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Synthesis and biological evaluation of novel steroid-modified ether phospholipids

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Abstract

Platelet activating factor is one of the most potent inflammatory ether phospholipid mediators known and structurally modified analogues are of considerable interest as potential therapeutic preparations. Inspired by the proposed structure for a novel endogenous hydroxy-PAF analogue isolated recently from gingival crevicular fluid, we designed and prepared two novel steroid-modified ether phospholipids. These two novel compounds exhibit marked chemical and biological similarities to their endogenous prototype and they antagonize it being less active in inducing washed platelet aggregation through PAF receptors.

Keywords: Steroid ether phospolipids; Platelets; Platelet activating factor; PAF-acetylhydrolase; Periodontal disease

1. Introduction

Platelet-activating factor (1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine, PAF) occurs naturally in cell membranes and is one of the most potent inflammatory ether phospholipid mediators known (Blank et al., 1981; Demopoulos et al., 1979; Montrucchio et al., 2000). PAF (1, Fig. 1) plays an important role in a number of physiological and pathological processes, such as allergy, hypotension, anaphylaxis, thrombosis, ischemia, acute infections in transplantation, nephritis, gastric ulcer, etc. (Snyder, 1987). Activated inflammatory cells challenged by bacterial lipopolysaccharides produce and secrete inflammatory mediators like PAF (Jakubowski et al., 2004), which is believed to be a key regulator of various diseases like periodontal disease (Antonopoulou et al., 2003). Moreover, PAF has been shown to stimulate platelet degranulation and aggregation (Snyder et al., 1989), to cause the contraction of smooth muscles, bronchoconstriction, and coronary

Abbreviations: Ac, acetyl; Bn, benzyl; LPC, lysophosphatidylcholine; PAF, platelet-activating factor; Ph, phenyl; SM, sphingomyelin; TBAF, tetrabutylammonium fluoride; TBDPS, tert-butyldiphenylsilyl; THF, tetrahydrofuran

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