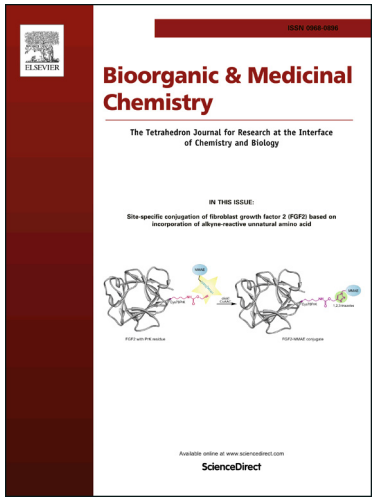
Accepted Manuscript



Synthesis of novel 1,2,5-oxadiazoles and evaluation of action against *Acinetobacter baumannii*

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Synthesis of novel 1,2,5-oxadiazoles and evaluation of action against *Acinetobacter baumannii*

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Graphical abstract

Abstract

With multidrug resistant bacteria on the rise, novel antibiotics are becoming highly sought after. In 2008, eleven compounds were identified by high throughput screening as inhibitors of BasE, a key enzyme of the non-ribosomal peptide synthetase pathway found in *Acinetobacter baumannii*. Herein, we describe the preparation of four structurally similar heterocyclic lead compounds from that study, including one 1,2,5-oxadiazole. A further library of 30 analogues containing the oxadiazole moiety was then generated. All compounds were screened against *Acinetobacter baumannii* and their minimum inhibitory concentration data is reported, with (*E*)-3-(2-hydroxyphenyl)-*N*-(4-methyl-1,2,5-oxadiazol-3-yl)acrylamide **32** found to have an MIC of 0.5 mM. This work provides the foundation for further investigation of 1,2,5-oxadizoles as novel inhibitors of *A. baumannii*.

Keywords

1,2,5-Oxadiazoles; *Acinetobacter baumannii;* BasE inhibitors; Antibiotic resistance

Introduction

The rise of multidrug resistant bacteria is becoming a significant problem worldwide. In 2013, the Centers for Disease Control and Prevention reported that there are at least two million infections and 23,000 deaths caused by multidrug resistant pathogens each year in the United States alone.[1] Surgical patients, those undergoing chemotherapy and the critically ill are all in acute need of effective antibiotics and many commonplace medical treatments would not be practical without ways to combat bacterial infection.[2] Resistance can be attributed to a spontaneous or acquired mutation resulting in the drug becoming ineffective against the target. Bacteria can also enhance their ability to remove compounds by more effective degradation enzymes or by improving their efflux systems. The evolution of resistance mechanisms is compounded by the inappropriate use of antimicrobial drugs and inadequate mechanisms to prevent and control the spread of infection.[3,4] Despite the increased need for effective treatments, the discovery of novel therapeutic antibiotics has lagged far behind, with only one new class of antibiotics introduced in the past decade.[5]

Acinetobacter baumannii is a Gram-negative organism known to cause pneumonia, meningitis and infections of the bloodstream, urinary tract, skin and wounds.[6] Commonly found in the hospital environment, *A. baumannii* can survive for long periods on inanimate surfaces due to its ability to form biofilms.[7] *A. baumannii* has a highly plastic genome and readily acquires new resistance mechanisms.[8] Alarmingly, there are now pan-resistant isolates of *A. baumannii* that are untreatable by antibiotic therapy.[8] New targets are urgently needed in order to develop novel antibacterial agents to combat rising drug resistance. One potential pathway of interest is the siderophore mediated iron acquisition pathway.

Bacteria require iron for growth and survival.[9, 10] At approximately 10^{-24} M,[11] the free iron concentration in a typical vertebrate host is too low to support bacterial virulence. In these circumstances, bacteria acquire iron through another mechanism comprising the release and recovery of siderophores. Siderophores are small, structurally diverse scavenger molecules that chelate iron(III) with high affinity. Released in iron deficient conditions, siderophores are essential for bacterial virulence.[9, 10]

First characterised in 1992 by Yamamoto *et al*., acinetobactin (Figure 1) is the siderophore produced by *A. baumannii*[12] and is synthesised via the non-ribosomal peptide synthetase pathway.[13] Initially, the aryl acid adenylating enzyme, BasE, catalyses the formation of 2,3-dihydroxybenzoate-adenosine monophosphate (DHB-AMP) from 2,3-dihydroxybenzoic acid and adenosine monophosphate. The DHB-AMP conjugate then undergoes acylation by BasE. This acylated complex forms the aryl cap, a common feature of all siderophores, and is transported by BasF to BasA, BasB and BasD for further processing. Inhibiting BasE would halt siderophore production, thus preventing bacteria from acquiring the iron essential for their

virulence. Notably, the genes of the BasE system are highly upregulated during *A. baumannii* infection and mutagenesis of the acinetobactin cluster has been shown to attenuate bacteria in a murine model of disease.[14] With no known homologues in humans, BasE is an ideal drug target for further study.[13]

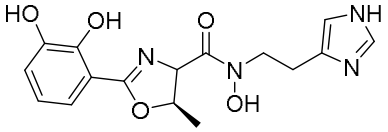


Figure 1. BasE siderophore acinetobactin.

In 2008, a series of compounds were identified as inhibitors of BasE by a high throughput screen (HTS) conducted by Neres and coworkers.[10] One of the compounds (HTS-23 in Figure 2), with a dissociation constant in the submicromolar range, was further developed and a series of analogues was described in 2013.[13] While the analogues of compound HTS-23 displayed potent enzyme inhibition of BasE, they lacked whole cell activity against *A. baumannii*.

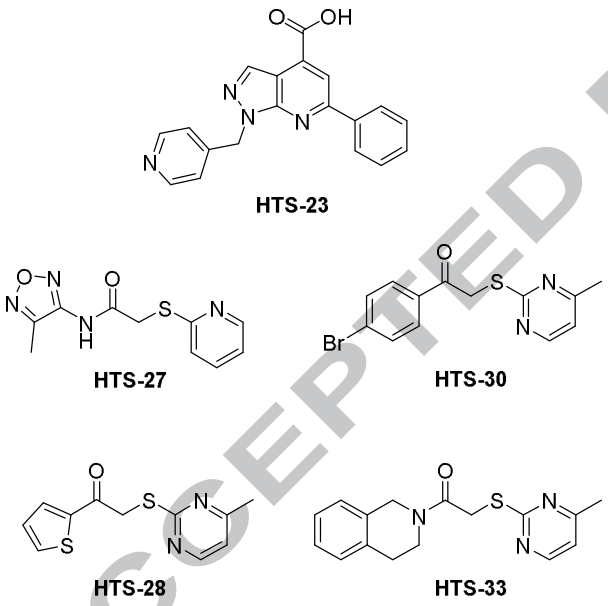


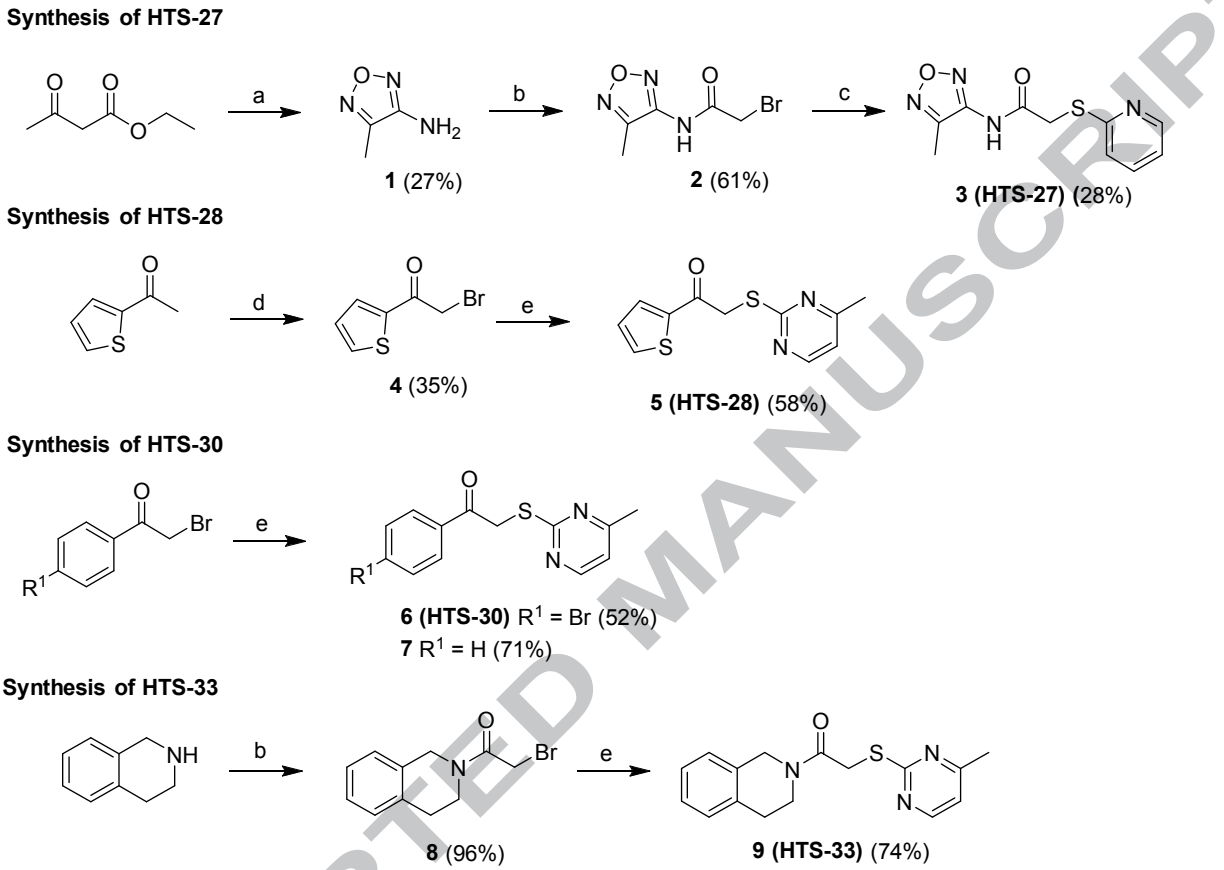
Figure 2. Selected HTS hit compounds identified against BasE in 2008.[10]

Interested in the whole cell activity of the remaining high throughput screen hit results, we herein describe for the first time the synthesis and characterisation of four of the structurally similar heterocyclics identified by Neres *et al.* (**HTS-27**, **HTS-28**, **HTS-30** and **HTS-33** in Figure 2). All contain two cyclic rings, mostly aromatic, linked by a thioether alongside either an amide or carbonyl group. Three of the compounds contain a methylpyrimidine ring while the fourth has a pyridine instead. Of the four known compounds

prepared and tested, **HTS-27** exhibited activity against *A. baumannii* under iron deficient conditions and a series of analogues of this hit were then synthesised for biological evaluation.

Results and discussion

The preparation of **HTS-27**, **HTS-28**, **HTS-30** and **HTS-33** was achieved as shown in Scheme 1. While all of these lead compounds are commercially available, their synthesis and characterisation is reported here, to the best of our knowledge, for the first time.



Scheme 1. Reaction conditions: (a) One pot reaction over 3 days; 1. NaOH, H_2O, 10 ˚C → rt. 2. $NaNO_2$, 20% $HClO_4$, 10 ˚C → rt. 3. NaOH, $NH_2OH.HCl$, 90 ˚C, urea, reflux. (b) Bromoacetyl bromide, DIPEA, CH_2Cl_2, -20 ˚C. (c) 2-Mercaptopyridine, Na_2CO_3, EtOH, H_2O. (d) Br_2, diethyl ether, 0 ˚C. (e) 2-Mercapto-4-methylpyrimidine, Na_2CO_3, EtOH, H_2O.

The synthesis of **HTS-27** was undertaken over a three step process. Preparation of 4-methyl-1,2,5-oxadiazole-3-amine **1** was undertaken from ethyl acetoacetate in a one pot reaction over three days as reported by Sheremetev *et al*.[15] Initially, freshly distilled ethyl acetoacetate was added to sodium hydroxide in water at 10 ˚C forming an emulsion, which was stirred to homogenization overnight. Sodium nitrite was added the following day, followed by perchloric acid to form an oxime which undergoes decarboxylation. On the third day, sodium hydroxide was added, followed by an excess of hydroxyl amine hydrochloride then a further addition of sodium hydroxide. The mixture was heated to 95 °C for two hours to facilitate the cyclisation process then urea, a dehydrating agent, was added in one portion to assist cyclisation and the reaction was refluxed for three hours. The product was extracted from the reaction mixture with multiple

washings of dichloromethane yielding 4-methyl-1,2,5-oxadiazol-3-amine **1** in 27% yield. Though the literature reports a 51% yield for this reaction, this result was unable to be replicated despite increasing the reaction time and equivalents of reagent. A number of side products were visualised via TLC but not isolated, thus contributing to a poor yield. The product was also found to be highly water soluble and required further extraction than the previously reported number of washes to reach the modest yield reported here.

Acylation of **1** was then undertaken with bromoacetyl bromide and base in dichloromethane at -20˚C, as adapted from the literature,[16] to form the corresponding amide **2** in a 61% yield. Finally, via procedures described by Loghmani-Khouzani and Hajiheidari,[17] the brominated compound **2** was coupled with 2-mercaptopyridine in aqueous ethanol with sodium carbonate to obtain **3** (**HTS-27)** in 28% yield after column chromatography. Unfortunately, a further fraction of product could not be satisfactorily purified.

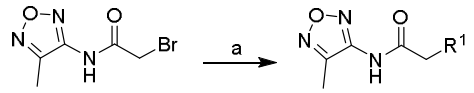
To prepare **HTS-28**, 2-acetylthiophene was initially brominated as reported by Sharma *et al.*[18] Coupling of the 2-(2-bromoacetyl)thiophene (**4**) with 2-mercapto-4-methylpyrimidine in aqueous ethanol with base gave **5 (HTS-28**), where acidification precipitated the desired product in 58% yield. The same procedure was applied to commercially available 2,4'-dibromoacetophenone and 2-mercapto-4-methylpyrimidine to give **6** (**HTS-30)** in 52% yield. Compound **7**, an analogue of **HTS-30** without the *para*-bromo substitution, was also synthesised in 71% yield when 2-bromoacetophenone was used as the starting material.

Finally, synthesis of **HTS-33** involved acylation of 1,2,3,4-tetrahydroisoquinoline with bromoacetyl bromide as reported in literature[16] to produce compound **8**, which was then coupled with the corresponding thiol in aqueous ethanol as previously employed, to give **9** (**HTS-33**) in 74% yield.

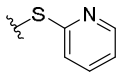
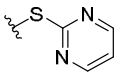
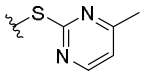
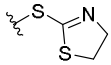
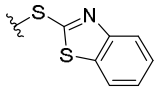
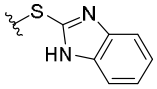
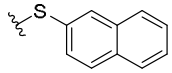
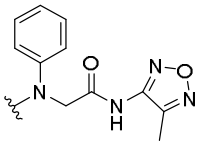
All compounds were subjected to testing for antibiotic activity against *A. baumannii* American Type Culture Centre (ATCC) 17978 via a minimum inhibitory concentration (MIC) assay. The iron chelator 2,2'-dipyridyl was added to the medium to simulate the iron depleted conditions under which siderophores are required for growth.[19,20] Results were obtained in triplicate and the median value identified as the MIC.

Compound **HTS-27** displayed antibiotic activity with a MIC of 2 mM, while an MIC of 4 mM was determined for **HTS-28**. Neither **HTS-30** or **HTS-33** had observable activity under the conditions tested, with an MIC > 4 mM. As a consequence, it was decided to pursue the synthesis of analogues of **HTS-27** to determine whether structural changes could improve potency. The analogues prepared are summarised in Tables 1 and 2 below.

Table 1. Chemical structures, synthetic yields and MIC against *A. baumannii* for thioether and dimeric analogues of **HTS-27**.

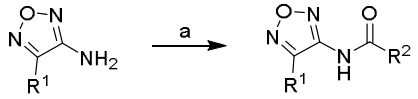


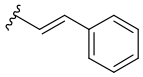
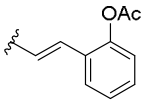
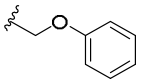
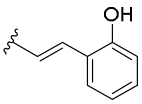
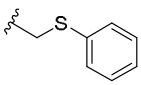
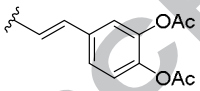
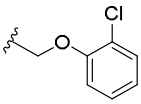
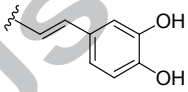
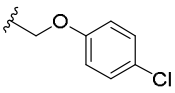
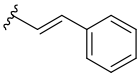
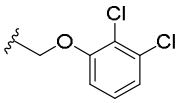
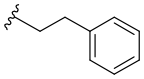
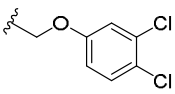
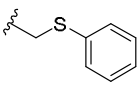
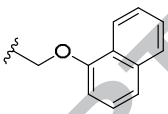
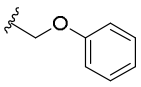
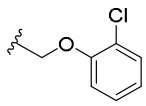
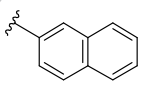
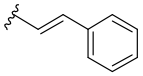
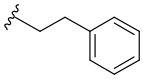
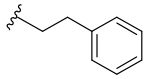
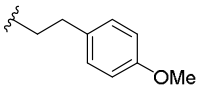
2

Compound	R^1	Yield (%)	MIC[a]
HTS-27		28	2 mM
10		94	4 mM
11		90	4 mM
12		76	2 mM
13		73	> 4 mM
14		85	2 mM
15		48	> 4 mM
16		12	> 4 mM

Reaction conditions: (a) Corresponding thiol, Na_2CO_3, EtOH, H_2O.
[a] Median MIC value for *Acinetobacter baumannii* (ATCC 17978) from a minimum of three independent experiments.

Table 2. Chemical structures, synthetic yields and MIC against *A. baumannii* for 2-, 3- and 4-substituted analogues of **HTS-27**.



Compound	R^1	R^2	Yield (%)	MIC[a]	Compound	R^1	R^2	Yield (%)	MIC[a]
18	CH_3		5[b]	1 mM	**31**	CH_3		33	2 mM
19	CH_3		73	2 mM	**32**	CH_3		95[c]	0.5 mM
20	CH_3		83	1 mM	**34**	CH_3		57	4 mM
21	CH_3		66	> 4 mM	**35**	CH_3		45[c]	> 4 mM
22	CH_3		57	1 mM	**37**	Ph		41	> 4 mM
23	CH_3		59	> 4 mM	**38**	Ph		26	> 4 mM
24	CH_3		68	1 mM	**39**	Ph		17	> 4 mM
25	CH_3		81	> 4 mM	**40**	Ph		43	> 4 mM
26	CH_3		79	1 mM	**41**	Ph		41	> 4 mM
27	CH_3		44	4 mM	**43**	Propyl		67	> 4 mM
28	CH_3		72	1 mM	**44**	Propyl		81	1 mM
29	CH_3		72	2 mM					

Reaction conditions: (a) Corresponding acid, PCl_5, CH_2Cl_2, reflux.
[a] Median MIC value for *Acinetobacter baumannii* (ATCC 17978) from a minimum of three independent experiments.
[b] Alternative procedure. Reaction conditions: (a) Cinnamic acid, $SOCl_2$. (b) 4-Methyl-1,2,5-oxadiazole-3-amine, THF, $NaHCO_3$.
[c] Obtained from deprotection of compounds **30** and **32** with methanolic ammonia.

Preparation of 2-bromo-*N*-(4-methyl-1,2,5-oxadiazol-3-yl)acetamide **2**, as described previously, followed by coupling to a variety of thiols resulted in the production of six analogues **10**-**15** in yields ranging from 48-94%. In addition, aniline was also reacted with compound **2** with the view to expand the scope of potential analogues. However, column chromatography of the crude material resulted in the isolation of the dimeric compound **16**, which was confirmed by NMR analysis and mass spectrometry.

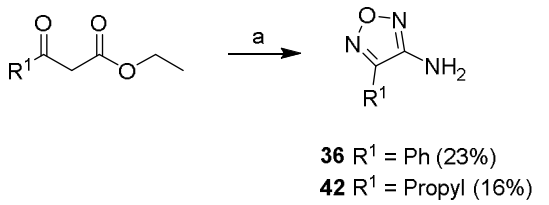
A further library of analogues was then prepared by acylating 4-methyl-1,2,5-oxadiazole-3-amine **1** with various acid chlorides. The first acid chlorides were prepared from the corresponding acids with thionyl chloride followed by coupling to 4-methyl-1,2,5-oxadiazole-3-amine **1** in dry tetrahydrofuran with sodium bicarbonate overnight, as described by Shin *et al.*[21] Cinnamic acid gave compound **18**, isolated by column chromatography in a 5% yield while compound **19**, prepared from phenoxyacetic acid, was isolated in a 25% yield. Due to these low yields, an alternative procedure was explored where the acid chloride was generated *in situ*, in order to eliminate the need for isolation.[22] Phenoxyacetic acid was refluxed with phosphorus pentachloride in dichloromethane for 30 minutes followed by the addition of 4-methyl-1,2,5-oxadiazole-3-amine **1** and further reflux for two hours. This method successfully obtained the product **19,** with an improved yield of 73% in sufficient purity following extraction.

Continuing to use the simplified and higher yielding procedure, a variety of analogues were synthesised from varying the corresponding acid. To explore the importance of the nitrogen in the pyridine ring, analogue **20** was prepared from thioacetic acid. Four chlorine substituted analogues of **19**, designated **21**-**24**, were then synthesised to determine the tolerance of electronegative groups around the ring. Three naphthalene derivatives were produced to give compounds **25**-**27**, two with a shortened linker to the oxadiazole while the third resulting in a larger aromatic derivative. Analogue **28** explores the effect of no heteroatom next to the aromatic system with the following compound **29** containing a *para* substituted methoxy group.

Compounds **31**-**32** and **34**-**35** are cinnamic acid derivatives, related to unsubstituted analogue **18**. Initially, 2-hydroxycinnamic acid was refluxed with phosphorus pentachloride without phenolic protection but purification resulted in recovery of the oxadiazole starting material and identification of two side products, coumarin and a dimer. NMR shifts were found to correspond to those reported by Kim *et al.* identifying formation of these products when 2-hydroxycinnamic acid was stirred with base in various solvents at room temperature.[23] To avoid this outcome, the 2-hydroxycinnamic acid and 3,4-dihydroxycinnamic acid were stirred in acetic anhydride and sulfuric acid at 0 ˚C to produce the acetylated product which was subsequently refluxed with phosphorus pentachloride and the oxadiazole, producing compounds **31** and **34**. To attain two further analogues the resulting derivatives were deprotected with methanolic ammonia solution to afford **32** and **35**.

To explore the role of the methyl substituent on the oxadiazole, a small series of analogues were also prepared with alternative functionality on the heterocyclic ring. 4-Phenyl-1,2,5-oxadiazol-3-amine (**36**) was

synthesised from ethyl benzoylacetate in a one pot reaction as described by Sheremetev *et al*[24] (Scheme 2). Subsequent coupling of **36** with five different acids, through the use of phosphorus pentachloride, produced the 4-phenyl compounds **37**-**41**. Additionally, two 4-propyl oxadiazole analogues **43** and **44** were prepared to see if a longer chain would be tolerated if the 4-phenyl group was not accepted.



36 R^1 = Ph (23%)
42 R^1 = Propyl (16%)

Scheme 2. Reaction conditions: (a) One pot reaction over 3 days; 1. NaOH, H_2O, 10 ˚C → rt. 2. $NaNO_2$, 20% $HClO_4$, 10 ˚C → rt. 3. NaOH, $NH_2OH.HCl$, 90 ˚C, urea, reflux.

All analogues were tested against *A. baumannii* (ATCC 17978) under the same conditions as previously described, however care must be taken when interpreting results where changes of less than an order of magnitude are observed. The alternate heterocycles trialled as thioethers **10**-**15** had undetectable activity, the exception being the 4,5-dihydrothiazole **12** and benzoimidazole **14** compounds with MIC values of 2 mM. The dimer **16** did not have detectable activity. However, removal of the pyridyl nitrogen from **HTS-27** to give compound **20** did not appear to be detrimental to activity, with MIC values of 2 mM for the lead and 1 mM for the benzene analogue. Changing the thioether of the lead to an oxygen or carbon bridge resulting in compounds **19** and **28** was also tolerated. Substitution of the ether **19** with 4-chloro and 3,4-dichloro functionality on the aromatic ring gave MIC values of 1 mM (analogues **22** and **24** respectively) but compounds **21** and **23**, with 2-chloro and 2,3-dichloro substitution respectively, were not potent. For compound **28**, the 4-methoxy analogue **29** was also acceptable. Naphthyl analogues **25**-**27** did not appear promising, though compound **26** had an MIC of 1 mM.

Interestingly, introducing rigidity through the alkene of compounds **18**, **31** and **32** gave a new synthetic direction to pursue. Unfortunately, the 3,4-subsituted analogues **34** and **35** were not active. Compound **32**, (*E*)-3-(2-hydroxyphenyl)-*N*-(4-methyl-1,2,5-oxadiazol-3-yl)acrylamide, returned the most promising MIC value of 0.5 mM, offering potential for further development. Finally, none of the 4-phenyl analogues **37**-**41** exhibited detectable activity while the influence of the 4-propyl substituent on the activity of analogues **42** and **43** requires further exploration.

These antibacterial results are comparable to those observed in 2013 by Neres and co-workers.[13] There are a number of potential explanations for the modest level of activity of these compounds against *A. baumanii* despite the previously demonstrated high affinity for BasE.[10] These include: (i) potential low compound solubility in water, (ii) an unknown ability to cross bacterial membranes, (iii) the possibility of export from the bacterial cell via broad-specificity multi-drug export systems of *A. baumannii*, and (iv) the ability of

other iron-acquisition systems to compensate for the loss of the acinetobactin cluster function. Solubility does not appear to be a significant influence on activity. Analogues with an MIC of 1 mM were found to have cLogP values in the range of 1.71 - 3.07. While compound **32** with an MIC 0.5 mM had a slightly lower cLogP value of 1.45, a decrease to cLogP of 0.77 was found for **HTS-27**, which had a higher MIC of 2 mM. While poor affinity cannot be ruled out, as direct testing against BasE has not yet been undertaken, compound **20** was tested in an environment with a normal iron concentration, and growth was not inhibited. This indicates that the inhibition is iron-related, and thus most likely siderophore related.

Conclusion

Four heterocyclic compounds previously reported as high throughput screen hits against BasE of *A. baumannii*[10] have been synthesised, characterised and had their antibiotic activity evaluated. Despite being promising inhibitors of BasE,[10] two of the HTS hits showed little to no antibacterial activity toward *A. baumannii* while the other two compounds indicated modest activity. A library of **HTS-27** analogues was then prepared, adapting and improving upon existing synthetic methods. Compound **32** was identified as the most potent analogue with a MIC of 0.5 mM against *A. baumannii* (ATCC 17978). These studies contribute to the exploration of BasE and siderophore biosynthesis as a target for novel antibiotics in *A. baumannii*.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at XXXX.

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