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CYCLIC HOMOPENTAPEPTIDES 2. SYNTHETIC MODIFICATIONS OF VIOMYCIN

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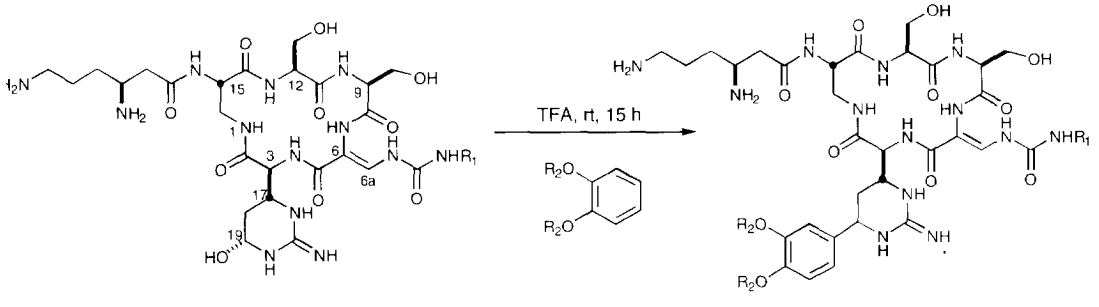
Abstract: This paper describes synthetic modifications of the C-19 position of tuberactinomycin B (viomycin) and related analogs. The in vitro antibacterial activity of selected analogs against *Pasteurella multocida*, *Escherichia coli* and methicillin-resistant *Staphylococcus aureus* is also discussed. Although C-19 arylation and thiolation did not improve antibacterial activity, C-19 benzyl carbamates, benzyl- and phenyl ureas were found to be more potent than the parent antibiotic. © 1997 Elsevier Science Ltd.

We described in an accompanying paper that the antibacterial activity and spectrum of tuberactinomycin B (viomycin) is significantly improved by replacing the C-6a urea moiety with substituted phenyl ureas and anilines.[1] The modification of alternative sites on viomycin was explored in an effort to further improve the antibacterial activity. The synthetic options are limited due to the highly functionalized and charged nature of viomycin. However, we felt that the C-19 position could be modified since, as reported in an accompanying paper, we were able to deoxygenate the C-19 position with triethylsilane in trifluoroacetic acid (TFA). Moreover, previous work published by Kitagawa et al. demonstrated that reductive ring-opening of the viomycidine residue of viomycin to the respective guanidino–alcohol could be achieved using sodium borohydride.[2]

Chemistry: A search was initiated for nucleophiles that could trap the presumed guanidiniminium cation formed in TFA. Treating viomycin in TFA with a tenfold excess of 1,2-dimethoxybenzene or 1,2-dihydroxybenzene cleanly gave the respective Pictet–Spengler type product with undetermined relative stereochemistry (see Scheme 1). These conditions worked equally well with C-6a substituted urea analogs of

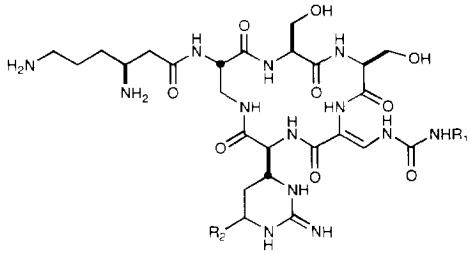
Scheme 1



viomycin. The yields of these reactions ranged from 50-90%. The arylation reaction was not successful with less nucleophilic aryl moieties such as 1,2-dichlorobenzene or benzene. Attempts to allylate the C-19 position with allyltrimethylsilane or allyltributyltin failed, presumably due to the instability of these reagents under strong protic acid conditions. Substitution at the C-19 position proved to be quite general, since thio, carbamate[3], sulfonamide, and urea derivatives could be prepared by treating viomycin, or one of its substituted urea analogs, with the appropriate nucleophile in TFA. The relative stereochemistry was not determined in any of these cases.

Antibacterial Activity: The antibacterial activity for selected compounds against key animal health pathogens and methicillin-resistant *Staphylococcus aureus* (MRSA) is shown below in Tables 1 and 2. Substituting the C-19 position of viomycin, or the C-6a 3,4-dichlorophenyl urea analog of viomycin, with aryl, thio, and *p*-methylsulfonamide groups did not improve activity (Table 1). However, substituting the C-19 position of vio-

Table 1

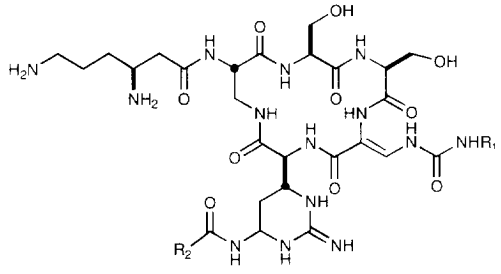


R_1	R_2	*P. multocida* MIC μg/mL	*E. coli* MIC μg/mL
H	OH	200	200
H	3,4-dimethoxyphenyl	>200	>200
H	3,4-dihydroxyphenyl	200	200
3,4-$Cl_2C_6H_3$	OH	3.12	50
3,4-$Cl_2C_6H_3$	3,4-dimethoxyphenyl	12.5	12.5
3,4-$Cl_2C_6H_3$	3,4-dihydroxyphenyl	12.5	12.5
3,4-$Cl_2C_6H_3$	$NH_2(CH_2)_2S$	3.12	25
3,4-$Cl_2C_6H_3$	L-cysteine	3.12	25
3,4-$Cl_2C_6H_3$	L-methylcysteine	3.12	25
3,4-$Cl_2C_6H_3$	N-acetylcysteine	6.25	50
H	4-$MeC_6H_4SO_2NH$	200	200

Abbreviations: MIC (minimum inhibitory concentration); MRSA (methicillin resistant *S. aureus*); N.T. (not tested)

mycin with benzyl carbamate, benzyl urea and phenyl urea groups significantly increased the antibacterial activity (Table 2). The best activity was observed when the phenyl ring was substituted with halogen or alkyl groups. The positioning of these groups on the phenyl ring does not seem to be important. Interestingly, C-19 substitution of 3,4-dichlorophenyl urea derivative of viomycin with substituted benzyl carbamate and phenyl urea groups did not further improve the antibacterial activity.

Table 2



R_1	R_2	*P.multocida* MIC μg/mL	*E. coli* MIC μg/mL	MRSA MIC μg/mL
H	$C_6H_5CH_2O$	25	50	N.T.
H	3,4-$Cl_2C_6H_3CH_2O$	6.25	25	3.12
H	3-$IC_6H_4CH_2O$	6.25	6.25	12.5
H	4-$IC_6H_4CH_2O$	3.13	12.5	12.5
H	2,3-$Cl_2C_6H_3CH_2O$	3.13	25	12.5
H	2-F,4-$ClC_6H_3CH_2O$	3.13	12.5	N.T.
H	4-t-$BuC_6H_4CH_2O$	12.5	25	N.T.
3,4-$Cl_2C_6H_3$	2,4-$Cl_2C_6H_3CH_2O$	6.25	3.13	12.5
H	3,4-$Cl_2C_6H_3NH$	1.56	6.25	25.0
3,4-$Cl_2C_6H_3$	3,4-$Cl_2C_6H_3NH$	6.25	6.25	25.0
H	3,4-$Cl_2C_6H_3CH_2NH$	3.13	12.5	N.T.
H	4-Cychex$C_6H_4CH_2NH$	N.T.	N.T.	25.0
H	3-CychexC_6H_4NH	N.T.	N.T.	12.5
Vancomycin		N.T.	N.T.	0.78

Abbreviations: MIC (minimum inhibitory concentration); MRSA (methicillin resistant *S. aureus*); N.T. (not tested)

References and Notes

1. Dirlam, J. P.; Belton, A. M.; Birsner, N. C.; Brooks, R. R.; Chang, S.-P.; Chandrasekaran, R. Y.; Clancy, J.; Cronin, B. J.; Dirlam, B. P.; Finegan, S. M.; Froshauer, S. A.; Girard, A. E.; Hayashi, S. F.; Howe, R. J.; Kane, J. C.; Kamicker, B. J.; Kaufman, S. A.; Kolosko, N. L.; LeMay, M. A.; Linde II, R. G.; Lyssikatos, J. P.; MacLelland, C. P.; Magee, T. V.; Massa, M. A.; Miller, S. A.; Minich, M. L.; Perry, D. A.; Petitpas, J. W.; Reese, C. P.; Seibel, S. B.; Su, W.-G.; Sweeney, K. T.; Whipple, D. A.; Yang, B. V. *Bioorg. Med. Chem. Lett.* preceeding paper in this series.
2. Kitagawa, T.; Miura, T.; Tanaka, S.; Taniyama, H. *J. Antibiotics* **1973**, *26*, 528.
3. Typical procedures using benzylcarbamates are as follows: A solution containing 500 mg of viomycin sulfate (0.547 mmol) in 5 mL of anhydrous TFA was stirred at room temperature under an atmosphere of dry nitrogen. An excess of 4-chloro-2-fluorobenzyl carbamate (1.10 g, 5.47 mMol) was added and the resulting reaction mixture was stirred at ambient temperature for 15 h. The reaction mixture was then diluted with 50 mL of water and 12 ml of 6 N hydrochloric acid. The aqueous layer was washed 6 times with 15 mL of ethyl acetate and then poured into 30 grams of activated Diaion HP-21 resin (Mitsubishi Kasei Corp.; a high porous polymer absorption resin that was activated by soaking in methanol for 45 min and then thoroughly washing with water). The resulting reaction mixture was shaken at ambient temperature for 45 min and then filtered. The HP-21 resin was thoroughly washed with 300 mL of water and transferred to a beaker containing 250 mL of methanol. The methanol mixture was shaken at ambient temperature for 45 min and then filtered. The filtrate was concentrated under reduced pressure to give 220 mg of the product as the tri-hydrochloride salt.

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