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Synthesis and Evaluation of Carbapenem/Metallo-β-Lactamase Inhibitor Conjugates

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Antibiotics, particularly the β-lactams, are a cornerstone of modern medicine. However, the rise of bacterial resistance to these agents, particularly through the actions of β-lactamases, poses a significant threat to our continued ability to effectively treat infections. Metallo-β-lactamases (MBLs) are of particular concern due to their ability to hydrolyze a wide range of β-lactam antibiotics including carbapenems. For this reason there is growing interest in the development of MBL inhibitors as well as novel antibiotics that can overcome MBL-mediated resistance. Here, we report the synthesis and evaluation of novel conjugates that combine a carbapenem (meropenem or ertapenem) with a recently reported MBL inhibiting indole carboxylate scaffold. These hybrids were found to display potent inhibition against MBLs including NDM-1 and IMP-1, with IC_{50} values in the low nanomolar range. However, their antibacterial potency was limited. Mechanistic studies suggest that despite maintaining effective MBL inhibiting activity in live bacteria, the new carbapenem/MBL inhibitor conjugates have a reduced ability to engage with the bacterial target of the β-lactams.

Introduction

Antibiotics are among the most important discoveries in the history of medicine. However, soon after their introduction into the clinic, it was found that bacteria can develop resistance to antimicrobial agents, complicating the treatment of bacterial infections. One of the most concerning types of antibiotic resistance is driven by β-lactamases. Bacteria equipped with these enzymes can hydrolyse and thus deactivate a broad range of beta-lactam antibiotics including penicillins, cephalosporins, and carbapenems. According to the Ambler classification, β-lactamase enzymes are divided into four categories: Class A, B, C and D.[1] The class A, C and D are serine β-lactamases (SBLs), which utilize a serine residue in their active sites to catalyze hydrolysis of the beta-lactam ring. The class B enzymes are the metallo-β-lactamases (MBLs), which rely on zinc-ion-mediated activation of an active site water molecule for their hydrolytic activity. Most prominent among the MBLs are the Verona integron-encoded metallo-β-lactamase (VIM), imipenemase (IMP), and New Delhi metallo-β-lactamase (NDM) enyzmes. Due to the now widespread presence of these resistance mechanisms among bacteria, β-lactam antibiotics, including carbapenems, which are often considered last-resort treatments, are progressively losing their effectiveness.

There are currently a handful SBLs inhibitors used in clinical practice, which include clavulanic acid, sulbactam and tazobactam (each of which also include the β-lactam moiety) and the structurally distinct diazabycloоctanes including avibactam, relebactam, and durlobactam.[2,3] These compounds are typically administered together with a β-lactam antibiotic and work by binding to and inactivating SBLs, thereby helping the antibiotic retain its activity against a wide range of bacteria. There are, however, no clinically approved β-lactamase inhibitors able to tackle the class B MBLs. This is due to the fundamental differences in the hydrolytic mechanism of the MBLs, which render SBL inhibitors ineffective. Furthermore, low homology between the zinc-binding active sites of the different MBLs makes the design of broad-spectrum MBL inhibitors challenging.[2–4] Moderate success has been achieved with inhibitors containing free thiol groups that can bind to zinc ions within the MBL active site.[5,6] More promising are the boronic acid-based β-lactamase inhibitors that in some cases exhibit activity against both SBLs and MBLs.[7,8] In recent years, carboxylate substituted heterocycles including 1,3-thiazole-4-carboxylates and indole-2-carboxylates have also have been reported as potent, MBL-specific inhibitors capable of competitively binding to the MBL active site.[9,10]

There are numerous reports in the literature describing attempts at enhancing the antibacterial properties of β-lactam antibiotics by covalently linking them to other bioactive moieties.[11–14] The most common such approaches explored to date have involved the conjugation of two β-lactams,[15–17] the linking of a β-lactam to a non-β-lactam,[18,19] or the covalent attachment of a siderophore to a β-lactam.[20] By contrast, a relatively unexplored approach is the conjugation of β-lactam antibiotics to MBL inhibiting motifs as a means of overcoming MBL-mediated resistance. To this end, our group recently

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reported the design and synthesis of novel cephalosporin conjugates coupled to thiol-based MBL inhibiting groups.[21,22] Building from these strategies, we here describe efforts aimed at generating novel carbapenems wherein meropenem and ertapenem are conjugated to a potent MBL-inhibiting indole-2-carboxylate moiety. These conjugates are conveniently prepared using the copper-catalysed azide-alkyne "click" ligation after which we assessed both their antibacterial activity and ability to inhibit NDM- and IMP-type MBLs.[23]

Results and Discussion

In designing the carbapenem-MBLi conjugates we were particularly drawn to the indole-2-carboxylate based compounds recently reported by Schofield and coworkers.[10,24] In a study aimed at comparing the relative activities of various MBL inhibitors, we also found the fluoro-substituted indole-2-carboxylate **3** (Figure 1) to be a highly effective inhibitor of NDM-1 and IMP-1 with the ability to also strongly potentiate the activity of meropenem against NDM-1 positive isolates.[25] The Schofield group also reported the triazole-substituted indole-2-carboxylate **4** as a potent MBLi.[10] With this in mind, we envisioned a click chemistry approach for the preparation of conjugates **5** and **6** wherein either meropenem and ertapenem could be directly linked to the indole-2-carboxylate scaffold by means of a triazole ring (Figure 1).

The preparation of conjugates **5** and **6** first required access to the appropriate alkyne substituted meropenem and ertapenem analogues as well as the necessary azide substituted indole-2-carboxylate building block. Schemes 1–3 outline the synthetic strategies used for preparing these key compounds. For the installation of the alkyne moiety on meropenem and ertapenem, intermediates **13** and **17** were first synthesized (Scheme 1).[26] In brief, the commercially available L-hydroxyproline (**9**) was protected as the *p*-nitrobenzyl carbamate (PNZ) and

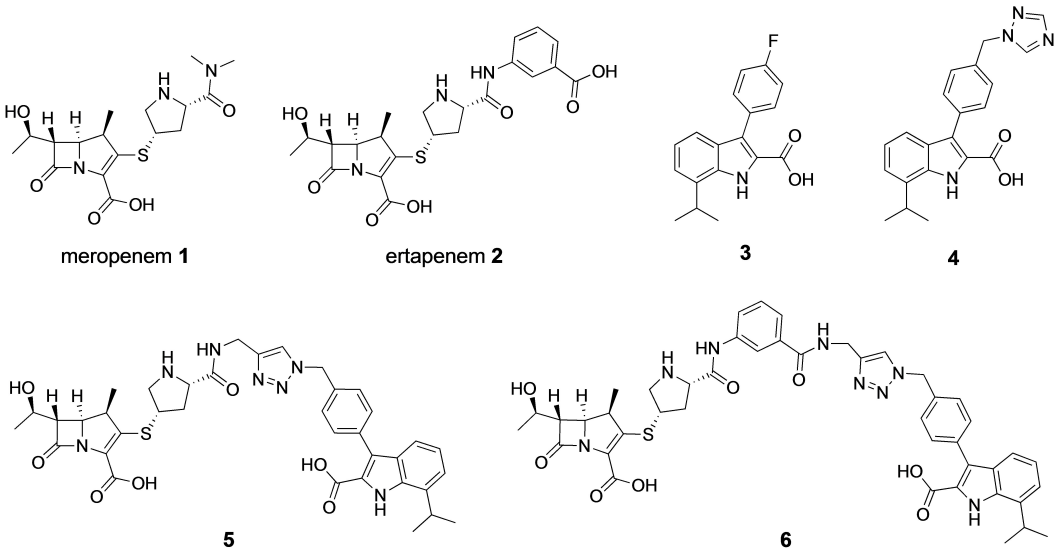
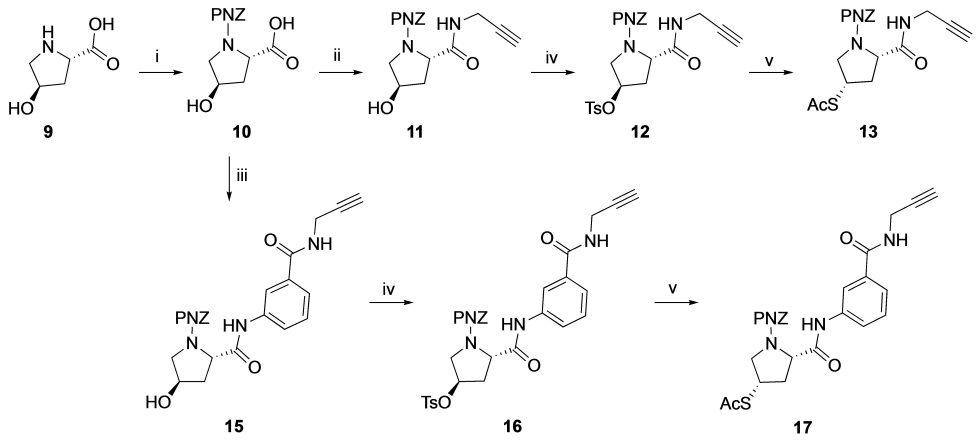
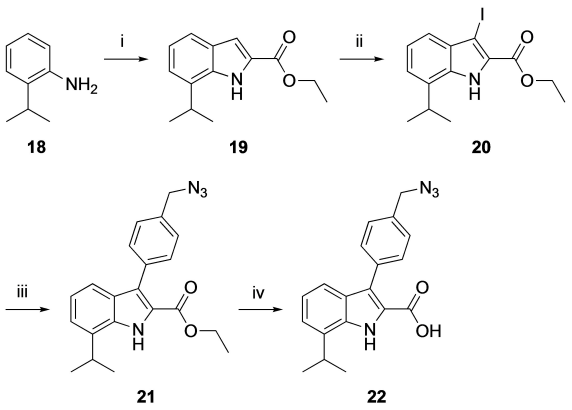


Figure 1. Structures of meropenem (**1**) and ertapenem (**2**), indole-based MBL inhibitors **3** and **4**, and the conjugates **5** and **6**.



Scheme 1. Reagents and conditions: i) 4-nitrobenzyl chloroformate, NaOH, water/DCM, 0 °C, 2 h, 97%; ii) EDC·HCl, HOBt, N-methylmorpholine, propargylamine, THF, rt, overnight, 68%; iii) 3-amino-N-(prop-2-yn-1-yl)benzamide **14**, HATU, DIPEA, DCM, rt, overnight, 66%; iv) TsCl, TEA, DMAP, DCM, rt, overnight, 82% for **12**, 81% for **16**; v) AcSK, DMF, 65 °C, 3.5 h, 80% for **13**, 98 % for **17**.

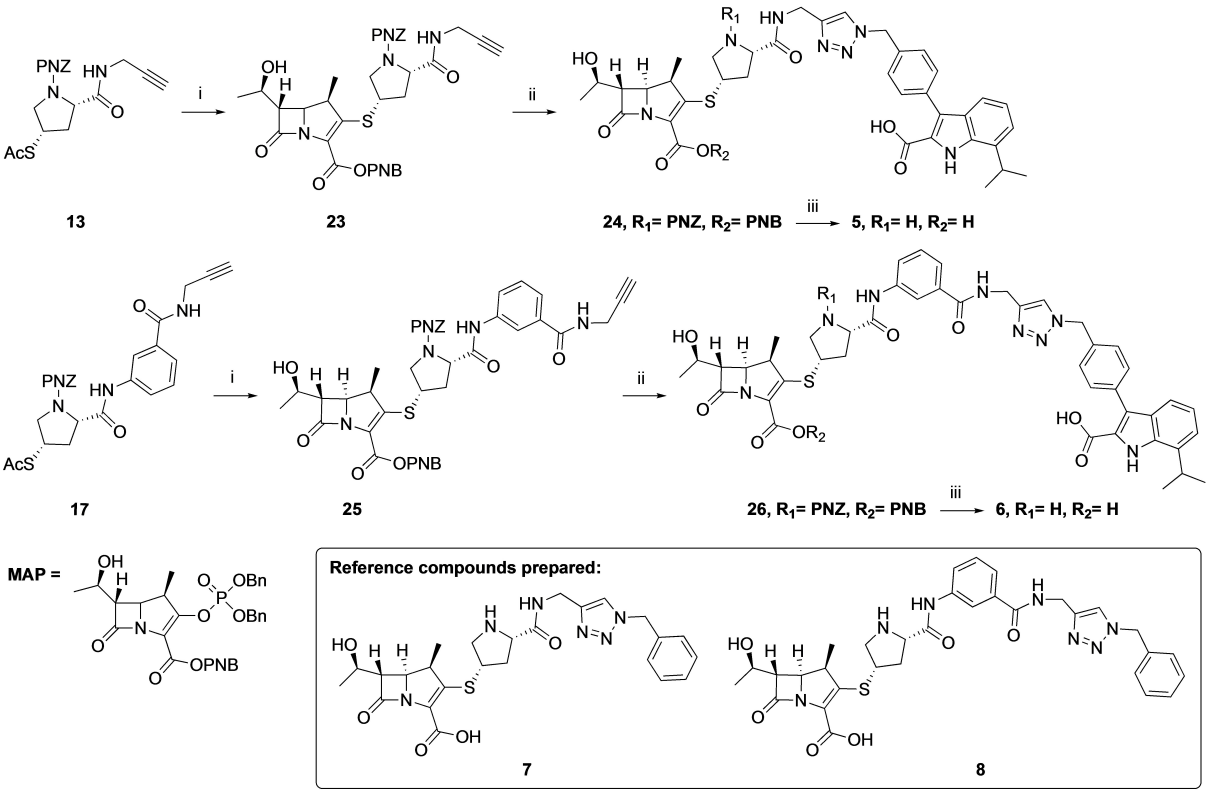


Scheme 2. Reagents and conditions i) $NaNO_2$, conc. HCl, water, 0 °C, 10 min; ethyl-2-methylacetoacetate, KOH, EtOH, rt, 1 h; p-TsOH, toluene, reflux, overnight, 40%; ii) NIS, DCM, rt, 81%; iii) 4-(azidomethyl)benzeneboronic pinacol ester, $PdCl_2dppf$, Na_2CO_3, water/dioxane, reflux, overnight, 55%; iv) NaOH, THF/EtOH (7:4), overnight, 97%.

then coupled with propargylamine to yield **11** or with 3-amino-*N*-(prop-2-yn-1-yl) benzamide (**14**) to give **15**. Subsequent activation of the alcohol moiety in both **11** and **15** by conversion to the tosylate, following by nucleophilic displacement with potassium thioacetate yielded the desired compounds **13** and **17**.

The synthesis of azide-substituted indole-2-carboxylic acid **22** was conducted according to established methods (Scheme 2).[24] Briefly, 2-isopropyl aniline (**18**) was treated with sodium nitrite to form the diazonium salt, which was then combined with ethyl acetoacetate to generate the transient arylhydrazone through a Japp-Klingemann reaction. Under the conditions used, this species tautomerises to the corresponding 'ene-hydrazine' and subsequently undergoes a sigmatropic rearrangement yielding indole **19** (Scheme 2). The corresponding iodo intermediate **20** was then generated by treatment with *N*-iodosuccinimide. Introduction of the azido group was next achieved by means of a Suzuki-Miyaura coupling with the commercially available 4-(azidomethyl)benzeneboronic pinacol ester to yield **21** after which ester hydrolysis furnished key azide building block **22** (Scheme 2).

The desired carbapenem-MBLi conjugates were finally prepared by first coupling alkyne building blocks **13** and **17** with the commercially available beta-methyl vinyl phosphate meropenem precursor commonly known as MAP (Scheme 3). This involved initial thioester hydrolysis of **13** and **17** under mild conditions after which MAP was added along with DIPEA and the mixture stirred overnight at reduced temperature. This led to the formation of intermediates **23** and **25**, both of which could be conveniently purified using column chromatography. Subsequent ligation with azide-substituted indolecarboxylate building block **22** was achieved using the copper-catalyzed azide-alkyne cycloaddition to yield triazole intermediates **24**



Scheme 3. Reagents and conditions. i) NaOH, water/MeOH, 0 °C, 20 min; TCEP·HCl, NaOH, water/THF, overnight; MAP, DIPEA, ACN, −10 °C, overnight, 36% for **23**, 39% for **25**; ii) compound **22**, sodium ascorbate, $CuSO_4{\cdot}5H_2O$, water/DMF, rt, 1 h, 28% for **24**, 54% for **26**; iii) Pd/C, H_2, THF/1 M $Et_3N{\cdot}H_2CO_3$ (1:1), pH 8.5, rt, overnight, 25% for **5**, 39% for **6**.

and **26**. Simultaneous deprotection of the PNZ and PNB groups was accomplished using hydrogenation to provide the target conjugates **5** and **6**. In addition, two reference compounds **7** and **8** were prepared following the same synthetic route by reacting **23** and **25** with benzyl azide in place of **22** to assess the compatibility of the reaction conditions with the carbapenem core. All final compounds were purified to >95% purity by preparative HPLC and their structures confirmed by ^{1}H-NMR, ^{13}C NMR, and HRMS (full experimental details provided in the Supporting Information).

With the carbapenem-MBLi conjugates in hand we first proceeded to confirm their ability to inhibit MBLs. To this end we determined the half-maximal inhibitory concentration (IC_{50}) values for conjugates **5** and **6**, as well as reference compounds **7** and **8**, against purified NDM-1 and IMP-1 enzymes. For these assays, we employed the fluorescent cephalosporin substrate FC5 previously described in the literature.[27] As summarized in Table 1, conjugates **5** and **6** both displayed remarkable potency against NDM-1 and IMP-1, with IC_{50} values in the low to sub-nanomolar range for both enzymes. By comparison, and in line with exception, the truncated reference compounds **7** and **8**, lacking the indole-2-carboxylate moiety, showed significantly lower inhibitory activity. Also included as a positive control was known MBLi **3** which has previously been reported as a potent inhibitor of both NDM-1 and IMP-1.[24,25] Interestingly, both **5** and **6** were also found to display a near 10-fold increase in inhibitory potency relative to **3** suggesting that the carbapenem moiety present in the two conjugates offers some enhancement of activity. To examine the stability of the β-lactam moiety in these conjugates in the presence of MBLs we conducted a time-course experiment wherein **5** was incubated with either NDM-1 or IMP-1 and monitored by LCMS (see Supporting Information Figure S2). These studies revealed little hydrolysis of the β-lactam moiety in the time scale used for the inhibition assays suggesting that the potent MBL inhibition measured for **5** and **6** is primarily governed by the indole-2-carboxylate moiety.

Having established that conjugates **5** and **6** are effective MBLs inhibitors, we next investigated their antibiotic properties by testing them against drug-resistant, MBL-expressing strains. To this end, we determined the minimum inhibitory concentration (MIC) values of meropenem **1** and ertapenem **2** (both alone and in combination with MBLi **3**), as well as conjugates **5** and **6**, and reference triazole analogues **7** and **8** against a panel of nine Gram-negative strains harbouring different MBLs (NDM-1, IMP-1, IMP-28 and VIM-1) as well as a standard carbapenem-susceptible strain (*E. coli* 25922). The results of these assays are presented in Table 2. As expected, meropenem and ertapenem were found to be highly active against the susceptible *E. coli* strain (MIC ≤0.03-0.06 μg/ml) and inactive against strains expressing MBLs with MIC values generally >64 μg/ml. Also in line with expectation, when combined with MBL inhibitor **3** in a 1:1 ratio, the activities of meropenem and ertapenem were effectively potentiated against MBL-positive strains of *E. coli* and *K. pneumoniae*, with a less pronounced effect against the *P. aeruginosa* strains tested. In contrast, the novel conjugates **5** and **6**, containing both the carbapenem scaffold and potent MBLi moiety, showed negligible antibacterial activity against MBL-positive strains (MICs >64 μg/ml). Furthermore, both **5** and **6** showed only moderate antibacterial activity towards the susceptible *E. coli* 25922 strain with MIC values of 8 and 16 μg/ml respectively (with similarly moderate activity observed

Table 1. IC_{50} values for carbapenem-MBLi conjugates against NDM-1 and IMP-1.

Compound	IC_{50} (μM)[a]	
	NDM-1	IMP-1
3	0.0016 ± 0.0004	0.095 ± 0.062
5	0.00025 ± 0.00001	0.0029 ± 0.0005
6	0.000115 ± 0.000003	0.000656 ± 0.000004
7	13.52 ± 3.02	0.67 ± 0.13
8	3.99 ± 0.80	0.57 ± 0.06

[a]The half-maximal inhibitory concentration values for each compound against NDM-1 and IMP-1 with FC5 used as the substrate. Values shown are averages of triplicate measurements ± SD.

Table 2. Minimum inhibitory concentration (MIC) values of compounds against bacterial strains expressing different MBL enzymes.

Bacterial strain and MBL enzymes evaluated		Antibacterial activity of compound(s) assessed: MIC values expressed as μg/ml							
Strain	MBL	**1**[a]	**2**[b]	**1** + **3** (1:1)	**2** + **3** (1:1)	**5**	**6**	**7**	**8**
E.coli 25922	–	0.03	≤0.06	≤0.06	≤0.06	8	16	≤0.5	≤0.5
E. coli RC0089	NDM-1	64	>64	2	8	>64	>64	>64	>64
E.coli 2018–015	NDM-1	>64	>64	2	8	>64	>64	>64	>64
P. aeruginosa NRZ08418	NDM-1	>64	>64	32	>64	>64	>64	>64	>64
P. aeruginosa NRZ03961	IMP-1	>64	>64	>64	>64	>64	>64	>64	>64
P. aeruginosa C017217	IMP-1	>64	>64	>64	>64	>64	>64	64	64
K. Pneumoniae 13443	NDM-1	>64	>64	64	>64	>64	>64	>64	>64
K. Pneumoniae JS022	NDM-1	>64	>64	4	16	>64	>64	>64	>64
K. Pneumoniae JS265	IMP-28	>8	>8	2	4	>64	>64	64	>64
K. Pneumoniae 1124	VIM-1	>64	>64	64	>64	>64	>64	>64	>64

[a]**1** = meropenem, [b]**2** = ertapenem.

against a panel of carbapenem-sensitive strains, see Table S1, Supporting Information). Notably, the smaller triazole analogues **7** and **8**, lacking the MBL inhibitor fragment, were found to exhibit potent activity against the susceptible strain (MIC $\leq$0.5 μg/ml). These findings indicate that while addition of the smaller benzyl triazole motif to the carbapenem scaffold is tolerated, incorporation of the larger indole-2-carboxylate group leads to loss of inherent antibacterial activity.

To assess whether the lack of antibacterial activity for conjugates **5** and **6** might be due to a decreased ability to permeate the Gram-negative outer membrane (OM), we next tested them in combination with polymyxin B nonapeptide (PMBN) a known potentiator of antibiotics with poor OM penetration.[28,29] To this end we performed checkerboard assays wherein combinations of PMBN and conjugate **5** or **6** were tested against the carbapenem susceptible *E. coli* 25922 strain. These studies revealed no enhancement of antibacterial activity for **5** or **6** (Figure 2A). The antibacterial activity of **5** and **6** was also assessed against *E. coli* strains bearing a compromised lipopolysaccharide (LPS) layer making it easier for antibiotics to cross the OM (see Table S2, Supporting Information). However, and in agreement with the PMBN synergy studies, the potency of **5** and **6** was only marginally improved against LPS-deficient strains further indicating that poor OM permeability is not likely the explanation for their reduced antibacterial effect.

We next evaluated whether or not conjugates **5** and **6** have the capacity to potentiate the activity of meropenem against MBL expressing bacteria. In our earlier enzymatic studies (Table 1), **5** and **6** were found to have potent MBL inhibitory activity. We therefore applied another checkerboard assay approach, this time evaluating combinations of meropenem with either known MBLi **3** or conjugates **5** and **6**, against an NDM-1 positive, meropenem-resistant strain of *E. coli*. As shown in Figure 2B, compounds **3**, **5**, and **6** all exhibit clear synergy with meropenem with FICI values of $<$0.155. Taken together, the data presented in Figure 2 indicate that compounds **5** and **6** can still penetrate the OM and effectively inhibit MBLs in live bacteria but are devoid of inherent antibiotic activity.

The lack of antibacterial activity observed for conjugates **5** and **6**, despite their ability to enter bacterial cells, suggests that they are not able to effectively inhibit the penicillin-binding proteins (PBPs) that are the targets of the carbapenems and all other β-lactam antibiotics. This apparent loss of PBP binding ability is presumably due to the introduction of the indole-2-carboxylate moiety in **5** and **6**. In contrast, analogues **7** and **8**, which only contain the benzyl triazole moiety at the same position, seem capable of effectively interacting with PBPs as

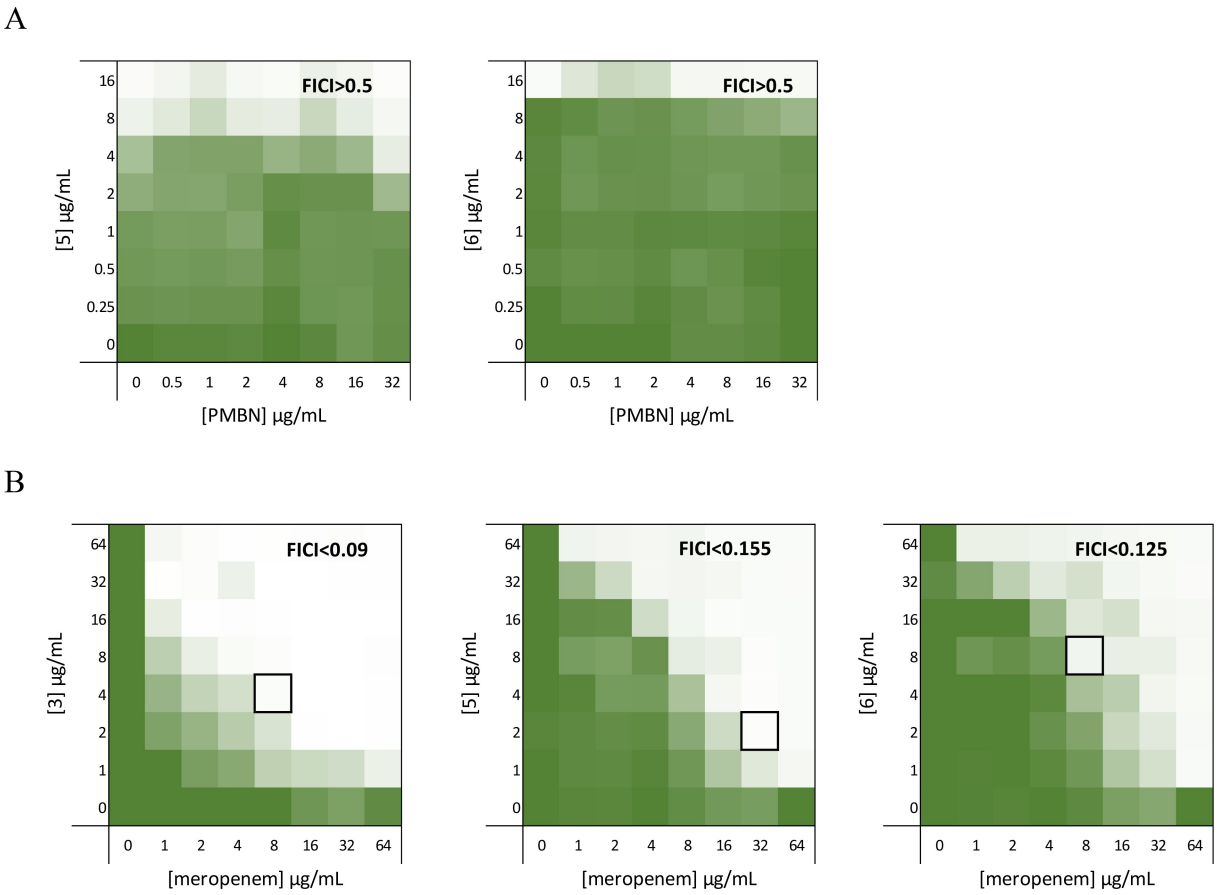


Figure 2. Checkerboard assay results. A) Synergy of conjugates **5** and **6** with PMBN against *E. coli* ATCC 25922; B) Synergy of compounds **3**, **5**, and **6** with meropenem against *E. coli* RC0089 (NDM-1). The combination which resulted in the lowest FICI is indicated by a black box. The mean optical density of the bacterial growth (OD600) is shown as a color gradient, with green signifying maximum bacterial growth and white no growth.

they maintain potent antibacterial activity. This finding is somewhat surprising given that the published crystal structures of meropenem bound to different PBPs all show the distal dimethylamide moiety of meropenem to be located outside the binding pocket and solvent exposed, suggesting it should be amenable to modification.[30–33] Based on our findings it would appear that there are limits to the size and/or functionality of the substituents that can be added at this position without impacting PBP binding.

Conclusions

The lack of a robust development pipeline for new drugs targeting antibiotic-resistant Gram-negative bacteria highlights the importance of strengthening the existing antibacterial arsenal. To this end we here report the design, synthesis, and evaluation of new bifunctional conjugates intended to both act directly as antibiotics and also inhibit MBLs. The strategy employed was guided by previous work demonstrating the synergistic relationship between meropenem and MBL inhibitors (such as indole-2-carboxylic acids) against MBL-producing bacterial strains. As a result, conjugates **5** and **6**, in which a triazole moiety bridges a carbapenem antibiotic and an MBL inhibitor fragment, were synthesised by means of copper-catalyzed azide-alkyne cycloaddition reactions.

Enzyme inhibition assays against NDM-1 and IMP-1 revealed nanomolar potency for compounds **5** and **6**, with IC_{50} values on par with established MBL inhibitors. However, the compounds were found to exhibit only moderate antibacterial activity with relatively high MIC values when tested against both carbapenem-sensitive strains as well as against MBL-positive pathogens. The antibacterial effect of conjugates **5** and **6** was not enhanced by combination with PMBN, nor were the compounds more active against LPS deficient strains, indicating that OM permeation is not likely to be the factor responsible for their limited activity. In addition, the finding that **5** and **6** are able to effectively potentiate the activity of meropenem against NDM-expressing strains further substantiates their ability to cross the Gram-negative OM and potently inhibit MBLs in live bacteria.

In conclusion, based on these findings it would appear that the introduction of the MBL-inhibiting indole-2-carboxylate moiety in conjugates **5** and **6** prevents effective engagement with the target PBP enzymes. While the efficacy of these conjugates against MBLs is evident, the antibacterial potency is limited. Future research will therefore focus on further developing this class of compounds, with an emphasis on optimising the linker between the two active moieties as a means of also maintaining inherent antibacterial activity.

Materials and Methods

Compounds Synthesis

Compounds **5**–**8** were prepared according to commonly used procedures with minor adjustments.[10,24,26] Full experimental details are provided in the Supporting Information.

Enzyme Expression and Purification

The NDM-1 and IMP-1 were prepared according to an established protocol.[25]

Enzyme Inhibition Assays

The half-maximal inhibitory concentration (IC_{50}) of each compound was determined against NDM-1 and IMP-1. All the test compounds were dissolved and serially diluted in 50 mM HEPES, pH 7.2, containing 0.01% Triton X-100 and 1 μM zinc sulfate. The MBLs enzymes 60 pM NDM-1 or IMP-1 were added to the wells and incubated at 25 °C for 15 min. Next, the fluorescent cephalosporin substrate FC5 (0.5 μM for NDM-1 or IMP-1) was added to the wells, and the fluorescence was monitored over 30–40 cycles (λ_{ex} = 360 nm, λ_{em} = 465 nm) on a Tecan Spark plate reader. The initial velocity data was used to produce the IC_{50} curves using GraphPad prism 7 software. The microplates used were μClear®, black half-area 96-well plate (Greiner Bio-one).

Antibacterial Assays

Bacterial Growth

The antibacterial activity of the compounds was determined by measuring their minimum inhibitory concentration (MIC) values using the broth microdilution method according to the Clinical and Laboratory Standards Institute guidelines (CLSI). For the MIC assays, bacteria were grown in cation-adjusted Mueller-Hinton broth (CAMHB) as recommended by the CLSI. To this end, MHB supplemented with 20–25 mg/liter of Ca^{2+} and 10 to 12.5 mg/liter of Mg^{2+}, according to CLSI recommendations. The addition of Ca^{2+} and Mg^{2+} was necessary to ensure bacterial growth.

MIC Assays

From glycerol stocks, bacteria were plated out on blood agar plates overnight at 37 °C. One colony was transferred to growth media (TSB) and grown at 37 °C at 200 rpm to exponential growth phase as determined by OD_{600}. At OD_{600} = 0.5, the bacterial suspension was diluted 100-fold to reach 10^6 CFU/mL in media CAMHB and 50 μL of this bacterial stock was then added to a 2-fold serial dilution series of test compound (50 μL) to reach a total volume of 100 μL per well. The 96-well polypropylene plates were sealed by breathable seals and incubated at 37 °C at 600 rpm overnight for 18–20 h, after which the plates were visually inspected for bacterial growth. MICs are reported as the median of triplicates.

Checkerboard Assays with PMBN

Dilution series of both the test compound to be evaluated and PMBN were prepared in freshly prepared CAMHB media. To evaluate synergy, 25 μL of the test compound solutions were added to wells containing 25 μL of the PMBN solution. This was replicated in three columns for each combination so as to obtain triplicates.

To the resulting 50 μL volume of test compound + PMBN was next added 50 μL of bacterial stock (see MIC assay protocol above) and the plates sealed. After incubation overnight (18–20 h for Gram-negative strains, 20–24 h for Gram-positive strains) at 37 °C while shaking at 600 rpm, the breathable seals were removed. The plates were then transferred to a Tecan Spark plate reader and following another brief shaking cycle (20 s) the density of the bacterial suspensions was measured at 600 nm (OD_{600}). The FICI of each combination was next established according to the following equation with a value of < 0.5 indicating synergy.

$$\mathbf{FICI} = \frac{\mathbf{MIC_{compound}\ in\ combination}}{\mathbf{MIC_{compound}\ alone}} + \frac{\mathbf{MIC_{PMBN}\ in\ combination}}{\mathbf{MIC_{PMBN}\ alone}}$$

Checkerboard Assays with Meropenem

Dilution series of both the test compound to be evaluated and meropenem were prepared in freshly prepared CAMHB media. To evaluate synergy, 25 μL of the test compound solutions were added to wells containing 25 μL of the meropenem solution. This was replicated in three columns for each combination so as to obtain triplicates. To the resulting 50 μL volume of test compound + meropenem was next added 50 μL of bacterial stock (see MIC assay protocol above) and the plates sealed. After incubation overnight (18–20 h for Gram-negative strains, 20–24 h for Gram-positive strains) at 37 °C while shaking at 600 rpm, the breathable seals were removed. The plates were then transferred to a Tecan Spark plate reader and following another brief shaking cycle (20 s) the density of the bacterial suspensions was measured at 600 nm (OD_{600}). The FICI of each combination was next established according to the following equation with a value of < 0.5 indicating synergy.

$$\mathbf{FICI} = \frac{\mathbf{MIC_{compound}\ in\ combination}}{\mathbf{MIC_{compound}\ alone}} + \frac{\mathbf{MIC_{meropenem}\ in\ combination}}{\mathbf{MIC_{meropenem}\ alone}}$$

Supporting Information

Synthetic procedures and analytical data for compounds prepared, supporting figures for inhibition studies and supporting tables for antibacterial assays. This material is available free of charge via the Internet.

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Antibiotics · Resistance · Metallo-β-Lactamases · Enzyme Inhibitors · Carbapenem Conjugates

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