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Review article

Development of combretastatins as potent tubulin polymerization inhibitors

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ABSTRACT

The combretastatins are isolated from South African tree *combretum caffrum kuntze*. The lead compound combretastatin A-4 has displayed remarkable cytotoxic effect in a wide variety of preclinical tumor models and inhibits tubulin polymerization by interacting at colchicine binding site of microtubule. However, the structural simplicity of C A-4 is favorable for synthesis of various derivatives projected to induce rapid and selective vascular shutdown in tumors. Majority of the molecules have shown excellent antiproliferative activity and are able to inhibit tubulin polymerization as well as possible mechanisms of action have been investigated. In this review article, the synthesis and structure-activity relationships of C A-4 and immense number of its synthetic derivatives with various modifications on the A, B-rings, bridge carbons and their anti mitotic activities are discussed.

Contents

1. Introduction

In several organisms, tubulin is one of several members of a small family of globular proteins. Numerous isoforms of the tubulins exist that are encoded by different genes. The most studied tubulins have been isolated from vertebrate brains. Among the

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family of tubulin proteins, α/β heterodimer is the essential building material for the microtubular cytoskeleton [1]. Both α and β-tubulins, that consist of around 450 amino acids, are homologous but not identical and have a molecular mass of approximately 50 kDa and about 4–5 nm of diameter [2,3]. However, the formation of microtubules is a dynamic process that involves assembly of the heterodimers formed by tubulin subunits and degradation of the linear polymers. The balance between these phenomena is important for the structure of the cytoskeleton, as well as for mediating intracellular transport. Tubulin polymerizes in presence of non-hydrolysable GTP to form stable microtubules because of the high affinity of the tubulin-GTP dimer for the end of the microtubule. The disassembly is determined by GTP hydrolysis, due to instability of the resulting GDP microtubule. Main role played by microtubule network during cellular division, ligands that interrupt the dynamic instability inherent to this system have been developed as antimitotic agents. Different types of naturally occurring drugs that inhibit tubulin polymerization have been reported in the literature, and there has been a continuing discovery of new agents with pronounced structural diversity [4].

Microtubule targeting agents are known to play a main role in chemotherapy and well known tubulin binders such as paclitaxel, vinca alkaloids (vincristine and vinblastine) are routinely employed as antimitotic agents. Microtubule targeting agents derived from natural or synthetic products, generally exert their effects as microtubule stabilizers or polymerizing agents, like paclitaxel and docetaxal [5]. Paclitaxel was isolated in the 1960s from bark of the Pacific yew, *Taxus brevifolia*, and was given the name taxol, acts by promoting the assembly of tubulin into microtubules. Paclitaxel binds specifically at the *N*-terminal 31 amino acids of the β-tubulin subunit of tubulin polymers, at the inner surface of the microtubule lumen and showed much affinity for tubulin in microtubules than for free tubulin in solution. Taxol inhibits chromosome transport in a dividing cell by binding in a pocket of β-tubulin. It is one of the most successful cancer drugs ever produced, being widely used in the treatment of breast, ovarian and lung carcinomas and the crystal structure of paclitaxel bound tubulin [6]. Among the semi-synthetic derivatives, docetaxel approved for clinical use to date for treating advanced NSCLC (Non-small cell lung cancer), that is refractory to primary therapy [7]. In contrast, microtubule destabilizers such as colchicinium [8], vinca alkaloids [9] and combretastatin A-4 [10] causes the depolymerization of microtubules. The vinca alkaloids, vincristine and vinblastine, isolated from the periwinkle plant, *Catharanthus roseus*, were the first to enter clinical use and are the most successful anticancer agents for the past few years [9]. They bind to β-subunit of tubulin dimers, a different site from the taxane drugs and colchicine, and thereby prevent tubulin assembly. Several synthetic analogues of vinca alkaloids are also in clinical use, most notably vindesine, used mainly to treat melanoma and lung carcinomas [11]. The fluorinated analogue vinflunine is in Phase II clinical development for the treatment of bladder, non-small cell lung and breast cancers [12,13]. In continuation, combretastatin A-4 (C A-4) is a powerful microtubule-destabilizing agent that inhibits microtubule assembly by binding to tubulin at the colchicine binding site [14].

The antivascular effect of this molecule derives from the role tubulin and microtubules play in determining the elongated shape of vascular endothelial cells. The cellular microtubule networks of the cytoskeleton plays a major role in maintaining cell shape, particularly in the case of the neovasculature. Further, combretastatin A-4 caused extensive necrosis in MAC 15A s.c. and orthotopic colon cancer and metastases, resulting in anti-tumor effects, suggesting a vascular mechanism of action [15]. As a result of the tubulin depolymerization, endothelial cells round up and very quickly block blood-flow through the vascular network [16]. It was the subsequent discovery that water-soluble disodium phosphate prodrug of C A-4 could inhibit tumor blood flow at concentrations 10-fold less than the maximum tolerated dose (MTD) that prompted the first clinical trials of C A-4 as a vascular targeting agent and it is successfully reduced tumor blood supply and consequently retarded tumor growth, thus stimulating significant interest in a variety of C A-4 analogues [17].

2. Isolation of combretastatins

Combretastatins are *Z*-stilbenoid natural products, consist of two substituted aromatic (aryl) rings (ring A and B) linked by an olefinic bridge. The combretastatins and their corresponding compounds like combretastatin A-1 (C A-1, **1**) (Fig. 1), combretastatin A-4 (C A-4, **2**), combretastatin A-5 (C A-5, **3**), and combretastatin A-6 (C A-6, **4**) and Combretastatin B-series (C A-B, **5**) were accomplished by professor Pettit and colleagues from Arizona State University [18–22]. The combretastatins were extracted from *Combretum caffrum*, a South African willow tree, were isolated and identified nearly 17 compounds by Pettit and colleagues with significant collaboration of U.S. National Cancer Institute (NCI) in 1982 [18,19]. In 1988 two more seventeen member macro cyclic lactone (**7**, **8**) (Fig. 1) were discovered [19,23,24]. The structure elucidation of combretastatin was accomplished using spectral

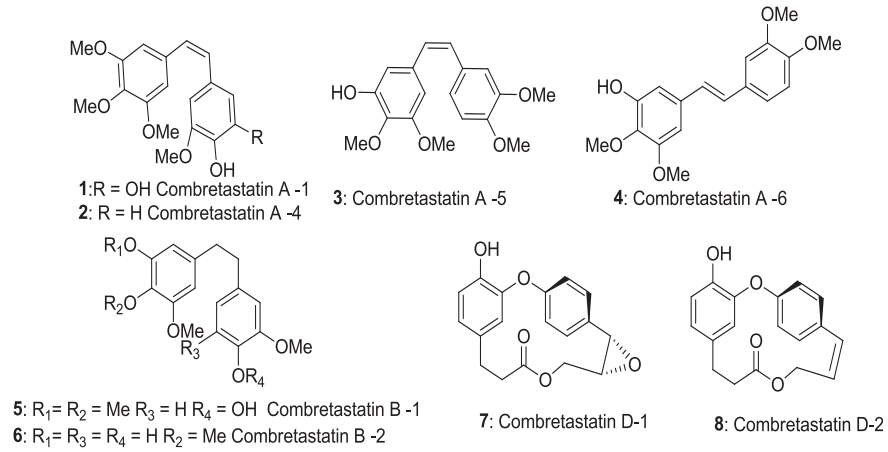

Fig. 1. Structure of combretastatin A-1 (1), combretastatin A-4 (2), combretastatin A-5 (3), combretastatin A-6 (4), combretastatin B-1 (5), combretastatin B-2 (6), combretastatin D-1 (7), combretastatin D-2 (8) as tubulin binding agents.