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CYCLIC HOMOPENTAPEPTIDES 3. SYNTHETIC MODIFICATIONS TO THE CAPREOMYCINS AND TUBERACTINOMYCINS: COMPOUNDS WITH ACTIVITY AGAINST METHICILLIN-RESISTANT *Staphylococcus aureus* AND VANCOMYCIN-RESISTANT ENTEROCOCCI

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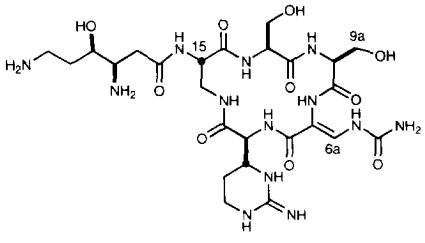
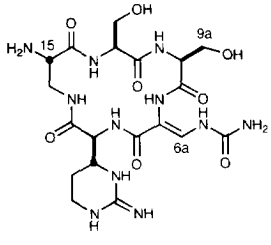
Abstract:. Modification and replacement of the β-lysine side chain of capreomycin and tuberactinomycin cyclic pentapeptide derivatives resulted in compounds with good antibacterial potency against multidrug-resistant pathogens. © 1997 Elsevier Science Ltd.

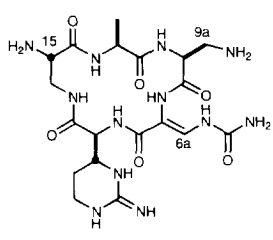
In the first paper of this series we reported the discovery of capreomycin and tuberactinomycin C-6a aryl ureas with excellent potency and efficacy against clinical isolates of vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA).[1] Here we describe our investigations of the effects of substitutions and modifications of the β-lysine moiety. The ultimate goal was to further improve potency or change physicochemical parameters that might be important for the in vivo performance of those analogues.



tuberactinomycin N (1)



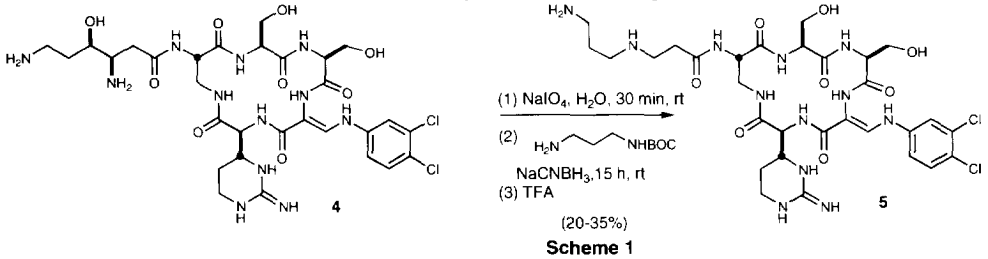
tuberactinamine N (2)



capreomycin IIB (3)

Figure 1

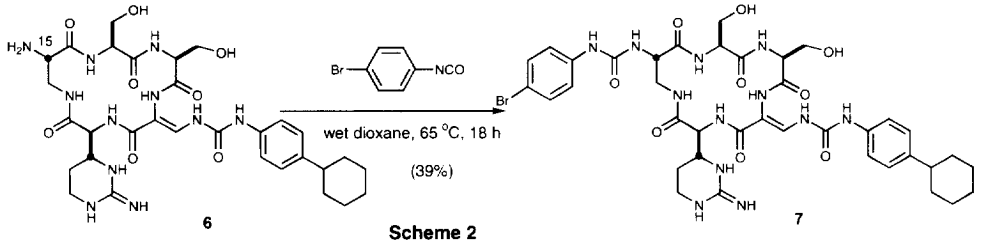
The earliest modifications were made to tuberactinomycin N (**1**), (Figure 1) in which the β-amino-γ-hydroxylysine side chain at C-15 provides a convenient vicinal amino alcohol for oxidative cleavage. Indeed, we found that treatment of tuberactinomycin N analogue **4**[1] with sodium periodate and reductive amination of



Scheme 1

the resultant cleavage product with *N*-*t*-butyloxycarbonyl-1,3-diaminopropane and $NaCNBH_3$ provided **5**. The yields for these transformations were generally 20-35%[2] (Scheme 1).

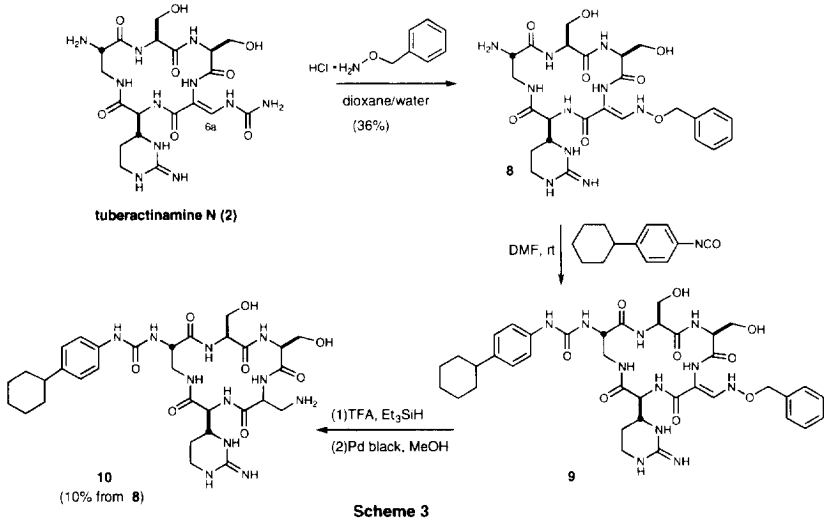
Tuberactinamine N analogues such as **6** could be directly modified and, with a single primary amine at C-15, they did not present the chemoselectivity issues found with capreomycin IIB (**3**). For example, treatment of **6** with 4-bromophenylisocyanate in DMF provided, in 39% yield, compound **7** (Scheme 2), which had a two fold improvement in potency against *S. aureus* (Table 1, entries 3 and 4). Modifications of this type to tuberactinamine N analogs generally resulted in compounds with improved potency against *S. aureus*.



6 **7**

Scheme 2

Earlier, we had shown that the olefin moiety was not essential at the C-6 position,[1] and the example above demonstrated that incorporation of an aryl urea at C-15 improved potency.[3] We felt that a primary amine at C-6 might be tolerated as long as a lipophilic moiety was appended at C-15. With this in mind, our goal became to install an aryl urea at C-15 and convert the vinyl urea to a primary amine. Displacement of the urea at C-6a of tuberactinamine N with *O*-benzylhydroxylamine provided oxime **8** in 36% yield (Scheme 3). Treatment with 4-cyclohexylphenylisocyanate afforded **9**. Reduction of the olefin using TFA/Et_3SiH provided an *O*-benzylhydroxylamine, which subsequently underwent hydrogenolysis with Pd black in methanol to afford **10** in 10% yield from **8**. These changes did not have the desired effect as compound **10** was much less active against the organisms tested than tuberactinamine N analogue **6** (Table 1, entries 3 and 5).



tuberactinamine N (2)

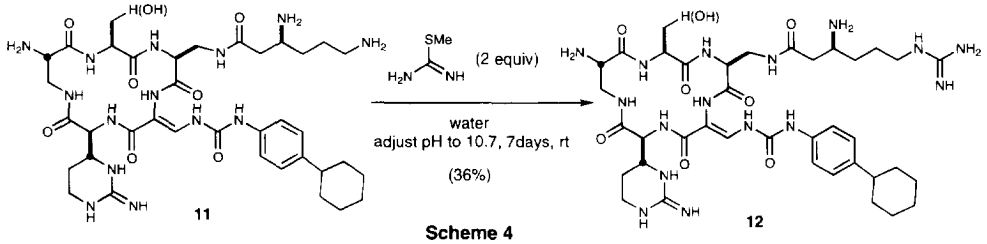
8

9

10
(10% from **8**)

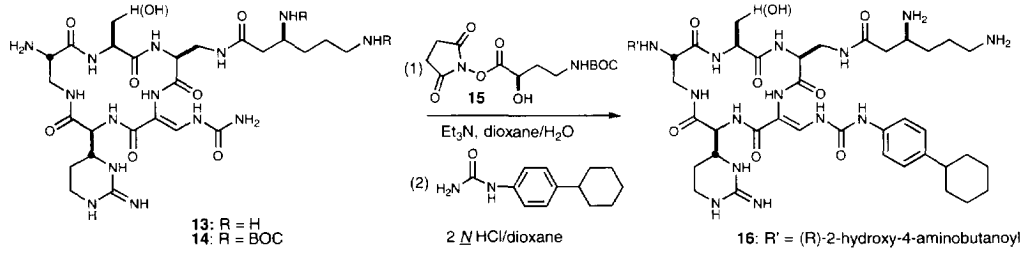
Scheme 3

The effect of increased basicity on potency was examined. Installation of a guanidine moiety at the ω-amine of the β-lysine side chain of **11** provided **12** (Scheme 4). This transformation was achieved, in 36% yield after HPLC purification, by carefully controlling the pH of the reaction mixture[4] over several days. This substantial change in basicity of the compound had no effect on potency against any of the three strains examined (Table 1 entries 6 and 7).



Scheme 4

It had been shown that tuberactinomycin N could be selectively acylated with activated amino acids[5] and beginning with protected intermediate **14**[4] we achieved a similar transformation with capreomycin, (**13**). Acylation of **14** with *N*-hydroxysuccinimide ester **15**[6] followed by a one pot incorporation of 4-cyclohexylphenyl urea and removal of the *t*-butylcarbamate protecting groups gave **16** in less than 10% yield. The potency of compound **16** is slightly less than that of **11**, the corresponding compound without the additional side chain but much better than that of capreomycin.



Scheme 5

In conclusion, we have reported five analogues representing structurally interesting changes to the capreomycins and the tuberactinomycins. Only compound **10** did not demonstrate improved potency over capreomycin, and compounds such as **7**, **12**, and **16** retained useful potency against clinical isolates of multidrug-resistant pathogens, an increasingly difficult therapeutic problem.[7]

TABLE 1
IN VITRO ACTIVITY (MIC μg/mL)[8]

entry	compound	*S. aureus* ery^r, meth^r, cip^r	*E. faecalis* van^r, meth^r, cip^r	*E. faecium* van^r, ery^r, cip^r
1	**4**	12.5	50	25
2	**5**	50	50	50
3	**6**	25	12.5	3.12
4	**7**	12.5	12.5	6.25
5	**10**	>100	>100	>100
6	**11**	1.56	3.12	3.12
7	**12**	1.56	3.12	3.12
10	capreomycin (**13**)	100	>1000	>1000
11	**16**	3.12	6.25	6.25
12	vancomycin	0.78	>100	>100

Abbreviations: ery^r(erythromycin-resistant), meth^r (methicillin-resistant), cip^r (ciprofloxacin-resistant),and van^r (vancomycin-resistant).

References and Notes

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2. The highly charged, highly water soluble cyclic homopentapeptide capreomycins and tuberactinomycins are not soluble in most organic solvents other than methanol or DMF. Most of the chemistry, therefore, was carried out in water or with water as a co-solvent.

3. This result plus the results described in the preceding paper suggested that incorporation of a lipophilic group at any position might lead to improved activity. Lyssikatos, J. Chang, S.-P.; Clancy, J.; Dirlam, J. P.; Finegan, S. M.; Girard, A. E.; Hayashi, S. F.; Larson, D. P.; Lee, A.; Linde II, R. G.; MacLelland, C. P.; Petitpas, J. W.; Seibel, S.; Vu, C. B. *Bioorg. Med. Chem. Lett.* preceding paper

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6. (a) Takahashi, S.; Yanagida, Y. European Patent Application 0 430 234 A2, Kanegafuchi Chemical Industry Co., Ltd. (b) Kawaguchi, H.; Naito, T.; Nakagawa, S.; Fujisawa, K. *J. Antibiot.* **1972**, *25*, 695.

7. The in vivo efficacy of representative cyclic homopentapeptides will be described in a subsequent report.

8. MIC=minimal inhibitory concentration as determined by NCCLS document 197-A3, December, 1993. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. 3rd Edition.

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