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Journal of Pharmaceutical and Biomedical Analysis
35 (2004) 513–522
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Simultaneous determination of Z-SU5416 and its interconvertible geometric E-isomer in rat plasma by LC/MS/MS

Yeping Zhao[1], Juthamas Sukbuntherng, Lida Antonian*

Department of Bioanalysis, Metabolism and Phamacokinetics, SUGEN Inc., 230 E. Grand Ave., South San Francisco, CA 94080, USA

Received 9 September 2002; received in revised form 19 June 2003; accepted 16 August 2003

Available online 27 March 2004

Abstract

SU5416 is a selective inhibitor of vascular endothelial growth factor (VEGF) receptor, which plays a major role in vascular angiogenesis. SU5416 exists as the thermodynamically stable and pharmacologically active *cis* isomer (Z-isomer) in the solid state. In light-exposed solutions the unstable *trans* isomer (E-isomer) is formed. The E-isomer is unstable for synthesis and isolation and the analytical standard of the E-isomer is unavailable. A new, simple, fast and reliable LC/MS/MS method was developed to quantify both isomers simultaneously in rat plasma samples in order to support the study of disposition kinetics of Z- and E-SU5416. This method is sensitive (LOQ = 0.5 ng/ml), reproducible, and has a wide linear range (0.5–2500 ng/ml).

Keywords: Z-SU5416; LC/MS/MS; E- and Z-isomers

1. Introduction

SU5416, referred to as the Z-isomer in this manuscript, is an angiogenesis inhibitor with selectivity for the vascular endothelial growth factor (VEGF) receptor. 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. It acts by blocking the signaling pathway of VEGF and its receptor, fetal liver kinase-1/kinase insert domain-containing receptor (Flk-1/KDR), which is found on the surface of the endothelial cell lining in blood vessels. Flk-1/KDR is a primary driver of angiogenesis in most solid tumors, and its inhibition by SU5416 was extensively studied in our efforts in cancer research [1–4].

SU5416 exists in two stereoisomeric forms, the E (*trans*) or Z (*cis*) isomer around the double bond between 2-oxindole and the pyrrole ring as seen in Fig. 1. The solid substance exists only as the Z-isomer, which is the thermodynamically stable form. However, in solution it can spontaneously convert to its E-isomer when exposed to light. Specifically, the photoisomerization of the Z to E-isomer in methanol or acetonitrile at pH 10 (basified with NaOH) reaches equilibrium within 5–6 h. The Z-isomer is completely stable in acidified (pH 2) methanol or acetonitrile [5]. The E-isomer is not stable in solution, and readily

* Corresponding author. Tel.: +1-650-837-3761; fax: +1-650-837-3311.
E-mail address: lida-antonian@sugen.com (L. Antonian).
[1] Present address: Exelixis, 170 Harbor Way, South San Francisco, CA 94083, USA.

0731-7085/$ – see front matter © 2004 Published by Elsevier B.V.
doi:10.1016/j.jpba.2003.08.017