Send Orders for Reprints to reprints@benthamscience.ae

Inhibitors of Angiogenesis in Cancer Therapy – Synthesis and Biological Activity

Monika Gensicka, Agnieszka Głowacka, Krystyna Dzierzbicka* and Grzegorz Cholewinski

Department of Organic Chemistry, Gdansk University of Technology, Narutowicza St 11/12, PL 80-233 Gdansk, Poland

Abstract: Angiogenesis is the process of formation of new capillaries from preexisting blood vessels. Angiogenesis is involved in normal physiological processes, and plays an important role in tumor invasion and development of metastases. Vascular endothelial growth factor (VEGF) plays a key role in angiogenesis. VEGF is a mitogen for vascular endothelial cells and stimulates their proliferation. By inhibiting the biological activity of VEGF, and then signal cascades with neutralizing VEGF antibodies and signal inhibitors, may negatively regulate the growth and metastasis. Anti-angiogenesis therapy is less toxic than chemotherapy. Angiogenesis is a multistep and multifactorial process, and therefore, can be blocked at different levels. In this review article, the authors present the synthesis of novel inhibitors of angiogenesis, together with the results of biological tests *in vitro*, and in some cases, state trials.

Keywords: Angiogenesis, biological activity, cancer therapy, inhibitors of angiogenesis, synthesis.

1. INTRODUCTION

Mostly all of us possess occult, cancerous lesions that for many will not progress to symptomatic disease. Thus, for most people, tumor will become dormant and not progress, while only in some cases will it become a symptomatic disease. Cancer dormancy is defined by stable or very slow tumor growth, which can occur at the cellular level as a malignant cell remaining quiescent for a long period before awakening. The explanation, proposed for tumor dormancy is based on the achievement of a balance between stimulation and inhibition of angiogenesis. This mechanism describes a phenomenon known as concomitant tumor resistance (CR) [1]. CR is a phenomenon in which the growth of secondary tumor implants does not affect the tumor-bearing host [2].

Angiogenesis is a process based on the formation of new blood capillaries from pre-existing vessels [3, 4]. It is not only involved in normal physiological processes such as pregnancy, organ development, menstrual cycle and wound healing, but also plays a crucial role in tumor growth, invasion and development of metastasis [3, 5].

*Address correspondence to this author at the Faculty of Chemistry, Department of Organic Chemistry, Gdansk University of Technology, G. Narutowicza St 11/12, 80-233 Gdansk, Poland;
Tel: (48 58) 347-20-54; Fax: (48 58) 347-26-94;
E-mail: krydzier@pg.gda.pl

As a result of physiological angiogenesis the fully formed functional new blood vessels characterized by the correct shape and size, are regular, and the vascular network has a full differentiation arterio-venous [6]. In the case of carcinogenesis, the newly formed vessels characterized by immaturity with numerous openings along their walls are highly disorganized due to bizarre form [3].

Angiogenesis is regulated by endogenic stimulators, such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), angiopoietins, platelet derived growth factor (PDGF), hepatocyte growth factor (HGF/SF), angiogenin, angiopoietins-1 (Ang-1), platelet-derived endothelial cell growth factor (PDECGF), interleukin-8 (IL-8), insulin-like growth factors (IGFs), prostaglandin E (PG-E), tissue factor (TF), transforming growth factor β (TGF-β) [7-13], and by endogenic inhibitors, such as thrombospondin-1 (TSP-1), angiostatin, endostatin, restin, vasostatin, angiopoietin-2 (Ang-2) and the digestion product of osteopontin [11, 14-16].

The process of angiogenesis is also facilitated by enzymes proteolytic extracellular matrix, fibrinolytic factors, and integrins [11, 17].

Of the many the above-mentioned factors stimulating angiogenesis process vascular endothelial growth factor (VEGF) plays a key role [18]. It regulates both

1875-533X/15 $58.00+.00 © 2015 Bentham Science Publishers

Personal Use Only Not For Distribution