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2-NAPHTHYLCARBAPENEMS: BROAD SPECTRUM ANTIBIOTICS WITH ENHANCED POTENCY AGAINST MRSA

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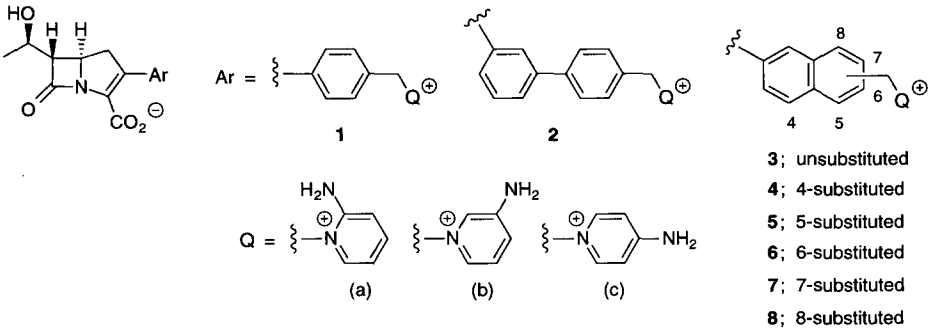
Abstract: A regioisomeric set of 2-naphthylcarbapenems featuring cationic substituents was synthesized. Optimal placement of the cationic group was found to markedly improve activity against methicillin-resistant staphylococci while maintaining a good spectrum of gram-negative activity.

Introduction: Previous reports from these laboratories have described the synthesis and biological activity of zwitterionic 2-phenylcarbapenems such as **1**.[1,2] These compounds showed potent antibacterial activity against a wide range of gram-positive and gram-negative bacteria and good stability to the mammalian DHP-I enzyme. However, they lacked activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase-negative staphylococci (MRCNS), pathogens of increasing clinical importance.[3] More recently, 2-biphenylcarbapenems such as **2** have been disclosed that possess excellent gram-positive activity, including against MRSA/MRCNS, but only very weak gram-negative activity.[4] We now report the synthesis and biological evaluation of the related 2-naphthylcarbapenems **3–8**. In this class of antibacterial agents, appropriate positioning of the cationic group has been found to lead to enhanced activity against MRSA and MRCNS while maintaining a good spectrum of gram-negative activity.



Chemistry: The synthesis of 2-naphthylcarbapenems **3–8** parallels that previously described for the corresponding 2-phenyl- and 2-biphenylcarbapenems and is illustrated in Scheme 1 by the synthesis of **6a–c**.[1,4] The key 2-pyridylthioester intermediate **9** was prepared by a modification of the procedure described by Guthikonda.[2b] Reaction of **9** with the Grignard reagent prepared from bromonaphthalene **10a**[5–7] provided keto-phosphorane **11a** in excellent yield. Desilylation of **11a** under acidic conditions gave carbinol **11b** which was cyclized in an internal Wittig reaction by heating in refluxing *p*-xylene (138 °C, 2 h) to yield the

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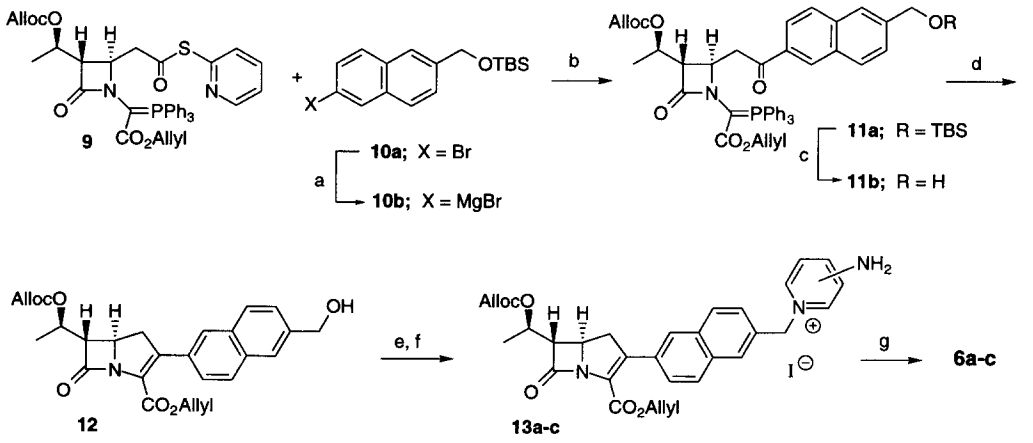
bis-protected 2-naphthylcarbapenem **12** in good yield. Carbapenem **12** was converted to the corresponding iodide via mesylation (MsCl, Et_3N, CH_2Cl_2) followed by Finkelstein reaction (NaI, acetone, 87%). Reaction with 2-, 3-, or 4-aminopyridine then gave pyridinium salts **13a**, **13b**, and **13c**, respectively, which were isolated by precipitation from Et_2O - CH_2Cl_2. Removal of the two allyl protecting groups of **13a–c** by the method of McCombie and Jeffrey[8] followed by reverse phase chromatography yielded carbapenems **6a–c**. The regioisomerically substituted 2-naphthylcarbapenems **4**, **5**, **7**, and **8** were prepared analogously by starting with the appropriate regioisomer of **10a**[9] and **3** was synthesized starting with 2-bromonaphthalene.

Scheme 1. Synthesis of 2-Naphthylcarbapenems



(a) i. *t*-BuLi, THF, -70 °C; ii. $MgBr_2$; (b) THF, -70 °C to -30 °C, 98%; (c) H_2SO_4, MeOH, 0 °C, 76%; (d) *p*-xylene, 138 °C, 2h, 89%; (e) i. MsCl, Et_3N, CH_2Cl_2; ii. NaI, acetone (87%); (f) 2-, 3-, or 4-aminopyridine, CH_3CN (35-82%); (g) $BuCH(Et)CO_2K$, $BuCH(Et)CO_2H$, $Pd(PPh_3)_4$, CH_2Cl_2, EtOAc (17 - 37%).

Biological Evaluation: The antibacterial activity of 2-naphthylcarbapenems **3–8** is shown in Table 1 with **1a** and **2a** included for comparison. These compounds possessed generally good gram-positive activity, slightly less than that of imipenem against methicillin-susceptible staphylococci (MSSA) while being somewhat more active against enterococci. However, against MRSA and MRCNS the cationic-substituted 2-naphthyl-carbapenems **4–8** were in most cases substantially more active than imipenem. For example, compound **6a** was 28-fold more active than imipenem against MRSA and more than 300-fold more active against MRCNS. It is noteworthy that the parent naphthyl compound, **3**, did not show this enhanced MRSA/MRCNS activity. Compounds **4–8** were also generally significantly more active against MRSA/MRCNS than the 2-phenylcarbapenem **1a**, although not as active as the 2-biphenylcarbapenem **2a**. The MRSA/MRCNS activity of **4–8** was not greatly affected by the location of the heteroarylium moiety, except in the case of the 2-aminopyridinium group, which was clearly disfavored at the 4-position (**4a**) and to a lesser extent at the 8-position (**8a**). By contrast, the gram-negative activity of **4–8** was dramatically dependent on the point of attachment of the cationic moiety. Compounds **6a–c** showed excellent gram-negative activity, greater than that of imipenem against *E. coli*, *Serratia*, and *Proteus* and nearly equal to imipenem against *Enterobacter* and *Klebsiella*. The regioisomeric compounds **4** and **8** on the other hand were nearly inactive against the gram-

negative organisms, while **5** and **7** were intermediate in their activity. The unsubstituted 2-naphthylcarbapenem **3** also showed generally poor gram-negative activity, further emphasizing the importance of the cationic group for activity against gram-negative organisms. As has generally been found with 2-arylcarbapenems,[1,2] none of the 2-naphthylcarbapenems described herein showed significant activity versus strains of *Pseudomonas aeruginosa*. All of the 2-naphthylcarbapenems displayed good stability to the mammalian dehydropeptidase, DHP-I, although compounds **6a–c** were somewhat more susceptible than the others.

Table 1. Antibacterial Activity[a] and DHP-I Stability of Carbapenems **1-8**

		Imipenem	1a	2a	3	4a	4b	4c	5c	6a	6b	6c	7c	8a	8c
Species (No.)		MIC (μg/mL)[b]	Fold Improvement in Activity vs Imipenem[c]												
MRSA (1)	G+	33 – 47	2.0	154	3.3	1.4	6.9	11	12	28	13	18	16	4.9	20
MRCNS (1)		70 – 72	1.6	232	2.7	1.9	12	24	77	323	44	77	55	8.0	40
MSSA (4)[d]		0.01 – 0.03	0.5	0.43	0.5	0.13	0.39	0.42	0.42	0.39	0.53	0.45	0.53	0.10	0.15
Enterococcus (3)		1.8 – 3.3	12.9	6.2	2.6	2.2	3.2	2.2	2.7	4.4	2.3	2.7	4.9	2.1	2.4
E. coli (5)	G-	0.19 – 0.70	1.7	0.11	0.31	0.04	0.09	0.06	0.40	1.4	1.3	1.4	0.33	0.04	0.09
Enterobact (6)		0.18 – 0.34	3.0	0.04	0.1	0.01	0.02	0.02	0.18	0.85	0.64	0.92	0.17	0.01	0.03
Klebsiella (5)		0.29 – 0.67	1.1	0.04	0.08	0.02	0.01	0.02	0.21	0.38	0.43	0.40	0.25	0.03	0.04
Serratia (2)		0.29 – 0.86	4.4	0.11	0.09	0.02	0.03	0.02	0.69	2.0	3.0	1.8	0.97	0.05	0.07
Proteus (5)		0.69 – 1.1	4.2	0.38	2.8	0.10	0.13	0.19	15	5.0	6.5	10	3.2	0.22	0.48
Ps. aeruginosa (5)		0.36 – 0.57	0.02	0.01	0.01	0.01	0.01	0.01	0.02	0.02	0.02	0.02	0.01	0.02	0.01
DHP-I Suscept[e]		1.0	0.11	0.04	0.09	0.01	0.01	0.01	0.03	0.20	0.15	0.26	0.07	0.00	0.01

(a) Agar disc diffusion assay (refs 10 and 11). Where more than one strain per species was tested, a geometric mean of the MICs (species index) was calculated. (b) Range of imipenem species indices from several tests. (c) Relative potency, based on species indices for an individual test, calculated by dividing the species index of imipenem by the species index of the test compound. (d) Methicillin-susceptible *S. aureus*. (e) DHP-I (porcine) susceptibility is rate of hydrolysis relative to that of imipenem (ref 12).

Several 2-naphthylcarbapenems were selected for further evaluation against panels of clinically relevant MRSA and MRCNS organisms and their activities were compared to **2a**, imipenem and vancomycin (Table 2). These compounds were all substantially more active than imipenem (8- to 16-fold), but were not as active as the 2-biphenylcarbapenem **2a**. The most potent 2-naphthylcarbapenem, **6a**, displayed activity against MRSA and MRCNS which compared favorably with that of vancomycin, the therapeutic agent of choice for the treatment of infections due to these pathogens.[3c]

Table 2. Anti-MRSA/MRCNS Activity[a] of 2-Naphthylcarbapenems

	MRSA (n = 9)			MRCNS (n = 4)	
Compound	Range	(MIC_{50})	(MIC_{90})	Range	(MIC_{50})
2a	0.5 – 2	1	2	2 – 4	2
6a	0.25 – 8	2	4	4 – 16	8
6c	1 – 8	4	8	8 – 16	8
8c	2 – 16	8	8	16 – 32	16
vancomycin[b]	1 – 2	2	2	2 – 8	4
imipenem[b]	1 – 128	32	64	64 – >128	128

(a) Broth microtube dilution method. Mueller-Hinton Broth + 2% NaCl, inoculum ~10^5 cfu/mL, incubation at 35 °C for 48 h. MICs (μg/mL) read to no visible growth. See ref 13 for description of strains. (b) Data reflect the mode of four measurements of each panel.

Conclusions: The 2-naphthylcarbapenems described herein showed good gram-positive activity in general and enhanced activity against MRSA and MRCNS relative to imipenem and the corresponding 2-phenylcarbapenems. Optimal positioning of the quaternary ammonium group was found to be critical to achieving a good spectrum of gram-negative activity. The best compound, **6a**, combined MRSA and MRCNS activity approaching that of vancomycin with gram-negative activity (excluding *Ps. aeruginosa*) comparable to that of imipenem.

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5. All new compounds described herein exhibited spectral properties in accord with the depicted structures.
6. Prepared from 6-bromo-2-naphthoic acid (ref 7) by reduction (BH_3, THF) followed by silylation (TBSCl, Et_3N, CH_2Cl_2).
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9. Prepared from the corresponding bromo-naphthoic acid as described in ref 6.
10. Antibacterial activities were determined by a disc diffusion assay using imipenem as an internal standard. Inhibitory concentration at the edge of the zone of inhibition was computed for each compound and for imipenem by a rearrangement of equation 3 in ref 11, which takes into account the differing molecular weights and the resultant diffusion constants of each compound. Strains were individually calibrated for their critical times.
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13. The staphylococcal strains used in this study were clinical isolates from the Merck Clinical Culture Collection. MRSA included one homotypic/heterotypic strain and eight heterotypic strains. MRCNS included two heterotypic *S. hominis* and two homotypic *S. haemolyticus* strains.