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# Heterocyclic methylsulfone hydroxamic acid LpxC inhibitors as Gram-negative antibacterial agents

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#### ABSTRACT

The synthesis and antibacterial activity of heterocyclic methylsulfone hydroxamates is presented. Compounds in this series are potent inhibitors of the LpxC enzyme, a key enzyme involved in the production of lipopolysaccharide (LPS) found in the outer membrane of Gram-negative bacteria. SAR evaluation of compounds in this series revealed analogs with potent antibacterial activity against challenging Gramnegative species such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*.

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As resistance to existing antibiotic treatments for hospital acquired Gram-negative bacterial infections becomes more prevalent, the need to develop medicines which target these bacteria is increasingly urgent.<sup>1</sup> Of particular concern are infections caused by Pseudomonas aeruginosa (Pae), Klebsiella pneumoniae (Kpn) and Acinetobacter baumannii (Aba), which all show resistance to standard treatments such as ciproflaxacin and aztreonam,<sup>2,3</sup> and highlight the need for new agents which inhibit novel antibacterial targets and pathways.<sup>4</sup> LpxC (UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase) is an enzyme present in all Gram-negative bacteria and plays a crucial role in the pathway leading to the construction of Lipid A.<sup>5</sup> Lipid A is a component of the outer membrane of Gram-negative bacteria, without which, bacteria have increased susceptibility to anti-bacterial agents.<sup>6</sup> Indeed, in Pae it has been shown that LpxC activity is essential for growth and that inactivation of the LpxC gene suppresses bacterial growth.<sup>7</sup> The LpxC enzyme therefore represents an attractive target for the development of a new class of antibiotics.

Numerous inhibitors of LpxC have been reported since the discovery of this enzyme target, although none of these inhibitors have yet successfully progressed through clinical trials.<sup>8</sup> We have

\* Corresponding author. Tel.: + 1 860 715 0346. E-mail address: laura.mcallister@pfizer.com (L.A. McAllister). recently reported sulfone hydroxamic acid compounds **1** and **2** (Fig. 1) as potent inhibitors of LpxC, with excellent whole cell activity in *Pseudomonas* strains.<sup>9</sup> Compound **2** has an impressive minimum inhibitory concentration (MIC) of 0.5  $\mu$ g/ml in the wild-type, efflux pump competent, *Pseudomonas* strain PAO1, and shows favorable physicochemical properties for further development as an intravenous antibiotic. X-Ray co-crystal structures of compounds in this class with the *Pseudomonas aeruginosa* LpxC enzyme revealed the key structural features which are crucial to their potency; a hydroxamic acid head group binds to the zinc atom in the active site; a methyl sulfone moiety where the oxygen atom makes a hydrogen-bonding interaction with a lysine residue (Lys238); and a hydrophobic tail group which interacts with a hydrophobic tunnel in the enzyme. As part of our program to find



Figure 1. Methylsulfone hydroxamate LpxC inhibitors.

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 Table 1

 SAR of 5-membered heterocyclic methylsulfone hydroxamic acids



Compound	nd R <sup>1</sup> Pae LpxC IC <sub>50</sub> (nM)			MIC (µg/ml)			
			PA-7	PA-3060	PA-3919	PAO1	
1		1.4	1	1	0.008	0.125	
2	C C N	3.6	1	2	0.06	0.05	
3a	ON SA	0.511	0.5	1	<0.06	0.5	
3b	N <sup>N</sup> N <sup>A</sup>	0.85	2	4	0.03	1	
3c	N N X	1.61	1	2	0.015	0.5	
3d	N <sup>o</sup>	3.02	1	2	<0.06	0.5	
<b>3e</b> <sup>a</sup>		3.00	16	32	0.5	8	
3f <sup>a</sup>		13.5	32	64	0.5	8	
3g <sup>a</sup>	N N NH	>100	>64	>64	64	>64	
3h <sup>a</sup>		>100	32	>64	0.5	16	
<b>3i</b> <sup>a</sup>	NN	>100	>64	>64	4	>64	
<b>3j</b> <sup>a</sup>	N N N	>100	32	64	0.5	32	

<sup>a</sup> Racemic compound tested.



Scheme 1. (a) (i) 4-Bromo-1-butene, Cs<sub>2</sub>CO<sub>3</sub>, THF; (ii) NalO<sub>4</sub>, OsO<sub>4</sub>, pyridine; (b) NH<sub>2</sub>OH·HCl, Na<sub>2</sub>CO<sub>3</sub>, EtOH; (c) Phenylacetylene, NaOCl, CH<sub>2</sub>Cl<sub>2</sub>; (d) LiOH, THF-H<sub>2</sub>O; (ii) THP-hydroxylamine, CDMT, NNM, 2-MeTHF; (iii) HCl, EtOH; (e) Cs<sub>2</sub>CO<sub>3</sub>, THF.



Scheme 2. (a) (i) Cs<sub>2</sub>CO<sub>3</sub>, DMF, 60 °C; (b) (i) LiOH, THF-H<sub>2</sub>O; (ii) THP-hydroxylamine, CDMT, NNM, 2-Me THF; (iii) HCl, EtOH (c) NaN<sub>3</sub>, DMF; (d) (i) Phenylacetylene, CuSO<sub>4</sub>, sodium ascorbate, EtOH-H<sub>2</sub>O; (ii) HCl, EtOH.



Scheme 3. (a) Benzaldehyde oxime, NaOCl, CH<sub>2</sub>Cl<sub>2</sub>; (b) (i) LiOH, THF-H<sub>2</sub>O; (ii) THP-hydroxylamine, CDMT, NNM, 2-MeTHF; (ii) HCl, EtOH (c) PhN<sub>3</sub>, Cul, dimethylcyclohexaadimine sodium ascorbate, DMSO/H<sub>2</sub>O (5:1).

improved LpxC inhibitors in this series, we undertook a body of work investigating the effects of replacing the central pyridone ring in **2** with 5-membered heterocycles. We aimed to improve parameters such as potency and antibacterial spectrum over lead compounds in the sulfone hydroxamate series. In addition, we hoped to improve fraction unbound in plasma, which is a crucial



Scheme 4. (a) CDI, Acetophenone, THF; (b) NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O, EtOH, 70 °C; (c) (i) LiOH, THF-H<sub>2</sub>O; (ii) THP-hydroxylamine, CDMT, NNM, 2-MeTHF; (iii) HCl, EtOH; (d) Pyridine, reflux.

Table 2 Triazole SAR



Compound	R <sup>1</sup>	Pae LpxC IC <sub>50</sub> (nM)	MIC (µg/ml)			
			PA-7	PA-3060	PA-3919	PAO1
3b		0.85	2	4	0.03	1
25a	CI	0.657	1	1	0.008	0.5
25b		0.912	2	2	0.06	2
25c	MeOF	1.2	2	4	0.06	2
25d		1.39	4	8	0.125	2
25e	CI CI	1.67	2	2	<0.06	1
25f	FF	1.87	4	4	0.06	4
25g		1.95	4	4	<0.06	2
25h	MeOCI	4.71	8	8	0.125	8
25i	F F	8.08	4	8	0.125	4

component in achieving the necessary free AUC exposures for efficacy, especially in an intraveneously administered drug that is predicted to have high clearance.<sup>10</sup>

We began by replacing the central ring of **1** and **2** with 5-membered heterocycles and assessed the potency of these analogs in a Pseudomonas aeruginosa LpxC enzyme assay (Table 1, compounds **3a–3j**). In addition, we examined MIC values in a few representative *Pseudomonas* strains to assess whole cell activity. PA-3919 is a multi efflux pump knockout strain which is used to assess whether the compound of interest is a substrate for these pumps.<sup>11</sup>

# Table 3

# Isoxazole SAR



Compound	$\mathbb{R}^1$	Pae LpxC IC <sub>50</sub> (nM)	MIC (µg/ml)				
			PA-7	PA-3060	PA-3919	PAO1	
3a	And	0.511	0.5	1	<0.06	0.5	
26a	MeO	2.32	0.5	1	0.125	0.5	
<b>26b</b> <sup>a</sup>	CI	2.66	ND <sup>b</sup>	2	0.06	$ND^{b}$	
<b>26c</b> <sup>a</sup>	F	6.75	ND <sup>b</sup>	4	<0.06	ND <sup>b</sup>	
<b>26d</b> <sup>a</sup>	C F	8.31	2	2	0.060	1	
3d		3.02	1	2	<0.06	0.5	
<b>27a</b> <sup>a</sup>	Me	2.93	2	2	<0.06	1	
27b	MeOF	4.4	2	2	<0.06	1	
27c	F OMe	5.32	4	8	<0.06	2	
<b>27d</b> <sup>a</sup>	F F	6.81	2	4	<0.06	2	

<sup>a</sup> Racemic compound tested.

<sup>b</sup> Not determined.

PAO1 and PA-7 are common strains with fully functioning efflux pumps. In addition, MICs were measured against PA-3060, which is a quinolone resistant Pseudomonas strain. As previously observed for this class of LpxC inhibitors, a Pae  $IC_{50}$  value of less than 5 nM is generally required to observe meaningful antibacterial activity. Isoxazole isomers **3a** and **3d** emerged as potent LpxC inhibitors with sub-nanomolar IC<sub>50</sub>s in LpxC and impressive MICs (both with PAO1 =  $0.5 \,\mu g/ml$ ). MICs at PA-7 and PA-3060 show the heteroatom arrangement in **3a** to be slightly more favorable than that in 3d. This is also reflected in their relative Pae IC50 values. Pyrazole 3c showed comparable enzyme potency MICs at PAO1 to the isoxazoles 3a and 3d. Triazole 3b was half as potent as 3c across all Pseudomonas strains, possibly as a result of increased polarity in the hydrophobic tunnel of the enzyme creating unfavorable interactions. Linking the terminal phenyl ring through the N-atom of the heterocycle, as in **3e** and **3f**, is disfavored; resulting in an increase in MIC vs PAO1 (8 µg/ml). Similarly, it appears that the presence of heteroatoms on opposing sides of the central heterocyclic ring, such as in **3h** and **3j**, and the presence of hydrogen bond donors (analogs **3i** and **3g**) results in a dramatic fall off in potency.

A diverse array of chemistry was employed to access the heterocyclic systems evaluated in Table 1. A general outline of synthetic routes to compounds 3a-3j is described in Schemes 1-4. Compounds 3a, 3f and 3g can be accessed from sulfone ester intermediate 4 (Scheme 1). Alkylation of 4 with bromobutene, followed by oxidative cleavage, yielded aldehyde 5. Aldehyde 5 was condensed with hydroxylamine, and then converted to oxazole **7** by an in situ oxidation to the nitrile oxide, and subsequent cycloaddition onto phenylacteylene. Conversion of ester 7 to the hydroxamic acid 3a was achieved through hydrolysis to the acid, CDMT promoted coupling to O-THP protected hydroxylamine, followed by acid catalyzed removal of the THP group. Pyrazole 3f and triazole 3g can be obtained by alkylation of 4 with the appropriate iodide intermediates 8 and 10 respectively, followed by conversion of the ester to the hydroxamate using our standard protocol (Scheme 2). Pyrazole 3c and triazoles 3b and 3j can be obtained from bromide interme-

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Compound		MIC 90 (µg/ml)			LogD (pH 7.4)	c Log D	Mwt	hFu
	Pae	Eco	Kpn	Aba				
1	4	2	16	32	2.24	2.17	347	0.02
<b>2</b> <sup>a</sup>	2	8	16	32	0.8	0.51	364.4	0.14
3a <sup>a</sup>	2	4	32	>32	1.31	0.61	338.4	0.016
3d <sup>a</sup>	2	1	4	>32	0.99	-0.14	338.4	0.013
3c <sup>b</sup>	4	32	>64	>256	1.04	0.67	337.4	0.048
<b>25a</b> <sup>a</sup>	2	1	2	>32	1.34	0.54	390.8	ND <sup>d</sup>
<b>25c</b> <sup>a</sup>	4	16	>32	>32	1.36	0.61	386.4	0.085
27b <sup>c</sup>	4	4	8	32	1.23	0.98	386.4	0.072

Table 4							
MIC90s, LogD	measured a	and calculated)	, Mwt,	and	free fraction	of selected	analogs

<sup>a</sup> Pae, Kpa (*n* = 22), Eco,Aba (*n* = 11).

<sup>b</sup> Pae (*n* = 51), Eco, Kpn, Aba (*n* = 11).

<sup>c</sup> Pae (*n* = 22), Kpa (*n* = 21),Eco (*n* = 11) Aba (*n* = 10).

<sup>d</sup> Not determined.

diate **12.**<sup>12</sup> Alkylation of phenyl pyrazole **13** with **12** and standard conversion of the ester to the corresponding hydroxamic acid gave 3c. Triazole 3j was obtained similarly by alkylation of phenyltriazole 15 with 12. Treatment of 12 with sodium azide followed by conversion of the ester functionality to THP-protected hydroxamate, resulted in the key azide intermediate 14. Reaction of 14 with phenylacetylene under 'click chemistry'<sup>13</sup> conditions installed the triazole core, then deprotection of the THP group gave the hydroxamic acid 3b. Alkyne intermediate 16 was used to prepare oxazole 3d via cycloaddition chemistry and 3e utilizing 'click chemistry' (Scheme 3). Carboxylic acid 19 was converted to diketone 20 by activation with CDI and addition of acetophenone. Condensation of 20 with hydrazine gave the desired intermediate pyrazole 21 which could be converted to hydroxamic acid 3i (Scheme 4). Similarly, oxadiazole 3j was acquired by conversion of **19** to the acid chloride followed by subsequent reaction with hydroxyamidine **23** to give oxadiazole intermediate **24**.

In view of the promising activity of triazole **3b**, and isoxazoles **3a** and **3d**, we decided to prepare a more focused set of analogs with these heterocyclic cores. Although pyrazole 3c also showed promising activity, further work based on this core is not described here. Previous work on the sulfone hydroxamate series indicated that we could improve potency over compounds 1 and 2, by addition of appropriately positioned substituents (e.g. chloro, fluoro, methoxy) on the terminal phenyl ring. An array of triazole analogs (25a-25i) was prepared, varying the substituents on the terminal phenyl ring (Table 2). We were pleased to find that the 2-fluoro-4-chloro analog 25a had a one dilution improvement in MIC values at PAO1 and PA7, and a fourfold improvement at PA-3060, compared to the simple phenyl analog 3b. Analogs 25b and 25e, both bearing 4-position chloro substituents had comparable activity to the parent unsubstituted compound 3b. Two libraries of isoxazole isomers 26a-26d and 27a-27d were prepared; applying the chemistry detailed in Schemes 1 and 3. The most active compounds from these libraries are shown in Table 3. In this series, activity in the Pae LpxC enzyme assay translated into better MIC values than expected in comparison to the triazoles. For example, 2-fluoro, 4-methoxy compound 26a had equal MIC activity to parent compound **3a** despite  $\sim$ 4.5-fold lower enzyme potency. Notably. isoxazole isomer 27b was much less active than 26a, again suggesting that the latter arrangement of heteroatoms in the oxazole core is preferred. Disappointingly, we did not find a compound with superior potency to the parent in either isoxazole series.

Some of the most active compounds from each series were evaluated in MIC90 panels for activity against a wider spectrum of Gram negative bacteria, including *Escherichia coli*, *Klebsiella pneumonia* and *Acinetobacter baumannii* (Table 4). With the exception of *Acinetobacter baumannii*, we observed excellent MIC90 activity across the species. Isoxazole 3d displayed an impressive MIC90 of 4 µg/ml versus Klebsiella pneumoniae and 1 µg/ml versus E. coli Isoxazole isomer 3a had comparable MIC90 values against Pseudomonas aeruginosa however, Klebsiella and Ecoli activity was more modest, with values of 32  $\mu$ g/ml and 4  $\mu$ g/ml respectively. A particularly impressive spectrum of activity was observed for substituted triazole compound 25a. In addition to an MIC90 value of 1 µg/ml against Pseudomonas aeruginosa, 25a had MIC 90 values of 2 µg/ml versus Klebsiella and 1 µg/ml at Ecoli. These values represent a significant enhancement in antibacterial spectrum compared with pyridone 2. Pyrazole 3c was also tested in MIC 90 panel against all four species but unfortunately it exhibited poorer spectrum than pyridone 2. Surprisingly, some of the 5-membered heterocyclic series compounds in Table 4 had significantly higher measured  $\log D$  values than compound **2** and correspondingly much greater plasma protein binding. We saw some evidence that this high plasma protein binding could be mitigated by addition of substituents on the terminal phenyl ring. Indeed, in fluoro-methoxy substituted triazole **25d** and isoxazole **27b** we observed that fraction unbound in human plasma was increased compared with unsubstituted compounds 3a, 3d and 3c However, these analogs did have somewhat reduced MIC90 values and hFu did not quite match levels observed in pyridone 2. Nonetheless, we were greatly encouraged by the improved Gram-negative antibacterial spectrum observed in the isoxazole and triazole series, which opens avenues for further exploration to enhance free fraction while maintaining the superior spectrum.

In summary, we have explored the SAR of a diverse range of 5membered heterocyclic sulfone hydroxamate LpxC inhibitors. We have identified two promising new series of LpxC inhibitors based upon the triazole and isoxazole cores. In addition to excellent activity against *Pseudomonas*, compounds from these series, such as **3d** and **25a**, display impressive antibacterial spectrum against challenging species such as *Klebsiella*. These compounds represent promising leads for further exploration as antibacterial agents.

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