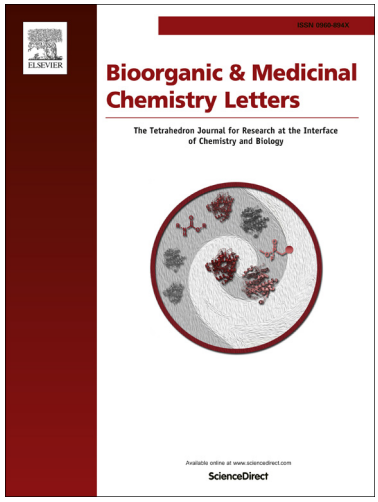

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Strategies for the modulation of phase II metabolism in a series of PKCε inhibitors.

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ABSTRACT

Extensive phase II metabolism of an advanced PKCε inhibitor resulted in sub-optimal pharmacokinetics in rat marked by elevated clearance. Synthesis of the *O*-glucuronide metabolite as a standard was followed by three distinct strategies to specifically temper Phase II metabolic degradation of the parent molecule. In this study, it was determined that the introduction of proximal polarity to the primary alcohol generally curbed O-glucuronidation and improved PK and physical chemical properties while maintaining potency against the target. Utilization of a Jacobsen hydrolytic kinetic resolution to obtain optically enriched final compounds is also discussed.

In the discovery and development of novel drug candidates, drug metabolism is an area of intense scrutiny as undesirable metabolic instability can alter the pharmacokinetics and pharmacodynamics of a compound while potentially producing metabolites leading to toxicity by various mechanisms.[1-2] Conjugative phase II metabolism specifically renders typically lipophilic xenobiotics much more polar, increasing their clearance potential and suppressing exposure of the parent compound.[3] Although often observed as a post-phase I oxidation event, *O*-glucuronidation can occur directly on compounds containing alkyl alcohols, phenols and carboxylic acids. This type of metabolic pathway is a significant contributor to the clearance of drugs such as propofol, morphine and various NSAIDS.[4-5] When significantly observed, the attenuation of this metabolic clearance pathway is therefore pursued in the development of drug candidates.

Protein kinase C epsilon (PKCε) is a serine/threonine kinase belonging to the novel class of the greater family of PKC enzymes. PKCε signaling has been implicated in immunologic, nervous and inflammatory systems leading to investigation of the enzyme as a therapeutic target for diseases such as chronic pain and cancer.[6-12] Although diversely expressed, PKCε is abundantly present in neuronal cells and has been implicated specifically in primary afferent nociceptor sensitization as well as mechanical hyperalgesia.[13] As part of a program targeting therapeutics for neuropathic pain, we identified a series of PKCε inhibitors represented by compound **1** which demonstrated potent activity (PKCε K_i = 25nM, Figure 1). In an effort to attenuate observed *O*-glucuronidation of **1** resulting in metabolite **2**, a rationally designed set of diverse functionalities was introduced in place of the metabolically susceptible ethyl alcohol sidechain. The synthesis of **1** as well as related analogues relied on key intermediates **6** and **7**, the syntheses of which are shown in Scheme 1.

Commercially available 2-fluoro-4-iodonicotinaldehyde is treated with in situ generated trifluoromethyl anion giving aldol product **3**. Manganese oxide oxidation followed by cyclization with hydrazine affords pyrazolopyridine compound **5**. Protection

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