



[Science Archives \(ISSN:2582-6697\)](https://doi.org/10.47587/SA.2023.4304)

Journal homepage: www.sciencearchives.org



<https://doi.org/10.47587/SA.2023.4304>

Review Article



Novel β -lactamase inhibitors and the pursuit of MBL inhibitors to combat antibiotic-resistant bacteria: a review

Ahmed A. Saleh & Ahmed A. J. Mahmood 

Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, Iraq.

Received: June 19, 2023/ Revised: July 18, 2023/Accepted: July 25, 2023

(✉) Corresponding Author: ahmedsot@gmail.com

Abstract

Bacterial resistance is spreading internationally and poses a serious threat to humans. β -lactam resistance has enhanced to an uncontrolled rate due to many reasons. The most significant form of resistance is destruction of the β -lactam ring by a bacterial enzyme named β -lactamase enzyme which is essential for antibacterial activity. There are currently six β -lactamases inhibitors that can be used clinically in conjugation with the antibiotic in order to protect them from enzymatic attacks. They bind the β -lactamase enzyme thus the β -lactam antibiotic catches the transpeptidase (PBP) which has the responsibility of peptidoglycan synthesis and disables it thus causing cell wall lysis. However, in order to tackle the fast escalating β -lactam resistance, additional research is needed in order to create novel drugs with broad-spectrum. Herein we represent the recently published works of the β -lactamases inhibitors. Until nowadays there are no clinically approved MBL inhibitors, Efforts should be put to discover and evaluate novel MBLi to impede the spread of pathogenic-resistant bacteria and minimize their global health impact. The scientists realize this fact and emphasize their effort toward MBL inhibitors.

Keywords: Bacterial Resistance, β -lactam ring, β -lactamases Inhibitors.

Introduction

Penicillins, cephalosporins, carbapenems, and monobactams all are vital β -lactam antibiotics that currently battling bacterial resistance (Abodakpi et al., 2019). Bacterial resistance is spreading globally and poses a serious threat to human health (Liscio et al., 2015) β -lactam resistance has accelerated to an uncontrolled rate due to many reasons like increased consumption, poor prescribing strategies, and abuse of the antibiotics to treat minor infections etc (Liscio et al., 2015). The most significant form of resistance is the generation of β -lactamases enzyme by the pathogenic bacteria which destroy the β -lactam ring which is essential for antibacterial activity (Blizzard et al., 2014).

Serine beta-lactamases (SBLs) (ambler class A, C, D) which are most clinically significant, they utilize a nucleophilic serine moiety for β -lactam ring hydrolysis. While in metallo β -lactamases (MBLs) the water molecule trigger by zinc ion to

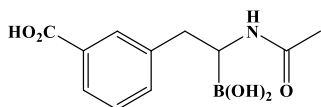
hydrolyze β -lactam antibiotics, they are also getting a lot of interest these days due to their robust carbapenemase activity and incredibly broad substrate profile (Ehmann et al., 2013; Rotondo & Wright, 2017). There are currently six β -lactamases inhibitors that can be used in clinically in conjugation with the antibiotic in order to protect them from enzymatic attacks (Ju et al., 2018), they bind the β -lactamase enzyme thus the β -lactam antibiotic catches the transpeptidase (PBP) which has the responsibility of peptidoglycan synthesis and disable it thus causing cell wall lysis (Ju et al., 2018). The majority of the existing SBL-mediated resistance, in instance, is susceptible to the recently licenced beta-lactamase inhibitors avibactam and relebactamexists (Rotondo & Wright, 2017; Ju et al., 2018).

However, in order to tackle the fast escalating β -lactam resistance, additional research is needed in order to create novel drugs with broad-spectrum MBL and SBL inhibitors.

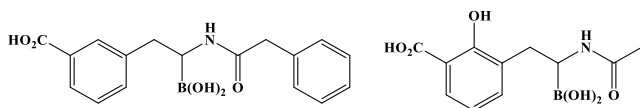
Herein we represent the recent published works of the β -lactamases inhibitors.

The production of one or two tetrahedral intermediates and transition states alongside the reaction pathway is a common characteristic of all types of β -lactamases (Docquier and Mangani, 2018). As a result, substances that can imitate these intermediates make for great candidates for enzyme inhibitors.

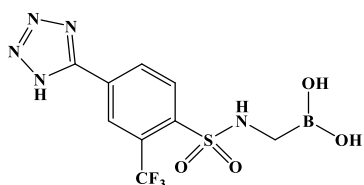
A powerful boronic acid derivatives inhibitor of class A TEM-1 enzyme, distinguished by the crystal structure of TEM-1 from *E. coli*, was designated as such by Strynadka and coworkers in 1996 (Strynadka et al., 1992; Ehmman et al., 2013).



These compounds were then more improved to produce the strong inhibitors (Ness et al., 2000; Yuan & Ingleson, 2022).



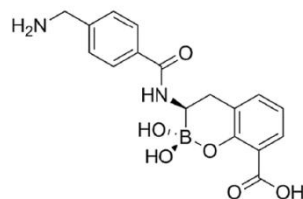
Then sulfonamide boronic acid which is capable to triplicate the continuation of mice infected with *E. coli* that produces ampC after administration with cefotaxime as compared to the antibiotic alone (Ness et al., 2000; Yuan & Ingleson, 2022).



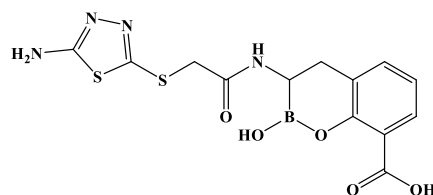
Boronate-based substances are being evaluated as a second novel scaffold for the development of non-lactam β -lactamase inhibitors. Because of its propensity to take on a tetrahedral geometry, boron can be used to model transitory tetrahedral species produced by hydrolytic processes (Cahill et al., 2017), boronates have been discovered as inhibitors of either the acylation or deacylation processes' tetrahedral transition states (Rojas et al., 2016).

Meropenem and the cyclic boronate vaborbactam have recently been introduced to the clinic through the

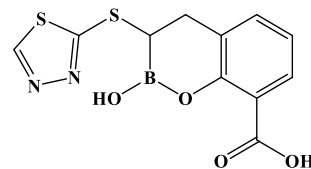
development of cyclic boronates with broad spectrum inhibitors of serine β -lactamases (Thomas et al., 2022) was Accepted in 2017 for treatment complicated urinary tract infections. The efficiency of cefepime and carbapenems against a number of clinical isolates containing class A/C/ or D β -lactamases is significantly increased by the presence of vaborbactam, a potent broad-spectrum inhibitor against most serine- β -lactamases subclasses (KPC/CTX-M/ SHV/ CMY). (Li et al., 2017).



Rempex Pharmaceuticals' scientists were able to present additional chemical alterations to the inhibitor's molecule to significantly increase its inhibitory efficacy against metallo-lactamases (Shi et al., 2019). With the addition of an aminothiadiazole side chain, the inhibitor's initial optimisation was established. This side chain retained nanomolar strength against serine carbapenemase and demonstrated a promising inhibition of the NDM-1 metallo-lactamase.

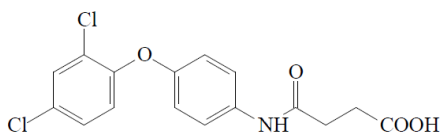


However, a more extreme modification to the molecule, in which the amide group was substituted by a sulphur atom, followed by a similar thiadiazole moiety, was necessary to provide the most significant increase in the effectiveness of inhibition against metallo- β -lactamases. This substance demonstrated broad-spectrum β -lactamase inhibition, being equally efficient against serine- and metallo- carbapenemases (Brem et al., 2016) (Li et al., 2021).

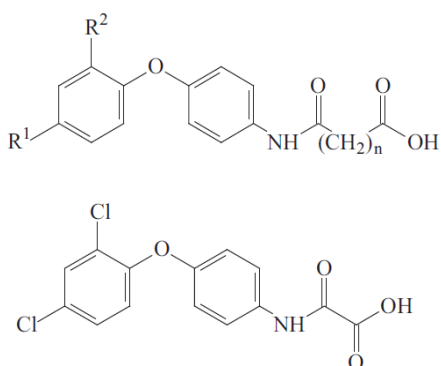


Grigorenko et al. (2016) by utilizing computer-assisted screening of scaffolds correlated to those of recognized as

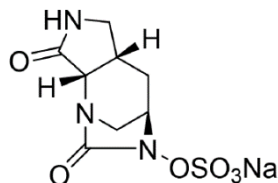
low-affinity inhibitors, were synthesized PA-34 inhibitor from reaction of succinic acid anhydride with dichlorophenoxyaniline in toluene. Which is a new inhibitor of broad range class A β -lactamases (Grigorenko et al., 2016).



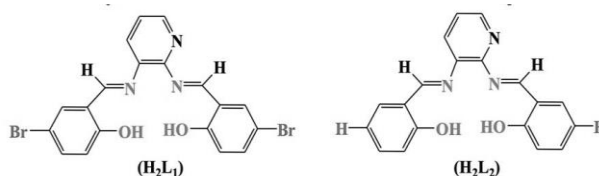
As TEM-class β -lactamase inhibitors, Antipin et al. (2017) synthesised new modules of acylated phenoxyanilide and thiourea compounds and tested them for their capacity to block TEM type β -lactamase enzyme (Antipin et al., 2017).



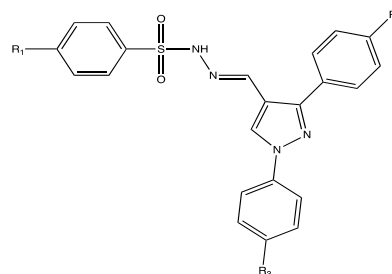
IID572, a novel broad spectrum BLI of the diazabicyclooctane (DBO) family that was synthesised by Reck et al., 2019, has the ability to revive piperacillin's antibacterial activity against piperacillin/tazobactam-resistant clinical isolates. IID572 differs from other DBOs by having a wide β -lactamase inhibition and not having any antibacterial activity (Reck et al., 2019; Zhang et al., 2018).



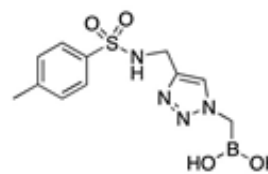
Zakia et al. in 2020 Two tetradentate Schiff base ligands, H2L1 and H2L2, are created via condensation of 1,2-diaminopyridine on bromosalicylaldehyde and salicylaldehyde, respectively. The two Schiff base ligands employed here serve as inhibitors of the MBLs, which were isolated from Acinetobacter baumannii. They exhibit a considerable inhibitory effect (Wang et al., 2018).



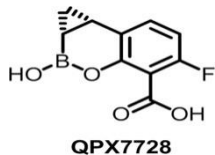
Aryl sulfonyl hydrazones and 1,3-diaryl pyrazoles are used by Shaaban et al. (2020) to target metallo-beta-lactamases (MBLs) 26. Significant inhibition constants against the in vitro MBLs NDM-1, IMP-1, and AIM-1 were seen at low micromolar ranges (1.5–16.4 μ M). Additionally, all medications re-sensitized the K. pneumoniae (K5) strain of resistance to meropenem and cefalexin (Shaaban et al., 2020).



Caselli et al. 2020 describe a novel class of Boronic acid transition state inhibitors (BATSI) in which a bioisostere triazole replaces the amide group. A 26 α -triazolylmethaneboronic acids was chemically synthesized and evaluated against clinically significant Acinetobacter-derived cephalosporinase (Caselli et al., 2020). The best inhibitor places a tolyl group close to Arg340, resulting in favorable cation interactions. These findings support the α -triazolylboronic acids' potential as a template for future inhibitor development (Zhao et al., 2021).



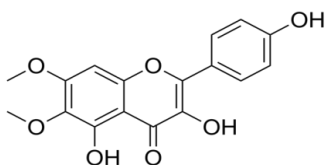
In vitro Activity of the Ultrabroad-Spectrum-Beta-Lactamase Inhibitor QPX7728 against Carbapenem-Resistant Enterobacterales (CRE) with Varying Intrinsic and Acquired Resistance Mechanisms is studied by Nelson et al. (2020) when compared to other beta-lactamase inhibitor combinations, meropenem and QPX7728 were the most successful beta-lactam-BLI combinations tested against all groups of CRE with various resistance routes (Yu et al., 2018).



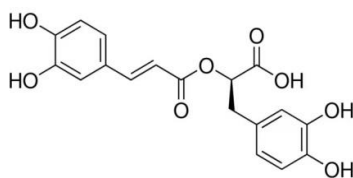
De-Yun Cui et al. (2020) find that H2dedpa is as a competent NDM-1 inhibitor, a series of H2dedpa derivatives were systematically prepared (Cui et al., 2020). These compounds had strong anti-NDM-1 action. Meropenem's efficacy against *Klebsiella pneumoniae*, *Escherichia coli*, and *Proteus mirabilis* with either NDM or IMP could be restored invitro by compounds 6k and 6n. When these two compounds were combined with meropenem, the activity of meropenem against *E. coli* generating NDM-4 might be increased by up to 5333 times (Viivi et al., 2021).



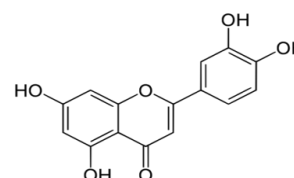
Somalapora et al. (2020) Explore the impact of MBL inhibitors generated from natural sources, such as eupalitin, rosmarinic acid, and luteolin by performing molecular docking and molecular dynamics investigations (Parida et al., 2021).



Eupalitin



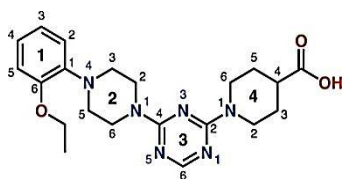
Rosmarinic acid



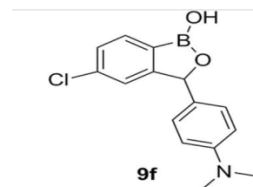
Luteolin

Taylor et al. (2020) use the DNA-encoded chemistry technology for rapid search for substances that bind to and may inhibit OXA-48 (Taylor et al., 2020). This method led to the discovery of the successful chemical CDD-97, which has submicromolar potency ($K_i = 0.53 - 0.08 M$) against OXA-48. However, due to weak accumulation inside *E. coli*, CDD-97 has poor synergy with beta-lactam antibiotics to limit the growth of bacteria expressing OXA-48 (Taylor et al., 2021).

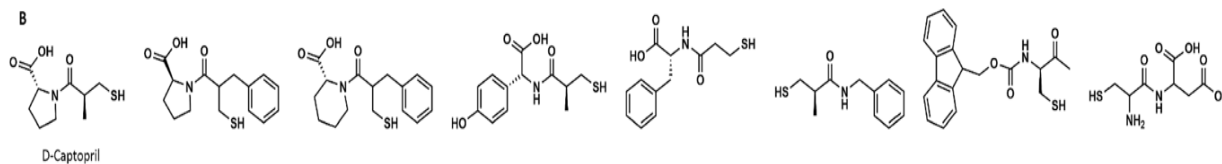
The most effective inhibitor showed micromolar inhibitory action toward MBLs and an IC_{50} value of 86 nM for KPC-2 SBL (Gangadharappa et al., 2020).



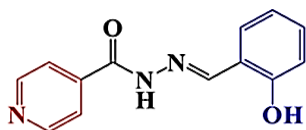
Yan et al. (2021) Identify several 3-aryl substituted benzoxaborole compounds that displayed broad-spectrum inhibition against illustrative serine- and metallo- beta-lactamases (SBLs) and MBLs (Yan et al., 2021).



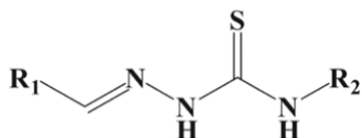
Ma et al. (2021) based on structure-guided design report series D-captopril derivatives that can inhibit the activity of New Delhi metallo- β -lactamase 1 NDM-1 in vitro and at cellular levels (Ma et al., 2021). based on the structure of D-captopril sequence of compounds with changes to the methyl group, the carboxylate position, and the ring structure were synthesized. NDM-1 activity is effectively inhibited by compounds with a 6-membered ring structure and a carboxylate group in either the ortho- or para-position in vitro and in living cells (Shi et al., 2019).



Gao et al. (2021) investigation into the N-acylhydrazone scaffold as a powerful ML inhibitor. Biological activity testing revealed that the synthesised N-acylhydrazones predominantly inhibited ML NDM-1 (Gao et al., 2021). The examination of the IC₅₀ data showed that the compounds' capacity to inhibit NDM-1 was improved by the pyridine and hydroxylbenzene substituents at the 2-position. The synthesised N-acylhydrazones exhibited synergistic antibacterial activity with meropenem and decreased meropenem's MIC on *E. coli* that produces NDM-1 by 4–16 fold (Bush et al., 2019).

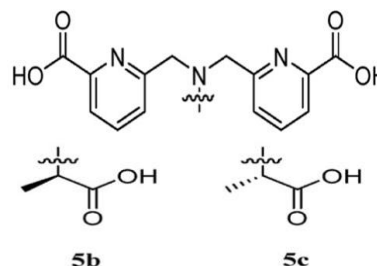


Li et al. (2021) investigate diaryl-substituted thiosemicarbazone as potent scaffold for inhibition of metallo-β-lactamases (MβLs) (Li et al., 2021). They report 26 compounds that specifically inhibit NDM-1, with an IC₅₀ range of 0.038-34.7 M. Synthetic thiosemicarbazones' structure-activity relationship showed that the diaryl-substitutes, particularly 2-pyridine and 2-hydroxybenzene, enhanced the inhibitors' inhibitory effects. The MIC of meropenem was decreased by 2-512-fold as a result of the synergistic antimycobacterial activities of the thiosemicarbazones on *E. coli*-NDM-1 (Bouza et al., 2017).

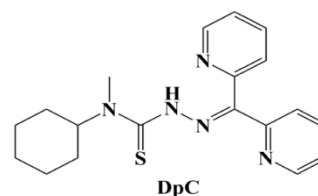


Chen et al. (2021) developed a number of pentadentate-chelating H₂dpa derivatives and their ability to inhibit MBLs was tested. Imipenemase, New Delhi metallo-lactamase (NDM), and Verona integron-encoded metallo-lactamase were clinically important MBLs that were inhibited by similar medicines with IC₅₀ values of 1-4.9 M. The most

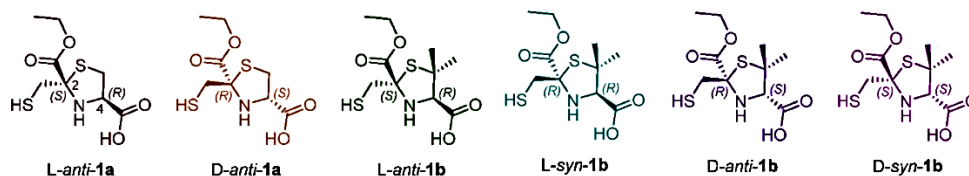
promising molecules in vitro are 5b and 5c (Chen et al., 2021; Zhen et al., 2019).



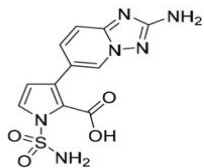
Li et al. (2021) A dipyridyl-substituted thiosemicarbazone (DpC), with an IC₅₀ value in the range of 0.021-1.08 M, was discovered to be the broad-spectrum inhibitor of M-Ls (NDM-1, VIM-2, IMP-1, ImiS, and L1). It suppressed NDM-1 in a reversible and competitive manner with a K_i value of 10.2 nM (Li et al., 2021). The MIC of meropenem against EC-MLs, EC01-EC24, and *K. pneumonia* were each reduced by 2-16, 2-8, and 8-fold respectively, as a result of it having a synergistic antibacterial impact on MβLs-producing bacteria (Wong & Van Duin, 2017).



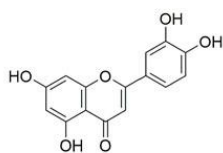
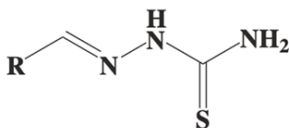
Hinchliffe et al. (2021) previously defined 2-mercaptomethyl thiazolidines (M.M.T.Zs) as B1 metallo beta-lactamase inhibitors (e.g. new delhi metallo betalactamase-1) (Hinchliffe et al., 2021). There are three subtypes of MBLs: B1, B2, and B3. They have recently demonstrated that inhibition also has a clinically meaningful impact on B2 and B3 enzymes. According to X-ray crystallography, inhibition occurs when the M.M.T.Z thiol directly interacts with the mono- or dizinc centers of (B2) and (B3), one-to-one. This is further enhanced by sulfur-interactions with a conserved active site tryptophan (Linciano et al., 2018).



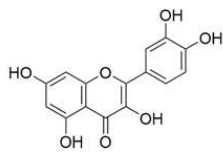
Farley et al. (2021) synthesize and describe NSPCs (N-sulfamoylpyrrole-2-carboxylates), which are powerful inhibitors of significant B1 subclass metallo beta-lactamases, including NDM-1. According to crystallography, the N-sulfamoyl NH₂ group displaces the B1 MBLs' dizinc bridging (hydroxide-water) (Farley et al., 2021). Meropenem efficiency in clinically derived *K. pneumoniae* and *E. coli* bla_{NDM-1} is restored in the presence of an NSPC (Christoff et al., 2017).



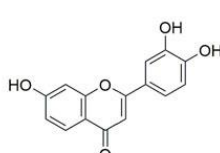
Ge et al. (2021) developed and assayed thirteen thiosemicarbazones (1a-1m). With an IC₅₀ in the range of 0.88-20.2 M, the synthesised compounds preferentially inhibited NDM-1, with 1a and 1f being the most powerful inhibitors (IC₅₀ = 1.79 and 0.88 M), respectively (Bouza et al., 2017; Messasma et al., 2021).



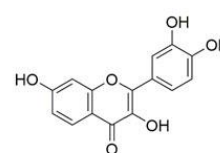
Luteolin
81% inhibition at 50 μM



Quercetin
87% inhibition at 50 μM



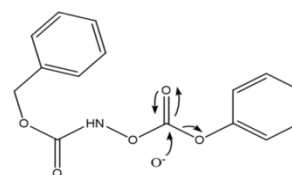
3',4',7-trihydroxyflavone
80% inhibition at 50 μM



Fisetin
90% inhibition at 50 μM

Perbandt et al. (2022) where the Covalently bound Bortezomib and Ixazomib are used to analyse the crystal structures of the -lactamase CTX-M-14 at high resolutions of 1.3 and 1.1, respectively. Both inhibitors mimic the beta-lactam hydrolysis deacylation transition state by replacing the

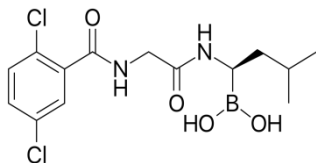
Chigan et al. (2021) synthesized and assayed thirteen novel O-aryloxycarbonyl hydroxamates against MβLs (Chigan et al., 2022). The obtained compounds have an IC₅₀ value between 0.10-18.42 and 0.23-22.33 M for imipenemase-1 and New Delhi metallo-β-lactamase-1, respectively. Using cefazolin and meropenem as substrates, with an IC₅₀ of between 0.1 and 0.23 M, hydroxamate 5 was found to be the most efficient inhibitor (Gavara et al., 2021).



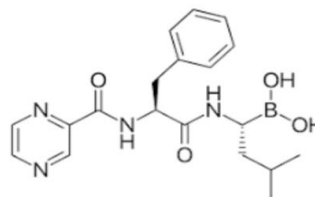
Qin et al. (2022) found luteolin, fisetin, quercetin, 3',4',7-trihydroxyflavone, apigenin, taxifolin and kaempferol, as efficient inhibitors of OXA-48 enzyme with IC₅₀ ranging from 0.47 to 4.54 μM. The structure-activity relationship (SAR) showed that quercetin and its analogs have superior inhibitory effects against OXA-48 due to the substitution (-OH) groups in rings A and B (Legru et al., 2021). The antibacterial activity of piperacillin or imipenem against *E. coli* producing OXA-48 was successfully restored by luteolin, fisetin, quercetin, and 3',4',7-trihydroxyflavone, resulting in a 2-8nM fold decreased MIC (Ventola, 2015).

deacylating water molecule with a different water molecule. Finally they suggest using Bortezomib/Ixazomib as starting compounds for development of novel BLIs (Perbandt et al., 2022; Chigan et al., 2022).

Ixazomib

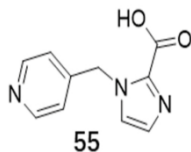


Bortezomib



Chigan et al. (2022) synthesized and assayed more than thirty molecules quinolinyl sulfonamides (1a-p) and sulphonyl esters (2a-o). The obtained compounds specifically inhibited new delhi metallo beta-lactamase-1, and 1e and 1f were determined to be the most powerful inhibitors, with an IC₅₀ of 0.02 μM using meropenem as substrate. The acquired molecules 1a-p and 2a-o exhibited an IC₅₀ value in the range of 0.02-1.4 and 8.3-24.8 M, respectively (Yan et al., 2022). The structure-activity connection shows that the inhibitory impact of quinoline derivatives on NDM-1 is greatly improved by replacing phenyl and phenyl with a halogen atom (Liu et al., 2018).

Yan et al. (2022) By examining how to occupy with the active-site flexible loops and increase diffusion into Gram-negative bacteria, they describe X-ray structure-guided optimisation of 1H-imidazole-2-carboxylic acid (ICA) derivatives. 55 of the assessed ICA inhibitors shown potent synergistic antibacterial effect with meropenem on engineered *E. coli* strains and even untreatable clinically isolated *Pseudomonas aeruginosa* generating VIM-2 MBL. (Yan et al., 2022; Liu et al., 2018).



Bognanni et al. (2023) have been explored and synthesized. a number of chelators for zinc chelators for their capacity to disrupt the interactions between Zn-ions in the MBL active site⁶⁴. They evaluated the inhibitory activity of novel polyimidazole ligands N,N,N,N'-tetra((imidazol-4-yl-methyl)-ethylenediamin, N,N,N'-tris((imidazol-4-yl)methyl)-ethylenediamine, N,N'-bis((imidazol-4-yl)methyl)-ethylenediamine, against three diverse subclasses B1 MBLs, NDM-1, VIM-1, and IMP-1 by in vitro assays. The active site of VIM-1 can accommodate all four imidazole rings of the tetra-imidazole ligand. The substance had the strongest anti-metallo-lactamase inhibitory action (Venkata et al., 2021).

Conclusion

Microorganisms are one of most offensive enemy on the earth; of them are the bacteria which still develop mechanistic resistance against powerful and newly synthesized antibiotics. Beta-lactamase enzyme inhibitors is one of valuable strategy to fight against globally disseminated bacteria, as there are no clinically approved MBL inhibitors effort should put to discover and evaluate novel MBLi to impede the spread of pathogenic resistant bacteria and minimize their global health impact. The scientists realize this fact and emphasize their effort toward MBL inhibitors.

Conflict of Interest

The author hereby declares no conflict of interest.

Consent for publication

The author declares that the work has consent for publication.

References

- Abodakpi, H., Wanger, A., & Tam, V. H. (2019). What the clinical microbiologist should know about pharmacokinetics/pharmacodynamics in the era of emerging multidrug resistance: focusing on β-lactam/β-lactamase inhibitor combinations. *Clinics in Laboratory Medicine*, 39(3), 473-485. <https://doi.org/10.1016/j.cll.2019.05.006>
- Antipin R. L., Beshnova D. A., Petrov R. A., Shiryaeva A. S., Andreeva I. et al. (2017) Synthesis, SAR and molecular docking study of novel non-β-lactam inhibitors of TEM type β-lactamase. *Bioorganic & Medicinal Chemistry Letters*. <http://dx.doi.org/10.1016/j.bmcl.2017.02.025>.
- Blizzard, T. A., Chen, H., Kim, S., Wu, J., Bodner, R., Gude, C., & Hammond, M. L. (2014). Discovery of MK-7655, a β-lactamase inhibitor for combination with Primaxin®. *Bioorganic & medicinal chemistry letters*, 24(3), 780-785. <https://doi.org/10.1016/j.bmcl.2013.12.101>
- Bouza, A. A., Swanson, H. C., Smolen, K. A., VanDine, A. L., Taracila, M. A., Romagnoli, C., & Wallar, B. J. (2017). Structure-based analysis of boronic acids as inhibitors of Acinetobacter-derived cephalosporinase-7, a unique class C β-lactamase. *ACS infectious diseases*, 4(3), 325-336. <https://doi.org/10.1021/acinfecdis.7b00152>
- Brem, J., Cain R., Cahill S., McDonough M.A., Clifton I.J., et al. (2016) Structural basis of metallo-beta-lactamase, serine-beta-lactamase and penicillin-binding protein inhibition by cyclic boronates. *Nat. Commun.* 7, 12406.
- Bush, K., Bradford, P.A. Interplay between β-lactamases and new β-lactamase inhibitors. *Nat Rev Microbiol* 17, 295-306 (2019). <https://doi.org/10.1038/s41579-019-0159-8>
- Cahill, S.T., Cain R., Wang D.Y., Lohans C.T., Wareham D.W., et al. (2017) Cyclic boronates inhibit all classes of β-lactamases. *Antimicrobial Agents and Chemotherapy*. April, Vol. 61, Issue 4, e02260-16 <https://doi.org/10.1128/AAC.02260-16>.

- Caselli, E., Fini, F., Introvigne, M. L., Stucchi, M., Taracila, M. A., Fish, E. R., & Prati, F. (2020). 1, 2, 3-Triazolylmethaneboronate: a structure activity relationship study of a class of β -lactamase inhibitors against *Acinetobacter baumannii* cephalosporinase. *ACS infectious diseases*, 6(7), 1965-1975. <https://doi.org/10.1021/acinfecdis.0c00254>
- Chen, F., Bai, M., Liu, W., Kong, H., Zhang, T., Yao, H., & Qin, S. (2021). H2dpa derivatives containing pentadentate ligands: An acyclic adjuvant potentiates meropenem activity in vitro and in vivo against metallo- β -lactamase-producing Enterobacterales. *European Journal of Medicinal Chemistry*, 224, 113702. <https://doi.org/10.1016/j.ejmech.2021.113702>
- Chigan, J. Z., Li, J. Q., Ding, H. H., Xu, Y. S., Liu, L., Chen, C., & Yang, K. W. (2022). Hydroxamates as a potent skeleton for the development of metallo- β -lactamase inhibitors. *Chemical Biology & Drug Design*, 99(2), 362-372. <https://doi.org/10.1111/cbdd.13990>
- Christoff, R. M., Murray, G. L., Kostoulias, X. P., Peleg, A. Y., & Abbott, B. M. (2017). Synthesis of novel 1, 2, 5-oxadiazoles and evaluation of action against *Acinetobacter baumannii*. *Bioorganic & Medicinal Chemistry*, 25(24), 6267-6272. <https://doi.org/10.1016/j.bmc.2017.08.015>
- Cui, D. Y., Yang, Y., Bai, M. M., Han, J. X., Wang, C. C., Kong, H. T., ... & Zhang, E. (2020). Systematic research of H2dedpa derivatives as potent inhibitors of New Delhi metallo- β -lactamase-1. *Bioorganic Chemistry*, 101, 103965. <https://doi.org/10.1016/j.bioorg.2020.103965>
- Docquier, J. and Mangani S. (2018) An update on β -lactamase inhibitor discovery and development. *Drug Resistance Updates*, 36, 13–29 <https://doi.org/10.1016/j.drup.2017.11.002>
- Ehmann, D. E., Jahić, H., Ross, P. L., Gu, R. F., Hu, J., Durand-Réville, T. F., & Fisher, S. L. (2013). Kinetics of avibactam inhibition against class A, C, and D β -lactamases. *Journal of Biological Chemistry*, 288(39), 27960-27971. <https://doi.org/10.1074/jbc.M113.485979>
- Eidam, O., Romagnoli C., Dalmasso G., Barelier S., Caselli E., et al. (2012) Fragment-guided design of subnanomolar β -lactamase inhibitors active in vivo. *Proc. Natl. Acad. Sci. U. S. A.*, 109, 17448–17453. <http://dx.doi.org/10.1073/pnas.1208337109>.
- Farley, A. J., Ermolovich, Y., Calvopiña, K., Rabe, P., Panduwawala, T., Brem, J., & Schofield, C. J. (2021). Structural Basis of Metallo- β -lactamase Inhibition by N-Sulfamoylpyrrole-2-carboxylates. *ACS Infectious Diseases*, 7(6), 1809-1817. <https://doi.org/10.1021/acinfecdis.1c00104>
- Gangadharappa, B. S., Sharath, R., Revanasiddappa, P. D., Chandramohan, V., Balasubramaniam, M., & Vardhini, T. P. (2020). Structural insights of metallo-beta-lactamase revealed an effective way of inhibition of enzyme by natural inhibitors. *Journal of Biomolecular Structure and Dynamics*, 38(13), 3757-3771. <https://doi.org/10.1080/07391102.2019.1667265>
- Gao, H., Li, J. Q., Kang, P. W., Chigan, J. Z., Wang, H., Liu, L., & Yang, K. W. (2021). N-acylhydrazones confer inhibitory efficacy against New Delhi metallo- β -lactamase-1. *Bioorganic Chemistry*, 114, 105138. <https://doi.org/10.1016/j.bioorg.2021.105138>
- Ge, Y., Kang, P. W., Li, J. Q., Gao, H., Zhai, L., Sun, L. Y., ... & Yang, K. W. (2021). Thiosemicarbazones exhibit inhibitory efficacy against New Delhi metallo- β -lactamase-1 (NDM-1). *The Journal of Antibiotics*, 74(9), 574-579. <https://doi.org/10.1038/s41429-021-00440-3>
- Grigorenko, V.G., Andreeva I.P., Rubtsova M.Y., Deygen I.M., Antipin R.L., et al. (2016) Novel non- β -lactam inhibitor of β -lactamase TEM-171 based on acylated phenoxylaniline, *Biochimie*, 132, 45-53. doi: 10.1016/j.biochi.2016.10.011.
- Hinchliffe, P., Moreno, D. M., Rossi, M. A., Mojica, M. F., Martinez, V., Villamil, V., & Spencer, J. (2021). 2-Mercaptomethyl thiazolidines (MMTZS) inhibit all metallo- β -lactamase classes by maintaining a conserved binding mode. *ACS Infectious Diseases*, 7(9), 2697-2706. <https://doi.org/10.1021/acinfecdis.1c00194>
- Hirvonen, V. H., Spencer, J., & Van Der Kamp, M. W. (2021). Antimicrobial resistance conferred by OXA-48 β -lactamases: towards a detailed mechanistic understanding. *Antimicrobial Agents and Chemotherapy*, 65(6), 10-1128. <https://doi.org/10.1128/AAC.00184-21>
- Ju, L. C., Cheng, Z., Fast, W., Bonomo, R. A., & Crowder, M. W. (2018). The continuing challenge of metallo- β -lactamase inhibition: mechanism matters. *Trends in pharmacological sciences*, 39(7), 635-647. <https://doi.org/10.1016/j.tips.2018.03.007>
- Li, G. B., Abboud M.I., Brem J., Someya H., Lohans C.T., et al. (2017) NMR-filtered virtual screening leads to nonmetal chelating metallo-beta-lactamase inhibitors. *Chem. Sci.*, 8, 928–937.
- Li, J. Q., Gao, H., Zhai, L., Sun, L. Y., Chen, C., Chigan, J. Z., & Yang, K. W. (2021). Dipyrrolyl-substituted thiosemicarbazone as a potent broad-spectrum inhibitor of metallo- β -lactamases. *Bioorganic & Medicinal Chemistry*, 38, 116128. <https://doi.org/10.1016/j.bmc.2021.116128>
- Li, J. Q., Sun, L. Y., Jiang, Z., Chen, C., Gao, H., Chigan, J. Z., & Yang, K. W. (2021). Diaryl-substituted thiosemicarbazone: A potent scaffold for the development of New Delhi metallo- β -lactamase-1 inhibitors. *Bioorganic Chemistry*, 107, 104576. <https://doi.org/10.1016/j.bioorg.2020.104576>
- Li, R., Chen, X., Zhou, C., Dai, Q. Q., & Yang, L. (2022). Recent advances in β -lactamase inhibitor chemotypes and inhibition modes. *European Journal of Medicinal Chemistry*, 114677. <https://doi.org/10.1016/j.ejmech.2022.114677>
- Linciano, P., Cendron, L., Gianquinto, E., Spyarakis, F., & Tondi, D. (2018). Ten years with New Delhi metallo- β -lactamase-1 (NDM-1): from structural insights to inhibitor design. *ACS infectious diseases*, 5(1), 9-34. <https://doi.org/10.1021/acinfecdis.8b00247>
- Liscio, J. L., Mahoney, M. V., & Hirsch, E. B. (2015). Ceftolozane/tazobactam and ceftazidime/avibactam: two novel β -lactam/ β -lactamase inhibitor combination agents for the treatment of resistant Gram-negative bacterial infections. *International journal of antimicrobial agents*, 46(3), 266-271. <https://doi.org/10.1016/j.ijantimicag.2015.05.003>
- Liu, S., Jing, L., Yu, Z. J., Wu, C., Zheng, Y., Zhang, E., ... & Li, G. B. (2018). ((S)-3-Mercapto-2-methylpropanamido) acetic acid derivatives as metallo- β -lactamase inhibitors: synthesis, kinetic and crystallographic studies. *European Journal of Medicinal Chemistry*, 145, 649-660. <https://doi.org/10.1016/j.ejmech.2018.01.032>
- Ma, G., Wang, S., Wu, K., Zhang, W., Ahmad, A., Hao, Q., ... & Zhang, H. (2021). Structure-guided optimization of D-captopril for discovery of potent NDM-1 inhibitors. *Bioorganic & Medicinal Chemistry*, 29, 115902. <https://doi.org/10.1016/j.bmc.2020.115902>
- Messasma, Z., Aggoun, D., Houchi, S., Ourari, A., Ouennoughi, Y., Keffous, F., & Mahdadi, R. (2021). Biological activities, DFT calculations and docking of imines tetradentates ligands, derived from salicylaldehydic compounds as metallo-beta-lactamase inhibitors. *Journal of Molecular Structure*, 1228, 129463. <https://doi.org/10.1016/j.molstruc.2020.129463>
- Nelson, K., Rubio-Aparicio, D., Sun, D., Dudley, M., & Lomovskaya, O. (2020). In vitro activity of the ultrabroad-spectrum-beta-lactamase inhibitor QPX7728 against carbapenem-resistant Enterobacterales with varying intrinsic and acquired resistance mechanisms. *Antimicrobial Agents and Chemotherapy*, 64(8), e00757-20. <https://doi.org/10.1128/aac.00757-20>
- Ness, S., Martin R., Kindler A.M., Paetzel M., Gold M., et al. (2000) Structure-based design guides the improved efficacy of deacylation transition state analogue inhibitors of TEM-1 β -lactamase. *Biochemistry* 39, 5312–5321. <http://dx.doi.org/10.1021/bi992505b>.
- Parida, P., Bhowmick, S., Saha, A., & Islam, M. A. (2021). Insight into the screening of potential beta-lactamase inhibitors as anti-bacterial chemical agents through pharmacoinformatics study. *Journal of Biomolecular Structure and Dynamics*, 39(3), 923-942. <https://doi.org/10.1080/07391102.2020.1720819>
- Reck, F., Birmingham A., Blais J., Casarez A., Colvin R., et al. (2019) IID572: A New Potentially Best-In-Class β -Lactamase Inhibitor. *ACS Infect. Dis.*, 5, 1045–105, DOI: 10.1021/acinfecdis.9b00031
- Rojas, L. J., Taracila M.A., Papp-Wallace K.M., Bethel C.R., Caselli E., et al. (2016) Boronic acid transition state inhibitors active against KPC and other class A betalactamases: structure–activity relationships as a guide to inhibitor design. *Antimicrob. Agents Chemother.*, 60, 1751–1759.
- Rotondo, C. M., & Wright, G. D. (2017). Inhibitors of metallo- β -lactamases. *Current opinion in microbiology*, 39, 96-105. <https://doi.org/10.1016/j.mib.2017.10.026>
- Shaaban, M. M., Ragab, H. M., Akaji, K., McGeary, R. P., Bekhit, A. E. A., Hussein, W. M., ... & Bekhit, A. A. (2020). Design, synthesis, biological evaluation and in silico studies of certain aryl sulfonyl hydrazones conjugated with 1, 3-diaryl pyrazoles as potent metallo- β -lactamase inhibitors. *Bioorganic Chemistry*, 105, 104386. <https://doi.org/10.1016/j.bioorg.2020.104386>
- Shi, X. F., Wang, M. M., Huang, S. C., Han, J. X., Chu, W. C., Xiao, C., & Qin, S. (2019). H2dedpa: an acyclic adjuvant potentiates meropenem activity in vitro against metallo- β -lactamase-producing enterobacterales. *European Journal of Medicinal Chemistry*, 167, 367-376. <https://doi.org/10.1016/j.ejmech.2019.01.083>

- Strynadka, N. C., Adachi H., Jensen S.E., Johns K., Sielecki A., *et al.* (1992) Molecular structure of the acyl-enzyme intermediate in β -lactam hydrolysis at 1.7 Å resolution. *Nature*, 359, 700–705. <http://dx.doi.org/10.1038/359700a0>.
- Taylor, D. M., Anglin, J., Hu, L., Wang, L., Sankaran, B., Wang, J., ... & Palzkill, T. (2021). Unique Diacidic Fragments Inhibit the OXA-48 Carbapenemase and Enhance the Killing of Escherichia coli Producing OXA-48. *ACS Infectious Diseases*, 7(12), 3345-3354. <https://doi.org/10.1021/acinfeddis.1c00501>
- Taylor, D. M., Anglin, J., Park, S., Ucisik, M. N., Faver, J. C., Simmons, N., & Palzkill, T. (2020). Identifying oxacillinase-48 carbapenemase inhibitors using DNA-encoded chemical libraries. *ACS Infectious Diseases*, 6(5), 1214-1227. <https://doi.org/10.1021/acinfeddis.0c00015>
- Thomas, P. W., Cho, E. J., Bethel, C. R., Smisek, T., Ahn, Y. C., Schroeder, J. M., & Fast, W. (2022). Discovery of an effective small-molecule allosteric inhibitor of New Delhi metallo- β -lactamase (NDM). *ACS Infectious Diseases*, 8(4), 811-824. <https://doi.org/10.1021/acinfeddis.1c00577>
- Wang, M. M., Chu, W. C., Yang, Y., Yang, Q. Q., Qin, S. S., & Zhang, E. (2018). Dithiocarbamates: efficient metallo- β -lactamase inhibitors with good antibacterial activity when combined with meropenem. *Bioorganic & Medicinal Chemistry Letters*, 28(21), 3436-3440. <https://doi.org/10.1016/j.bmcl.2018.09.028>
- Wong, D., & Van Duin, D. (2017). Novel beta-lactamase inhibitors: unlocking their potential in therapy. *Drugs*, 77(6), 615-628. DOI :<https://doi.org/10.1007/s40265-017-0725-1>
- Yan, Y. H., Li, Z. F., Ning, X. L., Deng, J., Yu, J. L., Luo, Y., & Xiao, Y. C. (2021). Discovery of 3-aryl substituted benzoxaboroles as broad-spectrum inhibitors of serine-and metallo- β -lactamases. *Bioorganic & Medicinal Chemistry Letters*, 41, 127956. <https://doi.org/10.1016/j.bmcl.2021.127956>
- Yu, Z. J., Liu, S., Zhou, S., Li, H., Yang, F., Yang, L. L., & Li, G. B. (2018). Virtual target screening reveals rosmarinic acid and salvianolic acid A inhibiting metallo-and serine- β -lactamases. *Bioorganic & Medicinal Chemistry Letters*, 28(6), 1037-1042. <https://doi.org/10.1016/j.bmcl.2018.02.025>
- Yuan, K., & Ingleson, M. (2022). trans-Haloboration of o-Alkynyl Phenols Generates Halogenated Bicyclic-Boronates Relevant to Broad Spectrum Beta-Lactamase Inhibitors. <https://doi.org/10.26434/chemrxiv-2022-9cq8q>
- Zhang, E., Wang, M. M., Huang, S. C., Xu, S. M., Cui, D. Y., Bo, Y. L., ... & Qin, S. (2018). NOTA analogue: A first dithiocarbamate inhibitor of metallo- β -lactamases. *Bioorganic & Medicinal Chemistry Letters*, 28(2), 214-221. <https://doi.org/10.1016/j.bmcl.2017.10.074>
- Zhao, B., Zhang, X., Yu, T., Liu, Y., Zhang, X., Yao, Y., & Qin, S. (2021). Discovery of thiosemicarbazone derivatives as effective New Delhi metallo- β -lactamase-1 (NDM-1) inhibitors against NDM-1 producing clinical isolates. *Acta Pharmaceutica Sinica B*, 11(1), 203-221. <https://doi.org/10.1016/j.apsb.2020.07.005>
- Zhen, X., Lundborg, C. S., Sun, X., Hu, X., & Dong, H. (2019). Economic burden of antibiotic resistance in ESKAPE organisms: a systematic review. *Antimicrobial Resistance & Infection Control*, 8, 1-23. DOI: <https://doi.org/10.1186/s13756-019-0590-7>

How to cite this article

Saleh, A. A. & Mahmood, A. A. J. (2023). Novel β -lactamase inhibitors and the pursuit of MBL inhibitors to combat antibiotic-resistant bacteria: a review. *Science Archives*, Vol. 4(3), 199-207. <https://doi.org/10.47587/SA.2023.4304>

This work is licensed under a [Creative Commons Attribution 4.0 International License](https://creativecommons.org/licenses/by/4.0/)



Publisher's Note: MD International Publishing stays neutral about jurisdictional claims in published maps and institutional affiliations.