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Natural Product Evodiamine with Borate Trigger Unit: Discovery of Potent Antitumor Agents against Colon Cancer

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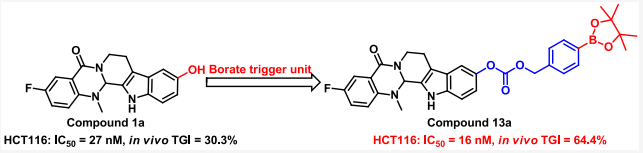
ABSTRACT: In order to improve the antitumor potency of the natural product evodiamine, novel boron-containing evodiamine derivatives were designed by incorporating boronic acid and boronate as trigger units. Boronate derivative **13a** could be triggered by reactive oxygen species (ROS) in the HCT116 colon cancer cell line and showed excellent antitumor activity *in vitro* and *in vivo*. It induced apoptosis in HCT116 cancer cells in a dose-dependent manner and cell growth arrest at the G2 phase.



KEYWORDS: *Evodiamine, borate unit, ROS, antitumor, Top1, Top2*

Boron is an essential element of diverse cells and is ubiquitous in nature.[1] It has an empty p-orbital with an electrophilic property, which can form covalent bonds with biological nucleophiles including amine and hydroxyl groups in nucleic acids. Moreover, the sp^2 boron center can be easily changed to sp^3 hybridization under certain physiological conditions.[2−6] Given the special characteristics of the boron atom, boron-containing compounds (BCCs) have attracted great interests in medicinal chemistry, and several of them have been approved (e.g., bortezomib, tavaborole, Figure 1)[7,8] or under clinical trials (e.g., crisaborole, GSK8175, Figure 1).[9,10]

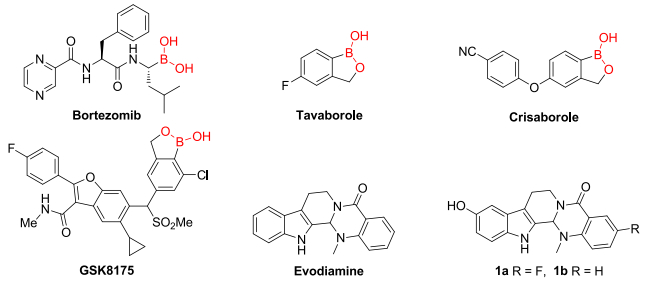


Figure 1. Chemical structures of bortezomib, tavaborole, crisaborole, GSK8175, evodiamine, and evodiamine derivatives.

Reactive oxygen species (ROS), including hydrogen peroxide (H_2O_2), which act as a pivotal part in cell signaling and homeostasis, are natural byproducts of normal oxygen metabolism.[11] In particular, cancer cells exhibit an exclusive feature of increased ROS (mainly H_2O_2),[12−14] which can be used to design drugs for targeted cancer therapy.[15,16] Moreover, borates, including boronate and boronic acid, are ROS responsive functional groups.[11,17−22] Borates attached to carbon are easily cleavable by ROS.[11,17−22] Therefore, it is advantageous to attach borates as a "trigger unit" to improve the pharmacological activity and druggability of antitumor agents.[17−22]

In recent years, evodiamine (Figure 1) has been investigated as an antitumor lead compound that possesses multitargeting profiles.[23−26] Previously, systemic structural optimizations of evodiamine were performed by our group, and several highly active evodiamine derivatives (**1a** and **1b**, Figure 1) were identified.[27−29] Unfortunately, further development of evodiamine derivatives was hindered by the unsatisfied *in vivo* antitumor potency. In light of the success of borate in drug discovery,[17−22] herein, a series of novel boron-containing evodiamine analogues were reported by incorporating borates as trigger units at the C10 position of compounds **1a** and **1b** through various cleavable linkers with an aim to improve their *in vivo* antitumor efficacy (Figure 2).

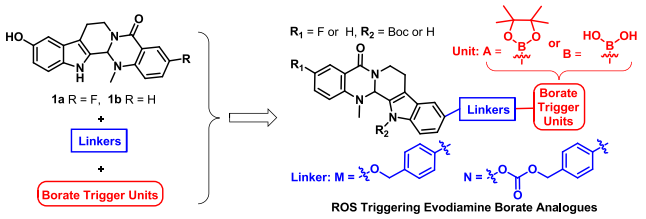


Figure 2. Design of ROS triggering evodiamine borate analogues.

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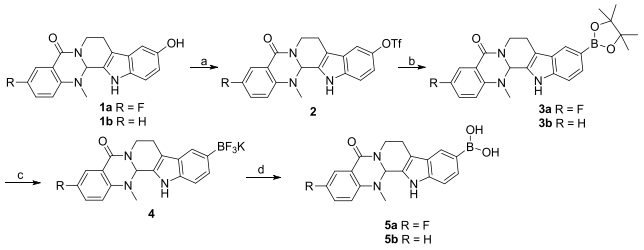
The syntheses of evodiamine borates were depicted in Schemes 1−3. First, starting from evodiamine derivatives **1**,

Scheme 1. Chemical Synthesis of Compounds 3 and 5[a]

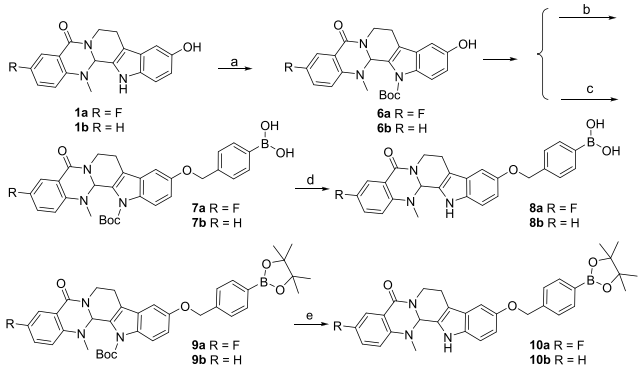


[a]Reagents and conditions: (a) Tf_2O, pyridine, DCM, 0 °C, 3 h, yield 87%; (b) bis(pinacolato)diboron, Pd(dppf)Cl_2, KOAc, 1,4-dioxane, 100 °C, 8 h, yield 90−93%; (c) KHF_2, MeOH, rt, 30 min, yield 63−68%; (d) TMSCl, H_2O, MeCN, 2 h, yield 95−98%.

triflates **2** were prepared according to the literature.[22] Then, the Miyaura reaction was performed with **2** to afford boronoates **3**. Deprotection of **3** in the presence of potassium difluorohydride (KHF_2) and methanol at room temperature gave potassium trifluoroborates **4**, followed by hydrolysis under acid conditions to yield target compound **5** (Scheme 1).

Target compounds **7**−**10** were synthesized as shown in Scheme 2. The NH groups of compounds **1** were protected

Scheme 2. Chemical Synthesis of Compounds 7−10[a]

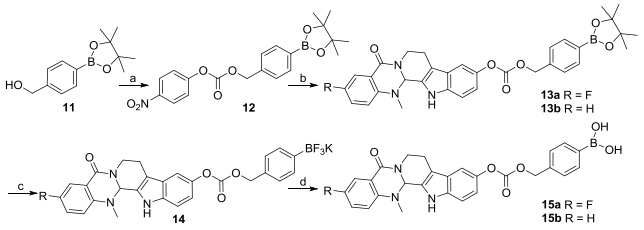


[a]Reagents and conditions: (a) (1) DMAP, $(Boc)_2O$, THF, 2 h; (2) K_2CO_3, MeOH, 4 h; (3) AcOH, 1 h, yield 62−65%; (b) NaH, 4-bromomethylphenylboronic acid, DMF, 0 °C, 8 h, 1 N HCl, pH = 2, yield 80−83%; (c) NaH, 4-bromomethylphenylboronic acid pinacol ester, DMF, 0 °C, 8 h, yield 82−83%; (d) TFA, DCM, rt, 2 h, yield 63−66%; (e) TFA, DCM, rt, 2 h, yield 45−48%.

with the Boc group via three steps to afford intermediates **6**. In the presence of NaH and 4-bromomethylphenylboronic acid or 4-bromomethylphenylboronic acid pinacol ester, phenylboronic acids **7** and phenylboronates **9** were obtained, respectively. Finally, Boc deprotection was conducted to give target compounds **8** and **10**.

As depicted in Scheme 3, evodiamine boronate derivatives with carbonate linker (**13** and **15**) were prepared. Boronate pinacol ester **11** was reacted with 4-nitrophenyl chloroformate and trimethylamine (TFA) in tetrahydrofuran (THF) to afford intermediate **12**, which was reacted with compounds **1** to give target compounds **13** with high yields. Then, target compounds **15** were prepared using similar synthetic methods as described for derivatives **5**.

Scheme 3. Chemical Synthesis of Compounds 13 and 15[a]



[a]Reagents and conditions: (a) 4-nitrophenyl chloroformate, TEA, THF, rt, 6 h, yield 58%; (b) **1**, K_2CO_3, THF, 70 °C, 10 h, yield 76−80%; (c) KHF_2, MeOH, rt, 30 min, yield 74−76%; (d) TMSCl, H_2O, MeCN, 2 h, yield 59−62%.

The *in vitro* antitumor activities of evodiamine borates (Table 1) were assayed against HCT116, MCF-7,and A549

Table 1. *In Vitro* Antitumor Activity of Borate Evodiamines (IC_{50}, μM)

Compds	HCT116	MCF-7	A549
3a	0.17 ± 0.004	0.96 ± 0.2	0.11 ± 0.14
3b	0.22 ± 0.03	0.39 ± 0.075	0.17 ± 0.022
5a	0.063 ± 0.003	0.094 ± 0.006	0.040 ± 0.006
5b	0.069 ± 0.005	0.16 ± 0.031	0.10 ± 0.008
7a	4.91 ± 0.97	2.39 ± 0.48	2.13 ± 0.15
7b	0.52 ± 0.36	1.58 ± 0.32	7.20 ± 1.4
8a	0.083 ± 0.001	0.059 ± 0.010	0.073 ± 0.003
8b	0.12 ± 0.04	0.11 ± 0.021	0.074 ± 0.014
9a	2.17 ± 0.47	7.85 ± 0.92	2.23 ± 0.43
9b	4.18 ± 0.79	4.13 ± 0.83	3.44 ± 0.65
10a	0.15 ± 0.014	0.097 ± 0.016	0.12 ± 0.001
10b	0.10 ± 0.06	0.16 ± 0.031	0.39 ± 0.075
13a	0.016 ± 0.003	0.033 ± 0.008	0.037 ± 0.002
13b	0.065 ± 0.022	0.086 ± 0.017	0.10 ± 0.006
15a	0.041 ± 0.005	0.032 ± 0.006	0.044 ± 0.002
15b	0.052 ± 0.007	0.14 ± 0.028	0.13 ± 0.05
1a	0.027 ± 0.006	0.031 ± 0.008	0.029 ± 0.004
1b	0.055 ± 0.005	0.27 ± 0.006	0.084 ± 0.013
CPT	0.009 ± 0.003	0.084 ± 0.005	0.039 ± 0.008

cell lines using the CCK8 assay.[30] Evodiamine derivatives **1a** and **1b** and camptothecin (CPT) were selected as positive controls. As illustrated in Table 1, boronic acids derivatives (**5a**, **5b**, **8a**, **8b**, and **15b**) generally showed better antitumor activity than the corresponding boronates (**3a**, **3b**, **10a**, **10b**, and **13b**). Most N13-Boc protected intermediates (**7a**, **7b**, **9a**, and **9b**) showed decreased antitumor activity against the three cell lines. Interestingly, excellent antitumor activity was retained for evodiamine borates with a carbonate linker (**13** and **15**). Most boronic acid derivatives showed comparable antitumor activity to lead compounds **1a** and **1b**. In particular, compound **13a** exhibited excellent antiproliferative activity (IC_{50} range: 16−37 nM), whose efficacy against HCT116 cells (IC_{50} = 16 nM) was superior to that of lead compound **1a** (IC_{50} = 27 nM).

Previously, topoisomerase I (Top1) and topoisomerase II (Top2) were identified as targets of compounds **1a** and **1b**. Herein, evodiamine borates with good cytotoxicity were selected to investigate their Top inhibitory activities. As depicted in Figure 3A, all the compounds showed strong inhibitory effect against Top1 at 500 μM. At a lower

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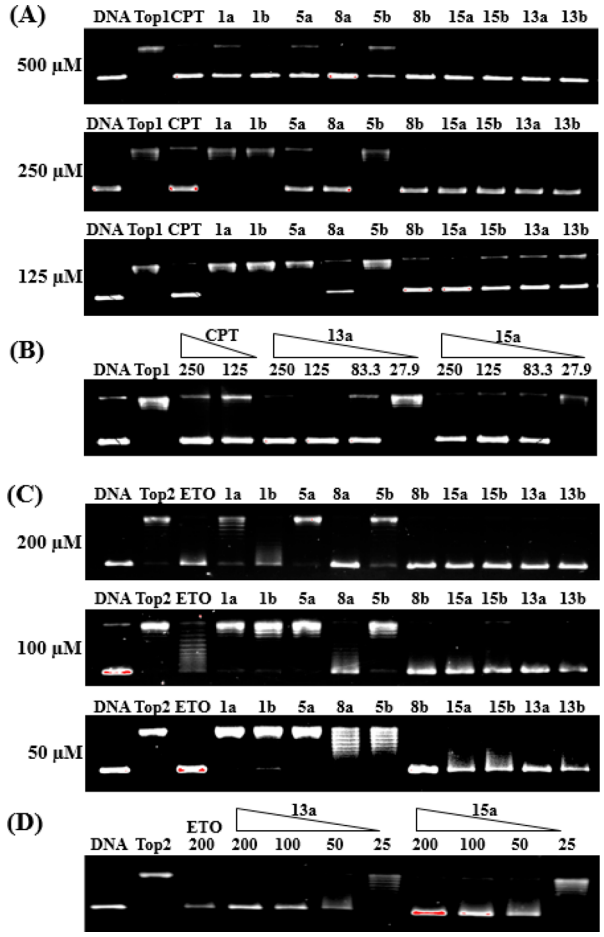

Figure 3. (A) Top1 inhibitory activity assay of evodiamine borate derivatives at 500, 250, and 125 μM, respectively. (B) Top1 inhibitory activity assay of compounds **13a** and **15a** ranging from 27.9 to 250 μM. (C) Top2 inhibitory activity assay of evodiamine borate derivatives at 200, 100, and 50 μM, respectively. (D) Top2 inhibitory activity assay of compounds **13a** and **15a** ranging from 25 to 200 μM.

concentration of 125 μM, six compounds (**8a**, **8b**, **13a**, **13b**, **15a**, and **15b**) were still effective. Particularly, the activity of compounds **13a** and **15a** were active at 83.3 μM (Figure 3B). Moreover, five compounds, namely, **8b**, **13a**, **13b**, **15a**, and **15b**, retained Top2 inhibitory potency at 50 μM (Figure 3C,D), and three of them (**8a**, **13a**, **15a**) exhibited comparable potency to the reference drug etoposide (ETO). Given that 3-chloro-10-hydroxy thio-evodiamine was identified as a Top1/Top2/tubulin inhibitor, the tubulin inhibitory activities of compounds **13a**, **13b**, **15a**, and **15b** were further determined.[28] However, only compound **15b** was active with an IC_{50} value of 25.7 μM (Table S3). On the basis of the above results, compounds **8b**, **13a**, **13b**, and **15a** were proven to be Top1/Top2 dual inhibitors, indicating that these borate compounds might act by a similar antitumor mechanism to that of lead compounds **1a** and **1b**.[29]

To better illuminate the binding mode with Top1 and Top2, compounds **1a**, **1b**, **13a**, and **15a** were subjected to molecule docking. Similar to compounds **1a** and **1b** (Figure S1A,B), the A-ring of compound **13a** formed $\pi-\pi$ interactions with the TGP11 base pair, enhancing the base stacking at the active site of Top1 (Figure 4A). The carbonyl group and carbonate carbonyl group formed hydrogen bonding interactions with Try426 and Asn722, respectively. The boric acid group of

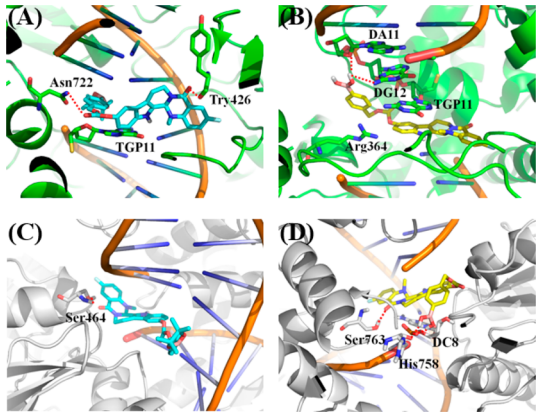

Figure 4. Binding modes of compounds **13a** (A, C) and **15a** (B, D) with the Top1−DNA complex (PDB code: 1T8I) and ATPase domain of Top2α (PDB code: 5GWK).

compound **15a** additionally formed a hydrogen bond with DA11 and DG12 (Figure 4B). Additional hydrogen bonds were also found for compounds **13a** and **15a** in the active site of Top1. Moreover, the four compounds fitted well into the ATPase of Top2α. For compounds **1**, hydrogen bonds between the hydroxy group and Top2α were the predominant interactions (**1a**, DC8 and His758; **1b**, DC8 and Ser763, Figure S1C,D). However, compounds **13a** and **15a** bound to the active domain of Top2 through different ways. For compound **13a**, the D-ring carbonyl group participated in the formation of a hydrogen bond with Ser464 (Figure 4C). For compound **15a**, the D-ring carbonyl group formed a hydrogen bond with Ser763 and the boric acid group formed hydrogen bonds with His758 and DC8, respectively (Figure 4D).

On the basis of *in vitro* antitumor activities, two different types of evodiamine borates **13a** and **15a** were selected to test the ability to induce apoptosis and cell-cycle arrest in the HCT116 cell line. As shown in Figure 5A, compounds **13a** and **15a** demonstrated significant apoptosis-inducing activity in a dose-dependent manner in HCT116 cells. The percentages of apoptotic cells were increased significantly (**13a**: from 42.28% to 61.73%; **15a**: from 44.40% to 64.47%) as compared to the control population (6.25%). The cell-cycle arrest of compounds **13a** and **15a** in HCT116 cells was evaluated by the flow cytometric method (Figure 5B). After exposure to compound **13a** at 0.05, 0.2, and 0.4 μM, the percentages of cells in the G2 fraction were 26.88%, 45.49%, and 56.25%, respectively. Similarly, the percentages of cells exposed to compound **15a** at the G2 phase were changed dramatically (29.47%, 43.45%, and 51.23%, respectively). As compared with the ratio (10.8%) of the untreated cells at the G2 phase, compounds **13a** and **15a** were confirmed to induce cell-cycle arrest in HCT116 cells at the G2 phase, which was consistent with that of lead compound **1a**.[29]

Compounds **13a** and **15a** were selected to investigate the ability to release compound **1a** by treating different concentrations of H_2O_2 in PBS (pH = 7.4) using high performance liquid chromatography (HPLC). At 0.05 mM H_2O_2, compound **1a** could be detected with relative drug release rates for compounds **13a** and **15a** of 11.6% and 20.8%, respectively. Compound **1a** could be released in a concentration-dependent manner, indicating that it can be activated by H_2O_2 (Figures S1 and S2). Furthermore, ultraperformance liquid chromatography quadrupole time-of-flight mass spec-

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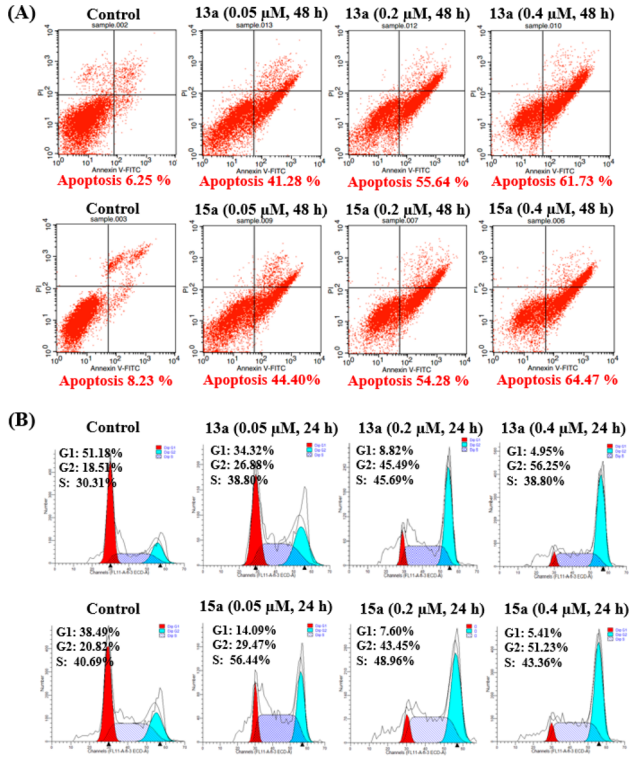
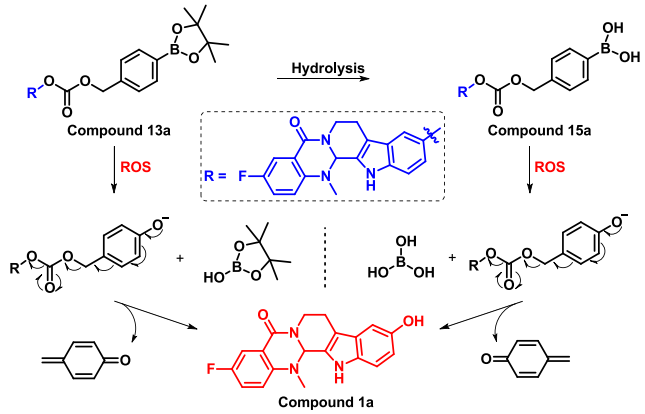


Figure 5. Apoptosis and cell-cycle arrest induced by compounds **13a** and **15a**. (A) HCT116 cells were incubated with 0.05, 0.2, and 0.4 μM of compounds **13a** or **15a** for 48 h. Apoptosis was assayed by flow cytometry (n = 3). (B) Cell-cycle effect of compounds **13a** and **15a**. HCT116 cells were incubated with 0.05, 0.2, and 0.4 μM of compounds **13a** or **15a** for 24 h. At least three independent experiments were done for each condition.

trometry (UPLC-QTOF/MS) was used to assess the cleavage of borate derivatives undergoing intracellular ROS in HCT116 cancer cells. The concentrations of compounds **13a**, **15a**, and **1a** in cell culture media were analyzed after incubation with HCT116 cancer cells for 8, 48, and 72 h. Relative drug release rates were measured by relative peak areas. Compound **15a** (retention time: 8.6 min) was directly converted into compound **1a** (retention time: 7.3 min) with the relative drug release rates of 18.5%, 24.5%, and 35.5%, respectively (Figures S4−S6). In contrast, compound **13a** (retention time: 11.4 min) was first converted to compound **15a** (78.6%, 43.7%, and 36.3%, respectively) and then transformed to compound **1a** (13.6%, 39.9%, and 53.1%, respectively, Figures S4−S6). Thus, compounds **13a** and **15a** could be triggered by ROS in HCT116 cells (Scheme 4). The relative drug release rates were increased in a time-dependent manner. Reactive quinone methide (QM) precursor 4-(chloromethyl)phenyl acetate was also used to test its antiproliferative effect for cancer cells, and it was almost inactive against cancer cells (Table S1), suggesting the released QM has little effect on cancer cells. Furthermore, *in vitro* metabolic stabilities of compounds **13a**, **15a**, and **1a** were evaluated through the liver microsome assay. Compound **13a** had a terminal half-life ($t_{1/2}$) of 8.36 min, which was much longer than that of compounds **15a** ($t_{1/2}$ = 0.74 min) and **1a** ($t_{1/2}$ = 3.69 min, Table S2). The cLogP values of compounds **13**, **15**, and **1** were also predicted (Table S4). Compounds **13** had better *in vitro* antitumor potency, possibly due to their tumor penetration with increased lipophilicity of the boronate units.

Scheme 4. Proposed Reaction Mechanism of Evodiamine Borate Analogues with ROS



Finally, compound **13a** was administrated intraperitoneally (IP) at 10 mg/kg to evaluate its *in vivo* antitumor activity in a HCT116 xenograft model in mice. After 21 consecutive days, compound **13a** achieved the tumor growth inhibition (TGI) of 64.4% (Figure 6A), which was superior to compound **1a** (TGI

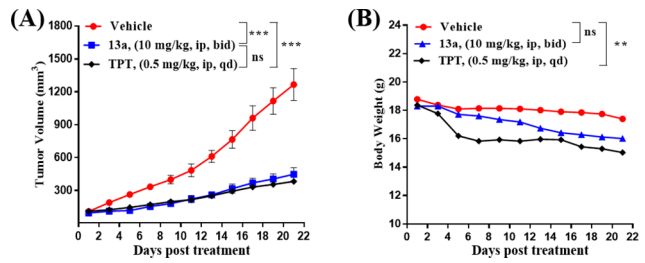


Figure 6. Antitumor activity of compound **13a** and TPT in a HCT116 tumor xenograft model. (A) Tumor growth inhibition. (B) The change of body weight. Data are presented as the mean ± SEM: *P < 0.05, **P < 0.01, and ***P < 0.001 vs vehicle group, determined with Student's t test.

= 30.3% at 2 mg/kg,[29] highly toxic at 10 mg/kg, Figure S7) and comparable to the control TPT (TGI = 68.8%). Meanwhile, compound **13a** had no significant effects on the decrease of the body weight (P > 0.05, Figure 6B). In contrast, TPT had significant toxicity on the treated mice (P < 0.01), suggesting that the toxicity of compound **13a** might be lower than that of TPT.

In summary, novel boron-containing evodiamine analogues were reported by incorporating boronic acid and boronate as trigger units. In particular, compound **13a** showed excellent antitumor activity in a HCT116 xenograft model in mice, which induced apoptosis in a dose-dependent manner and cell growth arrest at the G2 phase. Compound **13a** acted as a ROS triggering evodiamine borate analogues and showed improved *in vivo* antitumor potency compared to parent evodiamine derivative **1a**. Taken together, this study demonstrated a good example of using borates as trigger units to improve the *in vivo* antitumor potency of a natural product. Compound **13a** represents a promising antitumor lead compound, and further structural optimization and antitumor mechanism studies are currently in progress.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.9b00513.

Chemical synthesis and structural characterization of the target compounds; protocols of the biological assays; relative drug release; NMR spectra; HPLC purity of representative compounds; certificate of STR analysis (PDF)

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Author Contributions

▽X.L., S.W., and G.D. contributed equally to this work. D.L. and C.S. designed the experiments and revised the manuscript. X.L., S.W., and G.D. synthesized evodiamine borate derivatives and carried out the biological experiments. S.C. and Z.M. assisted with the biological experiments and in the preparation of the manuscript. All authors discussed the results and commented on the manuscript. All authors read and approved the final manuscript.

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

BCCs, boron-containing compounds; ROS, reactive oxygen species; CPT, camptothecin; ETO, etoposide; Top1, topoisomerase I; Top2, topoisomerase II; HPLC, high performance liquid chromatography; UPLC-QTOF/MS, ultra performance liquid chromatography quadrupole time-of-flight mass spectrometry; IP, intraperitoneally; TGI, tumor growth inhibition.

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