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SCOPE OF AZETIDINONE HYBRIDS FOR DIVERSE PHARMACOLOGICAL ACTIVITIES; A REVIEW

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Keywords:

Azetidinones, Azetidinone hybrids, β-lactams

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ABSTRACT: Azetidinones (Azetidin-2-ones), more commonly known as β-lactams, are well-known heterocyclic moieties among the medicinal compounds mainly because of their diverse pharmacological activities such as antimicrobial, anti-inflammatory, anticonvulsant, anti-HIV, anti-parkinsonian, antidiabetic and antitubercular activities. Various comparative studies of current azetidinone derivatives show an alarming increase in the bacterial resistance to the β-lactam nucleus may be due to irrational usage, which unfortunately led to less therapeutic usage. Hence new hybrids of Azetidinones with other drugs containing different heterocyclic rings found to possess broad-spectrum efficacy against various types of bacteria with β-lactamase inhibition to find great scope for future needs. This concept of hybrid molecules of different heterocyclic drugs would be a cost-effective and time-saving experiment in the process of drug discovery and development. In today's world of diseases and expensive drugs which are not affordable for countries like India, this attempt would be noon. Hence this review is an attempt to focus on the possible hybrid molecules of Azetidinones with other heterocyclic drugs for various diseases.

INTRODUCTION: 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].

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β-lactams are well-known heterocyclic compounds among the medicinal compounds because their diverse pharmacological activities mainly include 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 gene/s. 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: The parent heterocyclic ring of azetidinones is azetidine. Azetidine is a 4 member heterocyclic ring system with nitrogen as heteroatom. 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].

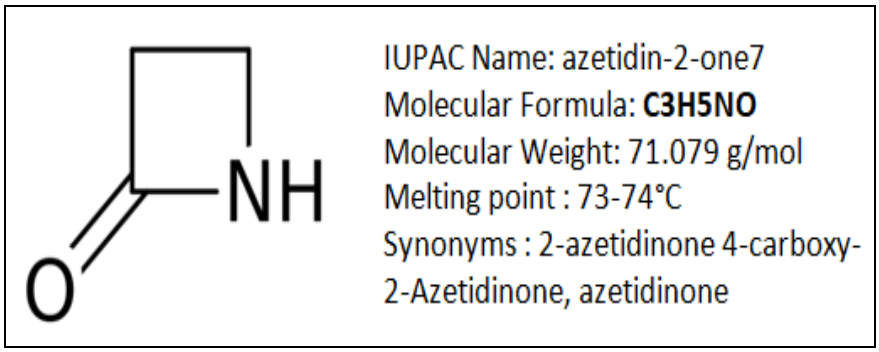
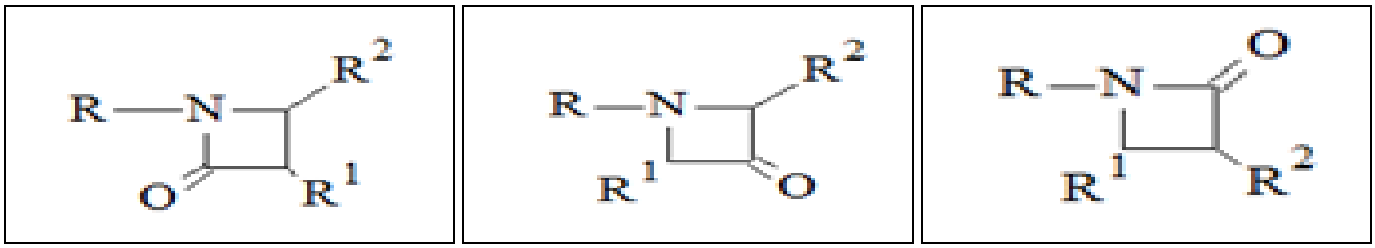


FIG. 1: CHEMICAL STRUCTURE OF AZETIDIN-2-ONE

Reactivity of Azetidinones:



AZETIDINE-2-ONE **AZETIDINE-3-ONE** **AZETIDINE-4-ONE**

FIG. 2: DIFFERENT POSSIBLE AZETIDINONE RING STRUCTURES

Hybrid Compounds of Azetidinones: The combination of two different and independently acting compounds into one covalently linked hybrid compound can convey synergy from the effects of both independently acting moieties to the new composite compound, leading to a pharmacological potency greater than the sum of each individual moiety's potencies, such are known as a hybrid molecule. The dual function compounds consist of two different moieties the covalent bond represented by a black line) acting simultaneously on a molecular target at a time point. Multifunction compounds are similar to dual-function compounds, with the addition of a third moiety linked by a covalent bond acting independently at a subsequent time point [5].

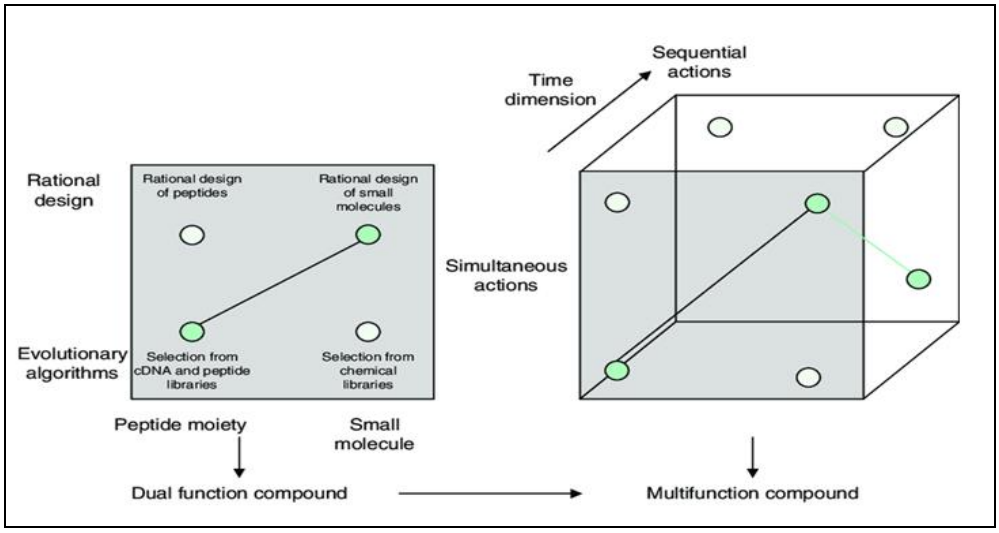


FIG. 3: REACTIVITY PROFILE OF AZETIDINONE

In the light of above discussion, we have attempted to make a review of work reported by different researchers on Azetidinone hybrids for various pharmacological activities, which may further enlarge the knowledge of medicinal chemists for drug discovery.

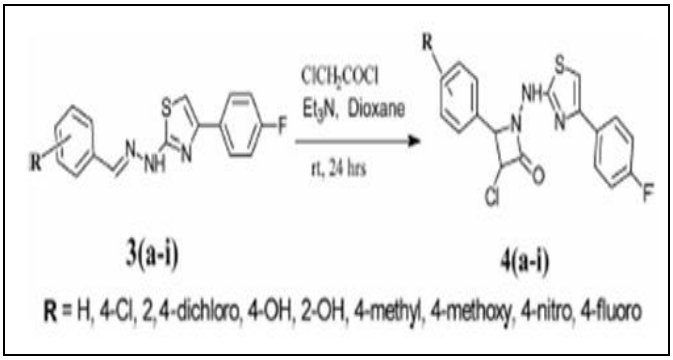


FIG. 4: SYNTHESIS 3-CHLORO - 4 - [(4-FLUOROBENZYLIDENE) – 1 - {4-(SUB-STITUTEDPHENYL) - 1, 3 – THAIAZOL - 2YL} AMINO] AZETIDIN – 2 - ONE

MATERIALS AND METHOD: Chaljin A *et al.*, reported that they had synthesized 3-Chloro-4-[(4-fluorobenzylidene)-1-{4-(substitutedphenyl)-1,3-thaiazol-2yl} amino] azetidin-2-ones from fusing Azetidinones with Thiazolyl moiety in different steps and various derivatives were prepared, characterized by spectral data [7].

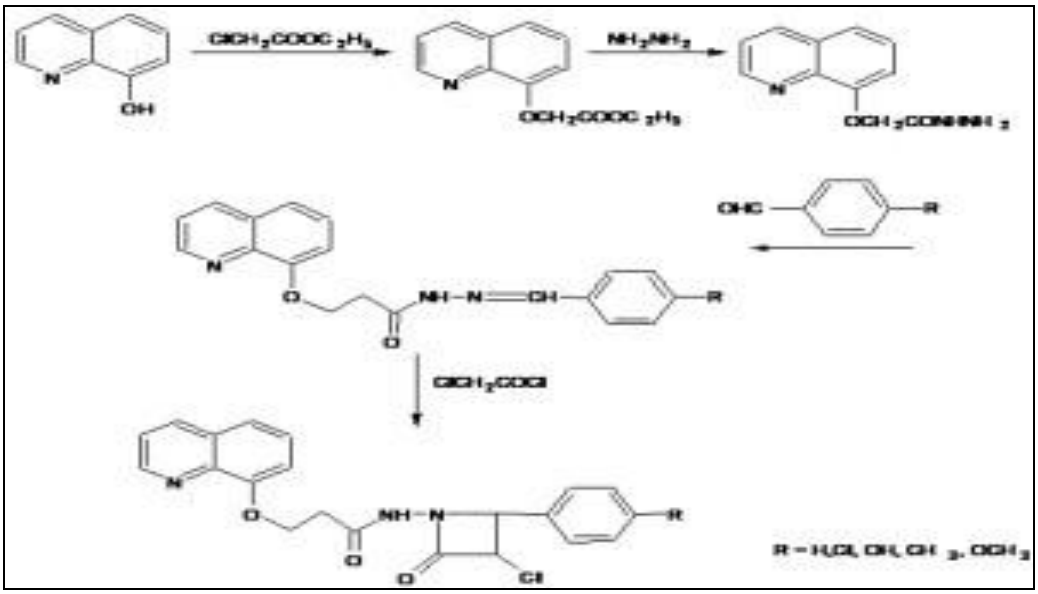


FIG. 5: SYNTHESIS OF NOVEL AZETIDINONES WITH QUINOLONE DERIVATIVES

Antimicrobial Screening: Sangu *et. al.*, synthesized some novel azetidinones with quinolone derivatives. The incorporated oxy-methylcarbamide at 8th position of the quinoline ring which was found to influence the biological activities of the molecules. Some of the new

quinolinyloxymethyl azetidinones were synthesized from 8-hydroxy quinolone through (quinolin-8-yl-oxy) acetyl hydrazide intermediate. All the synthesized compounds were found to possess antimicrobial activity [7]. Singh *et al.,* in their article, reported on the synthesis of synthesis of some 1, 2, 4-triazole derivatives. They have synthesized several derivatives, characterized them using elemental analysis and spectral data. They have reported that the synthesized compounds were evaluated for antibacterial activity against *S. aureus, E. coli, P. vulgaris, K. pneumonia,* and antifungal activity against *A. fumigatus, C. albicans, C. albicans,* and *C. krusei*. Some of them were found to be potent antibacterial and antifungal agents when compared with standard drugs [8].

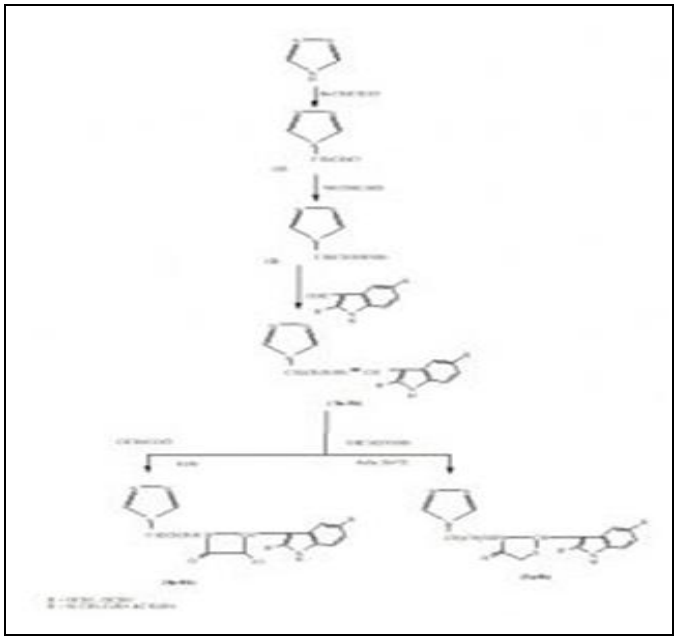


FIG. 6: SYNTHESIS OF 1, 2, 4-TRIAZOLE DERIVATIVES

Sai Padmini D *et al.,* reported on the synthesis and screening for antimicrobial activity of Novel 6h-Indolo (2, 3-b) Quinoxaline Fused Azetidinones. They have reported that the synthesized compounds contained both quinolyn and azetidinone moieties fused together which were novel and characterized by spectral data. The novel compounds were screened for antbacterial potency against gram-positive *Staphylococcus aureus* and *B. subtilis* and gram-negative *Proteus vulgaris* and Klebsiella by disc diffusion method. It was reported that the compounds had shown promising results as antibacterials. Similarly, the synthesized compounds were evaluated for their antifungal activity against *Aspergillus niger* and *C. albicans*. It was reported that all compounds had shown antifungal activity [9].

Chopra B *et al.,* in their report on the synthesizing of Naphthylamine analogs containing Azetidinone and Thiazolidinone Moiety, mentioned that the synthesized new coupling of azetidinone with thiazolidinones, characterized with spectral analysis and later evaluated for antimicrobial activity.

The *in-vitro* antibacterial study was conducted against *B. subtilis*, *St. aureus*, *E. coli,* and *P. aeruginosa* as well as antifungal activity against *C. albicans*. They have reported among all derivatives; four compounds exhibited a broad spectrum of activity [10].

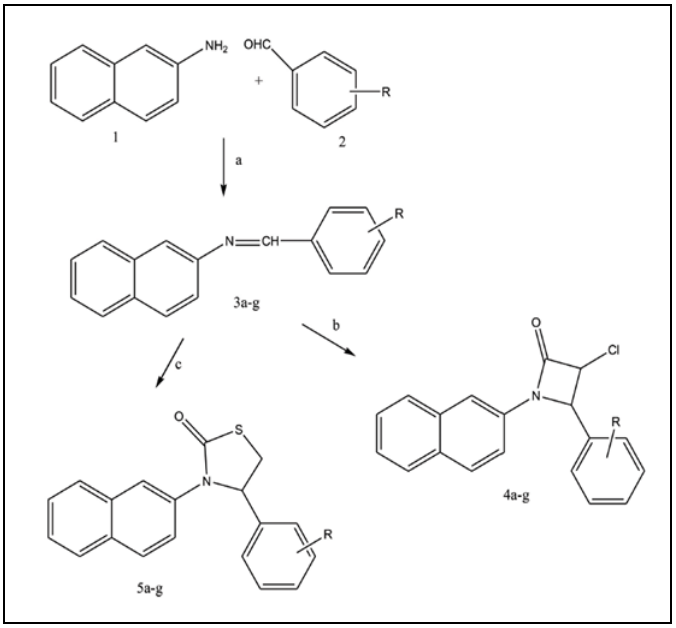


FIG. 7: SYNTHESIS OF NAPHTHYLAMINE ANALOGS CONTAINING AZETIDINONE AND THIAZOLIDINONE

Desai N C *et al.,* evaluated the antimicrobial efficacy of quinolone hybrids of azetidinones synthesized by the fusion of heterocyclic rings like thiazolidinones, azetidinones and oxadizoles bearing quinoline motif, which were screened for antibacterial and antifungal activities. They reported that the synthesized novel molecules were potent against bacteria such as *E. coli*, *P. aeruginosa*, *S. aureus*, *S. pyogenus*, and fungi such as *C. albicans, A. niger*, and *A. clavatus* and the results showed that these compounds were potent antimicrobial agents [11].

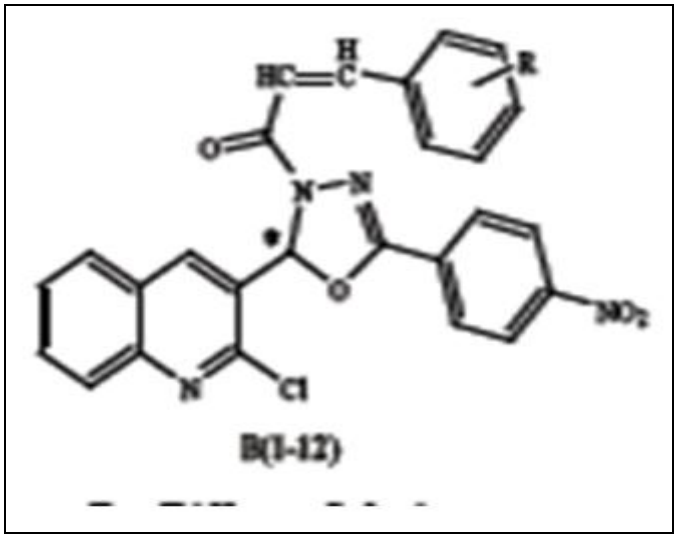


FIG. 8: QUINOLONE HYBRIDS OF AZETIDINONES

Dani R *et al.*, reported that they have synthesized novel Coumarinyl-oxadiazolyl-azetidinone & thiazolidinone derivatives using $POCl_3$, Carbon disulphide, Chloro acetyl chloride, and Thioglycolic acid. These synthesized compounds were characterized by spectral analysis and evaluated for *in-vitro* antibacterial activity against Gram-positive (*Staphylococcus aureus* and *Streptococcus pyogenes*) Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria and antifungal activity against (*Candida albicans*, *Aspergillus niger*, and *Aspergillus clavatus*) strains by using broth dilution technique. They have reported that some of the compounds were potent antibacterial and antifungal agents [12].

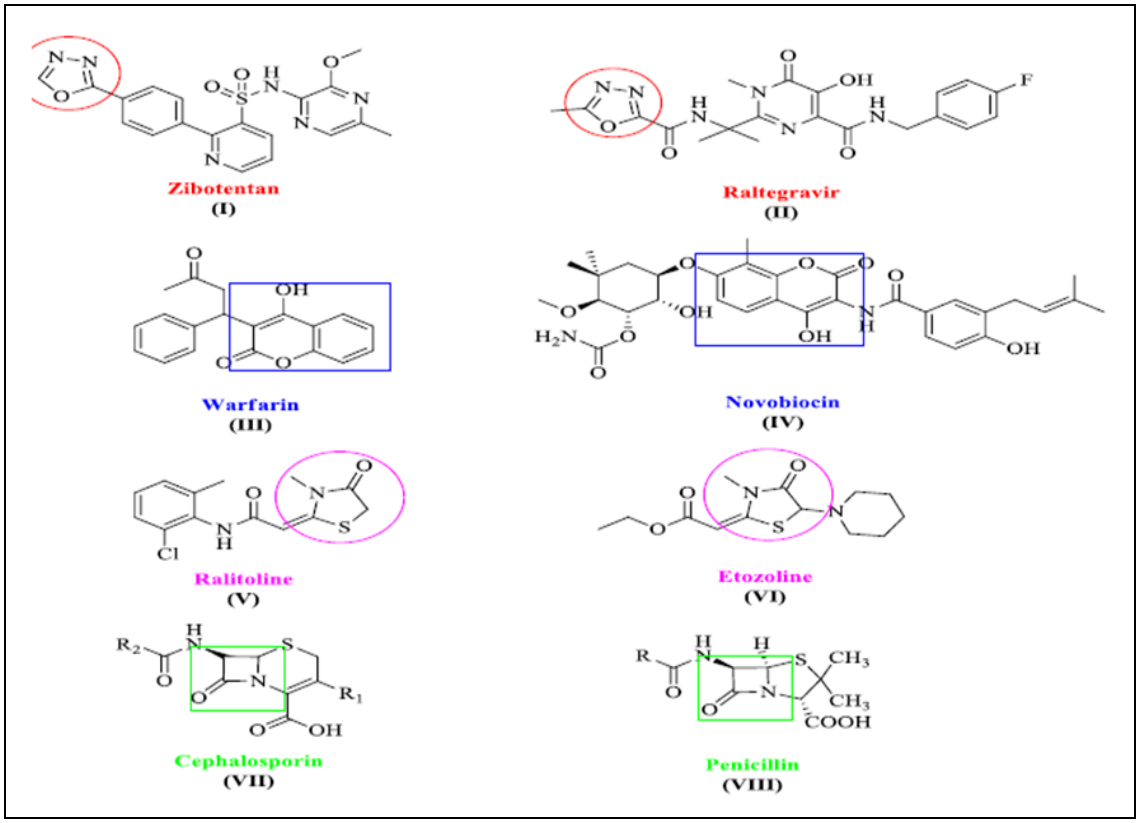


FIG. 9: SYNTHESIS OF NOVELCOUMARINYL – OXADIAZOLYL – AZETIDINONE & THIAZOLIDINONE DERIVATIVES

Antibacterial Activity: Jays J *et al.*, reported that they have designed new funan coupled Azetidinone rerivatives (16) and attempted molecular docking of these with 4 different targets of *E. coli* Dihydrofolate reductase, DNA gyrase, Enoyl reductase, and methionine aminopeptidase on software to study the is silico antibacterial potentials. The results obtained for the molecular docking of the compounds with enoyl reductase of *E. coli* has produced promising results and encouraged them to synthesize the molecules later [13]. Agarwal S *et al.*, reported that A new series of 1-(3-chloro-2-oxo-4-substituted phenyl azetidin-1-yl)-3-(substituted benzo[d]thiazol-2-yl) urea were synthesized, characterized, by elemental analysis and spectroscopic data (IR, 1H NMR and Mass) and evaluated for antimicrobial activity. The minimum inhibitory concentrations of the chemical compounds were carried out by broth microdilution method using Two Gram-positive (*Bacillus cereus*

MTCC 4317 and Staphylococcus aureus MTCC 3160) and two Gram-negative (*Escherichia coli* DH5 alpha MTCC 1652 and *Pseudomonas aeruginosa*, *Aspergillus niger* MTCC 282, *Alternaria solani* MTCC 2101, *Fusarium culmorum* MTCC 2090 and *Rhizopus stolonifer* MTCC 2591 strains were used for antifungal activity using Ampicillin sodium salt and Fluconazole as standards. antibacterial and antifungal drugs, respectively. The compounds showed good to moderate inhibition against the various strains [14].

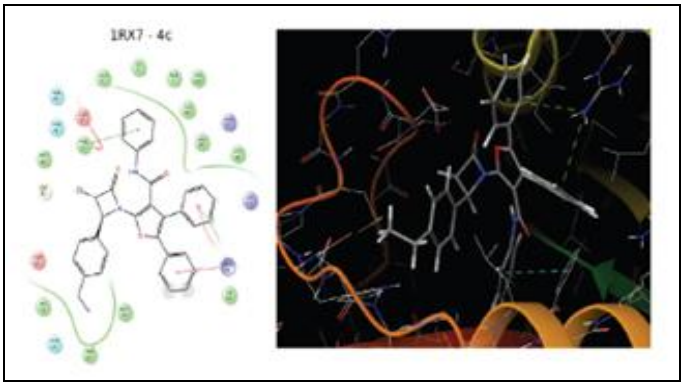


FIG. 1: XP DOCKED POSE OF COMPOUND 4E WITH ENOYL REDUCTASE OF *E. COLI* (PDB ID: 1014)

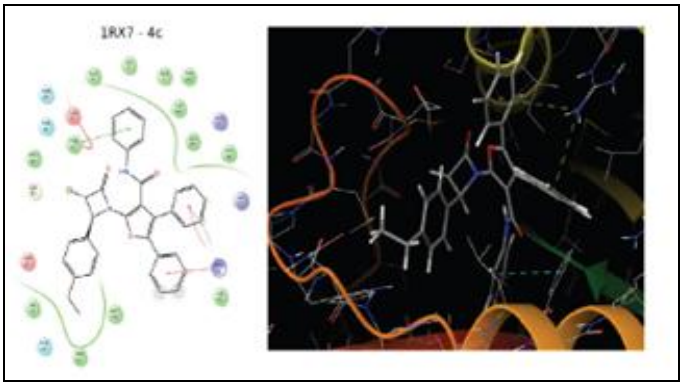


FIG. 2: XP DOCKED POSE OF COMPOUND 4C WITH DHFR OF *E. COIL* (PDB ID: 1RX7).

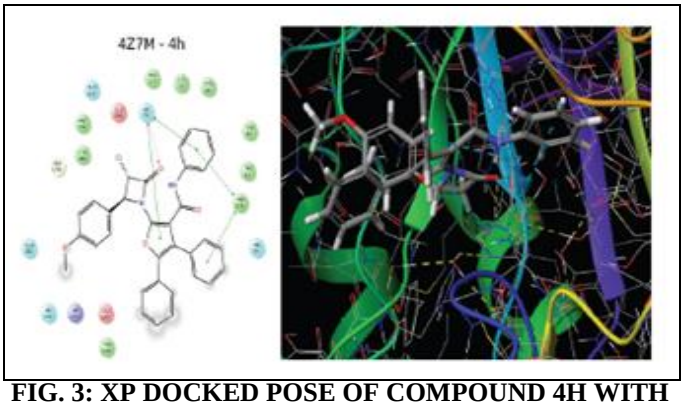


FIG. 3: XP DOCKED POSE OF COMPOUND 4H WITH METHIONINE AMIOPEPETIDASE (PDB ID: 4Z7M)

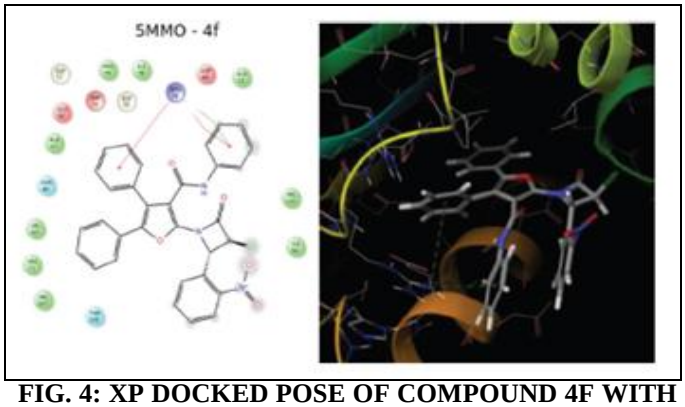


FIG. 4: XP DOCKED POSE OF COMPOUND 4F WITH DNA GYRASE OF *E. COIL* (PDB ID: SMMO)

FIG. 10: MOLECULAR DOCKING RESULTS OF FUNAN COUPLED AZETIDINONERERIVATIVES

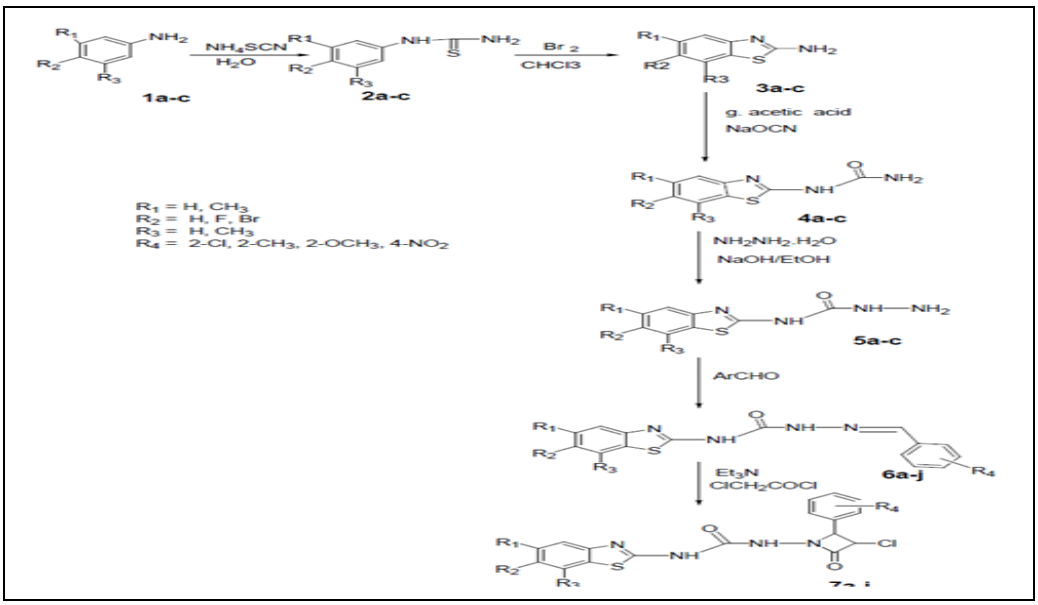
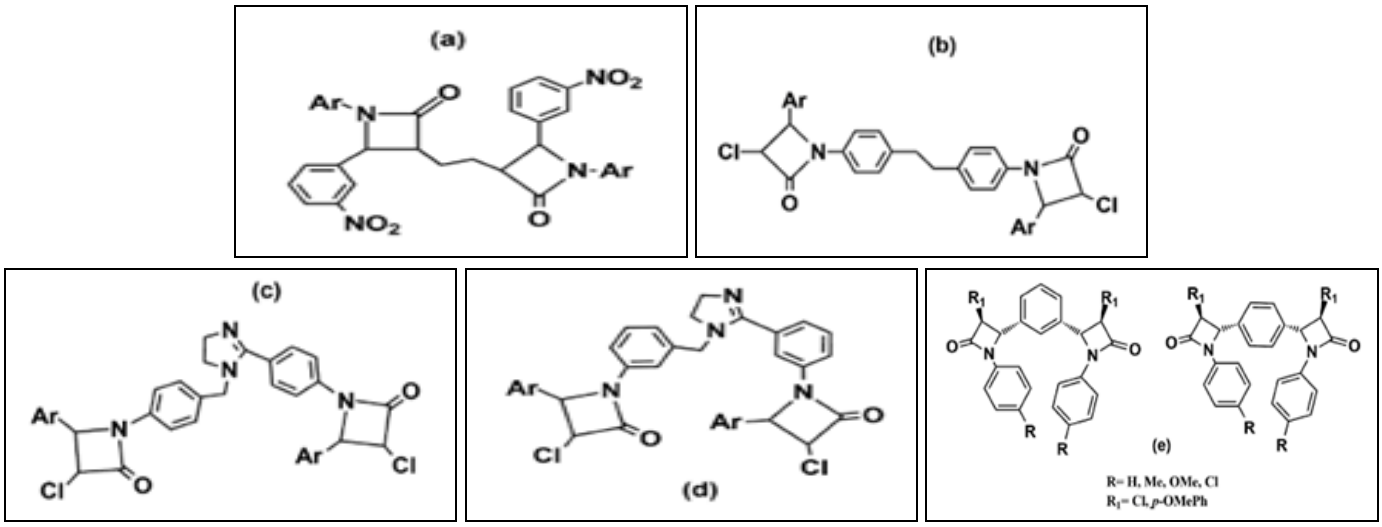


FIG. 11: SYNTHESIS OF 1-(3-CHLORO-2-OXO-4-SUBSTITUTED PHENYL AZETIDIN-1-YL)-3-(SUBSTITUTED BENZO [D] THIAZOL-2-YL) UREA

A review by Margherita De Rosa *et al.,* on coupling of azetidinones to yield various bis-azetidinone moieties with better antibacterial efficacy was reported citing various derivatives which are under clinical trials presently. This review enlightens us with the scope of coupling the two azetidinones with better efficacy [15].



CHEMICAL STRUCTURES OF BIT-AZETIDINONE CONNECTED BY SPACERS OF DIFFERENT TYPES. COMPOUNDS (A-D) ARE REPORTED IN REFS. [20-22], COMPOUNDS (E) IN REF [23]

FIG. 12: VARIOUS BIS-AZETIDINONE MOIETIES

Jays J *et. al.,* reported that they have novel furan-azetidinone hybrid compounds have been synthesized based on the molecular docking studies of the designed molecules on the four target sites-Dihydrofolate reductase (PDB: 3SRW), DNA gyrase (-PDB: 5BS3), Dihydropteroate synthetase (PDB: 1AD4) and pyruvate kinase (PDB: 3T07 of *S. aureus*.

They have observed that one of the compounds 4b forms H-bonding interaction with PHE 36 at the active site of the protein, which was comparable to the standard drug.

This study results encouraged them to synthesize new inhibitors for *S. aureus* [16].

Antitubercular Activity: It was reported by Joshi SD *et al.,* on the design and synthesis of quinolinyl Schiff bases and azetidinones as enoyl ACP-reductase inhibitors. The synthesized compounds were screened for *in-vitro* antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Vibrio cholera* and antitubercular activity against *Mycobacterium tuberculosis* H37Rv.

These compounds have exhibited good anti-bacterial and antitubercular activities. The molecular docking of these into active sites of enoyl ACP-reductase was performed on 2H7M.PDB and 4JX8.PDB files to understand ligand-protein interactions [17].

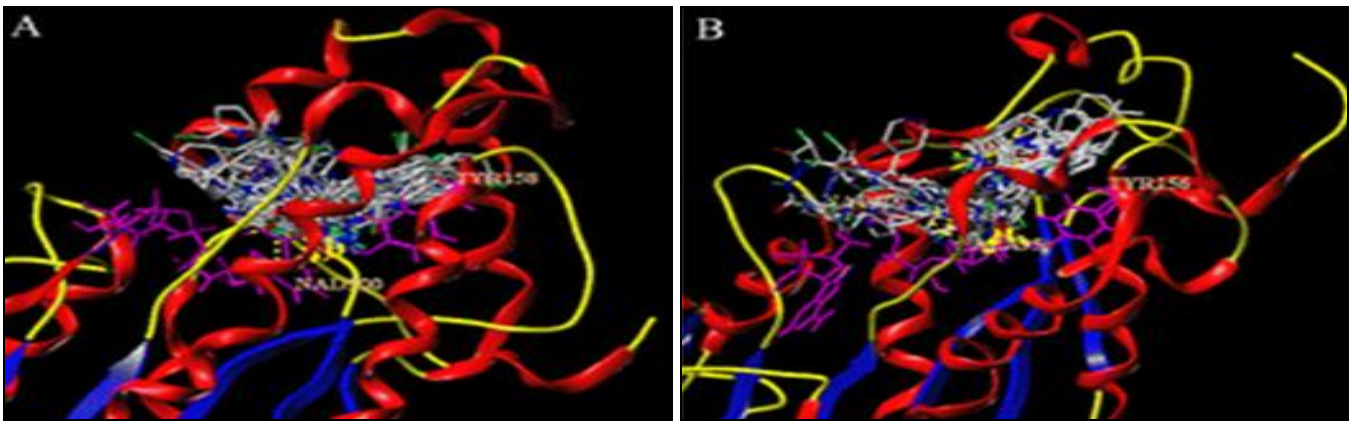


FIG. 13: MOLECULAR DOCKING OF QUINOLINYL SCHIFF BASES AND AZETIDINONES

Mallikarjunaswamy C *et al.,* reported Synthesis of Some New Pyrimidine-Azitidinone Analogues and evaluated for antimicrobial as well as antitubercular potency by *in-vitro* tuberculosis activities against Mycobacterium tuberculosis H37Rv and the results indicated that pyrimidine analogues were active against mycobacteria and displayed the highest inhibition at a constant concentration level (6.25 μg/mL) against M. tuberculosis H37Rv [18].

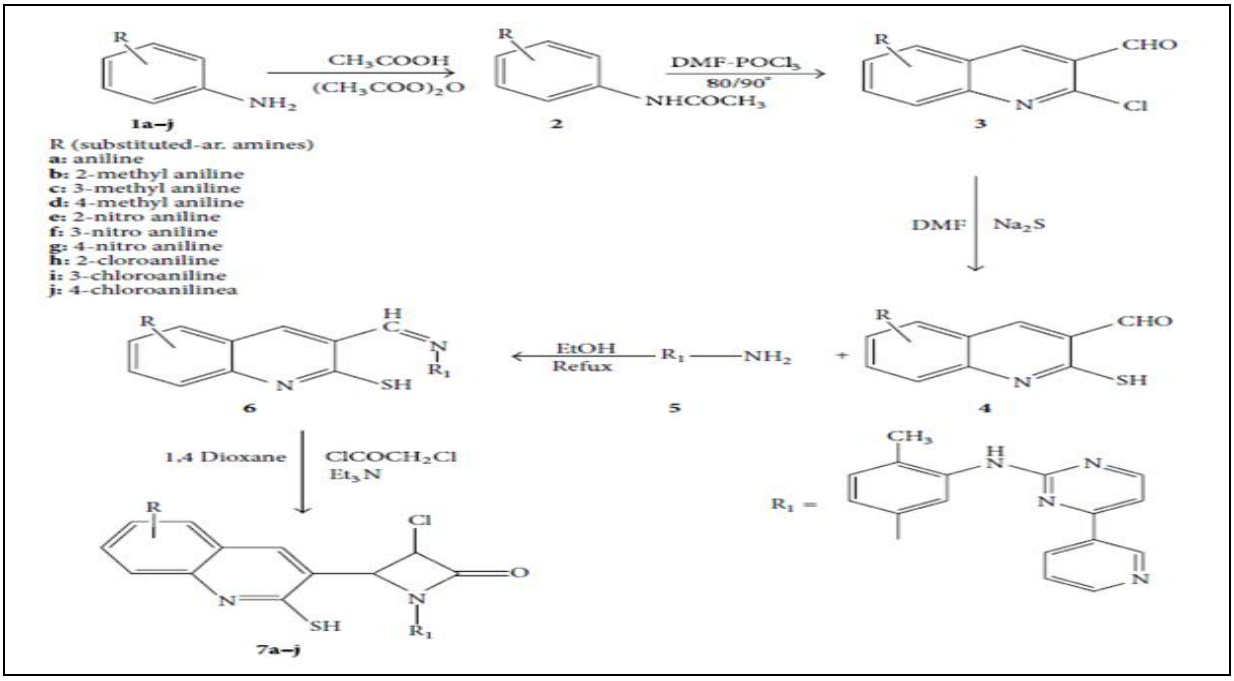


FIG. 14: SYNTHESIS OF SOME PYRIMIDINE-AZITIDINONE ANALOGUES

Pramod N *et al.,* reported that they have synthesized novel pyridine containing azetidinone derivatives and evaluated for antitumour activities and characterized from spectral data. Later, the synthesized compounds were screened for anti-tubercular potency using Microplate Alamar Blue Assay (MABA) method and found that some derivatives were more potent than the standard [19].

Synthesis of Pyridine Containing Azetidinone Derivatives:

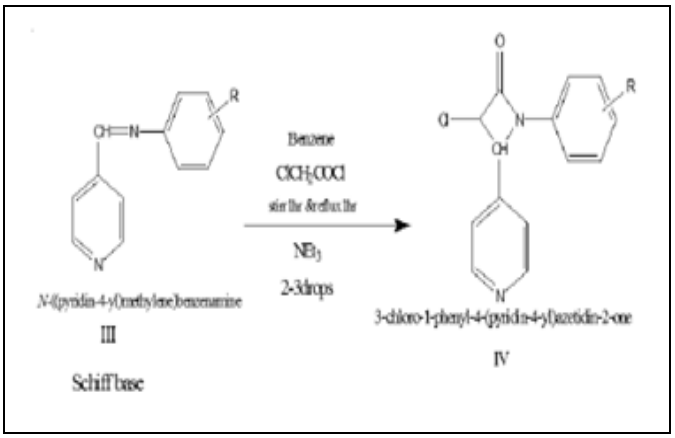


FIG. 15: SYNTHESIS OF PYRIDINE CONTAINING AZETIDINONE DERIVATIVES

Natarajan A *et al.,* (2020) reported that they have synthesized stereo, regioselective hydrids of novel β-lactam grafted spirooxindolopyrrolidine and screened for antimycobacterium tuberculosis potency against *Mycobacterium tuberculosis* H37Rv. This synthesis was carried out in multiple steps, and the synthesized compounds were characterized by spectral data. It was noticed that the derivatives with unsubstituted and chloro substituted oxindole had shown good activity, which was better than standard drug ethambutol [20].

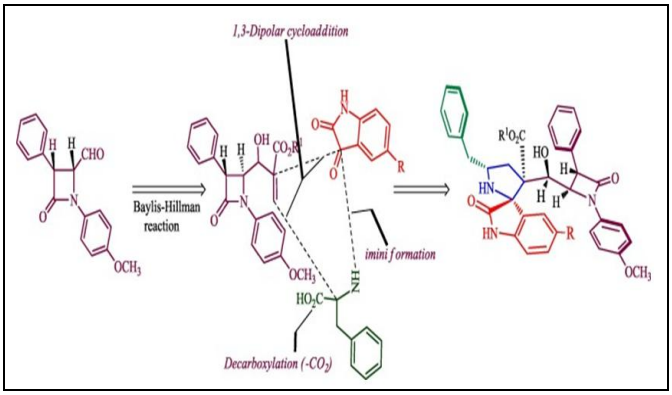
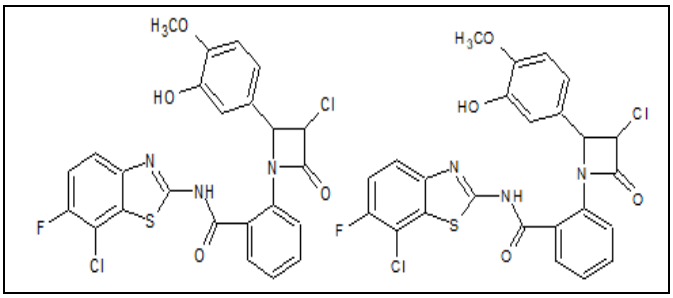


FIG. 16: SYNTHESIS OFSTEREO, REGIO-SELECTIVEHYDRIDS OF NOVEL B-LACTAM GRAFTED SPIROOXINDOLOPYRROLIDINE

Anti-inflammatory Activity: Various derivatives of 2-azetidinone derivatives dihydropyrimidinone incorporating the quinoline motif have been synthesized **Fig. 17** by Shaikh A *et al.,* by microwave technique (62- 84%) and reported that the synthesized cdompounds were characterized by spectral analysis and elemental analysis. The synthesized compounds were screen for their in vivo anti-inflammatory and analgesic activities on Wistar albino rats using Diclofenac and Indomethacin as standard reference drugs respectively and showed moderate to good anti-inflammatory activity. These compounds were screened for *in-vitro* anti-bacterial activity against some Gram positive and Gram negative strains of bacteria using Ampicillin and Streptomycin as standard reference [21].



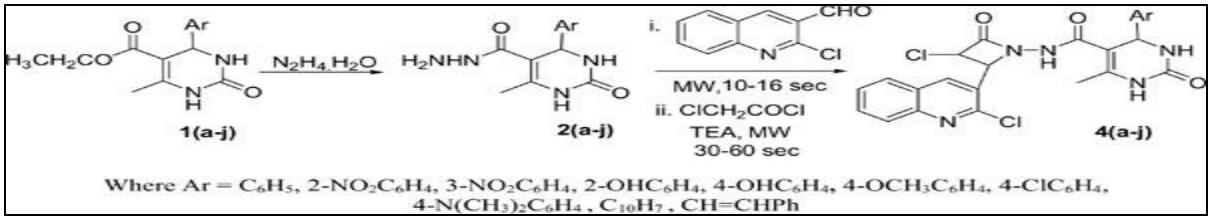


FIG. 17: MICROWAVE SYNTHESIS OF 2-AZETIDINONE DERIVATIVES DIHYDROPYRIMIDINONE INCORPORATING THE QUINOLINE

Anticancer Activity/Antiproliferative Activity: Alegaon S G *et al* reported that, a new quinoline-azetidinone hybrid template have been designed, synthesized and screened for their cytotoxic activity against human cancer cell lines such as Hep G2, and Hep 3B by the MTT assay and results were compared with paclitaxel, 5-fluorouracil and doxorubicin. Interestingly, some of the compounds were found significantly active against both cell lines. The compound 6f (IC_{50} = 0.04 ± 0.01 µM) exhibited potent antiproliferation activity against Hep G2 cell line, and 6j compound (IC_{50} = 0.66 ± 0.01 µM) demonstrated potent antiproliferation activity against Hep 3B cell line and provide to be more potent as cytotoxic agents than standard drugs [22].

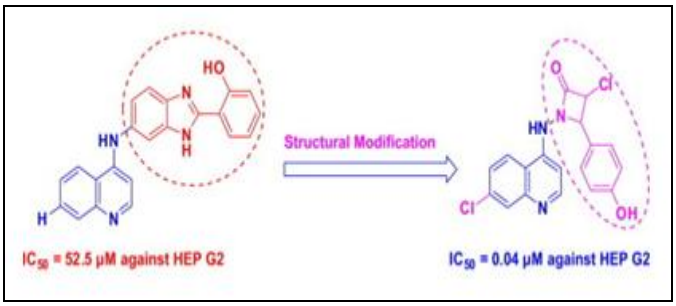


FIG. 18: SYNTHESIS OF QUINOLINE-AZETIDINONE HYBRID

Greene T F *et al.,* reported that Structure-activity relationships for a series of 3-phenoxy-1,4-diarylazetidin-2-ones were investigated, leading to the discovery of a number of potent anti-proliferative compounds, including trans-4-(3-hydroxy-4-methoxyphenyl)-3-phenoxy-1-(3,4,5-trimethoxyphenyl)azetidin-2-one and trans-4-(3-amino-4-methoxyphenyl)-3-phenoxy-1-(3, 4, 5-trimethoxyphenyl)azetidin-2-oneThese compounds displayed IC_{50} values of 38 and 19 nM, respectively, in MCF-7 breast cancer cells, inhibited the polymerization of isolated tubulin *in-vitro*, displayed minimal cytotoxicity, and was shown to interact at the colchicine-binding site on β-tubulin. Phosphate and amino acid prodrugs of both 78b and 90b were synthesized, of which the alanine amide 102b retained potency and is a promising candidate for further clinical development [23].

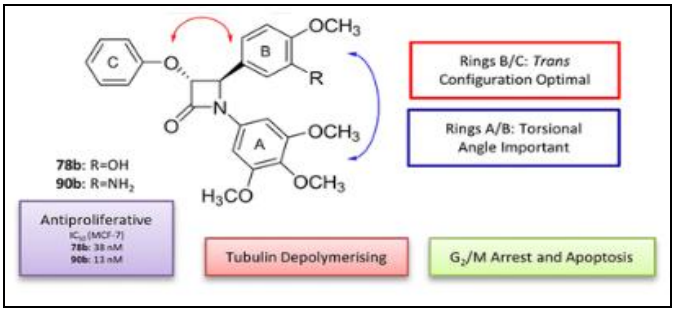
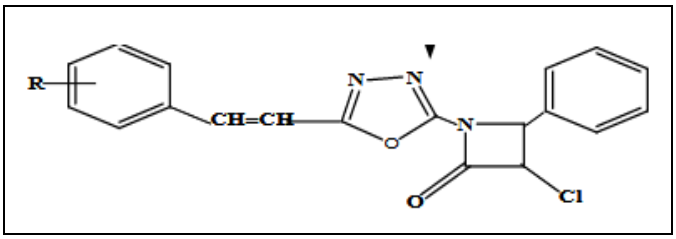


FIG. 19: STRUCTURE–ACTIVITY RELATIONSHIPS FOR A SERIES OF 3-PHENOXY-1,4-DIARYLAZETIDIN-2-ONES

Antioxidant Activity: Mishra PS *et al.* have synthesized a new series of Azetidinobe derivatives –Oxaziazole hybrids and screened them for free radical scavenging activity using Ascorbic acid as standard. Among the various synthesized molecules, 4c {2-hydroxy-5-nitro substituted derivatives} exhibited more activity [24].



AZETIDINONE DERIVATIVE

FIG. 20: SYNTHESIS OF NEW SERIES OF AZETIDINOBE DERIVATIVES–OXAZIAZOLE HYBRID

Antimalarial Activity: Aboubakr HA *et al.*, reported on the synthesis of new Quinazolyl fused derivatives for antimalarial study. In this research, they had reported that they had synthesized different derivatives of Quinazolin-2,4-Dione hybrids with different molecules including Azetridinones, characterized from spectral data. They have also conducted the In silico molecular docking studies of these hybrids with binding modes the putative active site of Plasmodium falciparum Dihydroorotate dehydrogenase (pfDHODH). The results revealed that the interactions were promising in comparison with the standard drug. And also, the pharmacokinetic properties were calculated, which were found to be good [25].

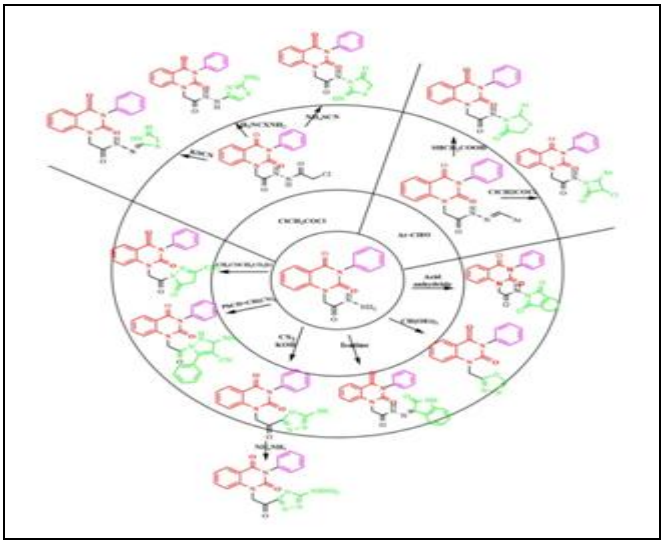


FIG. 21: QUINAZOLYL FUSED AZETIDINONEDERIVATIVES

RESULTS AND DISCUSSION: Several hybrid derivatives of amides (Azetidinones) which were synthesized and screened for various pharmacological activities were reviewed and found to possess antimicrobial, antitubercular, anti-inflammatory, antimicrobial activities, *etc.* An attempt is made to discuss recent developments in the synthesis, molecular docking studies, and pharmacological evaluation of various Azetidinone hydrid derivatives.

Several reports on synthesis and evaluation foe different pharmacological potentials of Azetidinone hybrids coupled with various heterocyclic drugs were reviewed and found to possess various biological activities such as antimicrobial, antitubercular, anti-inflammatory, angiotensin, anti-malarial activities. Literature survey reveals that, a large number of antibiotics contain amide linkage (Azetidino-2-one) such as Quinoline/pyridine-azetidinone hybrid (anti-microbial/antimalarial), azetidinones with 1, 2, 4-triazoles (anti-microbial/antitubercular) *etc.*

It was found that Energy minimization of the compounds was carried out, the protein was optimized and minimized, a 3-dimensional grid was generated at the active site; the results obtained from molecular docking of title compounds with N-myristoyl transferase of *C. albicans* is quite promising. It can be concluded that compound 4e (2,4- dichloro derivative) is predicted to have good antifungal activity. The study suggests that the compounds are specific in binding at the active site of N-myristoyl transferase.

A new series of thiazolyl-azetidinone derivatives was synthesized from a multistep approach involving the formation of thiosemicarbazone and then benzylidenehydrazinylthiazole derivatives cyclisation to have target compounds. The formation of all the compounds was confirmed with IR, NMR, and mass spectral analysis. These target molecules can be considered for biological screening in order to develop active pharma-ceautical compounds.

It was found that Antibacterial activity of the compounds azetidinones coupled with benzothiazolyl was carried out against gram-positive and gram-negative bacteria. The antifungal

activity of furan derivatives containing the azetidinone moiety against fungal strains by disc diffusion or cup and plate method to determine zone of inhibition (in mm). During the study, appropriate standard antibacterial and antifungal drugs, respectively, were used to compare the activities. It was found that Antitubercular activity was carried out on azetidinones hybrids with 1,2,4-triazoles by Middle brook 7H9 agar medium against Mycobacterium tuberculosis H37 RV strain. It was found that Anti-inflammatory activity was evaluated for the synthesized N-Substituted 3-chloro-2-azetidinone by treating fluoro-chloroaniline with KSCN in the presence of bromine and ammonia.

A series of Azetidine-Oxazole hybrids were synthesized and evaluated for antioxidant potentials by the free radical scavenging method, and some of them have shown promising results. It was also found that new Quinazolyl fused azetidinone hybrids were synthesized, characterized, docked into enzyme's energy pockets by *in-silico* method, and evaluated for antimalarial study which has produced promising docking results.

This review is an attempt to explore the potentials of Azetidinone hybrids with different heterocyclic molecules for different biological activities and try to enlarge the knowledge about it. This is an alternative method for new drug synthesis by utilizing the existing drugs by coupling reactions.

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CONFLICTS OF INTEREST: Nil

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