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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 4-UREIDO TRINEMS.

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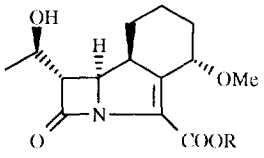
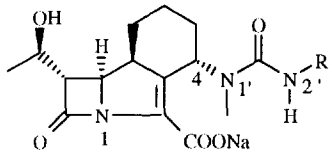
Abstract: This article describes studies carried out on the synthesis and biological activity of 4-ureido trinems **1** obtained by the condensation of various isocyanates and the intermediate **6**. Among others, 4-*N*-methyl-*N*'-alkyl ureido trinems showed a promising antimicrobial activity against Gram-negative bacteria. Copyright © 1996 Elsevier Science Ltd

β-Lactams constitute one of the most important classes of antibiotics, due to their broad spectrum of activity usually associated with low levels of toxicity.

However, the increasing development of resistant strains has necessitated the search for new classes of antibacterial agents. In the light of such need, trinems[1] (formerly referred to as tribactams) were discovered and studied in our laboratories. The 4-methoxy trinem sanfetrinem[2] and its orally active ester pro-drug sanfetrinem cilexetil (**Fig. 1**) showed an impressive biological profile both *in vitro* and *in vivo*, combining a broad spectrum with high potency, stability to human DHP and to β-lactamases. These compounds are currently in phase II clinical trials.

Further studies allowed us to identify other promising series of trinem derivatives. In this Letter we report the preliminary biological results achieved within the new class of 4-ureido trinem.





R = Na Sanfetrinem **1**

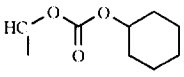
R =  Sanfetrinem cilexetil

Fig. 1

This class of molecules was readily accessed from the advanced intermediate **6** by its reaction with various commercial or synthesised isocyanates (**Scheme 1**).

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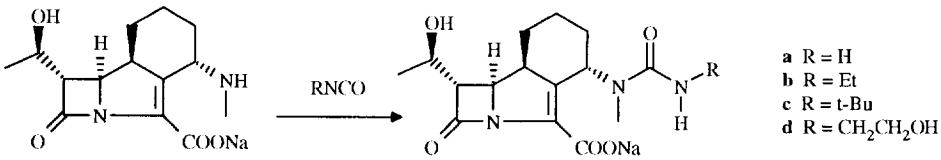
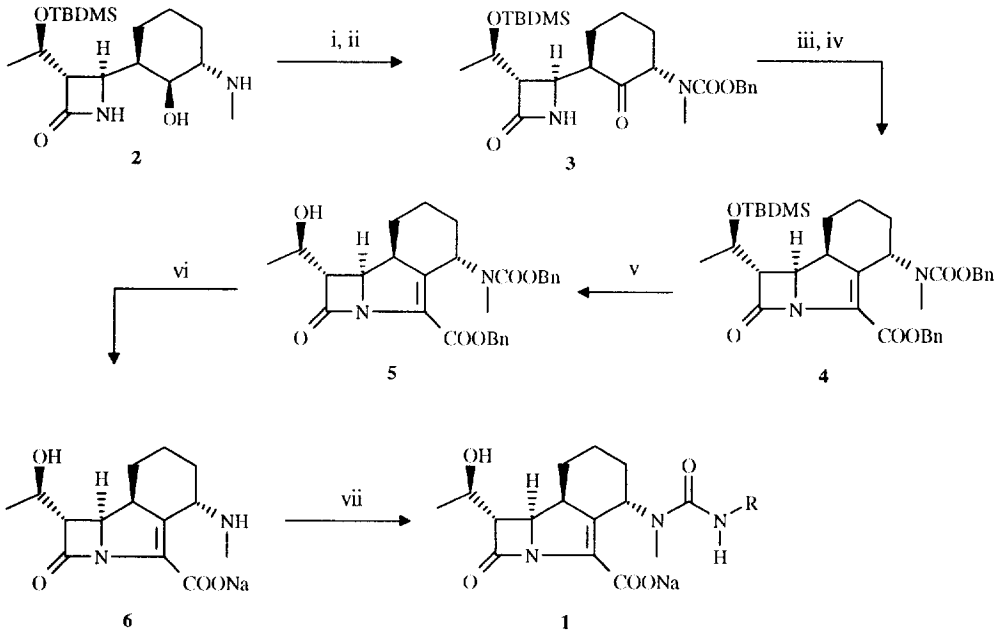


6 1a-d

Scheme 1

The 4-methyl-amino trinem **6** was obtained from the already known amino alcohol **2**[1a,3d] applying the same methodology reported in the literature by using benzyl carbamate and benzyl ester as protecting groups instead of the corresponding allyl derivatives. Protection of the amino group of **2** was carried out with benzylchloroformate and DIPEA; the subsequent oxidation of the secondary alcohol by treatment with oxalylchloride, dimethylsulfoxide and triethylamine in methylene chloride gave the desired ketone **3**. This compound was converted into the corresponding trinem **4** by means of a two step sequence involving *N*-1 acylation with benzyloxalyl chloride followed by treatment with $P(OEt)_3$ to give an intramolecular Wittig-type cyclisation.[4] The silyl protecting group was removed by a standard method using TBAF and acetic acid. Palladium catalyzed hydrogenation and subsequent treatment with a solution of $NaHCO_3$ afforded the key intermediate **6** by simultaneous deprotection of carbamate and ester functions without reduction of the double bond. This compound was then converted to the desired 4-ureido trinems **1a-d** by reaction with the appropriate isocyanate (**Scheme 2**).



2 3 4 5 6 1

i) DIPEA, $BnCO_2Cl$, CH_2Cl_2; ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60°C; iii) K_2CO_3, Py, $ClCOCO_2Bn$; iv) $P(OEt)_3$, xylene, 120°C; v) TBAF, CH_3COOH, THF, rt; vi) 10% Pd/C, H_2, iPrOH, H_2O, $NaHCO_3$; vii) RNCO, H_2O.

Scheme 2

Trinem **1c** was prepared using *t*-butyl isocyanate, which was in turn synthesised from the corresponding 2,2-dimethyl propionic acid. The acid was converted by treatment with diphenylphosphoryl azide to the azide which underwent the Curtius rearrangement upon heating.[5]

Table 1 reports the *in vitro* antibacterial activity (MIC μg/ml) of compounds **1a-d** in comparison with sanfetrinem and imipenem, as determined by microtiter broth dilution test (MIC values).

Table 1

	S. aureus 853	*S. pneum.* 3512	*E. coli* 1850 WT	*E. coli* 1919 PM	*C.perfr.* 615	*B.frag.* 2017	*P. aer.* 2032 WT	*P. aer.* 1911
1a	≤0.12	≤0.12	0.25	≤0.12	≤0,12	≤0.12	1	8
1b	0.25	≤0.12	2.00	0.25	≤0.12	0.50	4	16
1c	0.50	≤0.12	4.00	0.50	≤0.12	0.50	2	16
1d	0.25	≤0.12	0.50	≤0.12	≤0.12	0.25	8	16
Sanfetrinem	0.25	≤0.01	0.50	0.50	0.03	0.06	16	>32
Imipenem	0.10	≤0.01	0.50	0.50	0.03	0.06	4	4

Minimum Inhibitory Concentrations (MIC) determined in Mueller Hinton broth; Anaerobes Schadler broth; inoculum = $5x10^5$ CFU/ml. *S. aureus* 853 = *Staphylococcus aureus* 853E β-lactamase producing strain; *S. pneum.* = *Streptococcus pneumoniae* 3512E; *E. coli* 1850 = *Escherichia coli* 1850E wild type; *E. coli* 1919 = *Escherichia coli* 1919E β-lactamase producing permeable strain; *C. perfr.* 615 = *Clostridium perfringens* 615E; *B. frag.* 2017 = *Bacteroides fragilis* 2017E; *P. aer.* 2032WT = *Pseudomonas aeruginosa* 2032 wild type; *P. aer.* 1911 = *Pseudomonas aeruginosa* 1911 permeable strain.

The preliminary results obtained for 4-*N*-methyl-*N'*-alkyl ureido trinems **1a-d** show them to have good antibacterial activity across the range of representative bacteria studied. Moderate permeability problems were observed for compounds **1b** and **1c** against Gram-negative strains, highlighted by the difference in activity between the wild type *E. coli* 1850 and the permeable strain *E. coli* 1919. All of the compounds exhibited stability to β-lactamase enzymes as shown by the observed activity against β-lactamase producing strains, as well as stability to DHP-I.

In conclusion the promising antimicrobial activity shown by this class of compounds, particularly against *P. aeruginosa* as highlighted by compound **1a**, together with the ready accessibility of the advanced intermediate **6**, has prompted us to consider this class of antibacterial agents as deserving further investigation.

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