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3-TRIFLUOROMETHYLCARBACEPHEMS: SYNTHESIS OF BROAD SPECTRUM ANTIBACTERIAL COMPOUNDS

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Abstract. The enhanced stability of the carbacephem nucleus over the corresponding cephalosporin nucleus has allowed the synthesis of 7-arylglycyl-3-trifluoromethyl-carbacephems. These unique carbacephems possess broad spectrum activity and high stability to both plasmid and chromosomally mediated ß-lactamases.

Introduction. Carbacephems are structurally related to cephalosporins, differing only by replacement of the sulfur atom with a methylene group. First reported in the early 1970's,[1] the carbacephems maintain the potent antibacterial activity characteristic of the parent cephalosporins.[2] More recently, a cephalosporin vs. carbacephem comparative study demonstrated carbacephem analogs possess enhanced chemical stability.[3] We recognized the carbacephem's equipotent biological activity concomitant with decreased chemical reactivity provided potential medicinal chemistry opportunities.[4-6]

D-(-)-arylglycyl side chains attached to the C-7 position of cephalosporin antibiotics allow active transport across the intestinal barrier.[7,8] Cefaclor **24,** the leading oral cephalosporin, is used to treat Gram positive and a limited number of Gram negative organisms. We focused our efforts on obtaining oral carbacephalosporins that possessed a broader antibacterial spectrum and/or enhanced Gram negative activity compared to cefaclor. Considering the carbacephalosporin's enhanced chemical stability, we targeted arylglycylcarbacephems whose cephem counterparts demonstrated low potency in vitro, presumably due to chemical instability. Our target in this study was the 3-trifluoromethyl-7-arylglycylcarbacephems whose cephem analogs were virtually inactive against bacteria at pH 7.[9] Lack of in vitro activity of the 3-CF_3-7-arylglycylcephems at physiological pH can probably be attributed to chemical instability of the zwitterion form, since activity greater than cephalexin was reported at pH 5.[9] Table I shows a number of representative 3-CF_3 carbacephalosporins acylated with a variety of arylglycyl side chains.

Chemistry. Synthesis of the 7-arylglycyl-3-trifluoromethyl-carbacephems[10] **11–23** proceeded according to Scheme 1. We hoped to incorporate the 3-trifluoromethyl group from readily available *p*-nitrobenzyl (6R,7S)-7-(phenoxyacteamideo)-1-carba-1-dethia-3-[[(trifluoromethyl)sulfonyl]oxy]-3-cephem-4-carboxylate **1**.[11] Triflate conversion to vinyl bromide[12] provided a useful substrate for investigating the applicability of known [CF_3M] couplings to aryl halides.[13] Replacement of the *p*-nitrobenzyl ester with benzhydryl was required due to the difficulty of PNB removal at a later stage. Displacement of the triflates **1** and **2** with LiBr in 2,6-lutidine produced the bromides as a mixture of Δ-2 and Δ-3 isomers that could be isomerized with DBU and crystallized to give the desired Δ-3-vinyl bromides **3** and **4**. Pregeneration of Burton's[14] [CF_3Cu] reagent using CF_2Br_2/DMF/zinc/CuBr and subsequent coupling with the bromides (**3** and **4**) gave the desired trifluoromethyl derivatives **5** and **6**. The zwitterion **8**, used to obtain compounds **11**, **12**, **16**, and **20–23** was obtained from **5** in three steps: (1) the *t*-Boc protecting group was first added to the amide of the phenoxyacteyl side chain using

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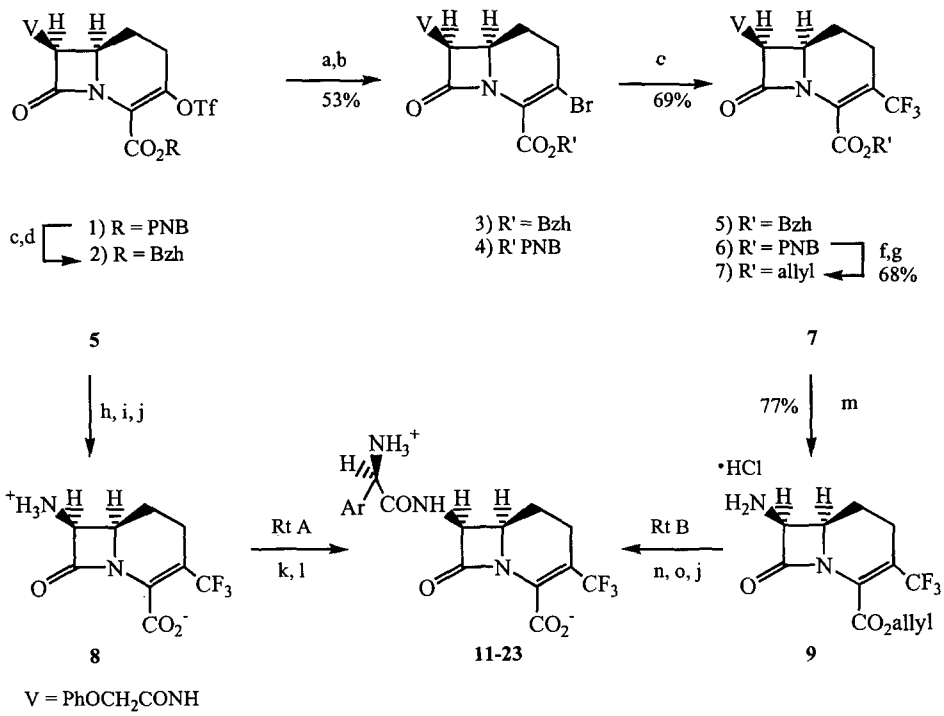
Boc anhydride, (2) treatment with mild base at ice bath temperature removed the phenoxyacteyl group to yield *t*-Boc amide,[15] and (3) deprotection with TFA/triethylsilane removed the *t*-Boc amide and benzhydryl ester. Acylation with a *t*-Boc phenylglycyl isobutanyl mixed anhydride, *t*-Boc removal with TFA, and subsequent purification using reverse phase chromatography gave the desired 3-trifluoromethyl-7-arylglycyl carbacephems **11, 12, 16,** and **20–23**.

Scheme 1



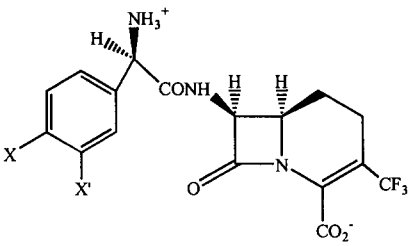
(a) LiBr, Lutidine, DMF. (b) DBU, CH_2CL_2. (c) Zn/HCl. (d) Ph_2CN_2, CH_3CN. (e) Zn, CF_2Br_2, DMF, CuBr. (f) Zn/HCl. (g) allylBr, Bu_4NHSO_4. (h) *t*-Boc anhydride, DMAP. (i) LiOH. (j) TFA, Et_3SiH. (k) *t*-Boc-arylglycyl mixed anhydride. (l) TFA. (m) PCl_5, *i*-BuOH. (n) *t*-Boc-arylglycine, 1-Chloro-3,5-dimethoxytriazine, NMM, CH_2Cl_2. (o) $Pd(PPh_3)_4$, N-Bu_3SnH.

Compounds **13–15** and **17–19** were made by the following procedure: PNB ester removal from 6 with zinc/HCl and esterification of the tetrabutylammonium salt with allyl bromide yielded **7** whose phenoxyacetyl side chain was cleaved with PCl_5 and butanol to give **9**. The amino acid was activated with 1-chloro-3,5-dimethoxytriazine[16] and coupled to the 7-amino group. Deallylation with $(Ph_3)_4Pd^{\circ}$/tributyltin hydride[17] and reverse phase chromatography provided the desired 3-trifluoromethyl-7-phenylglycyl carbacephems **13–15** and **17–19**. Racemic *t*-Boc amino acids were used in the acylation when chiral amino acids were not available (see Table I) and the diastereomers were separated during reverse phase chromatography.

Table I: Arylglycyl Compds

Compd	X	X'	Route	Yield
11	H	H	A	43%
12	OH	H	A	40%
13	F	H	B	14%
14	H	Br	B	9%
15	NH_2	H	B	10%
16*	CH_3	H	A	2%
17	H	$NHSO_2Et$	B	12%
18	H	F	B	14%
19	H	CF_3	B	11%
20*	H	CH_3	A	13%
21	H	$NHSO_2CH_3$	A	39%
22	OH	Cl	A	41%
23*	Cl	Cl	A	3%

* Racemic amino acid starting material



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In Vitro Activity. The 3-CF_3 carbacephems' microbiological activity is displayed in Tables 2 and 3 with cefaclor **24** as reference. Overall activity against gram positive organisms (e.g., *Staphylococcus sp.* and *Streptococcus s.p.*) is comparable to cefaclor. Methicillin-resistant *S. aureus,* X400 and S13E, do show a tendency towards less resistance to these compounds than to cefaclor. The 3-CF_3 carbacephems show the same potent activity as cefaclor against Gram negative *H. influenza* and *E. coli* strains, but in several other Gram negative organisms the majority of analogs show significantly more activity than cefaclor. Surprisingly lower MIC's for plasmid and chromosomally mediated ß-lactamase producing strains (e.g., *Klebsiella KAE* and *Enterobacter cloacae 265A*) indicated significant ß-lactamase stability that is virtually unseen in comparator compounds. In addition, many Gram negative organisms including *Serratia sp., Citrobacter sp., Proteus sp.,* and *Acinetobacter sp.* are notably more susceptible to these new carbacephems in vitro. More details regarding these findings will be published later.

Several arylglycyl analogs have potency comparable to or greater than the parent compound (**11**). 4-OH-Phenylglycine **12** is slightly less potent than the parent **11** against Staphylococcal organisms, but in most other cases, is 1-2 dilutions more potent. Similiarly, 4-OH, 3-Cl-phenylglycine **22** shows 1-2 dilutions lower MIC's than **11** against most organisms. With several exceptions, all compounds show good activity against Gram positive bacteria as well as *H. influenza, E. coli,* and *Klebsiella.* Aryl substituents other than hydroxyl result in reduced potency against the Gram negative organisms in Table 3, particularly 3-CF_3-phenylglycine and 3,4-diCl-phenylglycine **19** and **23**.

Table 2: Microbiological Activity I*

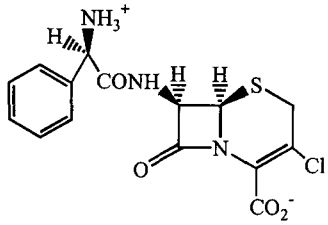
	Staphylococcus			*Streptococcus sp.*			*H. influ*		*E. coli*		*Klebsiella*	
	aureus			*Gp. A*	*pneu.*	*D*	*Amp-S*	*B-lact*	*sens*	*B-lact*	*pneumoniae*	
Compd	**X1.1**	**X400**	**S13E**	**C203**	**PARK**	**2041**	**C.L.**	**76**	**EC14**	**TEM**	**X26**	**KAE**
11	0.5	32	8	0.03	0.25	16	1	1	0.5	1	0.25	4
12	0.5	64	32	0.01	0.03	4	0.5	0.5	0.25	0.5	0.06	1
13	1	64	32	0.06	0.25	32	0.5	1	1	1	0.5	8
14	1	16	8	0.13	0.13	8	0.5	1	4	4	0.25	16
15	2	64	64	NG	NG	16	1	1	0.5	1	0.5	16
16	1	4	4	0.06	0.13	8	2	4	2	4	0.5	8
17	4	32	32	0.06	0.13	32	1	4	1	1	0.25	32
18	2	64	32	0.06	0.25	32	2	2	4	2	2	16
19	2	16	16	NG	0.13	16	1	1	8	16	1	64
20	1	4	4	0.03	0.25	8	1	2	2	4	1	16
21	2	16	16	0.06	0.13	16	2	2	0.5	1	0.5	16
22	1	8	8	0.03	0.06	4	0.5	0.5	0.5	1	0.13	4
23	0.5	64	8	0.02	0.13	16	2	2	32	16	1	64
24	0.5	128	128	0.06	0.5	32	2	1	1	2	0.25	128+

MIC's (minimum inhibitory concentrations) were determined by a standardized agar-dilution method (ref 18) using Mueller-Hinton agar (BBL Microbiology System, Cockeysville, MD) and an inoculum of approximately 10,000 CFU/spot.

* See ref 19 for organism descriptions.

Table 3: Microbiological Activity II*

	Enterobacter				**Salm.**	**Serratia**			**Providencia**		**Citro**	**Acin**
	aerogenes		**cloacae**					**morg.**	**stu.**	**rett.**		
Compd	**C32**	**EB17**	**EB5**	**265a**	**X514**	**X99**	**SE3**	**PR15**	**PR33**	**C24**	**CF17**	**AC12**
11	4	2	4	8	0.25	8	16	32	4	8	4	32
12	0.25	0.5	1	1	0.06	2	16	16	1	4	4	16
13	8	8	8	8	0.5	16	32	16	8	8	8	64
14	16	32	64	64	4	128	128	16	16	16	32	16
15	8	4	16	32	0.25	16	32	8	32	16	16	64
16	8	8	16	32	4	16	64	8	16	16	16	16
17	16	16	32	32	1	64	128	16	16	32	32	64
18	16	8	16	32	2	32	64	32	16	16	16	32
19	128	128	4	128	32	128	128+	32	32	64	128	32
20	32	4	16	32	8	16	32	8	8	16	16	32
21	2	4	16	32	2	16	32	8	8	16	16	64
22	2	1	8	16	0.125	4	16	4	4	4	4	32
23	128	128	128	128	32	128+	128+	32	32	64	128	128
24	32	8	32	128+	0.5	64	128+	128+	64	64	128+	128



24 (Cefaclor)

Summary. A new series of compounds, the 3-trifluoromethyl-7-arylglycyl-carbacephems, has been synthesized by 3-vinyl bromide coupling with in situ generated [CF_3Cu]. Microbiological potency of this series is high at pH 7 with incubation at 37°C and, in most cases, is comparable to cefaclor. These compounds show surprising activity against strains with plasmid and chromosomally mediated ß-lactamases. In vivo activity of compounds **11–12** will be reported in due course.

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