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Beta-Lactamases Inhibitors: A Perspective on the Existing and the Potential Admixtures to Synergize Beta-lactams Versus Resistant Superbugs

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β-lactam antibiotics are considered the safest bactericides, and upon wide clinical use of benzyl penicillin G in 1945, outbreaks of resistance came out. The frequent semi-synthetic strategies revealed β-lactam generations that are of broad-spectrum activity. The new agents as well as their concomitant use with known inhibitors of β-lactamases potentiate their effectiveness versus higher numbers of resistant pathogens. However, the extremely resistant pathogens are still representing a burden. Efforts had been continued to find more inhibitors of β-lactamases to combine with β-lactams to provide good management of infections by extremely resistant microbes. The purpose of this work is to overview the conventional and the recently introduced β-lactamases in clinical applications, as well as some reported effective inhibitors of β-lactamases. The review pinpoints the inhibitors that can be mixed and/or merged with the beta-lactam antibiotics to effectively treat the microbial infections producing resistant-β-lactamases. ClogP for these drugs and candidate inhibitors is introduced as suggestions to open a door for developers to admix derivatives with suitable pharmacokinetics.

Keywords: Antibacterial; β-lactamases inhibitors; Clinical investigations; Multi-resistant strains.

The strategies for the discovery of new â-lactam-antibiotics related to subclasses as penicillins, cephalosporins and monobactams in addition to carbapenems are not enough policies to kill superbugs. Historically, Abraham and Chain [1] noticed manifestation of resistance against penicillin from some bacterial cultures. The resistance involving deactivation by enzymes, mentioned later as β-lactamase.[2,3] Most of the β-lactam-antibiotics are vulnerable to inactivation by β-lactamases. The persistent exposure of some bacterial strains to a multitude of β-lactam-antibiotics has led to overproduction and mutation of β-lactamases. β-Lactamases are produced by many gram-positive and gram-negative strains.[2,4] Many β-lactamases have been reported and two systems were introduced to verify their types. The first one is Ambler system (1980) which utilizes amino acid sequence to define molecular phylogenies and grouping β-lactamases into four broad classes: A, B, C, and D.[4] The second is Karen Bush in 1988. Ambler A, C, and D classes are

serine β-lactamases (SBLs, Figure 1, Equation 1) while class B enzymes are Metallo-β-lactamases (MBLs, Figure 1, Equation 2). The Figure 1 simply configures the generalized fate of penicillin-β-lactamase-mediated hydrolysis to ring-opened penicilloic acid.[1] In continuation of our interest in medicinal chemistry area we report this work since it complies with our efforts in skeletons of specified biological activities and targeting as well as naturally active agents[5-25]. This is an updated review describing most of β-lactamases, along with reports on the ongoing status and information concerning the recent inhibitors to date 2021. In addition, a demonstration, concerning the strategies applied during the process of drug discovery to identify new β-lactamase inhibitors is also introduced.

β-Lactamases Hydrolyzing Effects

As mentioned by WHO in 2019, superbug's infections of the lower respiratory system represented the third top reason of worldwide deaths (https://www.who.int/data/gho/data/themes/ mortality-and-global-health-estimates) and if one adds superbug's infections in other body organs, it will be shifted to the top reason of deaths. In addition, a warning alarm mentions that mortality resulting from infections by resistant microbes will be increased by 2050 and will kill more people than cancer do.[26] There are attempts for production of wide-range-spectrum of β-lactamase inhibitors able to inhibit many β-lactamases, such as cephalosporinases along with serine-based carbapenemase, (Table 1) which severely limit therapeutic options by hydrolyzing β-lactam entity in β-lactam antibiotics. The (Figure 1), simply configures the generalized fate of penicillin-β-lactamase-mediated hydrolysis to ring-opened penicilloic acid. [1,25-28]

Clinically Useful β-Lactamases Inhibitors

To date the clinically used inhibitors of β-lactamases must be newly classified as follows:

i- Beta (β)-lactam β-lactamase inhibitors such as clavulanic acid, sulbactam and tazobactam.

ii- Gamma (ã)-lactam β-lactamase inhibitors such as avibactam and relabactam.

iii- Oxaborinane β-lactamase inhibitors such as vaborbactam.

The combination of β-lactams with β-lactamase inhibitors led to effective therapeutic properties. The known common combination are Amoxicillin combined with Clavulanic acid (Table 2, Compound 1) approved by FDA 1984 (https://www.medicinenet.com/amoxicillinclavulanic acid_tablet_875mg125mg/article.htm), Ticarcillin with Clavulanic acid, approved 1985, Piperacillin combined with Tazobactam (Table 2, Compound 2) approved by 1993, and Ampicillin combined with Sulbactam (Table 2, Compound 3) approved 1997. All of these combinations are introduced and widely used as major drugs for community-acquired contaminations as well as hospital-infection. [4]

Recently, Relebactam (MK 7655, Table 2, Compound 4) is a bicyclic none β-lactam β-lactamase inhibitor, gained FDA approval as part of the combination product Recarbrio[C$] in July 2019. [29-30] It is currently available in a combination product includes Imipenem and Cilastatin to treat complicated urinary tract infections (UTIs), pyelonephritis, and complicated intra-abdominal infections in adults. It is a last-line treatment option.

Avibactam (NLX104) (Table 2, Compound 5) [31-32] is another new none β-lactam β-lactamase inhibitor that is available in combination with Ceftazidime (Avycaz[C$]).[33-34] The FDA approved this combination in 2015 for the treatment of complicated intra-abdominal infections in combination with metronidazole, and the treatment of complicated urinary tract infections caused by resistant-and multi-drug resistant gram-negative bacterial pathogens. Avibactam is a potent and broad-spectrum inhibitor than the previously discussed inhibitors such as the widely prescribed clavulanic acid. It maintains the ability to covalently acylate β-lactamases. [32]

Vaborbactam (Table 2, Compound 6) is a β-lactamase inhibitor; a cyclic boronic acid derivative approved by FDA 2017 as Vabomere[C$] consists of Vaborbactam and Meropenem. Used mainly for complicated urinary tract infections (UTI) by intravenous administration. Vaborbactam is intended for serine beta-lactamases, Ambler class A and C enzymes.[35-39]

β-Lactam Antibiotics and Superbugs Resistance

β-Lactam bearing drugs are among the most used antibiotics. [40-46] Their main mechanism is to target and interrupt biosynthesis of cell wall via irreversible inhibition of trans-peptidases, and what is recognized as penicillin-binding proteins (PBPs). PBPs represent a group of enzymes that

are included in the final steps of peptidoglycan cross-linking of bacterial cell walls. [46-50] Superbugs represent a serious global health threat in this century. [51-52] Existing drugs become less effective against these resistant pathogens even in the presence of therapeutic-dose levels of the drugs because of their production of β-lactamases that irreversibly hydrolyze β-lactam ring. [54-55]

The Resistant Superbugs and β-Lactamases Classes

The resistance to antibiotics by superbugs gained through chromosomal mutation side-by-side with horizontal transfer of resistance genes by bacterial plasmids. The bacterial families bearing resistance are related to: 1- Some Gram-positive bacteria such as *Staphylococcaceae* (*Staphylococcus* aureus). 2- Gram-negative bacteria such as *Enterobacteriaceae* (*Klebsiella pneumonia, Citrobacter, Proteus vulgaris*, *Morganella*, *Salmonella*, *Shigella*, *Escherichia coli*), *Pasteurellaceae* (*Haemophilus influenza)*, *Neisseriaceae (Neisseria gonorrhoeae)*, *Pseudomonadaceae (Pseudomonas aeruginosa*) and 3- Neither *Gram*-positive nor *Gram*-negative; *acid-fast* bacteria such as *Mycobacteriaceae* (*Mycobacterium tuberculosis*).

Because of the variety of β-lactamases discovered the Ambler system is identified as molecular based classes depending on the sequence of amino acid. Classes are declared by letters A, B, C, and D. The second classification system recognized as the Bush that focuses on different aspects of β-lactamases, such as enzyme inhibition profile, hydrolysis rate, and binding affinity categorized as 3 groups based on their substrate and inhibitory profiles. Ambler's system appears to be more widely accepted. [56-64] Ambler and Bush classification systems and the main enzymes involved are outlined in Table 1. [43-66] Enzymes are characterized according to the sequencing of proteins. [62] Ambler's classes A, C, and D utilizes serine-OH group as nucleophile (Figure 1, equation 1) while class B (metallo-β-lactamases) involves divalent zinc as metal ions (Figure 1, equation 2) for substrate hydrolysis. [43,66] Extended-Spectrum β-Lactamases (ESBLs) are rapidly growing group.[65] Examples are class A TEM-type β-lactamases (plasmid-mediated) frequently encountered in *E. coli* and *K. pneumoniae* as well as in some strains of Gram-negative bacteria. [61,66] TEM 1 differs from TEM-2 by single amino acid and from TEM-3 by two amino acids. Other TEM-types differ by 3, 4 or more amino acids different from the parent TEM-1 and to-date over 140 TEM-enzymes were identified.[67-69]

Class A, SHV-1 (sulfhydryl SH) is also a chromosomally encoded-enzyme detected in *K. pneumonia* isolates, and isolated among samples of *Enterobacteria*.[66-71] The gene encoding SHV-1 incorporated is later included within the plasma which facilitated its spread to *Enterobacteria* species.[72] SHV-2 differs from SHV-1 by replacement of glycine by serine at particular position in the active site. [71] SHV-1 β-lactamase has structure resemblance with TEM-1.[62] SHV-5 and SHV-12 are among the common types of ESBLs.[61]

Class A, CTX-M-type β-lactamases are resistant to cephalosporins and originated in *Kluyvera* species. These enzymes acquire gene transfer via plasmid and detected in multiple strains of *Salmonella enteric*, *Typhimurium, E. coli*, and other *Enterobacteriaceae*.[69-73] To date, more than 172 CTX-M protein variants have been reported classed under 6 groups based on their amino acid sequencing. They include CTX-M-1, CTX-M-2, CTXM-8, CTX-M-9, CTX-M-25 and KLUC named after the first group which was detected. [60-62] It has been proven that the part associated with CTX-M β -lactamases is the serine residue at position 237.[70-72]

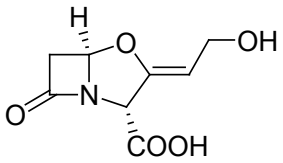
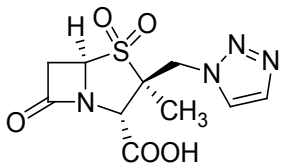
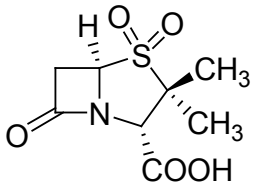
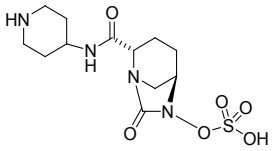
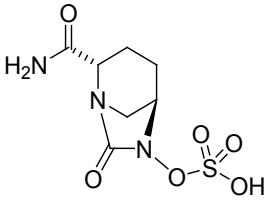
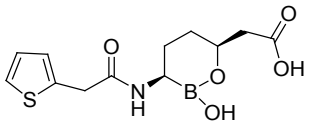
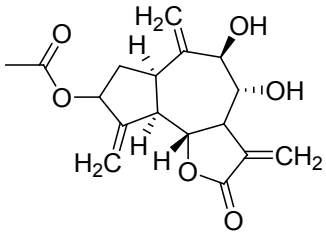
Class A *carbapenemases* enzymes were obtained from *Enterobacteriaceace*, in which they are involved with chromosomal encoding. [72-75] Carbapenemases represent the most diverse of the β-lactamase family that composed from two classes the Class A-serine-type and Class-B metallo-β-lactamases depending on the reactive site of the enzymes. They can be categorized under 3 different Ambler and 2 different Bush-Jacoby groups.[76-78] The enzymes identified in this Class A-type include the chromosomally encoded (NMC-A, SME, and IMI-1) and others are the plasmid-encoded (KPC, IMI-2, some GES variants). [74-76]

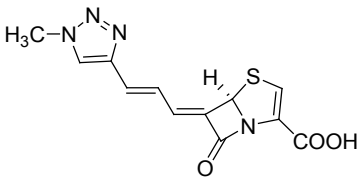
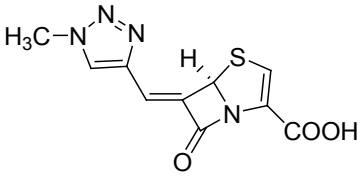
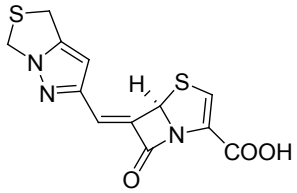
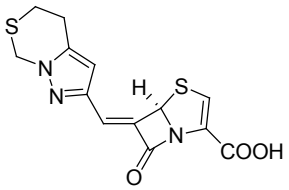
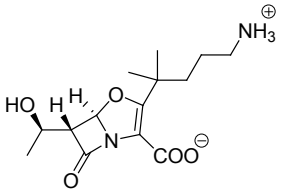
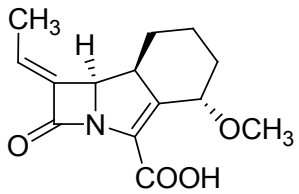
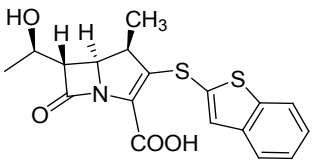
Class C-serine cephalosporinases [77-79] mentioned as AmpC are isolated from *Enterobacteriaceae* and identified as two types the chromosomal (inducible) Amp and plasmid mediated AmpC enzymes. Plasmid mediated type are becoming prevalent and generated through the transfer of chromosomal genes on to plasmids.[79-81]

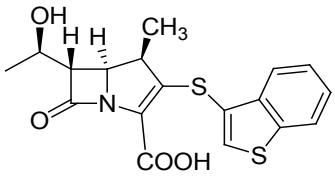
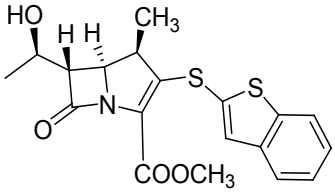
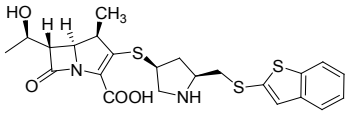
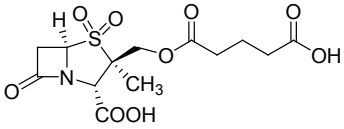
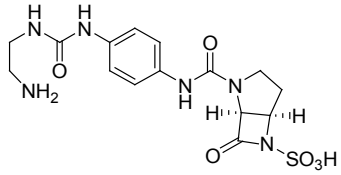
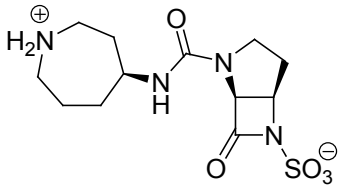
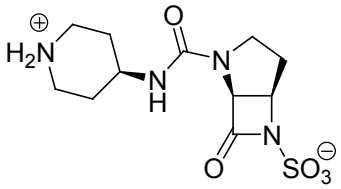
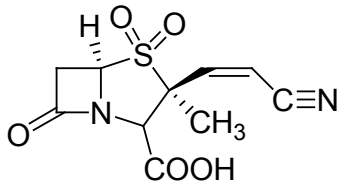
Table 1. Classification of â-lactamases, substrates, sensitivity to common inhibitors and examples. Ambler and Bush *et.al* systems [58-61]

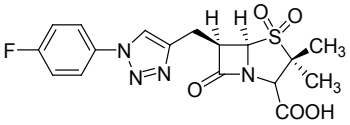
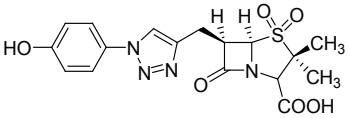
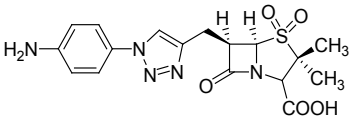
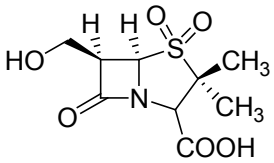
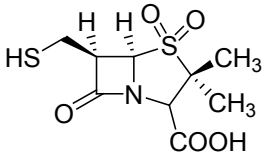
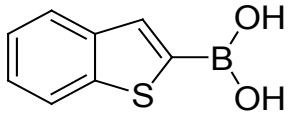
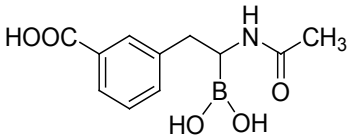
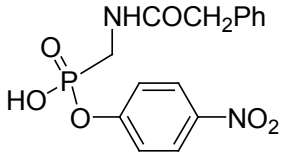
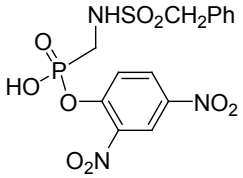
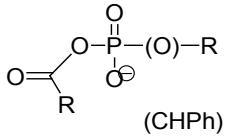
Ambler Mol class	Bush *et. al* Sub-group	Substrate Name	Inhibition Clavulanic	Tazobactam	EDTA	Enzymes
A	2a	Penicillins	Yes	No	No	AmpC, ACT-1
	2b	Penicillins & 1st, 2nd ceplalosporins	Yes	No	No	GC-1, CMY-37
	2be	Extended spectrum cephalosporins, Monobactams	Yes	No	No	PC-1
	2br	Penicillins	No	No	No	TEM-1, TEM-2, SHV
	2c	Carbenicillin	Yes	No	No	TEM-3, SHV-2, CTX-M-15
	2ce	Carbenicillin, cefepime	Yes	No	No	TEM-30, SHV-10
	2e	Extended spectrum cephalosporins	Yes	No	No	CepA
	2f	Carbapenems	Variable	Variable	No	KPC-2, SME-1
B	3a	Carbapenems	No	Yes	Yes	IMP-1, NDM-1
	3b	Carbapenems	No	Yes	Yes	CphA, Sfh-1
C	1	Cephalosporins	No	No		Ampc, ACT-1
	1e	Cephalosporins	No	Yes		GC-1, CMY-37
D	2d	Cloxacillin	Variable	No	No	OXA-1, OXA-10
	2de	Extended spectrum cephalosporins	Variable	No	No	OXA-11, OXA-15
	2df	Carbapenems	Variable	No	No	OXA-23, OXA-48

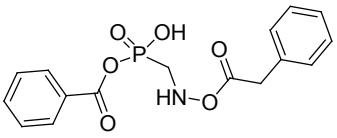
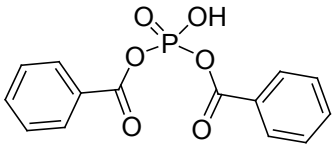
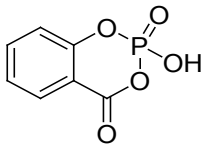
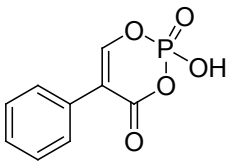
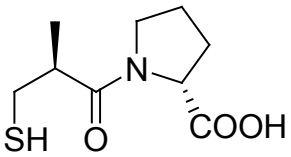
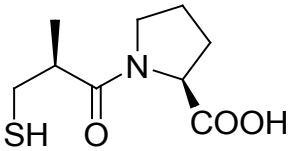
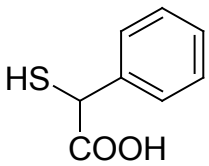
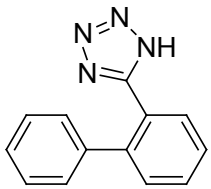
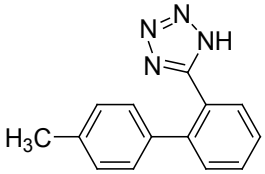
Table 2. The list of active derivatives as β-lactamase inhibitors

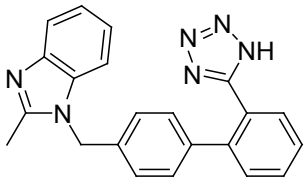
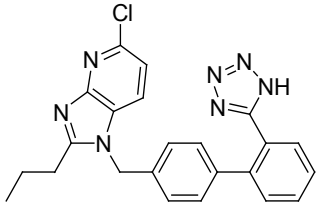
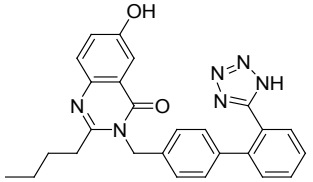
Compound Number, cLogP=	Chemical Structure	cLog P	Reference
Clavulanic acid; **Compound 1** cLogP= -1.065		Against class A, C and D β –lactamases	Ref. [96-99]
Tazobactam; **Compound 2** cLogP= -0.65		Against class A, C and D β –lactamases	Ref. [98-110]
Sulbactam; **Compound 3** cLogP= 0.314		Against class A, C and D β –lactamases	Ref. [98-110]
Relebactam; **Compound 4** cLogP= -1.749		Against class A, C and D β –lactamases	Ref. [31-33]
Avibactam; **Compound 5** cLogP= -1.628		Against class A, C and D β –lactamases. Also, against class B metallo-²-lactamase	Ref. [31-33,112]
Vabor-bactam; **Compound 6** cLogP= 0.525		Against class A and C with no . inhibitory actions on D or B	Ref. [35-41,152]
SB236050; **Compound 7** cLogP= -0.253		Against class B metallo-β-lactamase	Ref. [90-101]

SYN 1012; **Compound 8** cLogP=-0.041		Against class A, C and D β –lactamases	Ref. [100-104]
BRL 42715; **Compound 9** Log P: -0.35 cLogP= -0.495		Against class A, C and D β –lactamases	Ref. [100-104]
Compound 10 Log P: 0.64 cLogP= 0.372		Against class A, C and D β –lactamases	Ref. [105-110]
Compound 11 cLogP= 0.551		Against class A, C and D β –lactamases	Ref. [105-110]
AM-112; **Compound 12** cLogP= -1.894		Against class C and D β –lactamases	Ref. [109-113]
LK-157; **Compound 13** Log P: -0.37 cLogP= 0.270		Against class A, C and D β –lactamases. It inhibits AmpC-lactamase with 2,000-fold more potency than clavulanic acid.	Ref. [112-116]
J-110,441; **Compound 14** LogP= 1.42 cLogP= 3.383		Against class B metallo- β-lactamases	Ref. [115-117]

Compound 15 cLogP= 3.383		Against class B metallo- β-lactamases	Ref. [115-117]
Compound 16 cLogP= 4.356		Against class B metallo-β-lactamases	Ref. [115-117]
Compound 17 cLogP= 0.727		Against class B metallo-β-lactamases	Ref. [115-117]
SA2-13; **Compound 18** Log P: -1.58 cLogP= 0.471		Against class A β-lactamases	Ref. [86-88]
BAL29880; **Compound 19** cLogP: -1.271		Against Class C and some Class D	Ref. [116-118]
MK-8712; **Compound 20** cLogP= -0.11059		Against class A β-lactamases	Ref. [117-121]
Compound 21 cLogP= -0.67		Against class A β-lactamases	Ref. [117-121]
Compound 22 Log P: -0.95 cLogP: -0.0544		Against class C β-lactamases	Ref. [120-122]

Compound 23 cLogP= Log P: 1.18 CLogP: 2.033		Against class A, C and D β –lactamases.	Ref. [121-126]
Compound 24 cLogP= Log P: 0.63 CLogP: 1.484		Against class A, C and D β –lactamases.	Ref. [121-126]
Compound 25 cLogP= Log P: 0.22 CLogP: 0.90		Against class A, C and D β –lactamases.	Ref. [121-126]
Compound 26 cLogP: -0.044		Against both serine and metallo--lactamases	Ref. [121-126]
Compound 27 cLogP: 1.042		Against both serine and metallo--lactamases	Ref. [121-126]
ZBTH2BB; **Compound 28** cLogP: 2.625		Against class C β–lactamases	Ref. [129-131]
Compound 29 cLogP: -0.995		Against class C β–lactamases	Ref. [129-131]
Compound 30 cLogP: 0.624		Against class A and C β–lactamases	Ref. [130-134]
Compound 31 cLogP: 0.428		Against class A and C β–lactamases	Ref. [130-134]
Compound 32		Against class A and C β–lactamases	Ref. [130-134]

Compound 33 cLogP: 2.239		Against class A and C β–lactamases	Ref.[130-134]
Compound 34 cLogP: 2.328		Against class A and C β–lactamases	Ref. [132-136]
Compound 35 cLogP: -0.09		Against class A and C β–lactamases	Ref. [130-135]
Compound 36 cLogP: 1.158		Against class A and C β–lactamases	Ref. [130-135]
D-Captopril; **Compound 37** cLogP: 0.89		Against (MBL–Zn(II)) –lactamases More potent than L-captopril.	Ref. [134-138]
L-Captopril; **Compound 38** cLogP: 0.89		Against (MBL–Zn(II)) –lactamases	Ref. [134-138]
Compound 39 cLogP: 1.417		Against metallo-β-lactamase inhibitor	Ref. [134-141]
L-809, 022, **Compound 40**		Against metallo-β-lactamase inhibitor IC50 (cLogP:**880** 2.923 60	Ref. [140-145]
L-158, 507, **Compound 41**		Against metallo-β-lactamase inhibitor IC50 (cLogP: **160** 3.422 20	Ref. [140-145] β

L-809, 559, **Compound 42**		Against metallo-β-lactamase inhibitor IC50 (cLogP:**4**4.3991	Ref. [121-148]
L-158,678, **Compound 43**		Against metallo-β-lactamase inhibitor IC50 (cLogP:**3.5** 5.1010.4	Ref. [121-148]
L-159, 061, **Compound 44**		Against metallo-β-lactamase inhibitor IC50 (cLogP: **1.9** 5.3650.2	Ref. [121-148]

Class D-serine such as oxacillinases are over 498 OXA β-lactamases have been detected and divided into OXA ESBLs and *carpabenemases* detected in *P. aeruginosa* widespread in *Enterobacteriaceae, Acinetobacter* and in *K. pneumoniae*. They vary in amino acid sequence and mentioned as OXA-11, OXA-14, OXA-16, OXA-19, OXA-31, etc. (60, 69), OXA-23, OXA-48, OXA-51, OXA-143 and OXA-48 which is detected in *K. pneumoniae*.[61-83] Subgroups 2d, 2de, and 2df are related to molecular class D known as oxacillinases.[84]

Class B; metallo-β-lactamases (MBLs) also known as metallo-carbapenemase, that necessitate zinc ions in their active sites with mechanistic differences.[72-85] Metallo-β-lactamases have been recognized in *P. aeruginosa* and their encoding genes can be either chromosomal structure or situated on plasmids that can be spread among species. MBLs are subdivided into three classes; subclass B1 (includes IMP, VIM and NDM variants) and subclass B3 require two zinc (II) ions in their active sites. In contrast, subclass B2 enzymes utilize only one zinc (II) ion.[84-87]

Brief Mechanisms of Inhibition of β-Lactamases by FDA Approved Drugs

β-lactamases from classes A, C, and D follow the same interaction with the β-lactam-antibiotic and similarly with inhibitors. The (Figure 2), represents the initial location at the binding sites of enzymes and the FDA-approved drugs such as clavulanic acid (representing the 4-membered β-Lactamases group such as clavulanic acid, sulbactam and tazobactam), avibactam (representing 5-membered lactams such as avibactam and relebactam) and vaborbactam as borane derivative. The main amino acids catalyzing the interaction are mention.[88] The mechanism of interaction is reported elsewhere in which the amino acids lining the binding site interact and stretch the inhibitor molecule (similar to the antibiotics penicillins or cephalosporins) and facilitating the nucleophilic attack of ser-70 to form covalent bond with the vulnerable group of the inhibitor.[57-84]

The interaction of these β-lactamases with the inhibitors of different types (Figure 3) lead to hanging-up these enzymes through the formation of variable types of bonding.

a. In case of the first group of inhibitors namely clavulanic acid, sulbactam and tazobactam an irreversible covalent bond (ester) between the ser-70 hydroxyl group with the carbonyl of the inhibitor [89]. Further strong covalent bond may form

between amino group of lys-73 or ser-130 with carbon-6 followed by inhibitor degradation and inactivation of the enzyme (Figure 3: A, B, C). [90]

b. In case of the second group of inhibitors namely avibactam and relebactam a carbamate ester can be formed between ser-70 hydroxyl group with the carbonyl of theses inhibitors. Carbamate esters are less susceptible for hydrolysis (Figure 3: D).

c. In case of vaborbactam which represents a different type of inhibitors, a strong co-ordinate covalent bond is formed between ser-70 hydroxyl group with boron of the inhibitor (Figure 3: E).

In contrast to serine β-lactamases; MBLs are not associated with a covalent bond between the β-lactam antibiotic and an amino acid lining the active site. The metal-particles in MBLs are two zinc(II) ions the first zinc(II) ion coordinates to His-residues while the second zinc(II) ion coordinated with Asp120, His, and Cys-residues. The first zinc (II) ion acts as a Lewis acid and decreases the pKa value of the bridging water molecule which results in the formation of hydroxide ion that initiates the nucleophilic attack on the β-lactam antibiotic or the inhibitor vulnerable groups.[52-91]

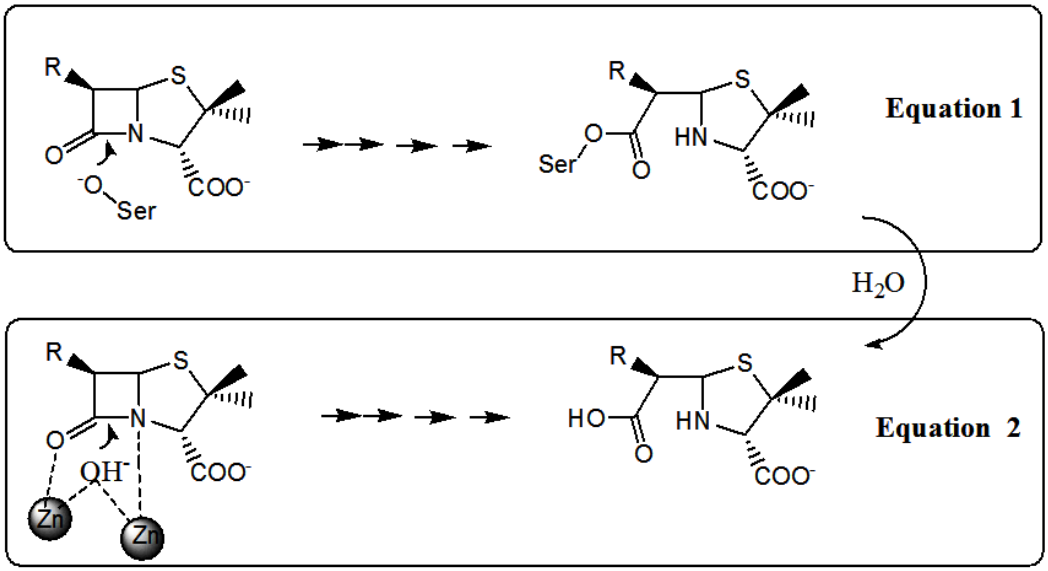


Fig. 1. A simplified chart of hydrolysis of penicillin by of â-lactamases. Equation 1: Serine â-lactamases (SBLs) hydrolysis pathway. Equation 2: Metallo-â-lactamases (MBLs) hydrolysis pathway utilizing two zinc ions

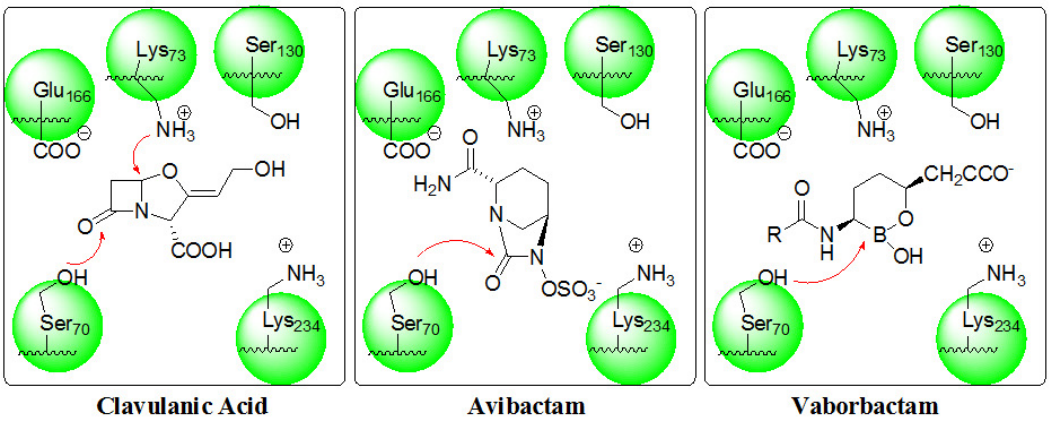


Fig. 2. Simplified initial interaction of â-lactamases of classes A, C and D with the â-lactamase inhibitors

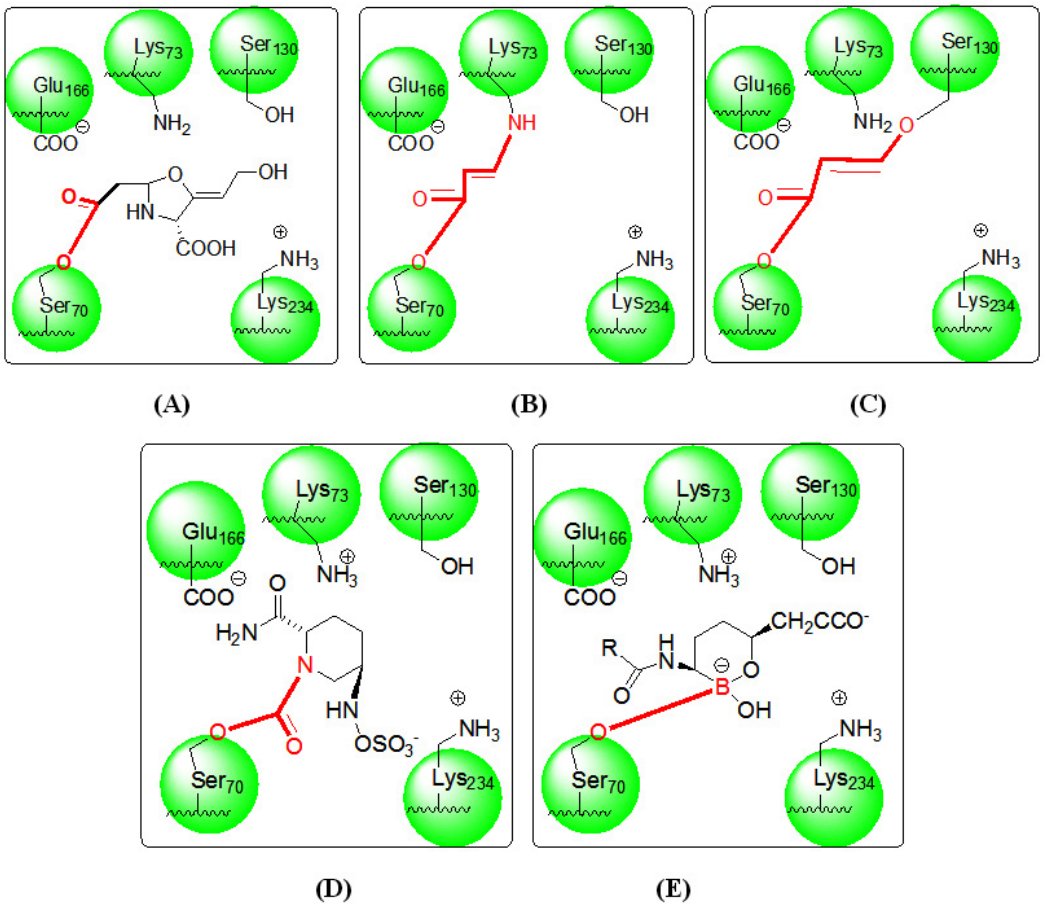


Fig. 3. The simplified feature of the inhibited â-lactamases of classes A, C, D with the â-lactamase inhibitors. The covalent bonds between amino acids ling active site with inhibitors are colored red

Another important point is that the amino acids lining the MBLs active site and interacting with the β-lactam antibiotic differ than those of classes A, C and D. Payne et. al. descried the interactions between the enzyme and a natural tricyclic structure SB236050 (Table 2, Compound 7) mentioned as MBLs inhibitor and provided antibacterial synergy with meropenem on some MBLs.[92] This compound has inhibitory activity versus IMP-1, and CfiA. Zn (II) coordinated with water and Asn193, His99, His101, His162, Zn (II) also coordinated with the same water molecule Asp103, Cys181, His223, and the inhibitor.

Structures of FDA-Approved Drugs, Patents and Developments of β-lactamase Inhibitors to Date

There is a serious need to search for new β-lactamase inhibitors in light of emerging of resistant superbug. To conquer this risk, scientists could introduce inhibitors to synergize the β-lactams effects. Developing inhibitors is a difficult aspect because of the different classes of β-lactamases. As an example, MBLs and OXA β-lactamases create a challenge and represent a highly significant problem due to their ability to inactivate nearly all β-lactam antibiotics.[93-95]

Regardless of the worldwide spread of MBLs, their inhibitors have not yet emerged in clinical use.[94] MBLs inhibitors have been reported, but the mechanism of inhibition is unknown for many of these inhibitors yet becoming more prevalent and problematic. On the other hand, the OXA species are extremely diverse with other 500 variants; among these species they

differ in their hydrolytic activity with the other serine-based mechanism, thus a single β-lactam-β-lactamase inhibitor combination strategy that targets all clinically significant β-lactamases seems improbable.[86-97]

Table 2 outlines the structures of FDA-approved drugs, codes of registered compounds or by numbers for the compounds that reported of high activity. The structures, and the references that introduce and/or discuss the mechanisms of these compounds are also mentioned in this table. The cLog P from chemdraw (https://perkinelmerinformatics.com/products/research/chemdraw/) for each structure are computed and added in (Table 2) is to understand structure's hydrophilicity and hydrophobicity.

Clavulanic acid (Table 2, Compound 1) was the first β-lactamase inhibitor introduced into clinical. It is mixed with amoxicillin (Augmentin ®), and this allows the effective dose of amoxicillin to be decreased. Mixed with ticarcillin (Timentin) to be used (*i.v.*) to inhibit the enzyme β-lactamase and providing prompt effect. The success of clavulanic acid stimulated the development of semisynthetic penicillinic acid sulfones. It is classed as sentry drug because it's able to make two covalent bonds and the molecule will be cleaved (Figure 3: B & C).[96-99]

Penicillinic acid Sulfones as FDA-approved drugs are synthetized penicillanic acid derivatives. The sulfur atom is made as sulfonyl group to increase its electron withdrawal effect on C-5 to be similar in its electrophilicity and reactivity with nucleophies at the binding site to that of clavulanic acid for its inhibition mechanism (Figure 3: B& C).

Sulbactam (Table 2, Compound 2) is a penicillanic acid sulfone of broader spectrum but slightly less potent than clavulanic acid. It is mixed with ampicillin as capsules, pills or (*i.v.*) injectables (https://go.drugbank.com/drugs/DB09324).

Tazobactam (Table 2, Compound 3) is another penicillanic acid sulfone β-lactamase inhibitor of equal potency with clavulanic acid but much broader. The combination piperacillin-tazobactam acquires activity against TEM-type ESBL's, in which the enzymes are more susceptible to piperacillin-tazobactam than SHV type ESBL's. Moreover, such combination provides a 10-fold high activity against CTX-M when compared with calvulanic acid [98-100].

Relebactam (Table 2, Compound 4) is a bicyclic system bearing a five-membered lactam ring bearing an electrophilic carbonyl-carbon that forms ester when attacked by the nucleophile of the active site. The ester in this case is a stable urethane (carbamate ester).

Avibactam (Table 2, Compound 5) has the same bicyclic system of relebactam bearing a five-membered lactam ring with no piperidine moiety on the amide side chain. The acylation mechanisms are reported elsewhere and enzyme binding with either avibactam or relebactan is represented in Figure 3: D.[31-33]

Vaborbactam (Table 2, Compound 6) is a β-lactamase inhibitor; a cyclic boronic acid derivative approved by FDA 2017 as Vabomere[C$] consists of Vaborbactam and Meropenem. Used mainly for complicated urinary tract infections (UTI) by intravenous administration. Vaborbactam is intended for serine beta-lactamases, Ambler class A and C enzymes in Figure 3: E.[35-37]

Candidates and Active Derivatives as β-Lactamase Inhibitors

The following monographs collect the effective derivatives under common structural titles and verification names:

Chaeto-Chromones

These were isolated from crude extract of fungus *Chaetomium indicum* (CBS. 860.68).[90-101] Group of potent inhibitors versus metallo-beta lactamases are mentioned from those polyketides SB236050 (Compound 7, Table 2) had been investigated at the active site of a metallo-beta lactamase enzyme in crystal structure.[90-92]

Four-Membered-Ring Bearing Scaffolds as Inhibitors

SYN 1012 and BRL 42715 (Compounds 8 and 9, Table 2) are methylidene-penem derivatives possessing strong inhibition of serine β-lactamases of class A, C and D enzymes.[100-102] These agents having increased cell permeability and acting by a different mechanism than clavulanic acid.[101-105] Penems (Compounds 10 and 11, Table 2) are other methylidene penems related to compound 9 and aimed mainly to improve stability in solution and increase lipophilicity. The compounds have proven to be potent inhibitors of class A, C, and

D β-lactamases.[104-108] The two compounds are effective inhibitors of class D OXA-1 β-lactamases.[107-110]

AM-112 (Compound 12, Table 2)

It is a derivative of clavulanic acid. This compound was unstable however it gives a lead zwitterion compound which has a potent inhibition property against class C and D β-lactamases.[109-113]

LK-157 (Compound 13, Table 2)

It is a fused tricyclic bearing carbapenem structure. It significantly inhibits AmpC-lactamase with 2,000-fold more potency than clavulanic acid and about 28-fold more active than tazobactam.[114] The introduction of a methoxy group at C-4 position shows affinity towards both Class A and Class C.[113] Ethylidene entity at C-6 was intended to maintain stability of the β-lactamase inhibitor/β-lactamase complex, in addition it was speculated that the hydrophobic rings at position C-3 and C-4 intended to block water molecule from penetrating the acyl-enzyme complex and thus preventing enzyme recovery.[114-116]

β-Methylcarbapenems (Compound 14-17, Table 2)

These are carbapenem derivatives that contain a methyl group at C-1 and substituents at C-2 that are important in this scaffold for the inhibition of class B metallo-β–lactamases. Among these derivatives; J-110,441 (Compound 14, Table 2) was the most potent inhibitor of class B metallo-β-lactamases (IC_{50} of 0.1 mM).[115-117]

SA2-13 (Compound 18, Table 2)

It is a tazobactam-related derivative β-lactamase inhibitor. It is developed to increase the lifetime of the trans-enamine intermediate compared to tazobactam when interacting with the enzyme. SA2-13: SHV-1 intermediate has a 10-fold lower de-acylation rate than tazobactam: SHV-1 intermediate.[86-88]

BAL29880 (Compound 19, Table 2)

It has a chelating property to be combined with MBL-resistant monobactam antibiotic that is affected by cephalosporinases class C type AmpC and ESBLs. BAL29880 inhibits AmpC furthermore, clavulanic acid blocks the activity of other class A β-lactamases including ESBLs.[116-118]

MK-8712 (Compound 20 and 21, Table 2)

The first has better AmpC inhibitory activity and shows synergistic effects with imipenem than the latter.[119-121]

Ro 48-1220 (Compound 22, Table 2)

(Z)-2 β- acrylonitrile penam sulfone is a potent inhibitor. Comparing its inhibition with tazobactam, Ro 48-1220 was 15 times more effective against class C β-lactamases. In another study, the inhibitor enhanced the activity of ceftriaxone and ceftazidime against producers of TEM-1 type class A -lactamases.[122]

6-Substituted penam sulfones (Compound 23-27, Table 2)

These are nM to low M inhibitors of serine –lactamases.[88] Changing the stereochemistry and functional groups on the C-6 position of penam sulfones can affect the selectivity of inhibition to the different classes of -lactamases.[121-124]

The compounds 23-25 (Table 2) providing IC_{50} = 1.6, 0.7 and 0.6 M versus TEM-1, respectively and were found to be potent inhibitors of class A -lactamases. The other compounds having C-6-hydroxy-akyl and mercapto-alkyl penam sulfones and the compounds 26 and 27, (Table 2) were designed to act as chelators for metals in MBLs. Modification of the hydroxymethyl group by a mercaptomethyl group results in broader spectrum of inhibition, targeting both serine and metallo--lactamases.[122-126]

Non -Lactam -Lactamase Inhibitors

Boronic Acid Analogs

Boron atom has three electrons in its valence shell. Covalent bonding favor only six surrounding electrons and thus it represents a favored electrophilic center (as monobasic Lewis acid of boron). To reach octet it must receive electrons from attacking nucleophiles. Boronic acid β-lactamases inhibitors are one of the most promising classes of β-lactamase inhibitors in development.[125-129] They have been explored as serine β-lactamases inhibitors of mainly class A and C β-lactamases.

Boronic acids act as competitive inhibitors, forming a tetrahedral intermediate by binding to the catalytic serine residues of the enzymes through a coordinate covalent bond. The enzyme: inhibitor complex resembles the tetrahedral structure of the high-energy intermediate formed during the mechanism of β-lactam hydrolysis (Figure 3: E).[130]

ZBTH2BB (Compound 28, Table 2)

It is the benzothiophene-2-boronic acid, a potent nanomolar non-β-lactam inhibitor for class C β-lactamases with a Ki of 27 nM. Another

compound, 1-amido-2-(*meta*-carboxyphenyl) ethane boronic acid (Compound 29, Table 2) possess features to make it closer to β-lactams antibiotics during hydrolysis.[131]

Phosphonate Derivatives

Among non- β-lactam inhibitors, phosphonates showed good inhibition against serine β-lactamases. They inhibit the enzyme by acylation and phosphylration of the active site serine-70 residue and formation of a stable tetrahedral phosphonyl-enzyme complex.[132]

Phosphonate monoesters bearing phenyl rings (Compound 30 and 31, Table 2) have shown inhibition against class A and C β-lactamases. In addition, compound 30 has a weak antibacterial activity as demonstrated by its inhibition of the D-ala-D-ala trans peptidases in Streptomyces R61. Compound 32 (Table 2) was found to inhibit class C enzymes.[130-134] The acyl phosphonate Compound 33 (Table 2) showed irreversible inhibition of β-lactamases. Adding proper hydrophobic substituents on diacyl phosphonates Compound 34 (Table 2) can increase the potency of inhibition, achieving an inhibition constant in the piconanomolar range.[132-136] Other analogs like, cyclic phosphonates (Compound 35 & 36, Table 2), The acyl phosphonates showed irreversible inhibition of β-lactamases. Adding proper hydrophobic substituents on diacyl phosphonates can increase the potency of inhibition, achieving an inhibition constant in the piconanomolar range.[130-135]

Thiol Derivatives (Captopril)

Captopril is a well-known antihypertensive agent that inhibits the zinc-containing angiotensin-converting enzyme in humans to treat hypertension.[134-135] It has also shown effective inhibition against all classes of metallo--lactamases, which include classes of B1, B2 and B3 enzymes. Both diastereoisomers of captopril are capable of inhibiting these enzymes. However, the D-diastereoisomers (Compound 37, Table 2) is more potent in inhibiting some MBLs than the L- diastereoisomers (Compound 38, Table 2). The thiol group is important for binding. Lengthening of carboxylate group decreases the activity against the enzymes via complex formation (MBL-Zn(II)-inhibitor). The sulfhydryl group bridges the two active site zinc ions, displacing the nucleophilic water molecule that act as the nucleophile to attack the carbonyl carbon on -lactam antibiotics.[134-138]

Thiomendalic acid (Compound 39)

It is a simple thiol-containing compound able to inhibit different subclasses of MBLs, demonstrating that potent inhibitors are possible to design. Against the dizinc BcII enzyme thiomandelic acid provided Ki value of 0.09 μM for the R-isomer and 1.28 μM for the S-isomer, respectively. Varying the functional groups at the para-position of benzene bearing analogues didn't provide more promising derivatives. The inhibitory activity of thiomandelic acid was found to be highly dependent on the thiol group, which chelates the two Zn (II) atoms in the active site of MBLs.[134-141]

Biphenyl tetrazoles

The inhibitory activity of biphenyl tetrazoles through screening and molecular modeling studies of metallo-β-lactamase structure from imipenem-resistant *B. fragilis* had been realized. Biphenyl moiety form hydrogen bonds with the NH of Asn176 and His145, along with the NH_2 of Lys187, enhancing the binding affinity to the enzyme. However, changing the position of the tetrazole ring from the *ortho*- to the *meta*- or *para*-position, relative to the biphenyl rings, has resulted in a drastic loss of the inhibitory activity against the enzyme. L-809, 022 (Compound 40, Table 2) have shown to be a weak inhibitor of the MBL enzyme of B. fragilis, however, the added methyl group in L-158, 507 (Compound 41) improved the potency of the compound by 5-folds.[140-145]

Conjugation of the biphenyl system with substituted heterocyclic aromatic rings increased the potency.[140-146] For example, replacement of the methyl group in the parent compound with a *Z*-methyl-benzimidazole moiety provided L-809, 559 (Compound 42, Table 2) of 40-fold increase in potency. The addition of the substituted imidazo[4,5-b] pyridinyl entity gave L-158,678 (Compound 43, Table 2) of 50-fold increase in inhibition over the parent compound. L-159, 061 (Compound 44, Table 2) with R= Z-butyl-6-hydroxylquinazolinone, showed the highest potency with a 100-fold greater activity than the parent compound.[121,140-148]

Proposed selections of proper inhibitors for admixing with β-lactams

The (Table 2), includes CLogP parameter obtained from chemdraw ultra. The number of

candidates proved potent inhibitory activity to metallo-β-lactamases are 16 candidates, each representing the top of a series of compounds. Six of those are β–lactam-bearing derivatives. The CLogP of these 6 derivatives drop in hydrophobic area ranging from 0 to 3.4. The generally approved β-lactamase inhibitors that are in clinical use are of balanced hydrophilicity and hydrophobicity having CLogP range -1.75 to 0.53.[147-151] All of those admixtures are active versus classes A, C and D β-lactamase. On this basis, we can consider the mentioned physicochemical figure for the selection of β-lactamase inhibitors. The presence of polar groups is important to chelate one metal ion, at least, in the active site of metallo-β-lactamase (Figure 1, equation 2). However, the hydrophobicity also is of high importance in case of metallo-β-lactamase.[152]

In addition, it might be effective also if we mix broad-spectrum β-lactams with suitable amounts of the earlier generations such as phenoxymethyl-penicillin (Pen V). Pen V is a good substrate for β-lactamases and thus acts as suicidal inhibitor allowing the broad-spectrum β-lactams to be effective versus super bugs.[153-155]

CONCLUSION

The impact of antimicrobials has brought upon benefits to medicine. However, harms include the β-lactamase enzymes that are resistant to either one or multiple antibiotics; as a result, limiting their use as single agents. In this review, we revisited the classification systems used to categorize these enzymes; in addition, we collected the various scaffolds of β-lactamase inhibitory activities. Most of the candidates mentioned mainly focused on targeting broader classes of β-lactamases against all types.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise with this work.

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