The Combretastins A-1 and A-4 Prodrugs: A Mini-Review

Abstract

Both marine and terrestrial sources of natural products have afforded an impressive array of medicinally valuable compounds. The isolation and synthetic endeavors within the CRI at ASU has generated several candidates which are now in clinical development. Specifically, the compounds developed from the Eastern Cape South African Bushwillow tree, Combretum Caffrum, have always peaked a keen interest to the author.

Keywords: Synthetic derivatives; Combretastatin; Prodrug; Clinical trials; Stilbene

Abbreviations: CRI: Cancer Research Institute; ASU: Arizona State University; CA1P: Combretastatin A-1 Prodrug; CA4P: Combretastatin A-4 Prodrug

Introduction

The Cancer Research Institute at Arizona State University has isolated several marine and terrestrial natural products which have anti-cancer activity [1-5]. Tropical and subtropical shrubs and trees of the Combretaceae family represent a practically unexplored reservoir of new substances with potentially useful biological properties [6]. Illustrative of this is the genus Combretum (250 species), of which a number of their chemical constituents have found application in primitive medical treatment, although their structures have rarely been reported [6,7]. Primitive and tribal medical practices in India and Africa using the Combretum genus have found a broad range of use that include's the treatment of leprosy (Combretum sp. roots) [6,8], cancer (Combretum latifolium) [6,9], mental illness (Combretum micranthum) [6,10,11], and scorpion invenomation (Combretum zeyheri) [6,12]. Other species within the Combretaceae genus that have received scientific investigation include Combretum molle (phanenethrenes) [7,13], Combretum eleanoideas (triterpenoids) [7,14], Combretum quadrangulare (cycoartane-type triterpenes) [15] and the heartwood extracts from Combretum psidioides, Combretum hereroense, and Combretum apiculatum (9,10-dihydrophanenethrenes and phenanethrenes) [7,16]. Still other chemical examinations [17] of this genus have included the isolation of cycoartane glycosides [18] and tannins [19]. Specifically, the compounds isolated from the Eastern Cape South African Bushwillow tree, Combretum Caffrum, are of main interest. These natural products designated the combretasin were isolated in the 1980s and are shown in Figure 1 [6-7,20-23]. By far, the most active constituents are those from the A-series having a cis-stilbene moiety.

Discussion

To date the most interesting synthetic derivatives that are currently undergoing clinical development at Mateon Therapeutics (located in South San Francisco) are the combretastatin A-4 and combretastatin A-1 prodrugs [24-26]. Development of combretastatin A-4 (1d) to Phase I human cancer clinical trials was accelerated following synthesis of the phosphate prodrg 8 [27] and uncovering its very promising cancer antiangiogenesis effects [25,28-30]. The formation of water-soluble ester prodrugs has long been recognized as an effective means of increasing the aqueous solubility of drugs containing a hydroxyl group, with the aim of development of improved preparations for parenteral [31] or ophthalmic [32] administration [33]. Once administered, the phosphate prodrg is presumed to be converted into the parent drug via endogenous non-specific phosphatases and then transported intracellularly [25,27]. Phosphate 8 exhibited cytotoxicity similar to that of the parent compound (GI50 0.0004μg/mL, P388 cell line), but its aqueous solubility was much greater (20mg/mL) [34]. Prodrug 8 was also shown to induce vascular shutdown within murine metastatic tumors at doses less than one-tenth of the maximum tolerated dose [29]. A phosphate-type prodrg has also been shown to be a valuable synthetic modification for other anticancer drugs such as pancratistatin [35], taxol [36,37], tyrosine-containing peptides [38], and etoposide [39] owing to its ability to amplify drug solubility for enhanced delivery.

The preclinical development of combretastatin A-1 (1a) has been hampered owing to the instability (oxidation to the 1,2-quinone) of the 2,3-dihydroxy unit [40,41]. This was supported by the fact that acetylation of 1a significantly enhanced cytotoxicity 10-fold, while reducing inhibition of the tubulin assembly [40]. Interestingly, biosynthetic processes in Combretum kraussii have circumvented this problem by elaborating cis-stilbene 1a with a β-D-glucopyranosyl group at the 2-position of the B-ring [42] although biological evaluation has revealed it to be less active than the parent diphenol [43].

In spite of this superficially negative aspect, some biological properties exhibited by diphenol 1a (combretastatin A-1) make it attractive. For example, diphenol 1a may be the most potent antagonist of colchicine binding known, with nearly 99% inhibition at equal concentrations [40]. In addition, diphenol 1a was found to be more potent than monophenol 1d in its ability to increase intracellular daunorubicin (an antibiotic used in the treatment of acute leukemia) concentrations in MDR (multidrug resistant) cell lines [44]. Most importantly, the tubulin-binding
stilbenes 1a (A-1) and 1d (A-4) elicit irreversible vascular shutdown selectively within solid tumors [45]. The degree of reduction ranged from 50% with diphenol 1a (A-1) to 70% with monophenol 1d (A-4) [45]. When a tumor reaches a critical mass (2-3mm), it becomes starved of oxygen and its cells begin secreting a messenger molecule, vascular endothelial growth factor (VEGF), to stimulate endothelial cells lining nearby blood vessels to form new capillaries (angiogenesis) for supplying oxygen [45]. Angiogenesis, the development and recruitment of new blood vessels, is a necessity for all tumor growth, and cancer specific antiangiogenic drugs such as combretastatin A-1 (1a) and A-4 (1d) are essential components for the inhibition of the metastatic pathway and are an attractive way to approach the cancer problem [46,47]. Recent biological experiments have noted that the combination of conventional chemotherapeutic agents with antiangiogenic agents has given significantly better results in reducing tumor metastases than was found with either agent alone [46] Other natural products such as taxol, tamoxifen, and adriamycin, which are already in clinical use as antitumor agents, are also being found to have antiangiogenic activity, increasing their overall therapeutic value [25,45,48].

Figure 1: The combretastatins.
Designated fosbretabulin (8) and Oxi4503 (9), respectively, these two synthetic derivatives are being used in various anti-cancer therapies [49]. Figure 2 illustrates the both the combretastatin A-4 and combretastatin A-1 prodrugs.

**Figure 2:** The CA1P and CA4P.

**Conclusion**

Both the CA4P (8) and CA1P (9) are important synthetic derivatives from the natural products known as the combretastatins. Each compound has advanced into the clinic for the treatment of specific classes of tumors [49].

**Acknowledgement**

The author would like to acknowledge all the research, both isolation and synthetic, that has gone on in the past at the CRI at ASU.

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