Coordination Chemistry Reviews 453 (2022) 214317

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Metalloenzyme mimicry and modulation strategies to conquer antimicrobial resistance: Metal-ligand coordination perspectives

Yusuf Oloruntoyin Ayipo [a,b,*,1], Wahab Adesina Osunniran [b,1,*], Halimah Funmilayo Babamale [c,d], Monsurat Olabisi Ayinde [e], Mohd Nizam Mordi [a,*,1]

[a] Centre for Drug Research, Universiti Sains Malaysia, USM, 11800 Pulau Pinang, Malaysia
[b] Department of Chemistry and Industrial Chemistry, Kwara State University, P M B, 1530 Malete Ilorin, Nigeria
[c] School of Chemical Sciences, Universiti Sains Malaysia, USM, 11800 Pulau Pinang, Malaysia
[d] Department of Industrial Chemistry, University of Ilorin, P. M. B, 1515 Ilorin, Nigeria
[e] Department of Chemistry, University of Ibadan, Ibadan, Nigeria

ARTICLE INFO

Article history:
Received 16 July 2021
Accepted 8 November 2021
Available online 24 November 2021

Keywords:
Metalloenzymes
Antimicrobial resistance
Biomimetic
Catalysis
Metal-chelating inhibitors
Coordination chemistry

ABSTRACT

The incessant resistivity of pathogenic microbes to antibiotics continuously constitutes a major threat to human wellness, thus, searching for effective therapeutic approaches remains essential. Metalloenzymes such as erythromycin esterases, β-lactamases, N-acetyltransferases, staphylopine dehydrogenases significantly confer antibiotic resistance and cell defence in superbugs including *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia, Helicobacter pylori* and *Staphylococcus aureus*. These occur through various pathomechanisms including modulations of intracellular targets, hydrolytic cleavage and cellular metabolism of antibiotics, redox catalysis, and oftentimes *via* the attraction/donation of electrons during labile coordination to substrates. Several inhibitors of these therapeutic pathways have been reported including metal chelators and chelates. However, the overview of these innovative anti-resistance strategies remains sparse. We hereby present a comprehensive review of the coordination chemistry of metalloenzymes in the resistance development and modulatory potentials of metal-chelating and metal complex inhibitors for catalytic deactivation. These include the removal/replacement of biotic metal ions and/or chelating agents to induce loss of resistivity and specificity, and suppression of catalytic activities as potential therapeutic strategies. Selectively, **imipenem, meropenem, hesperidin, aspergillomarasmine A, picolinic, rosmarinic** and **salvianolic acids** represent potent metal-chelating inhibitors of the metallo-β-lactamases, ligands **B67-B78** as promising candidates against ureases, while **B79-B83** effectively suppressed catalysis of polyphenol oxidases. Some metal chelates also demonstrated potentials to mitigate the defence/resistivity of the metalloenzymes hypothetically through the acquisition of abiotic metals ions, accumulation of antimicrobial ligands and blockage of active metalloenzyme sites. This review represents a model for innovative therapeutic strategies to overcome antimicrobial resistance through metalloenzyme mimicry and modulation for further studies.

© 2021 Elsevier B.V. All rights reserved.

Contents

1. Introduction . . . 2
2. Effects of metal cofactors on mechanisms of antimicrobial resistance . . . 3
3. Enzymatic mimicry and modulation through metal–ligand coordination . . . 5
   3.1. Removal of biotic metal cofactors by metal chelators . . . 6
      3.1.1. Theoretical estimation of Zn(II) cofactor effects on the substrate specificity of metallo-β-lactamases . . . 8
      3.1.2. Factors that favour inhibitory chelation of metal cofactors by small molecules . . . 10
   3.2. Inhibition of metalloenzymes by metal chelates . . . 11
   3.3. Replacement of biotic metal cofactor . . . 14

* Corresponding authors.
E-mail addresses: yusuf.ayipo@kwasu.edu.ng (Y.O. Ayipo), wahab.osunniran@kwasu.edu.ng (W.A. Osunniran), mnizam@usm.my (M.N. Mordi).
[1] These authors contributed equally.

https://doi.org/10.1016/j.ccr.2021.214317
0010-8545/© 2021 Elsevier B.V. All rights reserved.

3.4. Suppression of catalytic activities of metalloenzymes . . . 15
4. Coordination complexes of metal cofactors as potential anti-resistant agents . . . 18
5. Conclusion and future challenges . . . 18
Declaration of Competing Interest . . . 19
Acknowledgements . . . 19
References . . . 19

1. Introduction

The incessant resistivity of pathogenic microbes to antibiotics continuously constitutes a major challenge to human healthcare. In 2019 for instance in the United States of America, over 2.8 million clinical cases were reportedly developed by antibiotic resistance, out of which over 35,000 resulted in mortality. The forecasted 10 million deaths per year by 2050 also constitutes a big threat and thereby makes the development of more effective therapeutic strategies to curb the menace remain crucial [1,2]. Enzymes play critical roles in catalytic-dependent biochemical transformations for functional biological systems. They are capable of speeding up systemic processes by up to 10^{17}-folds and efficiently enhance biological reactions through the lowering of activation energy [3,4]. Unlike inorganic catalysts, they are specific in actions. Naturally, the drug-targeted enzymes undergo periodic molecular modifications to evade therapeutic actions and eventually develop resistance especially after a long term exposure [2]. Bacterial enzymes contribute immensely to the development of antibiotic resistance through various pathomechanisms. Notably, gene encoding variability (in resistomes), modulations of intracellular targets, enzymatic transformation and cellular metabolism and disruptive hydrolysis of antibiotics [2,5]. Some resistant microbial infections are arduous to manage due to biochemical similarities between their vectors and mammalian cells, which could trigger indiscriminative cytotoxicity by antibiotics. More so, some opportunistic fungi tend to settle in certain areas of the body which are inaccessible to drugs [6]. These factors contribute significantly to the resistance and other efficacious challenges associated with various antibiotics.

Metal ions are essentially required for several functions within biological systems to maintain healthy living, as such, their inadequacy or excessiveness may trigger maladies. In addition, their presence in metalloenzymes of microorganisms contributes significantly to the resistance-related activities. These include the ions of the main group metals such as K^+, Na^+ and Ca^{2+}, and those of the transition family including Cu^{2+}, Ni^{2+}, $Fe^{2+/3+}$, Zn^{2+} and Co^{2+}. Although few such as the ions of Hg and Pb confer cytotoxicity even at low concentrations while some others could induce oxidation [7,8]. Metalloenzymes constitute almost 50% of all protein targets and catalyse several chemical reactions including the most complex ones within biological systems [9]. They are also involved in various transformations of natural products by microorganisms including hydrolytic, oxidation and reduction processes through metal ion cofactors at their active sites, with vitamins as major sources of the cofactors [10]. Examples are the radical S-adenosylmethionine (RaS) enzyme family which are predominantly implicated in the production of ribosomally-synthesised and post-translationally modified peptides (RiPPs), a class of natural products with diverse functions, and superoxide dismutase which destroys superoxide ions [11,12]. Others include phosphodiesterase, nitrogenase, vitamin B-inclined enzymes, cytochrome p450cam, carboxypeptidase A and staphylococcal nuclease. Their biological functions are strongly influenced by the coordination chemistry of the metal centres at the active sites as illustrated (Fig. 1A-C) [11]. For instance, in mycobacterial cells and mitochondrial respiratory chains, cytochrome bc_1-aa_3 supercomplex and cytochrome *bd* oxidase contain Fe and Cu ion cofactors. The metalloenzymes are used to generate a proton motive force to induce oxygen reduction by electron transfer from menaquinone to molecular oxygen, and across a series of membrane-bound multiprotein complexes to the terminal respiratory oxidases. The targets are regarded as primary respiratory routes for synthesising adenosine triphosphate (ATP), thereby optimising the bacterial cell growths. These make them a plausible drug target for inhibiting mycobacteria. Several natural and synthetic organic small-molecule inhibitors have been reported for the pathogenic strains including *Mycobacterium tuberculosis* and *Mycobacteriumbovis*, however, their inhibitory mechanisms are rarely along the metal chelation pathway [13-15]. Although, a few metal-chelating inhibitors of the cytochrome *c* in *Candida krusei,* a multidrug-resistant fungal pathogen in patients with immunocompromised and

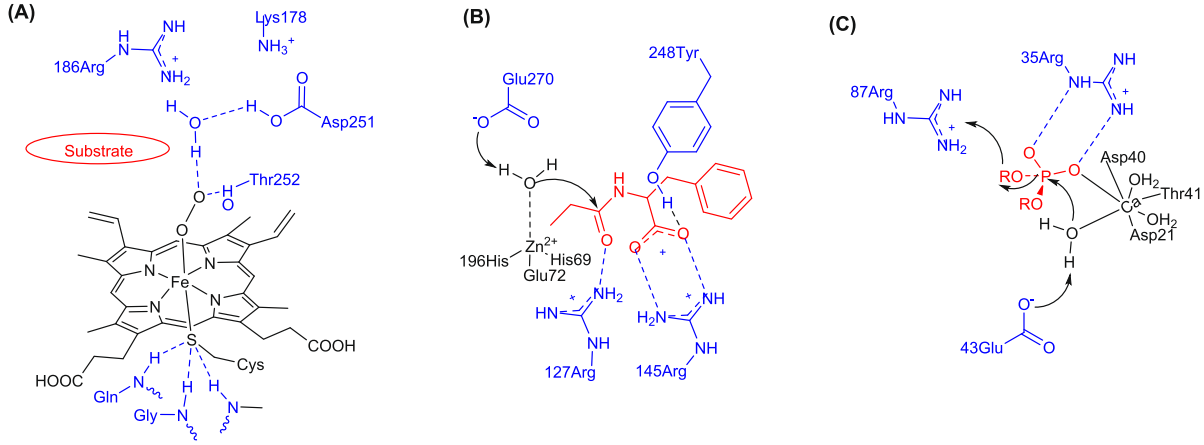


Fig. 1. Illustrations of some metalloenzyme active sites. (A) Cytochrome P450cam; (B) Carboxypeptidase A; (C) Staphylococcal nuclease. Metal cofactors in coordination to organic/inorganic ligands (black), spheres of hydrogen bonding interactions with surrounding moieties (blue) and guest molecules or substrates (red). (Reproduced with permission from [11], copyright 2017, Elsevier Ltd).

haematological malignancies has been documented. These include nalidixic acid, piromidic acid and 1,10-phenanthroline with a respective minimum inhibitory concentration of 13.4, 43.4 and 125 μM [16]. However, no further information was recently found in favour of their efficacy along the pathway under focus. Also, a complex modified cytochrome *c* adsorbent, N-metacryloyl-$_L$-histidine methyl ester was reported with an adsorption mechanism through Cu^{2+} cofactor chelation [14]. These pieces of evidence further buttress the implications of metalloenzymes in the pathogenic activities of antimicrobial resistance and their modification as an interesting therapeutic strategy.

Coordination and organometallic chemistry plays important roles and has been imparted greatly in everyday life. The biochemical properties of coordination compounds can be fine-tuned by restraining the centre oxidation state and choosing the most suitable ligands for each application [17]. For instance, the coordination chemistry of nucleating ligands has been explored through the modifications of dinuclear complexes, importantly for the production of novel catalysts, metalloenzymes and metalloproteinases. Dinuclear metalloproteinases are ubiquitous, mostly share crucial structural characteristics such as the spanning of the central metals at least by an Oxo species within the exogenous water, yet with significant differences in functionality, [18]. Thus, the analysis of the enzymatic modifications of antibiotic-targeted metalloenzymes and their mutants in resistance development could pave ways for the strategic designs of effective drugs to overcome the resistance menace [2]. The success stories of this innovative therapeutic science have been documented against multidrug-resistant bacteria including *Mycobacterium abscessus,* a mycobacterial species responsible for non-tubercular mycobacterial (NTM) infections, *E. coli, S. aureus* and *P. aeruginosa* [5,19,20].

The mimicry and modulation of the metalloenzymes through coordination chemistry constitutes a promising scientific strategy to overcome antimicrobial resistance. Several metal-chelating inhibitors have been reported to coordinate to the central metal cofactors, thereby sequestering the metal ion to deactivate the metalloenzymes with subsequent loss of substrate specificity and suppression of catalytic effects. Some other metal chelates from recent literature have also been demonstrated with the potentials to mimic the metalloenzymes and mitigate the defence/resistivity of the pathogenic microorganisms. Their activities are hypothesised mechanistically through the acquisition of abiotic metals ions by the enzymes, coordination of metal cofactors to antimicrobial ligands, increment of antimicrobial moieties and blockage of active sites by the complexes [3,4,21]. Additionally, the diversity in the coordinated protein ligands and ligand exchange processes significantly modify the metallic properties of the cofactor which in turn induces variation in the protein actions. These strategic modulations have become a subject of progressive research interests in recent times. However, the comprehensive overview of these innovative anti-resistance scientific strategies remains sparse. A recent review by Fatima and co-workers highlighted organism-based strategies for inhibiting the multidrug-resistant bacteria including those of β-lactamases (BLs), implicating inhibitors from natural plants, peptides, RNA engineering, bacteriophage, however with less focus on the mechanistic modulation of metalloenzymatic activities [22]. Also reported recently is a synopsis of general enzymatic modification as a therapeutic target against antibiotic resistance, however, the perspectives of molecular interplay and coordination chemistry of the metal cofactor centre were less considered [2]. Similarly, some renowned inhibitors of β-lactamases such as the combined therapy of clavulanic acid-amoxicillin, sulbactam-ampicillin and tazobactam-piperacillin labelled by trade name Augmentin®, Unasyn® and Tazocin® respectively exhibit diverged inhibitory mechanisms [23,24], as such less focused. Kontogiorghes and Kontogiorghes also surveyed the iron chelation effects of some ligands in mitigating proteins implicated in metabolism-related diseases including the cytochrome members, however, with rare attention to antimicrobial resistance [25]. We hereby present a comprehensive review of the analysis of the effects of the metal cofactors in the resistance-inclined activities of metalloenzymes and, their mimicry and modulation as potential strategies for deactivation. Furthermore, the potential loss of resistivity and specificity by the metalloenzymes were succinctly overviewed through multi mechanisms including the sequestering and/or displacement of biotic metal cofactors, modifications of coordinating ligands and modulation of catalytic activities from the coordination chemistry perspectives (Fig. 2). These scientific analyses interestingly potentiate therapeutic solutions for antimicrobial resistance and channels research pathways for further exploration.

2. Effects of metal cofactors on mechanisms of antimicrobial resistance

Metal cofactors are strongly involved in the biochemical activities of the metalloenzymes and metalloproteinases such as antibiotic resistance development. Some of the metalloenzymes consist of multimetallic centres which oftentimes strengthen their performance as a result of synergistic activation and transformation of substrates, and up-tuning of a metal cofactor effects by the other [26]. Several metal-dependent enzymes including the catalases, peroxidases and superoxide dismutases contain Mn as a cofactor, importantly involved in the cell defence mechanisms against oxidative damage and nitrosative attacks through the detoxification of peroxides and free oxygen radicals. Among the enzyme class, catalase-peroxidase (katG) confer drug resistance in *M. tuberculosis* through the catalytic oxidation of isoniazid to a less effective isonicotinic acid radical [27,28]. Others including the erythromycin esterases A and B confer antibiotic resistance to macrolides such as azithromycin and erythromycin. Although, their homolog proteins BcR135 and BcR136 are characterized by Ca^{2+} ions with an unclear contribution to catalysis, however, their pro-pathogenic activities are usually inhibited by chelating agents [5,29]. Among the phosphomycin-modifying enzymes, FosA, a glutathione-S-transferase and its FosB counterpart consist of K^{+}, Mg^{2+} and Mn^{2+} as cofactors, contributing to therapeutic pathways in some bacteria strains including *S. aureus* and *P. aeruginosa* [5].

The BLs are mainly responsible for the resistance of Gram-negative bacteria such as *P. aeruginosa, E. coli, K. pneumonia, Acinetobacter baumannii* and *Enterobacterales*. They represent the most threatening agents of antimicrobial resistance. Among the renowned families of the BLs are the cephalosporinases (AmpC), narrow-spectrum BLs, extended-spectrum BLs (ESBLs) and carbapenemases. The resistance development by the ESBL is mediated by amino acid substitution and acquisition of plasmid, a self-replicating extrachromosomal DNA fragment that spreads the β-lactam resistance gene. Notably among the resistance gene-encoding BLs of this class include TEM, SHV and CTX-M produced by *Enterobacteriaceae* such as *E. coli* and *K. pneumonia* [30-33]. The carbapenemase sub-class includes the metallo-β-lactamases (MBLs) such as the New Delhi metallo-β-lactamase-1 (NDM-1), imipenemase (IMP) and Verona integron-encoded metallo-β-lactamase (VIM) which contain catalytically active Zn^{2+} ion in the hydrophobic cavity, importantly for modulating structural and dynamic functions including substrate binding and specificity. Their mechanism of resistance to β-lactam antibiotics occurs mainly through the reactivity of the Zn centre in catalytic hydrolysis. The MBL as a coordination compound-catalyst tends to undergo a series of transformations along the course of catalysis. These include changes in the bonding mode, coordination number, geometry, ligand exchange among others [34]. The mechanisms of

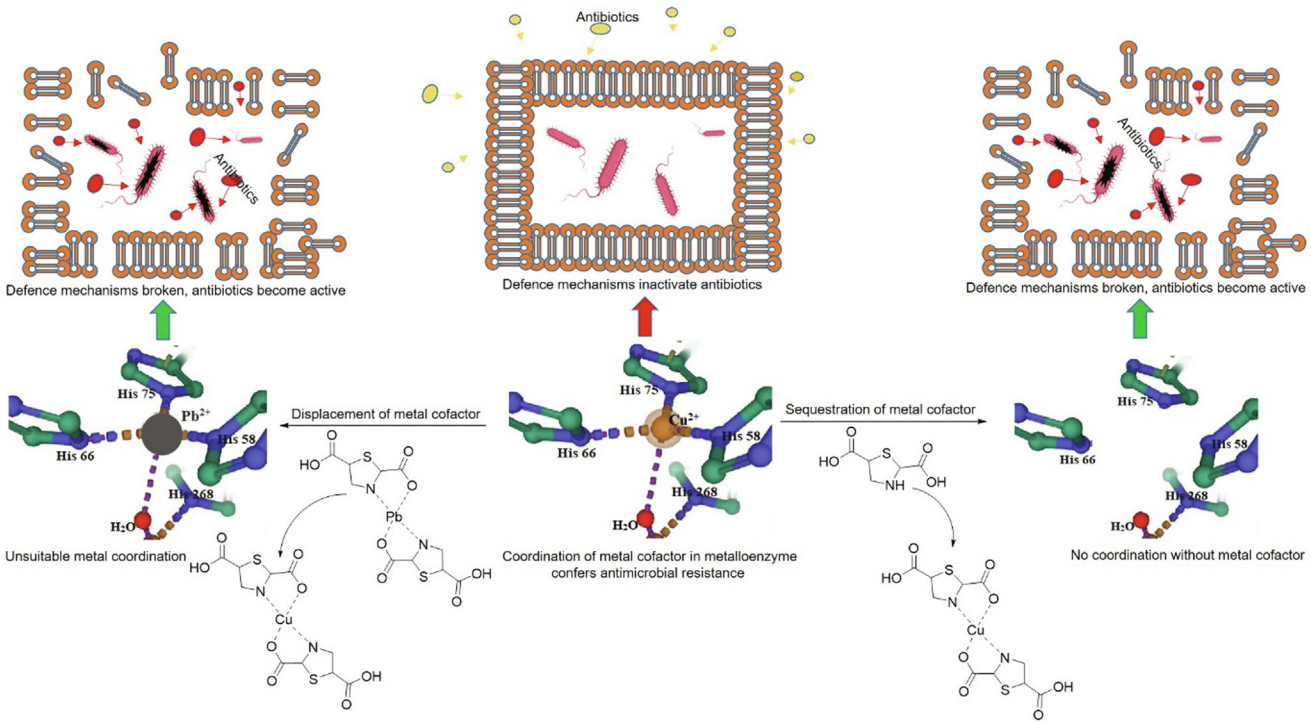


Fig. 2. Illustration of modulation of metalloenzymes by chelation to reverse antimicrobial resistance. Coordination of Cu(II) ion cofactor at the active site confers antimicrobial resistance (centre). The defence mechanism is reversed through the sequestration of metal cofactor by chelator (right) or displacement by ligand complex of abiotic metal (left) to induce loss of substrate specificity and weaken antibiotic resistance by disrupting the molecular coordination.

their resistance-inclined activities include the catalytic cleavage of the β-lactam rings in the drugs using the nucleophilic water molecules, thereby deactivating the inhibitors (Fig. 3) [5,35-40]. The study of biochemical and biophysical phenomena of the catalytic, hydrolytic cleavage of the β-lactam ring in imipenem, a carbapenem antibiotic by the mononuclear and binuclear Zn(II)-based NDM-1 was demonstrated by Lisa and co-workers. The analyses confirmed the participation of Zn(II) ion either as a mono- or binuclear cofactor in the activation of the enzyme for the resistance-inclined hydrolysis of the antibiotic. Summarily, the kinetic model (Fig. 3A) indicates the formation of two intermediate species (EI_1 and EI_2) from the reaction of the enzyme (E) with imipenem, a substrate (S). One is the Michaelis complex while the other is the anionic form of the drug. The characterization of the Michaelis complex at the resting, intermediate formation and product formation states was used to monitor the contribution of the Zn site in the hydrolysis stages. In both mono- and binuclear scenarios, the original coordination sphere of Zn in the enzyme was 4 in geometry, with direct coordination to two histidine residues, one aspartic acid and one water molecule (Fig. 3B and Fig. 3C) [41]. The coordination number increased to 5 and 6 respectively when the Zn sphere interacted with the electron-rich pyrrolyl N and hydroxyl O of the drug molecule, leading to the opening of the β-lactam ring. In the presence of water, the Zn complex products (EP) become hydrolysed to finally reproduce the molecular/radicalised enzyme as present initially and a deactivated anionic form of the drug without the β-lactam ring. Since, the coordination of Zn inestimably contributes to the destructive hydrolysis of the antibiotic drug, the removal of the Zn ion constitutes an essential strategy for protecting the molecular β-lactam ring, conserving the sensibility of the antibiotic and reversing the resistance aid of the metalloenzyme.

Selenium is essentially present at the active site of various selenoproteins including the deiodinases, glutathione peroxidases and thioredoxin reductases of several lactic acid bacteria (LAB) including *Fructobacillus tropaeoli and Lactobacillus plantarum*. It usually exists in form of selenocysteine, modulating microbial growth, metabolite distribution and several other enzymatic activities [42]. The activation of glutathione peroxidase, a Se-containing enzyme that regulates oxidative damage in organisms reportedly promotes anti-inflammatory response in the management of cancer and neurodegenerative diseases [4,43,44]. Similarly, certain pathogenic microorganisms such as the flesh-eating *Staphylococcus pyogenes* induce pains, redness and swollen surface during infection, and associated with inflammation, an immune-system response. Moreover, the bacteria are implicated in the pathophysiology of necrotizing fasciitis by eating away the tissue underneath the skin during infection, thereby triggering an inflammatory response. [45]. Although, the direct contributions of Se to these effects remain underexplored, however, hypothetically attributable to its activation of the enzymes.

Recently, *Klebsiella pneumonia*-carbapenemase 2 (KPC-2), a variant of the MBLs reportedly displayed a resistance-inclined dynamism through a rapid hydrolytic deacylation of the covalent intermediate in up to 20,000-folds of the popular TEM-1 analogue [46]. The incessant genetic mutations and transcriptions associated with the metalloenzymes of this deadly class constitute therapeutic snags and continuously pose a great threat to the global healthcare systems. For instance, the novel KPC-2 of *Klebsiella michiganensis* encoding the bla_{VIM-1} gene with a strange class 1 integron (In87), isolated in Switzerland from a Turkish patient was observed to acquire antibiotic resistance genes [46], indicating life-endangering threats. The metalloenzymes of these highly resistant pathogenic microorganisms consist of Zn(II) in coordination with amino acids and other ligands at their active sites for stability and substrate specificity as shown in Fig. 4A.

Also, the contribution of Mg^{2+} ions at the active site of the N-acetyltransferases (Fig. 4B) to biological activities cannot be over-

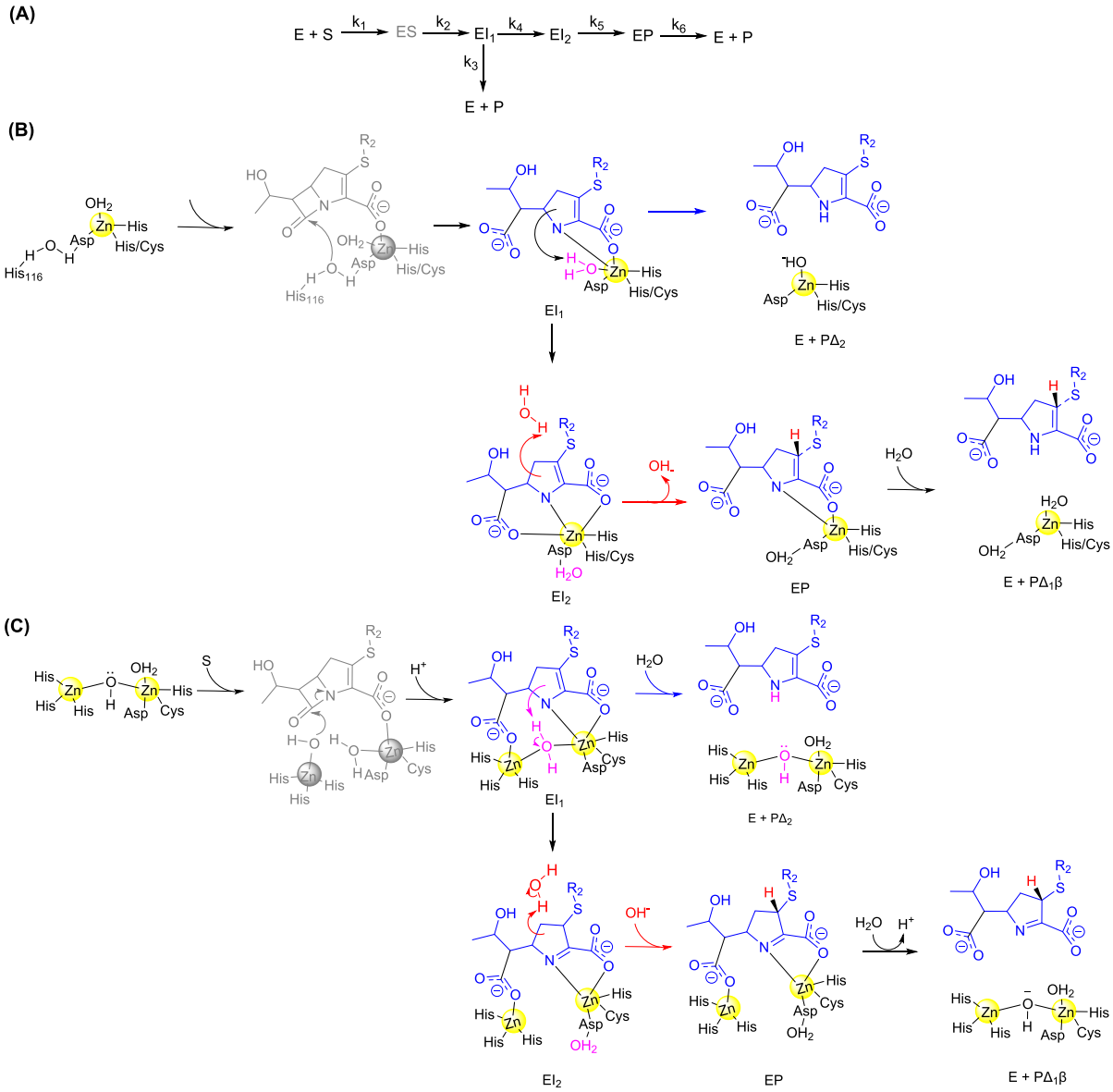


Fig. 3. General reaction mechanism for hydrolytic cleavage of the β-lactam ring of carbapenem by mononuclear metallo-β-lactamases (MBLs). (A) Summary of thermodynamic and kinetics of the catalytic process (E = intermediate; S = substrate; P = product). (B) Proposed mechanisms for carbapenem hydrolysis by mono-Zn(II)-MBLs. (C) Proposed mechanisms for carbapenem hydrolysis by bi-Zn(II)-MBLs. The Michaelis complex (ES) does not accumulate in all cases and is hence depicted in a different colour (grey). Its structure is proposed based on the ES detected for mononuclear MBLs. (Reproduced from [41], Licensed under CC BY 4.0).

ruled. The hemoproteinous catalase, peroxidase and cytochrome are essentially characterized by $Fe^{2+/3+}$ ions for catalytic activities. Metalloenzymes such as ascorbic acid oxidases, cytochrome oxidases and tyrosinases (TYRs), catechol oxidases (COs) (*Aspergillus oryzae*) also contain Fe and Cu, xanthine oxidase contains Mo, ATPase has Mg, while DNAase and acetyl-CoA carboxylases have Mn [4]. The structural analogues of COs and TYRs, aurone synthases and polyphenol oxidases (PPOs) also contain a type-III Cu centre [47]. Other metal–organic frameworks naturally present in the active sites of enzymes of organisms mainly bacteria include the nickel-pincer nucleotide (NPN) in the lactate racemase of *L. plantarum* (Fig. 4C), iron-guanylpyridinol in [Fe] hydrogenase, lanthanide-pyrroloquinoline quinone in alcohol dehydrogenase of *P. putida*, Cu^{2+} ions in catechol oxidase of *A. oryzae* (Fig. 4D) [48], tungsten-/molybdenum-pyranopterin in aldehyde oxidase of *Methylobacillus* sp. and nickel-tetrapyrrole coenzyme F430 in methyl coenzyme M reductase [49].

3. Enzymatic mimicry and modulation through metal–ligand coordination

Metal ions at the active sites of metalloenzymes contribute to biocatalysis and specific functions including defence mechanisms of organisms through the attraction/donation of electrons during labile coordination to substrates. In addition, a good number of biological proteins require metal ions for their functions. Since pathogenic microorganisms require the acquisition of metals ions from their host systems for survival and virulence activities such as hydrolytic reactions, respiration, energy metabolism, redox catalysis, DNA synthesis, Lewis acidity and functional diversity of metalloenzyme/proteome [51-53], the development of mimicking and modifications of ligand–metal coordination is reasonably hypothesised as a strategy for modulating pathogenesis and treatment strategies for resistant microbial diseases [51,54]. The mechanisms of the metalloenzyme-deactivating science include the

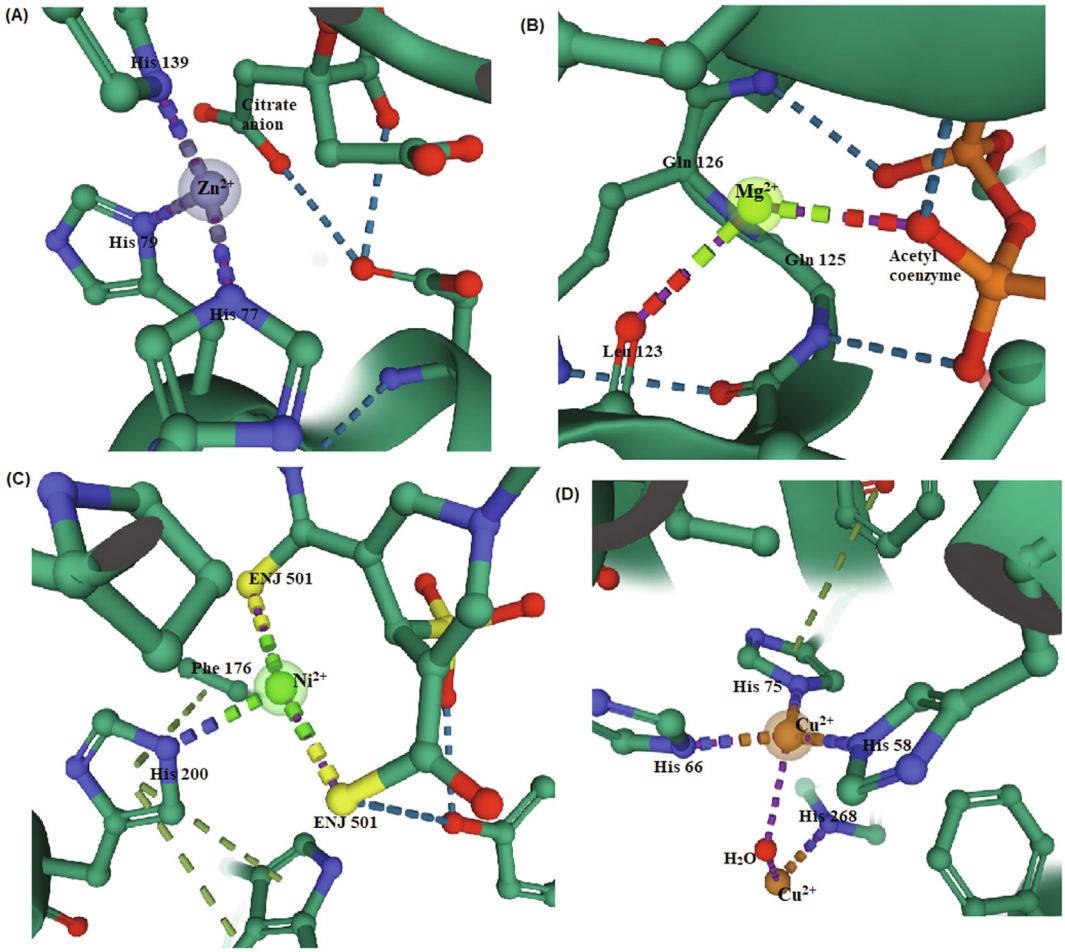


Fig. 4. Illustration of metal–ligand coordinations in the active sites of some metalloenzymes. (A) Zinc ion in coordination with some amino acid residues and citrate ion within the active site of B-lactamase, PDB 4F6Z; (B) Magnesium ion coordinated to amino acid residues and acetyl coenzyme in mutant N-acetyltransferase, PDB 6GTP; (C) Nickel-pincer nucleotide coordination in lactate racemase (ENJ 501 represents (4S)-5-methanethioyl-1-(5-O-phosphono-beta-D-ribofuranosyl)-4-sulfo-1,4-dihydropyridine-3-carbothioic S-acid, PDB 6C1W; (D) Copper ions in coordination with water and amino acids of catechol oxidase, PDB 4J3Q [50]. The low coordination number (2–4) of the metal spheres of the active sites of the enzymes allows more interactive coordination to substrates with minimal steric hindrance. It also favours the donation or attraction of electron pairs from donor ligands (drug or non-drug substrates) during the labile coordination, making them an interesting focus for the modulation of the enzymatic activities.

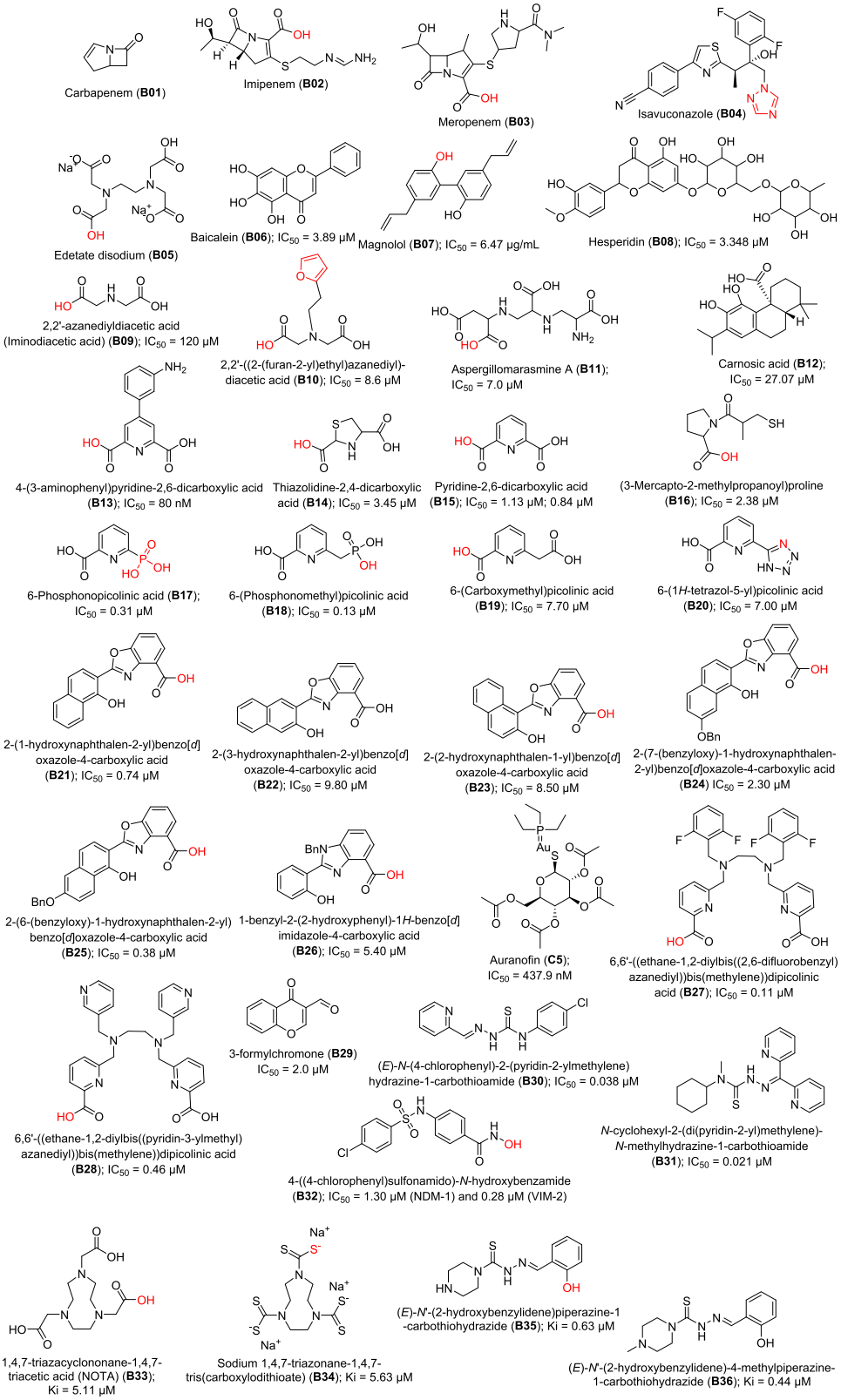
removal/sequester of the biotic metal cofactor *via* chelation, replacement of the biotic metal *via* ligand exchange, suppression of catalytic activities through the metal centre disruption and modulation of coordinating ligands.

3.1. Removal of biotic metal cofactors by metal chelators

The modifications such as the removal or replacement of the biotic metal ions induce loss of resistivity and specificity, implying a potential therapeutic approach [4,7]. A progressive innovation through the development of artificial and mutant enzymatic forms has been studied to facilitate this therapeutic opportunity [21,52]. For instance, in tuberculosis, the therapeutic advantage has been reported through the downregulation of matrix metalloproteinases levels to mitigate pathology of the bacterial infection *via* the induction of tissue damage by 1,25-dihydroxy vitamin D [55]. The N-acetyltransferases (in *E. coli*) are reportedly inhibited by various metallic cations through the increment of aminoglycoside effectiveness to overcome antimicrobial resistance [5]. From the previous section, Se-containing enzymes contribute to the devious activities of some microorganisms including the LAB [42], as such, the removal or replacement of Se at the actives sites could provide therapeutic pathways for modulating the activities through the mimicry of its chemistry. Similarly, Zn(II) reportedly plays a pivotal role in the resistance-inclined catalytic deactivation of β-lactam antibiotics by the MBLs of Gram-negative bacteria strains [36]. As such, the removal or replacement of the metal ion strategically through coordination chemistry could downregulate the enzymatic activities. Consequently, dozens of metal chelators have been experimented with potentials to inhibit the enzyme through the coordination chemistry-inclined Zn(II) ion chelation. The overall activities of these bioactive agents have impacted potent anti-resistance pharmacology on several deadly pathogenic bacterial and fungal strains including *E. coli, K. pneumonia, B. cereus, S. aureus* and *Proteus mirabilis* [37,56,57]. Interestingly, the flexible loops in some of the common antimicrobial resistance-inclined BL strains such as the NDM variants also support their activity modulation by various bioactive agents [58]. Some of these agents have been approved as prescription medicines including carbapenem (**B01**) and its derivatives, imipenem (**B02**) and meropenem (**B03**) [59], an antifungal drug, isavuconazole (**B04**) [37], while others have been reported with promising efficacy in various pre-clinical models. These include edetate disodium (**B05**) [36], baicalin (**B06**) [60], magnolol (**B07**) [61], hesperidin (**B08**) [62], iminodiacetic acid (**B09**), dipicolinic acid-furan derivative (**B10**) [38,63], aspergillomarasmine A (**B11**) [64,65], carnosic acid (**B12**) [66] and some

peptide macrocycles [67]. Others are small molecule carboxylic acids and picolinic acids (**B13-20**) [37,68], benzimidazole and benzoxazole derivatives with potent inhibitory IC_{50} in the range 0.38–9.80 μM and other natural products identified through an *in silico* study (**B21-26**) [69,70].

The inhibitory potential of meropenem was reportedly enhanced by 5333-folds upon combination with H_2dedpa derivatives, 6,6′-((ethane-1,2-diylbis((2,6-difluorobenzyl)azanediyl)) bis(methylene))dipicolinic acid (**B27**) and 6,6′-((ethane-1,2-diylbis((pyridin-3-ylmethyl)azanediyl))bis(methylene))dipicolinic



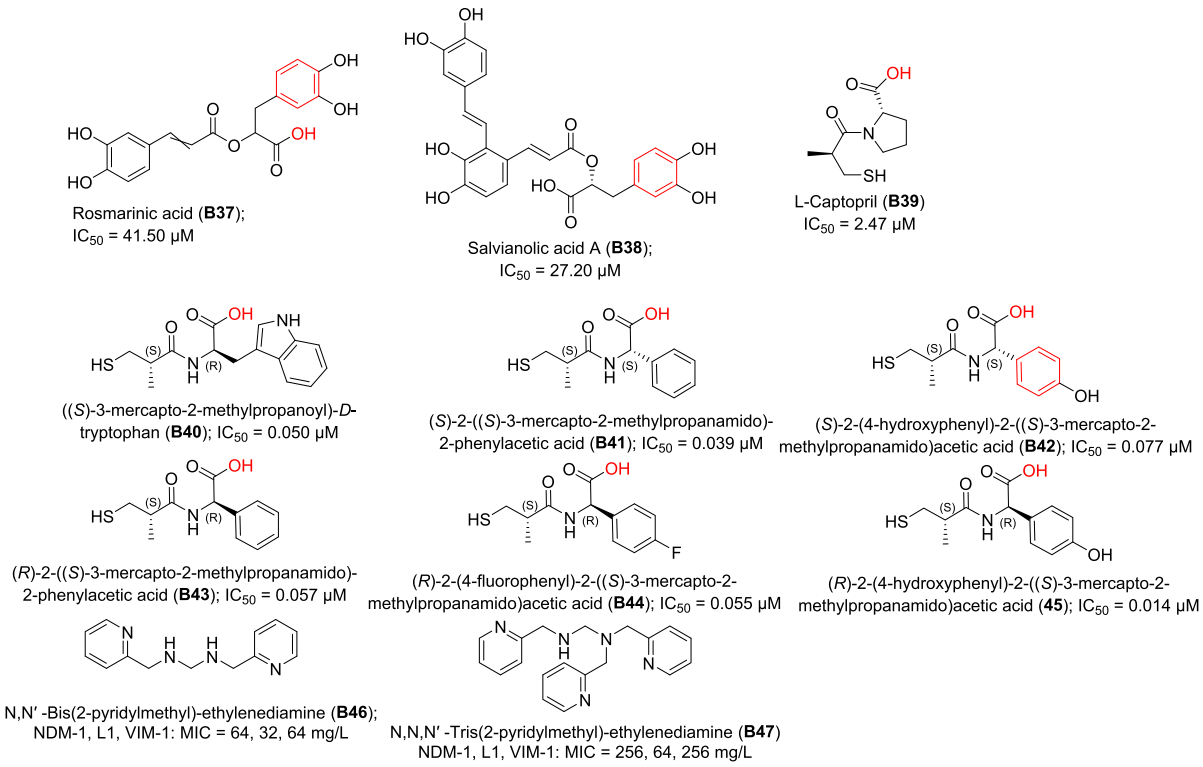
Scheme 1. Chemical structures of some potent metal-chelating inhibitors of NDM-1 with proposed active ligand (red) for Zn(II) chelation.

acid (**B28**), which also showed strong respective IC_{50} of 0.11 and 0.46 μM individually [56]. In another study, 3-formylchromone (**B29**) exhibited strong inhibition against the NDM-1 in a time-dependent manner, indicated by a drastic change in IC_{50} from 200 μM to 2 μM after just 10 min of incubation. The mechanism involved the reversible covalent bonding to the enzymatic residue, Lys 224, in addition to the possible metal chelation [71]. Similarly, some thiosemicarbazone derivatives, (E)-N-(4-chlorophenyl)-2-(pyridin-2-ylmethylene)hydrazine-1-carbothioamide (**B30**) and N-cyclohexyl-2-(di(pyridin-2-yl)methylene)-N-methylhydrazine-1-carbothioamide (**B31**) displayed potent inhibition of NDM-1 individually with respective IC_{50} of 0.038 and 0.021 μM, and percentage inhibition of >63 and >90. Synergistically, they restored the meropenem sensitivity and reduced its MIC in multi-folds with similar mechanistic chelation of Zn(II) ion [72,73]. In addition to therapeutic advantage yet to be fully investigated, highly toxic inhibitors such as **B30** and **B31** could be ideally developed into disinfectants for external applications such as agricultural biocides and sanitizers. A synthesised conjugate of benzenesulfonamide-hydroxamic acid, 4-((4-chlorophenyl)sulfonamido)-N-hydroxybenzamide (**B32**) reportedly demonstrated a reversible competitive inhibition against B3(L1), a subgroup of the MBLs and an analogue of NDM-1 with IC_{50} and *Ki* value of 1.3 and 2.5 μM respectively. [40]. Also, 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA) (**B33**), a renowned metal-chelating inhibitor of MBL and its analogue, sodium 1,4,7-triazonane-1,4,7-tris(carboxylodithioate) (**B34**) were reported with potent inhibitory effects against the NDM-1-encoded *E. coli* with a respective *Ki* value of 5.11 and 5.63 μM. The dual displayed additive therapeutic effects in the combination of each with meropenem, indicated by reductions in MIC against several multidrug-resistant clinical isolates of MBL-encoded bacteria. For instance, the MIC of meropenem and **B34** reduced from 10 and 8 ug/mL respectively to <0.0312 ug/mL when combined against the NDM-1-encoded *E. coli* [74]. Two hydrochloride compounds of thiosemicarbazone derivatives (E)-N'-(2-hydroxybenzylidene)piperazine-1-carbothiohydrazide (**B35**) and (E)-N'-(2-hydroxybenzylidene)-4-methylpiperazine-1-carbothiohydrazide (**B36**) excellently reversed MEM resistance in several positive clinical isolates of NDM-1 in a recent study by Zhao et al. The compounds were evaluated with inhibitory potentials against the NDM-1 with respective *Ki* values of 0.63 and 0.44 μM. Their mechanisms of MBL-disrupting activity were not different from those of the previously highlighted metal-chelating inhibitors. Interestingly, the compounds were proved to be non-haemolytic even at high concentrations, supporting systemic tolerability [75]. The molecular structures and activity potencies of the metal-chelating inhibitors of NDM-1 are presented in Scheme 1. The inhibitors displayed strong potentials for disrupting the active site of NDM-1 mostly by hijacking Zn(II) *via* chelation, while some through the formation of ternary complexes with Zn ion, either way, deactivating the enzymes [20].

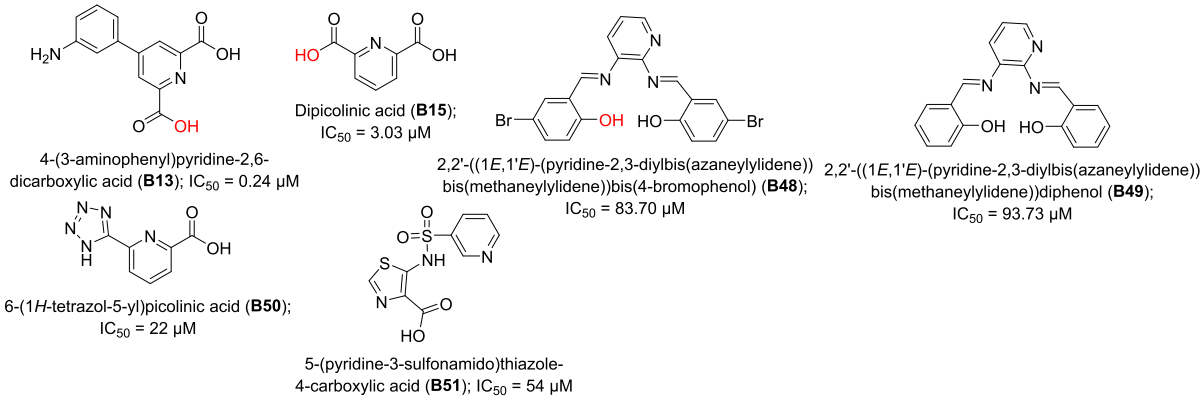
Some of the metal chelators (Scheme 2) also inhibited the VIM analogue significantly in a similar pattern. These include **B32** which was observed to bind very tightly to the active site Zn(II) through chelation using the O atoms of the hydroxamic acid moiety and interestingly showed lower IC_{50} of 0.28 μM against VIM-2 compared to its hydroxamic acid parent with >50 μM [40]. Rosmarinic acid (**B37**) and salvianolic acid A (**B38**) were identified among the natural metal-chelating inhibitors of VIM-2 with potent IC_{50} of 41.5 and 27.2 μM, although less active than a renowned inhibitor of this class, 1-captopril (**B39**) whose IC_{50} was reported as 2.47 μM. Further experimental investigations indicated that **B37** exhibited a dose-dependent reversible, competitive inhibition against VIM-2, however, showed weaker activity against the NDM-1 and serine-BL, TEM-1, while **B38** was observed to display strong potency against the strains with respective IC_{50} of 160.3 and 34.3 μM respectively [76]. Also reported among the VIM-2 metal-chelating inhibitors are the ((*S*)-3-mercapto-2-methylpropanamido)acetic acid analogues, **B40 – B45** with potent inhibitory IC_{50} between 0.014 and 0.077 μM [77]. Similarly, two polypyridine ligands, N,N′-Bis(2-pyridylmethyl)-ethylenediamine (**B46**) and N,N,N′-Tris(2-pyridylmethyl)-ethylenediamine (**B47**) displayed multitarget inhibitory pharmacology against several MBLs, NDM-1, L1 and VDM-1 with MIC values of 64/256, 32/64 and 64/256 mg/L respectively with mechanistic chelation of Zn ions to disrupt the metalloenzymatic activities of the targets. Meropenem (**B02**), a known metal-chelating inhibitor was assessed with respective MIC of 128, 256 and 16 mg/L against the strains, however, the tested compounds exhibited significant synergistic effects upon the combination with the antibiotic [78]. Messasma and co-researchers also reported two synthesised pro-antioxidants, multidentate Schiff bases, 2,2′-((1E,1′E)-(pyridine-2,3-diylbis(azaneylylidene))bis(methaneylylidene))bis(4-bromophenol) (**B48**) and 2,2′-((1E,1′E)-(pyridine-2,3-diylbis(azaneylylidene))bis(methaneylylidene))diphenol (**B49**) with potent inhibitory activities against the IMP-1, a BL subtype, indicated by IC_{50} of 83.70 and 93.73 μM respectively in comparison with EDTA which showed 1 mM [79]. Other reported metal-chelating inhibitors of IMP-1 include 6-(1H-tetrazol-5-yl)picolinic acid (**B50**), 5-(pyridine-3-sulfonamido)thiazole-4-carboxylic acid (**B51**), 4-(3-aminophenyl)pyridine-2,6-dicarboxylic acid (**B13**) and dipicolinic acid (**B15**) with respective IC_{50} of 22, 54, 0.24 and 3.03 μM (Scheme 3). Their common mechanisms of inhibition deduced from physical and biochemical characterisations also involve the coordination chemistry-inclined sequestering of Zn(II) ions from the active centre of the enzyme and restoration of β-lactam susceptibility, while some form ternary complexes with Zn(II) ion, all resulting in the loss of Zn, in the similitude of the NDM-1 metal-chelating candidates [38,80-82]. Some series of enethiol and rhodanine derivatives consisting of (Z)-2-mercapto-3-phenylacrylic acid backbone (**B52-B65**) were synthesised and evaluated with potent dual inhibitory activities with IC_{50} ranges 0.03–0.5 μM and 0.01–0.8 μM against the VIM-2 and IMP-1 respectively with similar mechanisms of Zn (II) chelation and ternary complex formation with the metalloenzymes (Scheme 4). Interestingly, the compounds were observed to be non-haemolytic even at a high concentration of ≈1000 mg/mL [83]. The shreds of evidence from the surveyed experimental studies further strengthen the coordination chemistry of metal cofactor of metalloenzymes as mimicry and modulatory components, and an effective anti-resistant therapeutic pathway. Although, the strategy is becoming inevitably essential to curb the menace of antibiotic resistance, however, unspecific binding of the chelators to the metalloenzymes could engender some serious complications due to their predominance in humans for pivotal life activities [84]. Moreover, it could lead to the scarcity of some essential biological minerals. As such, concerted scientific attention is required on the appropriate delivery of the inhibitors to the targets to ensure discriminative toxicity and safety to normal cells.

3.1.1. Theoretical estimation of Zn(II) cofactor effects on the substrate specificity of metallo-β-lactamases

Understandingly, the hydrolytic activity of the MBLs on antibiotics at a molecular level implicates the aspartic acids at the active site as crucial residues to their disruptive catalytic effects on the drugs. Moreover, histidine, asparagine and other side chain residues can effectively block substrates with aspartic acid to induce the loss of hydrolysis, all mostly in coordination chemistry with Zn(II) cofactor at the active sites [85]. As such, the interactive inhibition of the enzyme by substrates with favourable pharmacophores through the Zn(II) centre and the amino acid residues in the active pocket portrays an important anti-resistance study. Therefore, the impacts of the Zn(II) coordination on the substrate

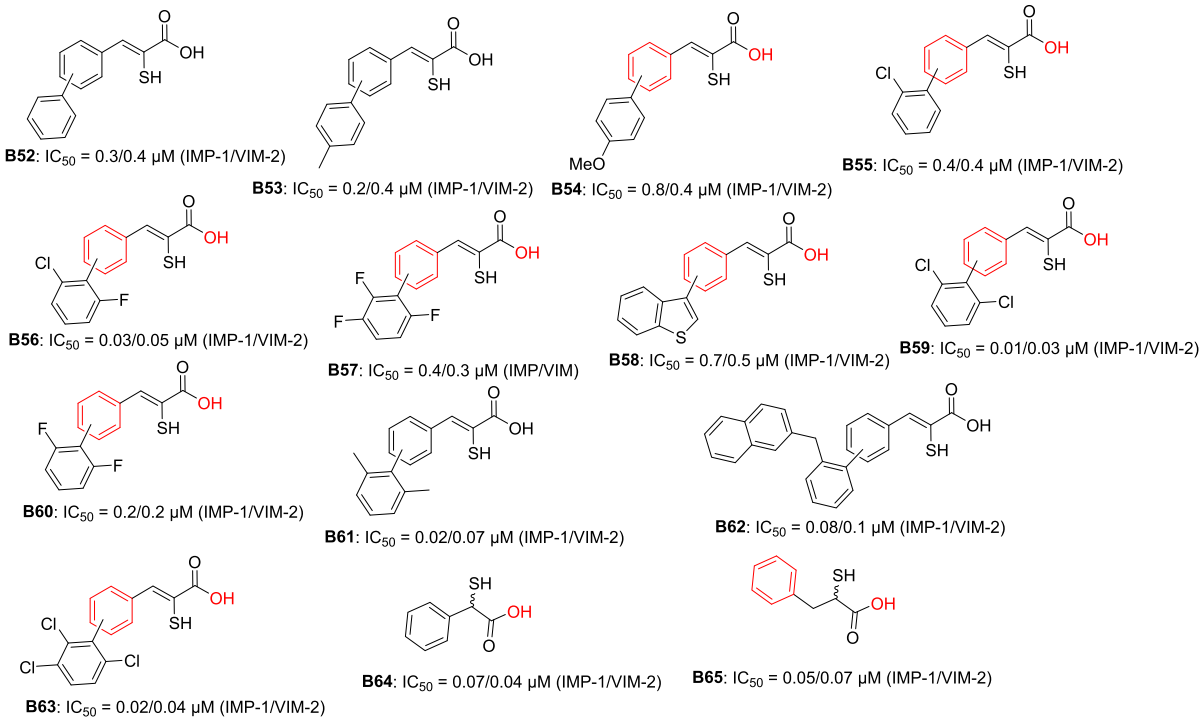


Scheme 2. Metal-chelating inhibitors of VIM-2 with proposed active ligand (red) for Zn(II) chelation.



Scheme 3. Chemical structures of some potent metal-chelating inhibitors of IMP-1 with proposed active ligand (red) for Zn(II) chelation.

specificity of MBLs were theoretically examined using a highly accurate extra precision (XP) Maestro 12.2 Glide ligand-receptor docking simulation (Glide, Schrodinger, LCC, New York, NY, 2021). From the simulation results (Table 1), the binding affinities represented by XP Gscores of the selected 20 top-ranked firmly bound chelators were arranged in ascending order in respect of the three observed scenarios. Firstly, the ligand-receptor simulation was conducted using a crystal structure of the NDM-1 in complex with imipenem, and containing Zn(II) ions cofactors along its chain A, as retrieved from the RCSB protein data bank (PDB 5YPL). Secondly, the protein receptor was remodelled by removing Zn(II) ions cofactors and in the third case, the receptor was remodelled by the replacement of biotic Zn(II) with abiotic Pb(II) ions. Generally, the highest theoretical binding affinities of the metal chelators to the receptor were recorded in the presence of Zn(II) ions cofactors. On average, the scores were higher in the absence of metal cofactor than when Pb(II) ions were included. These further implicate the crucial effects of Zn(II) ion cofactor to the substrate specificity and supports its chelation-inclined strategic removal or replacement with abiotic options as a plausible therapeutic pathway to overcoming the enzymatic activity-dependent resistance of the NDM-1 to antibiotics. As expected, imipenem (**B01**) and meropenem (**B02**) were among the chelators with the strongest inhibitory potentials against the receptor, while hesperidin (**B08**), aspergillomarasmine A (**B11**), 4-(3-aminophenyl)pyridine-2,6-dicarboxylic acid (**B13**), 6-(phosphonomethyl)picolinic acid (**B18**) 2-(6-(benzyloxy)-1-hydroxynaphthalen-2-yl)benzo[d]oxazole-4-carboxylic acid (**B25**) rosmarinic acid (**B37**) and salvianolic acid (**B38**) represent new promising metal-inhibitors of the NDM-1 for further studies. Some of the compounds are natural flavonoids with known interesting pharmacological potentials through interaction with matrix metalloenzymes in their ligand or complex forms [86]. It could also be observed that most of the top-ranked inhibitors coordinated to the metal centres through OH



Scheme 4. Chemical structures of some metal-chelating inhibitors of dual IMP-1 and VIM-2 with proposed active ligand (red) for Zn(II) chelation.

Table 1
Effects of Zn(II) on theoretical binding affinities of some metal chelators to NDM-1.

Compound	XP Gscore (kcal/mol)		
	Zn cofactor	No metal cofactor	Pb cofactor
B02	−12.271	−7.544	−10.999
B08	−11.893	−10.198	−7.163
B03	−11.847	−5.150	−6.254
B38	−11.225	−9.853	−7.239
B18	−10.901	−7.339	−7.717
B37	−10.789	−8.316	−8.183
B11	−10.689	−7.955	−7.167
B25	−10.317	−5.076	−6.572
B13	−10.067	−4.199	−6.008
B42	−9.930	−4.098	−7.126
B33	−9.837	−6.096	−4.191
B24	−9.828	−5.209	−4.986
B15	−9.658	−6.543	−5.997
B05	−9.595	−7.305	−4.470
B80	−9.594	−5.918	−7.771
B28	−9.580	−4.382	−5.609
B27	−9.431	−6.076	−5.863
B17	−9.241	−7.394	−6.485
B23	−9.223	−5.745	−5.090
B21	−9.044	−7.108	−3.748

and NH groups, which are capable of activating their O and N donor ligands, while some others including the picolinic acid derivatives consist of phosphate groups which influence their non-covalent interactions with the positively charged metal ions and the formation of ternary complexes [87,88]. They also interacted with essential amino acid residues implicated in the pathogenesis and prophylaxis of the resistant NDM-1 as illustrated by the binding poses (Fig. 5).

The Rsp is an AraC/XylS-type transcriptional regulator of the cntE gene in *S. aureus*, which influences its virulence factor in an *agr*-dependent manner. The expression of cnt by iron-dependent Fur and zinc-dependent Zur further provides a basis for their regulations to control the virulence activities of the bacteria [89,90]. Vancomycin, antibiotic medication for treating nosocomial infections caused by the β-lactam, methicillin-resistant *S. aureus* reportedly induced zinc homeostasis systems *in vitro* experimental model at 6.9 μM by binding to Zn(II) ion *via* chelation. The process resulted in the sequestration of Zn from the active centre, indicated by Zn accumulation by the ligand, thereby triggering the Zur-dependent Zn starvation response [91]. These pieces of evidence convincingly implicate the metal–ligand coordination approach of the removal of biotic metal cofactors as an indispensable strategy to curb antimicrobial resistance. The innovative strategy interestingly deserves further exploration as a potential real-time therapeutic breakthrough for debilitating antibiotic resistance.

Ureolytic bacteria contains ureases with catalytic enzyme activities depending strongly on the Ni(II) ion at their conserved active binding pockets [92,93]. Svane and co-workers recently screened some metal ion chelators for prospective urease inhibitors. Notably, EDTA (**B05**) and dimethylglyoxime were reported to significantly reduce the ureolytic activity and cellular uptake of Ni(II) ions and subsequently induced >25% inhibition of *K. pneumonia* [93]. The induction of the anti-urease activities by the chelators occurred through the inhibition of cellular uptake of the enzyme activity-dependent Ni(II) ion. Disulfiram, an FDA-approved drug for treating alcohol dependence and its Cu-containing metabolite reportedly inhibited the B1 and B2 subclasses of MBLs including the NDM-1 potently by binding covalently to the amino acid residue, Cys 208 to trigger the release of Zn(II) ion from the site, and through the oxidation of Zn(II) thiolate active site of the enzyme [94]. These further support the sequestering of biotic cofactor through coordination chemistry as a plausible therapeutic approach to ameliorate antimicrobial resistance.

3.1.2. Factors that favour inhibitory chelation of metal cofactors by small molecules

Essential characteristics of coordination compounds include the formation of coordinate covalent bonds between metal ions (Lewis acids) and donors of electron pairs (Lewis bases). As such, highly charged metal ions with small sizes such as the Zn(II) in MBLs,

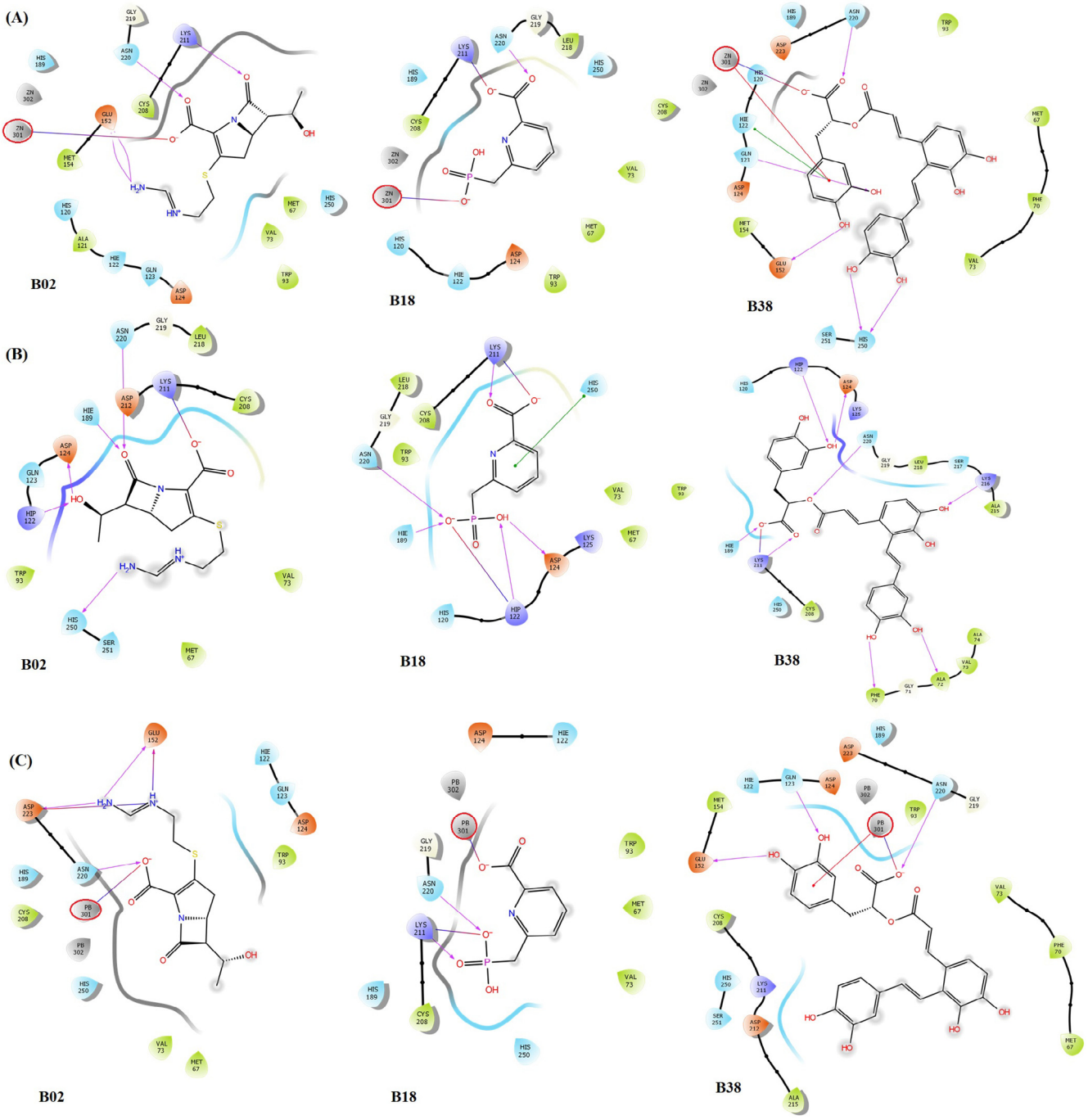
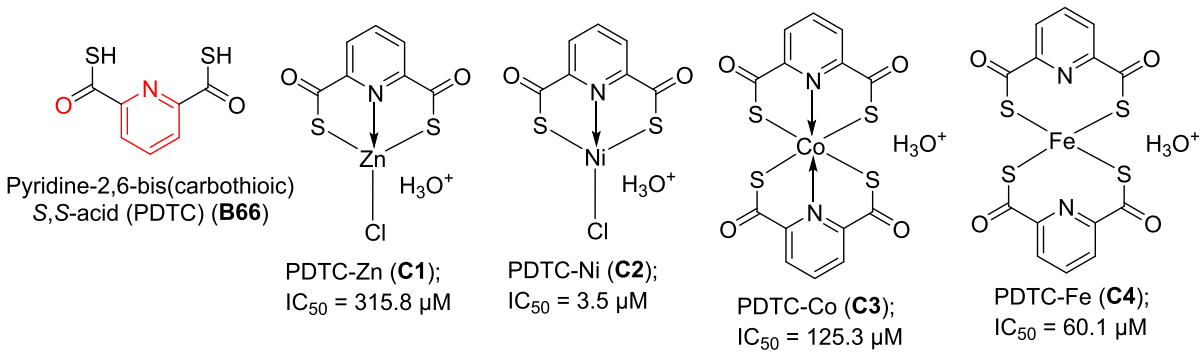


Fig. 5. Binding poses showing interactions of compounds **B02, B18** and **B38** with active site residues of NDM-1 (PDB 5YPL). (A) In the presence of the Zn(II) cofactor. (B) No metal cofactor. (C) Zn(II) replaced with Pb(II) (Images produced using Maestro Glide 12.2, Schrodinger, LCC, New York, NY, 2021).

Cu(II) in catechol and cytochrome oxidases possess high charge density that implies a strong affinity for electron-pair donors and can accommodate assemblies of negative charges from the electron pairs donated [34]. The minimal steric factor usually associated with complex formation between metal ions and low molecular weight small molecules favour the chelation effects of the highlighted small molecule inhibitors against the metalloenzymes [83]. The highlighted small molecules mostly form ternary complexes with the inclusion of water molecules of hydroxide ion to complete the tetrahedral or square planar geometry, either of which favours lability for isotopic ligand exchange, as a pathway to disrupt resistance. Most of the metalloenzymes of the highly resistant pathogenic organisms contain a central core Cu(II) or Zn (II) ion with d^8-d^{10} electronic configuration which supports complex stability and lability. Other influential factors include chelation effects, acidity, basicity, size and steric hindrance of the ligands as well as the electrochemical potentials of the metal ions [34,95,96], mostly supported by the small molecule inhibitors and metal cofactors previously outlined.

3.2. Inhibition of metalloenzymes by metal chelates

The coordination compounds of Zn, Ni, Co and Fe with pyridine-2,6-dithiocarboxylic acid (PDTC) (**B66**), annotated as PDTC-Zn (**C1**),



Scheme 5. Chemical structure of metal chelator PDTC and its metal complex inhibitors of NDM-1.

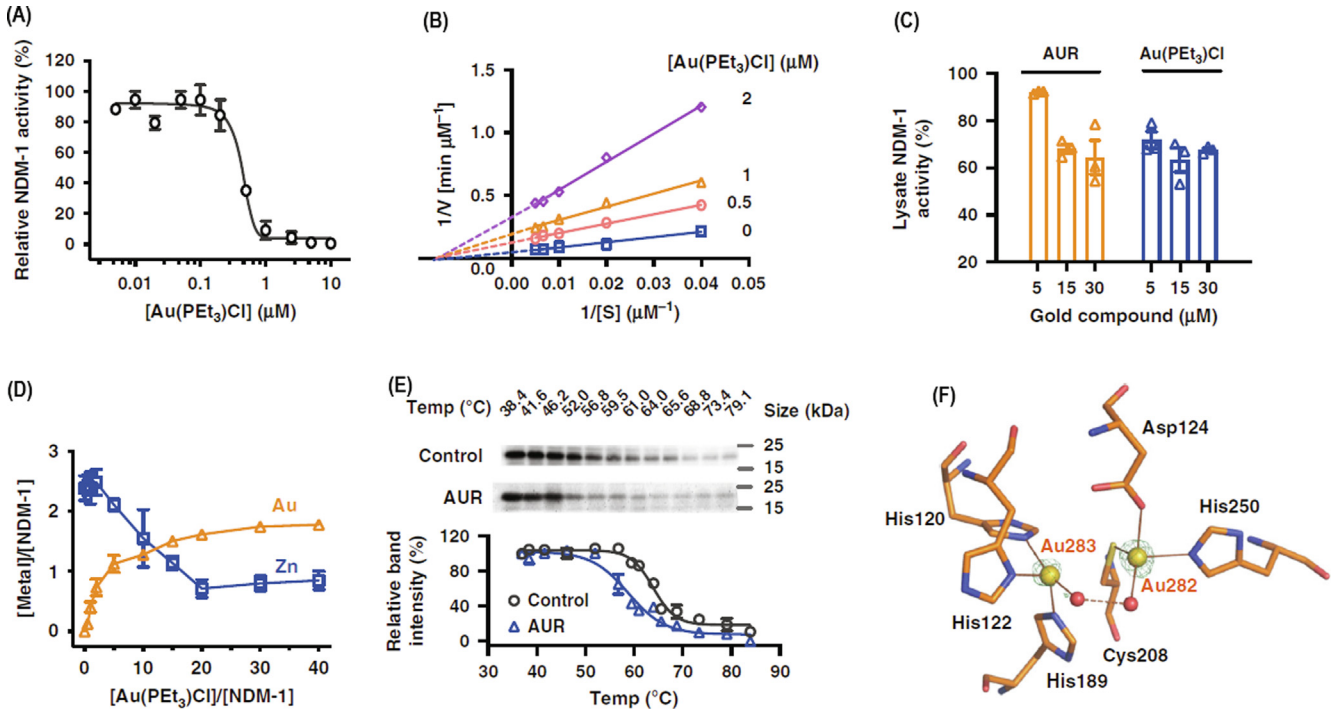


Fig. 6. Auranofin inhibits MBL activity *via* the displacement of Zn(II) cofactors. (A) Inhibition of NDM-1 activity by $Au(PEt_3)Cl$ with IC50 of 437.9 ± 29.1 nM. (B) Double reciprocal plot of substrate-dependent enzyme kinetics on inhibition of NDM-1 activity by $Au(PEt_3)Cl$. (C) Lysate NDM-1 activity from NDM-Rosetta treated with AUR or Au $(PEt_3)Cl$. (D) The substitution of Zn(II) in Zn2-NDM-1 by $Au(PEt_3)Cl$ by equilibrium dialysis. The metal content was determined by ICP-MS. (E) Cellular thermal shift assays showing the binding of Au(I) to NDM-1 in intact NDM-Rosetta cells. NDM-1 melting temperature was shifted from 63.7 to 58.6 °C for the control and AUR-treated groups, respectively. The images show the representative blottings of three independent experiments. (F) Structure of the active site of Au-NDM-1 (PDB ID: 6LHE) with the anomalous density peak of Au shown as yellow spheres and water molecules as red spheres, and anomalous density peak of Au in green mesh contoured at 7.0σ. (A), (C)–(E) Data are presented as mean values ± SEM, n = 3 biologically independent samples. Source data are provided as a Source Data file. (Reproduced from [98], Licensed under CC BY 4.0).

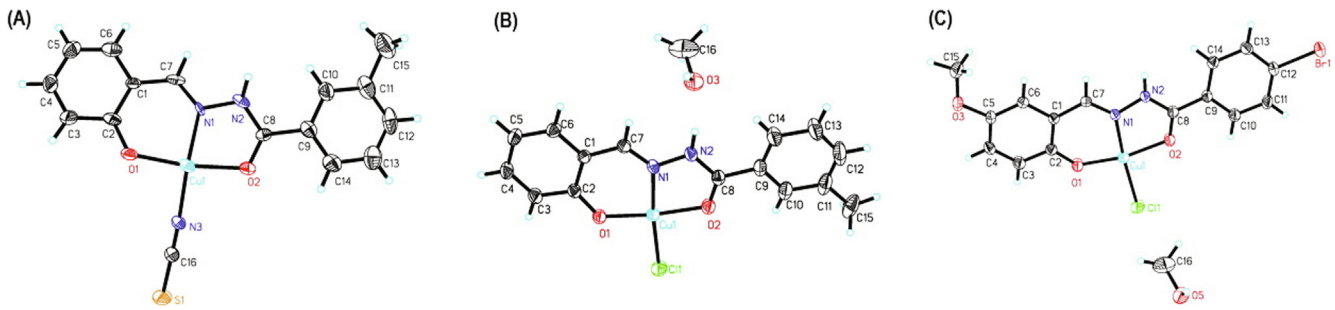


Fig. 7. Molecular structures of Cu complexes (A) **C11**, (B) **C12** and (C) **C13**, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. (Reproduced with permission from [100], Copyright (2016) Elsevier Inc.)

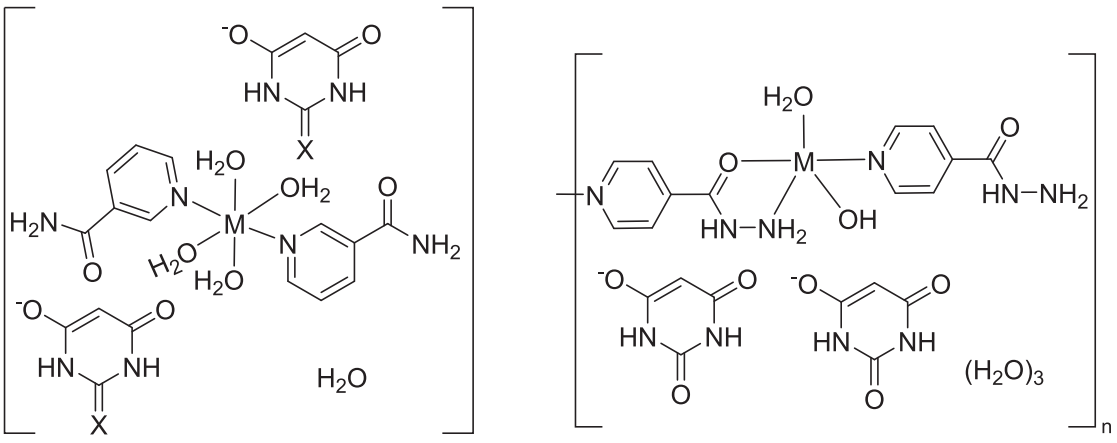
PDTC-Ni (**C2**), PDTC-Co (**C3**) and PDTC-Fe (**C4**) have also been reported with strong inhibitory potentials against the NDM-1 (Scheme 5). The kinetic studies indicated that the hydrolytic NDM-1 activity was significantly reduced upon the introduction of PDTC, with proposed mechanistic sequestration of Zn^{2+} from the enzyme active site [97]. Although, no detailed mechanism was reported in respect of the metal complexes, however, it could hypothetically occur through the additive antimicrobial effects of the aggregated **B66** as well as the blockade of the enzymatic active sites. Further study on these and the cytotoxicity of the agents remain important.

In addition to the inhibition of MBL hydrolytic activity, auranofin (**C5**), a gold-based antirheumatic drug reportedly abrogated the mobilised colistin resistance (MCR) enzyme irreversibly *via* the displacement of the functional Zn(II) cofactor from the active centre. The drug inhibited the NDM-1 activity excellently by ≈97% in a concentration-dependent manner with the IC_{50} recorded as 437.9 nM (Fig. 6). Synergistically with colistin antibiotic, it downregulated the growth of carbapenem- and colistin-resistant bacteria and rescued all mice infected with *E. coli*, expressing the MCR-1 and NDM-1 [98].

Furthermore, four Cu complexes have been evaluated with interesting inhibitory effects against the urease of *Helicobacter pylori* through the mechanistic interactions between their ligands and the Ni(II) ion cofactor and the blockade of the active centre of the metalloenzyme. The complexes are annotated as $[Cu(L^1)_2$-$].2NO_3.2CH_3OH$ (**C6**), $[Cu(L^2)_2].2Br$ (**C7**), $[Cu_2Cl_4(L^1)_2]$ (**C8**), $[CuL_3$(-NCS)] (**C9**) and $[CuClL^3].CH_3OH$ (**C10**), where L^1, L^2 and L^3 are zwitter ion of 4-methyl-2-((3-morpholinopropylimino)methyl)phenol, zwitter ion of 2-bromo-4-chloro-6-((2-(2-hydroxyethylamino) ethylimino)methyl)phenol and monoanionic 4-methyl-2-((pyridine-2-ylmethylimino)methyl)phenol respectively. They were recorded with respective inhibitory IC_{50} values of 0.37, 0.21, 0.03, 0.39 and 0.76 μM against the metalloenzyme [99]. Similarly, Pan and co-researchers reported potent inhibitory effects of some Cu complexes of aroylhydrazone ligands. The complexes were characterised with square planar geometries, resulting from the coordination of Cu ions to the NOO, Cl and/or N of the aroylhydrazone and thiocyanate donor ligands (Fig. 7). Annotatively, they were recorded with respective IC_{50} values of 5.14, 0.20, 4.06, 5.52 and 0.26 μM against the urease of *H. pylori* for $[CuL^4(NCS)]$ (**C11**), $[CuClL^4].CH_3OH$ (**C12**), $[CuClL^5].CH_3OH$ (**C13**), $[CuL^6(NCS)].CH_3OH$ (**C14**) and $[CuL^7(NCS)]0.0.4H_2O$ (**C15**), where L^4 = deprotonated forms of *N'*-(2-hydroxybenzylidene)-3-methylbenzohydrazide; L^5 = 4-bromo-*N'*-(2-hydroxy-5-methoxybenzilidine)benzohydrazide, L^6 = *N'*-(2-hydroxy-5-methoxybenzilidine)-3-methylbenzohydrazide and L^7 = 2-chloro-N'-(2-hydroxy-5-methoxybenzilidine)benzohydrazide. The study suggested that copper complexes with square planar geometry display better complementarity with the inhibitory binding mechanism to the urease active centre [100].

Some transition metal ions such as Zn(II) and Cu(II) play important roles as biometals since they are found in thousands of enzymes of living organisms. Their complexes of *N*- and *O*-donor ligands are known as good binders of DNA, radio protective, tumour photosensitizers, antidiabetic insulinomimetic and antibacterial agents. Moreover, recent studies reveal that their complexes could also potentiate anticancer effects due to their groove binding, low toxicity and low side effects. [101-103]. Consequently, Shah and co-workers reported interesting inhibitory activities of some transition metal complexes of N- and O-donor ligands against urease within IC_{50} range of 3.9–19.9 μM while the thiourea standard was recorded with 20.8 μM. These are mononuclear complexes, $[Co(NCA)_2(H_2O)_4].(BTA)_2{\cdot}H_2O$ (**C16**), $[Zn(NCA)_2(H_2O)_4].(BTA)_2{\cdot}H_2O$ (**C17**) $[Ni(NCA)_2(H_2O)_4].(TBA)_2{\cdot}H_2O$ (**C18**), and polymeric chains of $[Co(INZ)(H_2O)_3]$-$(BTA)_2(H_2O)_3$ (**C19**) and $[Zn(INZ)(H_2O)_3]$-$(BTA)_2(H_2O)_3$ (**C20**) where NCA, BTA, TBA and INZ are annotations for nicotinamide, barbituric acid, thiobarbituric acid and isoniazid respectively (Scheme 6). Although the mechanisms of actions could not be succinctly proposed, however, suggested being in association with the biochemical characteristics of the transition metals [103].

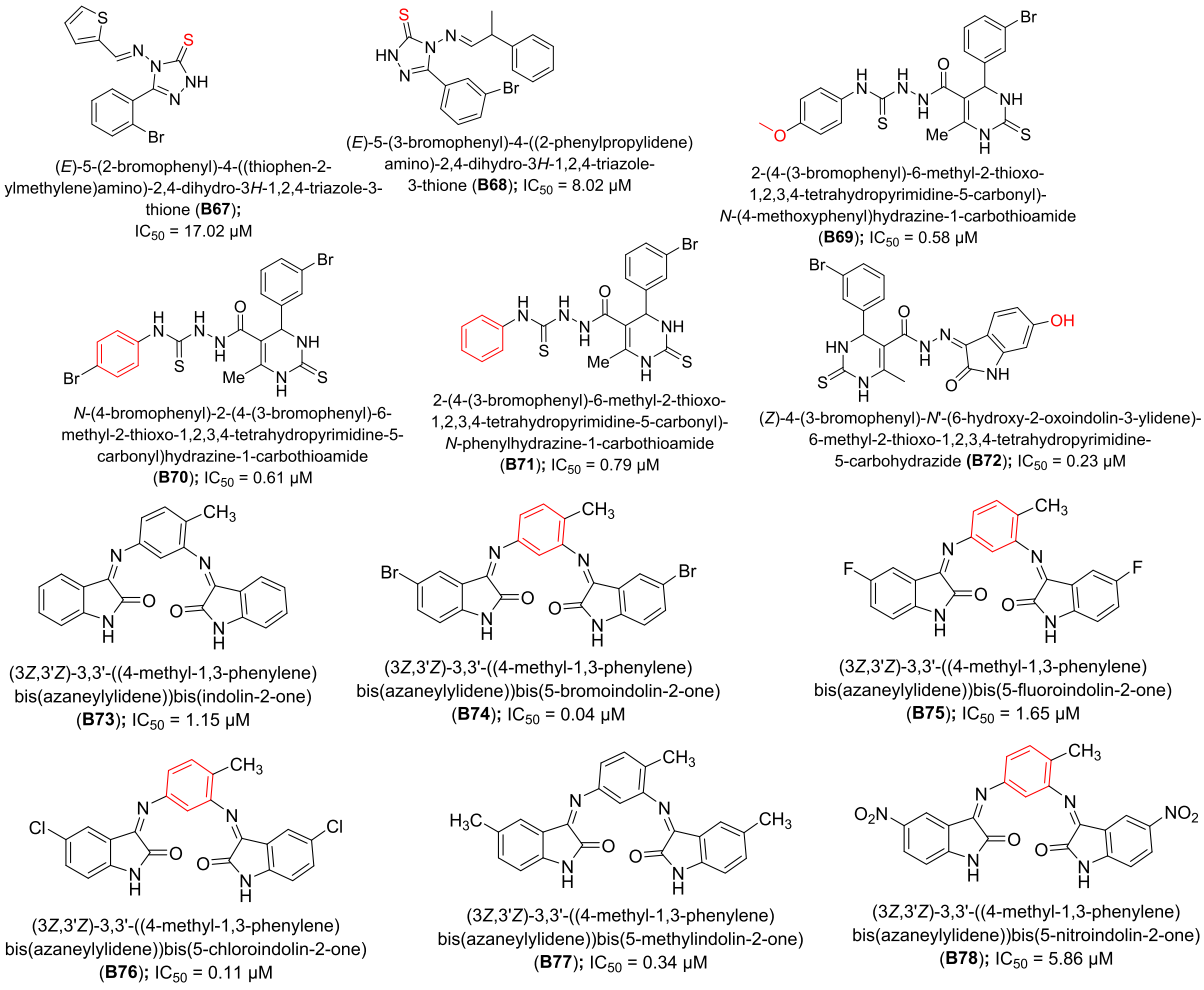
Furthermore, ureases are members of the amidohydrolase family containing Ni(II) ion, pivotal to their enzymatic activities at the conserved binding pockets. These enzymes are present in ureolytic bacteria including *Canavalia ensiformis, H. pylori* and *K. pneumonia,* accelerating the catalytic hydrolysis of urea to NH_3 and CO_2. The progression of their pathogenic activity results in some important medical conditions such as gastrointestinal and urinary tract infections due to the unpleasant increase in pH levels by the emission of NH_3 [92,93]. As such, some synthesised bioactive compounds have been demonstrated with potent inhibitory activities against them *in vitro* experimental models. These include the Schiff bases, (E)-5-(2-bromophenyl)-4-((thiophen-2-ylmethylene)amino)-2,4-dihydro-3H-1,2,4-triazole-3-thione (**B67**), (E)-5-(3-bromophenyl)-



C16: M = Co; X = O; IC_{50} = 7.5 μM
C17: M = Zn; X = O; IC_{50} = 18.1 μM
C18: M = Ni; X = S; IC_{50} = 3.9 μM

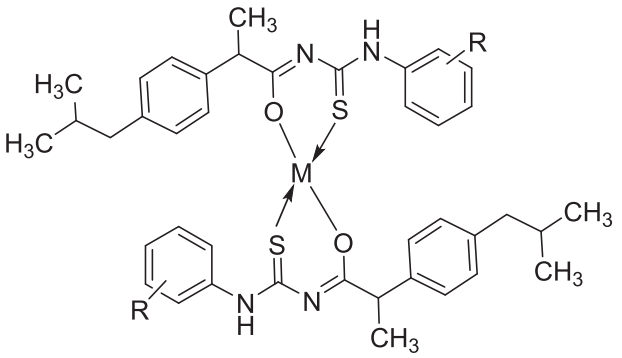
C19: M = Co; IC_{50} = 19.9 μM
C20: M = Zn; IC_{50} = 5.3 μM

Scheme 6. Proposed chemical structures of complex inhibitors of urease (**C16-20**) containing nicotinamide, barbituric acid, thiobarbituric acid and isoniazid.



Scheme 7. Chemical structures of some metal-chelating inhibitors of ureases with proposed active ligands (red).

4-((2-phenylpropylidene)amino)-2,4-dihydro-3H-1,2,4-triazole-3-thione (**B68**) [104], dihydropyrimidine derivatives, 1-(4-(3-bromophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4-(4-ethylbenzyl)pent-4-en-1-one (**B69**), N-(4-bromophenyl)-2-(4-(3-bromophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonyl)hydrazine-1-carbothioamide (**B70**), 2-(4-(3-bromophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonyl)-N-phenylhydrazine-1-carbothioamide (**B71**) and (Z)-4-(3-bromophenyl)-N'-(6-hydroxy-2-oxoindolin-3-ylidene)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (**B72**). The binding affinities of the compounds **B69-B72** to the active pocket of the metalloenzyme were strongly influenced by the coordination of their donor ligands to the Ni(II) centre, specifically, compounds **B69** and **B72** through the OCH_3 and OH group respectively in a structure–activity relationship (SAR) (Scheme 7) [105]. The compounds displayed more potency than thiourea reference inhibitor in most cases, as such, represent promising urease inhibitors for further studies.



Scheme 8. Proposed chemical structures of some metal(II)-complex inhibitors of urease.

3.3. Replacement of biotic metal cofactor

The replacement of the biotic metal cofactor by ligand exchange constitutes another pathway to metalloenzyme deactivation. The process depends on several factors including the variations in ligand binding strength, acidity/basicity, size, chelation effects, electrochemical potentials of metal cofactor and mechanisms of ligand exchange [34,96]. The catalytic activities of the cyclic amidohydrolase isatin of some aerobic, Gram-negative bacteria strains such as *Labrenzia aggregata* and *Ralstonia solanacearum* depends strongly on the motif bound Mn(II) ion at its active site. As such, the replacement of the catalytically active Mn(II) in the

substrate-binding pocket by Zn(II) has been demonstrated experimentally to distort the hydrolytic mechanisms of the metalloenzyme due to the variation in their coordination modes [106]. This interestingly provides a basis for the modification of the catalytic hydrolytic functions of the enzyme through the replacement of its active pocket Mn(II) ion as a plausible therapeutic strategy.

Consequently, two Schiff base complexes of Ag(I) were examined with impressive inhibitory effects against urease, quantitatively by IC_{50} of 3.5 and 3.8 μM for $[Ag(L_1)(H_2O)]$ (**C21**) and $[Ag(L_2)(H_2O)]$ (**C22**) where L_1 and L_2 are 4-((2-diethylaminoethylimino)methyl)phenecarboxylate and 4-([3-(morpholin-4-yl)propyl]iminomethyl)phenecarboxylate respectively [107]. Although, the mechanisms of inhibition of the complexes could not be provided by the author, however, the displacement of the more biotic Ni(II) ion by an abiotic Ag(I) was suggestively hypothesised for further evaluation. Other metal(II) complexes with potent inhibition of urease include **C23 – C26** whose respective activity was recorded as IC_{50} of 14.6, 16.5, 18.0 and 16.9 μM (Scheme 8) using Jack bean urease inhibitory assay [108]. The presence of Co(II) and Cl group at meta position implicatively enhanced the inhibitory effects of **C23** and **C24** [108], while the toxicity of Pb bioaccumulation could be responsible for others [109]. Moreover, the complexes containing toxic metals such as **C25** and **C26** could be useful for designing biocides and disinfectants for external, non-clinical applications such as control of agricultural diseases, sanitising hospital environments and other areas prone to deadly metalloenzyme-containing pathogens. Although the sensitivity of the metal-complex prodrugs to various stimuli such as redox, pH, light and importantly metalloenzymes supports their applicability in this perspective [110]. However, more explorations are required through the responses to understand the essential criteria for modulation to fulfil the quest of biotic metal replacement as an effective anti-resistance strategy.

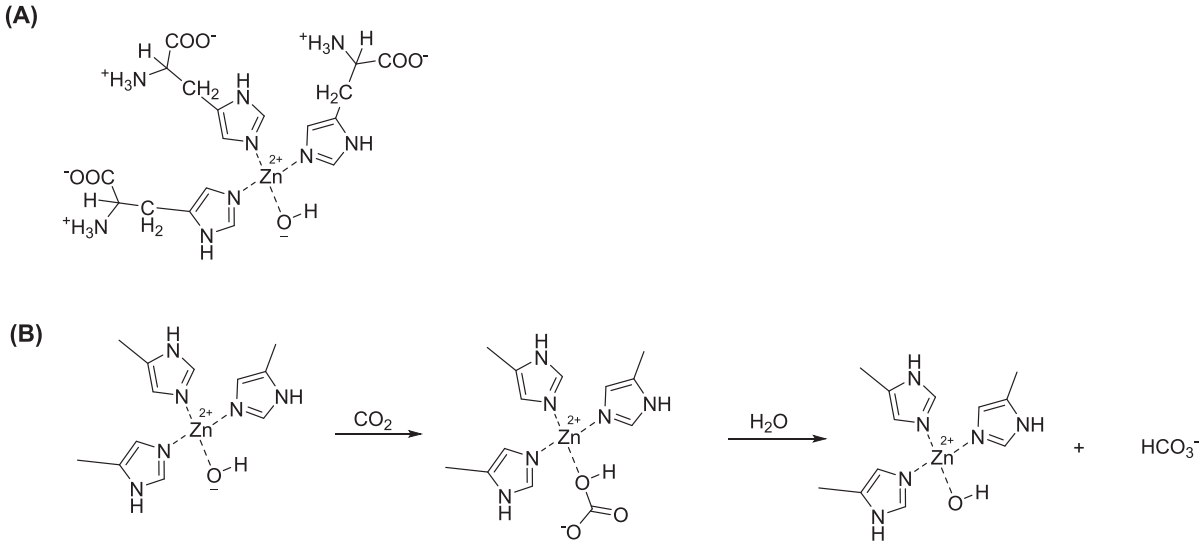
Contrastingly, some isatin-derived Schiff bases, **B73 – B78** reportedly demonstrate strong inhibitory potentials against Jack bean urease indicated by IC_{50} values between 0.04 and 5.86 μM while thiourea standard showed 22.3 μM. The potentials of the ligands were higher compared to their corresponding Cu(II complexes whose IC_{50} values were recorded in the range of 8.61–36.4 μM, except ligand **B77** with IC_{50} of 0.34 μM while its Cu(II) complex scored 0.03 μM. [111]. This could be due to the replacement of Ni (II) ion with more biotic Cu(II) ion, a renowned enhancer of enzyme activity and stability [112], favouring the enzymatic activity rather than its inhibition. The interesting hypothesis further supports the modulatory replacement of biotic cofactor as an ideal therapeutic strategy against microbial activities for more exploration.

3.4. Suppression of catalytic activities of metalloenzymes

The specificity of metalloenzymes for substrate and metal cofactor is associated with the influence of metal–ligand coordination on their catalytic activities. This has been established with shreds of experimental evidence from the biomimetic engineering and kinetic studies of the enzymatic activities influenced by the coordination chemistry of the metal cofactor centre. For instance, a kinetic analysis was conducted on dinuclear Cu(II) complex biomimetic models of catechol oxidase, {[Cu2(2-X-4,6-bis(di-2-picolylamino)-1,3,5-triazine where X = butan-1,4-diamine (**C27**) and X = N-methylpyrenebutan-1,4-diamine (**C28**) for enzymatic activity. The kinetic study on the oxidation of the substrate model, 3,5-di-*tert*-butylcatechol indicates that the spacer substituents, butan-1,4-diamine and pyrene enhanced the catalytic efficiency of the biomimetic systems. They supported the interactions between the complex and the substrate to exert oxidative and hydrolytic catalytic activities [113].

The catalytically efficient carbonic anhydrases (CAs, EC 4.2.1.1) and alcohol dehydrogenases are metalloenzymes present inclusively in vertebrates, bacteria, algae, protozoa and green plants with natural cofactors of Zn and Cu at their active sites. They enhance the catalysis of biological reactions and selectivity for substrates and mostly promote resistance of an organism to drugs. The Zn(II) ion at the active centre of CAs coordinates to three histidine residues and one hydroxide ion or water molecules, forming a tetrahedral geometry for enzymatic activities (Scheme 9A). The summarized mechanism of their catalytic activities involving the histidine residues such as the conversion of CO_2 into HCO_3^- ions is illustrated (Scheme 9B).

Recently, their artificial mutants and hybrids have been engineered to phantom therapeutic designs by suppressing their pro-resistance activities including catalysis through the incorporation of some other cofactors such as the transition metal ions of Cu, Fe, Mn, Ir and Rh. [3,4,21,114]. Examples of such artificial



Scheme 9. A representation of Zn(II) coordination site involved in catalysis by carbonic anhydrase. (A) Zinc structure is surrounded by three histidine molecules and one hydroxide ion or water molecule to give four bonds directed toward the corners of a tetrahedron. (B) The mechanism by which carbonic anhydrase converts CO_2 into HCO_3^- ions. Only the coordinated portions of the histidine residues are shown. (Reproduced with permission from [10], Copyright (2020) Elsevier Inc.)

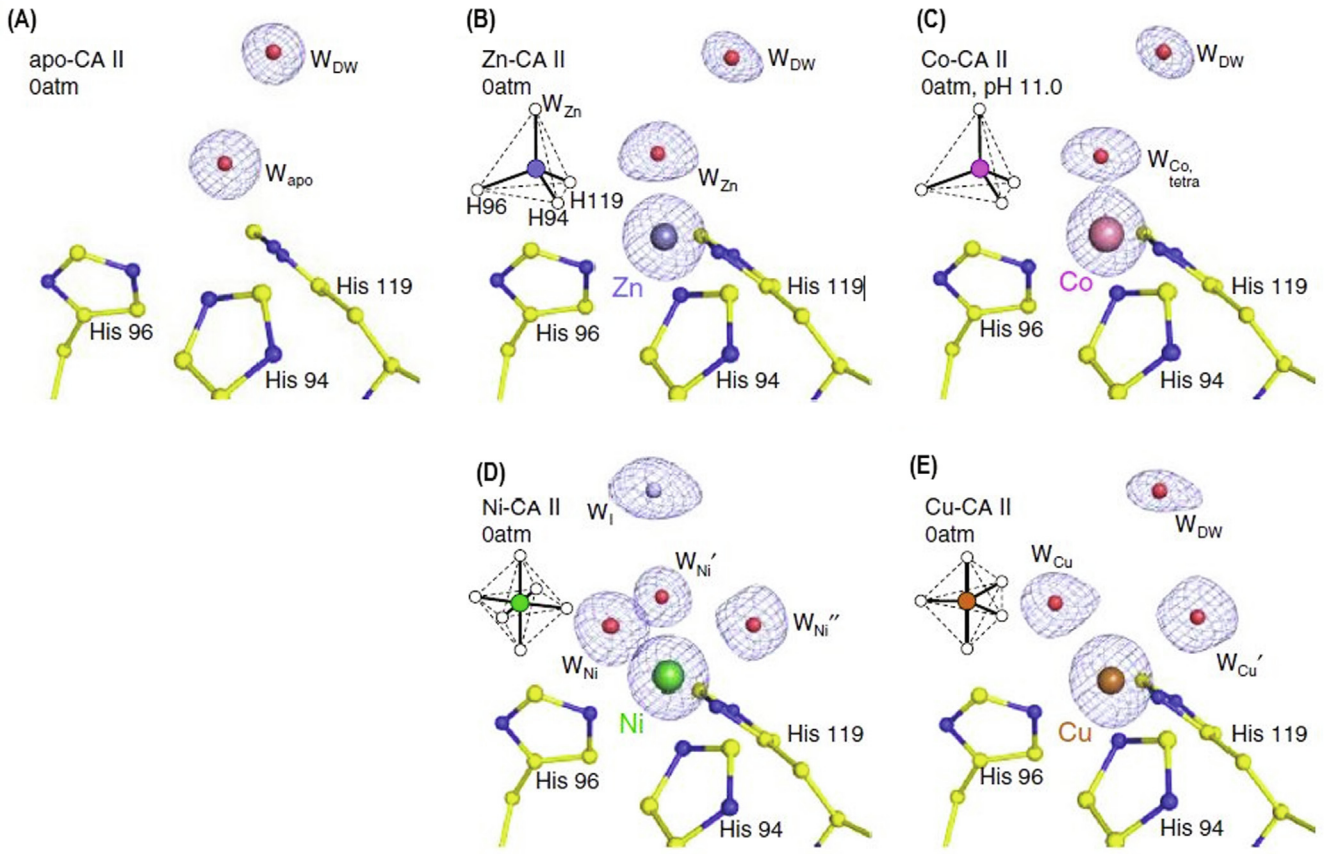


Fig. 8. Metal coordination geometry in CA II without CO_2 pressurization. (A) In apo-CA II, the metal-binding site is vacant; (B), (C) Zn- and Co-CA II show tetrahedral; (D) Ni-CA II octahedral, and (E) Cu-CA II trigonal bipyramidal coordination geometry. The electron density (2Fo–Fc, blue) is contoured at 2.2σ. All structures were obtained at pH 7.8 except for (C) which is obtained at pH 11.0. The intermediate water (W_I) in (D) is coloured in steel blue for clarity. (Reproduced from [116], licensed under CC BY-4.0).

metalloenzymes include Zn_8:$AB3_4$ and Zn_8:$AB5_4$), reportedly endowed with hydrolase activity and demonstrated with lactamase activity *in vivo*, indicating their ability to confer antibiotic resistance on *Escherichia coli* [52]. Moreover, the catalytic efficiency of metalloenzymes significantly changes when subjected to non-native metal substitution even within the same chemical environment. For instance, the variation in catalytic activities of CA II has been demonstrated in respect of change in geometries in the absence of CO_2 pressure. The organic ligands initially contained a vacant binding metal (Fig. 8A), the enzyme became tetrahedral in coordination to Zn^{2+} (Fig. 8B), octahedral forms with Co^{2+} and Ni^{2+} (Fig. 8C and Fig. 8D), and subsequently trigonal bipyramidal with Cu^{2+} (Fig. 8E). The change also induces electrostatic effects through the moderation of the water network at the active site of the enzyme [115]. The geometry plays a vital role in their interactions with biological targets such as the DNA, enzymes and protein receptors, and this, in turn, influences their biological activities (Topala et al 2019). For instance, metal complexes having a coordination number of 4 and square planar geometry are potent medicines in opposition to different diseases especially cancer [116]. These further support that the hypothesised modulation of enzyme-metal coordination in metalloenzymes through geometry represents an ideal strategy to mitigate microbial activities including resistance to drugs.

The suppression of undesired metalloenzyme-mediated activities was also enumerated. The PPOs are Cu-containing enzymes present in bacteria, fungi, plants and animals, renowned for catalytic oxidation of phenolic compounds to quinones, the promoters of brown pigments in tropical fruits and vegetables [47,117]. The effects of *Rosa roxburghii,* an edible perennial shrub on the rate of browning of apple fruits during storage was also demonstrated through the inhibition of PPO activity *in vitro* using inhibition and kinetic analyses. At 0.25–1.25% w/w, *R. roxburghii* juice significantly retarded the rate of browning and inhibited PPO activity (Fig. 9) hypothetically due to the presence of some prominent antioxidants such as ascorbic acid, quercetin, coumaric acid etc in the juice. Individually, ascorbic acid (**B79**) (1.67% w/w) showed strong anti-browning activity while some other phenolic inhibitors in the juice such as quercetin (**B80**) and morin (**B81**) displayed mixed-type and competitive inhibition of PPO activity with IC_{50} of 29.5 and 54.9 μM respectively (Scheme 10). Their activity is attributable to the electrostatic and hydrophobic interactions involving the biotic metal cofactor of the enzyme [117]. Similarly, Aksoy reported the competitive inhibitory activities of **B80** and curcumin (**B82**) on purified potato PPO in terms of IC_{50} of 0.018 and 0.029 mM respectively with the activity strongly linked to the catechol substrate. Quercetin (**B80**) selectively showed an improved potential with IC_{50} 0.0086 mM in the presence of 4-methylcatechol substrate, supporting the contributions of the catechol group in SAR [118]. The catalytic activity of PPO from Tuffles, *Terfezia arenaria* was also studied by Benaceur and co-workers through the purification and influence of metal ions using pyrocatechol and L-tyrosine. The enzymatic activity was recorded as 123 and 140% in the presence of Cu^{2+} ion for 5 mM procatechol and L-tyrosine substrate respectively. The respective activity reduced to 45 and 28% in Cd^{2+} and, 22 and 7% in Al^{3+}, supporting the significant contribution of change in metal cofactor coordination to the purification and enzymatic activities of the PPOs. The inhibitory

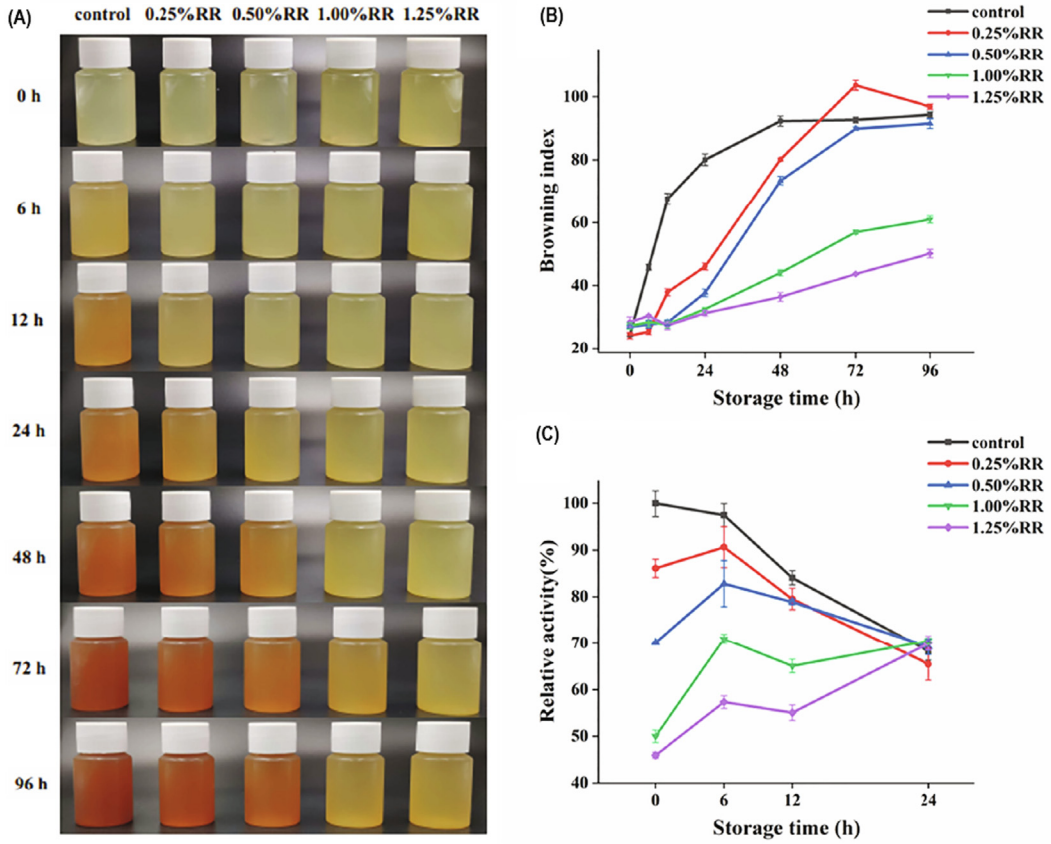
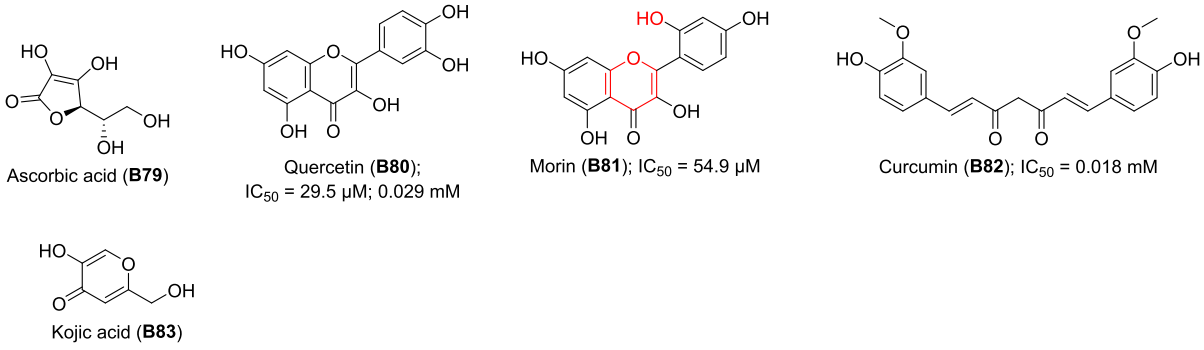


Fig. 9. Photographs of *Rosa roxburghii*-apple juice samples (A) and the changes in the browning index (B) and PPO activity (C) during storage. Control, 0.25% RR, 0.50% RR, 1.00% RR and 1.25% RR indicate adding 0, 0.25%, 0.50%, 1.00% and 1.25% (w/w) *Rosa roxburghii* juice to apple juice respectively. (Reproduced with permission from [118], Copyright (2021) Elsevier Ltd.)



Scheme 10. Chemical structures of some inhibitors of catalytic polyphenol oxidase.

effects of kojic acid (**B83**) at different concentrations on the enzyme were also observed under the influence of pH and temperature. Although, the enzyme maintained stability within a wide range of pH and temperature, however, **B83** sped up the enzymatic inactivation and destabilisation of PPO and thereby enhanced the antioxidant effects of truffles against browning [119]. Similarly, Torres et al recently reported the significant reduction in the activity of purified PPO from sweet potato by Zn(II) ion while Cu(II) enhanced its activation. The enzyme was also observed with the strongest affinity for 3,5-di-caffeoylquinic acid and 3,4,5-tri-caffeoylquinic acid among the tested substrates [120].

Ascorbate oxidases (AOs) are Cu-containing enzymes present in apoplasts of fruits. They are responsible for the reversible oxidation of ascorbic acid to monodehydroascorbic acid intermediate and subsequently to dehydroascorbic acid (DHA). Although the enzymes are mostly found in higher plants, however, few of their class are reportedly present in fungi [121,122]. The inhibitory suppression of AO activity was experimented *in vivo* to induce some biogenic transformations *via* the biosynthetic and recycling genes in melon fruit, thereby increasing the ascorbic acid level and altering the ascorbate redox state. Interestingly, the transient rate of ethylene production reportedly increased concurrently with the levels of 1-aminocyclopropane-1-carboxylic acid, OA activity and gene expression, thereby stimulating the ripening-mediated softening rate of the fruit. Although, the mechanisms of this important phenomenon remain complex, however, the DHA is mostly implicated in the loosening of the cell wall through the obstruction of the covalently cross-linking wall protein and interactions with

pectin or by the active removal of Ca^{2+} ion from the cell wall, thereby enhancing oxalate formation [121].

Nitrogen (II) oxide (NO) is a known inhibitor of catalase-induced hydrogen peroxide decomposition. The catalytic activity of the metal-containing catalase was reversibly inhibited by nitrite, glutathione (GSH), S-nitrosylglutathione (GSNO) and dinitrosyl iron complex (DNIC) in comparison with azide, a basic conjugate of hydrozoic acid. At pH 6, nitrite, DNIC/GSH and GSNO decreased catalase activity by 30% at a concentration of 0.13, 0.13 and 0.14 μM respectively compared to azide which showed 0.04 μM. The inhibitory effects became bolstered by up to 100-folds in the presence of halides (Br and Cl) and thiocyanate groups. The direct mechanisms involved the interactions of the compounds with the metal ion centre of the enzyme active site, leading to the production of positively charged NO (NO^+), protected from hydration by the halide and thiocyanate. The study suggests that a low concentration of cellular chloride significantly downregulate the inhibition of catalases by nitroso compounds [123]. Furthermore, the metallophore staphylopine in *S. aureus* constitute a cnt system through which the organism acquires metals such as iron, nickel, cobalt, copper and zinc from its host for survival and infection. Although, not significantly relevant to disease pathogenesis, however, the rate of biohydrogen production by N_2-fixing cyanobacteria such as the *Anabaena siamensis* was experimentally demonstrated to increase upon an increase in Fe, Mo and Ni cofactors of the catalytic metalloenzymes, nitrogenase and reversible hydrogenase [124]. This further indicates the modulatory influence of the metal cofactors on the catalytic activities of the metalloenzymes and as a plausible target for the activity regulations.

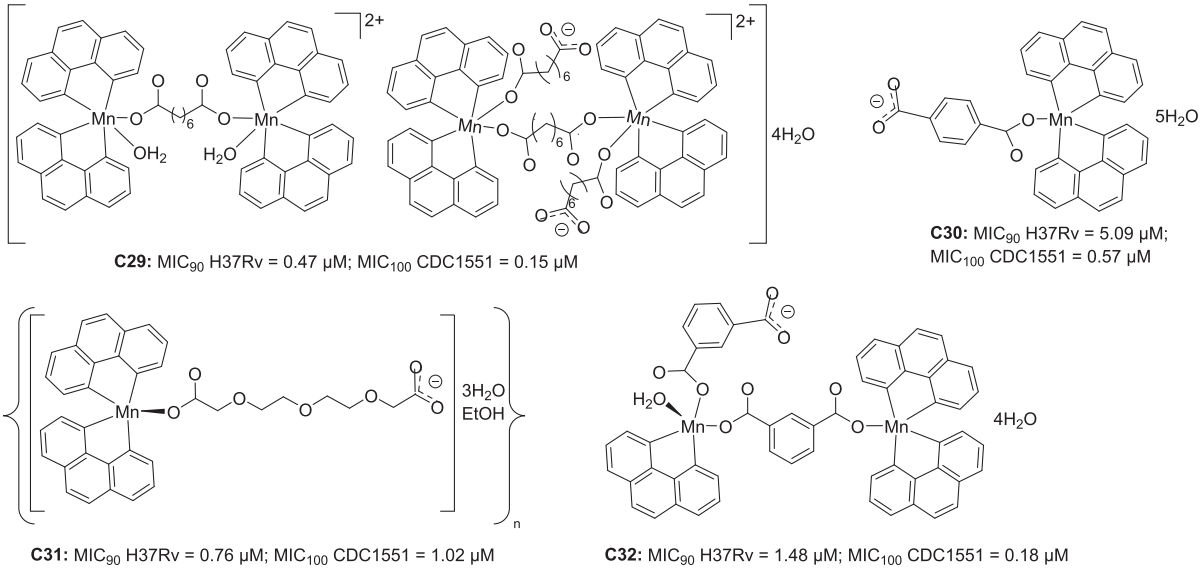
4. Coordination complexes of metal cofactors as potential anti-resistant agents

Generally, metal complexes usually possess characteristic features that favour enzyme inhibition. These include photochemical and photophysical properties such as facile 3D and planar structure for biocompatibility, photosensitivity, tunable pharmacophores for interaction with various biological targets, flexible geometry, inertness for substitution, additive ligand profiles, pH response and selectivity to chemical environments [103,110,125,126]. Their uniqueness in terms of ligand exchange and structural flexibility had fostered the atomistic understanding of their binding to metalloenzymes through kinetics and thermodynamics studies and supports the identification of metal-centred inhibitors of metalloenzymes [125]. In the development of enhanced medicinal compounds, metal complexes are of great importance. [17]. Thus, it is expected that the innovative growth of new and developed non-toxic metal-based drugs extremely extends with the strategic development of new and improved ligands for the metal elements [17].

Catalase-peroxidase is a katG gene-encoded protein that sometimes contains Mn cofactor centre, contributing to the resistance in *M. tuberculosis,* a bacterial disease with a significant effect on global health systems. It affects the bone, central nervous system, lung and several other organs, yet with limited therapeutic options while its symptoms are only being ameliorated by isoniazid [28]. Some Mn complexes were synthesised and evaluated as potent inhibitors of *M. tuberculosis.* Selectively. $[Mn_2(oda)(phen)_4(H_2O)_2][Mn_2(oda)(phen)_4(oda)_2].4H_2O$ (**C29**), $[Mn(tereph)(phen)_2].5H_2O$ (**C30**) {$[Mn(tdda)(phen)_2].3H_2O.EtOH$}n (**C31**) and $[Mn_2(isoph)_2(phen)_3].4H_2O$ (**C32**) where odaH2 = octanedioic acid, phen = 1,10-phenathroline, tdda = 3,6,9-trioxaundecanedioic acid, isophH2 = isophthalic acid and tereph = terephthalic acid displayed strong inhibitory potentials against *M. tuberculosis* H37Rv strain with MIC_{90} of 0.47, 5.09, 0.76 and 1.48 μM respectively, while they showed MIC_{100} of 0.15, 0.57, 1.02 and < 0.18 μM respectively (Scheme 11). Interestingly, their cytotoxicity against mammalian cells was recorded between IC_{50} of 70.06–947.3 μM, indicating their promising tolerability [28]. They are therefore suggested as potential antitubercular agents for further studies, although, the implications of the metalloenzyme, catalase-peroxidase in the anti-resistant activities of the complexes also remain underexplored.

5. Conclusion and future challenges

The enormous contributions of coordination-inclined metalloenzymes to antibiotic resistance and cell defence in superbugs such as *E. coli, P. aeruginosa, K. pneumonia, H. pylori, S. aureus* and several other deadly bacterial strains significantly constitute pathogenic disease threats. Recent scientific explorations to address the global menace which inestimably challenges human



C29: MIC_{90} H37Rv = 0.47 μM; MIC_{100} CDC1551 = 0.15 μM

C30: MIC_{90} H37Rv = 5.09 μM; MIC_{100} CDC1551 = 0.57 μM

C31: MIC_{90} H37Rv = 0.76 μM; MIC_{100} CDC1551 = 1.02 μM

C32: MIC_{90} H37Rv = 1.48 μM; MIC_{100} CDC1551 = 0.18 μM

Scheme 11. Chemical structures of metal chelates with anti-pathogenic-resistance activity.

well-being has been taken through interesting dynamisms. These involve the mimicry and modulation of coordination chemistry in metalloenzymes of some renowned resistant pathogenic organisms including the MBLs such as the IMP, NDM and VDM, the ureases, POs, CAs, targeting the metal cofactor active centres. The analysis of the enzymatic implications of these biomacromolecules and their mutants in resistance development was indicated to occur through various pathomechanisms including gene encoding variability, modulations of intracellular targets, hydrolytic reactions, cellular metabolism of antibiotics and redox catalysis. Oftentimes, the mechanisms involve the attraction/donation of electrons during labile coordination to substrates and these were largely overviewed.

The synopsis reveals that the metalloenzymes were effectively deactivated through strategic removal/replacement of biotic metal ions and/or chelating agents to induce loss of resistivity and specificity and suppression of catalytic activities. Several metal-chelating inhibitors from recent literature were shown to demonstrate promising potentials to mitigate the defence/resistivity of some notorious superbugs including *E. coli, K. pneumonia, S. aureus,* and *H. pylori*, targeting their respective metalloenzymes. Notably, imipenem (**B02**), meropenem (**B03**), hesperidin (**B08**), aspergillomarasmine A (**B11**), 4-(3-aminophenyl)pyridine-2,6-dicarboxylic acid (**B13**), 6-(phosphonomethyl)picolinic acid (**B18**) 2-(6-(benzyloxy)-1-hydroxynaphthalen-2-yl)benzo[d]oxazole-4-carboxylic acid (**B25**), rosmarinic acid (**B37**) and salvianolic acid (**B38**) displayed the highest potency against the MBL strains, NDM-1, VDM-2 and IMP-1 in both theoretical and experimental observations. The metal chelators, **B67-B78** were exceptionally potent as inhibitors of ureases. Their activities were observed as mechanistic sequestration of biotic metals ions, coordination-inclined replacement of biotic metal cofactors with abiotic type, leading to the deactivation and loss of substrate specificity by the metalloenzymes. Interestingly, most of the metal chelators are small natural molecules with biodiverse potentials, favouring safety and accessibility. They hijack the metal cofactors from the active sites of the metalloenzymes and potently form stable and labile ternary complexes with a minimised steric hindrance, supporting the assembling of bioactive ligands for synergistic antimicrobial effects. The ligands, **B79-B83** represent the suppressors of catalytic activities of the PPOs with modulatory effects proposedly through the ligand exchange and metal cofactor displacement. Among the coordination compound inhibitors, **C2, C4, C5, C18** and **C20** were efficient against the NDM-1 while complexes **C6-C15** potently deactivated the resistant ureases, all proposedly through the blockade of active sites, the additive antimicrobial effects of the ligands and ligand exchange. The complexes **C29-C32** also displayed interesting cytotoxicity against multidrug-resistant *M. tuberculosis*.

However, despite the promising anti-resistance pharmacology of the innovative strategic metal cofactor displacement from the metalloenzymes of the superbugs, unspecific chelation could engender mineral scarcity and trigger serious complications due to their predominance in biological functions. Since some of the metal cofactors such as Zn, Cu and Fe are essentially required for functional systemic activities, future scientific research is required for effective and appropriate delivery to target for discriminative actions. This could be achieved through the application of nanotechnology and would regulate the mineral levels for a healthy life. Indiscriminative cytotoxicity constitutes a major limitation to metal-based prodrugs. Therefore, more studies are necessarily required on the selective toxicity of the highlighted candidates, especially the metal complexes. The mechanisms of actions of some metal chelate inhibitors such as **C21-C24** were not succinctly reported. More research work is essential for promoting their interesting pharmacological potentials to real-life biomedical applications. The coordination chelates with biologically toxic metals such as **C25** and **C26** could be suitable for external applications such as biocides and disinfectants for agricultural practices and environmental sanitation upon further exploration. As prometallodrugs, the responses of the overviewed metal complexes to various stimuli essential for biomedical applications were less focused. Future studies on the effects of light, pH, temperature and other stimuli on the performance of the metal complexes remain worthy. Moreover, most of the overviewed works in this innovative therapeutic science were limited to basic preclinical modules without a comprehensive understanding of the pharmacokinetics, pharmacodynamics and druggability of the presented candidates. Furthermore, adequate excretion of the ternary complexes formed by the chelation or replacement of the enzymatic metal ions is very important to avoid a toxic accumulation of metal ions. As such, future exploration should be directed to the study of pharmacokinetics, pharmacodynamics, druggability and the effective removal of the bi-product complexes within biological systems. The experimental studies were also conducted mostly *via in vitro* models through which the undesired physiological side effects cannot be succinctly observed. Thus, future scientific work should incorporate extensive *in vivo* studies at basic and clinical levels. This is imperative for a complete translation of the promising candidates into real-life medicinal applications. The highlighted candidates are therefore recommended for further studies. This review represents a model for expanded exploration of the innovative and effective therapeutic science amenable for conquering antibiotic resistance of superbugs through metalloenzyme mimicry and modulation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by Tertiary Education Fund Nigeria, Fundamental Research Grant Scheme (203.CDADAH.6711955), Ministry of Higher Education of Malaysia and Universiti Sains Malaysia GA Scheme (grant no. 308.AIPS.415401).

References

[1] S. Kamal, N. Akhter, R. Noreen, M. Salman, S.G. Khan, T. Roheen, N. Yaqoob, A. Kamal, W.A. Siddique, A new approach to design 3(3-sulfamoylbenzamido) benzoic acid containing transition metal complexes: Characterization and biological activities, Pak. J. Pharm. Sci. 32 (2019) 2317–2324.
[2] A.J. Schaenzer, G.D. Wright, Antibiotic Resistance by Enzymatic Modification of Antibiotic Targets, Trends Mol. Med. 26 (2020) 768–782, https://doi.org/10.1016/j.molmed.2020.05.001.
[3] A. Angeli, F. Carta, C.T. Supuran, Carbonic anhydrases: Versatile and useful biocatalysts in chemistry and biochemistry, Catalysts. 10 (2020) 1–11, https://doi.org/10.3390/catal10091008.
[4] A. Blanco, G. Blanco, Enzymes are biological catalysts, Med. Biochem. (2017) 153–175, https://doi.org/10.1016/B978-0-12-803550-4/00008-2.
[5] A.M. Egorov, M.M. Ulyashova, M.Y. Rubtsova, Bacterial enzymes and antibiotic resistance, Acta Naturae. 10 (2018) 33–48.
[6] M.E. Helsel, E.J. White, S.Z.A. Razvi, B. Alies, K.J. Franz, Chemical and functional properties of metal chelators that mobilize copper to elicit fungal killing of: Cryptococcus neoformans, Metallomics. 9 (2017) 69–81, https://doi.org/10.1039/c6mt00172f.
[7] S.P Gupta, Roles of metals in human health, MOJ Bioorganic Org. Chem. 2 (2018) 221–224. 10.15406/mojboc.2018.02.00085.
[8] S. Kumar, R. Krishna Chaitanya, V.R. Preedy, Assessment of Antioxidant Potential of Dietary Components, Elsevier Inc., 2017. 10.1016/B978-0-12-809853-0.00020-1.
[9] A. Kulesha, J.H. Yoon, C. Chester, A.D. Souza, C. Costeas, O.V. Makhlynets, Contributions of primary coordination ligands and importance of outer sphere interactions in UFsc, a de novo designed protein with high affinity for metal ions, J. Inorg. Biochem. 212 (2020), https://doi.org/10.1016/j.jinorgbio.2020.111224 111224.

[10] J.E. House, Bioinorganic chemistry, in: Inorg. Chem., Third, Elsevier Inc., 2020: pp. 901–932. 10.1016/B978-0-12-814369-8.00023-6 901.
[11] A.J. Plaunt, M. de L. Betancourt-Mendiola, B.D. Smith, Biomolecule Recognition Using Transition Metal Ions and Hydrogen Bonding, in: Compr. Supramol. Chem. II, Elsevier Ltd, 2017: pp. 575–591. 10.1016/B978-0-12-409547-2.12576-4.
[12] R.M. Seyedsayamdost, A. Caruso, K. M.Davis, The Chemistry and Structural Enzymology of RiPP-Modifying Radical SAM Metalloenzymes, in: Compr. Nat. Prod. III, Third, Elsevier Ltd, 2020: pp. 49–64. 10.1016/B978-0-12-409547-2.14707-9.
[13] S. Bajeli, N. Baid, M. Kaur, G.P. Pawar, V.D. Chaudhari, A. Kumar, Terminal respiratory oxidases: A targetables vulnerability of mycobacterial bioenergetics?, Front Cell. Infect. Microbiol. 10 (2020) 1–22, https://doi.org/10.3389/fcimb.2020.589318.
[14] S. Emir, R. Say, H. Yavuz, A. Denizli, A new metal chelate affinity adsorbent for cytochrome c, Biotechnol. Prog. 20 (2004) 223–228, https://doi.org/10.1021/bp030033t.
[15] J. Liu, S. Chakraborty, P. Hosseinzadeh, Y. Yu, S. Tian, I. Petrik, A. Bhagi, Y. Lu, Metalloproteins containing cytochrome, iron-sulfur, or copper redox centers, Chem. Rev. 114 (2014) 4366–4369, https://doi.org/10.1021/cr400479b.
[16] S. Yamabe, The effect of nalidixic acid group compounds on reduction of cytochrome c from horse heart and Candida krusei, J. Gen. Microbiol. 105 (1978) 227–232, https://doi.org/10.1099/00221287-105-2-227.
[17] C. Bonaccorso, T. Marzo, D. La Mendola, Biological applications of thiocarbohydrazones and their metal complexes: A perspective review, Pharmaceuticals. 13 (2020), https://doi.org/10.3390/ph13010004.
[18] I. Casanova, M.L. Durán, J. Viqueira, A. Sousa-Pedrares, F. Zani, J.A. Real, J.A. García-Vázquez, Metal complexes of a novel heterocyclic benzimidazole ligand formed by rearrangement-cyclization of the corresponding Schiff base. Electrosynthesis, structural characterization and antimicrobial activity, Dalt. Trans. 47 (2018) 4325–4340, https://doi.org/10.1039/c8dt00532j.
[19] S. Luthra, A. Rominski, P. Sander, The role of antibiotic-target-modifying and antibiotic-modifying enzymes in mycobacterium abscessusdrug resistance, Front. Microbiol. 9 (2018) 1–13, https://doi.org/10.3389/fmicb.2018.02179.
[20] C.A. Thomas, Z. Cheng, K. Yang, E. Hellwarth, C.J. Yurkiewicz, F.M. Baxter, S.A. Fullington, A. Klinsky, J.L. Otto, A.Y. Chen, S.M. Cohen, W. Crowder, Probing the mechanisms of inhibition for various inhibitors of metallo- - lactamases VIM-2 and NDM-1, J. Inorg. Biochem. (2020), https://doi.org/10.1016/j.jinorgbio.2020.111123 111123.
[21] H.J. Davis, T.R. Ward, Artificial metalloenzymes: challenges and opportunities, ACS Cent. Sci. 5 (2019) 1120–1136, https://doi.org/10.1021/acscentsci.9b00397.
[22] H. Fatima, N. Goel, R. Sinha, S. Kumar, Recent strategies for inhibiting multidrug-resistant and β -lactamase producing bacteria: A review, Colloids Surfaces B Biointerfaces. 205 (2021), https://doi.org/10.1016/j.colsurfb.2021.111901 111901.
[23] S.S. Castle, Beta-Lactamase Inhibitors, in: XPharm Compr. Pharmacol. Ref., 2007: pp. 1999–2001.
[24] T. Kuriyama, T. Karasawa, D.W. Williams, Antimicrobial Chemotherapy: Significance to Healthcare, Elsevier Inc., 2014. 10.1016/B978-0-12-397043-5.00013-X.
[25] G.J. Kontoghiorghes, C.N. Kontoghiorghe, Iron and chelation in biochemistry and medicine: treating related diseases, Cells 9 (2020) 43 pages.
[26] A.C. Ghosh, C. Duboc, M. Gennari, Synergy between metals for small molecule activation: Enzymes and bio-inspired complexes, Coord. Chem. Rev. 428 (2021), https://doi.org/10.1016/j.ccr.2020.213606 213606.
[27] R. Crichton, Manganese - Oxygen generation and detoxification, in: Biol. Inorg. Chem., Third Edit, Elsevier B.V, 2019: pp. 459–473. 10.1016/B978-0-12-811741-5.00016-3.
[28] P. McCarron, M. McCann, M. Devereux, K. Kavanagh, C. Skerry, P.C. Karakousis, A.C. Aor, T.P. Mello, A.L.S. Santos, D.L. Campos, F.R. Pavan, Unprecedented in vitro antitubercular activitiy of manganese(II) complexes containing dicarboxylate ligands: increased activity, superior selectivity, and lower toxicity in comparison to their copper (II) analogs, Front. Microbiol. 9 (2018) 1–10, https://doi.org/10.3389/fmicb.2018.01432.
[29] T. Golkar, M. Zielinski, A.M. Berghuis, Look and outlook on enzyme-mediated macrolide resistance, Front. Microbiol. 9 (2018) 1–15, https://doi.org/10.3389/fmicb.2018.01942.
[30] Q. Ye, Q. Wu, S. Zhang, J. Zhang, G. Yang, Characterization of β-lactamase-producing enterobacteriaceae from retail food in China, Front. Microbiol. 9 (2018) 1–12, https://doi.org/10.3389/fmicb.2018.01709.
[31] D.L. Paterson, Infections due to other members of the enterobacteriaceae, multidrug-resistant strains, in: Goldman's Cecil Med. 24/E, Twenty Fou, Elsevier Inc., 2012: pp. 1874–1877. 10.1016/B978-1-4377-1604-7.00313-4.
[32] T. Singh, S. Ahmad, S. Das, S. Haque, Importance of efflux pumps in subjugating antibiotic resistance, Elsevier Inc., 2020. 10.1016/B978-0-12-818480-6/00010-2.
[33] M. Arshad, A. Nowalk, P.D. Tamma, Multidrug-Resistant Gram-Negative Infections in Transplant and Oncology Patients, in: Pediatr. Transpl. Oncol. Infect. Dis., 1st ed., Elsevier Inc., 2021: pp. 97–102. 10.1016/B978-0-323-64198-2.00023-3.
[34] J.E. House, Coord. Comps. Catal. (2020), https://doi.org/10.1016/b978-0-12-814369-8.00022-4.
[35] K. Bush, Past and present perspectives on β-lactamases, Antimicrob. Agents Chemother. 62 (2018) 1–20, https://doi.org/10.1128/AAC.01076-18.
[36] G. Rivière, S. Oueslati, M. Gayral, J.B. Créchet, N. Nhiri, E. Jacquet, J.C. Cintrat, F. Giraud, C. van Heijenoort, E. Lescop, S. Pethe, B.I. Iorga, T. Naas, E. Guittet, N. Morellet, NMR characterization of the influence of zinc(II) ions on the structural and dynamic behavior of the New Delhi metallo-βlactamase-1 and on the binding with flavonols as inhibitors, ACS Omega 5 (2020) 10466–10480, https://doi.org/10.1021/acsomega.0c00590.
[37] A.Y. Chen, Conversion of Metal Chelators to Selective and Potent Inhibitors of New Delhi Metallo-beta- lactamase, UC San Diego. Chen_ucsd_ (2020). https://escholarship.org/uc/item/8xk949p6.
[38] A.Y. Chen, P.W. Thomas, A.C. Stewart, A. Bergstrom, Z. Cheng, C. Miller, C.R. Bethel, S.H. Marshall, C.V. Credille, C.L. Riley, R.C. Page, R.A. Bonomo, M.W. Crowder, D.L. Tierney, W. Fast, S.M. Cohen, Dipicolinic acid derivatives as inhibitors of New Delhi Metallo-β-lactamase-1, J. Med. Chem. 60 (2017) 7267–7283, https://doi.org/10.1021/acs.jmedchem.7b00407.
[39] F. Di Pisa, C. Pozzi, M. Benvenuti, J. Docquier, F. De Luca, S. Mangani, Boric acid and acetate anion binding to subclass B3 metallo-β-lactamase BJP-1 provides clues for mechanism of action and inhibitor design, Inorg. Chim. Acta (2017), https://doi.org/10.1016/j.ica.2017.07.030.
[40] J. Li, C. Chen, M. Yao, L. Sun, H. Gao, J. Chigan, K. Yang, Hydroxamic acid with benzenesulfonamide: An effective scaffold for the development of broad-spectrum metallo-β-lactamase inhibitors, Bioorg. Chem. 105 (2020), https://doi.org/10.1016/j.bioorg.2020.104436 104436.
[41] M. Lisa, A.R. Palacios, M. Aitha, M.M. González, D.M. Moreno, M.W. Crowder, R.A. Bonomo, J. Spencer, D.L. Tierney, L.I. Llarrull, A.J. Vila, A general reaction mechanism for carbapenem hydrolysis by mononuclear and binuclear metallo-β-lactamases, Nat. Commun. 8 (2017) 1–11, https://doi.org/10.1038/s41467-017-00601-9.
[42] F.G. Martínez, G. Moreno-martin, M. Pescuma, Y. Madrid-albarrán, F. Mozzi, Biotransformation of selenium by lactic acid bacteria: formation of seleno-nanoparticles and seleno-amino acids, Front. Bioeng Biotechnol. 8 (2020) 1–17, https://doi.org/10.3389/fbioe.2020.00506.
[43] C. Li, X. Deng, X. Xie, Y. Liu, J.P.F. Angeli, L. Lai, Activation of glutathione peroxidase 4 as a novel anti-inflammatory strategy, Front. Pharmacol. 9 (2018) 1–12, https://doi.org/10.3389/fphar.2018.01120.
[44] B.R. Cardoso, D.J. Hare, A.I. Bush, B.R. Roberts, Glutathione peroxidase 4: A new player in neurodegeneration?, Mol Psychiatry. 22 (2017) 328–335, https://doi.org/10.1038/mp.2016.196.
[45] A. Dance, How bacteria cause pain and what that reveals about the role of the nervous system, Proc. Natl. Acad. Sci. U. S. A. 116 (2019) 12584–12586, https://doi.org/10.1073/pnas.1905754116.
[46] S.C. Mehta, I.M. Furey, O.A. Pemberton, D.M. Boragine, Y. Chen, T. Palzkill, KPC-2 β-lactamase enables carbapenem antibiotic resistance through fast deacylation of the covalent intermediate, J. Biol. Chem. (2020) 1–33, https://doi.org/10.1074/jbc.RA120.015050.
[47] I. Kampatsikas, A. Bijelic, A. Rompel, Biochemical and structural characterization of tomato polyphenol oxidases provide novel insights into their substrate specificity, Sci. Rep. (2019) 1–13, https://doi.org/10.1038/s41598-019-39687-0.
[48] N. Hakulinen, C. Gasparetti, H. Kaljunen, K. Kruus, J. Rouvinen, The crystal structure of an extracellular catechol oxidase from the ascomycete fungus Aspergillus oryzae, J. Biol. Inorg. Chem. 18 (2013) 917–929, https://doi.org/10.1007/s00775-013-1038-9.
[49] R.P. Hausinger, New metal cofactors and recent metallocofactor insights, Curr. Opin. Struct. Biol. 59 (2019) 1–8, https://doi.org/10.1016/j.sbi.2018.12.008.
[50] S.K. Burley, C. Bhikadiya, C. Bi, S. Bittrich, L. Chen, et al., RCSB Protein Data Bank: powerful new tools for exploring 3D structures of biological macromolecules for basic and applied research and education in fundamental biology, biomedicine, biotechnology, bioengineering and energy sciences, Nucleic Acids Res. 49 (2021) D437–D451, https://doi.org/10.1093/nar/gkaa1038.
[51] S. Luo, Y. Ju, J. Zhou, Q. Gu, J. Xu, H. Zhou, Crystal structure of CntK, the cofactor-independent histidine racemase in staphylopine-mediated metal acquisition of Staphylococcus aureus, Int. J. Biol. Macromol. 135 (2019) 725–733, https://doi.org/10.1016/j.ijbiomac.2019.05.169.
[52] F. Nastri, D. D'Alonzo, L. Leone, G. Zambrano, V. Pavone, A. Lombardi, Engineering metalloprotein functions in designed and native scaffolds, Trends Biochem. Sci. 44 (2019) 1022–1040, https://doi.org/10.1016/j.tibs.2019.06.006.
[53] L. Hernández, E. Del Carpio, W. Madden, G. Lubes, A. Perez, R.E. Rodríguez-Lugo, V.R. Landaeta, M.L. Araujo, J. Daniel Martínez, V., Lubes, Determination of stability constants of ternary copper(II) complexes formed with picolinic acid and several amino acids, Phys. Chem. Liq. 58 (2020) 31–48, https://doi.org/10.1080/00319104.2018.1534235.
[54] Z. Chen, Z. Wang, J. Ren, X. Qu, Enzyme mimicry for combating bacteria and biofilms, Acc. Chem. Res. 51 (2018) 789–799, https://doi.org/10.1021/acs.accounts.8b00011.
[55] M.A. Guevara, J. Lu, R.E. Moore, S.A. Chambers, A.J. Eastman, J.D. Francis, K.N. Noble, R.S. Doster, K.G. Osteen, S.M. Damo, S.D. Manning, D.M. Aronoff, N.B. Halasa, S.D. Townsend, J.A. Gaddy, Vitamin D and Streptococci: the interface of nutrition, host immune response, and antimicrobial activity in response to infection, ACS Infect. Dis. 6 (2020) 3131–3140, https://doi.org/10.1021/acsinfecdis.0c00666.
[56] D. Cui, Y. Yang, M. Bai, J. Han, C. Wang, Systematic research of H 2 dedpa derivatives as potent inhibitors of New Delhi Metallo-β-lactamase-1, Bioorg. Chem. 101 (2020), 103965, https://doi.org/10.1016/j.bioorg.2020.103965.

[57] A.T. Gordon, O.O. Abosede, S. Ntsimango, S. van Vuuren, E.C. Hosten, A.S. Ogunlaja, Synthesis, characterization, molecular docking and antimicrobial activity of copper(II) complexes of metronidazole and 1,10 phenanthroline, Inorg. Chim. Acta. 510 (2020), https://doi.org/10.1016/j.ica.2020.119744 119744.
[58] J.E. Raczynska, B. Imiolczyk, M. Komorowska, J. Sliwiak, J. Czyrko-horczak, K. Brzezinski, M. Jaskolski, Flexible loops of New Delhi metallo-β-lactamase modulate its activity towards different substrates, Int. J. Biol. Macromol. 158 (2020) 104–115, https://doi.org/10.1016/j.ijbiomac.2020.04.219.
[59] Y.A. Heo, Imipenem/cilastatin/relebactam: A review in gram-negative bacterial infections, Drugs 81 (2021) 377–388, https://doi.org/10.1007/s40265-021-01471-8.
[60] C. Shi, J. Bao, Y. Sun, X. Kang, X. Lao, H. Zheng, Discovery of Baicalin as NDM-1 inhibitor: Virtual screening, biological evaluation and molecular simulation, Bioorg. Chem. 88 (2019), https://doi.org/10.1016/j.bioorg.2019.102953 102953.
[61] S. Liu, Y. Zhou, X. Niu, T. Wang, J. Li, Z. Liu, J. Wang, S. Tang, Y. Wang, X. Deng, Magnolol restores the activity of meropenem against NDM-1-producing Escherichia coli by inhibiting the activity of metallo-beta-lactamase, Cell Death Discov. (2018), https://doi.org/10.1038/s41420-018-0029-6.
[62] C. Shi, J. Chen, B. Xiao, X. Kang, X. Lao, H. Zheng, Discovery of NDM-1 inhibitors from natural products, J. Glob. Antimicrob. Resist. 18 (2019) 80–87, https://doi.org/10.1016/j.jgar.2019.02.003.
[63] A.Y. Chen, C. Thomas, P.W. Thomas, K. Yang, Z. Cheng, W. Fast, M.W. Crowder, S.M. Cohen, Iminodiacetic acid as a novel metal-binding pharmacophore for New Delhi metallo-β-lactamase inhibitor development, ChemMedChem (2020), https://doi.org/10.1002/cmdc.202000123.
[64] J. Zhang, S. Wang, Q. Wei, Q. Guo, Y. Bai, S. Yang, F. Song, L. Zhang, X. Lei, Synthesis and biological evaluation of Aspergillomarasmine A derivatives as novel NDM-1 inhibitor to overcome antibiotics resistance, Bioorg. Med. Chem. 25 (2017) 5133–5141, https://doi.org/10.1016/j.bmc.2017.07.025.
[65] D. Sychantha, C.M. Rotondo, K.H.M.E. Tehrani, N.I. Martin, G.D. Wright, Aspergillomarasmine A inhibits metallo-β-lactamases by selectively sequestering Zn2+, J. Biol. Chem. (2021), https://doi.org/10.1016/j.jbc.2021.100918 100918.
[66] Y. Yang, Y. Guo, Y. Zhou, Y. Gao, X. Wang, J. Wang, Discovery of a novel natural allosteric inhibitor that targets NDM-1 against Escherichia coli, Front. Pharmacol. 11 (2020) 1–11, https://doi.org/10.3389/fphar.2020.581001.
[67] K.V. Mulligan, S. Workman, T. Sun, S. Rettie, X. Li, L.J. Worrall, T.W. Craven, D. T. King, P. Hosseinzadeh, A.M. Watkins, P.D. Renfrew, S. Guffy, J.W. Labonte, R. Moretti, R. Bonneau, N.C.J. Strynadka, D. Baker, Computationally designed peptide macrocycle inhibitors of New Delhi metallo- β -lactamase 1, PNAS. 118 (2021) 1–9, https://doi.org/10.1073/pnas.2012800118/-/DCSupplemental.Published.
[68] Q. Wang, Y. He, R. Lu, W. Wang, K. Yang, H.M. Fan, Thermokinetic profile of NDM-1 and its inhibition by small carboxylic acids, Biosci. Rep. 38 (2018) BSR20180244. 10.1042/BSR20180244.
[69] A. Salari-jazi, K. Mahnam, P. Sadeghi, M.S. Damavandi, Discovery of potential inhibitors against New Delhi from natural compounds: in silico - based methods, Sci. Rep. (2021) 1–20, https://doi.org/10.1038/s41598-021-82009-6.
[70] A.C. Jackson, T.B.J. Pinter, D.C. Talley, A. Baker-agha, D. Patel, P.J. Smith, K.J. Franz, Benzimidazole and benzoxazole zinc chelators as inhibitors of metallo-β -lactamase NDM-1, ChemMedChem 15 (2020) 1–9, https://doi.org/10.1002/cmdc.202000607.
[71] T. Christopeit, A. Albert, H.S. Leiros, Discovery of a novel covalent non-β-lactam inhibitor of the metallo-β-lactamase NDM-1, Bioorg. Med. Chem. (2016), https://doi.org/10.1016/j.bmc.2016.04.064.
[72] J. Li, L. Sun, Z. Jiang, C. Chen, H. Gao, J. Chigan, H. Ding, K. Yang, Diaryl-substituted thiosemicarbazone : A potent scaffold for the development of New Delhi metallo- β -lactamase-1 inhibitors, Bioorg. Chem. 107 (2021), https://doi.org/10.1016/j.bioorg.2020.104576 104576.
[73] J. Li, H. Gao, L. Zhai, L. Sun, C. Chen, J. Chigan, H. Ding, K. Yang, Dipyridyl-substituted thiosemicarbazone as a potent broad-spectrum inhibitor of metallo-β-lactamases, Bioorg. Med. Chem. 38 (2021), https://doi.org/10.1016/j.bmc.2021.116128 116128.
[74] E. Zhang, M. Wang, S. Huang, S. Xu, D. Cui, Y. Bo, P. Bai, Y. Hua, C. Xiao, S. Qin, NOTA analogue : A first dithiocarbamate inhibitor of metallo-b-lactamases, Bioorg. Med. Chem. Lett. 28 (2018) 214–221, https://doi.org/10.1016/j.bmcl.2017.10.074.
[75] B. Zhao, X. Zhang, T. Yu, Y. Liu, X. Zhang, Y. Yao, X. Feng, H. Liu, D. Yu, L. Ma, S. Qin, Discovery of thiosemicarbazones derivatives as effective New Delhi metallo-β-lactamase-1 (NDM-1) inhibitors against NDM-1 producing clinical isolates, Acta Pharm. Sin. B 1 (2020), https://doi.org/10.1016/j.apsb.2020.07.005.
[76] Z. Yu, S. Liu, S. Zhou, H. Li, F. Yang, L. Yang, Y. Wu, L. Guo, G. Li, Virtual target screening reveals rosmarinic acid and salvianolic acid A inhibiting metallo- and serine- b -lactamases, Bioorg. Med. Chem. Lett. 28 (2018) 1037–1042, https://doi.org/10.1016/j.bmcl.2018.02.025.
[77] S. Liu, L. Jing, Z. Yu, C. Wu, Y. Zheng, E. Zhang, Q. Chen, Y. Yu, L. Guo, Y. Wu, G. Li, ((S)-3-Mercapto-2-Methylpropanamido)acetic acid derivatives as metallo-β-lactamase inhibitors: Synthesis, kinetic and crystallographic studies, Eur. J. Med. Chem. (2018), https://doi.org/10.1016/j.ejmech.2018.01.032.
[78] L. La Piana, V. Viaggi, L. Principe, S. Di, F. Luzzaro, M. Viale, N. Bertola, G. Vecchio, Polypyridine ligands as potential metallo-β-lactamase inhibitors, J. Inorg. Biochem. 215 (2021), https://doi.org/10.1016/j.jinorgbio.2020.111315 111315.
[79] Z. Messasma, D. Aggoun, S. Houchi, A. Ourari, Y. Ouennoughi, F. Keffous, R. Mahdadi, Biological activities, DFT calculations and docking of imines tetradentates ligands, derived from salicylaldehydic compounds as metallo-beta-lactamase inhibitors, J. Mol. Struct. (2020), https://doi.org/10.1016/j.molstruc.2020.129463 129463.
[80] A.Y. Chen, P.W. Thomas, Z. Cheng, N.Y. Xu, D.L. Tierney, M.W. Crowder, W. Fast, S.M. Cohen, Investigation of dipicolinic acid isosteres for the inhibition of metallo- b -lactamases, ChemMedChem 14 (2019) 1271–1282, https://doi.org/10.1002/cmdc.201900172.
[81] S. Leiris, A. Coelho, C. Lozano, J. Bougnon, J. Bousquet, M. Everett, M. Lemonnier, N. Sprynski, M. Zalacain, T.D. Pallin, M.C. Cramp, N. Jennings, G. Raphy, M.W. Jones, R. Pattipati, B. Shankar, R. Sivasubrahmanyam, A.K. Soodhagani, R.R. Juventhala, N. Pottabathini, S. Pothukanuri, J. Docquier, D.T. Davies, SAR studies leading to the identification of a novel series of metallo-β-lactamase inhibitors for the treatment of carbapenem- resistant enterobacteriaceae infections that display efficacy in an animal infection model, ACS Dis. 5 (2019) 131–140, https://doi.org/10.1021/acsinfecdis.8b00246.
[82] H. Zhang, K. Yang, Z. Cheng, C. Thomas, A. Steinbrunner, C. Pryor, M. Vulcan, C. Kemp, D. Orea, C. Paththamperuma, A.Y. Chen, S.M. Cohen, R.C. Page, D.L. Tierney, M.W. Crowder, Spectroscopic and biochemical characterization of metallo-β-lactamase IMP-1 with dicarboxylic, sulfonyl, and thiol inhibitors, Bioorg. Med. Chem. 40 (2021), https://doi.org/10.1016/j.bmc.2021.116183 116183.
[83] D. Zhang, M.S. Markoulides, D. Stepanovs, A.M. Rydzik, A. El-hussein, C.A.M. Bon, J.J.A.G. Kamps, P.M. Collins, S.T. Cahill, D.Y. Wang, D.W. Timothy, J. Brem, M.A. Mcdonough, C.J. Schofield, Structure activity relationship studies on rhodanines and derived enethiol inhibitors of metallo- β -lactamases, Bioorg. Med. Chem. (2018), https://doi.org/10.1016/j.bmc.2018.02.043.
[84] G. Kumar, B. Issa, S. Biswal, D. Jain, A. Bhattacharjee, A.S. Ghosh, Glutamic acid at position 152 and Serine at position 191 are the key residues required for the metallo-beta-lactamase activity of NDM-7, Int. J. Antimicrob. Agents (2019), https://doi.org/10.1016/j.ijantimicag.2019.10.005.
[85] Y. Yu, X. Wang, Y. Gao, Y. Yang, G. Wang, L. Sun, Y. Zhou, X. Niu, Insight into the catalytic hydrolysis mechanism of New Delhi metallo-β-lactamase to aztreonam by molecular modeling, J. Mol. Liq. 282 (2019) 244–250, https://doi.org/10.1016/j.molliq.2019.03.006.
[86] M. Małecka, A. Skoczyńska, D.M. Goodman, C.G. Hartinger, E. Budzisz, Biological properties of ruthenium(II)/(III) complexes with flavonoids as ligands, Coord. Chem. Rev. 436 (2021), https://doi.org/10.1016/j.ccr.2021.213849.
[87] S.K. Dey, A. Mukherjee, Catechol oxidase and phenoxazinone synthase: Biomimetic functional models and mechanistic studies, Coord. Chem. Rev. 310 (2016) 80–115, https://doi.org/10.1016/j.ccr.2015.11.002.
[88] R. Jastrzab, M. Nowak, M. Zabiszak, A. Odani, M.T. Kaczmarek, Significance and properties of the complex formation of phosphate and polyphosphate groups in particles present in living cells, Coord. Chem. Rev. 435 (2021), https://doi.org/10.1016/j.ccr.2021.213810 213810.
[89] L. Vinué, D.C. Hooper, Rsp activates expression of the Cnt system in Staphylococcus aureus, BMC Microbiol. 20 (2020) 1–8, https://doi.org/10.1186/s12866-020-02013-0.
[90] B. Liu, B. Sun, Rsp promotes the transcription of virulence factors in an agr -independent manner in Staphylococcus aureus, Emerg. Microbes Infect. (2020) 1–42, https://doi.org/10.1080/22221751.2020.1752116.
[91] A. Zarkan, H.R. Macklyne, A.W. Truman, A.R. Hesketh, H.J. Hong, The frontline antibiotic vancomycin induces a zinc starvation response in bacteria by binding to Zn(II), Sci. Rep. 6 (2016) 1–9, https://doi.org/10.1038/srep19602.
[92] Â. de Fátima, C.deP. Pereira, C.R.S.D.G. Olímpio, B.G. de Freitas Oliveira, L.L. Franco, P.H.C. da Silva, Schiff bases and their metal complexes as urease inhibitors – A brief review, J. Adv. Res. 13 (2018) 113–126, https://doi.org/10.1016/j.jare.2018.03.007.
[93] S. Svane, J.J. Sigurdarson, F. Fin, T. Eitinger, H. Karring, Inhibition of urease activity by different compounds provides insight into the modulation and association of bacterial nickel import and ureolysis, Sci. Rep. 10 (2020) 1–14, https://doi.org/10.1038/s41598-020-65107-9.
[94] C. Chen, K.-W. Yang, L.-Y. Wu, J.-Q. Li, L.-Y. Sun, Disulfiram as a potent metallo-β-lactamase inhibitor with dual functional mechanisms, ChemComm 00 (2020) 1–3, https://doi.org/10.1039/C9CC09074F.
[95] V. Bhatt, Thermodynamics and kinetics of complex formation, Essentials Coord. Chem. (2016) 111–137, https://doi.org/10.1016/b978-0-12-803895-6.00004-5.
[96] L. Korala, A.L. Prieto, F. Collins, U. States, Chemical Functionalization of Colloidal Inorganic Nanocrystals (NCs) via Ligand Exchange, Elsevier Inc., 2017. 10.1016/B978-0-12-409547-2.14290-8.
[97] C.S. Thomas, D.R. Braun, J.L. Olmos, S.R. Rajski, G.N. Phillips, D. Andes, T.S. Bugni, Pyridine-2,6-dithiocarboxylic acid and its metal complexes: New inhibitors of New Delhi metallo β-Lactamase-1, Mar. Drugs. 18 (2020), https://doi.org/10.3390/md18060295.
[98] H. Sun, Q. Zhang, R. Wang, H. Wang, Y.T. Wong, M. Wang, Q. Hao, A. Yan, R.Y.T. Kao, P.L. Ho, H. Li, Resensitizing carbapenem- and colistin-resistant bacteria to antibiotics using auranofin, Nat. Commun. 11 (2020) 1–13, https://doi.org/10.1038/s41467-020-18939-y.

[99] Z. You, M. Liu, C. Wang, G. Sheng, X. Zhao, D. Qu, F. Niu, Inhibition studies of Helicobacter pylori urease with Schiff base copper(II) complexes, RSC Adv. 6 (2016) 16679–16690, https://doi.org/10.1039/C6RA00500D.
[100] L. Pan, C. Wang, K. Yan, K. Zhao, G. Sheng, H. Zhu, X. Zhao, D. Qu, F. Niu, Z. You, Synthesis, structures and Helicobacter pylori urease inhibitory activity of copper(II) complexes with tridentate aroylhydrazone ligands, J. Inorg. Biochem. (2016), https://doi.org/10.1016/j.jinorgbio.2016.02.017.
[101] I. Ali, L.M.A. Mahmood, Y.T.H. Mehdar, H.Y. Aboul-enein, Synthesis, characterization, simulation, DNA binding and anticancer activities of Co (II), Cu(II), Ni(II) and Zn(II) complexes of a Schiff base containing o- hydroxyl group nitrogen ligand, Inorg. Chem. Commun. (2020), https://doi.org/10.1016/j.inoche.2020.108004 108004.
[102] C.N. Banti, M. Poyraz, I. Sainis, M. Sari, G. Rossos, N. Kourkoumelis, S.K. Hadjikakou, The periodic table of urea derivative: small molecules of zinc(II) and nickel(II) of diverse antimicrobial and antiproliferative applications, Mol. Divers. 24 (2020) 31–43, https://doi.org/10.1007/s11030-018-09909-0.
[103] S.R. Shah, Z. Shah, M. Khiat, A. Khan, L.R. Hill, S. Khan, J. Hussain, R. Csuk, M.U. Anwar, A. Al-Harrasi, Complexes of N- And O-donor ligands as potential urease inhibitors, ACS Omega 5 (2020) 10200–10206, https://doi.org/10.1021/acsomega.0c01089.
[104] M. Rafiq, M. Saleem, F. Jabeen, M. Hanif, S.Y. Seo, S.K. Kang, K.H. Lee, Facile synthesis, biological evaluation and molecular docking studies of novel substituted azole derivatives, J. Mol. Struct. 1138 (2017) 177–191, https://doi.org/10.1016/j.molstruc.2017.03.013.
[105] F. Iftikhar, Y. Ali, F. Ahmad Kiani, S. Fahad Hassan, T. Fatima, A. Khan, B. Niaz, A. Hassan, F. Latif Ansari, U. Rashid, Design, synthesis, in vitro Evaluation and docking studies on dihydropyrimidine-based urease inhibitors, Bioorg. Chem. 74 (2017) 53–65, https://doi.org/10.1016/j.bioorg.2017.07.003.
[106] T. Sommer, K. Bjerregaard-Andersen, L. Uribe, M. Etzerodt, G. Diezemann, J. Gauss, M. Cascella, J.P. Morth, A fundamental catalytic difference between zinc and manganese dependent enzymes revealed in a bacterial isatin hydrolase, Sci. Rep. 8 (2018) 1–11, https://doi.org/10.1038/s41598-018-31259-y.
[107] Y. Zhang, Q. Liu, H. Jing, Y. Cai, Q. Wang, Y. Li, Synthesis, characterization, and antimicrobial activity of two Schiff base silver (I) complexes derived from 4-carboxybenzaldehyde, J. Coord. Chem. 8972 (2017), https://doi.org/10.1080/00958972.2017.1285399.
[108] A. Mumtaz, J. Arshad, A. Saeed, M.A.H. Nawaz, J. Iqbal, Synthesis, characterization and urease inhibition studies of transition metal complexes of thioureas bearing ibuprofen moiety, J. Chil. Chem. Soc. 63 (2018) 3934–3940, https://doi.org/10.4067/s0717-97072018000203934.
[109] K. Usman, M.H. Abu-Dieyeh, N. Zouari, M.A. Al-Ghouti, Lead (Pb) bioaccumulation and antioxidative responses in Tetraena qataranse, Sci. Rep. 10 (2020) 1–10, https://doi.org/10.1038/s41598-020-73621-z.
[110] X. Wang, X. Wang, S. Jin, N. Muhammad, Z. Guo, Stimuli-Responsive Therapeutic Metallodrugs, Chem. Rev. 119 (2018) 1138–1192, https://doi.org/10.1021/acs.chemrev.8b00209.
[111] H. Pervez, M. Ahmad, S. Zaib, M. Yaqub, M.M. Naseer, J. Iqbal, Synthesis, cytotoxic and urease inhibitory activities of some novel isatin-derived bis-Schiff bases and their copper(ii) complexes, MedChemComm 7 (2016) 914–923, https://doi.org/10.1039/C5MD00529A.
[112] S. Ma, J. Wang, G. Yang, J. Yang, D. Ding, M. Zhang, Copper (II) ions enhance the peroxidase-like activity and stability of keratin-capped gold nanoclusters for the colorimetric detection of glucose, Microchim. Acta 2 (2019) 2–8, https://doi.org/10.1007/s00604-019-3395-8.
[113] M.P. Silva, C. Saibert, T. Bortolotto, A.J. Bortoluzzi, G. Schenk, Dinuclear copper (II) complexes with derivative triazine ligands as biomimetic models for catechol oxidases and nucleases, J. Inorg. Biochem. 213 (2020), https://doi.org/10.1016/j.jinorgbio.2020.111249 111249.
[114] C. Perez-Rizquez, A. Rodriguez-Otero, J.M. Palomo, Combining enzymes and organometallic complexes: Novel artificial metalloenzymes and hybrid systems for C-H activation chemistry, Org. Biomol. Chem. 17 (2019) 7114–7123, https://doi.org/10.1039/c9ob01091b.
[115] J.K. Kim, C. Lee, S.W. Lim, A. Adhikari, J.T. Andring, R. McKenna, C.M. Ghim, C. U. Kim, Elucidating the role of metal ions in carbonic anhydrase catalysis, Nat. Commun. 11 (2020) 1–10, https://doi.org/10.1038/s41467-020-18425-5.
[116] Z. Gul, N.U. Din, E. Khan, F. Ullah, M. Nawaz Tahir, Synthesis, molecular structure, anti-microbial, anti-oxidant and enzyme inhibition activities of 2-amino-6-methylbenzothiazole and its Cu(II) and Ag(I) complexes, J. Mol. Struct. 1199 (2020) 126956. 10.1016/j.molstruc.2019.126956.
[117] K. Yu, L. Zhou, Y. Sun, Z. Zeng, H. Chen, J. Liu, Anti-browning effect of Rosa roxburghii on apple juice and identification of polyphenol oxidase inhibitors, Food Chem. 359 (2021), https://doi.org/10.1016/j.foodchem.2021.129855 129855.
[118] M. Aksoy, Protein expression and purification A new insight into puri fi cation of polyphenol oxidase and inhibition effect of curcumin and quercetin on potato polyphenol oxidase, Protein Expr. Purif. 171 (2020), https://doi.org/10.1016/j.pep.2020.105612 105612.
[119] F. Benaceur, R. Chaibi, F. Berrabah, A. Neifar, H. Gouzi, K. Benaceur, W. Nouioua, A. Rezzoug, H. Bouazarra, A. Gargouri, Purification and characterization of latent polyphenol oxidase from Truffles (Terfezia arenaria), Int. J. Biol. Macromol. (2019), https://doi.org/10.1016/j.ijbiomac.2019.09.126.
[120] A. Torres, G. Aguilar-osorio, M. Camacho, F. Basurto, A. Navarro-ocana, Characterization of polyphenol oxidase from purple sweet potato (I pomoea batatas L. Lam) and its affinity towards acylated anthocyanins and caffeoylquinic acid derivatives, Food Chem. 356 (2021), https://doi.org/10.1016/j.foodchem.2021.129709 129709.
[121] F. Chatzopoulou, M. Sanmartin, I. Mellidou, I. Pateraki, A. Koukounaras, G. Tanou, M.S. Kalamaki, S. Veljovi, S. Kostas, P. Tsouvaltzis, R. Grumet, A.K. Kanellis, Silencing of ascorbate oxidase results in reduced growth, altered ascorbic acid levels and ripening pattern in melon fruit, Plant Physiol. Biochem. 156 (2020) 291–303, https://doi.org/10.1016/j.plaphy.2020.08.040.
[122] V. Braunschmid, S. Fuerst, V. Perz, S. Zitzenbacher, J. Hoyo, C. Fernandez-sanchez, T. Tzanov, G. Steinkellner, K. Gruber, G.S. Nyanhongo, D. Ribitsch, G. M. Guebitz, A fungal ascorbate oxidase with unexpected laccase activity, Int. J. Mol. Sci. 21 (2020) 1–14, https://doi.org/10.3390/ijms21165754.
[123] V.Y. Titov, A.N. Osipov, V.Y. Titov, A.N. Osipov, Nitrite and nitroso compounds can serve as specific catalase inhibitors, Redox Rep. 0002 (2016), https://doi.org/10.1080/13510002.2016.1168589.
[124] S. Taikhao, S. Phunpruch, Effect of metal cofactors of key enzymes on biohydrogen production by nitrogen fixing cyanobacterium Anabaena siamensis TISIR 8012, Energy Procedia. 138 (2017) 360–365, https://doi.org/10.1016/j.egypro.2017.10.166.
[125] L. Riccardi, V. Genna, M. De Vivo, Metal–ligand interactions in drug design, Nat. Rev. Chem. 2 (2018) 100–112, https://doi.org/10.1038/s41570-018-0018-6.
[126] Y.O. Ayipo, W.A. Osunniran, M.N. Mordi, Metal complexes of β-carboline: Advances in anticancer therapeutics, Coord. Chem. Rev. 432 (2021), https://doi.org/10.1016/j.ccr.2020.213746 213746.