SYNTHESIS AND HUMAN LEUKOCYTE ELASTASE INHIBITORY ACTIVITY OF NOVEL 2-SPIRO(2',2'-DIPHENYLCYCLOPROPANE) CEPHALOSPORIN SULFONES

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A new series of 2-spiro(2',2'-diphenylcyclopropane) cephalosporin sulfones was synthesized as potent human leukocyte elastase inhibitors.

Proteolytic tissue damage by human neutrophil elastase (HNE) released from human polymorphonuclear leukocytes (PMN) by inflammatory stimuli, plays a major role in the destructive process associated with chronic inflammatory diseases such as rheumatoid arthritis [1], emphysema [2], adult respiratory distress syndrome [3], and cystic fibrosis [4]. It has been postulated that development of these degenerative diseases will result from genetic or chemically induced imbalance of the proteinase-antiproteinase system. Indeed, in the development of these pathologies, the natural plasma inhibitors of HNE, α1-AT (also called α1-PI), and (α2-macroglobulin) (α2-M) are thought to have diminished capacity to protect host connective tissues from degradation by the enzyme. Use of synthetic low molecular weight and selective HNE inhibitors that can be delivered to the site of unregulated PMN elastase activity could be an attractive approach in the treatment of the above-mentioned diseases. These possibilities have led to an intensive search for human neutrophil elastase inhibitors. Various modified cephalosporins have been found to be potential anti-elastase agents [5-14] in pathological conditions in which HNE is implicated. We have investigated the classes of 7a-methoxy-2-(1,3-dithiolan-2-ylidene)cephem sulfones [15] and found that some representatives are very potent inhibitors of HNE.

In the present study we will describe the synthesis and reactivity of a newly developed series of 2-spiro(2',2'-diphenylcyclopropane) cephem sulfones as potent and selective HNE inhibitors.

CHEMISTRY

In a general procedure, tert-butyl 7a-methoxy-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (I), which was prepared from 7-aminodeacetoxycephalosporanic acid (7-ADCA) in three steps based on the procedure described by Blacklock et al. [16], was converted to the 2-exomethylene derivative II under Mannich conditions. Compound II was reacted at room temperature with freshly prepared diphenyldiazomethane to give tert-butyl 7a-methoxy-2-spiro(2',2'-diphenyl)cyclopropane)-3-methyl-3-cephem-4-carboxylate 1,1-dioxide (III) as the major product in 85% yield along with the minor products IV-VI. The isolation of compound III as major product suggests that the addition of diphenyldiazomethane to the double bond was facially selective.

Removal of the tert-butyl protecting group from compound III with anhydrous formic acid at 35-40°C over 1 to 3 h or with TFA-anisole in methylene chloride at 0°C gave the corresponding acid (VII) in excellent yield (89-98%). The acid VII was then converted into the acid chloride VIII by reaction with oxalyl chloride in methylene chloride in the presence of a catalytic amount of DMF. The acid chloride VIII was smoothly transformed into various amides (IX) by reaction with appropriate amines in the presence of triethylamine. Similarly, the acid chloride VIII was

(a) aq. CH$_2$O—Me$_2$NH·HCl/1,4-dioxane/tert-BuOH; (b) Ph$_2$CN$_2$/DCM;
(c) HCOOH, 35...40 °C, 3 hrs; (d) (COCl)$_2$/DCM; (e) amines, DCM;
(f) Cul/THF/$R^2$MgX