



Simultaneous determination of SU5416 and its phase I and phase II metabolites in rat and dog plasma by LC/MS/MS

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Abstract

SU5416, Z-3-[(2,4-dimethylpyrrol-5-yl)methylidene]-2-indolinone, is a cytostatic substance in development as an anti-angiogenic agent. SU5416 has several phase I and phase II metabolites including SU9838, SU6595, SU6689, 5'-hydroxy glucuronide of SU5416 and 5'-acyl glucuronide of SU5416. In order to support the preclinical studies, a liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method for simultaneous determination of SU5416 and its metabolites in rat and dog plasma was developed. This method is fast, simple, sensitive (LOQ = 2.0 ng/ml), reproducible and has a wide linear range (2.0–5000 ng/ml for SU5416, 2.0–2000 ng/ml for SU6689 and 2.0–1000 ng/ml for SU9838 and SU6595). This method was applied to rat and dog plasma samples obtained from pharmacokinetic and toxicokinetic studies. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: SU5416; Drug analysis; Liquid chromatography; Mass spectrometry; LC/MS/MS

1. Introduction

SU5416, Z-3-[(2,4-dimethylpyrrol-5-yl)methylidene]-2-indolinone, is an angiogenesis inhibitor in development [1]. It is a synthetic molecule designed to inhibit the growth of solid tumors by preventing the formation of new blood vessels (angiogenesis) which are required for nourishing the tumors. SU5416 acts by blocking the signaling pathway of the Flk-1 receptor, which is found on the surface of endothelial cell lining of the blood vessel walls. Flk-1 is one of the primary drivers of

angiogenesis in most solid tumors, suggesting a very important opportunity for the development of an effective inhibitor of this receptor [1–4]. SU5416 is currently in phase II/III clinical trials as an anti-angiogenic agent for the treatment of cancer. The objective of this paper is to illustrate a sensitive and validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method developed to analyze SU5416 and its metabolites.

Biotransformation studies on SU5416 [6] have indicated that SU5416 has several metabolites including SU9838, SU6595, SU6689, 5'-hydroxy glucuronide of SU5416 and 5'-acyl glucuronide of SU5416 (Fig. 1). In order to support the pharmacokinetic and toxicological studies of SU5416 and

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