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Discovery of 3-aryl substituted benzoxaboroles as broad-spectrum inhibitors of serine- and metallo-β-lactamases

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ABSTRACT

The production of β-lactamases represents the main cause of resistance to clinically important β-lactam antibiotics. Boron containing compounds have been demonstrated as promising broad-spectrum β-lactamase inhibitors to combat β-lactam resistance. Here we report a series of 3-aryl substituted benzoxaborole derivatives, which manifested broad-spectrum inhibition to representative serine-β-lactamases (SBLs) and metallo-β-lactamases (MBLs). The most potent inhibitor **9f** displayed an IC_{50} value of 86 nM to KPC-2 SBL and micromolar inhibitory activity towards other tested enzymes. Cell-based assays further revealed that **9f** was able to significantly reduce the MICs of meropenem in clinically isolated KPC-2-producing bacterial strains and it showed no apparent toxicity in HEK293T cells.

Introduction

The β-lactams are the most widely used antibiotics in clinic for the treatment of bacterial infections.[1] However, the emergence and wide spread of resistance in bacteria compromised their efficacy, posing a great threat to public health.[2,3] The most important β-lactam's resistance determinant in bacteria is the production of β-lactamases, which hydrolyze the β-lactam ring to enable the β-lactams ineffective.[4,5] The β-lactamases can be classified into class A, B, C and D, according to their sequence and structural diversity.[6] Class A, C and D are nucleophilic serine β-lactamases (SBLs), while class B are metallo β-lactamases (MBLs) which utilize one or two zinc ions to catalyze the hydrolysis of β-lactam antibiotics.[7]

The combination of a β-lactam antibiotic with a β-lactamase inhibitor has been demonstrated as a clinically effective strategy to counter β-lactamase-mediated resistance.[8,9] The β-lactam ring-containing marketed inhibitors, clavulanic acid, sulbactam, and tazobactam, are mainly active against class A SBLs.[10] The clinical introduction of non-lactam-based inhibitor avibactam and its derivative relebactam was an important step because of their broad-spectrum inhibition against class A, C and D SBLs.[11,12] In contrast with the clinical success of SBL inhibitors, there are currently no clinically available MBL inhibitors. Of particular interest is to develop new agents with the ability to inhibit all β-lactamase producers, including MBLs.

Boron-containing compounds have been proved to have potential in broadly inhibiting both SBLs and MBLs.[13,14] Early work on boronic acid derivatives has led to the introduction of the first cyclic boronate-based SBL inhibitor, vaborbactam, which is approved by U.S. FDA for use in co-administration with meropenem for the treatment of adult patients with complicated urinary tract infections.[15] In addition, several other cyclic boronates, *e.g.* taniborbactam, RPX-7350, and QPX7728, (Fig. 1), are now in clinical or preclinical pipeline as broad-spectrum inhibitors for SBLs and MBLs.[13,16] As another important class of boronic acid derivatives, benzoxaboroles have been developed as anti-bacterial, anti-viral, anti-fungal, anti-protozoal and anti-inflammatory agents with interesting drug development perspectives;[17] we recently tested the FDA-approved anti-inflammatory drug crisaborole against SBLs, and identified that crisaborole had broad-spectrum SBL inhibition, particularly with an IC_{50} value of 0.67 μM to clinically important *K. pneumoniae* carbapenemase-2 (KPC-2) (Fig. S1). Based on the initial results and our previous efforts on the development of β-lactamase inhibitor (BLI),[18–20] we herein report the synthesis of a series of benzoxaboroles with various

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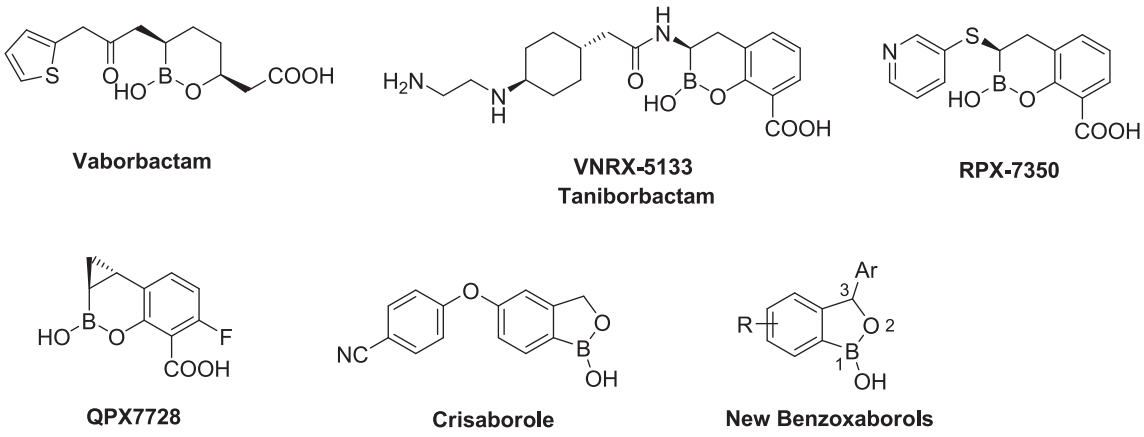
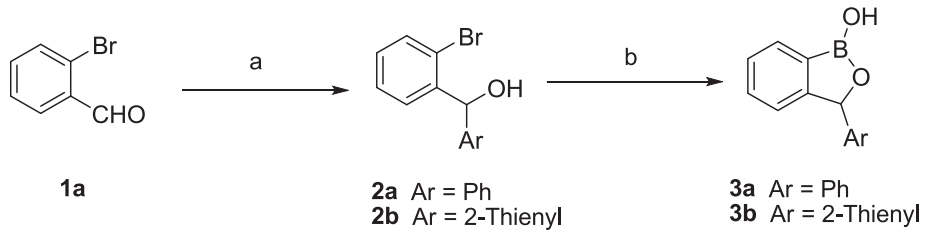
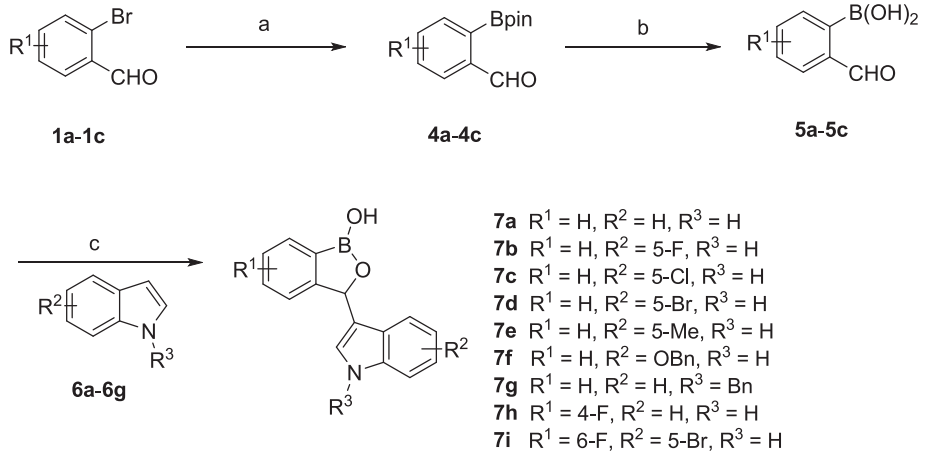


Fig. 1. Representative boron-containing SBL and MBL inhibitors.



Scheme 1. Synthesis of compounds **3a**–**3b**.‡ ‡Reaction conditions: (a) (i) ArMgBr, diethyl ether, 0 °C, overnight; (ii) NH_4Cl (aq.); (b) $Pd(PPh_3)_2Cl_2$, KOAc, DMSO, B_2Pin_2, 90 °C, 8 h.



Scheme 2. Synthesis of compounds **7a**–**7i**.‡ ‡Reaction conditions: (a) $Pd(PPh_3)_2Cl_2$ KOAc, 1,4-dioxane, B_2Pin_2, 90 °C, 8 h; (b) (i) 1) $NaIO_4$, THF/H_2O, rt, 20 min; (ii) HCl (aq.), 2 h; (c) THF, **6a**–**6g**, 60 °C, 24 h.

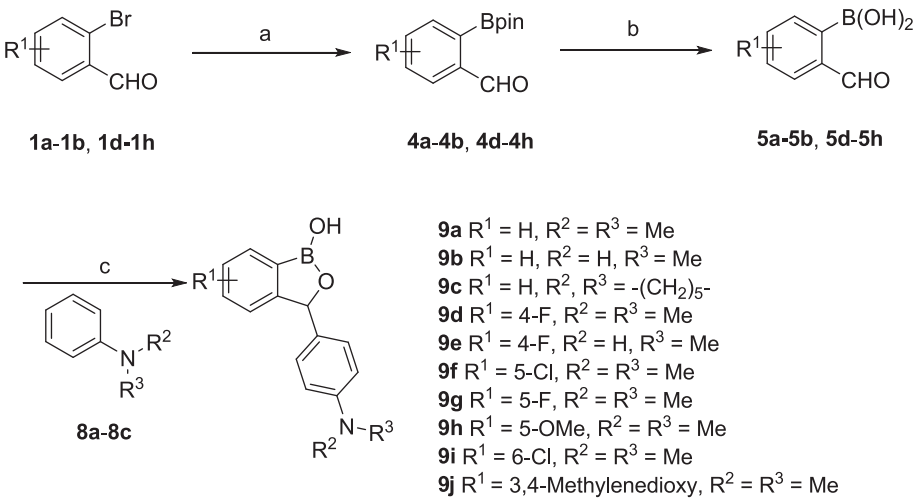
aryl substituents at C-3 position (Fig. 1) and investigation of their structure-activity relationship (SAR) with representative SBLs and MBLs. These benzoxaboroles can potently inhibit all of the tested SBLs and class B1/B2 MBLs, and the most potent compounds could restore meropenem resistance in clinically isolated KPC-2-producing bacterial strains, which provided a new starting point for the development of drug candidates against antibacterial resistance.

Results and discussion

Synthesis of 3-aryl substituted benzoxaborole derivatives

The synthesis of compounds **3a**–**3b** started from commercially available substituted 2-bromobenzaldehyde **1a**.[21] The reaction of 2-bromobenzaldehyde **1a** with Grignard reagent could afford the 2-bromobenzyl alcohols **2a**–**2b**, which were converted to the corresponding 3-aryl substituted benzoxaboroles **3a**–**3b** via palladium-catalyzed Miyaura borylation/cyclization cascade (Scheme 1).

On the other hand, 2-bromobenzaldehyde **1a**–**1c** could also be used for the synthesis of 3-indoxyl substituted benzoxaboroles **7a**–**7i**. In the first step, aryl boronates **4a**–**4c** could be accessed through Palladium-mediated borylation. After hydrolysis of the pinacol ester group to the corresponding 2-formylbenzeneboronic acid derivatives **5a**-–**5**c, final products **7a**–**7i** could be obtained by nucleophilic addition/cyclization cascade using substituted indoles **6a**–**6g** as nucleophile (Scheme 2).[22] Following the same synthetic sequence, 3-aniline substituted benzoxaboroles **9a**–**9j** were obtained using *N*-substituted anilines **8a**–**8c** as nucleophile (Scheme 3).



Scheme 3. Synthesis of compounds **9a**–**9j**.‡ ‡Reaction conditions: (a) $Pd(PPh_3)_2Cl_2$ KOAc, 1,4-dioxane, B_2Pin_2, 90 °C, 8 h; (b) (i) 1) $NaIO_4$, THF/H_2O, rt, 20 min; (ii) HCl (aq.), 2 h; (c) THF, **8a**–**8c**, 60 °C, 24 h.

Biochemical evaluation and SAR analyses

To investigate the inhibitory activity of the synthesized 3-substituted benzoxaborole derivatives to β-lactamases, we selected a panel of representative MBLs and SBLs, including serine enzymes class A KPC-2 and penicillinase TEM-1, class C AmpC, class D Oxacillinase-48 (OXA-48), and metalloenzymes class B1 New Delhi MBL-1 (NDM-1), B1 Verona integron-encoded MBL-1 (VIM-1) and class B2 Serratia fonticola MBL (Sfh-I). The protein production/purification are well-documented in our previous work[20,23–25]; all enzyme inhibition assays were carried out using the reported fluorescent substrate FC-5.[26] All the results are summarized in Tables 1 and 2.

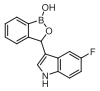
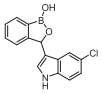
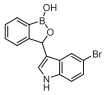
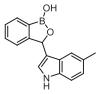
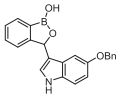
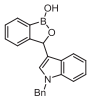
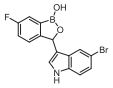
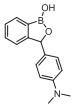
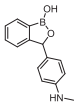
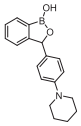
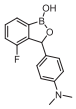
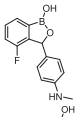
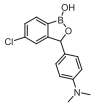
Compound **3a** with phenyl substituent at C-3 position showed broad-spectrum inhibition to all the tested β-lactamases at micromolar level. (Table 1). Compound **3b**, possessing a thiophene group substituent at C-3 position, exhibited comparable or slightly better inhibitory potency against SBLs and MBLs compared with **3a** (Table 1).

Compounds **7a**–**7i**, which bear 5-indole substituents at C-3 position, were then evaluated against these SBLs and MBLs. Compound **7a** displayed potent inhibition against KPC-2, AmpC, NDM-1, VIM-1 and Sfh-I with IC_{50} values of low micromolar level, while it had much lower inhibition to TEM-1 and OXA-48. Similar tendency were observed for compounds **7b**–**7e** (with fluoro-, chloro-, or methyl group at the indole substituent, please see Table 1); notably, **7b**, **7c**, and **7e** manifested IC_{50} of 0.36 μM, 0.20 μM, and 0.22 μM to KPC-2, respectively. Comound **7b** showed less potent inhibition than **7b**, **7c** and **7e** towards tested SBLs, probably indicated the size and electronegativity of the substituent may influent interaction with residues in the active site. Compounds **7f** and **7g**, with a large benzyl group at of 3-indole, had low inhibition against tested SBL enzymes, probably due to its steric hindrance with the active sites of these enzymes. Interestingly, **7g** had substantial inhibitory activity on the tested MBLs but **7f** did not. This may be due to the steric clash between the C-5 substitution on the indole ring of **7f** and the residues on the L10 loop of the MBL active site, while N-1 substituted indole ring of **7g** may enhance the interactions with the L3 loop. For compounds **7h** and **7i**, which had fluorine at C-4 and C-6 position respectively, we observed that **7h** showed stronger inhibitory activity than **7i** against KPC-2, AmpC and tested MBLs.

By replacement of the aromatic ring with the dimethylaminophenyl (*i.e.*, compound **9a**) at C-3 position, we observed a significant increase in inhibitory activity (Table 1), particularly for KPC-2 (IC_{50} = 0.18 μM), TEM-1 (IC_{50} = 0.73 μM), and NDM-1 (IC_{50} = 8.44 μM). Correspondingly, **9b** (with methylaminophenyl) and **9c** (with piperidinylphenyl) showed comparable inhibitory activity to OXA-48, VIM-1 and Sfh-I, but slightly lower activity to KPC-2, TEM-1, AmpC and NDM-1. These results suggested that dimethylaminophenyl is a preferred fragment to extensively accommodate with the active sites of all the tested enzymes. Thus, several analogs (**9d**, **9f**, **9g**, **9h**, **9i**, and **9j**) with C-3 dimethylaminophenyl were further synthesized and evaluated. Compared with **9a**, **9d** with fluorine at C-4 position showed reduced activity against all the tested enzymes except for Sfh-I, which is similar as that of the pair **7a**/**7h** (Table 1), suggesting that the fluorine substituent at C-4 position is not favorable for the inhibition to the tested β-lactamases (except for Sfh-I). Compound **9f** with the chlorine substituent at C-5 position showed better or comparable inhibitory potency compared with **9a**. Especially, **9f** had an IC_{50} value of 86 nM to the clinically important KPC-2. Compared to **9a**, **9g** (a fluorine substituent at C-5) and **9h** (a methoxy substituent at C-5) exhibited slightly decreased inhibitory activity against tested enzymes, with an exception of KPC-2. Compared with the moderate inhibition of **9a** and **9b** on VIM-1, the weak inhibition of **9d**–**9j** on VIM-1 indicated that the substitution on the phenyl group of the benzoxaborol core is unfavorable for binding with VIM-1. The introduction of a chlorine atom at C-6 position (*i.e.*, compound **9i**) was harmful for the inhibition of tested class A SBLs and B1 MBL but beneficial to inhibit class C SBL and B2 MBL. As a marketed beta-lactamase inhibitor, avibactam exhibited nanomolar to submicromolar inhibition potency against tested SBLs and B2 Sfh-I, but showed weak inhibitory activity against tested B1 MBLs. Compared to avibactam, the benzoxaborole compounds had less potent inhibition to tested SBLs. Nevertheless, some compounds showed good inhibition towards both tested SBLs and MBLs, *e.g.* **3b** and **9f**, indicating their potentiation for further optimization as broad-spectrum MBL/SBL inhibitors.

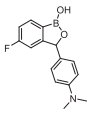
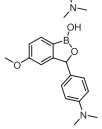
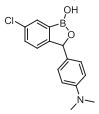
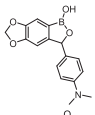
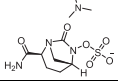
In order to investigate how **9f** binds with KPC-2 and NDM-1, we carried out docking simulations to predict the possible binding mode of **9f** with KPC-2 and NDM-1. Since the flexibility of Trp_{105} at L3 loop of KPC-2 was observed in our previous crystallographic analyses,[20] we selected the two crystal structures (PDB codes 6J8Q and 6JN3) as the docking templates. The best predicted binding mode is shown in Fig. 2A.

Table 1
Inhibitory Activity of synthesized 3-substituted benzoxaborole derivatives against representative SBLs and MBLs.[†]

Cpd ID	Chemical Structure	SBLs IC_{50} values (μM)				MBLs IC_{50} values (μM)		
		Class A KPC-2	Class A TEM-1	Class C AmpC	Class D OXA-48	Class B1 NDM-1	Class B1 VIM-1	Class B2 Sfh-I
3a		1.00	4.46	29.22	8.67	89.02	73.76	3.56
3b		0.41	6.97	18.74	5.45	22.41	17.39	2.47
7a		2.58	>100	3.66	>100	6.04	15.15	8.50
7b		0.36	88.83	7.27	>100	>100	62.47	6.58
7c		0.20	>100	5.66	>100	>100	ND[‡]	18.58
7d		9.43	>100	25.87	>100	23.97	13.13	14.93
7e		0.22	>100	8.52	>100	68.00	16.25	19.44
7f		>100	>100	>100	>100	>100	>100	>100
7g		>100	>100	>100	>100	15.87	10.64	9.60
7h		6.56	>100	10.75	>100	25.40	89.68	2.17
7i		>100	>100	>100	>100	>100	>100	>100
9a		0.18	0.73	8.27	2.41	8.44	39.36	2.52
9b		0.10	3.20	13.88	2.37	57.39	26.45	3.02
9c		0.51	32.96	32.22	3.44	11.69	18.44	5.27
9d		1.91	20.73	15.09	7.48	25.59	>100	1.83
9e		2.41	37.87	15.27	6.49	51.38	>100	1.15
9f		0.086	1.54	22.69	2.34	9.05	>100	3.81

(*continued on next page*)

Table 1 (*continued*)

Cpd ID	Chemical Structure	SBLs IC_{50} values (μM)				MBLs IC_{50} values (μM)		
		Class A KPC-2	Class A TEM-1	Class C AmpC	Class D OXA-48	Class B1 NDM-1	Class B1 VIM-1	Class B2 Sfh-I
9g		0.35	5.68	39.29	3.58	11.20	>100	3.64
9h		0.18	1.54	11.39	2.93	38.39	>100	4.23
9i		0.81	4.34	3.60	1.96	61.73	>100	0.47
9j		0.76	1.15	5.23	6.40	16.58	51.03	2.77
Avi[‡]		0.0037	0.0019	0.024	0.17	>100	>100	0.025

Avi: avibactam.

[†] All the IC_{50} curves (errors among triplet tests) are shown in Supporting Information Fig. S2.

[‡] ND: not determined.

Table 2
MICs of meropenem against bacterial strains expressing KPC-2, AmpC, and TEM-1 in the presence of **3b** and **9f**.[‡]

Bacterial strain	Characterized β-lactamase	MEM (μg/ml)	MEM + 100 μM **3b**	MEM + 10 μM **3b**	MEM + 100 μM **9f**	MEM + 10 μM **9f**
ATCC 25922	–	0.06	–	–	–	–
K. pneumonia C692	AmpC, TEM-1	>128	>128	>128	>128	>128
Escherichia coli BAA-2340	KPC-2	16	0.5	2	0.5	2
Escherichia coli 11119	KPC-2	64	2	32	8	32

[‡] MEM: meropenem.

We observed that similar to previous reports,[7,27,28] **9f** is likely to form a covalent bond with the catalytically important Ser_{70} of KPC-2, and make hydrogen bonds with Asn_{170} and Glu_{166}. The benzoxaborole likely binds near to Leu_{167} and Asn_{170}, and the chlorine is likely positioned to make Trp_{105} away from Leu_{167} (Fig. 2A). This binding mode may explain why substituents at C-6 position (*e.g.*, **7i** and **9i**) or big substituents on C-3 indole (*e.g.*, **7g**) lead to decreased inhibitory activity to KPC-2. For NDM-1, we observed that the sp^3 hybridized benzoxaborole of **9f** is likely to interact with zinc ions and form hydrogen bonding with Asn_{220} (Fig. 2B).

*Cell-based activity of **3b** and **9f***

Considering structural diversity and inhibitory activity, we chose compound **3b** and **9f** for further investigation of their activity in cells. Three SBL-producing clinical isolates, including *K. pneumoniae* C692 (with AmpC and TEM-1), *Escherichia coli* BAA-2340 (with KPC-2), and *Escherichia coli* 11119 (with KPC-2), were selected for antimicrobial susceptibility testing according to the CLSI guideline. We observed that **3b** and **9f** at 100 μM could significantly potentiated the activity of meropenem against the two KPC-2 producing *Escherichia coli* strains, *i.e.*, reducing the MIC of meropenem by 32-fold to 8-fold. Even, **3b** and **9f** at 10 μM could restore meropenem activity to combat KPC-2 producing *Escherichia coli* BAA-2340 (Table 2). Unfortunately, **3b** and **9f** were unable to potentiate meropenem activity in AmpC/TEM-1 producing *K. pneumoniae* (Table 2). The variable susceptibility on different bacterial strains may reflects the possible effect of other resistance mechanisms, *e.g.* active efflux pumps.

In addition, the cytotoxicity of these two compounds was also evaluated using human HEK293T cells. Compound **3b** and **9f** showed no apparent cytotoxicity to HEK293T cells at 100 μM and 10 μM (Fig. S3), suggesting this series of compounds are a good starting point for further structural optimization to develop more potent inhibitors to multiple clinically relevant SBLs and MBLs.

Conclusions

In summary, a series of 3-aryl substituted benzoxaborole derivatives were synthesized and evaluated against a panel of representative SBLs and MBLs. Most compounds have moderate to good inhibitory activity against all the tested enzymes, and some of them had nanomolar inhibition to clinically important KPC-2. The structurally distinct compounds **3b** and **9f** significantly reduced the MICs of meropenem against KPC-2 expressing clinical isolates and showed no apparent cytotoxicity to HEK293T cells at 100 μM. This study provided new chemotypes for developing broad-spectrum β-lactamase inhibitors, and suggested great potential of benzoxaboroles in inhibiting both MBLs and SBLs.

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.

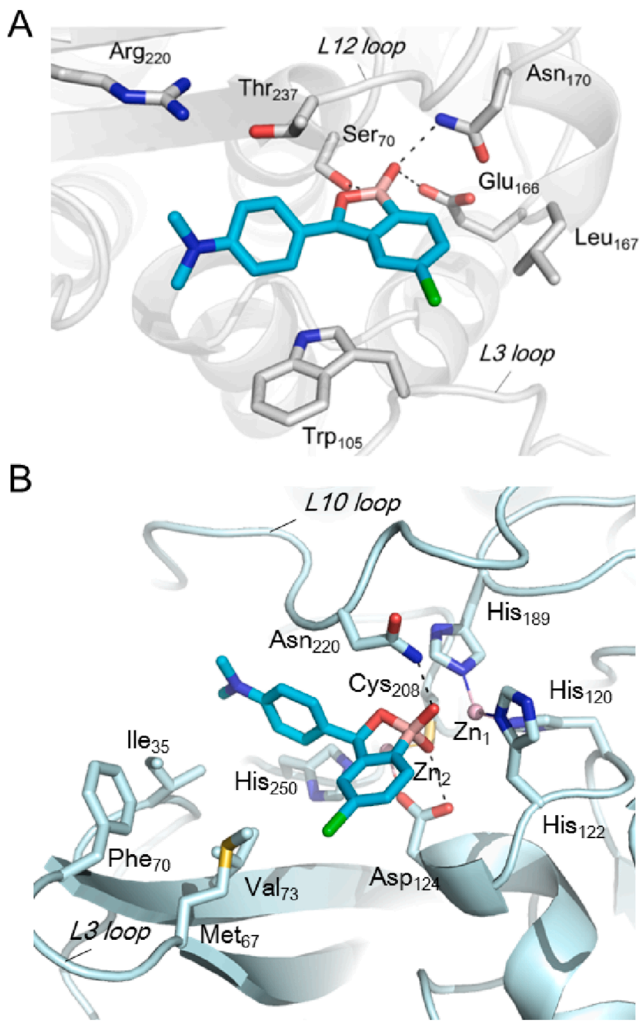


Fig. 2. The predicted binding mode of **9f** with (A) KPC-2 and (B) NDM-1, suggesting that the benzoxaborole is likely to form a covalent bond with the catalytically important KPC-2 Ser_{70} and to coordinate with NDM-1 zinc ions.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.127956.

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