New Carbapenemase Inhibitors

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Contributor: Alejandro Beceiro, Juan Carlos Vázquez-Ucha

Carbapenem resistance is a major global health problem that seriously compromises the treatment of infections caused by nosocomial pathogens. Production of carbapenemases (carbapenem-hydrolyzing enzymes) is the most important mechanism of carbapenem resistance. A new generation of promising carbapenemase inhibitors, together with the recently approved avibactam, relebactam and vaborbactam are being tested in clinical and pre-clinical trials.This review summarizes the main, most promising carbapenemase inhibitors synthesized to date.

Keywords: Carbapenemase ; inhibitor ; antibiotic resistance ; carbapenem resistance ; metallo-β-lactamases ; serine-β-lactamases

1. Introduction

β-lactams are the most diverse and widely used group of antibiotics in clinical practice. The mechanism of action of β-lactams is based on binding and blocking the penicillin binding proteins (PBPs), which are involved in the final steps of cell wall synthesis [1][2][3]. Carbapenems differ structurally from penicillins, cephalosporins and monobactams and have a wider spectrum of action and stability against β-lactamase enzymes. The longest established carbapenems are imipenem, meropenem and ertapenem, while more recently developed examples include doripenem, biapenem, panipenem, razupenem and tomopenem [4]. **The use of carbapenems in clinical settings increased in the 2000s due to the emergence and spread of extended spectrum β-lactamases (ESBLs). However, the massive use/overuse of these agents led to the emergence of resistance, as had previously occurred with other groups of antibiotics [5].**

In 2017 the World Health Organization (WHO) published a list of priority pathogens for which new treatments are required. The pathogens included in the highest category of urgency are carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa* and carbapenem- and third generation cephalosporin-resistant *Enterobacterales* [6]. This situation highlights the importance of β-lactam antibiotics, especially carbapenems, in the treatment of infections caused by nosocomial pathogens. **Production of carbapenemases (carbapenem-hydrolyzing enzymes) is the most important mechanism of carbapenem resistance [7], with examples in the four classes of β-lactamases, categorised according to the Ambler classification [8][9].** Among the carbapenemases identified, the following are the most important: **(i) class A carbapenemases, especially those coded in plasmids, such as KPC and GES.** The KPC group is the most widely distributed worldwide and the constituents are predominantly found in *Klebsiella pneumoniae* [8][9][10]**; (ii) class B carbapenemases (also known as metallo-β-lactamases, MBLs)** are usually found in pathogens such as *P. aeruginosa*, *A. baumannii* and *Enterobacterales*,and their prevalence has increased in recent years [8][11]. **The most common groups of MBLs are VIM, IMP and NDM [11]; (iii) class C carbapenemases are not numerous and have been identified recently.** Although, class C β-lactamases production does not offer carbapenem resistance, exceptionally five enzymes in this group are capable of hydrolyzing carbapenems (ACT-1, DHA-1, CMY-2, CMY-10 and ADC-68) [9], and **(iv) class D carbapenemases (also known as OXAs);** although discovered many years ago, the rapid spread of carbapenem hydrolyzing class D β-lactamase (CHDLs) is recent [12][13]. **OXA-48-like is widely disseminated in *Enterobacterales*, while the groups OXA-23-like, OXA-24/40-like, OXA-58-like, OXA-143-like and OXA-235-like are mainly responsible for resistance to carbapenems in *A. baumannii*** [13][14](Table 1).

Table 1. *Most clinically significant carbapenemases.*

Mechanism of Action	Class	Carbapenemase	More Common Enzymes

		KPC	KPC-2	KPC-3		
	A					
Serine-β-lactamases		GES	GES-2	GES-5	GES-6	
	D	OXA	OXA-23	OXA-24/40	OXA-58	OXA-48
		IMP	IMP-1	IMP-6	IMP-7	
Metallo-β-lactamases	B	VIM	VIM-1	VIM-2		
		NDM	NDM-1	NDM-4	NDM-5	

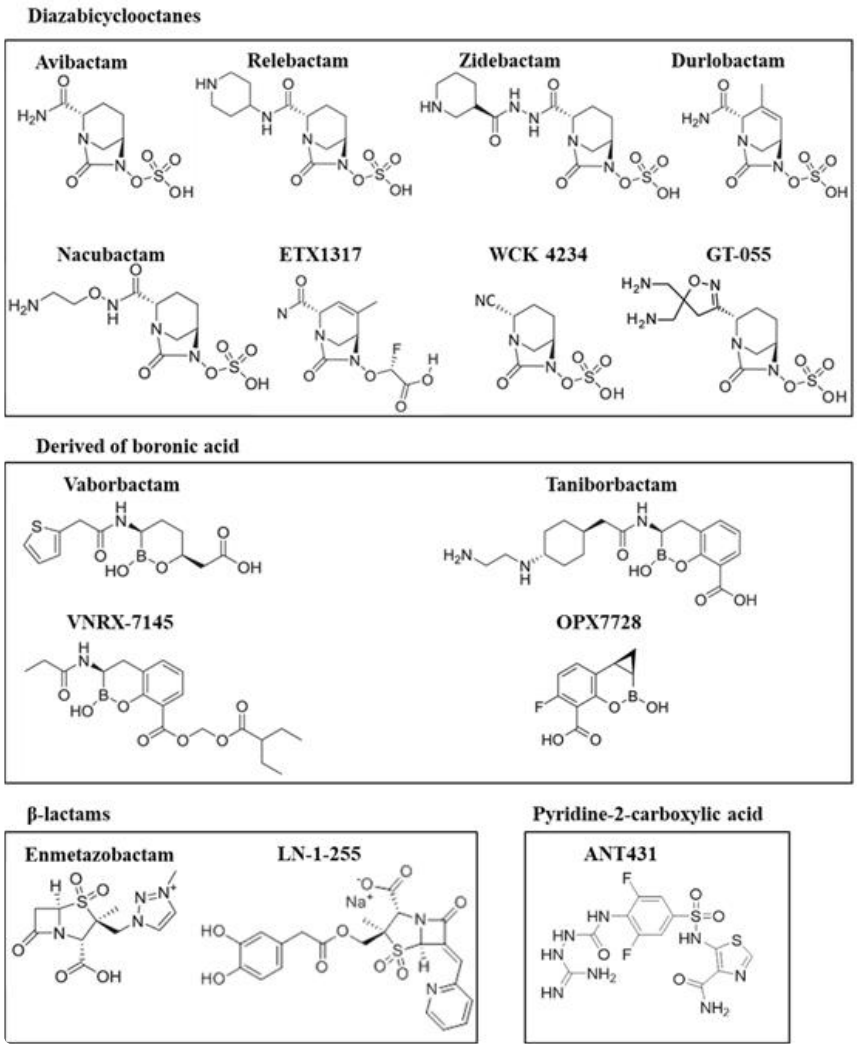
Although carbapenemase activity is the main cause of carbapenem resistance, other elements are also involved. Porins have been shown to be associated with the development of resistance to carbapenems in synergy with hyperexpression of AmpC and/or ESBLs [15][16][17]. Similarly, efflux pumps [15] and mutations in PBPs (PBP2 orPBP3) have also been implicated in resistance to carbapenems [18][19].

One of the main strategies used to restore the effectiveness of β-lactam antibiotics is to use β-lactamase inhibitors (molecules that are able to bind to the active site of the enzyme) to prevent the antibiotic being hydrolysed by the enzyme [20][21]. The first β-lactamase inhibitor discovered (in 1972) was **clavulanic acid**, followed by **sulbactam** (in 1978) and **tazobactam** (in 1984). These are the so-called classical β-lactamase inhibitors [20][21][22][23]. In recent years new groups of inhibitors have appeared, and some have already been approved by regulatory agencies and are now available in the clinical setting, thus extending and recovering the antimicrobial activity of some β-lactam antibiotics. The main new groups are diazobicyclooctanes (DBOs) (avibactam and relebactam have been approved by the FDA) and boronic acid derivatives (vaborbactam is currently the only inhibitor approved) [24][25] (Figure 1).

2. New Carbapenemase Inhibitors in Development

This review focuses on the recent studies of new carbapenemase inhibitors at preclinical or clinical stages of development (Figure 1, Tables 2 and 3).

Figure 1. *Structures of the recent carbapenemase inhibitors*



2.1. Diazabicyclooctane Derived Inhibitors

In the last few years the chemical scaffolds of the diazabicyclooctane class of β-lactamase inhibitors such as avibactam and relebactam have been modified to enhance the activity of these compounds [26]. Although DBOs do not exert inhibitory activity against class B β-lactamases, they can be combined with a monobactam, such as aztreonam, as these are stable to MBLs and need only to be protected from ESBL or AmpC enzymes [27]. **Indeed, some second generation developmental DBO inhibitors, such as durlobactam, zidebactam and nacubactam are "dual action inhibitors" and have high affinity for the PBP2 of many Gram-negative species, thus exerting an antimicrobial effect.** These DBOs thus exhibit "β-lactam enhancer" activity, potentiating partner β-lactams, and the new combination displays activity against carbapenemase-producing pathogens, including MBLs.

Table 2. *Inhibition of major carbapenemases by new carbapenemase inhibitors*

Table 3. *Potential therapies aimed at treating infections caused by priority carbapenem-resistant pathogens for which new drugs are urgently needed*

New B-lactam/B-lactamase Inhibitor	Main Bacterial Targets		
	Carbapenem Resistant *A. Baumanii*	Carbapenem Resistant	Carbapenem Resistant

2.1.1 Avibactam (aztreonam/avibactam)

Avibactam is capable of inhibiting ESBLs, AmpCs and the carbapenemases produced by *Enterobacterales*, such as KPC, GES, IMI, SME or OXA-48, but not MBLs [28][29][30]. A new combination is now being developed, aimed at MBLs, selecting the only monobactam approved to date, aztreonam.

2.1.2 Zidebactam (cefepime/zidebactam)

Zidebactam (formerly WCK 5107, Wockhardt, India), as well as other new generation DBOs such as nacubactam and durlobactam**, inhibit PBPs, β-lactamases and display synergy with β-lactams** [31]. **Zidebactam is a new bicyclo-acyl hydrazide which displays activity against of Gram-negative bacteria such as *Enterobacterales*, *P. aeruginosa* and *A. baumannii*, including strains producing different class A, C and D β-lactamases, such as CTX-**

M-like, AmpC or OXA-48 [32][33][34]. Although zidebactam is derived from a DBO scaffold, it has been designed with the objective of augmenting PBP2 binding rather than increasing the β-lactamase-inhibitory activity of the compound, thus enhancing β-lactam activity; however, it also displays moderate activity as a β-lactam inhibitor [31].

2.1.3 Durlobactam (sulbactam/durlobactam)

Durlobactam (previously ETX2514, Entasis Therapeutics, USA), a diazabicyclooctenone β-lactamase inhibitor of class A, C and D β-lactamases [35]**, displays some intrinsic antimicrobial activity against some *Enterobacterales*** [36]. It is being tested in combination with sulbactam, another β-lactamase inhibitor also able to inhibit class A and C β-lactamases. Sulbactam, commercially available in combination with ampicillin, displays antimicrobial activity against *Acinetobacter* spp. [37].

2.1.4 Nacubactam (meropenem/nacubactam)

Similarly to zidebactam, nacubactam (formerly RG6080/OP0595, Meiji Seika Pharma, Japan; Fedora Pharmaceuticals, Canada and Roche, Switzerland) **is a next generation DBO which also acts in different ways, by inhibiting class A and C β-lactamases, and as an antibiotic by inhibiting PBP2, thus enhancing the activity of the β-lactam partner** [38]. It has a high affinity for class A carbapenemases such as KPC, but not for class D carbapenemases such as OXA-23 and OXA-24/40, displaying highest activity against class A β-lactamases such as TEM and CTX-M. To our knowledge, data on the inhibitory activity of nacubactam against OXA-48 is lacking. In combination with meropenem, nacubactam shows good synergy against carbapenem-resistant KPC-producing *Enterobacterales* [38][39].

2.1.5 ETX1317 (Cefpodoxime/ETX1317)

ETX1317 (Entasis Therapeutics) is a new DBO that displays broad spectrum activity against class A and C serine-β-lactamases (SBLs). The ester prodrug of ETX1317 is the compound ETX0282, used in combination with cefpodoxime (an oral third-generation cephalosporin), and it is currently in development for treatment of multidrug-resistant and carbapenem-resistant *Enterobacterales* infections. This combination exhibits good antimicrobial activity in *Enterobacterales* isolates with multiple β-lactamases, including KPC-producing types [40]. As the high polarity and low pK_a of DBOs are well-suited to intravenous administration, but lead to low oral bioavailability, the main advantage of ETX0282 is the oral dosing availability [41].

2.1.6 WCK 4234 (meropenem/WCK 4234)

WCK 4234 (Wockhardt) displays potent inhibitory activity against class A and D carbapenemases and class C enzymes. It does not show antibacterial activity, unlike other DBOs considered in this review. It can enhance the activity of carbapenems against *Enterobacterales* producing OXA-48 or KPC carbapenemases, but not against MBLs-producing *Enterobacterales*. Importantly, the meropenem-WCK 4234 combination displays activity against OXA carbapenemases produced by *A. baumannii*, such as OXA-23, OXA-24/40 and hyperproduced OXA-51. WCK4234 did not display any activity against a collection of carbapenem-resistant isolates of *P. aeruginosa* [31][42][43].

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

The diazabicyclooctane inhibitor GT-055 (also referred to as LCB18-055, LegoChem Biosciences) exhibits intrinsic activity against many *Enterobacterales* isolates, which bind tightly to PBP2. It is being tested in combination with GT-1 (also known as LCB10-0200), a novel siderophore-dihydroxypyridone and a modified aminothiazolylglycyl cephalosporin, which exploits bacterial iron-uptake systems to enhance entry into Gram-negative pathogens using a “Trojan-horse” strategy. GT-055 is able to enhance the in vitro activity of GT-1 against many GT-1–resistant strains [42].

2.2. Boronic Acid Derived Inhibitors

2.2.1. Taniborbactam (Cefepime/Taniborbactam)

Taniborbactam (formerly VNRX-5133, Everest Medicines, New York, USA) **is a cyclic boronate with broad spectrum β-lactamase inhibitory activity against KPC, OXA-48 and MBLs (such as VIM and NDM, but not IMP)** [44][45]**.** It was probably the first inhibitor showing direct inhibitory activity against Ambler class A, B, C, and D enzymes [46]. Taniborbactam uses distinct mechanisms to inhibit both SBLs and MBLs. It inhibits SBLs with slow dissociation, while in MBLs, it behaves as a reversible competitive inhibitor, with low inhibitor constant (*K*i) values and rapid dissociation [46].

Taniborbactam is being developed for use in combination with cefepime and meropenem to treat complicated infections caused by MDR pathogens such as carbapenem-resistant *Enterobacterales* and carbapenem-resistant *P. aeruginosa*, including strains expressing serine carbapenemases and metallo-β-lactamases. Several phase I clinical trials have been undertaken to evaluate its PK/PD and safety. A phase III clinical trial is being conducted with cefepime/taniborbactam to evaluate the safety and efficacy of this combination against complicated urinary tract infections, including infections caused by MBL-producing strains.

2.2.2. VNRX-5236 (Ceftibuten/VNRX-7145)

VNRX-7145 (VenatoRx Pharmaceuticals, Malvern, PA, USA) **is a novel cyclic boronate β-lactamase inhibitor with good oral bioavailability.** In vivo, VNRX-7145 undergoes biotransformation to the active VNRX-5236, which **covalently and reversibly binds the active serine site of Ambler class A and D β-lactamases, including those that hydrolyze carbapenems, such as KPC and OXA-48.** VNRX-7145 is being developed in combination with ceftibuten, because of the good oral bioavailability of the cephalosporin [47][48].

2.2.3. QPX7728 (Meropenem/QPX7728)

QPX7728 (QPEX Biopharma) is an ultra-broad-spectrum cyclic boronic acid β-lactamase inhibitor with activity against both SBLs and MBLs [30]. In comparison with other β-lactamase inhibitor combinations (such as meropenem-vaborbactam, ceftazidime-avibactam and imipenem-relebactam), meropenem plus QPX7728 was found to be the most potent β-lactam-β-lactamase inhibitor combination tested against all groups of carbapenem resistant *Enterobacterales* with multiple resistance mechanisms, including KPC and MBLs carbapenemases [49]. Similarly, the meropenem/QPX7728 combination showed antimicrobial activity against a collection of carbapenem-resistant *A. baumannii* isolates producing CHDLs, NDM and KPC carbapenemases [49], and it was also being active against KPC-producing *P. aeruginosa* strains [50].

2.3. β-Lactam-Derived Inhibitors. Penicillin Sulfones

Penicillin-based sulfones, such as clavulanic acid, sulbactam and tazobactam, were the first inhibitors to be discovered. Unfortunately, none of these three compounds can inhibit carbapenemases. In recent years, within the group of penicillin sulfones, several molecules have emerged with higher or broader activity than the classical inhibitors, but only enmetazobactam and LN-1-255 have exhibited a relevant activity against carbapenemases.

2.3.1 Enmetazobactam (cefepime/enmetazobactam)

Enmetazobactam (formerly AAI101, Allecra Therapeutics), a novel penicillanic acid sulfone ESBLs inhibitor, also displays slight activity against some class C and D carbapenemases and also against some class A carbapenemases from *Enterobacterales* strains [51][52][53][54]. Enmetazobactam differs from tazobactam in the presence of a methyl group in the triazole moiety, which causes the compound to have a net neutral charge that enhances its activity [55]. The cefepime/enmetazobactam combination produced better results against MDR ESBLs-producing *Enterobacterales* strains than recently approved treatments such as ceftazidime/avibactam, ceftolozane/tazobactam and imipenem/relebactam [56]. Enmetazobactam is a good inhibitor of all class A β-lactamases, including the carbapenemases KPC-2 and KPC-3, with IC_{50} values in the nanomolar range, and it presents higher levels of inhibition than tazobactam and similar levels to those displayed by avibactam. However, the levels of inhibition observed against class C and D are significantly lower for enmetazobactam than for the other two compounds [55].

2.3.2 LN-1-255 (imipenem or meropenem/LN-1-255)

A group of penicillin sulfones with activity against class A, C and D β-lactamases have been synthesized by John D. Buynak and collaborators [57][58][59]. Among these, the LN-1-255 molecule is the most widely studied due to its ability to inhibit CHDLs, yielding good results in combination with carbapenems. **LN-1-255 displayed a significant ability to inhibit the carbapenemases typically produced by *A. baumannii* (OXA-23, OXA-24/40, OXA-51, OXA-58, OXA-143 and OXA-235) and the OXA-48 carbapenemase produced by *Enterobacterales*** [60][61][62][63]. LN-1-255 possesses a catechol group that is responsible for its effectiveness due to its ability to enhance internalization of the compound in the bacteria through iron uptake systems [25]. In vivo models of murine pneumonia showed a reduction in the bacterial load in mice treated with imipenem/LN-1-255, of between 1.7-4.5 logs, in lungs infected with CHDL-producing *A. baumannii* strains [64]. In 2020, Rodriguez and collaborators designed a series of six 6-arylmethylidene penicillin-based sulfones, derived from LN-1-255, through modifications in the pyridine ring. Some of these compounds improved the efficiency of action against CHDLs [65].

2.4. Other Promising MBL Inhibitors

MBLs are Zn(II)-dependent enzymes with the ability to hydrolyze β-lactam antibiotics. No clinically useful inhibitors of these enzymes have yet been approved. **In the last few years, new structures focused specifically on inhibiting MBLs have been developed, with the compound ANT2681 (Antabio) probably representing one of the most important examples**. This novel thiazole-carboxylate inhibitor, optimized from ANT431, is the result of a medicinal chemistry hit-to-lead program starting with pyridine-2-carboxylic acid, and it is a preclinical candidate with potential for clinical development as a specific inhibitor of MBLs [66]. **ANT2681 inhibits the activity of MBLs through interaction with the dinuclear zinc ion cluster present in the active site of these enzymes [67]. The inhibitor displays the highest affinity for NDM-1, lower affinity for VIM-1 and very poor affinity for IMP-1.** This inhibitor has shown efficacy in a mouse thigh model with an NDM-1-producing clinical isolate of *K. pneumoniae*. Although meropenem was ineffective at reducing tissue burden, its coadministration with ANT2681 yielded a statistically significant (1.8 log) reduction in colony forming units. Thus, ANT2681 is undergoing preclinical development with the intention of combining it with meropenem as a new treatment for serious infections caused by MBL-producing CRE.

In addition to the above-mentioned β-lactam-derived inhibitors, other compounds with a β-lactam core are capable of inhibiting carbapenemases, but which are at early stages of development. Thus, within the group of penicillin sulfones, C-6 substitutions affect the specificity of inhibition, displaying good activity against some class B β-lactamase [68]. In the group of penems, fusion of different bicyclic and tricyclic heterocycles with 6-methylidine penem yielded activity against class B carbapenemases [69][70][71]. CcrA and IMP-1, among others, were inhibited by J-110,441, a 1β-methylcarbapenem with a benzothenyl moiety at the C-2 position [72]. J-111,225, another new 1β-methylcarbapenem (with a trans-3,5 disubstituted pyrrolidinylthio moiety in C-2), inhibited IMP-1 [73] and showed bactericidal activity per se against *S. aureus* and *P. aeruginosa* [74]. Reverse hydroxamates (cephalosporins derived molecules) have exhibited activity against the MBL GIM-1 [75], or bisthiazolidines, also able to inhibit MBL enzymes [76].

3. Major Challenges in the Development of New Carbapenemase Inhibitors

As discussed above, a new generation of carbapenemase inhibitors is being developed. **Development of inhibitors of MBL type and *A. baumannii* CHDL enzymes is perhaps the most difficult challenge**. One of the main difficulties in designing inhibitors of class B β-lactamases is the wide genetic diversity among these enzymes. Thus, e.g. taniborbactam can inhibit NDM and VIM but not IMP enzymes. On the other hand, small molecules able to bind and chelate zinc ions have been reported to inhibit MBLs; however, they also inhibit human metalloenzymes and they may therefore be toxic to living tissues. Preclinical assays are also complicated to perform, due to the lack of zinc needed for appropriate behaviour of the MBLs at the infection sites [11][77]. In vitro conditions used for determining antibiotic susceptibility are very different from those that actually occur during infection [78]. It is therefore challenging to design and evaluate specific inhibitors for MBLs, and further research is necessary.

CHDLs, especially those produced by *A. baumannii*, are resistant to the action of most classical inhibitors [13]. The moderate capacity of CHDLs to hydrolyse carbapenems, combined with low permeability of *A. baumannii*, generates a high level of resistance to these antibiotics, which are considered the first choice for treating *A. baumannii*. **There is an urgent need to develop new compounds capable of restoring the susceptibility to carbapenems in CHDL-producing strains of *A. baumannii*.** So far, two compounds have exhibited useful activity against these enzymes: durlobactam [79] and LN-1-255 [80]. In both cases the key factor was the development of highly permeable compounds. Another important challenge is the coexistence of different β-lactams in the same pathogen. Thus, it is common to find numerous β-lactamases in *Enterobacterales*, for example strains co-producing bla_{NDM-1}, bla_{OXA-48}, $bla_{CTX-M-15}$, bla_{TEM-1} and $bla_{SHV-182}$ [81], often expressing two or more different carbapenemases or even MBLs.

Future inhibitors must be very potent and able to inhibit different classes of β-lactamases at the simultaneously, which requires complex structural and biochemical development [82]. Likewise, research must continue in order to develop new compounds that are effective against the main enzymatic resistance mechanism of this multi-drug resistant pathogen.

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