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Design and synthesis of 3,5-disubstituted boron-containing 1,2,4-oxadiazoles as potential combretastatin A-4 (CA-4) analogs

Bhaskar C. Das^{a,*}, Xiang-Ying Tang^b, Patrick Rogler^b, and Todd Evans^{a,*}

^aDepartment of Surgery, Weill Cornell Medical College, Cornell University, New York, NY 10065, USA

^bDepartment of Developmental & Molecular Biology, Albert Einstein College of Medicine, Bronx, NY 10461, USA

Abstract

We have designed and synthesized a small library of 3,5-disubstituted-1,2,4-oxadiazole containing combretastatin A-4 (CA-4) analogs. Our objective is to increase the efficacy of the CA-4 as an anti-tubulin and antimitotic agent by substituting the *cis*-alkene bond with one of its bioisosteres, the 1,2,4-oxadiazole ring. We also modified the substituents attached to both of the phenyl rings (ring A and B in Fig. 1) of CA-4 for the purpose of diversifying our analogs based on SAR. These compounds were synthesized via a coupling reaction between an amidoxime and a carboxylic acid in DMF solvent, with HOBt as a base, and utilizing EDCI as a coupling reagent. Using this protocol, we synthesized a small library of 10 compounds with moderate to good yields. A detailed biological study is currently undergoing in our laboratory to evaluate the activity of these compounds.

Keywords

3,5-Disubstituted 1,2,4-oxadiazole; Combretastatin A-4; Bioisosteres; Vascular disrupting agent; Tubulin; Boron-containing CA4 compound

Combretastatin A-4 (CA-4) is an antimitotic agent that binds to the colchicine site on tubulin causing inhibition of tubulin polymerization, and in cells microtubule depolymerization and mitotic block.¹ CA-4 exhibits potent cytotoxicity against a broad spectrum of human cancer lines, including multidrug resistance (MDR) lines, and also acts as a vascular disrupting agent (VDA).²

The mechanism of action of CA-4 involves reversible, high affinity binding in the colchicine site of tubulin.^{1b} Major limitations of CA-4 as a therapeutic candidate are its poor aqueous solubility, bioavailability, short biological half-life, isomerization of the ethene bond, and exhibition of many deleterious side effects.^{2g}

To improve the therapeutic regimen of CA-4 (Fig. 1,1a), many analogs have been developed over time that retain the biological actions of the parent molecule but have improved water solubility and better pharmacokinetic properties Figure 1.³ In addition to prodrug **1b**,

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*Corresponding author: Tel.: +1 212 746 3290; fax: +1 212 746 0201. bcd2004@med.cornell.edu (B.C. Das).

Supplementary data

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notable analogs undergoing clinical evaluations include CA-1 (**1c**), the derivative CA-1P (OXI-4503, **1d**⁴), the amino acid derivative AC-7739 (**2a**), and AVE8062 (**2b**). However, thus far no compounds have entered into clinical use, and there remains a need to develop new VDAs to treat solid tumors.

Based on structure–activity relationship studies, it was reported that the *cis*-configuration of the double bond and the 3,4,5-trimethoxy group on ring **A** is essential for the biological activity of CA-4.⁵ The key structural factor for the cytotoxic activity is the presence of the double bond (in *cis*-configuration) which forces the two aromatic rings to be at an appropriate distance and to have an optimal dihedral angle to maximize the interactions with tubulin. However, the *cis*-configuration is prone to isomerization, which reduces the potency and bioavailability. By comparing the minimal energy conformations for both colchicine and combretastatin, it has been demonstrated that it is possible to overcome the problem of the isomerization of the active *cis* double bond to the inactive *trans*-configuration, by introducing five-membered heterocycles in place of the olefin group without substantial loss of potency.⁶

Therefore, to improve the efficacy and potency of combretastatin a number of heterocyclic compounds as new possible bioisosteres of the double bond of the combretastatins have been prepared.^{5,3} As heterocyclic compounds are concerned, it was reported that substituted oxadiazoles including 3,4-disubstituted-1,2,5-oxadiazole (Combretafurazan),⁷ and 2,5-disubstituted-1,3,4-oxadiazole^{4c} are more potent than combretastatin itself. However, 1,2,4-oxadiazole substituted CA-4 has not yet been explored. Herein, we report for the first time, to the best of our knowledge, the synthesis of boron- containing 3,5-disubstituted 1,2,4-oxadiazole derivatives as potential new CA-4 analogs. The oxadiazole moiety should provide an optimal conformational geometry for interaction with the colchicine binding site of tubulin, while increasing the number of heteroatoms in the core structure. The net effect is an increase in the polarity of the molecule, which would also enhance water solubility.

Oxadiazoles are not only used as bioisosteres of ethene bonds but also as pharmacophore groups, known to possess a broad spectrum of biological activities,⁸ including anticancer activity.⁹ A number of oxadiazole derivatives, depending upon the substituents and positions of heteroatoms, namely 1,2,4- and 1,3,4-oxadiazoles, are known to have anticancer effects.¹⁰

Considering the potential importance of CA-4 and oxadiazole derivatives, we were interested in synthesizing a small library of new CA-4 derivatives to increase cytotoxicity and anti-tubulin activity. This is in the context of an ongoing chemical biology project, studying the role of key developmental signaling pathways during embryogenesis. Our goal is the development of new therapeutic and diagnostic agents for targeting these signaling pathways to modulate disease progression.¹¹

To increase the cytotoxicity and anti-tubulin activity of CA-4, we envisioned developing a set of boron-containing, 3,5-disubstituted, 1,2,4-oxadiazole derivatives as potential new analogs of CA-4, based on a hypothesis that (a) introduction of a constrained 1,2,4-oxadiazole ring system will protect *cis*–*trans* isomerization of the ethene group and improve water solubility, and (b) introduction of boronic acid as an acceptor-type functional group into the aromatic ring **B** in CA-4 may enhance biological activity, because it is expected that the boron atoms introduced into biologically active molecular frameworks may interact with a target protein not only through hydrogen bonds but also through covalent bonds, and this interaction would impact biological function.¹² Furthermore, CA-4P (a water-soluble prodrug of CA-4) is dephosphorylated in vivo to generate CA-4, and has a short plasma half-life. We anticipate that hydrolysis might not occur with our boronic acid and ester compounds, because the aryl carbon boron bond is not known to be prone to hydrolysis, and

thus would increase plasma half-life.^{12h} With these objectives in mind, we sought to synthesize the boron-containing 3,5-disubstituted-1,2,4-oxadiazole containing CA-4 analogs, substituting different functional groups in rings A and B of CA-4.

To synthesize these compounds, we first attempted to synthesize the model compound **5** (Fig. 2), keeping the trimethoxy-substituted A ring intact and substituting an ethene group with the oxadiazole moiety, and interchanging the methoxy and hydroxyl group positions in ring B. We introduced oxadiazole group in the place of ethene group with three objectives, (a) this will protect *cis-trans* isomerization, (b) oxadiazole moiety would provide an optimal conformational geometry for interaction with colchicines binding site, and (c) by increasing the number of heteroatoms in the core structure of the molecule would increase the polarity and enhance water solubility.

To synthesize compound **5**, we first synthesized amidoxime derivatives **4a–d** (Scheme 1).

The different substituted amidoximes were synthesized by refluxing an ethanolic solution of substituted phenyl nitriles and hydroxylamine hydrochloride using NaOH as base.¹³ The oxadiazole- containing CA-4 analog was synthesized by an amide coupling strategy¹⁴ using amidoxime **4a** and acid **3** (commercially available from Aldrich), which were readily available through simple transformations, as the substrates. Thus, the corresponding acid **3** was treated with 1.2 equiv of CDI (carbonyldiimidazole) in DMF for 30 min at room temperature. Then the amidoxime **4a** was added and the resulting reaction mixture was heated under reflux for about 12 h (or until the acid was consumed completely as monitored by TLC) (Scheme 1).¹⁵ Compound **5** was obtained as a yellow solid (mp 181–183 °C, 58% yield), after purification by silica-gel chromatography (Hexanes/EtOAc, 3:1). Using the same reaction protocol and different amidoximes **4b**, **4c**, and **4d** we synthesized the compounds **6**, **7**, and **8** in moderate to good yields (Fig. 3).¹⁵

In compound **8**, we replaced both the methoxy and hydroxyl groups in ring B by an acetylene derivative with an objective to derivatize different functional groups and thereby increase water solubility and binding potency to colchicines sites. To synthesize our target compound **9**, we first tried to synthesize amidoxime **12** (Scheme 2). Unfortunately, we failed to synthesize **12** despite using different bases [like NaOH/EtOH, K₂CO₃/DMSO, Et₃N/EtOH, and (*i*Pr)₂NH/EtOH] and reaction conditions (Scheme 2).¹⁶

The failure of amidoxime **12** (Scheme 2) preparation forced us to develop an alternative route for accomplishing the synthesis of the target compound **9**. Thus, a Suzuki coupling reaction was employed using bromide compound **7**¹⁵ and B₂Pin₂ (bis-pinocolatodiboron) as the substrates to give the boronic ester containing compound **9** in 45% yield as a white solid (Scheme 3).¹⁵

It has been shown that the *cis*-configuration of the double bond and the 3,4,5-trimethoxy group on ring A are the basic requirements for CA-4 cytotoxicity and anti-tubulin activity. However, Gaukroger et al. questioned the importance of the trimethoxyphenyl group for the anti-tubulin activity.¹⁷ Based on these observations, Pettit's group developed fluorcombstatins, where the methoxy group at the meta position in ring A of CA-4 was replaced with a fluorine group. In this case, the compounds showed antitubulin activity comparable to that of CA-4.¹⁸ Based on these observations, we attempted to generate a small library of CA-4 analogs by substituting the trimethoxy group in ring A with more hydrophobic chloro derivatives (Scheme 4).

Compounds **14–17** were synthesized by the protocol described above, where acid **13** (Purchased from Aldrich), was reacted with aldoximes **4a–d** in the presence of CDI as

coupling reagents to give oxadiazole containing products (**14–17**) in moderate to good yields (Fig. 4).¹⁵

To synthesize compound **18**, we used Suzuki coupling reaction conditions, as described above for compound **9** (Scheme 5).¹⁵

In conclusion, we have successfully synthesized a small library of 3,5-disubstituted boron-containing, 1,2,4-oxadiazole derivative compounds. In five compounds of this library (**5–9**), we substituted ring B of CA-4 (trimethoxy and hydroxyl groups) with different functional groups, including boronic ester. In five additional compounds (**14–18**), we substituted both ring A and ring B. In ring A, the three methoxy groups were replaced with dichloro groups and in ring B the trimethoxy and hydroxyl groups were replaced with different functional groups. In all 10 compounds the cis-alkene bond of CA4 was substituted with one of its bioisosteres, 1,2,4-oxadiazole ring. This is the first report, to our knowledge, of boron-containing 3,5-disubstituted 1,2,4-oxadiazole-containing CA-4 analogs. A detailed biological study is currently undergoing in our laboratory to evaluate the activity of these compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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15. *General procedure for synthesis of amidoximes:* nitrile compound (10.0 mmol), hydroxylamine hydrochloride (11.0 mmol, 754.0 mg), NaOH (11.0 mmol, 440.0 mg) and EtOH (20.0 mL) were added to a 50.0 mL RBF. The resulting mixture was stirred reflux overnight. After the reaction complete (Monitored by TLC), ethanol was removed under vacuum and the residue was purified by a silica-gel chromatography to give a white solid amidoxime product. *General procedure for synthesis of oxadiazole compounds:* Acid (0.5 mmol) and CDI (Carbonyl diimidazole) (97.3 mg, 0.6 mmol) were dissolved in 3.0 mL of DMF and stirred at room temperature. After 30 min, amidoxime (0.6 mmol) was added and the reaction mixture was heated under reflux for about 24 h (Monitored by TLC). Then the mixture was poured into water (20.0 mL), extracted with ethyl acetate (3 × 15.0 mL), and the combined organic extractions were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica-gel chromatography (hexanes/ethylacetate) to give the oxadiazole product. **Compound 5.** A yellow solid. Yield: 58%, mp 181–183 °C. ¹H NMR (CDCl₃, 300 MHz, TMS) 3.97 (s, 3H, CH₃), 4.01 (s, 6H, 2CH₃), 4.04 (s, 3H, CH₃), 5.94 (s, 1H, OH), 7.06 (d, *J* = 8.4 Hz, 1H, Ar), 7.47 (s, 2H, Ar), 7.67 (d, *J* = 1.5 Hz, 1H, Ar), 7.78 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.5 Hz, 1H, Ar); ¹³C NMR (CDCl₃, 75 MHz, TMS) 56.2, 56.4, 61.1, 105.4, 109.5, 114.7, 119.0, 119.5, 121.7, 142.1, 146.7, 148.4, 153.6, 168.8, 175.3. **Compound 6.** A yellow solid. Yield: 63%, mp 148–150 °C. ¹H NMR (CDCl₃, 300 MHz, TMS) 3.91 (s, 3H, CH₃), 3.97 (s, 3H, CH₃), 4.01 (s, 6H, 2CH₃), 7.04 (d, *J* = 8.7 Hz, 2H, Ar), 7.47 (s, 2H, Ar), 8.14 (d, *J* = 8.7 Hz, 2H, Ar); ¹³C NMR (CDCl₃, 75 MHz, TMS) 55.4, 56.4, 61.0, 105.4, 114.2, 119.4, 129.1, 142.0, 153.6, 161.9, 168.8, 175.3. **Compound 7.** A red solid. Yield: 62%, mp 155–157 °C. ¹H NMR (CDCl₃, 300 MHz, TMS) 3.97 (s, 3H, CH₃), 4.00 (s, 6H, 2CH₃), 7.46 (s, 2H, Ar), 7.67 (d, *J* = 8.4 Hz, 2H, Ar), 8.07 (d, *J* = 8.4 Hz, 2H, Ar); ¹³C NMR (CDCl₃, 75 MHz, TMS)

56.4, 61.0, 105.4, 118.6, 125.8, 125.9, 129.0, 132.1, 142.2, 153.6, 168.3, 175.9. Compound **8**. A white solid. Yield: 56%, mp 141–143°C. ¹H NMR (CDCl₃, 300 MHz, TMS) 3.23 (s, 1H, CH), 3.97 (s, 3H, CH₃), 4.01 (s, 6H, 2CH₃), 7.47 (s, 2H, Ar), 7.65 (d, *J* = 8.4 Hz, 2H, Ar), 8.17 (d, *J* = 8.4 Hz, 2H, Ar); ¹³C NMR (CDCl₃, 75 MHz, TMS) 56.4, 61.1, 79.3, 83.0, 105.4, 119.1, 125.0, 127.1, 127.4, 132.6, 142.1, 153.7, 168.4, 175.7. Compound **9**. A white solid. Yield: 45%, mp 161–163°C. ¹H NMR (CDCl₃, 300 MHz, TMS) 1.39 (s, 12H, 4CH₃), 3.97 (s, 3H, CH₃), 4.01 (s, 6H, 2CH₃), 7.48 (s, 2H, Ar), 7.96 (d, *J* = 8.4 Hz, 2H, Ar), 8.18 (d, *J* = 8.4 Hz, 2H, Ar); ¹³C NMR (CDCl₃, 75 MHz, TMS) 56.4, 61.0, 84.1, 105.4, 119.3, 126.6, 129.2, 135.1, 142.0, 153.6, 169.0, 175.6. Compound **14**. A yellow solid. Yield: 56%, mp 169–171°C. ¹H NMR (DMSO, 300 MHz) 3.88 (s, 3H, CH₃), 6.97 (d, *J* = 8.1 Hz, 1H, Ar), 7.57 (s, 1H, Ar), 7.59 (d, *J* = 1.8 Hz, 1H, Ar), 8.03 (dd, *J*_{1,2} = 1.8 Hz, 1H, Ar), 8.16 (d, *J* = 1.8 Hz, 1H, Ar), 9.84 (s, 1H, OH); ¹³C NMR (DMSO, 75 MHz) 56.6, 111.3, 116.8, 117.4, 121.8, 127.3, 127.5, 133.4, 136.2, 149.1, 151.2, 169.3, 173.6. Compound **15**. A yellow solid. Yield: 76%, mp 142–144°C. ¹H NMR (CDCl₃, 300 MHz, TMS) 3.88 (s, 3H, CH₃), 7.02 (d, *J* = 8.7 Hz, 2H, Ar), 7.58 (dd, *J*_{1,2} = 1.8 Hz, 1H, Ar), 8.08–8.11 (m, 4H, Ar); ¹³C NMR (CDCl₃, 75 MHz, TMS) 55.4, 114.3, 118.8, 126.4, 126.9, 129.1, 132.5, 136.0, 162.2, 168.9, 173.0. Compound **16**. A red solid. Yield: 67%, mp 168–170°C. ¹H NMR (CDCl₃, 300 MHz, TMS) 7.63 (br s, 1H, Ar), 7.68 (d, *J* = 8.7 Hz, 2H, Ar), 8.05 (d, *J* = 8.7 Hz, 2H, Ar), 8.12 (d, *J* = 1.8 Hz, 2H, Ar); ¹³C NMR (CDCl₃, 75 MHz, TMS) 125.4, 126.2, 126.4, 126.6, 129.0, 132.3, 132.7, 136.2, 168.5, 173.6. Compound **17**. A white solid. Yield: 59%, mp 153–155°C. ¹H NMR (CDCl₃, 300 MHz, TMS) 3.25 (s, 1H, CH), 7.63–7.67 (m, 3H, Ar), 8.12–8.16 (m, 4H, Ar); ¹³C NMR (CDCl₃, 75 MHz, TMS) 79.5, 82.9, 125.3, 126.4, 126.6, 126.7, 127.4, 132.6, 132.7, 136.1, 168.6, 173.5. Compound **18**. A white solid. Yield: 48%, mp 175–177°C. ¹H NMR (CDCl₃, 300 MHz, TMS) 1.40 (s, 12H, 4CH₃), 7.62 (dd, *J*_{1,2} = 2.4 Hz, 1H, Ar), 7.98 (d, *J* = 8.4 Hz, 2H, Ar), 8.14 (d, *J* = 2.4 Hz, 2H, Ar), 8.18 (d, *J* = 8.4 Hz, 2H, Ar); ¹³C NMR (CDCl₃, 75 MHz, TMS) 25.3, 84.6, 126.8, 127.1, 127.2, 129.1, 133.0, 135.7, 136.5, 169.6, 173.8.

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Figure 1.
Structures of several known biologically active combretastatin A-4 analogs.

Figure 2.
Structures of 3,5-substituted-1,2,4-oxadiazole derivatives.

Figure 3.
Structure of compounds **5–9**.

Figure 4.
Structure of compounds **14–18**.

Scheme 1.
Synthesis of compounds **5-8**.

Scheme 2. Attempt at synthesis of compound **12**.

Scheme 3.
Synthesis of compound **9**.

Scheme 4.
Synthesis of compounds **14**–**17**.

Scheme 5.
Synthesis of compound **18**.