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SYNTHESIS AND BIOLOGICAL EVALUATION OF 4-ALKOXY SUBSTITUTED TRINEMS. PART I

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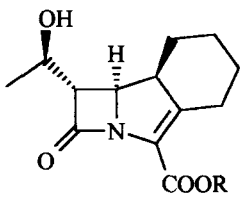
Abstract. Synthesis of new 4-alkoxy substituted trinems **4**, **5**, **6**, **7** and **8** together with their antibacterial profiles compared to imipenem and GV104326 (**2**) are described. The good antibacterial profile observed for derivatives **4-7** encouraged further exploration of these derivatives.

The intense interest in the study of β-lactam antibiotics has led, in the last fifteen years, to the continue introduction of new classes of compounds[1] endowed with a broad spectrum of activity associated with very low toxicity levels which ensure them an outstanding role in antibacterial chemotherapy.

Fig.1



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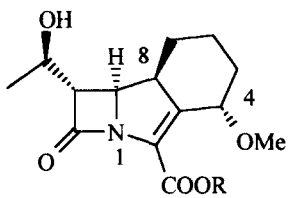
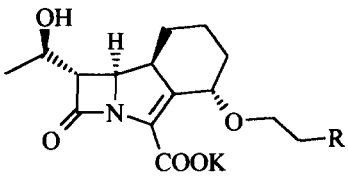
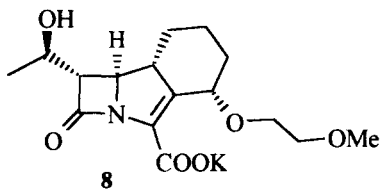


2, GV104326, R = Na
3, GV118819, R = $CH(CH_3)OCOOC_6H_{11}$

4, R = OMe
5, R = OH
6, R = CN
7, R = F

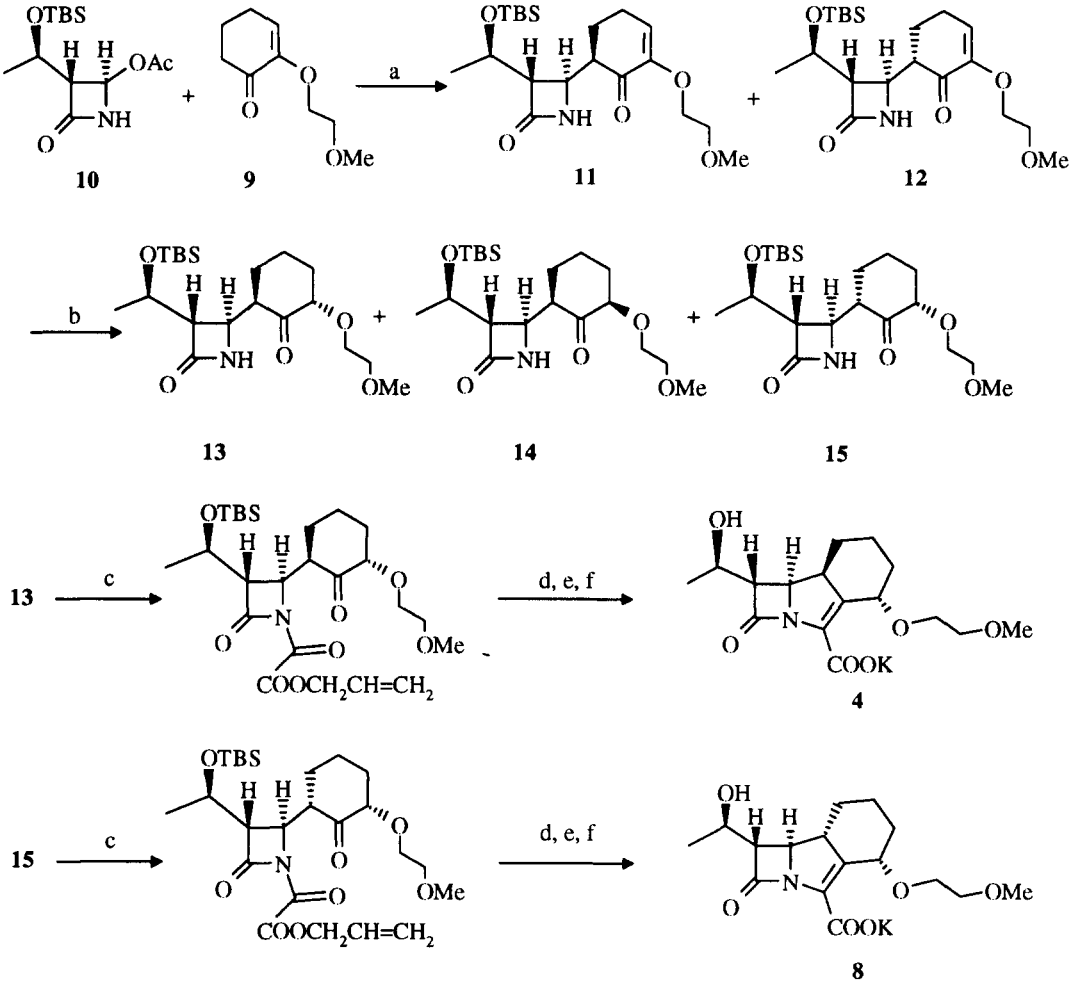




8

Some years ago, we at Glaxo[2] have identified a novel class of tricyclic β-lactam antibiotics, trinems (**1**, Fig. 1), formerly referred to as tribactams, which are characterised by high potency, high stability to both most relevant β-lactamases and to renal dehydropeptidases, associated with a good chemical stability. As a result GV104326, (**2**, Fig.1), and its metabolically labile ester GV118819 (**3**, Fig.1) were selected for development and are currently in phase II clinical trials.

Scheme 1



a) LHMDA, -78°C, THF; b) Pd/Al_2O_3, H_2 4.5 atm., EtOH; c) TEA, $ClCOCOOCH_2CH{=}CH_2$, CH_2Cl_2; d) $P(OEt)_3$, xylene, 120-140°C; e) TBAF, AcOH, THF; f) $Pd(PPh_3)_4$, potassium 2-ethylhexanoate.

With the aim to investigate biological properties of others 4-alkoxy derivatives, the synthesis of a series of analogues of **2** was undertaken in our laboratories, and this paper describes the synthesis and the preliminary antibacterial profile of compounds **4-8** (Fig. 1).

Trinems **4** and **8** have been prepared according to the procedure[3] utilised for compounds **2**, as outlined in Scheme 1. 2-(Methoxyethoxy)-cyclohex-2-en-1-one[4] **9** was reacted with commercially available