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Review

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Carbapenemase Inhibitors: Updates on Developments in 2021

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Abstract

Carbapenem resistance, an emerging global health problem, compromises the treatment of infections caused by nosocomial pathogens. Preclinical and clinical trials demonstrate that a new generation of carbapenemases inhibitors, together with the recently approved avibactam, relebactam and vaborbactam, would address this resistance. Our review summarizes the latest developments related to carbapenemase inhibitors synthesized to date, as well as their spectrum of activity and their current stage of development. A particular focus will be on β-lactam/β-lactamase inhibitor combinations that could potentially be used to treat infections caused by carbapenemase-producer pathogens. These new combinations mark a critical step forward the fight against antimicrobial resistance.

Keywords: Carbapenem resistance; Carbapenemase inhibitors; Pathogens

Introduction

Carbapenem resistance has been declared a worldwide problem as per the 2017 World Health Organization [1]. To address this global pandemic crisis, it is pivotal to understand the mechanism of resistance and better classify the responsible pathogens. The main mechanism of resistance is the hydrolysis of carbapenems via the production of carbapenem-hydrolyzing enzymes [2]. β-lactamase enzymes are classified by the Ambler Classification System into four groups (A, B, C, and D) based on their central catalytic domain and substrate preference [3]. In general, class A, B and D enzymes utilize carbapenemases for resistance while class C enzymes mainly hydrolyze cephalosporins. Moreover, class A, C and D enzymes have serine in their central catalytic domain, while class B enzymes have zinc and are considered metallo-β-lactamases (MBLs) [4] (Table 1).

Class A enzymes can be chromosomally encoded (SME, NmcA, SFC-1, BIC-1, PenA, FPH-1, SHV-38) or plasmid-encoded (KPC, GES, FRI-1) [5]. Chromosomally encoded class A carbapenemases are rare and are found in a limited number of *Serratia* and *Enterobacter* isolates [6-8]. However, plasmid-encoded class A carbapenemases are widely spread and have been isolated predominantly in *Klebsiella pneumoniae* [9, 10]. Specifically, the KPC family from class A has enzymes that can hydrolyze a huge variety of β-lactams substrates, which gives these carbapenemases the power to spread and develop resistance, making them one of the most difficult carbapenemases to control [11].

Class B carbapenemases are distinguished by having zinc ions on their active site. These ions interact with the β-lactams leading to their hydrolysis. The mechanism of action of these MBLs facilitates their inhibition by metal ion chelators, such as EDTA, but not by the regularly used lactam inhibitors. They are divided into chromosomal (CcrA, CphA, L1) and plasmid-encoded (VIM, IMP, GIM, SIM) variants. Chromosomally encoded class B carbapenemases are mainly found in opportunistic pathogens and are therefore not common in nosocomial bacteria. Since the spread of chromosomal MBLs is directly dependent on the prevalence of the offending pathogen, they are relatively rarer to detect [12, 13]. On the contrary, the plasmid-encoded class B carbapenemases are transferrable, so their prevalence has increased over the years, with some (VIM, IMP) even spreading beyond their countries of origin. They are found predominantly in *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Enterobacterales* [11, 14].

Class C enzymes, as mentioned earlier, are known to hydrolyze mainly cephalosporins. Recently five enzymes in this group (ACT-1, DHA-1, CMY-2, CMY-10, and ADC-68) were found to exhibit carbapenem catalytic activity as well, imposing further therapeutic threat against the use of multiple antibiotic classes [15].

Class D enzymes, also called OXAs (oxacillinases) due to their ability to hydrolyze isoxazolyl penicillin oxacillin,

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Table 1. Summary and Classification of Carbapenemases Enzymes

Ambler Classification System	Active site	Carbapenemases enzymes	
		Chromosomally encoded	Plasmid/transposon/ integron-encoded
Class A	Serine-beta-lactamases	SME, NmcA, SFC-1, BIC-1, PenA, FPH-1, SHV-38	KPC, GES, FRI-1, NmcA
Class B	Metallo-beta-lactamases	CcrA, CphA, L1	GIM, IMP, VIM, SIM
Class C	Serine-beta-lactamases	ACT-1, ADC-68	CMY-2, CMY-10, DHA-1
Class D	Serine-beta-lactamases	OXA-23, OXA-24/40, OXA-58, OXA-143, OXA-235a, OXA-134a, OXA-211, OXA-213, OXA-214, OXA-229	OXA-48, OXA-58, OXA-51

are widely found in gram-negative bacteria. Some of these enzymes are found to possess carbapenemase activity, thus given the name carbapenem-hydrolyzing class D β-lactamases (CHDLs). The majority of the clinically significant CHDLs (OXA-23, OXA-24/40, OXA-51, OXA-58, and OXA-143) are found in the *A. baumannii* strains. Of those, OXA-51 is the most widespread. OXA-48 is also found in *K. pneumonia* and less often in some members of the *Enterobacteriaceae* family [16-22].

Carbapenemase Inhibitors

Diazabicyclooctanes (DBOs) derived inhibitors

DBOs were thought to be potential β-lactam mimics; however, early synthetic DBOs had no antimicrobial uses [23, 24]. Nevertheless, continuing efforts in their development had made them potentially potent inhibitors of β-lactamases. DBOs consist of a five-membered ring with an amide group that carbamylates and subsequently deactivates the serine residues of class A and class C enzymes. Additionally, it has shown unpredictable activity against class D enzymes and no effect on class B metalloenzymes [24].

Avibactam

Up until 2015, antibiotics with extensive side effect profile, such as aminoglycosides and colistin, have been considered the optimal modality for managing carbapenem-resistant *Enterobacteriaceae* (CRE). In 2015, the Food and Drug Administration (FDA) approved the use of avibactam-ceftazidime, a combination of a β-lactam/β-lactamase inhibitor (BLI) [25, 26]. It has a broader spectrum of activity when compared to current BLIs (clavulanic acid, tazobactam, and sulbactam) [27]. Moreover, when paired with ceftazidime, a third-generation cephalosporin, it has restored the antimicrobial activity against a wide range of class A and C β-lactamases, along with *K. pneumoniae* carbapenemase (KPC) carbapenemases, extended spectrum beta-lactamases (ESBLs), and AmpC enzymes. A recent study by Niu et al proved that aztreonam-avibactam combination has an activity against MBL-producing *K. pneumoniae*, a matter which has been challenging for many antimicrobials [28]. Nevertheless, ceftazidime alone stands effective against OXA-48-like carbapenemases in addition to its good antipseudomonal activity. Together when combined they offer extensive action against β-lactamase producing *Enterobacteriaceae* as well as against *P. aeruginosa* with derepressed AmpC [29]. The combination of aztreonam in combination with ceftazidime-avibactam has provided an upgrade on the individual ability of aztreonam and ceftazidime-avibactam individually to fight against serine-beta-lactamase (SBL) and MBL-producing *Enterobacterales* (*P. aeruginosa*). In a study designed to evaluate the bactericidal activity of different antibiotic combinations against SBL and MBL-producing *P. aeruginosa* isolates, there was a significant increase in bactericidal activity in 4/5 of the isolates upon combining aztreonam with ceftazidime-avibactam, as opposed to using aztreonam, aztreonam-avibactam, and ceftazidime-avibactam which showed no bactericidal activity against any of the isolates [30].

Aztreonam-avibactam combination is superior to relebactam, clavulanate, and vaborbactam in the treatment of multidrug-resistant (MDR) *S. maltophilia*. Though there may be some decreased susceptibility by some strains in part due to overexpression of intrinsic beta-lactamases and efflux pumps [31].

Zidebactam (ZID) and WCK 5153

ZID and WCK 5153 are bicyclo-acyl hydrazides (BCHs), derivatives of the DBOs scaffold, and are used for the treatment of severe infections caused by highly drug-resistant gram-negative bacteria [32, 33]. ZID in combination with cefepime (FEP) is presently being evaluated in clinical trials for infections caused by MDR gram-negative pathogens such as *P. aeruginosa* and *A. baumannii* [32]. Despite being synthetized from a DBO scaffold, BCHs were developed with the goal of increasing penicillin-binding protein 2 (PBP2) binding in *P. aeruginosa* and *A. baumannii* rather than improving the compound's β-lactamase-inhibitory action [32, 34]. That contrasts with the first DBO, avibactam, which had a low PBP2 affinity in *Enterobacteriaceae*, followed by OP0595 (RG 6080), which had a higher PBP2 affinity but was only active against *Enterobacteriaceae*. ZID and WCK 5153 have shown in *P. aeruginosa* a high affinity for *A. baumannii* PBP2 with inhibitory concentration 50 (IC50) of 0.01 g/mL, which was 7 - 8 times lower than imipenem and like meropenem, although both are known to be powerful PBP2-binding drugs. For wild-type and

MDR *Acinetobacter bacteria*, the minimum inhibitory concentrations (MICs) of ZID and WCK 5153 were more than 1,024 µg/mL. Furthermore, combinations of FEP with 8 µg/mL ZID or WCK 5153 and sulbactam with 8 µg/mL ZID or WCK 5153 have resulted in four- and eight-fold decreases in MICs, respectively, and improved antimicrobial activity. Many of the different combinations resulted in complete bacterial elimination after 24 h [32].

Durlobactam (sulbactam/durlobactam)

Sulbactam/durlobactam, previously known as (sulbactam-ETX2514), constitutes a β-lactam/BLI combination used to treat severe *A. baumannii-calcoaceticus* complex (ABC) organisms, including MDR strains [35, 36]. This combination often inhibits PBP3 and therefore has an inherent action against *A. baumannii*. However, high MICs are often detected among isolates resistant to carbapenems. When compared to other drugs, sulbactam/durlobactam exhibits high *in vitro* effectiveness against *A. baumannii* isolates, including those resistant to imipenem/meropenem, amikacin, minocycline, and colistin. Moreover, it has been shown to be effective when used with current limited antimicrobials used to treat *A. baumannii*. Sulbactam/durlobactam was found to have a good safety profile, tolerability, and pharmacokinetic properties in phase 1 and phase 2 studies, and is currently being tested in a randomized, controlled phase 3 study in patients with *A. baumannii* infections, such as hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, and bacteremia [37].

Nacubactam

Nacubactam, a bridged DBO previously known as RG6080 and OP0595, is a class A and C BLI with intrinsic antibiotic and β-lactam "enhancer" action against *Enterobacteriaceae* [38, 39]. The structure of nacubactam can be distinguished from avibactam by an aminoethoxy group attached to the carbamoyl side chain. This modification is most likely responsible for nacubactam's relatively high antibacterial activity. Nacubactam inhibits *Escherichia coli* PBP2 in a similar manner as ETX2514, WCK 5153, and ZID. Furthermore, when coupled with β-lactams, nacubactam, like mecillinam and other DOBs (WCK 5153 and ZID), was found to act synergistically as a β-lactam enhancer. This is largely attributed to the ability of these combinations to target numerous PBPs. Nevertheless, nacubactam alone was proven to be effective against gram-negative bacteria such as *E. coli*, *Klebsiella spp*., *Enterobacter spp.*, and *Citrobacter spp.* When coupled with β-lactams, its effectiveness is extended to most *Enterobacteriaceae* isolates generating ESBLs, AmpCs, KPCs, MBLs, OXA-48, as well as ESBL- and AmpC-producing *Enterobacteriaceae* that lack porins and strains of *P. aeruginosa* with reduced AmpC, PER, or VEB ESBLs [39]. Of interest, there is growing evidence that meropenem/nacubactam reduces bacterial burden in the lungs of neutropenic mice infected with AmpC and KPC-positive *P. aeruginosa* [40].

ETX1317

ETX1217 is a DBO serine β-lactam inhibitor. Despite lacking a β-lactam core, EXTA1217 was found to acylate much serine β-lactamases, thus deactivating them [41]. Therefore, it is classified as an antagonist of class A, C, and D serine-lactamases [42]. A combination of its oral prodrug (ETX0282) and cefpodoxime proxetil (an oral prodrug of a third-generation cephalosporin) was also found to improve the efficacy of several β-lactams against a variety of MDR *Enterobacteria,* including CREs [41].

In vitro, ETX1317 preserves cefpodoxime's antibacterial activity against organisms immune to fluoroquinolones, cephalosporins, and carbapenems, including *Enterobacterales* [42]. Moreover, it was shown to be effective against drug-resistant isolates in preclinical infection models [41]. Therefore, ETX1317 has the potential to benefit both patients and the health system by decreasing the risk of nosocomial infections and minimizing the healthcare expenses associated with hospitalizations [42].

WCK

WCK 4234 is a new DBO with a nitrile side chain at the C-2 position; it has strong inhibitory action against carbapenemases of classes A and D, as well as class C enzymes [43]. In a study by Iregui et al, WCK 4234 increased carbapenem activity against isolates generating KPC, AmpC, and OXA-lactamases [44].

The combination of meropenem and WCK 4234 was effective in mouse models infected with carbapenem-hydrolyzing OXA-possessing *A. baumannii* [43]. Moreover, meropenem and WCK 4234 were shown to be highly effective against *Enterobacteriaceae*, including KPC-producing *K. pneumoniae* isolates [43, 44]. WCK 4234 also enhanced carbapenem activity against MDR *A. baumannii* expressing OXA-23, OXA-24/40, and OXA-58 carbapenemases and hyper-producing the chromosomal OXA-51 carbapenemases [44, 45]. Moreover, the combination of meropenem and WCK 4234 was effective *in vivo* against *A. baumannii* isolates generating OXA-23 or OXA-26 [44]. *In vivo* studies also showed an MIC for meropenem with WCK 4234 of 8 µg/mL against OXA-23 and OXA-26, indicating an eight-fold reduction when compared to meropenem alone (MIC: 64 µg/mL). The WCK 4234/meropenem combination was also found to be effective in the treatment of MDR *A. baumannii*-induced mouse peritonitis and neutropenic lung infection [45].

GT-055(GT-1/GT-055)

Many *E. coli*, *K. pneumoniae*, and *Acinetobacter spp*. MDR strains were shown to be susceptible to GT-1, a new siderophore cephalosporin [46, 47]. Some strains, however, have shown extremely high GT-1 MICs. Except for YMC2011/11/B144, non-susceptibility to GT-1 was frequently associated with the presence of AmpC-lactamase DHA-1, for which GT-1 MICs ranged from 4 to 64 g/mL. The high potency of the synergistic combination of GT-055 and GT-1 in the presence of -lactamases in CTX-M- (CTX-M-14, CTX-M-15, CTX-M-27, CTX-M-55, CTX-M-65), SHV- (SHV-12, SHV-83), DHA-1-,

and SIM-1-producing strains is another feature of this novel antibiotic [47]. Additionally, GT-055 has inherent action against several *Enterobacteriaceae* isolates, which likely contributes to its effectiveness against *E. coli* and *K. pneumoniae* isolates when combined with GT-1 [47].

Boronic acid derived inhibitors

Taniborbactam (FEP/taniborbactam)

VNRX-5133 (taniborbactam), a bicyclic boronate, is a novel BLI under clinical testing. VNRX-5133 inhibits SBLs and some MBLs, such as NDM-1 and VIM-1/2 [48, 49]. However, the activity of VNRX-5133 against IMP-1 and tested B2/B3 MBLs was reduced or non-existent. Crystallographic findings show that bicyclic boronates have the capacity to block SBLs and MBLs by adding a tetrahedral (sp3) boron species [50]. Moreover, a study by Wang et al has shown that taniborbactam enhanced FEP activity in the same way that avibactam promoted ceftazidime efficiency against 66 KPC-2 producers, 30 carbapenem-non-susceptible *Enterobacteriaceae*, and 28 meropenem-susceptible *P. aeruginosa*. Of interest, FEP/taniborbactam was more effective than ceftazidime/avibactam against 56 ESBL-producing, 61 AmpC-producing, 32 ESBL and AmpC co-producing *Enterobacteriaceae*, 87 NDM-producing, and 21 MBL-producing *Enterobacteriaceae* predicted by phenotypic mCIM and eCIM, 82 *Enterobacteriaceae* that were sensitive to all tested β-lactams as well as 22 carbapenem-non-susceptible *P. aeruginosa* [49]. Taniborbactam concentrations needed to restore the activity of FEP were 4 mg/L for *Enterobacterales*, 32 mg/L for *P. aeruginosa*, 4 mg/L for *E. coli*, and 16 mg/L for *K. pneumoniae* [51].

A 4 mg/L taniborbactam was required to achieve > 90% *Enterobacterales* isolate susceptibility to FEP. However, taniborbactam failed to reach similar susceptibility against *Pseudomonas* since seven isolates showed resistance even at a concentration of 32 mg/L [51].

Resistant *Enterobacterales* and *P. aeruginosa* species were found to have increased expression of VIM and AmpC genes [52].

Human studies done to assess pharmacokinetics of taniborbactam showed no added adverse effects when compared to placebo when treated with doses of up 1,500 mg for a single dose, and a total of 2,250 mg/day for 10 days. Increased doses of taniborbactam were not associated with increased adverse effects. No adverse effects on heart cardio-dynamics were noted (including QTcF changes, heart rate and T-wave morphology) [53].

VNRX-5236 (ceftibuten (CTB)/VNRX-7145)

VNRX-5236 is a very powerful inhibitor of all four Ambler types of β-lactamase enzymes that is also extremely efficient in a wide spectrum of gram-negative bacteria using a cyclic boronate template. The N-(2-aminoethyl)cyclohexylamine side chain of 20 (VNRX-5133) was shown to be important for broad-spectrum β-lactamase inhibition as well as improved gram-negative outer membrane permeability and periplasmic accumulation [54].

The combination of CTB/VNRX-7154 showed similar potency level to ceftazidime-avibactam (IV) and meropenem-avibactam against *Enterobacterales*-producing SBLs, in *in vitro* studies. This combination offers an alternative path to treatment since it is readily orally available [55].

CTB/VNRX-5236 has demonstrated potent antibacterial activity against beta-lactamases-producing *Enterobacterales* including KPC, CTX-M-15, P99AmpC, CMY-2, OXA-1, and OXA-48 [56].

In vivo, efficacy of CTB/VNRX-5236 was assessed in mice injected with *K. pneumoniae* strain resistant to CTB. Results showed that CTB/VNRX-5326 delivered orally or subcutaneously was able to rescue CTB with median effective dose (ED50) values of 12.9 and 13.5 mg/kg, respectively [56].

QPX7728 (meropenem/QPX7728)

QPX7728 is a BLI that was developed as part of the boronic acid pharmacophore program. It was the first medication from this class to be approved by the FDA and the European Medicines Agency (EMA). When compared to the newly licensed drugs such as avibactam, vaborbactam and relebactam, QPX7728 has a wider beta-lactamase inhibitory spectrum. Drugs from this class are strong inhibitors of *Enterobacteriaceae* class A carbapenemases, such as KPC, class C beta-lactamases and, some class D enzymes [57, 58]. Of note, this class was the only class among the newly licensed drugs to show significant activity against *Baumannii* class D carbapenems such as OXA-23, OXA 24/40 and OXA 58 as well as the B1 subclass such as NDM, VIM, and IMP [58, 59]. Other drugs such as durlobactam have shown significant activity against the *Acinetobacter* OXA enzymes but were not capable of inhibiting class B MBLs. Furthermore, taniborbactam inhibits certain MBLs; however, it has no effect on *Acinetobacter*'s OXA carbapenemases. Therefore, QPX7728 is a promising candidate for future research because of its ultrabroad-spectrum beta-lactamase inhibitory profile. In summary, antibiotics with QPX7728 are effective against bacteria producing class A ESBLs (CTX-M, SHV, TEM, VEB, PER) and carbapenemases (KPC, SME, NMC-A, BKC-1). QPX7728 also inhibits both plasmid (CMY, FOX, MIR, DHA) and chromosomally encoded (P99, PDC, ADC) class C beta-lactamases and class D enzymes, including carbapenemases such as OXA-48 from *Enterobacteriaceae* and OXA enzymes from *A. baumannii* (OXA-23/24/72/58). Many class B MBLs (NDM, VIM, CcrA, IMP, and GIM, but not SPM or L1) are likewise inhibited by QPX7728 [58].

β-lactam derived inhibitors, penicillin sulfones

Enmetazobactam (AAI101) (FEP/enmetazobactam)

AAI101, a new drug from the penicillanic acid sulfone family, is an ESBL inhibitor in phase I clinical studies [60]. Its structure is like that of tazobactam with one significant variation; AAI101 has a strategically positioned methyl group, which provides the inhibitor with a net neutral charge allowing it to

Table 2. Carbapenem-Resistant Pathogens and Their Therapies

New beta-lactam/beta-lactamase inhibitor	Main bacterial targets					
	Carbapenem-resistant *A. baumannii*		Carbapenem-resistant *P. aeruginosa*		Carbapenem-resistant *Enterobacteriaceae*	
	SBLs	MBLs	SBLs	MBLs	SBLs	MBLs
Diazabicyclooctane derived inhibitors						
Ceftazidime/avibactam			Y		Y	
Imipenem/relebactam						
Aztreonam/avibactam					Y	Y
Cefepime/zidebactam			Y	Y	Y	Y
Sulbactam/durlobactam	Y					
Meropenem (or cefepime, or aztreonem)/nacubactam			Y		Y	Y
Cefpodoxime/ETX1317					Y	Y
Meropenem/WCK 4234	Y	N			Y	N
GT-1/GT-055	Y	Y			Y	Y
Boronic acid derivative inhibitors						
Meropenem/vaborbactam						
Cefepime (or meropenem)/taniborbactam			Y	Y	Y	Y
VNRX-7145/ceftibuten					Y	
Meropenem/QPX7728	Y	Y	Y	Y	Y	Y
β-lactam derived inhibitors						
Cefepime/enmetazobactam					Y	
Imipenem/LN-1-255	Y				Y	

SBLs: serine β-lactamases; MBLs: metallo-β-lactamase; Y: yes; N: no.

penetrate bacterial cells more effectively [61]. AAI101 has an inhibitory action against class A lactamases, including ESBLs, carbapenemases, and clavulanic acid-resistant lactamases [61]. Moreover, its addition to FEP has shown to regain its efficacy against an immune population of *E. coli* and *K. pneumoniae* [62]. This provides a possible carbapenem-free treatment regimen for infections caused by *Enterobacteriaceae* ESBLs [61]. In summary, the combination of FEP/emetazobactam provides a novel therapy option for challenging gram-negative bacteria during an age of high bacterial resistance and limited therapeutic alternatives [62].

LN-1-255

Buynak's penicillin-based sulfone 1 (LN-1-255) has shown significantly more effectiveness than tazobactam and avibactam against relevant CHDLs in *A. baumannii* both plasmid-encoded OXA-23, OXA-24/40, OXA-58, OXA-143, and OXA-235, and chromosomally encoded OXA-51 as well as OXA-48 produced by *K. pneumoniae*. LN-1-255 increases imipenem's *in vitro* activity by 32- to 128-fold and has high therapeutic effectiveness *in vivo* [63]. Its efficacy stems from its ability to create an indolizine adduct that is resistant to hydrolysis which is generated by nucleophilic attack of the pyridine nitrogen atom on the conjugated initial imine adduct after the dioxothiazolidine ring is opened [63].

Table 2 summarizes the therapies aimed at treating infections caused by carbapenem-resistant pathogens.

Figure 1 shows the chemical structures of the various carbapenemase inhibitors (biomodel.uah.es).

Conclusion

Carbapenems, the most effective β-lactam antibiotics, display a broad spectrum of antibacterial activity. A carbapenem together with a β-lactam ring provides a great stability against hydrolysis by β-lactamases. These agents are mostly used as treatment against severe infections. Mediated by carbapenemases, carbapenem resistance drastically limits treatment options for gram-negative bacteria resistant to most β-lactams and/or all carbapenems. These pathogens often infer resistance to other antibiotics such as aminoglycosides and quinolones, which is problematic. Colistin and fosfomycin are usually the two antibiotics utilized in such scenarios, but their use has been limited due to their toxicity profile. Tigecycline has been utilized as a rescue therapy, but resistance is rapidly increasing as well [64, 65].

Finally, adequate antimicrobial stewardship programs and carbapenems-sparing strategies must be implemented in clini-

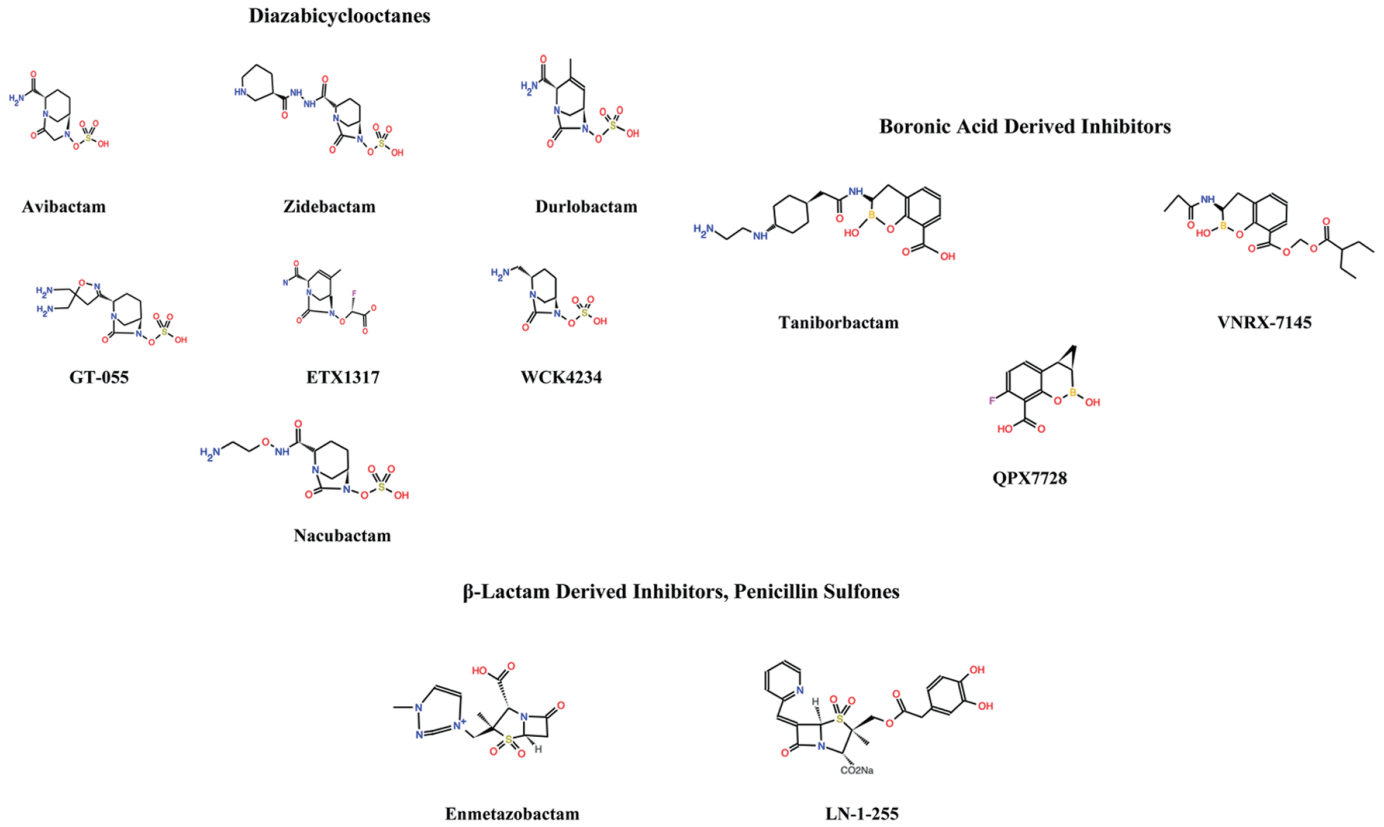

Figure 1. The chemical structures of the various carbapenemase inhibitors (biomodel.uah.es).

cal settings to preserve the effectiveness of these antibiotics [66]. Appropriate infection control and prevention measures along with the rationale use of carbapenems could offset carbapenem resistance and provide us with time to develop new inhibitory molecules.

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None to declare.

Conflict of Interest

None to declare.

Author Contributions

MBZ drafted the manuscript. NZ conceived the idea for the paper. All authors contributed to the discussion section. All authors have read and approved the final manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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