Strategies to combat New Delhi metallo- β-lactamase - where do we stand?

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Abstract
Antibiotic resistance to carbapenems is an emerging threat in global health care settings and poses a significant menace to the treatment of diseases spurred on by the multi-drug-resistant bacteria (MDR). New Delhi-metallo-β-lactamase-1 (NDM-1) was recently found and grouped into the broad-spectrum B1-subclass of metallo-β-lactamases (MBLs). The ability of the NDM-1 to hydrolyze diverse array of β-lactam antibacterial agents, notably carbapenems, has received a lot of interest. In general, NDM-1 offers a broad range of substrate binding affinity owing to its shallow active site and distinct electrostatic mechanism. In recent years, numerous NDM-1 inhibitors with different chemical structures have been found. Despite considerable progress in structural and mechanistic knowledge, it remains difficult to develop an effective NDM-1 inhibitor that will be approved for therapeutic use. This may be because NDM-1 has a flexible hydrolysis mechanism and many variants, that impede advent of clinically effective NDM-1 inhibitors. In-depth knowledge of the nature of inhibition and the structural relationship of the NDM-1 enzyme would be beneficial for the identification, synthesis, and development of biologically active inhibitor and would make it a promising drug candidate. In this report we summarize and categorize the significant recent progress in the identification and subsequent development of numerous NDM-1 inhibitors, along with their mechanism of action.
Key words: NDM-1, carbapenem resistance, NDM-1 inhibitors, structure-activity relationship, biological activity, adjuvants

1. Introduction

Antibiotics have a significant impact on the prevalence of bacterial ailments in clinics, lowering mortality and extending human life. Antibiotics, on the other hand, have promoted antibiotic resistance in microorganisms all over the world[1].Due to antibiotic resistance, it is predicted to result in 300 million casualties worldwide by 2050, as well as a catastrophic economic loss $100 trillion, resulting in millions of people becoming impoverished, most of whom will reside in economically deprived countries[2]. Despite their immense use, β-lactam antibiotics are still the most often recommended antibacterial agents and of their interaction with penicillin-binding proteins (PBPs) helps to prevent bacteria from forming cell wall [3]. Each bacterial species has its own collection of PBPs and can contain three to eight enzymes. Contrarily, bacteria have developed extensive resistance mechanism against β-lactam antibiotics, with the most complete and therapeutically important mechanism being the development of β-lactamases [4].Most bacterial species produce β-lactamases that render β-lactam antibiotics ineffective by cleaving their amide bond[5].

Ambler classified β-lactamases into two broad classes - Serine-β-lactamases (SBLs) and Metallo-β-lactamases (MBLs). Class A, C and D make up SBLs while MBLs constitute class B [6]. A number ofinhibitors for SBLs are available in the clinics including clavulanate, tazobactam and sulbactam. SBL inhibitors block the hydrolysis of β-lactam antibiotics by covalently binding to the serine-moiety[7]. Combining these substances with antibiotics has been successful in treating infections that are resistant to conventional treatments. In contrast, class B: β-lactamases are challenging to tackle since they typically hydrolyse β-lactam antibiotics and it is possible because the catalytic site of these enzymes contains zinc ions that interact with the carboxylate of the β-lactam ring to catalyse the hydrolysis of antibiotic.

The three sub-groups of MBLs are B1, B2, and B3. NDM-1, a newly discovered member of the B1 MBL superfamily, was originally detected in *Klebsiella pneumoniae (K. pneumoniae)* that was identified in 2008 from a Swedish patient [8]. *K pneumoniae, Escherichia coli (E. coli) and Acinetobacter spp.* are the major determinants of NDM-1[9]. All most all currently known β-lactam antibiotics, with the exception of monobactams like aztreonam, are hydrolysed by NDM-1 enzyme and its rapid spread among bacteria of the same or different species is predominantly mediated by the plasmids encoding NDM-1 gene, thereby limiting the efficacy of antibacterial therapies [10].

Effective NDM-1 inhibitors include sulphur analogues, captopril derivatives, sulfanilamide and some of the phytocompounds [11]. In addition, the combination of inhibitors with β-lactam antibiotics can enhance antibacterial activity and overcome resistance mediated by MDR bacteria. It remains difficult to design an efficient and accurate NDM-1 inhibitor for therapeutic application despite the review of physico-chemical characteristics including knowledge about the process NDM-1 catalysis [12].In this paper, we emphasised the important developments in NDM-1 inhibitor research. This study aims to identify the *in vitro* and *in vivo*inhibitory mechanism of inhibitors and compounds working in combination with β-lactam antibiotics to reinstate the antibiotic efficacy of therapeutically competent NDM-1 expressing bacteria.

2. Metallo-β-lactamases (MBLs)

MBLs are structurally and functionally distinct from SBLs, suggesting a divergent evolutionary origin. SBLs hydrolyze β-lactam antibiotics via a covalent acyl-enzyme intermediate that uses serine as the reaction nucleophile and exhibit a conserved serine-xaa/xaa: lysine motif [5]. Instead, a metal-activated water nucleophile drives the hydrolytic reaction in MBLs. These enzymes are not affected by commercially available inhibitors such as tazobactam, sulbactam, or clavulanic acid[13]. In addition, NXL-104, a therapeutic agent which is presently under clinical study to curtail SBLs of class A and C[14]. MBLs were considered as medical rarities occurring in geographically limited outbreaks. This paradigm has changed as AMR mediated by NDM, VIM, and IMP has become more prevalent worldwide in ESKAPE pathogens [15].

Since MBLs are typically observed in pathogenic organisms that are impervious towards many broad-spectrum antibiotics, including carbapenems, aminoglycosides, polymyxins, and other commonly used last line drugs, in addition to being insensitive to clinically used SBL inhibitors, curbing their activity is an urgent and growing medical nee[16]. B1 and B3 of the three MBL subclasses found to undergo broad substrate hydrolysis, encompassing penicillin, cephalosporin, and carbapenems, while subclass B2 can only hydrolyse carbapenem[13]. NDM is the leading MBL of subclass B1 that is gaining medical importance due to its transmissibility, diversity, and emerging mutations.

3. Active site structure of NDM-1

NDM-1 is a broad-spectrum B1 MBL enzyme with 27.5 KDa polypeptide chain and has 270 amino acid residues with N-terminal signal peptide of 28 amino acids with the features of 50-40-40 Å. Five α-spirals and twelve β-lamellar folds with two α-spirals on each side and α-α/β-βsandwich arrangementwithin the middle lamella make up the secondary structure of NDM-1 natural proteins(King &Strynadka, 2013). The three loop regions of the active site residues are identified as Leu3 (Leu65-Val73), Leu7 (Thr119-Met126), and Leu10 (Cys208-Leu221). At the bottom of each loop are two positively charged zinc ions: Zn1 and Zn2 with hydrolytic properties. Since, Zn1 interacts with His120, His122, His189and are described as histidine site while Zn2 interacts with Asp124, Cys208, and His250, that would be alluded to as cysteine site as well as exhibits a trigonal pyramidal co-ordination sphere (Figure 1)[17].

Figures:

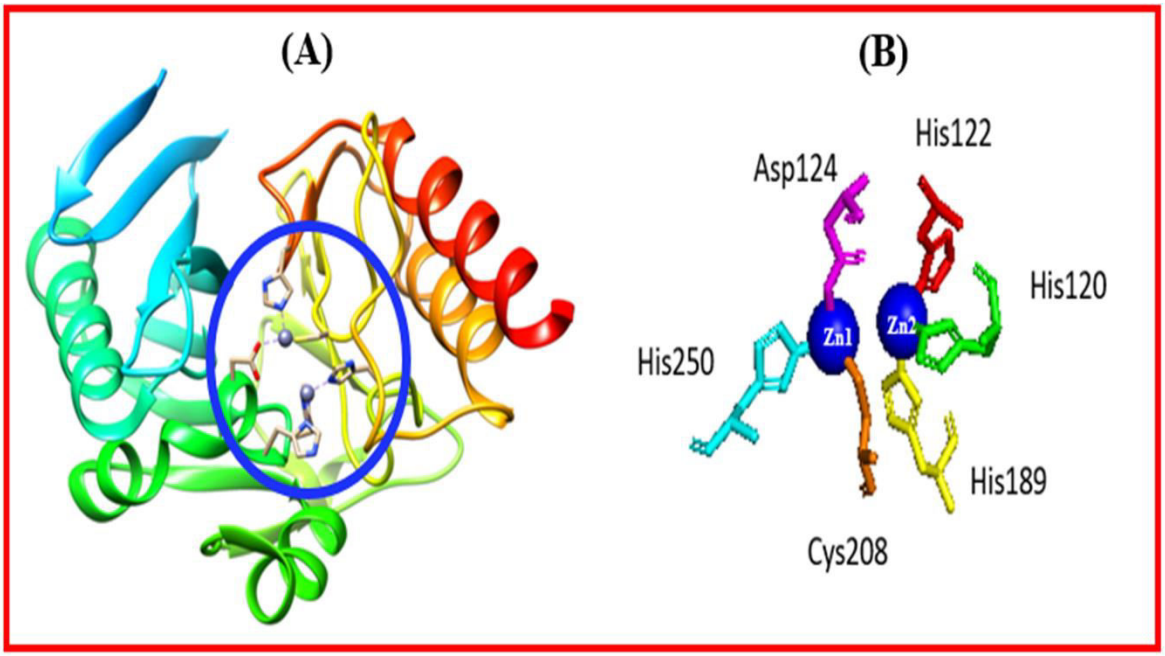

Figure 1. The structure of NDM-1 (PDB: 4EYL): a) Blue colour circle represents the active site of NDM-1 with two purple spheres displaying zinc ions b) The key active site amino acid residues of NDM-1

4. Mechanism of multi drug resistance by NDM-1

PBPs that prevent antibiotic penetration into bacterial cells, upregulation of β-lactamases, drug efflux pumps and altered outer membrane porins on the cell wall of bacteria that significantly increase antibiotic efflux from the bacterial cell are some of the underlying mechanisms of microbial resistance to antibiotics [18]. Accelerated transmission and recent incorporation of NDM-1 into the MBLs amplicon hydrolyze virtually all clinically available last resort β-lactam antibiotics including carbapenems imipenem (IPM) and meropenem (MEP)[15]. NDM-1-mediated hydrolysis is thought to occur in two steps: Amide bond breaking and protonation of the resulting intermediate compound [19]. To effectively hydrolyse the β-lactam group of antibiotics, zinc ions ($Zn2^{+}$), a water molecule situated in between $Zn2^{+}$and selective amino acids within the catalytic site are required. Two $Zn2^{+}$ions position the β-lactam substrate at the catalytic site and coordination with neighboring amino acidssuch as Lys224 and Asn233 stabilize it there for the duration of the hydrolysis reaction. The water molecule spanning two $Zn2^{+}$ ions act a potential nucleophile targeting the carbonyl group and starting the dissociation of the β-lactam ring. Since, the first Zn reacts with the newly produced carboxylate while the other Zn interacts with of amino group, the water molecule spanning two Zn ions is a potential nucleophile targeting the carbonyl group and starting the dissociation of the β-lactam ring[20]. Its subsequent protonation of an amine is thought to constitute the reaction's ratelimiting step[7]. The chemically hydrolysed substrate possesses no antibacterial properties and is totally in effective.

5. Current treatment options for NDM producers

5.1. Aztreonam-Avibactam

Even though aztreonam is resistant to MBLs, NDM-producing bacteria often contain ESBLs and or AmpC enzymes that can degrade it. Both aztreonam and avibactam have shown significant efficacy *in vitro* against Enterobacteriaceae that express ESBLs and yet are NDM-positive [21]. Aztreonam-avibactam is not currently approved for use in humans and is still in the clinical development stage.

5.2. Fosfomycin

In the United States, Fosfomycin is accessible as an oral drug, while in China and Europe it can also be administered intravenously. There has not been much extensive research conducted on sensitivity of Fosfomycin against NDM positive Enterobacteriaceae as well as there is insufficient evidence to justify administration of fosfomycin alone, but as mentioned previously, a fosfomycin-containing drug combination has shown promising effects [22].

5.3. New Antimicrobial Agents in Development

The new monobactam LYS -228 is impervious to hydrolysis of β-lactamases.Based on *in vitro* investigations, it showed considerable effectiveness against a huge portion of carbapenem resistant Enterobacteriaceae, notably NDM expressing bacterial isolates[23].Odilorhabdins remain an emerging class of antibiotics that target ribosomes to effectively prevent translation and are also potent against wide range of bacterial strains [24]. A systemic mouse model was developed to illustrate the efficacy of the drug NOSO-502 against CRE strains expressing different classes of β-lactamases including NDM [25]. Tilapia-piscidin-3 (TP-3) and Tilapia-piscidin-4 (TP-4), two antibacterial peptide compounds produced from fish, shown efficacy in invitro tests against NDM harbouring *K pneumoniae*. It was determined that TP-3 and TP-4 are safe and can be utilised to treat NDM-positive strains[26]. By decomposing bacterial cell walls, photoactivated 2,3-distyrylidoles, a chemical mainly focused upon a 2,3-distyrylindole structure, exhibit a broad spectrum of action towards MDR bacteria. As a result, photoactivated 2,3-distyrylbenzyl derivatives may have the potency to be locally administered [27].

5.4. Antimicrobial Adjuvants

We desperately require significant therapeutic alternatives due to the dearth of existing treatment options. Adjuvant-containing combinations are perhaps one method for tackling with this escalating crisis. Antibacterial adjuvants encompass a broad range of substances across many synthetic scaffolds as well as natural compounds in addition to antibacterial agents. Some of the antibiotic adjuvant compound proved to be effective are, having 320 µg/ml of oxalic acid as well as succinic acids in combination with colistin lowered its Minimum inhibitory concentration (MIC) by 8 to 0.5 µg /ml displaying the combination might possess the effect of lowering the dosage of colistin [28].

In conventional checkerboard studies, copper shows synergistic activity with carbapenems against *E. coli* expressing NDM gene. In addition, the Food and Drug Administration (FDA) approved copper pyrithione coordination was tested in combination with a relatively small amount of copper (10 µM) to demonstrate synergism between copper and carbapenems.Cefepime and zidebactam again had significant antibacterial activity on isolates of Enterobacteriaceae and *P. aeruginosa* expressing a wide range of therapeutically important β-lactamases, including NDM [29]. Chander et al.,found that extracts of *Hibiscus spp*. and *Combretum albidum G. Don* etc. significantly suppressed the enzyme NDM-1 when treated with colistin[30]. Liu Z et al., reported the effect of magnolol which had significantly reduced the activity of NDM-1 enzyme and had been able to reinstate MEPs potential to combat NDM-positive *E. coli*[31].

5.5. Immunotherapeutic agents

Immunotherapeutic agents are an innovative, useful approach to fight against diseases caused by the NDM producing bacteria. Using the mouse pneumonia model infected with *K. pneumoniae* possessing NDM gene, cystatin 9 and cystatin C, two recombinant human cysteine proteinase inhibitors, were investigated [32]. According to this study, infected mice treated with either inhibitor or left untreated fared significantly worse than mice treated with the inhibitor. This indicates that the cysteine proteinase inhibitor treatment strategy is a promising way to combat bacterial pneumonia.

5.6. NDM Inhibitors

The development of NDM inhibitors would be a promising approach to combat bacteria expressing the NDM gene. Although numerous NDM inhibitors from diverse categories were identified and studied, neither of these compounds have yet been received approval for clinical use.

6. NDM-1 inhibitors: Discovery and Advances

The development of new drugs has been financially and significantly supported in recent decades by increasing global demand. Despite various approved inhibitors for serine-β-lactamases and significant computational drug discovery and development efforts, the realisation of an intended and potent NDM-1 inhibitor for clinical use was still hindered due to limitations like a narrow catalytic site, a dearth of specificity of the inhibitor, and even a lack of unique scaffolds [35]. The advent of NDM-1 triggered a plethora of studies investigating and testing promising NDM-1 inhibitors with the potential to protect antibiotics from hydrolysis. In the last decade, numerous investigations on inhibitors targeting NDM-1 have been published in the past decade. The primary objective of the study is to report the wide range of inhibitors identified so far.

6.1. Mode of action of NDM- 1 inhibitors

6.1.1. Reversible inhibitors

Recently, it has been found that certain inhibitorshave an effect on amino acids at the active. However, in another study, MDR bacteria carrying the NDM-1 enzyme were found to be inhibited instead of metal sequestration. The discovery of a heteroaryl phosphonate structure by Orville A. Pemberton et al.,[34]was described as evidence of non-covalent interactions with cross-inhibition of typical carbapenemase, primarily KPC2, NDM-1, and VIM -2, including favourable in vitro ADME properties. A small collection of chemical compounds comprising heterocyclic compounds was designed, synthesized, and described by Wen Bin Jin et al.,[35]to test their cytotoxic activity and combinatorial effect with MEP over NDM-1 harbouring*E.coli* Tg-1. When tested on cell lines, the formulations demonstrated minimal cytotoxicity and significant combinatorial activity on a range of clinical isolates from NDM-1-positive CRE strains, offering intriguing biochemical compounds and prospects towards by a class of organ sulphur compounds (Dithiocarbamates -DCs) derivatives comprising azacycloalkanes. The *in vitro* results indicate that the DCs exhibited low cytotoxicity in L929 mouse cells and exerted the strongest antibacterial activity against the bacterium *E. coli* (NDM-1). This would apparently lead to new possibilities and approaches for the discovery and advancement of novel carbapenemase inhibitors.

Perhaps cyclic boronates are one of the majorities of known effective NDM-1 inhibitors discovered so far.Vaborbactam is the first generation cyclic boronic acid has been given approval from the FDA as an SBL inhibitor[20]. Regardless of whether the boronate scaffold is cumbersome against MBLs, this has spurred further progress and research. Most β-lactamase subclasses, particularly the class B MBLs, are inhibited by taniborbactam(VNRX-5133), a bicyclic boronate scaffold [14]. Subsequent studies to optimise boron by substitution of the aryl ring revealed that perhaps the most effective acylamine substituents are methylthioacetamide. Efficacy against class B enzymes was significantly increased by using a thiol bond (QPX7778) instead of an amine group, while oral absorption was about 53% at dosage of 30 to 100 mg/ kg in fasting mice [36]. The boronate QPX7728 potentiates NDM-1 through an identical mechanism of action as VNRX-5133, which is significant because it affects a wide range of enzymes, compromisingclass D SBL, IMP and B1 MBL. The results support the choice of boric acid as a scaffold for the synthesis of versatile β-lactamase inhibitors. In contrast, 3-bromopyruvic acid (3BP), an effective nucleophilic precursor of the cellular metabolite (pyruvate), was identified as NDM-1 suppressive [37]. In addition, 3BP was shown to be safe in cytotoxic effects against L929 mouse fibroblasts.

In another study, Tony Christopeit et al. 2016reported 3-formylchromone, a potent reversible covalent inhibitor targeting NDM-1. The mechanism of reversible covalent inhibition lends itself to the development of small molecule inhibitors that can help treat bacterial infections resistant to conventional antibiotics. Although the inhibitor still needs to be optimised for therapeutic application, it has the whole potential to be a lead NDM-1 inhibitor molecule[38].In addition, further studies are needed to determine effective doses for infection prophylaxis, chronic problems, and clinical outcomes in *in vivo* studies.

6.1.2. Competitive Inhibitors

In 2019, Bo Ma et al., demonstrated that the secondary metabolite thanatin damages the cell wall bacteria composing NDM gene by selectively depriving positively charged ions from the cell wall and causing the expulsion of lipo-polysaccharides[39].The cytotoxicity of thanatin showed significant specificity for the cell wall of bacteria but not for mammalian cells, and Jia-Qi Li et al., discovered dipyridyl-thio-semicarbazone (DpC), which is

considered a specific inhibitor of MBLs. MEP's antibacterial effect against NDM positive *E. coli*(XJ141026) found significantly increased. In MBLs-producing bacteria and in mouse studies, DpC was shown to exhibit synergistic bactericidal activity, suggesting that both DpC and MEP could be used together to combat the health threat posed by the transfer of resistance to NDM-containing bacteria[40].

Using X-ray crystallography, Jun-ichiWachino et al., investigated the interaction patterns of 2,5-diethyl-1-methyl-4-sulfamoylpyrrole-3-carboxylate (SFC)with MBLs, designed SFC for significantly more efficient inactivation of different β-lactamases notably NDM-1 then evaluated their efficacy *in vivo*[41].It was found that perhaps the co-administration of MEP and SFC greatly reduced the mortality rate of mice infected with either *K. pneumoniae* MS5674 or even *E. coli* NUBL-24 carrying the IMP1 gene. Considering the therapeutic application of MEP, Shampa Das et al., designed ANT2681, a competitive binding inhibitor of MBLs with significant effect on NDM activities. Antimicrobial susceptibility testing of 1,687 CRE comprising 1,108 strains of NDM positive. MEP combined with ANT-2681 was found to be a promising novel therapeutic approach for treating severe diseases caused by NDM-producing bacteria [42].

In addition, González and colleagues presented BTZ synthesised by the double distillation of amino-thiols and mercapto-acetaldehyde dimer, focusing the process on how NDM-1 recognizes and hydrolysis β-lactam antibiotics [43].In this way, BTZs comprising L-CS-319 and L-VC-26 and its stereoisomers, were found to competitively block NDM-1and enhance the effectiveness of carbapenems in clinical strains encoding NDM-1 gene. When the cytotoxic effect of L-CS-319 was tested on cell cultures, no adverse effects were observed in cell lines - HeLa and Hek-293, suggesting that the compound does not in itself infringe with the other vital human enzymes. The two major pharmacophores of the four BTZ analogues are mainly the carboxyl group that binds to Lys224 and possibly the thiol moiety that interacts with the Zn ions in the catalytic site of NDM-1 [44]. To further expand the range of synthesised drugs, the compound could be modified with certain other simple therapeutic agents.

6.1.3. Irreversible Inhibitors

A Cys208 residue of NDM-1 remains crucial in order to interact with Zn ions, which is required to maintain a stable catalytic site, making it a potential target for NDM-1 inhibitor development. Disulfiram (DSF), a novel NDM inhibitor established an irreversible interaction with the Cys208 residue by forming a disulphide bond[45]. Oxidation of the Zn (II) thiol group within the enzyme also rendered Cu (DTC), the copper-containing substrate of NDM-1 *in vivo*, inactive. When administered with IPM, most DSF derivatives showed synergistic effects over NMP-1, ImiS, NDM-1 harbouring *E. coli*; IMP-1, NDM-1 *P. aeruginosa* and *K. pneumoniae* strains. Both B1 and B2 subtypes of MBLs are eventually inhibited by cisplatin and Pd (II) compounds discovered by Cheng Chen.

The Lys211 protein had also been thought to serve as a potential "handhold" in the advent of covalent NDM-1 inhibitors. Cefaclor, a β-lactam antibiotic, inevitably deactivates NDM-1 over several mechanisms, as Pei W. Thomas et al.,discovered in 2014[46]. The same researchers also discovered in a different study that an O-aryloxycarbonyl hydroxamate affinity tag that was directed at the Lys211 rendered NDM-1 inactive by forging a long-lasting interaction with in the active site rather than being directly interacted with the zinc ions. According to Pei W. Thomas et al.,[47]their findings suggested a technique of labelling the Lys could be an effective approach for constructing scaffolds which may inhibit simultaneously SBLs and MBLs. The zinc chelator Tris-picolylamine (TPA) was constructed into ZN148 by OrjanSamuelsen, who further demonstrated that ZN148 inhibited MBLs in a time dependent manner and removed zinc ions from catalytic site. ZN148 is ideally positioned to join the drug development pipeline as another potential approved compound in order to address the imperative therapeutic problem of major global concern [48].

Ying Ge et al., 2021 developed thirteen thiosemicarbazones and tested to discover effective NDM-1 inhibitors. The experiments demonstrate that thiosemicarbazide is indeed a promising substrate towards the synthesis of novel inhibitors against NDM-1 expressing MDR bacteria since the synthesized compounds selectively blocked NDM-1[49]. Ebselen is perhaps a medication that is being tested on humans to address cerebral ischemia as well as stroke. It is quite efficient and is well accepted in experimental animals, does have very minimal side effects, and the minimum inhibitory levels of AM and MEP were lowered by ebselen but the propensity in developing drugs is constrained by toxicity of selenium component [50]. Current attempts could perhaps be focused on enhancing its selectivity towards MBL and lowering the cytotoxicity to certain other cysteine containing human enzymes. Following that, Cheng Chen et al.,devised dual irreversible inhibitors resulting selenide-sulfide bond (SeS) between Cys221 and ebselenand amide bond between ester and of Lys224 of NDM-1 at Zn2 of the enzymes active

site respectively. The results showed the effective suppression of NDM-1 expressing clinical strains and *E. coli* - BL21 in *in vitro* and *in vivo* experiments against B1 and B2 class of MBLs [51].
An effective covalent compound "ebsulfur" was identified by JianpengSu et al. in 2019for addressing NDM-1 enzyme inhibition by *in vitro* and *in vivo* studies. It had been observed that ebsulfurs curtailed NDM-1 activity. They have further exhibited minimal cell-toxicity whilst significantly restoring CZ antibacterial efficacy over *E. coli* that expressed NDM-1[52]. In their 2019 study Cheng Chen et al.,synthesised a structure composed of 1,2-benisoselenazol-3(2H)-1 and evaluated the efficacy of the compounds in successful restoration of the antimicrobial property of β-lactam antibiotics against NDM-1 expressing *E. coli*[53]. Colloidal bismuth sub-citrate (CBS), a potent drug used to cure diseases spurred by *Helicobacter pylori*, was shown to lower the MIC and FICI of MEP against NDM:HK [54].

6.1.4. Allosteric Inhibitors

Since many inhibitors were developed specifically to target catalytic site of the NDM-1 enzyme, allosteric inhibition might be advantageous given that a specific gene mutation might contribute to resistant strains. In addition, an inhibitor acting away from the catalytic site would prevent further mutations thus retaining inhibitory potency [55]. In a study by Yang et al., carnosic acid is recognized as a novel allosteric NDM-1 inhibitor. It strongly hinders NDM-1 action and reduces the total MIC of MEP in *E. coli*by approximately a four-fold reduction. It has been demonstrated that the loop 3 side-chains and the α-1 helix interact hydrophobically and form stable hydrogen bonds with carnosic acid. Additionallycompared to wild type, the mutants of NDM-1 constituted relatively weak bonds with the carsonic acid and had lower inhibition effect [56]whereas recently P.W. Thomas et al., identified QDP-1 as a potent inhibitor which significantly lowered the MIC of MEP in clinical NDM-1 expressing strains.

6.1.5. Inhibitors acting on Zinc ions (Zn^{2+})

$Zn^{2+}$are often a vital component for NDM-1's enzymatic activity; zinc starvation is one of the most significant factors that inhibit zinc dependent enzymes; and metal-chelators, such as EDTA, have been frequently reported to reduce MBL enzyme activity [57,58]. Consequently, indiscriminate cytotoxic activity has rendered chelating drugs unsuitable for therapeutic applicationin light of the presence of metallo-enzymes in human-body. Because of this, scientific experts have altered the architecture of such compounds to boost specificity and preclude cytotoxicity. For instance, Ca-EDTA, a combination comprising EDTA and its conjugate base, proved that Ca-EDTA might be used in healthcare settings as a potent NDM-1 inhibitor [59].An efficient zinc scavenger and among the most potential metal chelators, aspergillomarasmine A (AMA) reinstates bacteria that have been resistant to carbapenems and inhibits NDM-1 via by stripping the metallic ions [60]. Furthermore, in mice, AMA had been well absorbed and displayed a high level of bioavailability [4]
In the comparative study of acyclic and macrocyclic chelating agents as promising MBL inhibitors when used in conjunction withMEP[61] found TPEN, DPAtoo were able to lower MICs of MEP. Since macrocyclic chelators are relatively safe over acyclic chelators and display a greater specificity towards zinc. Further, researchers discovered 1,4,7-triazacyclononane (TACN), a cyclic synthetic compound pertaining to the NOTA and DOTA classes, which successfully restored MEP's activity over B1 MBLs [62]. The sulphur group within its diazole core of the spiro-indoline-thiadiazole structure was identified to be essential towards chelating metal ions as well as anti - bacterial action by F. Falconer et al.,[63].
Three constitutively active spiro (indoline-thiadiazole)compounds were found by the other team of scientists. The scaffold was identified to block NDM-1 and when combined with MEP, CD1 mice had considerable reductions in bacterial count and without any observable effects. Benzimidazole and benzoxazole scaffolds were examined by Abigail C. Jackson et al.,[64]as NDM-1 inhibitors, in which it was found that these compounds enhanced the MEP sensitivity in NDM-1-harbouring *E. coli*. De-Yun Cui et al.,discovered that the modified Para-alkyl complexes had the potential to positively affect and exhibit less cytotoxicity on HeLa cells, making them potential treatment option against MDR bacterial strains including MBLs[65].
The potency of Di-(2-picolyl) amine (DPA) and tris-(2-picolyl) amine (TPA) over various MBL types as well as their better binding specificity with NDM-1 were illustrated by Sphelele C. Sosibo et al.,[66]. One of most effective compounds was discovered to be TPA, which has three pyridyl moieties, trailed by DPA and MPA, respectively. Wang Bin Jin et al.,created pyrrolidines with trans-1,3,4-trisubstituted groups and investigated a key pyrrolidine

with considerable synergistic effects towards NDM-1 expressing CRE clinical isolates[67]. Jia-Qi Li et al., 2021investigated thiosemicarbazone, a promising scaffold. The association between the substrate specificity of chemically synthesized thiosemicarbazones showed further that diaryl-substitutes, in specific 2-Pyridone and 2-Hydroxylbenezene, significantly increased the therapeutic activity of the chelators and displayed potent inhibitory activity against *E. coli*, *K. pneumoniae*, and *P. aeruginosa* isolates expressing NDM-1 [40]. Chris S. Thomas et alinvestigation into PDTC action in combination with MEP against NDM-1-carrying CRE bacteria as well as NDM-1 kinetics experiments revealed, in parallel with the PDTC ligand, metal-bound PDTC complexes have been effective in suppressing the activity of NDM-1[68].As a step towards the thiol based MBL inhibitor, a study published by Yu-Hang Yan et al., 2020showed that meta and ortho-mercapto-propenamide substituted aryl-tetrazoles displayed important structural-activity relationships. They discovered that the compound chelated the catalytically active zinc ions using the thiol group. Both binding interactions and inhibition mechanism obtained in *in vitro* and *in vivo* experiments potentially support other investigators' structure - based designing even though chelating compounds typically have safety constraints that make them not suitable for therapeutic applications[20].

6.1.6. Natural compounds and their derivatives

Yet another area of research targeting NDM-1 inhibitors is natural products[73]. Magnolol was identified by Liu et al. as a potent inhibitor that significantly reduced NDM-1 enzyme expression. When combined with MEP, magnolol restored the antimicrobial efficacy of *E. coli*-ZC-YN3 harbouring NDM-1 gene[31]. A well-known polyphenol known as pterostilbene found in *Pterocarpus santalinus* (red sandal wood). Liu et al. investigated the bioburden and antibacterial efficacy and found that the compound effectively inhibited NDM-1 and significantly enhanced the antibacterial effect of MEP [71].In addition, according to Riche et al, patients with hyperlipidemia who received pterostilbene at doses of 100 to 250 mg per day had no significant side effects [72]. The inhibitory effect of Embelin on antibiotics was first described by Ning et al. Embelin has an excellent safety profile as demonstrated by acute toxicological studies in mice administered orally at a dose of 50 or even 100 mg/ kg, which showed any appreciable difference in body mass, morbidity, and observable toxicities. Thakur et al.,discovered that nimbolide and isomargolone had lower IC_{50} values than β-lactam antibiotics as well as showed significant binding near the catalytic site and they lack the structure advantage of a β-lactam ring, making them easier to resist the catalysis of hydrolytic activity of NDM-1 [69].

In a study conducted by Brinda Chandar et al., 2017,found that various *Hibiscus spp*. and other plant extracts exhibiting antibacterial properties and curbed the NDM-1 enzyme activity and exhibited synergism with MEP, tetracycline, and colistin[30]. When crude soy saponins were screened for β-lactamase inhibitory properties by Hitoshi Horie et al., [73]they were found to inhibit β-lactamases, particularly NDM-1. Therefore, to create potential agents targeting NDM-1, they could be subsequently optimised. Hesperidin, a major component of vitamin P and one of the effective inhibitors discovered by Chen Shi and team, exerts its effect on vital amino acids at the active site of NDM-1. It may be investigated as a precursor molecule for the advent of NDM-1 inhibitors owing to its low toxicity and biocompatibility[74].

Other natural products such as baicalin, the primary active ingredient from the radix of *Scutellariabaicalensis* used in traditional Chinese medicine, could reverse the sensitivity of NDM-positive *E. coli* BL21-DE3 to commonly prescribed β-lactam antibiotics. Due to its low toxicity, baicalin is an attractive lead molecule for further synthesis of compounds against NDM-1 enzyme[75]. Isoliquiritin from *Glycyrrhiza uralensis Fisch* was recently discovered by Yanling Wang and colleagues as a promising inhibitor of NDM-1, especially the FICI values of isoliquiritin in combination with MEP were lower against NDM-positive bacteria. As a result, it might be used as a lead compound in the future to develop significantly potent NDM-1 inhibitors[76].

7. Conclusion

Recent addition of NDM-1 into B1 subclass of MBLs is prevailing across the globe and is rapidly spreading within the bacterial population. The NDM-1 enzyme hydrolyses all major potential β-lactam antibiotics notably last resort carbapenems, which is extremely worrisome. Consequently, one of the most effective strategies to combat NDM-1-containing bacteria would be the successful identification of extremely potent inhibitors and their use in conjunction with β-lactam antibiotics. There are significant difficulties in developing inhibitors that are effective against NDM-1. NDM-1 and its variants use a flexible hydrolysis method, which increases their risk of causing

drug-resistant infections. Analysis of the crystalline structure shows that NDM-1 has a shallow catalytic site and a specific metal ion which enable it to target a wide range of compounds.The two Zn ions and distinct enzymatic activity of this β-lactamase group set it apart from other β-lactamases. Since no structural intermediate is established during hydrolytic mechanism between both the enzyme and substrate, it is particularly challenging to produce inhibitors.Only a few key residues have been identified as important covalent inhibitor domains. It is challenging to target these important amino acid residues in the active site while maintaining toxic effects. The interaction mechanism of NDM-1 with substrate should be better understood with the advent of bioinformatics, medicinal chemistry and various other interdisciplinary sciences and technologies. This study provides a comprehensive overview of NDM-1 and the progress in inhibitor development serving as a valuable tool for discovering and developing novel inhibitors.

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