Installation of an aryl boronic acid function into the external section of N-aryl-oxazolidinones: Synthesis and antimicrobial evaluation

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ABSTRACT

N-aryl-oxazolidinones is a prominent family of antimicrobials used for treating infections caused by clinically prevalent Gram-positive bacteria. Recently, boron-containing compounds have displayed intriguing potential in the antibiotic discovery setting. Herein, we report the unprecedented introduction of a boron-containing moiety such as an aryl boronic acid in the external region of the oxazolidinone structure via a chemoselective acyl coupling reaction. As a result, we accessed a series of analogues with a distal aryl boronic pharmacophore on the oxazolidinone scaffold. We identified that a peripheric linear conformation coupled with freedom of rotation and no further substitution on the external aryl boronic ring, an amido linkage with hydrogen bonding character, in addition to a para-relative disposition between boronic group and linker, are the optimal combination of structural features in this series for antimicrobial activity. In comparison to linezolid, the analogue comprising all those features, compound **20b**, displayed levels of antimicrobial activity augmented by an eight-fold to a thirty-two-fold against a panel of Gram-positive strains, and a near one hundred-fold against *Escherichia coli* JW5503, a Gram-negative mutant strain with a defective efflux capability.

1. Introduction

The evaluation of novel pharmacophores in known and/-or unprecedented drug-like scaffolds is key to explore broad areas of the chemical space and unveil drug candidates with uncharted therapeutic profiles [1]. This approach is of utmost relevance in the antibiotic discovery setting [2], amidst the pre-pandemic global emergence of antimicrobial resistance (AMR) [3], that combined with a complex confluence of economic [4], regulatory [5], and societal factors drastically restricts the development of novel first-in-class antimicrobial drugs [6]. Such threatening pharmaceutical scenario is aggravated by a gap in knowledge not only on the molecular basis underlying novel AMR mechanisms but also on the delicate balance of interplaying physicochemical properties t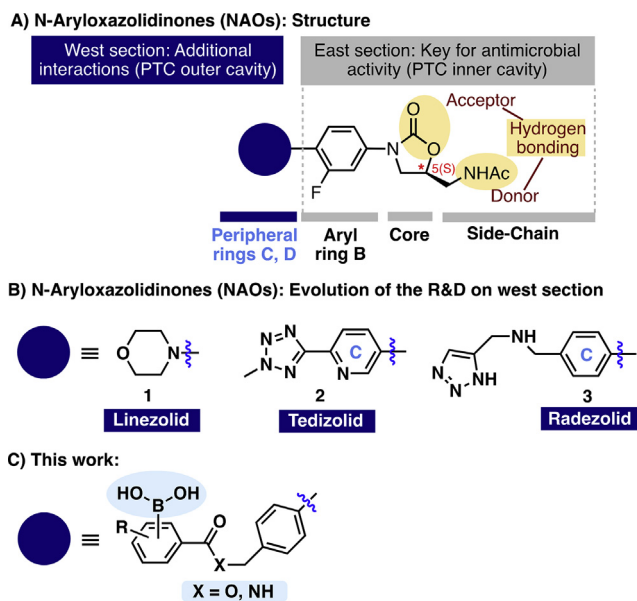hat translates into optimal intracellular accumulation and antimicrobial activity [7]. Consequently, there is an urge-pressing need to expand the molecular space covered by antimicrobial discovery programs. In this manner, we may strengthen our understanding of the structure-activity relationships (SAR) and predictive guidelines that may lead to the optimal design of broad-spectrum antimicrobials[2,6,8].

N-aryl-oxazolidinones (NAOs), such as linezolid (LZD) **1**, constitute the last family of discovered first-in-class synthetic antibiotics (Scheme 1b), and are used as the last resort therapy in major infections caused by multidrug-drug resistant (MDR) Gram-positive bacteria (GPB) [9]. The NAOs family is distinguished by a unique binding mode to the A-site pocket of the 50S subunit of bacterial ribosomes at the peptidyl transferase centre (PTC), that inhibits the formation of the 70S initiation ribosomal complex, an essential intermediate for protein synthesis and bacterial growth [10,11]. Furthermore, three characteristics define NAOs as a privileged platform for antimicrobial development. Firstly, a comprehensively studied SAR clearly establishes that an acetamide group or hydroxyl hydrogen-bonding donor at the C-5 side chain of the oxazolidinone core ring, and at least one fluorine atom in the meta-

A) N-Aryloxazolidinones (NAOs): Structure

B) N-Aryloxazolidinones (NAOs): Evolution of the R&D on west section

C) This work:

Scheme 1. Unprecedented oxazolidinones featuring an aryl boronic acid ring in their peripheral west section.

position of the adjacent aryl ring B (Scheme 1a), are the structural elements essential for antimicrobial activity [12]. Secondly, the prevalence of AMR against NAOs has been comparatively lower compared to other antibiotics, although the appearance of generic forms of NAOs already in the market (Scheme 1b) is expected to promote AMR cases [13]. Thirdly, their structure is relatively simple in relation to other antibiotics, enabling facile access to libraries of candidate molecules covering broader areas of SAR chemical space with less time and resources[14].

The majority of recent pharmaceutical research on NAOs has been focused on the introduction of a diverse array of polar substituents and heterocycles on their peripheral west section to raise additional biological interactions outside the cavity of the PTC [9,15].

Conversely, we aimed to explore the effects that a Lewis acid pharmacophore such a boronic acid could impart in the antimicrobial activity of NAOs. These pharmacophores are known to possess high specificity to bind diol residues near the active site of key enzymes in protein synthesis and gene translation, such as leucyl-*t*-RNA synthethases (LeuRS) or serine proteases [16]. Furthermore, boron-containing compounds have been shown recently to possess intriguing potential in the antimicrobial discovery setting as novel β-lactamase inhibitors [17], quorum sensing modulators [18], or as prospective inhibitors of the NorA efflux pump in MDR *Staphylococcus aureus* strains [19]. In this context, we herein disclose our findings on the synthesis and antimicrobial evaluation of a novel series of NAO analogues equipped with distal aryl boronic functional groups on their external section (Scheme 1c).

## 2. Results and discussion

2.1. Chemistry

We deemed that the east section of radezolid **3** (Scheme 1b) could be the most convenient synthetic platform to pursue the introduction of distal aryl boronic pharmacophores in an oxazolidinone scaffold. To that end, the presence in **3** of a *para*-substituted aryl ring C with a protic functional group such as an amine provides

a synthetic handle for further functionalization and assures a modular character for the synthetic approach. Additionally, radezolid is a second generation NAO antimicrobial with augmented pharmaceutical properties such as improved potency, activity against many LZD-resistant bacterial strains and even moderate activity against some Gram-negative bacteria (GNB) such as *Haemophilus influenza* and *Moraxella catarrhalis* [20]. To begin our studies, we selected the synthetic route reported by Frost and co-workers to prepare advanced intermediate **6** (Scheme 2) which they used as racemic synthon for the total syntheses of LZD, tedizolid and rivaroxaban.[21a] Although this route does not allow to control the configuration at the C-5 stereocentre of the central oxazolidinone ring, we considered that its relative efficiency, scalability, and modular character was quite convenient to swiftly access a series of aryl boronic analogues **10a-f** with different substituents on the terminal aryl boronic ring.

With the advanced intermediate **6** in hand, the targeted series of analogues **10a-f** were prepared through a straightforward two-step sequence comprising a Suzuki-Miyaura reaction [21b], followed by esterification of the resulting alcohol with a series of 4-carboxyphenylboronic acids **9a-f**. In this task, we were pleased to observe that a combination of 1-ethyl-3-(3-dimethylamino propyl) carbodiimide hydrochloride (EDC·HCl) and 4-dimethylaminopyridine (DMAP) furnished the corresponding aryl boronic analogues **10a-f** in good yield. Indeed, careful tuning of the reaction conditions and experimental procedure allowed us to supersede protodeboronation events, that are well-known to occur in acylation reactions using phenyl boronic as coupling agents [22], as well as the formation of trimeric boroxine anhydride species that are known to generate by dehydration of the parent boronic acid [23]. This is unambiguously confirmed by NMR spectroscopy and HRMS (see Appendix A). Surprisingly, the reaction tolerated well several phenyl boronic acids with *ortho*- and *meta*- electron-poor substituents such as Cl- and F-, as coupling partners, albeit delivered complex mixtures when the boronic acid featured an electron-rich methoxy substituent. For the syntheses of chiral aryl boronic derivatives we implemented the route adapted by Stoltz's group of the initial Upjohn & Pharmacia synthetic approach [24], that allows constructing the oxazolidinone core with full stereocontrol at C-5 in three steps from (*S*)-epichlorohydrin by using a *para*-chlorophenyl auxiliary to mask the amine group at the terminal alkyl chain (Scheme 2).

In our hands, the subsequent cleavage of that auxiliary in intermediate **12** and release of the free amino group was achieved in a straightforward and robust manner *via* transimination reaction with an excess of isobutylamine [25]. Next, acetylation of the free amino group followed by electrophilic iodination of the aryl ring B with NIS on TFA furnished intermediate **13**, that was then used as common building block to synthesize the series of chiral oxazolidinones with a distal aryl boronic fragment comprised in this study. For this task, the prior two-step sequence involving Suzuki-Miyaura and EDC-promoted acylation coupling reactions was competent to render chiral oxazolidinone analogues **16b**, **16g**, **18b**, **18g** and **23**, with an ester functionality linking the oxazolidinone and external aryl boronic fragments. Then, we converted the external primary hydroxyl in **17** into the amine group of radezolid intermediate **19** through a three-step sequence involving iodination followed by azidation and chemoselective hydrogenation. Finally, the chiral analogues **20b** and **20g** featuring an amide linkage between the oxazolidinone scaffold and the external aryl boronic fragment, such in radezolid, were also prepared in a facile manner by means of the EDC-promoted coupling of **19** with aryl boronic acids **9b** and **9g**, respectively.
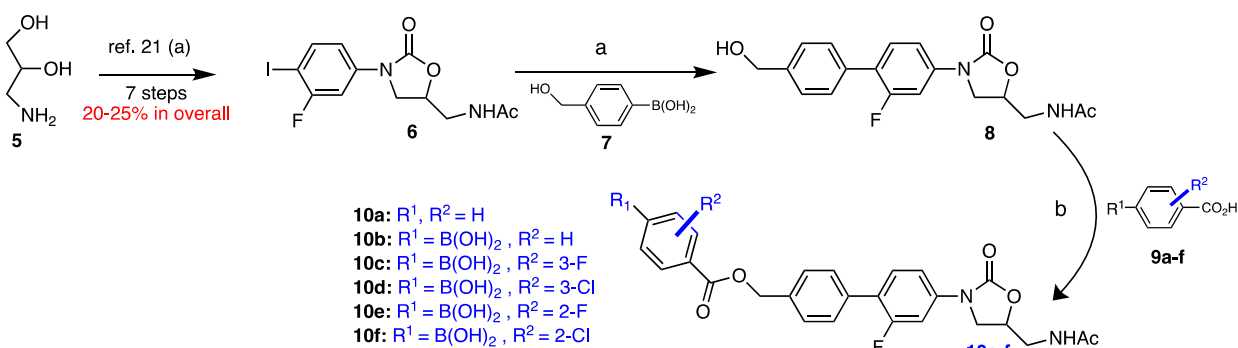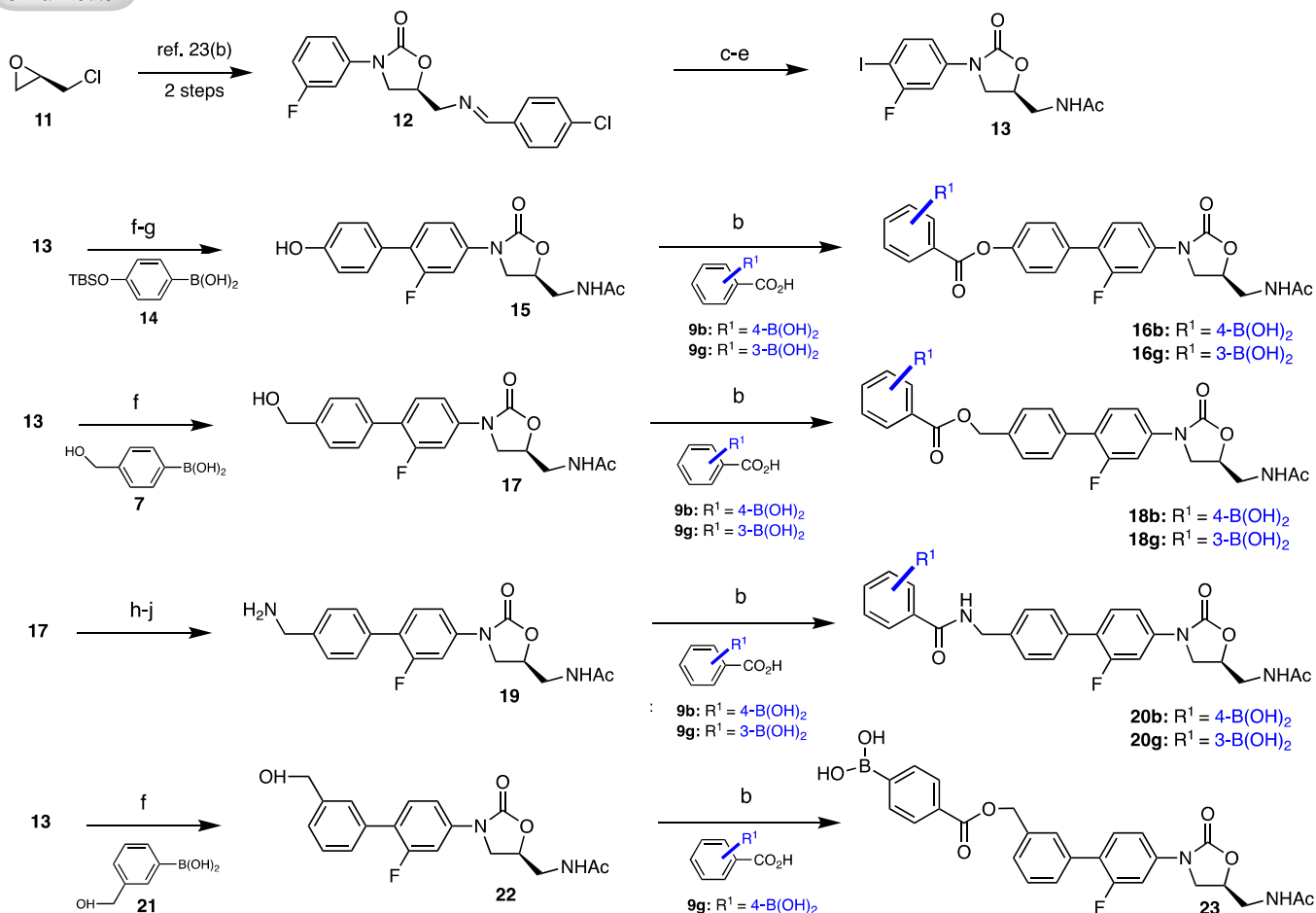
Scheme 2. Syntheses of racemic and chiral aryl boronic oxazolidinone derivatives. Reagents and conditions: (a) 4-(Hydroxymethyl)phenylboronic acid (1.4 equiv), K_2CO_3 (3 equiv), Pd(PPh$_3$)$_4$ (0.05 equiv), PhMe/EtOH/H$_2$O (4:1:1), reflux, 6 h, 90−95%; (b) Aryl carboxyl boronic acid **9a-f** (1.05−2.0 equiv), EDC•HCl (1.5−2.6 equiv), DMAP (0.4−1.0 equiv), DMF, rt, 24−96 h, 38−79%; (c) Isobutylamine (7−10 equiv), PhMe, 80−85 °C, 14 h, 85%; (d) Ac$_2$O (3.0 equiv), DMAP (0.05 equiv), Et$_3$N (4 equiv), DCM, rt, 2 h, 88%; (e) NIS (1.1 equiv), TFA, rt, 2 h, 77%; (f) 3 or 4-substituted phenylboronic acid (1.4 equiv), K$_2CO_3$ (3 equiv), Pd(PPh$_3$)$_4$ (0.05 equiv), PhMe/EtOH/H$_2$O (4:1:1), reflux, 6−10 h, 60−81%; (g) TBAF (1.2 equiv), THF, 0 °C, 30 min, 68%; (h) PPh$_3$ (2 equiv), imidazole (2.2 equiv), I$_2$ (2.5 equiv), THF, rt, 10 min, 68%; (i) NaN$_3$ (5.4 equiv), DMF, 70 °C, 14 h, 96%; (j) Pd/C (10 % wt), H$_2$ (1 bar), MeOH, rt, 2 h, 85%.

2.2. Antimicrobial activity

Initially, the antibacterial activity of racemic aryl boronic oxazolidinone analogues **10a-f** was evaluated against the ESKAPE panel of bacteria (for detailed information see the SI). All the compounds were additionally tested against wild-type *E. coli* ATCC 25922 and two *E. coli* mutant strains, JD17464 and JW5503. *E. coli* JD17464 is a lpxC deletion mutant with impaired outer membrane, while *E. coli* JW5503 is a tolC deletion mutant with defective efflux pump. Additionally, we examined their antimicrobial activity

Table 1
Minimum inhibitory concentration (MIC) of racemic aryl boronic analogues against selected Gram-positive strains and *E. coli* JW5503, a tolC deletion mutant.
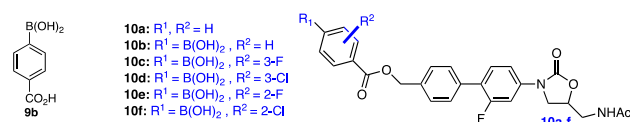
Compound	MIC (μM)[a]							Efflux ratio[b]
	E. coli JW5503	*E. faecalis* 29212	VR *E. faecalis* 51575	*E. faecium* 35667	VR *E. faecium* 700221	*S. aureus* 29213	MR *S. aureus* 43300	
LZD, **1**	75	6.25	6.25	12.5	6.25	6.25	6.25	>1[c]
9b	>50	>50	>50	>50	>50	>50	>50	ND
10a + 9b	>50	6.25	6.25	12.5	6.25	6.25	6.25	ND
10a	>50	3.13	3.13	6.25	3.13	3.13	3.13	ND
10b	6.25	3.13	1.56	3.23	1.56	3.13	1.56	>8
10c	25	1.56	1.56	1.56	1.56	1.56	1.56	>2
10d	25	3.13	3.13	3.13	3.13	3.13	3.13	>2
10e	12.5	1.56	0.78	1.56	1.56	1.56	1.56	>4
10f	25	1.56	1.56	1.56	1.56	1.56	1.56	>2

[a] Minimum inhibitory concentrations (μM) were determined after 24 h incubation (n = 3). Ciprofloxacin was used as a positive control for *E. coli* JW5503 (Δtolc) at 0.02 μM, and for both strains of *E. faecalis* and *S. aureus* at 3.0 and 1.5 μM, respectively. For *E. faecium* and VR *E. faecium* positive control LZD was used at 12 μM. VR = vancomycin-resistant; MR = methicillin-resistant; LZD = linezolid.
[b] Efflux ratio = MIC *E. coli* 25922/MIC *E. coli* JW5503. ND: not determined for compounds with MIC >50 μM for both strains.

against clinically relevant GPB, including MDR strains such as vancomycin-resistant (VR) *E. faecium* and *E. faecalis*, as well as methicillin-resistant (MR) *S. aureus.* The results of the antimicrobial assays are presented as percentage of bacterial growth inhibition (%) (Table S1). Overall, oxazolidinone analogues did not display significant inhibition of GNB (e.g. inhibitions were <90%), except for *E. coli* JW5503, which had similar results to GPB strains ($\geq$90%), excluding analogue **10a**. In line with previous reports, [15g,k] these results clearly indicate that bacterial efflux is the main phenomenon associated with the low intracellular accumulation and poor antimicrobial activity of NAOs against GNB.

Then, we sought to directly examine the relationship between the pattern of substitution on the aryl boronic pharmacophore of racemic oxazolidinone analogues **10a-f** and their antimicrobial potency against the GPB that initially had shown activity. Their minimum inhibitory concentration (MIC) values are summarized on Table 1. In general, all oxazolidinones equipped with a distal aryl boronic acid **10b-10f** exhibited lower MIC values than LZD that ranged from a two-to an eight-fold decrease (e.g. **10e** vs VR *E. faecalis* 51575). In particular, **10b**, that did not feature any substituent on the external aryl ring rather than the boronic acid, was the analogue of this series showing a better balance of antibacterial properties against all GPB isolates evaluated. Remarkably, **10b** also had the lowest MIC value against mutant GNB *E. coli* JW5503 (6.25 μM vs 75 μM for LZD), a result indicating that additional substitution in the external aryl boronic ring is detrimental to facilitate transport through GNB membranes, thus obstructing intracellular accumulation.

Critically, control experiments firmly confirmed that (i) the single 4-carboxylphenyl boronic acid compound **9b** does not exert any antimicrobial activity alone. Furthermore, (ii) the radezolid scaffold is not responsible itself for the observed increase of antimicrobial activity on GPB, even if analogue **10a** generally displays slightly lower MIC values than LZD, in fact those values are generally higher than those for aryl boronic oxazolidinone analogues **10b-f**. Foremost, (iii) the presence of the boronic function on the radezolid scaffold is the factor involved in the observed amplification of antibacterial activity against GPB and mutant GNB strain *E. coli* JW5503, since the simultaneous administration in a 1:1 ratio of both compounds **9b** (4-carboxylphenyl boronic acid) and **10a** (radezolid scaffold) does not reach the levels of antimicrobial

inhibition displayed by **10b** (radezolid scaffold that has the aryl boronic ring linked by an ester functional group).

With these preliminary results in hand, we next proceeded to evaluate the antimicrobial potency of the optimized series of chiral oxazolidinones with distal aryl boronic pharmacophores. MIC values are displayed on Table 2.

As it could be expected, the antimicrobial activity of all these chiral analogues was much higher than all of their racemic counterparts **10b-10f** and LZD. For instance, the MIC values for the chiral analogue **18b** were between a two-fold (*E. coli* JW5503 and MR *S. aureus*) and a four-fold lower (remainder of GPB strains) than the respective values for its racemic counterpart **10b**, which only differs on the presence of enantiomers with both stereochemical configurations at C-5 (*S* and *R*).

Moreover, all these chiral analogues exhibited higher antimicrobial activities than their control parent compounds, which have their terminal hydroxyl, phenol or amino protic group free before the acylation coupling with the aryl boronic carboxyl compounds **9b** and **9g**. These results suggest that the observed activity of the chiral oxazolidinone analogues does not arise as a result of metabolic cleavage of their ester or amide linkage under physiological conditions, a case in which we may expect that the activities of both control and acylated analogues are equal. Control compound **15** and its chiral acylated analogue **16b** constituted the exception to this rule since the latter exhibited lack of antimicrobial activity for all the GPB evaluated. We devise that such an effect can be ascribed to the fact that the phenol scaffold **15** is relatively rigid compared to **17** and **19**, and the aryl boronic fragment introduced on their acylated analogues **16b** and **16g** lies on a different plane forming an angle near 120° with respect to the rest of the molecule due to the intrinsic sp^2 trigonal geometry around the phenolic oxygen nuclei. As such, the limited rotation around the phenolic bond imposes molecules **16b** and **16g** to adopt rigid conformations far from the linearity that enables oxazolidinones reach their active site on the cavity of the ribosomal PTC.

Concerning the optimal position of the boronic acid group on the distal aryl ring in relation to the acyl functional group linking it to the rest of the molecule, the antimicrobial activity of analogues **16b** and **16g** against GPB were low for comparison due to the rigidity of their phenolic linkage (*vide ante*). However, we observed that in **18b** and **18g,** whereby the external aryl boronic ring is separated from the

Table 2
Minimum inhibitory concentration (MIC) of the chiral arylboronic acid analogue series against selected Gram-positive strains and *E. coli* JW5503, a tolC deletion mutant.

Compound	Structure R =	MIC (μM)							Efflux ratio[b]
		E. coli JW5503	*E. faecalis* 29212	VR *E. faecalis* 51575	*E. faecium* 35667	VR *E. faecium* 700221	*S. aureus* 29213	MR *S. aureus* 43300	
LZD, 1		75	6.25	6.25	12.5	6.25	6.25	6.25	>1
15 (control)		1.56	0.39	0.39	0.78	0.39	0.78	0.78	>32
16b		>50	>50	>50	>50	>50	>50	>50	ND
17 (control)		1.56	0.78	0.78	0.78	0.78	1.56	0.78	>32
18b		3.13	0.78	0.39	0.78	0.39	0.78	0.78	>16
18g		3.13	>50	0.78	>50	>50	1.56	0.78	>16
19 (control)		6.25	1.56	1.56	0.78	1.56	3.13	3.13	>8
20b		0.78	0.39	0.39	0.39	0.39	0.78	0.78	>64
20g		0.78	0.39	0.39	0.78	0.78	0.78	0.78	>64
22 (control)		3.13	1.56	3.13	1.56	1.56	3.13	1.56	>16
23		3.13	0.78	0.39	0.78	0.78	0.78	0.78	>16

[a]Minimum inhibitory concentrations (μM) were determined after 24 h incubation (n = 3). Ciprofloxacin was used as a positive control for *E. coli* JW 5503 (Δtolc) at 0.02 μM, and for both strains of *E. faecalis* and *S. aureus* at 3.0 and 1.5 μM, respectively. For *E. faecium* and VR *E. faecium,* LZD at 12 μM was used as positive control. VR = vancomycin-resistant; MR = methicillin-resistant; LZD = linezolid .
[b]Efflux ratio = MIC *E. coli* 25922/MIC *E. coli* JW5503.ND: not determined for compounds with MIC >50 μM for both strains.
[c]Compound **15** is the control for analogues **16b** and **16g**; compound **17** is the control for **18b** and **18g**, compound **19** is the control for **20b** and **20g**, and **22** is the control for **23**.

rest of the molecule by an ester linkage with an additional CH_2 fragment, *para*-is the optimal relationship between these two functional groups on the external ring (**18b** vs **18g**). This difference in antimicrobial activity is more pronounced in the case of **18b** and **18g** than between analogues **20b** and **20g**, in which the ester linkage is replaced by an amide group although that *para*-relative disposition remains optimal for **20b**. We additionally observed that deviation of the linearity in the relative conformation of the internal rings in analogue **23** was also deleterious for the antimicrobial activity.

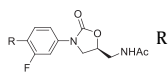### 2.3. Physico-chemical properties
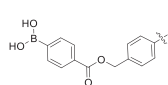
We then performed a quantitative structure-activity relationship (QSAR) analysis to get insight into the physico-chemical profile of this series of aryl-boronic-containing oxazolidinone analogues. Table 3 summarizes the main calculated descriptors for the selected chiral analogues **15**–**23** [7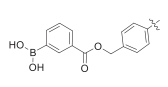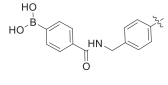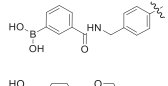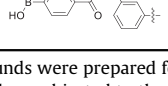a,26]. In general, the amplified antimicrobial activity of compounds containing the aryl boronic fragment, **18b**, **18g**, **20b**, **20g**, **23**, correlate with an increased lipophilicity (clogD and AlogP) and a larger contribution to the quantitative estimate of the drug-likeness (QED ALOGP). In connection with previous reports, [15k] the only parameter that seems to correlate with the augmented antimicrobial profile of **20b** and **20g** in relation to the rest of the analogues, is their increased ability to engage in hydrogen

bonding interactions due the presence of the amide linker. In this sense, further computational studies are ongoing in our laboratories to gain deeper insight into the fundamental questions concerning the origin of the observed enhancement of antimicrobial activity promoted by the installation of the aryl boronic fragment on the external section of the oxazolidinone analogues.

3. Conclusion

To summarize, with all the data at hand we can conclude that **20b** is the aryl boronic-containing oxazolidinone analogue with a combination of structural features ensuring better antimicrobial activities against the panel of clinically relevant GPB strains evaluated in this study. This may be attributed to the hydrogen bonding acceptor character of the amide bond in **20b** that may promote additional interactions in the outer cavity of the ribosomal PTC active site, combined with an optimal linear conformation with freedom for the external aryl boronic ring to rotate and adapt to the tight geometry of the PTC cavity. Compared to LZD, the amplified antimicrobial activity observed in **20b** varied between an eight-fold for *S. aureus* 29213 and MR 43300 strains (MIC of 0.78 μM for **20b** vs 6.25 μM for LZD), and a sixteen-fold to thirty-two-fold boost of antimicrobial activity for the rest of GPB, including the VR strains of *E. faecalis* and *E. faecium*. Remarkably, the antimicrobial activity

Table 3
Calculated physicochemical properties of the selected boronic analogues **15**−**23** using Discovery Studio 2019 (Accelrys Inc.).[a]

Name	R (structure)	cpKa[b]	cLogD[c]	Rotatable Bonds	ALogP[d]	HBD Count[e]	QED ALOGP[f]	ES Sum ssNH[g]
LZD, **1**	morpholine	3.51; 4.88	0.89	4.00	0.89	1.00	0.75	2.61
15	4-hydroxyphenyl	3.85; 6.64	1.82	4.00	2.32	2.00	0.98	2.59
17	4-(hydroxymethyl)phenyl	3.85	1.96	5.00	1.96	2.00	0.95	2.60
19	4-(aminomethyl)phenyl	3.85; 6.8	1.58	5.00	1.67	2.00	0.91	2.61
22	3-(hydroxymethyl)phenyl	3.85	1.96	5.00	1.96	2.00	0.95	2.60
18b	boronic ester	3.85; 8.97; 11.51	3.95	9.00	3.96	1.00	0.87	2.59
18g	boronic ester	3.85; 8.97; 11.51	3.95	9.00	3.96	1.00	0.87	2.59
20b	boronic amide	3.85; 8.97; 11.51	3.30	8.00	3.31	2.00	0.98	5.38
20g	boronic amide	3.85; 8.97; 11.51	3.30	8.00	3.31	2.00	0.98	5.36
23	boronic ester	3.85; 8.97; 11.51	3.95	9.00	3.96	1.00	0.87	2.59

[a] The compounds were prepared for descriptors calculations using the LigPrep module (Schrödinger LLC, USA) to produce a single, low-energy, 3D structure with correct chiralities and then subjected to the calculations of descriptors within the QSAR module of Discovery Studio 2019 (Accelrys Inc.).
[b] Calculated pKa values.
[c] Compound/Fragment octanol: aqueous buffer (at pH 7.4) distribution coefficient.
[d] Atomic contribution to the logP, octanol:water partition coefficient.
[e] Hydrogen bond donors count.
[f] ALOGP contribution to the Quantitative Estimate of Drug-Likeness.
[g] Electrotopological state descriptor of NH with two single bonds.

reached a near one hundred-fold level of amplification for **20b** and **20g** in relation to LZD and a four-fold increase in relation to the rest of chiral analogues **18b**, **18g**, and **23**, against the mutant GNB strain *E. coli* JW5503 with defective efflux pump (MIC of 0.78 μM for **20b** vs > 50 μM for LZD, and 3.13 μM for **18b**, **18g**, and **23**). Our results strongly suggest that the introduction of pharmacophores with Lewis character, such as aryl boronic acids into the peripheral section of oxazolidinone molecules with a linker capable of engaging in hydrogen bonding interactions such an amide group, and a linear but flexible conformation, may be a promising combination of structural features to expand the antimicrobial spectrum of oxazolidinone analogues and render them active against GNB bacteria. Further research is undergoing in our laboratories to reach this goal by overcoming the obstacle of efflux pumps and gaining further insight into the molecular basis of the observed antimicrobial activities.

Author contribution

C. D. C. Designed, conducted and supervised the antimicrobial evaluation of the compounds in this study. Contributed to the manuscript preparation. **P.W**. Assisted on the design and developed the syntheses of the compounds in this study. Contributed on the manuscript preparation. **K. M**. Conducted the Elemental and HRMS analyses and assisted to the chiral determination of the compounds in this study. **V. I**. Assisted on the syntheses of the compounds in this study. **H. M.** Assisted on the antimicrobial evaluation of the compounds in this study. **L. G.** Designed and conducted the calculation of the physicochemical properties for the compounds in this study. **S. H.** Assisted on the NMR structural determination of the compounds in this study. **P. T.** Contributed to design and supervised the antimicrobial evaluation of the compounds in this study. Contributed to manuscript preparation. **J. P. B.** Designed the syntheses of the compounds in this study, and wrote the manuscript. All authors have read, participated and approve this manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmech.2020.113002.

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