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Synthesis and Antimicrobial Activity of Binaphthyl-Based, Functionalized Oxazole and Thiazole Peptidomimetics

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Thirty two new binaphthyl-based, functionalized oxazole and thiazole peptidomimetics and over thirty five novel leucine-containing intermediate oxazoles and thiazoles were prepared in this study. This includes the first examples of the direct C-5 arylation of an amino acid dipeptide-derived oxazole. Moderate to excellent antibacterial activity was observed for all new compounds across Gram positive isolates with MICs ranging from 1–16 μg mL^{-1}. Results for Gram negative E. coli and A. baumannii were more variable, but MICs as low as 4 μg mL^{-1} were returned for two examples. Significantly, the in vitro results with a fluoromethyl-oxazole derivative collectively represent the best obtained to date for a member of our binaphthyl peptide antimicrobials.

Introduction

Bacterial resistance to antibiotic drugs is a critical problem facing modern healthcare.[1,2] The ever-growing use and misuse of antibiotics has led to the widespread development of multiple-drug resistant bacteria.[3] Key organizations including the World Health Organization (WHO) and the Centres for Disease Control (CDC) have recently issued reports on the impending threat of antibiotic resistance.[4,5] In the former, the WHO warned that "a post-antibiotic era – in which common infections and minor injuries can kill – is a very real possibility for the 21st Century."[4]

Resistance to our last resort antibiotics (e.g., vancomycin) has led to the emergence of bacterial "superbugs" resilient to virtually all available therapy.[6] As such, novel antibiotics with new modes of action are in high demand.[7] In recent times, the development of new antibiotics has received much less attention from industry,[8] leading to a shortage of novel therapies – the severity of this problem has been recognized by several authorities, including the European Innovative Medicine Initiative, which currently supports research in an attempt to stimulate the development of novel antibiotics.[9]

Previous work in our laboratory has led to the development of a novel class of cationic peptides (e.g., **1**, Fig. 1) for the potential treatment of multi-drug resistant bacteria.[10–13] These compounds contain a large, hydrophobic binaphthalene unit at the N-terminus of a tripeptide chain and exhibit *in vitro* minimum inhibitory concentrations (MICs) as low as 2–4 μg mL^{-1} against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE).[10–13]

The most active of our first generation compounds were based on an ester moiety at the C-terminus (R) bearing hydrophobic alkanes and arenes (e.g., **1**, Fig. 1).[10–12] Subsequent investigations were directed towards isosteric replacement with a 1,2,3-triazole (e.g., **2**), aimed at promoting metabolic stability and further probing structure-activity relationships (SARs) at the peptide terminus.[13] In related studies, we also prepared an oxazole isostere **3** with comparable activity to **1**.[10] Significantly, the efficacy of **3** was found to translate *in vivo* for systemic MRSA infection.[10] Encouraged by these results, we report here the synthesis of a library of oxazole and thiazole peptidomimetic analogous of **3**,[14] resulting in the discovery of several promising derivatives with equivalent or increased antimicrobial potency relative to **3** and other previous generation compounds.

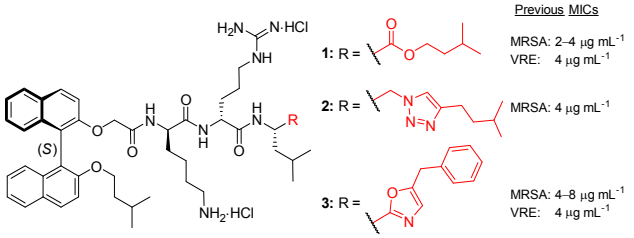

Fig. 1 Exemplary antibacterial compounds **1**–**3** developed previously in our laboratory.[10-13]

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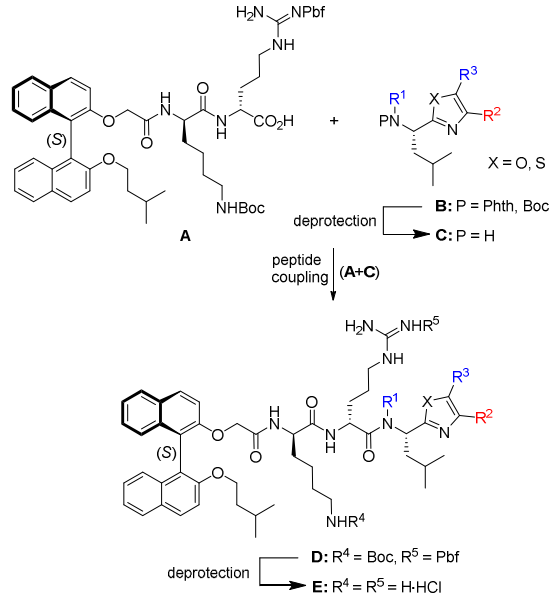
† Electronic Supplementary Information (ESI) available: Experimental procedures, compound characterization data, antibacterial testing methods, hemolysis data, NMR spectra and HPLC traces. See DOI: 10.1039/x0xx00000x

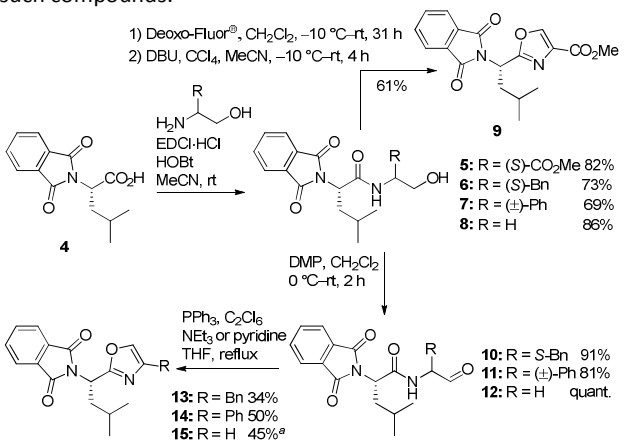
Results and Discussion

Our proposed synthetic strategy to the desired oxazole and thiazole peptidomimetics is illustrated in Scheme 1. The synthesis of key carboxylic acid **A** had been previously accomplished in our laboratory,[13] thus the initial focus of this work was the preparation of a library of *N*-protected leucine-based oxazole and thiazole derivatives **B** with variations at nitrogen (R^1), and the heterocyclic C-4 (R^2) and C-5 (R^3) positions for SAR studies. These compounds would be deprotected to provide amines **C** for subsequent coupling with **A** under standard conditions. Finally, potential antibacterial compounds **E** are revealed as di-hydrochloride salts after acidolysis of the Boc and 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf)[15] protecting groups. Notably, this is a modified, more convergent approach than that previously used to access lead oxazole **3**, which involved two peptide coupling steps.[10]



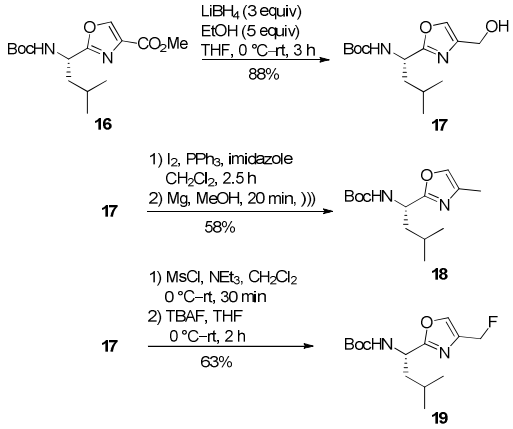
Scheme 1 Proposed synthetic strategy to oxa(thia)zole peptidomimetic derivatives.

Our initial synthetic studies were aimed at the preparation of a series of oxazoles with the opposite substitution pattern to lead compound **3** (Scheme 2). Thus, a small series of amino alcohols were coupled with *N*-Phth-leucine **4** to give amides **6**–**8** in 69–86% yield. The serine-containing dipeptide **5**, bearing a methyl ester, was also prepared to provide a versatile functional handle at C-4 (R^2) for subsequent derivatization. Treatment of **5** with Deoxo-Fluor®,[16] followed by formal dehydrogenation of the oxazoline intermediate with DBU/CCl_4,[16] gave **9** in 61% yield over two steps. Alternatively, oxazoles **13**–**15** were obtained by the reverse order of operations: oxidation by Dess-Martin periodinane (DMP) to the corresponding aldehyde, followed by cyclodehydation. The modest yields obtained in the cyclodehydration of aldehydes **10** and **11** with a PPh_3/C_2Cl_6 system[17] prompted us to survey alternative conditions for the formation of unsubstituted analogue **15**. Other common dehydrating conditions such as $POCl_3$/toluene/70 °C[18] and PPh_3/I_2/pyridine/rt[19] failed to promote the desired cyclization, resulting in decomposition or incomplete consumption of **12**. Eventually, **15** was obtained under the action of Hendrickson's POP reagent,[20] however the yield was again moderate (45%). Further efforts to improve the yields of **13**–**15** by incorporating the *N*-Boc protecting group into this reaction sequence were unsuccessful due to undesired formation of dihydropyrazines during DMP oxidation, which is consistent with an established route to such compounds.[21]



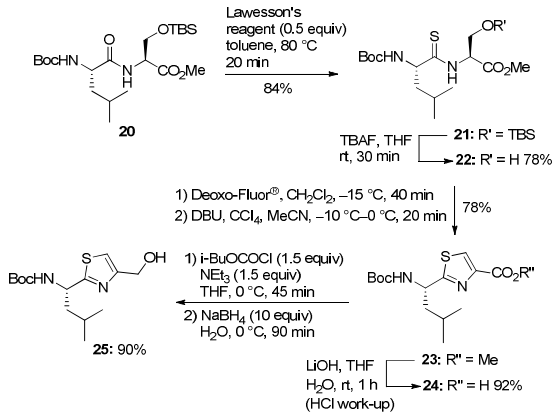
Scheme 2 Synthesis of oxazoles **9** and **13**–**15**. [a] Conditions: PPh_3O (2 equiv), Tf_2O (1 equiv), CH_2Cl_2, –78 °C–rt, 19 h.

In order to provide increased protecting group/reagent compatibility in transformations of the oxazole C-4-methyl ester, we also prepared the known Boc-protected analogue of **9** (compound **16** in Scheme 3) via a published route.[22] Reduction of ester **16** with a $LiBH_4$/EtOH system[23] gave the novel alcohol **17** in 88% yield (Scheme 3). This was further reduced to methyl oxazole **18** (58%) via iodination and treatment with Mg powder. Fluoromethyl derivative **19** was obtained (63%) via conversion of **17** to the mesylate ester and nucleophilic displacement with TBAF. Attempts to directly access **19** from alcohol **17** with Deoxo-Fluor® (1.1 equiv, –78 °C–rt)[24] resulted in poor yields with several unidentified products also present.



Scheme 3 Synthesis of oxazoles **17**–**19**.

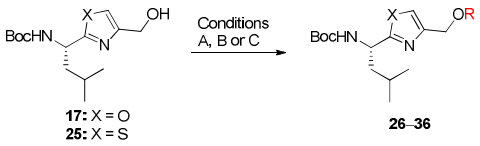
We next turned our attention to the synthesis of the corresponding hydroxy-thiazole **25** (Scheme 4). Previous routes to the known ester precursor **23** are based on condensation of cysteine with leucinal,[25] or the traditional Hantzsch thiazole synthesis,[26] however, we opted to pursue a cyclodehydration strategy by analogy with oxazoles **9** and **16**. Therefore, dipeptide **20**[27] was reacted with 0.5 equiv of Lawesson's reagent,[28] cleanly producing the required thioamide **21** in 84% yield. Treatment of the hydroxy derivative **22** with Deoxo-Fluor®, followed by oxidation gave **23** in good yield.[29] Encouraged by literature precedent,[30] we also attempted to shorten the sequence by direct conversion of Boc-Leu-Ser-OMe to dihydro-**23** (1 equiv of Lawesson's reagent), however this gave a mixture of the desired heterocycle and hydroxy-thioamide **22**, accompanied by significant decomposition. Nonetheless, our new route to **23** compares similarly with the previous methods in terms of step-economy and efficiency.[25,26] To access **25**, ester **23** was then saponified and reduced via a mixed anhydride. Interestingly, addition of the anhydride to a large excess of $NaBH_4$ proved essential to secure a high yield of **25** (90%), as the inverse reagent addition suffered from ester products arising from condensation of the mixed anhydride with **25** or isobutanol.



Scheme 4 Synthesis of hydroxyl-thiazole **25**.

With hydroxy-oxa(thia)zoles **17** and **25** in hand, a collection of ether derivatives **26**–**36** were synthesized in modest to good yields (Table 1). Etherification was best achieved by conversion to the mesylate ester and subsequent treatment with pre-formed alkoxides or phenoxide (Conditions A and B, entries 1–7), thus avoiding competing *N*-alkylation that occurred under alternate Conditions C (entries 8–11). The latter protocol, based on reaction of the *N*,*O*-dianion of **17** with methyl and benzyl halides, was unchanged from that reported for the highly selective mono-*O*-benzylation of the analogous valine-derived substrate,[23] suggesting that the decreased steric encumbrance proximal to the carbamate in **17** was responsible for the undesired *N*-alkylation in our case. Modifying the procedure to include only 1 equiv of NaHMDS did not improve the outcome, resulting in poor conversion of **17**.

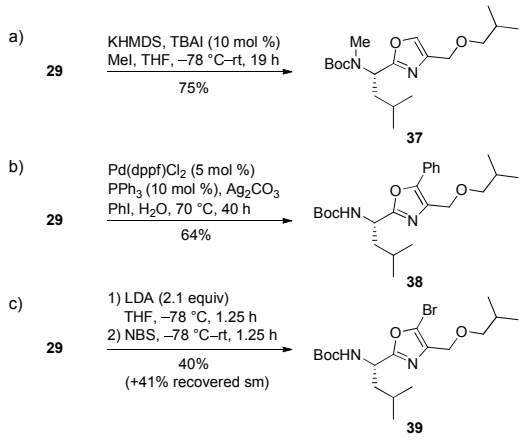
Table 1 Conditions and yields for etherification of oxazole **17** and thiazole **25**.



Entry		Conditions	X	R	Prod	Yield (%)
1	A:	1) MsCl, NEt_3 CH_2Cl_2, 0 °C–rt 2) ROH, NaHMDS TBAI (10 mol %) THF, −78 °C–rt	S	Me	**26**	73
2			O	i-Pr	**27**	81
3			S	i-Pr	**28**	48
4			O	i-Bu	**29**	80
5			O	i-Pentyl	**30**	70
6			O	(4-pyridyl)-Me	**31**	50
7	B:	1) MsCl, NEt_3 CH_2Cl_2, 0 °C–rt 2) ROH, Cs_2CO_3 acetone, rt	O	Ph	**32**	90
8	C:	NaHMDS (2 equiv) RX (1 equiv) TBAI (10 mol %) THF, −78 °C–rt	O	Me	**33**	59[a]
9			O	Bn	**34**	25[b]
10			O	4-Cl-Bn	**35**	43
11			O	4-F-Bn	**36**	34

[a] Along with 10% isolated *N*,*O*-dimethylated product. [b] Along with 48% isolated *N*,*O*-dibenzylated product. TBAI = tetrabutylammonium iodide.

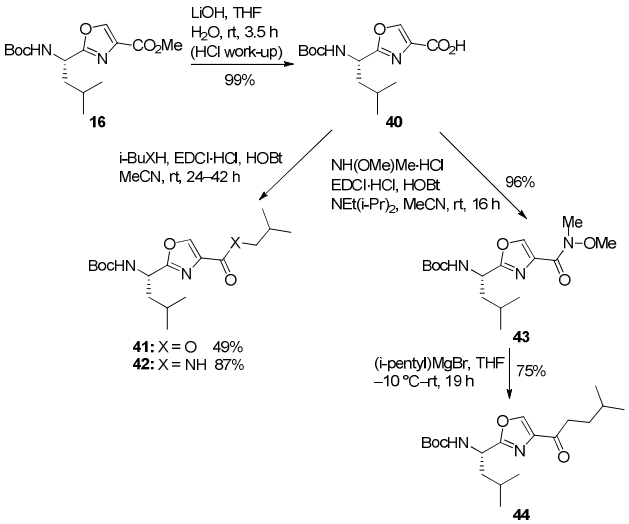
Various derivatives of isobutyl ether **29** were subsequently pursued (Scheme 5). *N*-Methylation proceeded smoothly to give secondary Boc-amine **37** in 75% yield (Scheme 5a). Functionalization at the C-5 position (R^3 in Scheme 1) proved more challenging. To our knowledge, there are only two previous examples of the C–H functionalization of an amino-acid derived peptidomimetic oxazole at the C-5 position, both involving C–C bond formation via lithiation.[23,31] We were interested in exploring a direct arylation approach using Pd-catalysis.[32] Preliminary attempts to introduce a phenyl group were performed with esters **9** or **16** using a $Pd(OAc)_2/P(Cy)_3$ combination with K_2CO_3 at 110 °C (Schemes S1a and S1b, ESI†).[33] Encouragingly, the reaction with *N*-Phth protected substrate **9** proceeded to completion to give the desired product in 61% yield (Scheme S1a, ESI†), however, this material was optically inactive, indicating that racemization had occurred under the basic conditions. In contrast, the Boc-protected analogue **16** produced an optically active arylation product, albeit with a moderate conversion (Scheme S1b, ESI†). Improved results were obtained with a milder heterogeneous arylation method developed by Greaney,[34] enabling phenyl-derivative **38** to be obtained in a respectable 64% yield, with full conversion of **29** (Scheme 5b). Furthermore, this product (**38**) was optically active and produced no detectable diastereomer when deprotected and coupled to stereochemically pure **A** (*vide infra*), establishing that racemization had not occurred. Notably, we also successfully applied Greaney's "on water" arylation protocol to hydroxy oxazole **17** (65% yield, Scheme S1c, ESI†). Further examination of this C-5 functionalization method with respect to other amino acid-derived oxa(thia)zoles and (hetero)aryl halides will likely be the subject of future studies.



Scheme 5 Synthesis of oxazoles **37**–**39**.

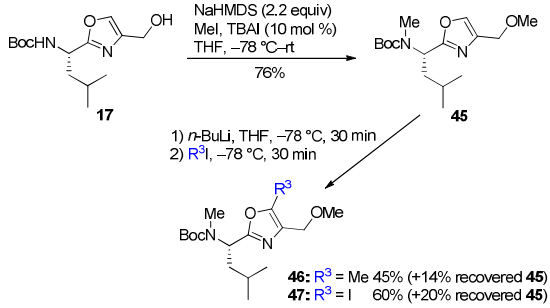
Initial efforts to introduce a halogen (I/Br) at C-5 of the oxazole ring were carried out with test substrates **9**, **16**, and **17** under various electrophilic halogenation conditions,[35] however, we could not isolate the desired product in any case (Schemes S2–S4, ESI†). Therefore, in order to brominate **29**, we resorted to a metalation/halogen quenching approach[36] via the *N*,*C*-5-dianion,[23] affording **39** in a modest, but satisfactory 40% yield (Scheme 5c). Attempts to identify an improved metalation procedure using ester **9** or TIPS-protected alcohol **17** were met with limited success (Schemes S2 and S5, ESI†).

Derivatives from the carboxylic acid oxidation state might be expected to have lower enzymatic stability than their ethereal and hydrocarbon analogues. Nonetheless, to better establish SAR at R^2 (oxazole C-4), a small set of ester, amide and ketone derivatives **41**–**44** were prepared from ester **16** in moderate to good yields via standard methods (Scheme 6). In keeping with lead compounds **1** and **2**, we opted to focus only on branched hydrophobic termini in these cases. A sample of the more polar Weinreb amide intermediate **43** was also preserved for later coupling with carboxylic acid **A**.



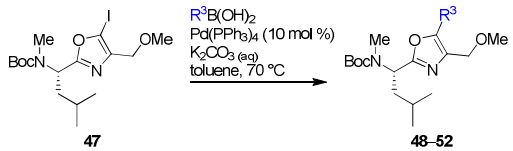
Scheme 6 Synthesis of oxazoles **41**–**44**.

Concurrent to the aforementioned investigations into direct arylation (Scheme 5b and Scheme S1, ESI†), we pursued an alternative entry into variations at R^3 via more established C–C bond forming technologies (Scheme 7 and Table 2).[37] Towards this end, hydroxy oxazole **17** was subjected to a global *N*,*O*-methylation to give **45** (76%, Scheme 7). C-5 lithiation, followed by quenching with MeI and separately, I_2, gave **46** and **47** in 45% and 60% yields, respectively. Subsequent Suzuki coupling of iodooxazole **47** was carried out with a range of (hetero)aryl boronic acids affording **48**–**52** in good to excellent yields (Table 2, entries 1–5).[37a]



Scheme 7 Synthesis of oxazoles **45**–**47**.

Table 2 Suzuki coupling reactions of oxazole **47**.



Entry	R^3	Prod	Yield (%)
1	Ph	**48**	95
2	4-(i-Pr)-Ph	**49**	76
3	4-CF_3-Ph	**50**	84
4	2,4-F,F-Ph	**51**	91
5	4-(3,5-Me,Me)-isoxazolyl	**52**	85

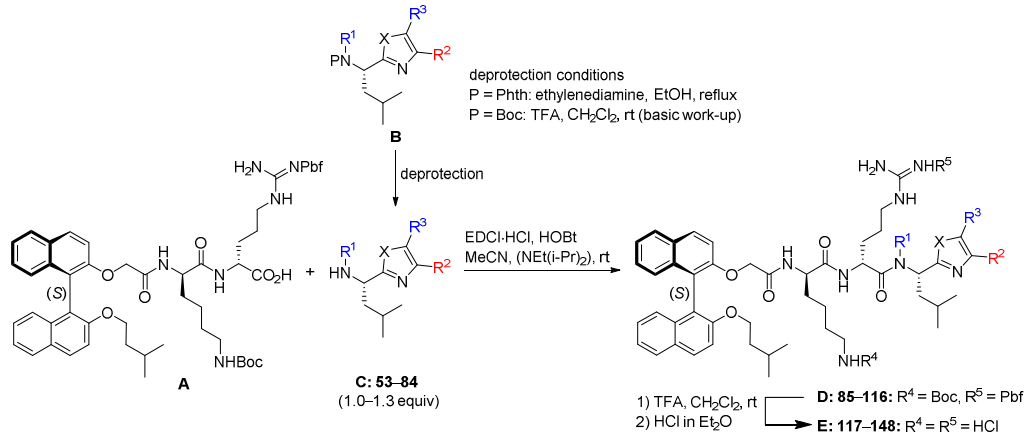
With an extensive collection of oxazoles and thiazoles of type **B** prepared, the target cationic peptidomimetic derivatives **E** were obtained using standard deprotection and coupling methods (Table 3, entries 1–32). The identity and purity of final compounds was established by full characterisation including NMR spectroscopy and high resolution mass spectrometry. Compounds **144**–**148** (entries 28–32), bearing a methyl group at R^1 and (hetero)aromatic groups at R^3, gave poorly resolved NMR spectra due to the presence of rotamers, and thus were additionally analyzed by HPLC to confirm purity (see ESI†).

For the earliest derivatives **117** and **118** (entries 1 and 2), penultimate scaffold **D** was obtained from **B** by a less effective iterative peptide coupling sequence, akin to lead compound **3** (see Scheme S7, ESI†).[10] Otherwise, moderate to excellent yields were generally observed throughout the illustrated three step sequence (entries 3–32). In all cases however, the yield of **D** was affected, albeit to varying degrees, by competing lactamization of **A**, a side reaction observed previously with other sulfonyl-protected arginine residues.[38,39] To suppress lactamization in our case, a slight excess of amine **C** (up to 1.3 equiv) was employed when possible, although the

small scale of the reactions (0.03–0.11 mmol of **A**) made it impractical to increase the (initial) reactant concentrations beyond 0.2–0.3 M, which may have provided further benefits.

Removal of the phthalimide group from amines is usually accomplished with hydrazine[40] or ethylenediamine[41] in alcoholic solvents (60–80 °C). Although deprotection of **13** and **14** with ethylenediamine gave the corresponding amines **53** and **54** in good yields (Table 3, entries 1 and 2), partial racemization was revealed by the formation of diastereomers in subsequent peptide coupling steps (see Scheme S7, ESI†). Fortunately, these minor epimers could be removed during purification by flash chromatography. Nonetheless, these results prompted us to use an alternative multistep, one-pot deprotection procedure[42] to unveil amine **55** (entry 3). Once again, a minor diastereomer, epimeric at leucine (ratio 9:1), emerged after coupling with **A**, which was in this case inseparable from **D** and thus retained in the final product **119**. In an effort to bypass the phthalimide removal step completely,[43] we also tried to synthesize **55** via Boc-deprotection and decarboxylation of **40** (depicted in Scheme 6), although this route was ultimately unsuccessful (Scheme S6, ESI†).[44]

Table 3 Synthesis of oxa(thia)zole peptidomimetic derivatives **117**–**148**.



Entry	B	P in B	X	R^1	R^2	R^3	C	Yield C (%)	D	Yield D (%)[a]	E	Yield E (%)
1	**13**	Phth	O	H	Bn	H	**53**	78	**85**	21[b]	**117**	50
2	**14**	Phth	O	H	Ph	H	**54**	87	**86**	12[b]	**118**	65
3	**15**	Phth	O	H	H	H	**55**	75[c]	**87**	73[d]	**119**	64[d]
4	**18**	Boc	O	H	CH_3	H	**56**	quant.[e,f]	**88**	nd	**120**	35[g]
5	**19**	Boc	O	H	CH_2F	H	**57**	quant.[e,f]	**89**	86	**121**	79
6	**17**	Boc	O	H	CH_2OH	H	**58**	78	**90**	94	**122**	93
7	**33**	Boc	O	H	CH_2OMe	H	**59**	84	**91**	66	**123**	95
8	**26**	Boc	S	H	CH_2OMe	H	**60**	85	**92**	69	**124**	71
9	**27**	Boc	O	H	CH_2O(i-Pr)	H	**61**	96[e]	**93**	85	**125**	95
10	**28**	Boc	S	H	CH_2O(i-Pr)	H	**62**	71	**94**	63	**126**	88
11	**29**	Boc	O	H	CH_2O(i-Bu)	H	**63**	100	**95**	82	**127**	100
12	**30**	Boc	O	H	CH_2O(i-pent)	H	**64**	89	**96**	85	**128**	81
13	**32**	Boc	O	H	CH_2OPh	H	**65**	97	**97**	53	**129**	92
14	**34**	Boc	O	H	CH_2OBn	H	**66**	73	**98**	36	**130**	90
15	**35**	Boc	O	H	CH_2O(4-Cl-Bn)	H	**67**	97	**99**	82	**131**	97
16	**36**	Boc	O	H	CH_2O(4-F-Bn)	H	**68**	82	**100**	79	**132**	100
17	**31**	Boc	O	H	CH_2O(4-pyridyl-Me)	H	**69**	96[e]	**101**	81	**133**	76
18	**37**	Boc	O	Me	CH_2O(i-Bu)	H	**70**	65	**102**	39	**134**	87
19	**38**	Boc	O	H	CH_2O(i-Bu)	Ph	**71**	91	**103**	78	**135**	67
20	**39**	Boc	O	H	CH_2O(i-Bu)	Br	**72**	88	**104**	71	**136**	72
21	**41**	Boc	O	H	CO_2(i-Bu)	H	**73**	82	**105**	64	**137**	91
22	**42**	Boc	O	H	CONH(i-Bu)	H	**74**	94	**106**	79	**138**	100
23	**43**	Boc	O	H	CONMe(OMe)	H	**75**	81	**107**	43	**139**	97
24	**44**	Boc	O	H	CO(i-pent)	H	**76**	quant.[e,f]	**108**	75	**140**	82
25	**45**	Boc	O	Me	CH_2OMe	H	**77**	82	**109**	47	**141**	97
26	**46**	Boc	O	Me	CH_2OMe	Me	**78**	69	**110**	69	**142**	95
27	**47**	Boc	O	Me	CH_2OMe	I	**79**	90	**111**	37	**143**	52
28	**48**	Boc	O	Me	CH_2OMe	Ph	**80**	80	**112**	81	**144**	96
29	**49**	Boc	O	Me	CH_2OMe	4-(i-Pr)-Ph	**81**	94[e]	**113**	65	**145**	96
30	**50**	Boc	O	Me	CH_2OMe	4-CF_3-Ph	**82**	97[e]	**114**	86	**146**	86
31	**51**	Boc	O	Me	CH_2OMe	2,4-F,F-Ph	**83**	97[e]	**115**	86	**147**	97
32	**52**	Boc	O	Me	CH_2OMe	4-(3,5-Me,Me)-isoxazolyl	**84**	94[e]	**116**	75	**148**	98

[a] Yield based on **A**. [b] Overall yield of **D** from **C** synthesized in an alternative linear peptide-coupling sequence, see Scheme S7 in the ESI†. [c] Conditions of phthalimide deprotection: 1) $NaBH_4$, i-PrOH, H_2O, rt, 20 h; 2) AcOH, 80 °C, 8 h; 3) HCl in Et_2O (isolated as HCl salt). [d] Obtained as a *ca.* 90:10 mixture of inseparable diastereomers, epimeric at leucine. [e] No aqueous work-up was performed, **C** obtained as the TFA salt. [f] Residual TFA present in the **C**·TFA salt. [g] Overall yield of **E** from **B**.

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In vitro biological testing results for the thirty two new peptidomimetic oxa(thia)zoles (**117**–**148**) against a selection of common bacterial pathogens are presented in Table 4 (entries 4–35). Lead compounds **1**–**3** were included as positive controls throughout (entries 1–3), in addition to vancomycin and chloramphenicol for Gram positive and Gram negative strains, respectively (entries 36 and 37).

Encouragingly, moderate to excellent activity was observed for all new compounds across Gram positive isolates with MICs ranging from 1–16 μg mL^{-1} (Table 4, entries 4–35), demonstrating equivalent or enhanced potency relative to lead compounds **1**–**3** in many cases. Results for Gram negative *E. coli* were more variable (MICs ≤128 μg mL^{-1}), but MICs as low as 4 μg mL^{-1} were returned (compounds **121** and **125**), representing a minimum four-fold increase in activity relative to previous compounds **1**–**3**.

A number of useful SAR trends emerged from closer inspection of the data in Table 4. Comparison of MICs for 4-benzyloxazole **117** (Table 4, entry 4) with those for its 5-benzyl regioisomer **3** (entry 3) revealed a clear benefit to oxazole-substitution at C-4 (R^2) over C-5 (R^3). Further exploration of derivatives at R^2 established improved antimicrobial potency through incorporation of smaller non-polar moieties (R^2 = H or CH_3, entries 6 and 7) or short chain aliphatic ethers (R^2 = CH_2OMe or CH_2O(i-Pr), entries 10–13). Longer chain aliphatic and aromatic ethers were less effective (entries 14–19), as were more polar functional groups such as an alcohol (entry 9) and a Weinreb amide (entry 26). Similar activities were observed when the oxazole terminus was exchanged with the corresponding thiazole (e.g., entry 12 *versus* entry 13). The most potent compound overall was oxazole **121**, bearing a fluoromethyl substituent at R^2 (entry 8). This derivative inhibited Gram positive bacterial growth at concentrations of 1–2 μg mL^{-1}, rivalling the efficiency observed for vancomycin (MICs 0.5–4 μg mL^{-1}, entry 36), as well as *E. coli* inhibition at only 4 μg mL^{-1}. Significantly, these *in vitro* results (with **121**) collectively represent the best obtained to date for a member of our binaphthyl peptide antimicrobials.[10–13]

Fully functionalized oxazoles (R^2 and R^3 ≠ H) containing a phenyl or bromo group at R^3 (Table 4, entries 22 and 23, respectively) and a common isobutoxymethyl group at R^2 generally gave higher MICs than their C-5 unsubstituted analogue (R^3 = H, entry 14). The adverse effect of C-5 substitution in these cases was particular prominent with respect to *E. coli*, for which activity was significantly attenuated (MIC increase from 8 μg mL^{-1} to 64/128 μg mL^{-1}). Methylation of the leucine nitrogen (R^1 = Me) appeared to result in decreased activity (Table 4, entry 10 *versus* entry 28; entry 14 *versus* entry 21), although, interestingly, when R^1 = Me, full functionalization of the oxazole terminus with a phenyl or isoxazolyl moiety at C-5 (R^3) was well tolerated with respect to preservation of antibacterial potency (entries 31 and 35), indicating a possible conformational change relative to the aforementioned related *N*-H compounds (R^1 = H, entries 22 and 23). Substitution of the C-5 phenyl group resulted in decreased antimicrobial activity in all cases (entry 31 *versus* entries 32–34).

A selection of our most active compounds (**121**, **123**–**127**) was tested further against additional bacterial isolates *in vitro* (Table 5). Similar to our best lead compound **1** (entry 1), moderate to excellent activity was observed across all strains including Gram negative *A. baumannii*, Gram positive *C. difficile*[45] and vancomycin-resistant *E. faecalis* (VRE) (entries 4–9). Comparison of data for VRE (Table 5) to that obtained for vancomycin-susceptible *E. faecalis* (Table 4), showed that MICs were largely the same or one dilution different, suggesting that vancomycin resistance does not have a significant impact on susceptibility to the title compounds.

Preliminary toxicity screening has also provided encouraging results. Our most active compounds (e.g., **121**, **123**–**126**) exhibited <4% hemolysis of sheep erythrocytes at concentrations above their average MICs (see Table S3, ESI†). Larger scale synthetic throughput of selected antibacterial oxa(thia)zoles in Table 5 is currently in progress as we progress to *in vivo* studies with these promising new antimicrobials.

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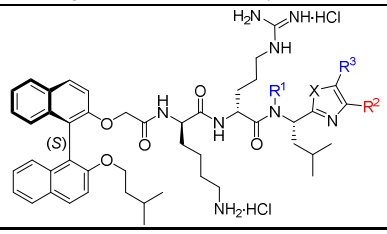
Table 4 Antibacterial activity of oxa(thia)zole peptidomimetics as minimum inhibitory concentrations (MICs) in μg mL^{-1}.

Entry	Compound	X	R^1	R^2	R^3	*S. aureus* ATCC 29213	MRSA[a] NCTC 10442	*E. faecalis* ATCC 29212	*S. pneumoniae* ATCC 49619	*E. coli* ATCC 25922
1	**1**[b]	-	-	-	-	2	2	2	2	16
2	**2**[b]	-	-	-	-	4	4	4	8	16
3	**3**	O	H	H	Bn	8	8	8	8	32
4	**117**	O	H	Bn	H	4	4	4	4	32
5	**118**	O	H	Ph	H	8	8	8	8	64
6	**119**	O	H	H	H	2	2	4	4	8
7	**120**	O	H	CH_3	H	4	4	4	8	8
8	**121**	O	H	CH_2F	H	1	2	2	2	4
9	**122**	O	H	CH_2OH	H	4	4	8	4	16
10	**123**	O	H	CH_2OMe	H	2	2	2	2	8
11	**124**	S	H	CH_2OMe	H	2	2	4	4	8
12	**125**	O	H	CH_2O(i-Pr)	H	2	2	2	2	4
13	**126**	S	H	CH_2O(i-Pr)	H	2	2	2	4	8
14	**127**	O	H	CH_2O(i-Bu)	H	2	4	4	2	8
15	**128**	O	H	CH_2O(i-pent)	H	4	4	4	4	32
16	**129**	O	H	CH_2OPh	H	4	4	8	4	8
17	**130**	O	H	CH_2OBn	H	4	4	4	4	16
18	**131**	O	H	CH_2O(4-Cl-Bn)	H	4	4	4	4	32
19	**132**	O	H	CH_2O(4-F-Bn)	H	4	4	4	2	16
20	**133**	O	H	CH_2O(4-pyridyl-Me)·HCl	H	4	4	8	8	8
21	**134**	O	Me	CH_2O(i-Bu)	H	4	4	8	8	32
22	**135**	O	H	CH_2O(i-Bu)	Ph	8	8	8	16	128
23	**136**	O	H	CH_2O(i-Bu)	Br	4	4	4	4	64
24	**137**	O	H	CO_2(i-Bu)	H	4	4	4	4	32
25	**138**	O	H	CONH(i-Bu)	H	2	4	4	4	8
26	**139**	O	H	CONMe(OMe)	H	8	8	8	8	32
27	**140**	O	H	CO(i-pent)	H	4	4	4	4	64
28	**141**	O	Me	CH_2OMe	H	4	4	4	2	8
29	**142**	O	Me	CH_2OMe	Me	2	2	4	4	8
30	**143**	O	Me	CH_2OMe	I	4	8	2	4	16
31	**144**	O	Me	CH_2OMe	Ph	2	2	4	2	8
32	**145**	O	Me	CH_2OMe	4-(i-Pr)-Ph	8	8	8	8	32
33	**146**	O	Me	CH_2OMe	4-CF_3-Ph	8	8	8	8	64
34	**147**	O	Me	CH_2OMe	2,4-F,F-Ph	4	4	4	4	32
35	**148**	O	Me	CH_2OMe	4-(3,5-Me,Me)-isoxazolyl	2	2	4	2	8
36	vancomycin	-	-	-	-	1	1	4	0.5	-
37	chloramphenicol	-	-	-	-	-	-	-	-	4

[a] Methicillin-resistant *S. aureus*. [b] See Fig. 1 for compound structure.

Table 5 Further biological screening of selected compounds. Results are given as minimum inhibitory concentrations (MICs) in μg mL^{-1}.



						C. difficile			*S. aureus*	*A. baumannii*		*E. faecalis*	
Entry	Compound	X	R^1	R^2	R^3	M7404 (RT027)	R20291 (RT027)	1470 (RT017)	Mu50 (VISA)	ATCC 19606	ATCC 15308	ATCC 51299 (VRE)	clinical (VRE)
1	**1**[a]	-	-	-	-	8	8	8	2	4	8	4	4
2	**2**[a]	-	-	-	-	8	8	8	-	-	-	-	-
3	**3**	O	H	H	Bn	-	-	-	16	16	16	4	4
4	**121**	O	H	CH_2F	H	8	8	8	4	4	4	2	2
5	**123**	O	H	CH_2OMe	H	16	16	16	8	8	8	4	4
6	**124**	S	H	CH_2OMe	H	8	16	8	4	8	8	4	4
7	**125**	O	H	CH_2O(i-Pr)	H	16	8	8	4	4	8	4	4
8	**126**	S	H	CH_2O(i-Pr)	H	8	8	8	4	4	4	2	2
9	**127**	O	H	CH_2O(i-Bu)	H	16	16	8	8	16	8	4	4
10	vancomycin	-	-	-	-	2	2	2	8	-	-	64	32
11	ciprofloxacin	-	-	-	-	-	-	-		1	0.5	-	-

[a] See Fig. 1 for compound structure.

Conclusions

In conclusion, thirty two new binaphthyl-based, functionalized oxazole and thiazole peptidomimetics have been prepared. Further, over thirty five novel leucine-containing oxazoles and thiazoles were also prepared as intermediates in this study, including the first examples of the direct C-5 arylation of an amino acid dipeptide-derived oxazole. Moderate to excellent antibacterial activity was observed for all new compounds across Gram positive isolates with MICs ranging from 1−16 μg mL^{-1}. Results against Gram negative *E. coli* and *A. baumannii* were more variable, but MICs as low as 4 μg mL^{-1} were returned for two compounds (compounds **121** and **125**). Significantly, the *in vitro* results with the fluoromethyl-oxazole derivative **121** collectively represent the best obtained to date for a member of our binaphthyl peptide antimicrobials.

Experimental section

Synthesis and characterization methods. All reactions were carried out in standard laboratory glassware with magnetic stirring. Thin layer chromatography (TLC) was performed on aluminum-backed 0.20 mm silica gel plates. Visualization was accomplished with UV light, a ninhydrin staining solution in *n*-butanol and/or an aqueous ceric ammonium molybdate solution. Flash chromatography and silica pipette plugs were performed under positive air pressure using Silica Gel 60 of 230−400 mesh (40−63 μm). Optical Rotations were measured at 25 °C in the specified solvent with a path length of 1.0 dm on a Jasco P-2000 Digital Polarimeter (λ = 589 nm). Concentrations (*c*) are given in g/100 mL. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury 300 MHz spectrometer, a Varian Inova 500 MHz spectrometer or a Varian VNMRS PS54 500 MHz spectrometer. Spectra aquired in $CDCl_3$ are reported relative to tetramethylsilane (^{1}H: δ = 0.00 ppm) and solvent resonance (^{13}C: δ = 77.0 ppm). Spectra acquired in CD_3OD are reported relative to solvent resonance (^{1}H: δ = 3.31 ppm; ^{13}C: δ = 49.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (abbreviations: s = singlet, bs = broad singlet, d = doublet, bd = broad doublet, app. d = apparent doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, app. t = apparent triplet, q = quartet, ABq = AB quartet, quin = quintet, sex = sextet, sep = septet, m = multiplet and bm = broad multiplet), coupling constant (Hz) and integration. Infrared (IR) spectra were obtained on a Shimadzu IRAffinity-1 FTIR Spectrometer with neat samples. Low resolution mass spectrometry (MS) was performed on a Shimadzu LC-2010 Electrospray Ionization (ESI) Mass Spectrometer. High resolution mass spectrometry (HRMS) was performed on a Waters Quadrupole-Time of Flight (QTOF) Xevo Spectrometer via ESI with Leucine-Enkephalin as an internal standard. For isolated ammonium salts of basic amino compounds, "M" refers to the mass of the corresponding *neutral* molecule. High performance liquid chromatography (HPLC) was performed on a reverse-phase Phenomenex C18 column (ϕ = 4.6 × 150 mm) using water/acetonitrile (both containing 0.1% TFA) as the mobile phase at a flow rate of 1.0 mL/min, with a detection wavelength (λ) of 254 nm.

Synthesis materials. Nitrogen (N_2) was dried by passage through self-indicating silica gel (2−4 mm bead size). Unless otherwise noted, anhydrous solvents (obtained from commercial sources) were utilized. Carboxylic acid **A** was prepared according to a published procedure.[13] Other known reagents that were not obtained commercially were prepared according to literature procedures cited within the ESI†. All other reagents were purchased reagent grade and used as received.

General synthetic procedures

General Procedure 1 for Amide Bond Formation. A reaction vessel was charged in air with the carboxylic acid (1.0 equiv), EDCI·HCl (1.2 equiv), HOBt (1.2 equiv) and the amine (1.0−1.3 equiv). If the latter was an ammonium salt, a slight excess of NEt(i-

$Pr)_2$ was also added. To this was added HPLC grade MeCN to a concentration of 0.2−0.3 M in the carboxylic acid (unless otherwise specified) and the resulting mixture was stirred at rt in an air atmosphere until TLC analysis indicated complete consumption of the carboxylic acid. After removal of the solvent under reduced pressure (for reactions with less than 5 mL of MeCN this is not necessary), the residue was dissolved in EtOAc (20 mL for reactions with ≤1 mmol of acid; or 20 mL/mmol of acid for larger scale) and washed sequentially with 1 M HCl (2×20 mL; to remove any excess amine, EDCI and the urea by-product), saturated $NaHCO_3$ (2×20 mL; to remove HOBt) and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. If required, purification was carried out by flash chromatography with the indicated eluent.

General Procedure 2 for Suzuki Coupling of Oxazole 47. A mixture of iodinated compound **47** (1.0 equiv), a boronic acid (1.0 equiv), aqueous K_2CO_3 (2 M, 2.0 equiv), $Pd(PPh_3)_4$ (10 mol %) and toluene (20 mL/mmol of **47**) was heated at 70 °C under N_2 for 7−72 h. After cooling to rt, EtOAc (20 mL) was added, followed by 1 M NaOH (20 mL). The organic layer was separated and the aqueous layer further extracted with EtOAc (20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated. Flash chromatography gave the desired C−C coupling product.

General Procedure 3 for Boc Deprotection of Type B Oxa(thia)zoles. To a solution of the Boc-protected compound **B** (1.0 equiv) in reagent grade CH_2Cl_2 (1.0 mL/0.10 mmol of substrate) was added neat TFA (15.0 equiv) and the solution was stirred at rt in an air atmosphere until TLC analysis (ninhydrin staining solution) indicated complete consumption of the starting material (reaction times typically 2−6 h). The mixture was diluted with CH_2Cl_2 (15 mL) and 1 M NaOH (15 mL). The organic layer was separated and the aqueous layer further extracted with CH_2Cl_2 (15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide the desired amine **C** with no further purification necessary. In cases where an aqueous work-up was not performed (noted within), at the completion of the reaction, the CH_2Cl_2 and excess TFA were removed under reduced pressure. Further drying under vacuum for several hours provided the corresponding amine·TFA salts.

General Procedure 4 for Pbf/Boc Deprotection of Type D Peptidomimetics. To a solution of the *N*-protected peptide **D** in reagent grade CH_2Cl_2 (3.3 mL/0.1 mmol of substrate) was added TFA (3.3 mL/0.1 mmol of substrate) and, where specified, H_2O (20 equiv), and the solution was stirred at rt in an air atmosphere for 16 h. The solvents were removed under reduced pressure and the residue dried under high vacuum. This was taken up in CH_2Cl_2 (*ca.* 0.5 mL) and an aliquot of excess ethereal HCl (2 M in Et_2O, 1.6 mL/0.1 mmol of substrate) was added to exchange the TFA anion with chloride. The mixture was again concentrated and dried under reduced pressure. The remaining sticky solid was dissolved in minimal MeOH (≤10 drops from a Pasteur pipette for ≤0.05 mmol of product) and reagent grade Et_2O (5 mL) was rapidly added, resulting in instantaneous precipitation of the product. The precipitate was collected via vacuum filtration and the original vessel (containing significant product deposited on the glass) and filter cake were washed with Et_2O (3×10 mL). The filter cake was transferred back into the original vessel (containing the remainder of the product) via dissolution with MeOH (*ca.* 10 mL). Concentration and drying under reduced pressure provided the desired hydrochloride salts **E** as thin films which routinely gave easily-handled powders upon scratching with a spatula.

Representative synthesis of compound 127 from oxazole 16

(*S*)-*tert*-Butyl (1-(4-(hydroxymethyl)oxazol-2-yl)-3-methylbutyl)carbamate (17). To a solution of the known oxazole ester **16**[22] (1.08 g, 3.46 mmol) in THF (10 mL) at 0 °C under N_2 was added a solution of $LiBH_4$ (2.0 M in THF, 5.2 mL, 10.4 mmol) followed by dropwise addition of absolute EtOH (1.0 mL, 17.1 mmol). The mixture was allowed to warm to rt with stirring over 3 h, then EtOAc (5 mL) was added. After an additional 30 min, the reaction mixture was re-cooled to 0 °C and quenched by the dropwise addition of 1 M HCl (10 mL) until the evolution of H_2 had ceased. The mixture was poured into water (20 mL) and the product extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated to give alcohol **17** (870 mg, 88%) as a pale yellow gum. TLC (50% EtOAc/pet. ether) R_F = 0.49; TLC (5% MeOH/CH_2Cl_2) R_F = 0.48; $[\alpha]_D^{25}$ −57.9 (*c* 1.94, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 5.09 (bm, 1H), 4.98 – 4.89 (m, 1H), 4.58 (d, *J* = 5.8 Hz, 2H), 2.48 (t, *J* = 6.1 Hz, 1H), 1.78 – 1.59 (m, 3H), 1.44 (s, 9H), 0.95 (d, *J* = 5.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 155.1, 140.2, 134.9, 79.9, 56.1, 47.3, 43.5, 28.3, 24.6, 22.5, 22.1; MS (ES^+) *m/z* 307 (100%, M+Na), 285 (100%, M+H); HRMS (ES^+) Calcd. for $C_{14}H_{25}N_2O_4$: 285.1814 (M+H), Found: 285.1811.

(*S*)-*tert*-Butyl (1-(4-(isobutoxymethyl)oxazol-2-yl)-3-methylbutyl)carbamate (29). This compound was prepared in two steps from alcohol **17** via the mesylate ester intermediate. Thus, to a solution of **17** (56.9 mg, 0.20 mmol) and NEt_3 (32.4 mg, 0.32 mmol) in reagent grade CH_2Cl_2 (1.0 mL) at 0 °C in an air atmosphere was added a solution of MsCl (36.7 mg, 0.32 mmol) in CH_2Cl_2 (1.0 mL) and the mixture was allowed to warm to rt with stirring over 45 min. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated to give the mesylate intermediate (72.5 mg, quant.) as a yellow gum which was used directly without further purification. TLC (5% MeOH/CH_2Cl_2) R_F = 0.63. To generate the sodium alkoxide for the second step, to a solution of i-BuOH (0.37 mL, 4.00 mmol) in THF (0.5 mL) under N_2 at −78 °C was added a solution of NaHMDS (1.0 M in THF, 1.2 mL, 1.2 mmol) and the mixture was stirred at −78 °C for 15 min. To this was added a solution of the mesylate (72.5 mg, 0.20 mmol) and TBAI (7.4 mg, 0.020 mmol) in THF (2.0 mL) and the mixture was allowed to warm to rt with stirring for 24 h. The mixture was diluted with Et_2O (20 mL) and washed with 1 M HCl (20 mL) and saturated $NaHCO_3$ (20 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (6% EtOAc/pet. ether) gave **29** (54.4 mg, 80% over two steps) as a colorless gum. TLC (10% EtOAc/pet. ether) R_F = 0.23; $[\alpha]_D^{25}$ −43.9 (*c*

0.15, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1H), 5.07 (bm, 1H), 4.98 – 4.88 (bm, 1H), 4.40 (s, 2H), 3.27 (d, *J* = 6.7 Hz, 2H), 1.89 (sep, *J* = 6.7 Hz, 1H), 1.77 – 1.60 (m, 3H), 1.43 (s, 9H), 0.94 (d, *J* = 6.4 Hz, 6H), 0.91 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 155.0, 138.2, 135.7, 79.7, 77.7, 64.9, 47.4, 43.6, 28.33, 28.26, 24.6, 22.6, 22.1, 19.3; MS (ES^+) *m/z* 379 (18%, M+K), 363 (100%, M+Na), 341 (49%, M+H), 285 (58%, M+HCOOH−Boc); HRMS (ES^+) Calcd. for $C_{18}H_{32}N_2NaO_4$: 363.2260 (M+Na), Found: 363.2256.

(*S*)-1-(4-(Isobutoxymethyl)oxazol-2-yl)-3-methylbutan-1-amine (63). This compound was prepared according to *General Procedure 3* using Type **B** protected amine **29** (34.0 mg, 0.10 mmol) to give **63** (24.2 mg, 100%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (s, 1H), 4.38 (s, 2H), 4.04 (t, *J* = 7.0 Hz, 1H), 3.26 (d, *J* = 6.5 Hz, 2H), 1.88 (sep, *J* = 6.5 Hz, 1H), 1.73 – 1.58 (m, 5H), 0.93 – 0.87 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 138.0, 135.5, 77.8, 65.0, 48.3, 45.1, 28.3, 24.7, 22.8, 22.0, 19.3; MS (ES^+) *m/z* 241 (100%, M+H); HRMS (ES^+) Calcd. for $C_{13}H_{25}N_2O_2$: 241.1916 (M+H), Found: 241.1928.

***tert*-Butyl ((*R*)-6-(((*R*)-1-(((*S*)-1-(4-(isobutoxymethyl)oxazol-2-yl)-3-methylbutyl)amino)-1-oxo-5-(-2-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino)pentan-2-yl)amino)-5-(2-(((*S*)-2'-(isopentyloxy)-[1,1'-binaphthalen]-2-yl)oxy)acetamido)-6-oxohexyl)carbamate (95).** This compound was prepared according to *General Procedure 1* using carboxylic acid **A** (84.1 mg, 0.080 mmol) and Type **C** amine **63** (24.0 mg, 0.10 mmol). Flash chromatography (100% CH_2Cl_2 to 1.5% MeOH/CH_2Cl_2) gave **95** (83.8 mg, 82%) as a white solid. TLC (5% MeOH/CH_2Cl_2) R_F = 0.45; $[\alpha]_D^{25}$ −42.1 (*c* 0.77, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (t, *J* = 8.6 Hz, 2H), 7.88 – 7.83 (m, 2H), 7.54 – 7.19 (m, 9H), 7.18 – 7.11 (m, 2H), 6.28 (bs, 2H), 6.13 (bd, *J* = 6.1 Hz, 1H), 5.17 (dd, *J* = 14.7, 7.8 Hz, 1H), 4.82 (bs, 1H), 4.57 – 4.38 (m, 3H), 4.31 (s, 2H), 4.11 – 3.96 (m, 2H), 3.87 (dd, *J* = 15.4, 6.8 Hz, 1H), 3.25 – 3.00 (m, 4H), 2.92 (s, 2H), 2.87 – 2.78 (m, 2H), 2.56 (s, 3H), 2.49 (s, 3H), 2.07 (s, 3H), 1.92 – 1.70 (m, 4H), 1.68 – 1.53 (m, 2H), 1.51 – 1.35 (m, 15H), 1.30 – 1.05 (m, 8H), 0.99 – 0.83 (m, 13H), 0.83 – 0.70 (m, 2H), 0.53 (d, *J* = 6.3 Hz, 3H), 0.48 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 171.2, 169.4, 164.5, 158.6, 156.2, 156.0, 154.3, 152.1, 138.2, 138.0, 135.8, 133.8, 133.5, 133.1, 132.1, 129.74, 129.72, 129.2, 128.0, 127.9, 126.7, 126.5, 125.4, 124.9, 124.4, 124.2, 123.9, 120.2, 119.5, 117.3, 116.0, 114.1, 86.2, 78.9, 77.7, 68.5, 68.0, 64.9, 53.0, 52.5, 46.0, 43.2, 42.1, 40.4, 40.0, 37.9, 31.0, 29.2, 29.0, 28.5, 28.4, 28.3, 25.4, 24.6, 24.4, 22.8, 22.5, 22.3, 22.0, 21.7, 19.3, 19.2, 17.9, 12.4; MS (ES^+) *m/z* 1312 (25%, M+K), 1296 (98%, M+Na), 1274 (100%, M+H); HRMS (ES^+) Calcd. for $C_{70}H_{97}N_8O_{12}S$: 1273.6947 (M+H), Found: 1273.6965.

(*R*)-6-Amino-*N*-((*R*)-5-guanidino-1-(((*S*)-1-(4-(isobutoxymethyl)oxazol-2-yl)-3-methylbutyl)amino)-1-oxopentan-2-yl)-2-(2-(((*S*)-2'-(isopentyloxy)-[1,1'-binaphthalen]-2-yl)oxy)acetamido)hexanamide·dihydrochloride (127). This compound was prepared according to *General Procedure 4* using Type **D** protected peptide **95** (77.4 mg, 0.061 mmol) to give **127** (60.2 mg, 100%) as a white solid. $[\alpha]_D^{25}$ −24.9 (*c* 2.51, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 8.06 – 7.99 (m, 2H), 7.91 (d, *J* = 8.1 Hz, 2H), 7.78 (s, 1H), 7.54 (d, *J* = 9.0 Hz, 1H), 7.49 (d, *J* = 8.9 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.27 – 7.20 (m, 2H), 7.11 – 7.04 (m, 2H), 5.18 – 5.11 (m, 1H), 4.52 (ABq, $\Delta\delta_{AB}$ = 0.08, *J* = 14.8 Hz, 2H), 4.41 – 4.31 (m, 3H), 4.17 – 4.07 (m, 2H), 4.01 – 3.92 (m, 1H), 3.25 (d, *J* = 6.6 Hz, 2H), 3.22 – 3.11 (m, 2H), 2.85 – 2.75 (m, 2H), 1.91 – 1.40 (m, 12H), 1.33 – 1.09 (m, 5H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 6H), 0.57 (d, *J* = 6.5 Hz, 3H), 0.52 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 173.7, 173.3, 171.0, 165.8, 158.5, 155.9, 154.0, 138.9, 138.3, 135.2, 135.0, 131.3, 130.8, 130.6, 129.3, 129.1, 127.6, 127.5, 126.4, 125.9, 125.1, 124.8, 121.6, 120.5, 116.8, 115.9, 78.5, 69.2, 68.9, 65.2, 54.3, 53.9, 47.1, 42.8, 41.9, 40.3, 39.2, 32.0, 30.0, 29.5, 27.6, 26.4, 25.8, 25.6, 23.2, 23.0, 22.8, 22.6, 22.1, 19.7; MS (ES^+) *m/z* 921 (<5%, M+H), 461 (100%, M+2H); HRMS (ES^+) Calcd. for $C_{52}H_{73}N_8O_7$: 921.5602 (M+H), Found: 921.5599.

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