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REVIEW ARTICLE

Synthesis of Combretastatin A-4 Analogs and their Biological Activities

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

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

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Abstract: Combretastatin A-4 (CA-4) is a natural product, which consists of two phenyl rings, linked by an ethylene bridge. CA-4, inhibitor of polymerization of tubulin to microtubules, possesses a strong antitumor and anti-vascular properties both *in vitro* and *in vivo*. Previous studies showed that disodium phosphate salt of CA-4, a water-soluble prodrug is well tolerated at therapeutically useful doses. However, it should be noted that the *cis*-configuration of the double bond and the 3,4,5-trimethoxy group on ring A is necessary for the biological activity of CA-4. Structure of CA-4 renders the compound readily susceptible to isomerization, which reduces the potency and bioavailability. To circumvent this problem, a lot of scientists in the world synthesized a series of *cis*-restricted CA-4 analogs, where the double bond has been replaced by introduction of non-heterocyclic groups or heterocyclic groups like β-lactam and oxadiazole. This paper reviews the most important approaches in analogs of combretastatin synthesis and presents structure-reactivity relationships for these compounds.

Krystyna Dzierzbicka

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1. INTRODUCTION

In the last two decades many anticancer compounds were received, however, a special attention is paid to the ones that cause the reorganization of microtubules [1]. Microtubules are fibrous, cylindrical tubes having a diameter of 25-26 nm. They are formed by polymerization of tubulin proteins and represent one of the components of the cytoskeleton [2]. Microtubules play a central role in the functioning of cells, influence cell division, motility, intracellular transport direction, to maintain cell shape, arrangement and movement of organelles, and vesicles and cytosolic proteins. For the maintenance of normal structure they are responsible for polymerization and depolymerization processes that extend over the ends of the filaments. Some biologically active compounds influence the poles of tubulin, which can cause excessive microtubule polymerization or its inhibition. Microtubules are attractive for pharmacological target killing of tumor cells [3,4].

Colchicine **1** (Fig. **1**) was the first tubulin-binding agent noted to have some antivascular action, producing hemorrhagic necrosis in experimental tumors that resembled that produced by bacterial toxins [3]. Furthermore, it was noted that the endothelial cells of growing capillaries appeared sensitive to its toxic actions [4].

Combretastatin **2** (Fig. **1**) was isolated from the bark of an African willow Combretum caffrum. Although it exists as two isomers, only the cis isomer exhibits a biological activity and it is a potent inhibitor of tumor cell growth. Combretastatin has antiangiogenic effects by inhibiting tubulin polymerization leading to the breakdown of microtubules [5-7]. CA-4 induces apoptosis of proliferating endothelial cells of the tumor [5,8].

Pettit *et al.* [9-19], during their many years of research, isolated compounds from the group of combretastatins 2, 3-5, 6, 7-10 (Fig. **1**) and demonstrated their anti-cancer properties. The strongest activity was characterized by the CA-4 **2**. Combretastatin A-4 is made up of two aryl rings connected by an ethylene bridge [8].

Combretastatin, despite the fact that it showed significant biological activity *in vitro,* was not acceptable for clinical studies because of low solubility in water, which reduces the efficacy of the compound *in vivo* [20].

2. COMBRETASTATIN A-4 ANALOGS

2.1. Modification of Double Bond of Combretastatin A-4

Lee and co-workers [21] presented the synthesis of hydroxyethyl-analogs of combretastatin A-4 (CA-4) **11** that contain the 1-(1'-hydroxyethyl)-1-(3",4",5"-trimethoxyphenyl)-2-(substituted phenyl) ethene (Fig. **2**). Derivatives **11** were prepared in two steps from the respective benzaldehyde [21].

All synthesized compounds **11** were tested for biological activities against L1210 and B16 cells (murine lymphoma and melanoma respectively) using a 72h continuous exposure MTT assay. The most active were derivatives **12a** (IC_{50} = 3.9 μM for L1210 and IC_{50} = 17,5 μM for B16) and **12b** (IC_{50} = 4.1 μM for L1210 and IC_{50} = 16.1 μM for B16). Other analogs exhibited lower activity or were inactive. Studies revealed that substitution at the 4-position is significant, both size and electronic characteristic strongly influenced potency, and the highest cytotoxicity gave methoxy group. Additionally, substitution on the 3-position further affected the potency of the compounds. For instance, compound **12b** containing a hydroxy group on the 3-position and a methoxy group on the 4-position, was similarly active as compound **12a**. But if the 3-position contained bulkier substituent such as nitro or methoxy one, activity decreased clearly. Derivative **12b**, which holds a substitution pattern closest to CA-4, was tested also in terms of its mechanism of action, aqueous solubility, and tested *in vivo* using DBA2 female mice that were inoculated with L1210 mouse lymphocytic leukemia cells. Analogue **12b** demonstrated promising antitumor activity in mice with no toxicity. In addition, compound **12b** showed a much greater aqueous solubility than CA-4 [21].

Babu group [22] synthesized new acetyl-CA-4 analogs **15a-d** (Fig. **3**), which contained 3,4,5-trimethoxyphenyl group, and a variety of aromatic moieties instead of ring B. The compounds were prepared by Claisen-Schmidt condensation using 3,4,5-trimethoxy-phenylacetone **13**, aldehydes (**14a-d**) and suitable catalysts such as piperidine and benzoic acid (Scheme **1**) [22].

It was found that the conformation of the obtained compounds was similar to those observed in the X-ray structure and molecular formulas of combretastatin A-4, suggesting that the products **15a-d**

*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

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