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THE DISCOVERY AND SYNTHESIS OF 2-BIPHENYLCARBAPENEMS ACTIVE AGAINST METHICILLIN RESISTANT STAPHYLOCOCCI

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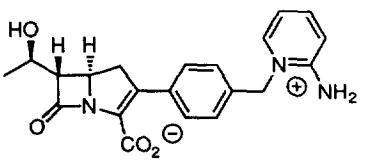
Abstract: The discovery and synthesis of the arylcarbapenem **2b** possessing potent activity against highly resistant strains of methicillin resistant staphylococci are disclosed.

Recently, we reported on the *in vitro* antimicrobial activity of quaternary ammoniomethyl-phenylcarbapenems, such as **1**, which were shown to be potent, broad spectrum antibacterial agents with stability toward mammalian dehydropeptidase.[1] In an attempt to further improve upon the activity profile and pharmacokinetics of **1**, we focused on increasing serum protein binding by increasing the overall lipophilicity of the molecule, and thus initially targeted the biphenyl variants **2**. Of the three possible biphenyl arrays, we opted to synthesize the more readily accessible *para* and *meta* dispositions utilizing the chemistry previously developed for the construction of the related carbapenems **1**.



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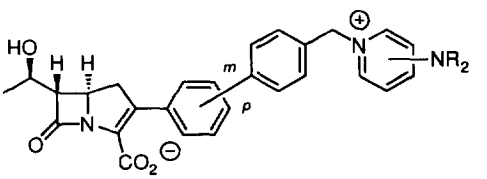

2

The synthesis of molecules **2** is outlined in the Scheme in which the key doubly protected 2-pyridylthioester-azetidinone synthon **3**, prepared by a modification of the route detailed by Guthikonda,[2] underwent Grignard reaction with the magnesium reagents derived from either 4'-dimethyl-t-butylsilyloxymethyl-4-bromobiphenyl (**4a**) or the 3-bromobiphenyl isomer **4b** in THF solution at -10°C for 0.5 hour to afford adducts **5a,b**.[3] Desilylation of the TBDMS group was accomplished with a 10% H_2SO_4 methanolic solution at ambient temperature for one hour to give alcohols **6a,b**, which then underwent intramolecular Wittig reaction in refluxing p-xylene during the course of one hour to provide the requisite, doubly protected carbapenem biphenylcarbinols **7a,b**. Activation of the benzylic position by conversion of the hydroxyl group to the more reactive iodide was accomplished in a straight forward manner as previously described.[1] Displacement reactions of the iodides were performed in acetonitrile at ambient temperature with 4-N,N-dimethylaminopyridine and 2-aminopyridine, respectively, to generate the pyridinium salts **8a,b**. As previously detailed,[1] the removal of the two allyl derived protecting groups was simultaneously accomplished by the method of McCombie and Jeffrey[4] to provide the target class **2**.

Scheme

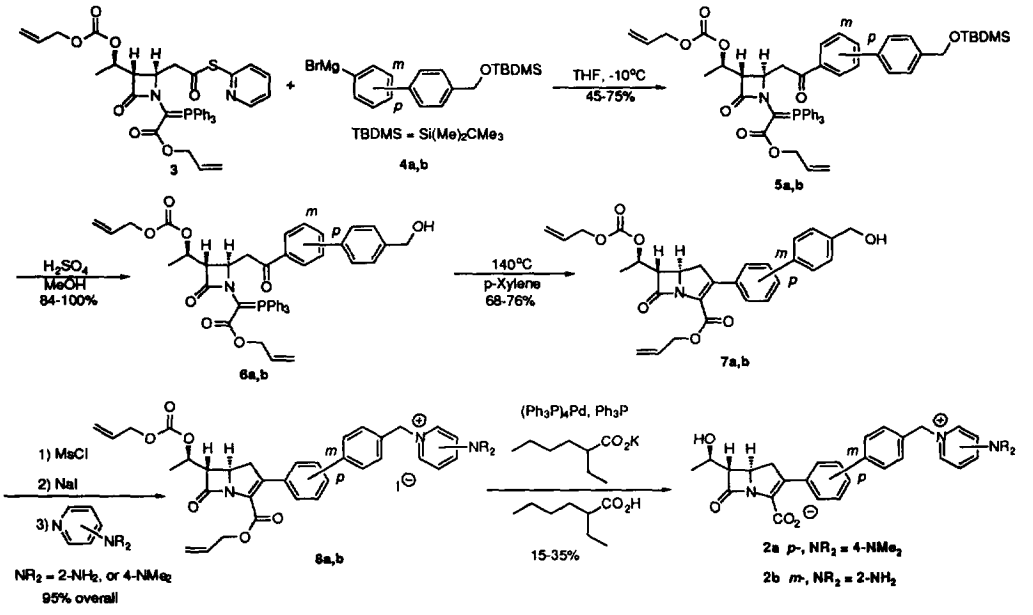

TABLE 1: *In Vitro* Antibacterial Activity [a] and DHP-I Stability of Carbapenems **1, 2a** and **2b**

Species (No.)	MIC[b], μg/mL Imipenem	Fold Improvement in Activity vs. Imipenem[c] 1	2a	2b
Methicillin-Resistant *S. aureus* (1)	33 - 45	2.0	3.9	*154*
Methicillin-Sensitive *S. aureus* (4)	0.01 - 0.27	0.5	0.16	0.43
Enterococcus spp. (3)	1.8 - 2.7	12.9	2.0	6.2
E. coli (5)	0.19 - 0.31	1.7	0.31	0.11
Enterobacter spp. (6)	0.18 - 0.33	3.0	0.12	0.04
Klebsiella spp. (5)	0.29 - 0.39	1.1	0.04	0.04
Serratia spp. (2)	0.29 - 0.77	4.4	0.26	0.11
Proteus spp. (5)	0.78 - 0.95	4.2	0.44	0.38
P. aeruginosa (5)	0.36 - 0.57	0.02	0.013	0.01
		DHP-I Susceptibility Relative to Imipenem[d]		
	Imipenem	1	2a	2b
DHP-I susceptibility	(1.0)	0.11	0.46	0.04

a. Agar disc diffusion assay method (See Ref. 5). In the instances where more than one strain per species was tested, a geometric mean of the MICs (referred to as a species index) was calculated for each species. b. Range of imipenem species indices achieved from several tests given as a reference. c. Relative potency, based on species indices for an individual test, is calculated by dividing the species index of imipenem by the species index of test compound. d. DHP-I (porcine) susceptibility is given as the subject compound hydrolysis rate divided by the hydrolysis rate with imipenem as substrate (See Ref. 6).

In contrast to **1**, the antibacterial profile exhibited by derivatives **2** was markedly altered. As shown in Table 1, both compounds were practically devoid of Gram negative activity and **2a**, the *para*-biphenyl isomer, had reduced activity against the "sensitive" *Staph. aureus* strains. Surprising however, was the anti-methicillin resistant S. *aureus* (MRSA) activity displayed by the *meta*-biphenyl isomer **2b**, as judged by its relative potency to imipenem. Such a level of activity was unprecedented in our primary assay and therefore, warranted further evaluation. Thus, **2b** was subjected to challenge by a panel of clinically relevant strains of MRSA and MRCNS (methicillin-resistant coagulase negative staphylococci), the result of which is depicted in Table 2.

TABLE 2: Anti-MRS Activity of Carbapenem **2b**

		MIC, μg/mL[a]			
Microorganism	ID	**2b**	Vancomycin	Imipenem	Methicillin
Staphylococcus aureus (methicillin-resistant)	CL 714	2	2	32	512
	CL 792	1	2	32	512
	CL 1395	2	2	64	512
	CL 1983	0.5	1	1	64
	CL 1985	1	1	1	64
	CL 1989	0.5	1	2	64
	CL 1990	1	2	4	128
	CL 1991	1	1	1	64
	CL 3025	1	2	2	64
	CL 3031	2	1	32	256
	CL 3033	2	2	128	>512
	CL 3043	1	1	16	128
	Range	0.5 - 2	1 - 2	1 - 128	64 - >512
	MIC_{50}	1	1	4	128
	MIC_{90}	2	2	64	512
Coagulase-negative staphylococci (methicillin-resistant)	CL 171	4	8	>128	>512
	CL 202	2	8	>128	>512
	CL 227	2	2	64	512
	CL 546	2	4	64	>512
	Range	2 - 4	2 - 8	64 - >128	512 - >512
	MIC_{50}	2	4	64	>512
	MIC_{90}	4	8	>128	>512

a. Broth microtube dilution method (See Ref. 7). Mueller-Hinton Broth + 2% NaCl, Inoculum ~10^5 CFU/mL, Incubation at 35°C for 46 hr. MICs read to no visible growth.

When compared to vancomycin, the therapeutic agent of choice for these pathogens,[8] **2b** was equipotent against MRSA and twice as active against MRCNS. Since methicillin-resistant staphylococci are a major cause of nosocomial infections and have become a significant clinical problem,[9] the need for alternative therapy prompted us to pursue the remarkable specificity of activity exhibited by the biphenyl platform, and an extensive program aimed at the development of an optimal anti-MRS carbapenem was initiated. Thus, future publications from these laboratories will detail the results of subsequent studies with *meta*-biphenylcarbapenems and related aromatic platforms.

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5. (a) The antibacterial activity of the synthetic carbapenems was 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 eq. 3 in ref 5b, which takes into account the differing molecular weights and resultant diffusion constants for each compound. Strains were individually calibrated for their critical times. The ratio of inhibitory concentration to that of imipenem is stated in the tables. For comparison, the range of MICs for imipenem are shown for the strains employed. (b) Humphrey, J.H.; Lightbrown, J.W. *J. Gen. Microbiology*, **1952**, *7*, 129.

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