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THE SYNTHESIS AND ANTI-MRSA ACTIVITY OF AMIDINIUM-SUBSTITUTED 2-DIBENZOFURANYLCARBAPENEMS

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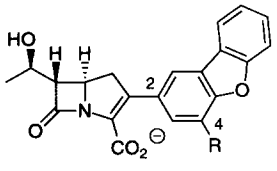
Abstract: A series of amidinium-substituted 2-dibenzofuranylcarbapenems with potent activity against MRSA has been synthesized via a Stille cross-coupling reaction. These new carbapenems show reduced serum protein binding and improved in vivo efficacy as a consequence of the positively charged amidinium substituent.

Introduction: Infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase negative staphylococci (MRCNS) are becoming an increasingly serious clinical problem worldwide.[1] In these laboratories, there has been an ongoing effort to identify carbapenem antibiotics to combat these infections. Investigation of various 2-arylcarbapenems led to the discovery of 2-*meta*-biphenyl-carbapenems with excellent activity against MRSA/MRCNS.[2] Increased potency was achieved by incorporating the biphenyl moiety into a planar tricyclic ring system such as a dibenzofuran, carboline, or fluorenone.[3] In addition, it has been found that an electron withdrawing substituent at the 4-position of a 2-dibenzofuranylcarbapenem (e.g., **1b,c**) results in a further enhancement of MRSA/MRCNS activity. However, hydrophobic analogs such as **1** show extremely high levels of binding to serum proteins and, as a result, are not highly efficacious in vivo. As a means of overcoming this problem, we have employed positively charged amidinium substituents as electronegative groups at the 4-position of the dibenzofuranyl moiety. The resulting zwitterionic carbapenems **2** have been found to be less highly bound to human plasma proteins than the net anionic derivatives **1** and in most cases retain excellent in vitro activity against MRSA and MRCNS. Improved in vivo efficacy in a mouse systemic infection model has also been demonstrated for carbapenems **2**.



1 ; R = -H (a) -CN (b) -$CONH_2$ (c)

2 ; R = (a) (b) (c)

(d) (e) (f) (g) (h)

Chemistry: The 2-dibenzofuranylcarbapenems **2** were synthesized via a slight modification of our previously described Stille cross-coupling method (Scheme 1).[4] The known β-ketoester **3** was converted to the corresponding enol triflate (Tf_2O, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, -70 °C) followed by in situ protection of the

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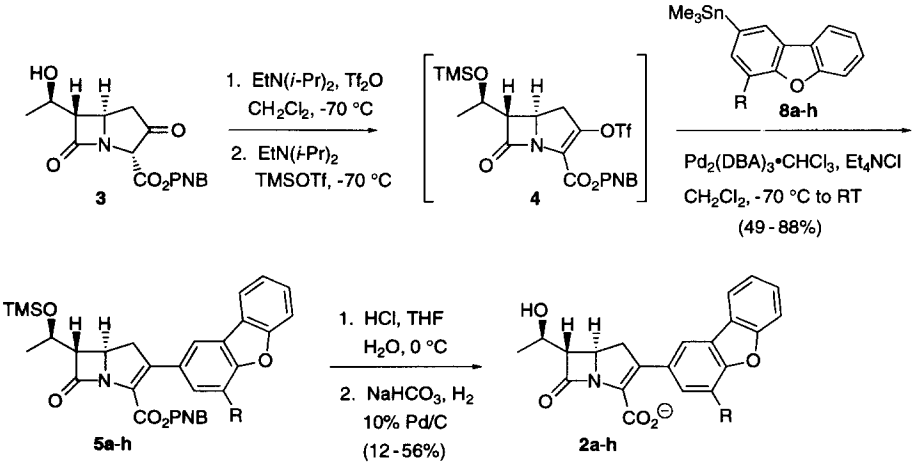
hydroxyethyl sidechain as its TMS ether [TMSOTf, EtN(*i*-Pr)$_2$] to give **4**. Without isolation, enol triflate **4** was reacted with the requisite aryl-stannane **8a–h** employing $Pd_2(dba)_3$•$CHCl_3$ as catalyst and Et_4NCl as a soluble chloride source (CH_2Cl_2, -70 °C to RT). After conventional aqueous work-up, coupled products **5a–h** were isolated in 49–88% yield by precipitation from CH_2Cl_2 - Et_2O. Significantly, this procedure accomplished introduction of the dibenzofuran sidechain with the fully elaborated amidinium substituent in a one-pot sequence. Acidic hydrolysis of the silyl group followed by hydrogenolysis of the *p*-nitrobenzyl ester and finally reverse-phase chromatography gave the desired carbapenems **2** in 12–56% yield.

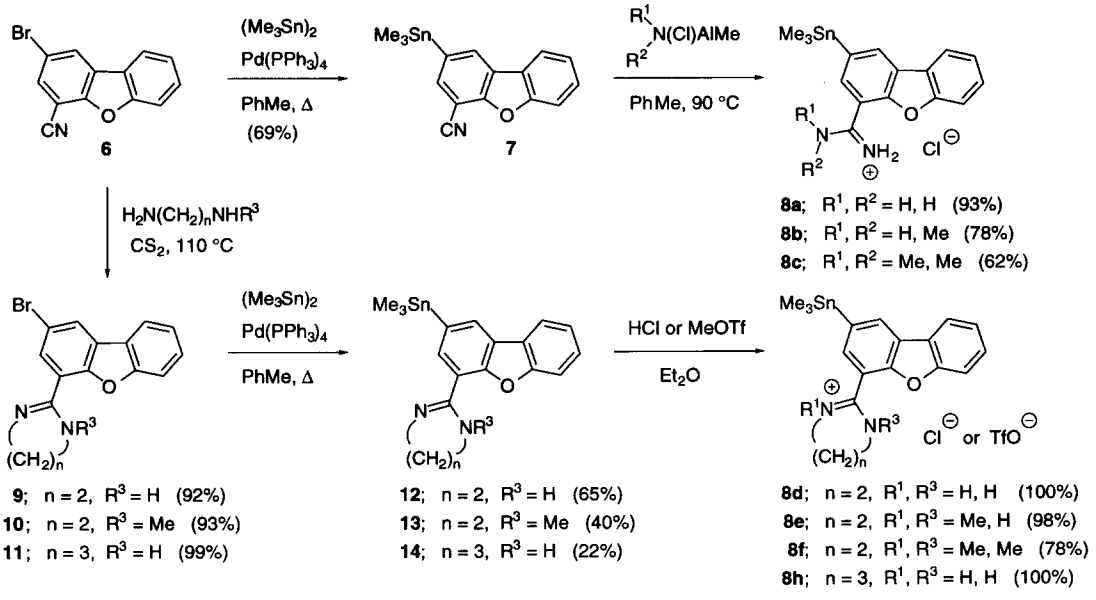
Scheme 1. Synthesis of 2-Dibenzofuranylcarbapenems **2a-h** by Stille Cross-Coupling



The amidinium-stannanes **8a–h** were synthesized as shown in Scheme 2 starting with 2-bromo-4-cyano-dibenzofuran **6**.[5,6] Stannylation of **6** in standard fashion with hexamethylditin provided **7**. Conversion of nitrile **7** to the amidines **8a–c** was accomplished by the one-step method of Garigipati,[7] employing the appropriate aluminum amide reagent[8] in each case. Amidines **8a–c** were isolated as hydrochloride salts after chromatography on silica gel (EtOAc, MeOH, CH_2Cl_2). The cyclic amidines were synthesized by heating nitrile **6** with a large excess of the appropriate 1,2-ethylenediamine or 1,3-propylenediamine derivative and catalytic carbon disulfide[9] to provide **9–11**. Stannylation followed by protonation or methylation then yielded stannanes **8d–f** and **8h**. Stannane **8g** was synthesized from intermediate **10** by dehydrogenation with barium manganate followed by stannylation and methylation.[10,11]

Biological Activity: As shown in Table 1, the simple amidine substituted compounds **2a** and **2d** retained the excellent anti-MRSA/MRCNS activity of compounds **1**. When compared to vancomycin, the therapeutic agent of choice for these pathogens, **2a** and **2d** were 1–2 times as active against MRSA and 4–8 fold more active against MRCNS. However, further substitution of the amidine resulted in a progressive loss of anti-MRS activity. This was particularly striking in the cyclic amidine series where **2e** and **2f** were 4 fold and 32 fold less active than **2d** respectively. This may reflect a requirement for co-planarity of the amidine with the aromatic ring system for optimal activity. Such a conformation would be highly disfavored in compound **2f**. Interestingly, the imidazolium analog **2g** was somewhat more active than **2f**. In addition, the 6-membered cyclic amidine compound, **2h**, was found to be 2–4 fold less active than its 5-membered counterpart **2d**.

Scheme 2. Synthesis of Amidinium Stannanes **8a-h**



8a; R^1, R^2 = H, H (93%)
8b; R^1, R^2 = H, Me (78%)
8c; R^1, R^2 = Me, Me (62%)

9; n = 2, R^3 = H (92%)
10; n = 2, R^3 = Me (93%)
11; n = 3, R^3 = H (99%)

12; n = 2, R^3 = H (65%)
13; n = 2, R^3 = Me (40%)
14; n = 3, R^3 = H (22%)

8d; n = 2, R^1, R^3 = H, H (100%)
8e; n = 2, R^1, R^3 = Me, H (98%)
8f; n = 2, R^1, R^3 = Me, Me (78%)
8h; n = 3, R^1, R^3 = H, H (100%)

As expected, the amidinium substituted compounds **2a–h** were much less highly serum bound than carbapenems **1**. For example, compound **1b** was found to be 98% bound to human plasma proteins whereas **2a** and **2d** were only 71% and 34% bound respectively (Table 2). In addition, **2a** and **2d** showed little or no MIC elevation in the presence of serum, while the MICs of **1b** and **1c** were highly serum antagonized. This proved to be predictive of the in vivo performance of the compounds. In a mouse systemic infection model, against a challenge dose of *S. aureus* MB2985 (methicillin-susceptible), amidines **2a** and **2d** were both more than 10 fold more efficacious than **1b** and 4–5 times more active than **1c**.

Table 1. Anti-MRSA/MRCNS Activity[a] of **1** and **2**

Compd	MRSA (12) Range	MRSA (12) MIC_{50}	MRSA (12) MIC_{90}	MRCNS (9) Range	MRCNS (9) MIC_{50}	MRCNS (9) MIC_{90}
1a	0.5-8	2	4	0.5-8	4	8
1b	0.125-2	0.5	1	0.125-1	1	1
1c	0.25-2	0.5	1	0.25-2	2	2
2a	0.25-4	1	2	0.5-4	1	2
2b	0.5-4	1	4	0.5-2	2	2
2c	1-8	2	8	1-8	4	8
2d	0.25-2	1	1	0.25-1	1	1
2e	1-8	2	4	1-8	2	4
2f	2-32	8	32	8-32	16	32
2g	2-16	4	8	4-16	8	16
2h	0.5-4	1	2	1-4	2	4
VAN[b]	1-2	1	2	2-8	4	8
IPM[b]	1-128	32	128	32->128	128	>128

(a) MICs (μg/mL) were determined using the broth microtube dilution method. Mueller-Hinton Broth + 2% NaCl, inoculum ~10^5 cfu/mL, incubation at 35°C for 46 h. MICs read to no visible growth (ref 2).
(b) VAN = vancomycin; IPM = imipenem. Data reflect the mode of 9 measurements of each panel of strains.

Table 2. In Vivo Efficacy of **1** and **2** in a Mouse Systemic Infection Model[a]

Compd	%PB[b]	MIC (μg/mL)	Plasma MIC[c] (μg/mL)	ED_{50} (mg/kg)
1b	98	<0.016	>32	1.44
1c	95	0.031	1	0.55
2a	71	0.031	0.031	<0.096
2d	34	≤0.016	0.063	0.135
IPM (n=5)	≤5	0.010 (±0.004)	0.014 (±0.004)	0.026 (±0.006)

(a) Charles River CD-1 female mice. Infecting organism *S. aureus* MB2985 (methicillin-suscept). Challenge Dose 4.0 x 10^7 cfu IP in brain heart broth. Antibiotics administered SC at 0 h.
(b) Percent binding to human albumin fraction V.
(c) MIC in presence of human albumin fraction V (21.5 mg/mL).

Conclusions: Positively charged amidinium substituents were employed to reduce the serum protein binding and improve the in vivo performance of a series of 2-dibenzofuranylcarbapenems, while in most cases maintaining excellent activity against MRSA and MRCNS. The most potent compounds, **2a** and **2d**, were more active than vancomycin against MRSA and MRCNS in vitro and demonstrated good in vivo efficacy in a mouse infection model. The compounds described herein thus represent a step forward in our quest to identify new carbapenem antibacterial agents for the treatment of infections due to these troublesome pathogens.

References and Notes

1. (a) Voss, A.; Doebbeling, B. N. *Int. J. Antimicrob. Agents* **1995**, *5*, 101. (b) Brumfitt, W.; Hamilton-Miller, J. M. T. *Drugs Exptl. Clin. Res.* **1994**, *20*, 215. (c) Chambers, H. F. *Clin. Microbiol. Rev.* **1997**, *10*, 781. (d) Ayliffe, G. A. J. *Clin. Infect. Dis.* **1997**, *24* (Suppl 1), S74.
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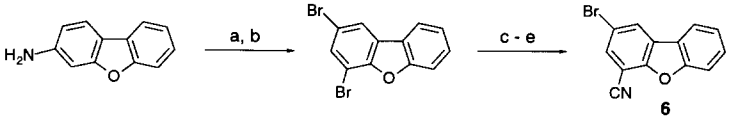
5. Prepared from 3-aminodibenzofuran (ref 6) in 5-steps:



(a) Br_2, dioxane, 2N NaOH, 89%; (b) *t*-BuONO, DMF, 50 °C, 68%; (c) i. *n*-BuLi, THF, -70 °C; ii. DMF, -50 °C; (d) $H_2NOH \cdot HCl$, pyridine, EtOH, 100%; (e) Tf_2O, Et_3N, CH_2Cl_2, -70 °C, 77%.

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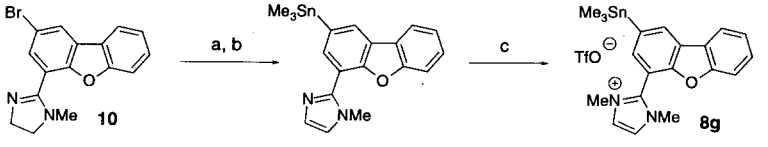
10. Synthesis of stannane **8g**:



(a) $BaMnO_4$, CH_2Cl_2, 45 °C, 83% (ref 11); (b) $(Me_3Sn)_2$, $Pd(PPh_3)_4$, PhMe, Δ, 83%; (c) MeOTf, CH_2Cl_2, 90%.

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