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NH-1,2,3-Triazole Inhibitors of the VIM-2 Metallo-β-Lactamase

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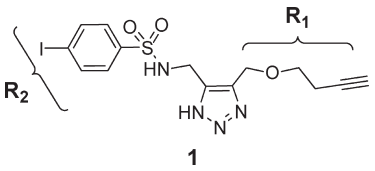
ABSTRACT Metallo-β-lactamases (MBLs) are an emerging cause of bacterial resistance to antibiotic treatment. The VIM-2 β-lactamase is the most commonly encountered MBLs in clinical isolates worldwide. Described here are potent and selective small molecule inhibitors of VIM-2 containing the arylsulfonyl-NH-1,2,3-triazole chemotype that potentiate the efficacy of the β-lactam, imipenem, in *Escherichia coli*.

KEYWORDS Metallo-β-lactamases, VIM-2, *N*H-1,2,3-triazole-based inhibitors, bacterial resistance, *Escherichia coli*



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Metallo-β-lactamases (MBLs) are an emerging class of enzymes with the ability to degrade most β-lactam antibacterial agents.[1] As a consequence of the rising rates of infections attributed to bacteria with acquired MBL genes, enzymes of this class represent new targets for adjuvant antibacterial therapy.[2,3] The VIM-2 enzyme is currently the most widespread MBL found in clinical isolates worldwide,[4−6] and as such, small molecule inhibitors of this enzyme may prove useful in the treatment of resistant infections. Several MBL inhibitors have been reported,[7,8] with the most potent VIM-2 inhibitor, a 3-mercaptopropionic acid derivative, exhibiting a K_i of 190 nM.[9] However, apart from *p*-chloromercuribenzoic acid (*p*CMB), a nonspecific cysteine-reactive reagent, no VIM-2 inhibitor has been shown to potentiate the antibacterial effects of β-lactams in VIM-2-expressing bacteria.[10] We recently identified a family of 4,5-disubstituted NH-1,2,3-triazoles (Figure 1) of selective VIM-2 inhibitors through the biochemical screening of a focused NH-1,2,3-triazole library with 267 members.[10]

The most potent candidate from this study, compound **1**, *N*-((4-((but-3-ynyloxy)methyl)-1*H*-1,2,3-triazol-5-yl)methyl)-4-iodo-benzenesulfonamide, exhibited submicromolar activity $K_i = 0.41 \pm 0.03$ μM against VIM-2 while being inactive toward the related MBL, IMP-1.[10] Unfortunately, this compound did not potentiate the antibacterial effects of a β-lactam antibiotic, imipenem.

Herein, we describe our efforts to examine structure−activity relationships (SARs) for this chemotype with the goal of improving the potency of the lead compound **1** and identifying VIM-2 inhibitors with the ability to potentiate β-lactam antibacterials. In our study, substituents on the C-4 methyl of the triazole (R_1) or the arylsulfonamide (R_2) were systematically varied. NH-triazole-containing sulfonamides were readily prepared as shown in Figure 2. The key transformation was the Banert cascade reaction of propargyl azides with various nucleophiles.[11] The sequence began with the synthesis of *N*-(4-chlorobut-2-ynyl)-sulfonamide derivatives (b) obtained from propargyl amines (a) and sulfonyl chlorides under the Schotten−Baumann conditions. Nucleophilic substitution of the chloride with sodium azide gave the desired propargyl azides (c), which, upon heating, underwent a facile rearrangement to triazafulvenes (d), highly reactive intermediates that could be readily captured with different nucleophiles.

From our initial work with arylsulfonyltriazole VIM-2 inhibitors, we noted that an alkoxy substituent on the C-4 methyl of the triazole moiety was important for activity.[10] We speculate that the oxygen of the alkoxy group, a hydrogen-bond acceptor, is important for effective inhibition of VIM-2, possibly through polar interactions between this atom and the active site amino acid residues. Consequently, to expand the SAR around the VIM-2 inhibitor **1**, five new analogues bearing an alkoxy appendage on the C-4 methyl of the triazole moiety were synthesized (compounds **2**−**4**, **5**, and **8** in Table 1) and examined in a nitrocefin biochemical assay[10] using VIM-2 cloned from a *Pseudomonas aeruginosa* clinical strain (COL-1). Three of the five new analogues exhibited improved potency as compared to the original hit, **1**.

Next, to further explore the substitution requirements of the triazole moiety and to show that VIM-2 inhibition was not

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unique to analogues containing a 4-iodobenzene group, a diverse series of 4-chlorobenzenesulfonyl derivatives were prepared and tested (Table 2). Inhibitors with submicromolar IC_{50} values were identified from this group of candidates (compounds **12**−**16**); all of them contained an amine at the C-4 methyl of the triazole ring. As for the SAR, the potency of the 4-chlorobenzene sulfonamides was strongly dependent on the nature of the C-4 methyl triazole substituent. In this series, hydrophobic amino (e.g., **12**, IC_{50} = 0.29 μM) and alkoxy derivatives (e.g., **17**, IC_{50} = 1.1 μM) were excellent inhibitors, while alkyl derivatives (i.e., **25**, **27** and **28**) were poorly active or inactive toward VIM-2. A sulfide **30**, which is the thioether analogue of **22**, was inactive. These findings

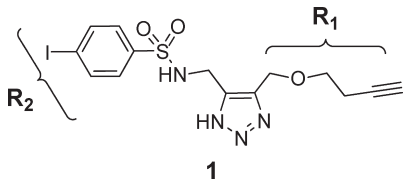

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Figure 1. 4,5-Disubstituted NH-1,2,3-triazoles with substituents on C-4 methyl of the triazole (R_1) or the arylsulfonamide (R_2). Candidate **1** is shown.

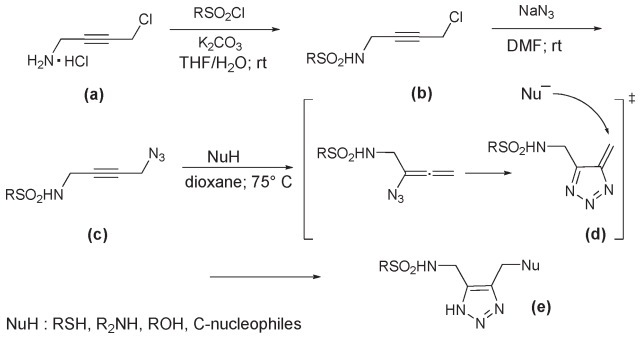


Figure 2. Synthesis of candidate compounds.

lend further support to our hypothesis that a hydrogen-bond acceptor of the C-4 methyl of the triazole is important for inhibitor−protein interactions, with nitrogen being superior to oxygen. However, with respect to VIM-2 binding and inhibition, sulfur does not appear to be a good replacement, probably as a consequence of its larger size and more diffuse electronic properties, leading to poor hydrogen-bond acceptor properties.

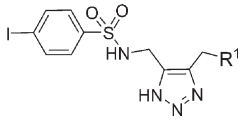
A series of unsubstituted arylsulfonamides were also examined (Table 3). Again, amino substitution on the C-4 methyl of the triazole resulted in the most potent compounds, with the adamantyl (**32**) and cyclohexyl (**33**) derivatives approaching IC_{50} = 100 nM.

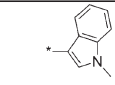
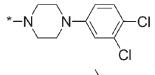
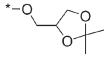
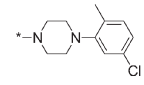
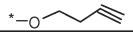
Next, we looked at the effect of aromatic substituents. The equivalent, unsubstituted 4-iodobenzenesulfonyl and 4-chlorobenzenesulfonyl derivatives (Table 3) exhibited at most a 3-fold difference in potency, demonstrating that changes at the para-position provide minor improvements in inhibitor binding.

To further explore the contribution to binding provided by the arylsulfonamide moiety, we prepared analogues with the same triazole derivative but with differing aromatic substituents (Table 4). Again, halide aromatic substitution had discrete effects. For example, the potency of **2**, a 4-iodobenzenesulfonyl derivative, and **36**, a 2,5-dichlorobenzenesulfonyl derivative, which both share an isopropyl appendage on the triazole, differed by 2-fold. Similarly **42**, a 4-methoxybenzenesulfonyl derivative, and **14**, a 4-chlorobenzenesulfonyl derivative, both sharing a dipropylamine appendage on the triazole, were equipotent. In contrast, derivatives with very bulky aromatic para-substituents (i.e., **38**−**40**) were poorly active or inactive against VIM-2.

During the course of lead optimization of **1**, we recognized that the most potent inhibitors contained a dichlorobenzene group (Table 5) and an amine substituent on the C-4 methyl of the triazole. Table 5 compares the most potent VIM-2 inhibitor **44** with other amino and alkoxy derivatives in the

Table 1. SAR of Triazolylmethyl 4-Iodobenzenesulfonamides with Respect to the C-4 Methyl Substituent



ID	R^1	IC_{50}[a]	ID	R^1	IC_{50}[a]	ID	R^1	IC_{50}[a]
2	O^{i}Pr	0.29 ± 0.03	**5**	-OBu	5.2 ± 0.7	**9**[b]		11%
3	-O^{t}Bu	1.1 ± 0.3	**6**[b]	-OMe	7.3 ± 1.9	**10**[b]		5.3%
4	-OEt	1.6 ± 0.3	**7**[b]		31%	**11**[b]		0%
1[b]		3.3 ± 0.4	**8**	-OBn	23%	-	-	-

[a] IC_{50} ± error (μM) was reported as the standard deviation of three replicates. IC_{50} values were obtained using a four-parameter sigmoidal dose−response curve with adjustable baseline using GraphPad Prism. Maximum inhibition (at 56 μM) was reported for compounds that do not achieve 50% inhibition. [b] Compounds were reported previously.[10]

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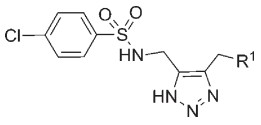
Table 2. SAR of Triazolylmethyl 4-Chlorobenzenesulfonamides with Respect to the C-4 Methyl Substituent



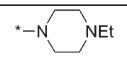
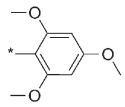
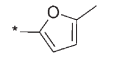
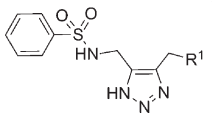
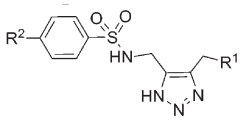
ID	R^1	IC_{50} (μM)	ID	R^1	IC_{50} (μM)	ID	R^1	IC_{50} (μM)
12	-NHPh	0.29 ± 0.02	**19**	-O^{t}Bu	1.4 ± 0.1	**26**		34 %
13	-NHcyclohexyl	0.39 ± 0.02	**20**	-Npyrrolidine	3.0 ± 0.02	**27**		0 %
14	-NPr$_2$	0.45 ± 0.02	**21**	-Nmorpholine	3.8 ± 0.6	**28**		0 %
15	-Nindoline	0.58 ± 0.05	**22**	-OBu	19 ± 6	**29**	-N(Bis(2-methoxyethyl))	0 %
16	-NHadamantyl	0.67 ± 0.01	**23**	-OMe	21 ± 5	**30**	-SBu	0 %
17	-O^{i}Pr	1.1 ± 0.1	**24**	-N^{i}Pr$_2$	45 %	**31**	-N(Me)Bn	0 %
18	-NH^{t}Bu	1.1 ± 0.2	**25**		36 %	-	-	-

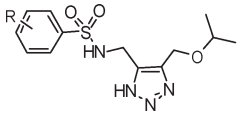
Table 3. SAR of Triazolylmethyl Arylsulfonamides with Respect to the C-4 Methyl Substituent

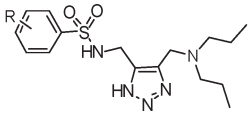


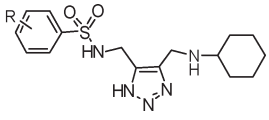


ID	R^1	IC_{50} (μM)	ID	R^1	R^2	IC_{50} (μM)	ID	R^1	R^2	IC_{50} (μM)
32	−NHadamantyl	0.12 ± 0.01	**2**	−O^{i}Pr	−I	0.29 ± 0.03	**11**	−OBu	−I	5.2 ± 0.70
33	−NHcyclohexyl	0.13 ± 0.01	**17**	−O^{i}Pr	−Cl	1.1 ± 0.1	**22**	−OBu	−Cl	18.9 ± 6.00
34	−NHpyrrolidine	0.19 ± 0.01	**3**	−O^{t}Bu	−I	1.1 ± 0.3	**6**	−OMe	−I	7.3 ± 1.9
35	−O^{i}Pr	0.85 ± 0.07	**19**	−O^{t}Bu	−Cl	1.4 ± 0.1	**23**	−OMe	−Cl	21 ± 5

Table 4. SAR of Triazolylmethyl Arylsulfonamides with Varying Aromatic Substituents







ID	R	IC_{50} (μM)	ID	R	IC_{50} (μM)	ID	R	IC_{50} (μM)
2	4-I	0.29 ± 0.03	**41**	2,5-dichloro-	0.10 ± 0.01	**44**	2,5-dichloro-	0.07 ± 0.003
36	2,5-dichloro-	0.61 ± 0.09	**42**	4-OMe	0.33 ± 0.03	**45**	3,4-dichloro-	0.07 ± 0.007
35	4-H	0.85 ± 0.07	**14**	4-Cl	0.45 ± 0.02	**34**	4-H	0.13 ± 0.01
17	4-Cl	1.10 ± 0.10	**43**	4-F	1.03 ± 0.003	**13**	4-Cl	0.39 ± 0.02
37	4-Br	1.10 ± 1.00						
38	4-NHAc	30%						
39	4-CF$_3$	4.3%						
40	4-^{t}Bu	0%						

2,5-dichlorobenzenesulfonyl series. Compounds **44** and **47** only differ by replacement of nitrogen by oxygen and clearly demonstrate a 20-fold improvement in potency of the amino over the alkoxy derivative.

To ascertain the biochemical selectivity for this chemical class, all compounds reported here were tested against another class B1 MBL, IMP-1. Because VIM-2 and IMP-1 show considerable sequence divergence in their active sites

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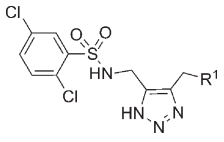
Table 5. SAR of Triazolylmethyl 2,5-Dichlorobenzenesulfonamides with Respect to the C-4 Methyl Substituent



ID	R^1	IC_{50} (μM)	ID	R^1	IC_{50} (μM)	ID	R^1	IC_{50} (μM)
44	−NHcyclohexyl	0.07 ± 0.003	**41**	$-NPr_2$	0.10 ± 0.01	**47**	−Ocyclohexyl	1.40 ± 0.50
46	−NHadamantyl	0.07 ± 0.01	**36**	$-O^iPr$	0.61 ± 0.09			

Table 6. Results of K_i and MIC Potentiation Studies

					imipenem MIC (μg/mL)		
ID	R_1	R_2	K_i(μM)[a]	mechanism[b]	50 μM[c]	20 μM[c]	10 μM[c]
46	−NHadamantyl	2,5-Cl	0.01 ± 0.002	C	0.617	0.617	1.851
45	−NHcyclohexyl	3,4-Cl	0.02 ± 0.002	C	0.617	0.617	0.617
41	−NHdipropyl	2,5-Cl	0.02 ± 0.004	C	0.617	0.617	1.851
44	−NHcyclohexyl	2,5-Cl	0.03 ± 0.003	C	0.617	0.617	1.851
33	−NHcyclohexyl	H	0.03 ± 0.01	C	0.617	0.617	1.851
34	−NHpyrrolidine	H	0.03 ± 0.004	C	0.617	0.617	1.851
42	−NHdipropyl	methoxy	0.06 ± 0.01	M	0.617	0.617	1.851
15	−Nindoline	Cl	0.06 + 0.01	C	0.617	0.617	1.851
12	−NHPh	Cl	0.08 ± 0.01	C	0.617	1.851	1.851
32	−NHadamantyl	H	0.01 + 0.001	C	0.617	0.617	1.851
14	−NHdipropyl	Cl	0.12 + 0.03	C	0.617	1.851	1.851
47	−Ocyclohexyl	2,5-Cl	0.17 ± 0.02	C	0.617	1.851	1.851
18	−NH*t* butylamino	Cl	0.18 + 0.03	C	0.617	0.617	1.851
13	−NHcyclohexyl	Cl	0.04 ± 0.01	C	0.617	0.617	1.851

[a] K_i values were calculated by nonlinear regression (hyperbolic equation) using GraphPad Prism. [b] C = competitive inhibition, and M = mixed inhibition. [c] Inhibitor concentration used in the potentiation assay.

(33% overall sequence identity), the arylsulfonyltriazoles were not expected to inhibit both enzymes unless behaving through promiscuous mechanisms. Indeed, all 47 compounds were inactive against IMP-1.

Docking studies with **44**[12] suggest that this inhibitor binds to VIM-2 in the same mode as was predicted for the parent, **1**, which is described elsewhere.[10] SAR studies show that the best inhibitors (i.e., **41** and **44**−**46**) display hydrophobic groups at the C-4 methyl substituent of the triazole. Our docking and modeling studies have identified a cavity that can accommodate a compact hydrophobic group such as adamantyl or cyclohexyl.[10,12] Consistent with SAR findings, smaller triazole appendages cannot take full advantage of this cavity, while groups larger or more extended than adamantyl would be detrimental to binding due to steric clashes.

Currently, only *p*CMB, a slowly reversible/irreversible VIM-2 inhibitor, has been shown to have a synergistic effect with β-lactam antibacterials in VIM-2-expressing bacteria.[10] However, this cysteine-reactive reagent is known to have several off-target activities, lessening its value for mechanistic studies. To demonstrate potentiation by the arylsulfonyltriazoles in bacteria, we assessed the ability of these compounds to affect the growth of parental (BL21) and VIM-2-transformed (BL21/VIM-2) *Escherichia coli*, in the presence or absence of a carbapenem, imipenem. Relative to the parental (BL21) strain, the MIC (minimum inhibitory concentration) for imipenem increased approximately 9-fold when cells were transformed with the VIM-2-encoding plasmid (imipenem MIC = 0.21 μg/mL in BL21 vs imipenem MIC = 1.85 μg/mL in BL21/VIM-2). This decrease in antibacterial potency reflects the ability of VIM-2 to degrade imipenem. When tested at 50 μM, 14 of the 47 arylsulfonyltriazoles potentiated imipenem and consequently were tested at lower doses (Table 6). Compound **45**, with the best potentiation, improved the MIC of imipenem by 3-fold from 1.85 to 0.617 μg/mL at 10 μM (Table 6). To ascertain whether this class of inhibitor can fully potentiate imipenem, compound **45** was tested at higher concentrations. Indeed, the MIC for imipenem was fully restored to that observed for the parental strain (i.e., lacking VIM-2) when **45** was tested at 150 μM. Furthermore, in parental (BL21) cells, the MIC for imipenem was unaffected by the presence of **45** as high as 150 μM. It was also established that none of these 14 compounds exhibited intrinsic antibacterial activity since *E. coli* cell growth was unaffected when they were tested at 150 μM.

The mechanism of inhibition for the 14 VIM-2 inhibitors active at 50 μM in VIM-2-expressing *E. coli* was further evaluated through kinetic studies (Table 6). The best inhibitors

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exhibited K_i values as low as 10 nM (i.e., **46**), and all but one exhibited classical competitive inhibition and hence bind at the active site. Only **42** exhibits a mixed mode of inhibition with features of both competitive and noncompetitive inhibition. While inhibition kinetics for **42** are somewhat different as compared to the other 13 compounds, a competitive inhibition component still suggests that binding of **42** occurs at the active site.

In conclusion, the fidelity and robustness of the Banert cascade have been used to rapidly assemble an NH-1,2,3-triazole library from diverse arrays of highly functionalized fragments. Medicinal chemistry efforts progressed via three iterative steps and resulted in the synthesis of 320 unique compounds. The starting compound exhibited moderate biochemical potency toward VIM-2 while being inactive toward IMP-1. Substitution at the arylsulfonamide produced subtle improvements in potency. On the other hand, analogues bearing amino substitution on the C-4 methyl of the triazole generated highly potent VIM-2 inhibitors that potentiate imipenem antibacterial activity. The best inhibitors exhibit as much as 40-fold increase in potency in biochemical assays over **1** and represent the most potent VIM-2 inhibitors to date. Furthermore, these are the first reported inhibitors to be active against VIM-2 in bacteria (*E. coli*), with no apparent off-target effects.

SUPPORTING INFORMATION AVAILABLE Method of enzyme inhibition, microbial inhibition, docking studies, and synthetic procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See the Supporting Information for docking studies with compound **44**.

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