activity. *International J of Pharmaceutical and Clinical Research* 2015; 7: 84-91
4. Shaveta, Mishra S and Singh P: Hybrid molecules: The privileged scaffolds for various pharmaceuticals. *EJMC* 2016; 124: 500-36.
5. V. Guner, S. Yildirir, B. Ozcelik and U. Abbasoglu, *I.l.Farmaco*, vol. 55, pp. 147, 2000.
6. V. N. Pathak, R. Gupta and M. Garg, *Heteroatom chemistry*, vol. 15, pp. 494, 2004.
7. K. Mistry, K. R. Desai, *Cheminform*, pp. 36, 2005.
8. G. S. Singh, B. J. Mmolotsi, *I.l.Farmaco*, vol. 60, pp. 727, 2005.
9. K. H. Patel, A. G. Mehta, *E- J. Chem.*, vol. 3, pp. 267, 2006.
10. A. K. Halve, D. Bhadauria, R. Dubey, *Bioorg. Med. Chem. Lett*., vol. 17, pp. 341, 2007.
11. T. Singh, V. K. Srivastava, K. Saxena, S. L. Goel, A. Kumar, *Archiv der Pharmazie*, vol. 339, pp. 466, 2006.
12. G. S. Singh, E. Mbukwa, ,*Arkivoc*, vol. 9, pp. 80, 2007.
13. G. S. Singh, T. Pheko, *Ind. J. Chem*., vol. 47B, pp. 159, 2008.
14. M. C. Sharma, D. V. Kohli, N. K. Sahu, S. Sharma, S. C. Chaturvedi, *Digest Journal of anomaterials and Biostructures*, vol. 4, pp. 339, 2009.
15. G. S. Singh, P. Luntha, *Eur. J. Med. Chem*., vol. 44, pp. 2265, 2009.
16. [31] R. Dua, S. K. Srivastava, *Int. J. Pharma. Bio Sci.*, vol. 1, pp. 1, 2010.
17. [32] V. Kumar, S. Sharma, S. Singh, A. Kumar, S. Sharma, *Archiv. der Pharmazie*, vol. 343, pp. 98, 2010,.
18. [33] H. Ceric, M. Sindler-Kulyk, M. Kovacevic, M. Peric, A. Zivkovic, *Bioorg. Med. Chem.*, vol. 18, pp. 3053, 2010.
19. [34] U. Sahoo, A. K. Seth, A. Sen, B. Dhanya, J. Patel, R. Chawla, *Res. J. Pharm. Bio. Chem. Sci.*, vol. 1, pp. 102, 2010.
20. R. S. Keri, K. M. Hosamani, H. S. Reddy, R. V. Shingalapur, *Archiv. der Pharmazie*, vol. 343, pp. 237, 2010.
21. V. P. Singh, K. K. Saxsena, S. K. Bhati, A. Kumar, *J. Global Pharma Tech.*, vol. 2, pp. 42, 2010.
22. G. Veinberg, I. Shestakova, M. Vorona, I. Kanepe, E. Lukevics, *Bioorg. Med. Chem. Lett.*, vol. 14, pp. 147, 2004.
23. A. S. Narute, P. B. Khedekar, K. P. Bhusari, *Ind. J. Chem.*, vol. 47B, pp. 586, 2008.
24. B. K. Banik, F. F. Becker, I. Banik, *Bioorg. Med. Chem.*, vol. 12, pp. 2523, 2004.
25. G. Veinberg, R. Bokaldere, K. Dikovskaya, M. Vorona, I. Kanepe, I. Shestakova, E. Yashchenko, E. Lukevics, *Chem. Het. Comp.*, vol. 39, pp. 587, 2003.
26. G. Veinberg, K. Dikovskaya, M. Vorona, I. Turovskis, I. Shestakova, I. Kanepe, E. Lukevics, *Chem. Het. Comp*., vol. 41, pp. 93, 2005.

27. D. P. Maia, D. V. Wilke, J. Mafezoli, J. N. Junior, M. O. Moraes, C. Pessoa, L. V. Costa-Lotufoa, *Chemico-Biological Interactions*, vol. 180, pp. 220, 2009.
28. C. Beauve, M. Bouchet, R. Touillaux, J. Fastrez, J. Marchand-Brynaert, *Cheminform*, vol. 31, 2000.
29. S. Gerard, G. Dive, B. Clamot, R. Touillaux, J. Marchand-Brynaert, *Tetrahedron*, vol. 58, pp. 2423, 2002.
30. Y. Wang, H. Zhang, W. Huang, J. Kong, J. Zhou, B. Zhang, *Eur. J. Med. Chem.*, vol. 44, pp. 1638, 2009.
31. P. Sharma, A. Kumar, S. Sharma, *Ind. J. Chem.*, vol. 43B, pp. 385, 2004.
32. Sugumaran M, Sethuvani S, Poornima M Synthesis, characterization and antimicrobial evaluation of 2-azetidinone and thiazolidine derivatives . *Research Journal of Pharmaceutical, Biological and Chemical Sciences.* Volume 3 issue 2 2012 page no. 625- 631.
33. Parmar S, Sah P. "Synthesis and antimicrobial activity of some new 1-methyl [(N-alkyl pthalyl)-Benzimidazolo]-3'- chloro-4'-substituted azetidin-2-ones". *Indian J Heterocyclic Chem.* 16, 2007, 367-370
34. H. Panwar, R. S. Verma, V. K. Srivastava, A. Kumar, *Ind. J. Chem.*, vol. 45B, pp. 2099, 2006.
35. . Singh GS, Pheko T., "Formation and antimicrobial activity of 2-azetidinones from selective ester cleavage in 1, 3, 3- trisubstituted 4-[2'-(o-diarylacyl)hydroxyphenyl]-2- azetidinones", *Indian J Chem.* 47B, 2008, 159-162.
36. S. Tan, V. A. Guner, A. Ergene, *Turkish J. Pharm. Sci.*, vol. 2, pp. 11, 2005
37. S,K.Gawande and R.E.Khadsan. Synthesis, Characterization Of Some 2-Azetidinone Derivatives From 4-Nitro Ethyl Benzoate By Microwave Method And Evaluation Of Their Antimicrobial Activity. *International journal of pharmaceutical sciences and research* volume 5 issue 7 2014 pg no- 2966-2971.
38. Kumar A, Sharma P, Sharma R, Mohan P, "Synthesis and anti-microbial screening of N-substituted-3-chloro-4- dithiocarbamatoazetidine-2-ones" *Indian J Chem*. 42B, 2003, 416-420.
39. P. K. Patel, V. N. Patolia, A. J. Baxi, *J. Ind. Chem. Soc.*, vol. 67, pp. 599, 1990.
40. Jubie S, Gowramma B, Muthal N, Kalirajan R, Gomathi S and Elango K., "Synthesis and Antimicrobial Evaluation of some 2-Azetidinone derivatives", *IJCRGG* , 1(2), 2009, 153- 157
41. Adlington R. M., Baldwin J. E., Becker G. W., Chen B, Cheng L, Cooper S. L., "Design, Synthesis, and Proposed Active Site Binding Analysis of Monocyclic 2-Azetidinone Inhibitors of Prostate Specific Antigen", *J. Med. Chem.*, 44(10), 2001, 1491–1508
42. K. Shankar, V. Srivastava, A. Gulati, *Ind. J. Chem.*, vol. 26(B), pp. 652, 1987.
43. D. Petter, P. Haken, M. Vivekananda, *J. Med. Chem.*, vol. 38, pp. 1380, 1995.
44. P. D. Mehta, N. P. S. Sengar, E. V. S. Subruhmanyam, *Ind. J. Pharm. Sci.*, vol. 68(I), pp. 103, 2006.
45. V. Srivastava, G. Palit, S. Singh, *J. Ind. Chem. Soc.*, vol. 67, pp. 335, 1990.
46. Kaythara P, Upadhayaya T, Doshi R and Parel H. *Indian J Hetero Chem*., 2000;10:09-12
47. Parikh Khyathi A, Oza PS, Bhatt SB and Parlik AR. *Indian J Chem 2000;*39B:09-12
48. Thakar KM, Kachhadia VV and Joshi HS. *Indian J Chem.,* 2000;39B:716-718
49. Narute AS, Khedekar PB, Bhusari KP., "QSAR studies on 4- thiazolidinones and 2-azetidinones bearing benzothiophene nucleus as potential antitubercular agents". *Indian J Chem.*, 47B, 2008, 586-591
50. R Pridarshini, R Vijayraj, T K Ravi & M Prabha, *Ind J Heterocycl Chem,* vol.14, pp. 165, 2004
51. Gurupadayya BM, Gopal M, Padmashali B and Manohara YN. *Indian J Pharma Sci.*, 2008;572-577.
52. Rajesh Agarwal. *Indian J Chem*., 1989;28B;893-896
53. Basak A, Rudra KR, Bdour HMM. Use of nitrones in the synthesis of potential antihypercholesterolemic and antibacterial mono and tricyclic β-lactams. *Indian J Chem.* 42B, 2003, 1508-1513.
54. K.P. Bhusari, N. B. Charbe, A.P. Mehere, A.S. Warokar, J.W. Kakde and A.P. Mishrab. "Synthesis, cholesterol absorption inhibition and anti-bacterial activity of some novel 2-azetidinone derivatives", *IJRPC*. 1(4), 2011, 2231- 2781
55. Srivastava S.K, Srivatsava S. and Srivastava S.D, "Synthesis of new carbazolylthiadiazol-2-oxo-azetidines", *Indian Journal of Chemistry*, 38B, 1999, 183-187
56. Preethi PJ, Bindu KS, Rajavel R, Sivakumar T. *Asian J Pharm Res,* 2012; 2(2): 63.
57. Vijay Kumar MMJ, Yogananda R, Snehalatha, Shameer H, Jayachandran E, Sreenivasa GM. *J. Pharm Sci and Res*., 2009;1(2):83-92
58. Sharma P, Indapurkar P, Mandloi A. "Antibacterial screening of N-arylamino-3-chloro-4-(4'-dimethylamino)phenyl-azetidin-2-ones", *Indian J Pharm Sci.,* 60(3), 1998, 128-131.
59. Chavan A. A., and Pai N. R., "Synthesis and biological activity of N-substituted 3-chloro-2-azetidinones", *Molecules*. 12(11), 2007, 2467-2477.
60. Mistry K, Desai KR. "Synthesis of pyrazole imines and azetidinone compounds using conventional and microwave technique and studies of their antibacterial activity". *Indian J Chem.*, 44B, 2005, 1452-1455.