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STRUCTURE-GUIDED DESIGN OF BETA-LACTAM ANTIBIOTICS AND BETA-LACTAMASE INHIBITORS AGAINST MULTIDRUG-RESISTANT PATHOGENS

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ABSTRACT: Beta-lactam antibiotics remain essential in treating bacterial infections due to their broad-spectrum efficacy and low toxicity. However, the increasing prevalence of beta-lactamase-mediated resistance, particularly among multidrug-resistant Gram-negative bacteria, undermines their clinical effectiveness. Recent advances in structural modification and new beta-lactamase inhibitors, such as *Cefiderocol*, *Avibactam*, *Relebactam*, and taniborbactam, have shown promising results against resistant pathogens like *Carbapenem-resistant Enterobacterales* and *Pseudomonas aeruginosa*. Structure-activity relationship (SAR) studies significantly improved antibiotic stability, bacterial membrane penetration, and resistance evasion. Innovative approaches, including monocyclic beta-lactams and siderophore-conjugated antibiotics, further expand therapeutic options. Additionally, targeted modifications against penicillin-binding proteins have enhanced beta-lactam efficacy. Despite these improvements, challenges persist, notably variability in therapeutic drug monitoring (TDM), limited inhibitor spectrums, and rapid resistance emergence. Future research should prioritize developing broad-spectrum, irreversible beta-lactamase inhibitors with optimized pharmacokinetics and minimal adverse effects, to maintain beta-lactams as effective tools against antimicrobial resistance.

INTRODUCTION: Beta-lactam antibiotics offer several advantages in clinical pharmacy. They have strong antibacterial activity, low toxicity, broad-spectrum of activity, and good clinical efficacy. The chemical structure of beta-lactam antibiotics enables modifications to the side chains, leading to a diverse range of antibiotics with different action spectra and distinct clinical pharmacological properties [1].

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However, the development of microbial resistance to these drugs presents a significant challenge for modern antibiotic therapy. Bacteria primarily use beta-lactamase-producing enzymes as their defense mechanism against beta-lactam antibiotics. These enzymes cleave the amide bond in the beta-lactam ring, rendering the antibiotic molecules inactive [2].

Furthermore, variability in exposure of critically ill patients to beta-lactam antibiotics, due to changes in volume of distribution and elimination, poses a challenge. Therapeutic drug monitoring (TDM) of beta-lactams has been recommended to overcome this variability, but clinical evidence supporting the benefits of TDM for beta-lactams is not well established [3].

Despite these challenges, beta-lactam antibiotics remain widely used and have a positive impact on the treatment of severe bacterial infections [4].

Justification for Studying the Structure-Activity Relationship for New Antibiotics: Investigating the structure-activity relationship (SAR) of antibiotics offers significant advantages. SAR studies provide valuable information for the rational design of new molecules active against multidrug-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and Gram-negative bacteria [5]. These studies allow for the optimization of existing drugs, leading to the development of more potent and less toxic antimicrobial resistance-modifying agents (ARMs) [6]. Furthermore, SAR studies help in selecting molecules with optimal activity, favorable pharmacokinetic profiles, and reduced toxicity [7]. By understanding the relationship between the chemical structure of antibiotics and their antimicrobial activity, SAR studies contribute to the development of more advanced candidates for antibiotic applications [8]. Additionally, SAR studies contribute to the discovery of new chemical structures with potential antimicrobial properties, which can be further explored for the rational design and development of derivatives.

Theoretical Foundations of the Structure-Activity Relationship: The basic principles of the structure-activity relationship in the context of beta-lactam antibiotics involve understanding the interactions between antibiotics and their target proteins, such as penicillin-binding proteins (PBPs) and serine β-lactamases. Beta-lactam antibiotics interact covalently with PBPs, inhibiting the synthesis of peptidoglycan and disrupting bacterial cell wall formation [9]. The affinity and acylation rate of beta-lactam antibiotics with PBPs are important factors determining their effectiveness [10]. Bacteria develop resistance to beta-lactams primarily through the production of β-lactamase enzymes, which hydrolyze the antibiotic's β-lactam ring. To counteract this resistance, β-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam have been developed. These inhibitors irreversibly bind serine β-lactamases, restoring β-lactam antibiotic efficacy. However, their effectiveness is limited as they do not inhibit metallo-β-lactamases, which are increasingly prevalent and confer resistance to all β-lactams, including carbapenems [11]. It is also important to understand the physicochemical properties of beta-lactam antibiotics, such as lipophilicity and hydrophilicity, to determine their spectrum of activity against different types of bacteria [12].

The molecular structure of beta-lactams can be used to determine their antimicrobial activity. The synthesis of monocyclic cis-β-lactam derivatives has proven to be completely diastereoselective, leading to the formation of exclusively cis-stereoisomers [13]. Furthermore, the study of different classes of beta-lactam antibiotics has revealed their stability, susceptibility to β-lactamases, mechanism of action, and antimicrobial activity spectrum [9]. Developing new β-lactamase inhibitors is also very promising, as it would allow for the continued use of effective and safe antimicrobial drugs. Additionally, the structural modulation of spiro-β-lactams involved replacing the four-membered β-lactam ring with a five-membered γ-lactam ring, and the observed results suggest that the β-lactam core is essential for antimicrobial activity [14].

Main Classes of Beta-lactams: The main classes of beta-lactams include penicillins, cephalosporins, carbapenems, and monobactams [9].

Penicillins are characterized by a β-lactam ring fused with nitrogen and the adjacent tetrahedral carbon to form a second heterocycle, typically a 5-membered thiazolidine ring. The presence of a functionalized amino group at the 6β position of the β-lactam ring and a carboxyl group at the 3-position of the thiazolidine ring is common in biologically active penicillins. The structural parameters of the β-lactam ring remain consistent across different penicillins, with a tendency toward planarity [15]. The penicillin core is referred to as penam, C5H7NOS, and penicillins are generally 6-acylamino-2,2-dimethylpenam-3-carboxylic acids [16]. The crystalline structures of penicillin derivatives have been studied, confirming the agreement of bond distances and angles with other penicillin derivatives. Mass spectrometry experiments have provided a better understanding of the fragmentation pathways of penicillins, particularly those related to the β-lactam ring, and

have provided structural information about the β-lactam ring and side chains [17].

Cephalosporins possess a β-lactam cyclic structure similar to penicillin. They are derived from the Acremonium mold (formerly known as Cephalosporium) [18]. Cephalosporins have different generations, each with structural modifications to increase effectiveness against a broader range of bacteria [19]. The antibiotics work by interfering with the synthesis of the bacterial cell wall, leading to the degradation of the infectious organism. Cephalosporins can bind to penicillin-binding proteins after crossing the bacterial cell wall. Binding interactions with proteins in cephalosporins have been studied, and certain functional groups have been found to be significantly correlated with protein binding, such as the tetrazole (positive association), and pyridinium, primary amine, and quaternary amine (negative associations) [19]. Metal-cephalosporin complexes have also been studied, and spectroscopic techniques have been used to elucidate their structure. The structural and electronic properties of the β-lactam ring in cephalosporins do not change significantly between different cephalosporins, but the three-dimensional structure of ceftobiprole facilitates increased reactivity.

Carbapenems are a class of antibiotics with specific structural characteristics. They are frequently observed in Gram-negative bacteria, particularly in the Enterobacteriaceae family [20]. The structural formula of carbapenems is not explicitly mentioned in the summaries provided. However, the summaries note that carbapenems have good activity against Gram-negative bacteria, including strict aerobes. They are also known for their stability, ability to penetrate cell membranes, and similarity to a peptide bond [21]. Carbapenems are used in the treatment of various diseases and may play a role in drug-target interaction or enhance the biological activity of parent molecules [22].

Monobactams are a class of antibiotics that possess a unique structural feature known as the monocyclic β-lactam ring [23]. This cyclic structure provides resistance to zinc metallo-β-lactamases and makes monobactams effective against carbapenem-resistant Enterobacteriaceae [24]. The structure of monobactams can be modified to incorporate functional groups that enhance their antibiotic activity. Overall, the structural features of monobactams, including the monocyclic β-lactam ring and N-sulfonated fraction, contribute to their broad-spectrum antibacterial activity, highlighting their potential.

New Beta-lactam Antibiotics: New beta-lactams have been synthesized with different molecular structures. One compound includes the acid (6R, 7R)-7-(4-amino benzene sulfonyl)amino-8-oxo-5-sulfur-1-aza-bicyclo[4.2.0]-2-octylene-2-carboxylic acid and the acid (2S, 5R, 6R)-6-(4-amino benzene sulfonyl) amino-3,3-dimethyl-7-oxo-4-sulfur-1-aza-bicyclo[3.2.0] structures of heptane-2-carboxylic acid [25]. Another type of beta-lactam compound possesses a central monocyclic azetidinone structure with specific substituents at different positions of the ring. Furthermore, new 4-alkylthio monocyclic beta-lactams have been designed and synthesized, containing substructures provided by the cleavage of the C (2)-C (3) bond in penicillins. The specific molecular structures of these new beta-lactams offer opportunities for the development of compounds with unique biological properties and enhanced antibacterial activity [25].

New generation of cephalosporins: Fifth-generation cephalosporins, such as ceftolozane, have been developed to treat infections resistant to other beta-lactams. These new antibiotics are designed to be effective against difficult-to-treat pathogens, such as multidrug-resistant *Pseudomonas aeruginosa*. For example:

Cefiderocol: Cefiderocol is a new siderophore cephalosporin that exhibits potent activity against multidrug-resistant Gram-negative pathogens, particularly *Acinetobacter baumannii* (CRAB) and carbapenem-resistant *Pseudomonas aeruginosa*. Research indicates cefiderocol exhibits greater activity compared to other beta-lactam antimicrobials. It surpasses new beta-lactams combined with beta-lactamase inhibitors, ciprofloxacin, and minocycline [26]. The drug's innovative cell permeation mechanism contributes to its excellent antibacterial activity, although resistance mechanisms have been identified, emphasizing the importance of rational clinical use

[27]. *In-vitro* studies have demonstrated that cefiderocol is active against most *P. aeruginosa* isolates, even those with limited alternative treatment options, with variable clinical response rates depending on the MIC values [28].

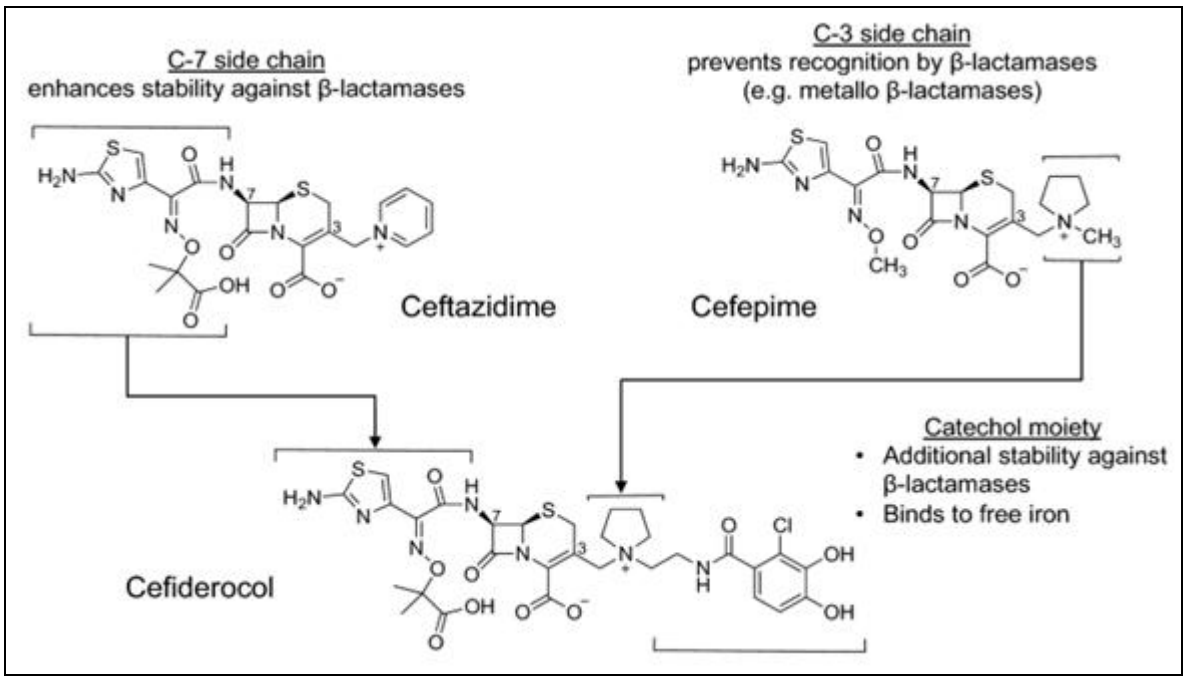

FIG. 1: SYNTHESIS OF CEFIDEROCOL

Cefiderocol, a new siderophore cephalosporin targeting Gram-negative bacteria, possesses a unique chemical structure that contributes to its effectiveness against carbapenem-resistant pathogens. The structural characteristics of cefiderocol resemble both ceftazidime and cefepime, allowing it to resist hydrolysis by beta-lactamases. A distinctive feature of cefiderocol is the addition of a catechol moiety to the C-3 side chain, which enables iron chelation, mimicking natural siderophores. This chelation process facilitates active transport across the bacterial cell's outer membrane to the periplasmic space via specialized iron transport channels. Additionally, cefiderocol demonstrates stability against hydrolysis by various beta-lactamases, including clinically relevant carbapenemases, such as *Klebsiella pneumoniae* carbapenemase and New Delhi metallo-beta-lactamase, demonstrating promising antibacterial activity both *in-vitro* and *in-vivo* [29].

Ceftolozane: Ceftolozane, a cephalosporin antibiotic combined with tazobactam, offers distinct advantages compared to other antibiotics. It has broad spectrum activity against Gram-negative pathogens, particularly *Pseudomonas aeruginosa*, including multidrug-resistant and carbapenem-resistant strains [30]. Research indicates that ceftolozane-tazobactam exhibits significant clinical and microbiological efficacy in the treatment of Gram-negative bacterial infections, especially those caused by *P. aeruginosa*, with higher rates of clinical cure and microbiological eradication compared to other antibiotics such as polymyxins/ aminoglycosides or levofloxacin [31]. Furthermore, ceftolozane-tazobactam presents a lower risk of acute kidney injury compared to some other antimicrobials, making it a safer option in certain cases. The stability of ceftolozane once reconstituted at room temperature enables safe and effective dosage optimization, which is particularly beneficial for frail and critically ill patients [32].

The latest antibiotics discovered in the beta-lactam family include recent innovations aimed at combating growing bacterial resistance. Some of these new antibiotics combine beta-lactamase inhibitors to enhance their efficacy against resistant bacteria. For example, a new drug combining a beta-lactam and a beta-lactamase inhibitor has recently been highlighted for its ability to treat infections caused by multidrug-resistant bacteria, including some strains of *E. coli* and *Pseudomonas*.

Additionally, research is ongoing to develop beta-lactams that can circumvent resistance mechanisms in Gram-negative bacteria. A notable example is the development of antibiotics targeting specific proteins in the bacterial cell wall, such as lipopolysaccharide transporters, which play a crucial role in the structure and resistance of Gram-negative bacteria.

These advancements are crucial in the fight against nosocomial infections and other serious infections caused by pathogens resistant to traditional antibiotics.

New Beta-Lactamase Inhibitors: Developing beta-lactamase inhibitors (BLIs) has been essential in combating antibiotic resistance and restoring the efficacy of beta-lactam antibiotics. Stereoselective approaches have been developed to access different stereoisomers of beta-lactams, allowing the use of their distinct properties [33]. Regarding BLIs, several inhibitors have been approved for clinical use, with a focus on targeting serine beta-lactamases (SBLs) and metallo-beta-lactamases (MBLs) [34]. These inhibitors have revitalized the effectiveness of beta-lactam antibiotics and have shown promise in treating infections caused by various classes of beta-lactamases. Efforts are also underway to identify new potentiators of beta-lactams to combat antibiotic resistance and reduce the global burden of antimicrobial resistance (AMR). For example:

Avibactam:

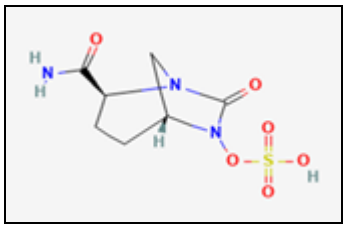

FIG. 2: CHEMICAL STRUCTURE OF AVIBACTAM

Avibactam targets class A and C beta-lactamases but does not inhibit class C beta-lactamase synthesis in *Enterobacter cloacae*. Chemically, avibactam is known as [(2S, 5R)-2-carbamoyl-7-oxo-1,6-diazabicyclo [3.2.1] octan-6-yl] hydrogenosulfate, with a molecular mass of 265.25 g/mol and a unique structure that lacks a beta-lactam ring. It possesses a sulfate group at C6, mimicking the carbonyl group of ceftazidime, and a carbonyl group that imitates cephalosporins, contributing to its mechanism of action. Its mechanism involves reversible inhibition, unlike other beta-lactamases, and it forms an acyl-enzyme intermediate to halt the hydrolysis of beta-lactams. This unique feature enables avibactam to effectively inhibit beta-lactamases while preserving the integrity of the antibacterial structure. Clinically, avibactam is used in the treatment of infections caused by Gram-negative bacteria, including urinary tract infections, intra-abdominal infections, and nosocomial pneumonia, demonstrating its effectiveness against a wide range of pathogens [35, 36].

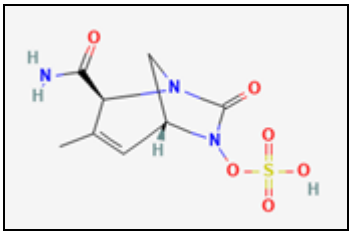

FIG. 3: CHEMICAL STRUCTURE OF DURLOBACTAM

Durlobactam: Durlobactam is chemically known as the hydrogenosulfate of [(2S, 5R) -2-carbamoyl-3-methyl-7-oxo-1,6-diazabicyclo [3.2.1] oct-3-en-6-yl], with a molecular mass of 277.26 g/mol. It contains a diazocyclooctene ring with a carbamoyl group, a methyl group, and a sulfate. The structure of Durlobactam enables it to inhibit serine beta-lactamases of classes A, C, and D, as well as carbapenem-resistant strains, with the exception of class B beta-lactamases. The mechanism of Durlobactam involves attacking and modifying the enzyme at the active serine site, leading to the establishment of a covalent bond, ultimately inhibiting the beta-lactamase activity. Durlobactam is used in combination with sulbactam to treat infections caused by *Acinetobacter baumannii*, showing greater activity than existing inhibitors [37].

Enmetazobactam:

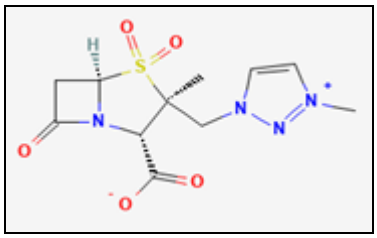

FIG. 4: CHEMICAL STRUCTURE OF ENMETAZOBACTAM

Enmetazobactam is chemically known as (2S, 3S, 5R) -3-methyl-3-[(3-methyltriazol-3-ium-1-yl) methyl]-4, 4, 7-trioxo-4lambda6-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate, with a molecular formula of $C_{11}H_{14}N_4O_5S$ [38].

Enmetazobactam is an N-methyl derivative of Tazobactam, effective against serine beta-lactamases of classes C and D, inhibiting carbapenemases produced by enterobacteria [39]. It lowers the MIC90 of cefepime for various bacterial isolates, thereby enhancing the antibiotic activity against enterobacteria [40]. It contains a beta-lactam ring with a cyclic thiopentane derivative from the triazole, enhancing its drug activity.

Enmetazobactam is a zwitterion whose structure is similar to Tazobactam, except for the methyl group on the triazole ring, which further boosts its activity. It is clinically used to treat urinary tract infections and nosocomial infections, demonstrating its effectiveness against Gram-negative bacteria.

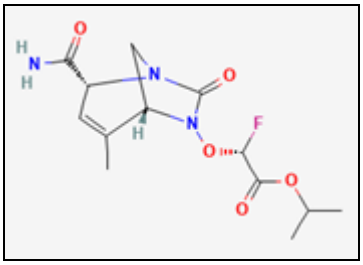

FIG. 5: CHEMICAL STRUCTURE OF ETX0282

ETX0282: ETX0282 is a prodrug of ETX1317, a beta-lactamase inhibitor, targeting serine beta-lactamases of classes A, C, and D. It has the chemical structure of propan-2-yl (2R) -2- [[(2R, 5R) -2-carbamoyl-4-methyl-7-oxo-1,6-diazabicyclo [3.2.1] oct-3-en-6-yl] oxy] -2-fluoroacetate [45].

ETX0282 is under development for oral treatment of infections caused by multi-drug resistant (MDR) Gram-negative organisms and carbapenem-resistant enterobacteria. It is being developed in combination with cefpodoxime proxetil (CPDP) for oral treatment for multidrug-resistant Gram-negative bacterial infections. ETX0282 contains a cyclic carbon-carbon double bond and a fluoroacetate activating group, showing broad-spectrumactivity against serine beta-lactamases of classes A, C, and D [41, 42]. This new diazabicyclooctane (DBO) beta-lactamase inhibitor, ETX0282, represents a significant advancement in the fight against antibiotic resistance by restoring the antibacterial activity of various beta-lactams, including third-generation cephalosporins such as cefpodoxime [43].

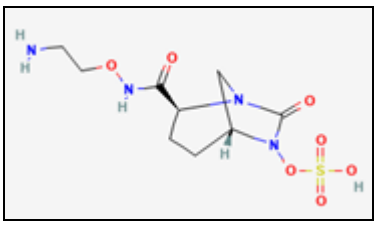

FIG. 6: CHEMICAL STRUCTURE OF NACUBACTAM

Nacubactam: Nacubactam has the chemical structure of [(2S, 5R)] -2- (2-aminoethoxycarbamoyl) -7-oxo-1,6-diazabicyclo [3.2.1] octan-6-yl] hydrogen sulfate with a molecular formula of C9H16N4O7S [44].

Nacubactam, a bridged diazabicyclooctane (DBO), is a potent beta-lactamase inhibitor that effectively inactivates class A and class C beta-lactamases [45]. It differs from avibactam by also inhibiting penicillin-binding proteins in enterobacteria, making it a promising agent against resistant strains. Research indicates that the Meropenem-Nacubactam combination significantly reduces the minimum inhibitory concentrations (MICs) of *Klebsiella pneumoniae* strains, particularly those carrying KPC or OXA-48 beta-lactamases [46]. Moreover, Nacubactam has proven effective against Mycobacterium species, inhibiting the growth of Mycobacterium smegmatis and *Mycobacterium tuberculosis*. These findings highlight the potential of Nacubactam as a key tool to combat multidrug-resistant bacteria and mycobacterial infections [46].

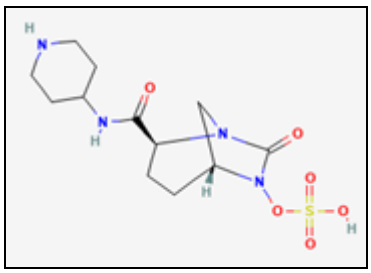

FIG. 7: CHEMICAL STRUCTURE OF RELEBACTAM

Relebactam: Relebactam has the chemical structure of [(2S, 5R) -7-oxo-2- (piperidin-4-ylcarbamoyl) -1,6-diazabicyclo [3.2.1] octan-6-yl] hydrogen sulfate, with a molecular mass of 348.38

g/mol and a central ureide structure similar to the beta-lactam ring of avibactam.

Relebactam is a beta-lactamase inhibitor that has demonstrated significant potential in restoring antibiotic sensitivity in various bacterial isolates. Research indicates that Relebactam enhances the activity of imipenem against both imipenem-sensitive and imipenem-resistant *Pseudomonas aeruginosa* and *Enterobacterales* strains [47, 48]. It has been shown to restore imipenem sensitivity in a considerable percentage of imipenem-resistant isolates, particularly in carbapenemase-producing enterobacteria and carbapenemase-negative *P. aeruginosa* [49]. The efficacy of Relebactam extends to various sensitivity categories, with notable ability to also improve Imipenem activity against sensitive isolates [50]. Overall, Relebactam has proven promising in combating antibiotic resistance by restoring beta-lactam antibiotic sensitivity in various clinical isolates, making it a key tool to combat multidrug-resistant bacteria.

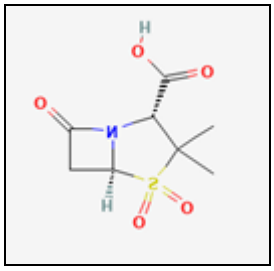

FIG. 8: CHEMICAL STRUCTURE OF SULBACTAM

Sulbactam: Sulbactam has the chemical structure of (5R) -3,3-dimethyl-4,4,7-trioxo-4l6-thia-1-azabicyclo [3.2.0] heptane-2-carboxylic acid, with a molecular mass of 233.24 g/mol and a pKa of 2.62 to 0.40. It is a semi-synthetic irreversible inhibitor with a boiling point of 567.7°C at 50.0°C and a melting point of 154°C to 157°C [51].

Sulbactam exhibits a broad-spectrum activity, making it a key tool to combat bacterial infections. It acts as a competitive and irreversible inhibitor of beta-lactamase, effectively restoring the efficacy of beta-lactam antibiotics against resistant organisms [52].

Sulbactam also has intrinsic antibacterial activity against certain bacterial species, including *Acinetobacter baumannii*, by inhibiting penicillin-binding proteins PBP1 and PBP3 [53]. The combination of sulbactam and ampicillin is particularly useful for treating polymicrobial aerobic or anaerobic infections, uncomplicated gonorrhea, and non-pseudomonal anaerobic and Gram-negative infections [52]. Additionally, sulbactam has been shown to be specific to intact sulbactam without interference from other antibiotics or degradation products, enabling precise quantification at concentrations as low as 0.2 µg/mL.

Tazobactam:

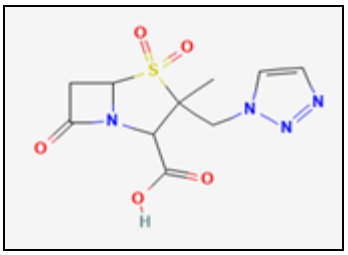

FIG. 9: CHEMICAL STRUCTURE OF TAZOBACTAM

Tazobactam is a beta-lactamase inhibitor used in combination with antibiotics to expand the antibacterial activity against various pathogens. It is effective against both Gram-positive and Gram-negative organisms, broadening treatment options for infections.

Chemically, tazobactam is known as (2S,3S, 5R) -3-methyl-4,4,7-trioxo-3- (triazol-1-ylmethyl) -4l 6 -thia-1azabicyclo [3.2.0] heptane-2-carboxylic acid, with a molecular mass of 300.29 g/mol [54].

Tazobactam forms an irreversible acyl-imine complex with beta-lactamase enzymes, inhibiting their activity and enhancing the effectiveness of antibiotics. Tazobactam, a sulfone beta-lactamase inhibitor, has a broadspectrum of activity against various pathogens. It is effective against beta-lactamase-producing enterobacteria, including CTX-M strains, making it useful in combating antimicrobial resistance[55]. The piperacillin-tazobactam combination is a common pairing that provides protection against Gram-negative bacteria, including Pseudomonas, and anaerobic bacteria, though rare side effects such as bicytopenia have been reported [56]. Developing tazobactam involves a series of intermediates, culminating in a high-purity final product suitable for industrial production. The ceftolozane-tazobactam combination, a new pairing, has demonstrated effectiveness against MDR organisms, including ESBL strains and *P.*

aeruginosa, making it a potential option for infections where carbapenems are not preferred [53]. The mechanism of action of tazobactam involves forming stable intermediates with beta-lactamases, contributing to its superior clinical efficacy [57].

Taniborbactam:

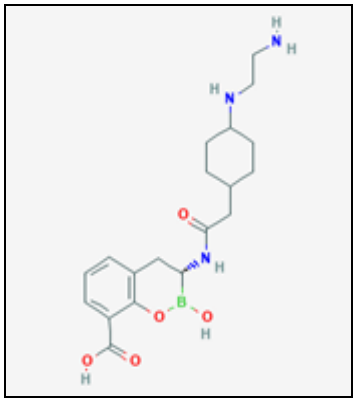

FIG. 10: CHEMICAL STRUCTURE OF TANIBORBACTAM

Chemically, Taniborbactam is known as (3R) -3-[[2-[4-(2-aminoethylamino) cyclohexyl] acetyl] amino]-2-hydroxy-3, 4-dihydro-1, 2-benzoxaborinine-8-carboxylic acid. It has the molecular formula C19H28BN3O5 and a molecular mass of 389.3 g/mol, containing a benzoxaborine ring with a carboxylic acid group and a cyclohexane chain linked by the carbamoyl fraction. Taniborbactam is a novel beta-lactamase inhibitor with a broadspectrum of activity against both serine and metallo-beta-lactamases, including carbapenemases [58, 59]. It has demonstrated efficacy in restoring the sensitivity of carbapenem-resistant *Pseudomonas aeruginosa* and enterobacteria to beta-lactam antibiotics [60]. Research indicates that Taniborbactam, in combination with cefepime, exhibits powerful activity against extended-spectrum beta-lactamase (ESBL) producers, restoring the sensitivity of enterobacteria and a significant proportion of *P. aeruginosa* isolates [61, 62]. Overall, Taniborbactam's spectrum of activity and efficacy make it a promising candidate in the fight against multidrug-resistant bacterial infections.

Vaborbactam: Chemically, Vaborbactam is known as 2- [(3R, 6S)-2-hydroxy-3-[(2-thiophene-2-ylacetyl) amino] oxaborinan-6-yl] acetic acid, with the molecular formula C12H16BNO5S and a molecular mass of 297.14 g/mol.

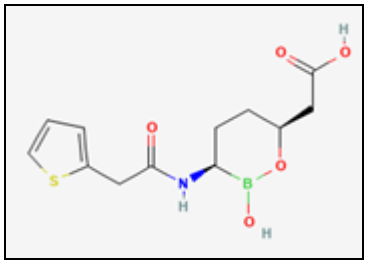

FIG. 11: CHEMICAL STRUCTURE OF VABORBACTAM

Vaborbactam penetrates the body via the outer membrane porins and forms a non-covalent complex with the enzyme before a covalent interaction occurs to inhibit the enzyme [63]. Vaborbactam, a new beta-lactamase inhibitor, has shown efficacy in treating infections caused by multidrug-resistant (MDR) Gram-negative bacteria, especially those producing KPC carbapenemases [64, 65]. It has been approved for conditions such as hospital-acquired pneumonia, ventilator-associated pneumonia, and bacteremia, demonstrating potent activity against carbapenem-resistant enterobacteria, including KPC-producing isolates. Research indicates that Vaborbactam, when combined with meropenem, leads to higher cure rates, reduced mortality, and fewer side effects in patients with Gram-negative infections, including those caused by carbapenem-resistant pathogens [66]. While generally well-tolerated, potential side effects of Vaborbactam include nephrotoxicity, hepatotoxicity, and skin rashes, though these are rare [67].

WCK-4234:

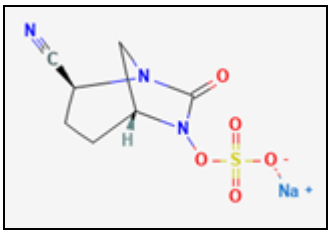

FIG. 12: CHEMICAL STRUCTURE OF WCK-4234

Chemically, WCK-4234 is known as sodium; [(2S, 5R)-2-(5-methyl-1, 3, 4-oxadiazol-2-yl)-7-oxo-1,6-diazabicyclo [3.2.1] octan-6-yl] sulfate, with the molecular formula C9H11N4NaO6S and a molecular mass of 326.26 g/mol. It contains a diazo-octane ring with methyl and aminosulfate groups. WCK-4234, a novel diazabicyclooctane, shows strong inhibitory activity against various carbapenemases and beta-lactamases in Gram-

negative pathogens, making it effective in treating multidrug-resistant infections [68]. When combined with meropenem, WCK-4234 significantly enhances the sensitivity against carbapenem-resistant isolates, particularly *Klebsiella pneumoniae* producing *Klebsiella pneumoniae* carbapenemase (KPC) and *Acinetobacter baumannii* [69]. Moreover, WCK-4234 shows promising activity against *Pseudomonas aeruginosa*, though its effect is more modest [70].

Notably, WCK-4234 does not establish a correlation between sensitivity and specific resistance mechanisms in *A. baumannii* and *P. aeruginosa*, but higher minimum inhibitory concentrations (MICs) are observed in isolates containing extended-spectrum beta-lactamases (ESBLs) [71]. Although the data suggest WCK-4234's potential in combating multidrug-resistant pathogens, further research is needed to determine potential side effects and optimize its clinical use.

CONCLUSION: The spread of antibiotic-resistant bacteria remains one of the most pressing public health challenges today. The growing emergence of antimicrobial resistance raises major concerns about the future effectiveness of beta-lactams. To counter this resistance, the use of beta-lactamase inhibitors is crucial, especially when these inhibitors can irreversibly neutralize the enzymatic activity. Unlike reversible inhibitors, which allow the reactivation of enzymes through non-covalent interactions, irreversible inhibitors covalently bind to enzymes, rendering them inactive even in the presence of alternative substrates.

Metallo-beta-lactamases, in particular, pose a significant challenge due to the shallow localization of their active site, complicating their inhibition. Taniborbactam, despite its role as an inhibitor of metallo-beta-lactamases, has not demonstrated broad spectrum efficacy, while captopril, another inhibitor in this group, presents undesirable side effects.

In contrast, clavulanic acid is currently considered the most effective beta-lactamase inhibitor due to its ability to target both Gram-positive and Gram-negative bacteria with a minimal side effect profile. Future research should prioritize developing broad-spectrum, irreversible beta-lactamase inhibitors with minimal side effects by optimizing molecular parameters such as polarity and pKa.

However, it is crucial to recognize that resistant bacteria to these inhibitors have recently been identified. To deepen our understanding of the spread and evolution of these resistant strains, it is imperative to study alterations in transmembrane proteins, often propagated by plasmids, in order to devise more effective strategies to combat this growing threat.

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