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# Diaryl-Substituted Azolylthioacetamides: Inhibitor Discovery of New Delhi Metallo-β-Lactamase-1 (NDM-1)

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The emergence and spread of antibiotic-resistant pathogens is a global public health problem. Metallo-\beta-lactamases (MBLs) such as New Delhi MBL-1 (NDM-1) are principle contributors to the emergence of resistance because of their ability to hydrolyze almost all known  $\beta$ -lactam antibiotics including penicillins, cephalosporins, and carbapenems. A clinical inhibitor of MBLs has not yet been found. In this study we developed eighteen new diaryl-substituted azolylthioacetamides and found all of them to be inhibitors of the M $\beta$ L L1 from Stenotrophomonas maltophilia ( $K_i < 2 \mu M$ ), thirteen to be mixed inhibitors of NDM-1 ( $K_i < 7 \mu M$ ), and four to be broad-spectrum inhibitors of all four tested MBLs CcrA from Bacteroides fragilis, NDM-1 and ImiS from Aeromonas veronii, and L1 ( $K_i < 52 \mu M$ ), which are representative of the B1a, B1b, B2, and B3 subclasses, respectively. Docking studies revealed that the azolylthioacetamides, which have the broadest inhibitory activity, coordinate to the  $Zn^{II}$  ion(s) preferentially via the triazole moiety, while other moieties interact mostly with the conserved active site residues Lys224 (CcrA, NDM-1, and ImiS) or Ser221 (L1).

Antibiotic resistance is an emerging worldwide epidemic,<sup>[1]</sup> and  $\beta$ -lactamases are the most significant threat to the continued use of  $\beta$ -lactam antibiotics.<sup>[2]</sup> There have been more than 1000 distinct  $\beta$ -lactamases identified, and these enzymes have been categorized into classes A–D, based on their primary sequence homologies.<sup>[3]</sup> Class A, C, and D enzymes are collectively called serine  $\beta$ -lactamases, which use an active site serine as a nucleophile. Class B enzymes are called metallo- $\beta$ -lactamases (M $\beta$ Ls), and these enzymes use either one or two equivalents of Zn<sup>II</sup> to catalyze  $\beta$ -lactam hydrolysis.<sup>[4]</sup> M $\beta$ Ls have been further divided into subclasses B1–B3, based on primary sequence homologies and Zn<sup>II</sup> content,<sup>[3–5]</sup> and separation of the B1 subclass into B1a (all B1 enzymes but NDM-1) and B1b (NDM-1) was recently

suggested owing to significant sequence diversity.<sup>[6]</sup> The emergence of NDM-1 heralds a new era of antibiotic resistance because of this enzyme's ability to hydrolyze almost all known βlactam-containing antibiotics and the rapid spread of the plasmid-encoded NDM-1 gene.<sup>[7]</sup> Bacteria harboring the NDM-1 gene are not susceptible to any common antibiotics, except colistin and tigecycline, because they contain multiple antibiotic resistance genes.<sup>[8]</sup> Both B1- and B3-subclass enzymes contain two Zn<sup>II</sup> ions and have broad-spectrum substrate profiles that include penicillins, cephalosporins, and carbapenems. Subclass-B1 enzymes have been found in strains of Bacillus, Bacteroides, Pseudomonas, Serratia, and Chryseobacterium, and subclass-B3 enzymes in strains of Stenotrophomonas, Legionella, Fluoribacter, Janthinobacterium, and Caulobacter.<sup>[9,10]</sup> In contrast, the B2-subclass enzymes contain only one Zn<sup>II</sup> ion and primarily hydrolyze carbapenems, which have been called one of the "last resort" antibiotics.<sup>[11]</sup> The co-administration of  $\beta$ lactam antibiotics with  $\beta$ -lactamase inhibitors has proven to be an effective strategy for combating antibiotic-resistant bacterial infections,<sup>[12]</sup> but  $\beta$ -lactamase inhibitors such as clavulanate, sulbactam, and tazobactam do not inhibit MBLs, and there are no clinically useful inhibitors of MBLs yet available.<sup>[13]</sup> Consequently, there is a pressing need for broad-spectrum  $M\beta L$  inhibitors.

Given the enormous biomedical importance of MBLs, there has been a large amount of effort in identifying novel inhibitors of these enzymes.<sup>[12,14]</sup> The succinic acid derivatives,<sup>[15a]</sup> Dcaptopril,<sup>[15b]</sup> thiomandelic acid,<sup>[15c]</sup> picolinic acid,<sup>[15d]</sup> hydroxamic acid derivatives,<sup>[15b]</sup> propionic acid,<sup>[15e]</sup> penicillin-based inhibitors, [15f] N-arylsulfonyl hydrazones, [15b] and pyrrole-based inhibitors have recently been reported.[15g] However, most of these reports involved studies on one or two of the MBLs, and to the best of our knowledge, only three classes of sulfur compounds—thiols,<sup>[15b,c]</sup> thiophosphonates,<sup>[15h]</sup> and analogues of penams<sup>[2]</sup>—have been reported to be broad-spectrum inhibitors of the MBLs. Our research group has been engaged in the synthesis and development of MBL inhibitors. We recently developed thioazoles which show inhibitory activity against MBLs with K<sub>i</sub> values in the micromolar range.<sup>[16]</sup> Based on this information we decided to develop new diaryl-substituted azolylthioacetamides by conjugation of the thioazoles with arylacetamide in an attempt to find broad-spectrum inhibitors of MBLs. Eventually, these compounds could be used in drug/inhibitor combinations to combat bacterial infections.

Toward this goal, 18 diaryl-substituted azolylthioacetamides were synthesized as shown in Supporting Information Scheme S1 and characterized by NMR and MS. The structures

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Figure 1. Structures of the synthesized diaryl-substituted azolylthioacetamides as potential broad-spectrum inhibitors of metallo- $\beta$ -lactamases.

of the synthesized compounds are shown in Figure 1. Briefly, arylcarboxylates were prepared by esterifying aromatic carboxylic acids and converting them into hydrazides by condensing with hydrazine. The hydrazides reacted with NH<sub>4</sub>SCN or CS<sub>2</sub> under basic conditions to give aroylthiourea or aroyldithiocarbazates, respectively.<sup>[17]</sup> The dithiocarbazates were treated with cold concentrated sulfuric acid to give 2-thio-1,3,4-thiadiazoles, which were held at reflux with potassium hydroxide to afford 2-thio-1,3,4-oxadiazoles,<sup>[18]</sup> and the thiourea was stirred with potassium hydroxide at reflux to afford 2-thio-1,3,4-triazoles.<sup>[19]</sup> N-Benzothiazolyl-2-chloroacetamide and N-phenyl-2-chloroacetamide were prepared as previously reported<sup>[20]</sup> and crosslinked with the thiadiazoles, oxadiazoles, and triazoles under various basic conditions to give the diaryl-substituted azolylthioacetamides 1-18 (detailed synthetic procedures are available in the Supporting Information).

To test whether compounds **1–18** are inhibitors or even broad-spectrum inhibitors of the M $\beta$ Ls, the following representative enzymes from the distinct M $\beta$ L subclasses were chosen for evaluation: CcrA (B1a), NDM-1 (B1b), ImiS (B2), and L1 (B3). The data listed in Table 1 summarize  $K_i$  values and modes of inhibition for the azolylthioacetamides.

The azolylthioacetamides **2**, **4**, **5**, and **7** were found to be broad-spectrum inhibitors of all four M $\beta$ Ls tested, exhibiting  $K_i$  values < 16  $\mu$ M, except **5** against CcrA with a  $K_i$  value of 52  $\mu$ M. Compound **4** exhibited the strongest inhibition against L1 with a  $K_i$  value of 73 nM. Presumably, these compounds exhibit greater inhibition of CcrA, NDM-1, and L1 than ImiS, because the former three enzymes contain two Zn<sup>II</sup> ions as opposed to a single Zn<sup>II</sup> ion, as in ImiS. Compound **10** was found to be a very potent inhibitor ( $K_i$  values < 2  $\mu$ M) of all tested enzymes except CcrA, which is clinically not very important.

All azolylthioacetamides **1–18** showed significant inhibitory activity against L1, with  $K_i$  values  $< 2 \,\mu$ M. We tested the intermediates arylthiazolyl-, aryloxazolyl-, and aryltriazolylthiols as inhibitors of L1, but these compounds exhibited no inhibitory activity. It is possible that the thiol groups on the compounds

Compd	<i>К</i> <sub>і</sub> [µм]			
	B1a, CcrA <sup>[a]</sup>	B1b, NDM-1 <sup>[a]</sup>	B2, ImiS <sup>[b]</sup>	B3, L1 <sup>[a]</sup>
1	$6.3 \pm 0.1$	$0.35\pm0.01$	> 300	$0.25\pm0.03$
2	$7\pm1$	$6.1\pm0.2$	$15\pm2^{[c]}$	$0.65\pm0.09$
3	-	$0.81\pm0.07$	-	$1.8\pm0.1$
4	$0.30\pm0.09$	$0.43\pm0.03$	$2.2\pm0.2$	$0.073 \pm 0.00$
5	$52\pm5$	$0.60\pm0.07$	$3.3\pm0.2^{\text{[d]}}$	$0.34 \pm 0.02$
6	-	$0.64 \pm 0.03$	>300	$0.51\pm0.03$
7	$8.5\pm0.2$	$5.6\pm0.1$	$0.75\pm0.02$	$0.34 \pm 0.05$
8	-	$45\pm 6$	$1.10 \pm 0.03$	$0.82\pm0.08$
9	-	$6.8\pm0.4$	>300	$0.33\pm0.02$
10	-	$0.42\pm0.02$	$1.3\pm0.4$	$0.25\pm0.04$
11	-	$0.23\pm0.01$	>300	$0.43\pm0.09$
12	-	$1.2\pm0.1$	-	$0.38\pm0.02$
13	-	$5.3\pm0.3$	>300	$0.86\pm0.09$
14	-	-	-	$1.0\pm0.1$
15	-	-	-	$1.4\pm0.4$
16	-	$4.3\pm0.3$	>300	$0.54\pm0.04$
17	-	-	-	$0.51\pm0.04$
18	-	-	-	$0.39\pm0.06$

**Table 1.** Inhibition constants of metallo-β-lactamases by diaryl-substitut-

interact with the cysteine residues to form a disulfide bridge in L1 rather than binding to the active site.<sup>[21]</sup>

inhibition. [d] Uncompetitive inhibition; -: no inhibition.

Recently, structural and mechanistic studies on NDM-1 have been reported,<sup>[5, 22a-d]</sup> but no tight-binding inhibitors of the enzyme have been reported to date. In this work, we found the azolylthioacetamides **1–13** and **16** to be inhibitors of NDM-1, exhibiting  $K_i$  values  $< 7 \,\mu$ M, except **8**, with a  $K_i$  value of 45  $\mu$ M. However, **14**, **15**, **17**, and **18** had no inhibition observed against CcrA, NDM-1, and ImiS, whereas they showed  $K_i$  values  $< 2 \,\mu$ M against L1, suggesting the 2-(3-pyridyl)-1,3,4-thiadiazolyl and 2-(3-pyridyl)-1,3,4-oxadiazolyl moieties on the compounds may play an important role in selecting B3-subclass enzymes.

Inhibition of ImiS was also observed, and the most potent inhibitors were **2**, **4**, **5**, **7**, **8**, and **10**, exhibiting  $K_i$  values  $< 15 \,\mu$ m. Compounds **1**, **2**, **4**, **5**, and **7** were found to be inhibitors of CcrA, with  $K_i$  values  $< 10 \,\mu$ m. It is not clear why **3**, **6**, **8**–**13**, and **16** inhibited NDM-1 and L1, but not CcrA, although these three enzymes are all dinuclear M $\beta$ Ls.

To assess the inhibition mode of these compounds, steadystate kinetic studies were conducted with CcrA, NDM-1, ImiS, and L1. Azolylthioacetamides **1–18** yielded Lineweaver–Burk plots that indicate mixed inhibition of the binuclear M $\beta$ Ls CcrA, NDM-1, and L1. For the mononuclear M $\beta$ L ImiS, compounds **4**, **7**, **8**, and **10** exhibited mixed inhibition, whereas **2** and **3** showed noncompetitive and uncompetitive inhibition, respectively. Inhibitor **4** was taken as an example to show its inhibition mode against NDM-1 and L1 as representative M $\beta$ Ls (Figure 2).

For docking calculations we focused on triazole **4**, which inhibited all tested enzymes, and **10**, which inhibited all enzymes but CcrA (computational details along with more detailed re-

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**Figure 2.** Lineweaver–Burk plots of inhibition of a) NDM-1- and b) L1-catalyzed hydrolysis activity by *N*-phenyl-5-(2-phenolyl-1,3,4-triazolyl)thioacetamide **4.** Cefazolin was used as substrate of NDM-1 and L1. Data points show inhibitor **4** concentrations of 0 (**■**), 0.625 ( $\square$ ), 1.25 (**▼**), and 2.50 µM ( $\bigtriangledown$ ).

sults and discussion are available in the Supporting Information). In summary, docking calculations were carried out as previously described<sup>[23]</sup> using the program AutoDock 4.2,<sup>[24]</sup> treating the enzyme as a rigid receptor and the synthesized compounds as flexible ligands. Fifty conformations were generated for each enzyme-inhibitor complex and analyzed under consideration of clustering and binding energies. We assume that inhibition is indeed due to compounds binding to the active site rather than depriving them of Zn<sup>II</sup> ions, because these enzymes bind Zn<sup>II</sup> tightly, and Zn<sup>II</sup> was provided in excess (50 µм) in the assay buffer. In the mononuclear CphA-4 and CphA-10 complexes, the triazole coordinated Zn2, just like the nitrogen atom derived from  $\beta$ -lactam hydrolysis<sup>[25]</sup> (Figure S1). In addition, the 2-phenolyl hydroxy group in 4 interacted with Lys224 (BBL standard numbering<sup>[26]</sup> is used throughout), and the amide carbonyl in 10 interacted with Asn233 (Figures S1 A and S1B). The former interaction is usually made by the C3/C4 carboxylate in penicillins and carbapenems/cephalosporins (Figure 3 c and Figure S1 C),<sup>[21d, 24]</sup> while the latter is reminiscent of the interaction between the  $\beta$ -lactam carbonyl group and Asn233.<sup>[27,28]</sup> In the binuclear complexes of CcrA, NDM-1, and L1 with deprotonated triazoles (see Supporting Information for rationale and details), the triazole coordinated the two Zn<sup>II</sup> ions, and the N-phenylthioacetamide moiety of 4 and 10 either bound to the R<sup>1</sup> or R<sup>2</sup> binding site with the 2-phenolyl (4) or 4-pyridyl (10) moiety binding to the other site, respectively (Figure 3 a,b). The interaction of the triazole with the Zn<sup>II</sup> ions resembles the binding mode of a biphenyl tetrazole inhibitor of CcrA.<sup>[29]</sup> Conformations in which the N-phenylthioacetamide bound to the R<sup>1</sup> binding pocket (Figure 3a) closely resemble hydrolyzed benzylpenicillin found in a crystal structure of NDM-1<sup>[22d]</sup> (Figure 3c), with the 2-phenolyl hydroxy group of 4 adopting the role of the C3 carboxylate to interact with Lys244 in CcrA (Figure S1D) and NDM-1<sup>[22d]</sup> (Figure 3a) and Ser221 in L1<sup>[30]</sup> (Figures S1E and S1F). The presence of the hydroxy group in 4 could explain why it inhibits CcrA if it interacts with Lys224, but 10 does not. However, both 4 and 10 efficiently bind to NDM-1 and L1, and we can currently not explain this difference in binding.



**Figure 3.** a), b) Two different low-energy conformations of **4** docked into NDM-1 (PDB code: 4EYL) with binding energies of -8.8 and -9.2 kcal mol<sup>-1</sup>, respectively. c) Crystal structure of a complex between NDM-1 and hydrolyzed benzylpenicillin (PDB code: 4EYF). The backbone of the enzyme is depicted as a green ribbon. Compound **4**, hydrolyzed benzylpenicillin, and key protein residues are shown as sticks (H, white; C, gray; N, blue; O, red; S, yellow). The backbone of Gln123 (BBL numbering Gln119, the side chain points to the left, away from the active site) and the side chain of Lys211 (BBL numbering Lys224) are shown. Zinc ions are shown as magenta spheres; the lower (front) one is Zn1 and the upper (back) one is Zn2.

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### **Experimental Section**

Synthetic procedures, <sup>1</sup>H and <sup>13</sup>C NMR data and physical properties of inhibitors, biochemical procedures, inhibition studies. and docking calculations are provided in the Supporting Information.

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Diaryl-Substituted Azolylthioacetamides: Inhibitor Discovery of New Delhi Metallo-β-Lactamase-1 (NDM-1) New inhibitors for NDM-1: Azolylthioacetamides 1–18 were obtained and all of them were found to be inhibitors of metallo-β-lactamases (MβLs) L1 ( $K_i < 2$ µM). Compounds 1–7, 9–13, and 16 are mixed inhibitors of NDM-1 ( $K_i < 7$  µM), and 2, 4, 5, and 7 are broad-spectrum inhibitors of all four tested M $\beta$ Ls: CcrA, NDM-1, ImiS, and L1 ( $K_i < 52 \ \mu$ M). Docking studies revealed that **4** and **10** coordinate to the Zn<sup>II</sup> ion(s) via the triazole moiety, while other moieties interact with the conserved active site residues Lys224 or Ser221.