Bioorganic & Medicinal Chemistry Letters 19 (2009) 3010–3013

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Binaphthyl scaffolded peptoids via ring-closing metathesis reactions and their anti-bacterial activities

Adel Garas [a], John B. Bremner [a,*], Jonathan Coates [b,†], John Deadman [b,†], Paul A. Keller [a,*], Stephen G. Pyne [a,*], David I. Rhodes [b,†]

[a] School of Chemistry, University of Wollongong, Wollongong, NSW 2522, Australia
[b] Avexa Ltd, 576 Swan St, Richmond, Vic 3121, Australia

ARTICLE INFO

Article history:
Received 9 March 2009
Revised 7 April 2009
Accepted 8 April 2009
Available online 18 April 2009

Keywords:
Antibacterial
Peptoid
Cationic
Binaphthyl

ABSTRACT

An efficient synthesis of four new acyclic and four new cyclic binaphthyl-based cationic peptoids is described. These compounds had anti-bacterial activities with MIC values of 4–62 μg/mL against *Staphylococcus aureus*.

With the increasing spread of antibacterial resistance,[1–3] including resistance by pathogenic bacteria to vancomycin,[4,5] there is a strong imperative for new antibacterials.[6,7] In this context, we have undertaken a programme investigating the design and synthesis of cyclic cationic peptoids linked by a hydrophobic scaffold as potential antibacterial agents, and thus far, have shown the binaphthyl (**1**)[8] and carbazole (**2**) scaffolds[9,10] within these cyclic peptoids produce antibacterial agents, whilst the smaller indole and phenyl based cyclic peptoids (**3**)[11] and (**4**)[12] had weak activities or were inactive (Fig. 1). Therefore, as part of this programme targeting new peptoid derivatives as antibacterial agents we investigated the preparation of further novel binaphthyl cyclic cationic peptides, **11a**,**b** and their acyclic analogues **9a**,**b**. In this study the peptide moieties are attached to the 2 and 2' positions of the binaphthyl system, rather than the 3 and 3' positions as in peptoid **1**. This modification made these new derivatives synthetically more accessible than our earlier compounds (compound **1** was obtained in twelve synthetic steps) and avoided the problems associated with the extra, uncontrolled stereogenic centre in the peptoid side chain.[8] Furthermore, these target compounds maintained the key structural units that we have found that are important for antibacterial activity, (1) a basic amino acid residue for potential electrostatic interaction with the carboxy group of terminal D-Ala or D-Lac; (2) a peptoid moiety for potential H-bonding interactions with both D-Ala or D-Lac; and (3) a hydrophobic 1,1′-binaphthyl system.[8]

These target peptoids were prepared in four and five steps, respectively from the known and racemic mono-*O*-allylbiphathyl **5**[13] as shown in Scheme 1. The phenolic group of **5** was O-alkylated under basic conditions with ethyl bromoacetate and ethyl 4-bromobutyrate to give the esters **6a** and **6b**, respectively. Saponification of these esters with aqueous lithium hydroxide/THF and then acidification of the final reaction mixture resulted in production of their respective carboxylic acids, **7a** and **7b** (Scheme 1). A peptide coupling reaction of these carboxylic acids with D-lys-N^{ε}-Boc-L-allylglycine[14] under standard conditions[12] gave the dipeptoids **8a** and **8b**, respectively in good yields (85–88%). *N*-Boc deprotection of **8a** and **8b** by exposure to TFA, followed by anion exchange with HCl, provided the hydrochloride salts **9a** and **9b**, respectively (Scheme 1).[12] Treatment of **8a** and **8b** with 10 mol % Grubbs' first generation ruthenium catalyst $[(Cy_3P)_2Ru[CHPh]Cl_2]$ resulted in successful ring-closing metathesis reactions and gave the cyclic peptoids **10a** and **10b**, respectively in good to excellent yields (77–93%, the *E*/*Z* ratios could not be readily determined due to peak overlap) (Scheme 1). *N*-Boc deprotection of these compounds by treatment with TFA,[15] followed by anion exchange with HCl, realised the hydrochloride salts **10a** and **10b**, respectively (Scheme 1).[15,16]

Compounds **9a**,**b** and **11a**,**b** underwent N-guanidination reactions by treatment with *N*,*N*′-bis(*tert*-butoxycarbonyl)-*N*″-triflylguanidine to give their respective homoarginine analogues **12a**,**b**

---

* Corresponding author. Tel.: +61 2 4221 4287; fax: +61 2 4221 4692.
E-mail addresses: jbremner@uow.edu.au (J.B. Bremner), keller@uow.edu.au (P.A. Keller), spyne@uow.edu.au (S.G. Pyne).
† Tel.: +61 3 9208 4094; fax: +61 3 9208 4100.

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.04.046

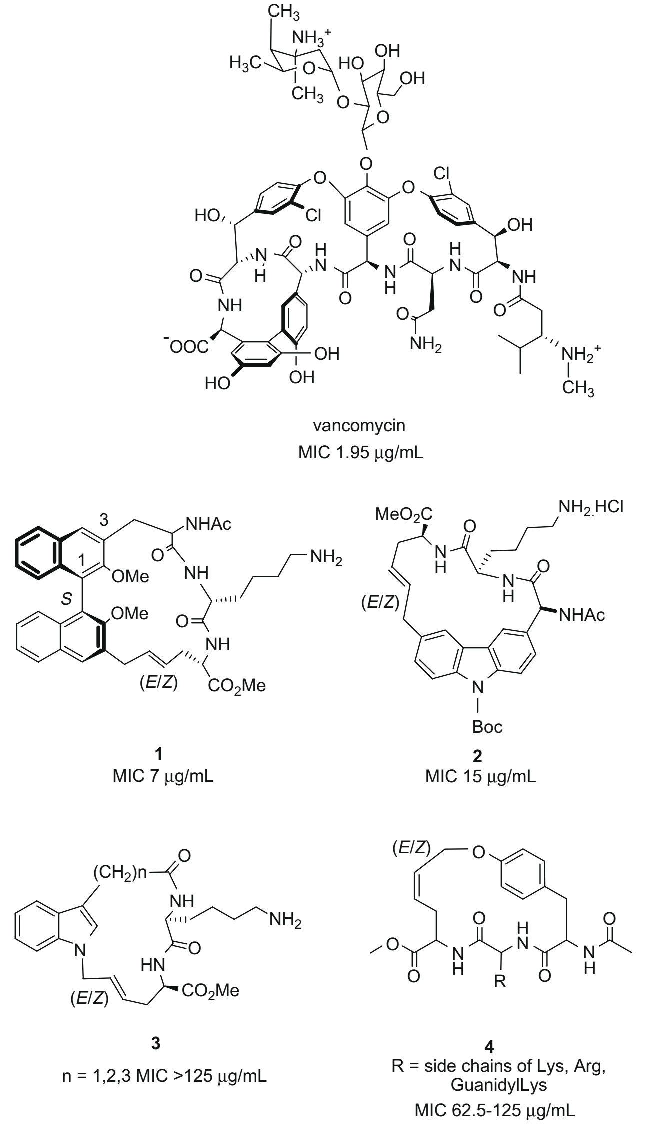
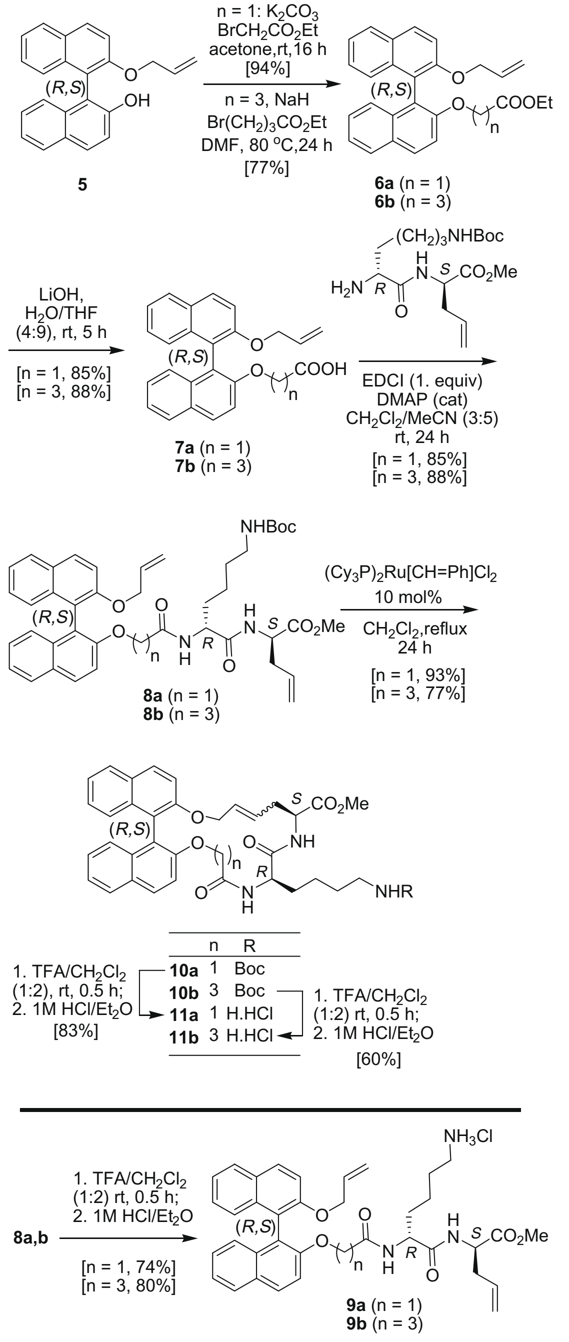


Figure 1. MIC values against *S. aureus* of vancomycin and cyclic peptoids **1**–**4**.

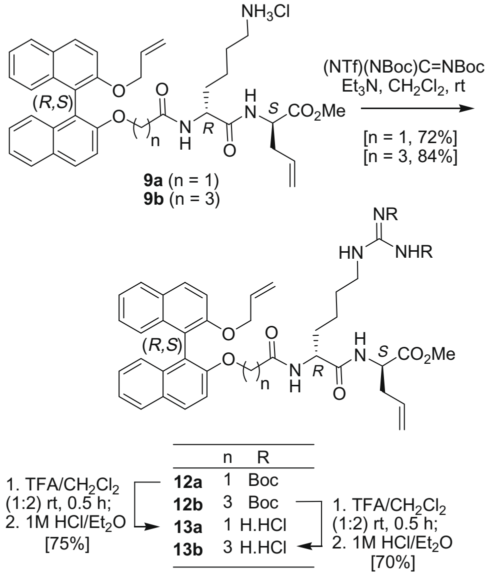
and **14a**,**b**, respectively (Schemes 2 and 3).[16] These compounds were then converted to their hydrochloride salts **13a**,**b** and **15a**,**b**, as shown in Schemes 2 and 3.

To assist with SAR studies on the above set of deprotected compounds the mono-peptoid **17** was prepared as shown in Scheme 4. A coupling reaction of the carboxylic acid **7a** with D-lys-N^{ε}-Boc(OMe) under standard peptide conditions using DCC and HOBt in MeCN[12] gave the peptoid **16** in 71% yield. *N*-Boc deprotection of **16** with TFA, followed by anion exchange with HCl provided the hydrochloride salt **17** (Scheme 4).

The synthesized cationic peptoids **9a**, **9b**, **11a**, **11b**, **13a**, **13b**, **15a**, **15b** and **17** were tested against the Gram-positive bacterium Staphylococcus aureus (ATCC6538) and the results are shown in Figure 2. The positive control, vancomycin, showed a MIC value of 1.95 μg/mL. The acyclic peptoid **9a** showed the highest antibacterial activity with a MIC value of 4 μg/mL. This compound was more active than its cyclic counterpart **11a** which had a MIC value of 15–31 μg/mL. Their three carbon chain elongated and ring enlarged analogues **9b** and **11b**, respectively, were significantly less active. Surprisingly, the acyclic and cyclic peptoids having a homoarginine side chain, **13a**, **13b**, **15a** and **15b**, all had MIC values of 8 μg/mL. Thus, except for **9a**, all homoarginine derivatives were more active than their lysine counterparts. This suggested that the more basic and multi-N-centred guanidine residue was responsible for this enhanced activity. In contrast, the mono-peptoid **17** was not as active (MIC of 32 μg/mL) as the related dipeptoids **9a** and **9b** suggesting that the C-terminal allylglycinate residue also contributes to antibacterial activity. Svendsen[17] has provided a pharmacophore model for peptoid antibacterial compounds which indicates that two hydrophobic and two cationic sites are important for antibacterial activity. In our case the C-terminal allylglycinate residue of **9a**, **9b**, **13a** and **13b** would represent the second, albeit considerably smaller, hydrophobic group when compared to the binaphthyl residue. These results highlight the importance of hydrophobicity within the peptoid for antibacterial activity and indicate that in this series cyclic and acyclic peptoids have

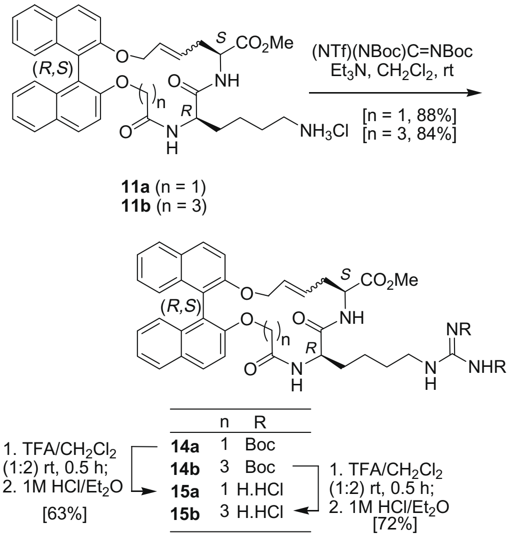


Scheme 1.



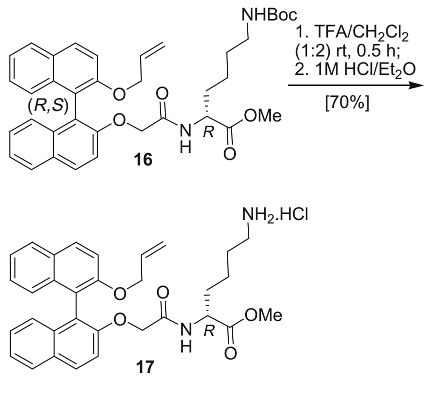
	n	R
12a	1	Boc
12b	3	Boc
13a	1	H.HCl
13b	3	H.HCl

Scheme 2.

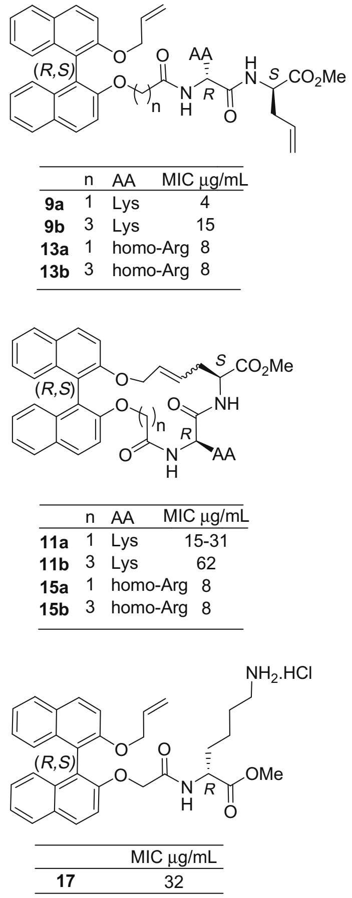


	n	R
14a	1	Boc
14b	3	Boc
15a	1	H.HCl
15b	3	H.HCl

Scheme 3.



Scheme 4.



	n	AA	MIC μg/mL
9a	1	Lys	4
9b	3	Lys	15
13a	1	homo-Arg	8
13b	3	homo-Arg	8

	n	AA	MIC μg/mL
11a	1	Lys	15-31
11b	3	Lys	62
15a	1	homo-Arg	8
15b	3	homo-Arg	8

	MIC μg/mL
17	32

Figure 2. MIC values against *S. aureus* of acyclic and cyclic peptoids as their hydrochloride salts.

similar anti-bacterial activities. While the configuration of the binaphthyl unit in the tested compounds was *R,S* we have found in earlier studies that the configuration of the binaphthyl unit had little impact on antibacterial.[18]

In conclusion, the acyclic cationic peptide **9a** can be readily prepared in four synthetic steps and has greater antibacterial activity against *S. aureus* than the structurally more complex and synthetically more challenging cyclic peptoid **1**. The study thus provides a platform for further development of antimicrobial agents with improved activity against *S. aureus.* We are currently extending these studies to molecules that incorporate two hydrophobic residues and two cationic residues and these studies will be reported in the future publications.

Acknowledgments

We thank the former Amrad Operations Pty Ltd and Avexa Limited, the University of Wollongong and the National Health and Medical Research Council (Development Grants 303415 and 404528) for their support, and Dr. Susan Cox for her support in the initial development of this project.

References and notes

1. Nordmann, P.; Naas, T.; Fortineau, N.; Poirel, L. *Curr. Opin. Microbiol.* **2007**, *10*, 436.
2. Nicolaou, K. C.; Boddy, C. N. C. *Sci. Am.* **2001**, *284*, 54.
3. Noble, W. C.; Virani, Z.; Cree, R. G. A. *FEMS Microbiol. Lett.* **1992**, *93*, 195.
4. Kahne, D.; Leimkuhler, C.; Lu, W.; Walsh, C. *Chem. Rev.* **2005**, *105*, 425.

5. Appelbaum, P. C. *Clin. Microbiol. Infect.* **2006**, *12*, 16.
6. Rice, L. B. *Am. J. Med.* **2006**, *119*, S11.
7. Wright, G. D.; Sutherland, A. D. *Trends Mol. Med.* **2007**, *13*, 260.
8. Bremner, J. B.; Coates, J. A.; Coghlan, D. R.; David, D. M.; Keller, P. A.; Pyne, S. G. *New J. Chem.* **2002**, *26*, 1549.
9. Bremner, J. B.; Coates, J. A.; Keller, P. A.; Pyne, S. G.; Witchard, H. M. *Synlett* **2002**, 219.
10. Bremner, J. B.; Coates, J. A.; Keller, P. A.; Pyne, S. G.; Witchard, H. M. *Tetrahedron* **2003**, *59*, 8741.
11. Au, V. S.; Bremner, J. B.; Coates, J. A.; Keller, P. A.; Pyne, S. G. *Tetrahedron* **2006**, *62*, 9373.
12. Boyle, T. P.; Bremner, J. B.; Coates, J. A.; Deadman, J.; Keller, P. A.; Pyne, S. G.; Rhodes, D. *Tetrahedron* **2008**, *64*, 11270.
13. Nakamura, Y.; Hollenstein, R.; Zsindely, J.; Schmid, H.; Oberhaensli, W. E. *Helv. Chim. Acta* **1975**, *58*, 1949.
14. Boyle, T. P.; Bremner, J. B.; Coates, J. A.; Deadman, J.; Keller, P. A.; Pyne, S. G.; Somphol, K. *Eur. J. Med. Chem.* **2009**, *44*, 1001.
15. Boyle, T. P.; Bremner, J. B.; Coates, J. A.; Keller, P. A.; Pyne, S. G. *Tetrahedron* **2005**, *61*, 7271.
16. Yields refer to material that had been purified by column chromatography. All compounds (unless specified as mixtures of diastereomers) were homogeneous by TLC analysis and judged to be of >95% purity based upon ^{1}H NMR analysis. Structures were confirmed by NMR and MS analysis.
17. For work on other cationic peptides and a pharmocophore model see: (a) Strom, M. B.; Haug, B. E.; Skar, M. L.; Stensen, W.; Stiberg, T.; Svendsen, J. S. *J. Med. Chem.* **2003**, *46*, 1567; (b) Haug, B. E.; Stensen, W.; Stiberg, T.; Svendsen, J. S. *J. Med. Chem.* **2004**, *47*, 4159; (c) Haug, B. E.; Stensen, W.; Svendsen, J. S. *Biorg. Med. Chem. Lett.* **2007**, *17*, 2361.
18. Unpublished results from our laboratory.