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# Chalcone–benzoxaborole hybrids as novel anticancer agents

Jiong Zhang [a], Fei Yang [a], Zhitao Qiao [a], Mingyan Zhu [a], Huchen Zhou [a,b,*]

[a] State Key Laboratory of Microbial Metabolism, School of Pharmacy, Shanghai Jiao Tong University, Shanghai, China
[b] Chemical Biology Division of Shanghai Universities E-Institutes, Key Laboratory of Cell Differentiation and Apoptosis of Chinese Ministry of Education, Shanghai Jiao Tong University School of Medicine, Shanghai, China

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ABSTRACT

In this study, we report the synthesis of a series of chalcone–benzoxaborole hybrid molecules and the evaluation of their anticancer activity. Their anticancer potency and toxicity were tested on three human cancer cell lines and two normal cell lines. The 4-fluoro compound **15** was found to be the most potent compound with an $IC_{50}$ value of 1.4 μM on SKOV3 cells. The 4-iodo compound **18** and 3-methyloxy-4-amino compound **47** showed good potency on SKOV3 cells while exhibiting low toxicity on normal cells. This work extended the application of benzoxaboroles to the field of anticancer research.



Cancer, as one of the major causes of death, seriously endangers human health.[1] In 2015 alone, an estimated 2.8 and 0.6 million cancer deaths occurred in China[2] and United States,[3] respectively. While chemotherapy remains the main treatment, clinically used anticancer drugs are generally limited by toxicity, side effects, and resistance.[4,5] Consequently, it remains urgent to develop novel anti-cancer agents. During the past decade, boron-containing compounds have started to attract much attention from medicinal chemists.[6,7] The boronic acid-containing drug bortezomib (Velcade) (Fig. 1), a proteasome inhibitor,[8] was approved in 2003 to treat multiple myeloma.[9] An interesting class of cyclic boron-containing compounds, benzoxaboroles, were first synthesized in 1957[10] while its medicinal usage had remained unexplored for fifty years until tavaborole (Kerydin) (Fig. 1) was approved in 2014 for the treatment of fungal infection of the toenails.[11,12] To date, benzoxaboroles have been investigated for their antifungal, antibacterial, anti-parasite, antiviral, and anti-inflammatory properties.[11–19] However, an investigation of their anticancer activity has been lacking. Although Kunar and coworkers tested a few benzoxaboroles against cancer cell lines, their compounds failed to show any significant inhibitory activity.[20] Li and coworkers reported benzoxaborole-containing phenylalanine analogs which have potential applications in boron neutron capture therapy (BNCT), but subsequent study was not reported.[21]

In order to develop novel anticancer agents and extend the range of application of benzoxaboroles, we screened a series of benzoxaboroles against three human cancer cell lines, SKOV3 (ovarian carcinoma), MDA-MB231 (breast cancer), and HCT116 (colon colorectal carcinoma), and two human normal cell lines, MCF-10A (human mammary epithelial cells) and WI-38 (lung fibroblast) by MTT assay.[22] The chalcone–benzoxaborole hybrid molecule **8** showed inhibitory activity against SKOV3, MDA-MB231, and HCT116 cell lines with $IC_{50}$ value of 3.4, 2.3, and 6.1 μM, respectively. It also showed an 8-fold selectivity between human cancer cells (MDA-MB231) and normal cells (WI-38). Further investigation of the derivatives of compound **8** led to the discovery of anticancer agents with $IC_{50}$ value as low as 1.4 μM (compound **15**) and compounds **18** and **47** which possess both high potency and good selectivity.

The compounds were synthesized according to our previously reported methods.[23] As shown in Scheme 1, 2,6-dimethylbromobenzene (**1**) was oxidized to 2-bromoterephthalic acid **2** which was subsequently converted to methyl ester **3**. Reduction of ester **3** gave benzyl alcohol **4** which underwent protection and treatment with *n*-BuLi and triisopropyl borate, followed by deprotection and

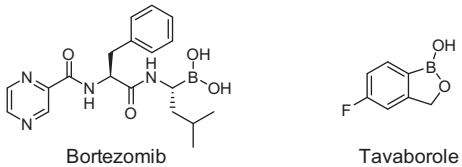


**Figure 1.** Structures of bortezomib and tavaborole.

* Corresponding author. Tel.: +86 21 3420 6721.
*E-mail address:* hczhou@sjtu.edu.cn (H. Zhou).

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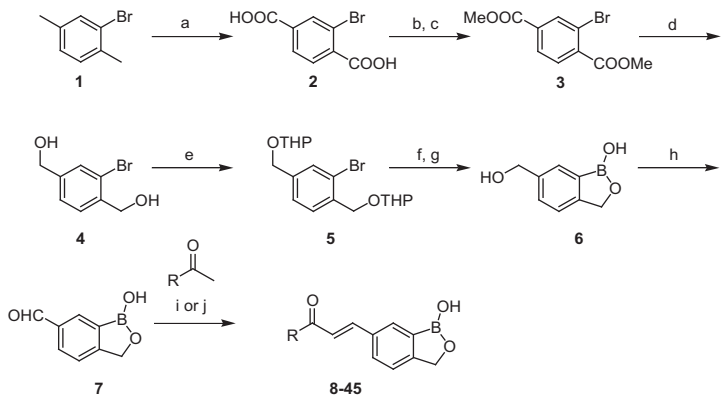
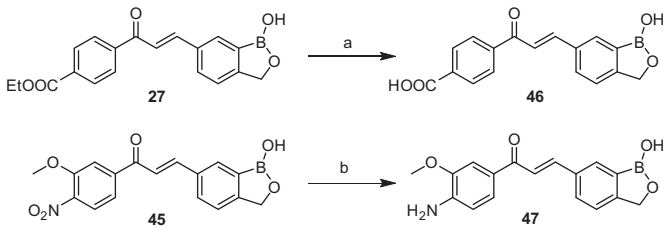



**Scheme 1.** Reagents and conditions: (a) $KMnO_4$, *t*-BuOH, $H_2O$, 70 °C; (b) $SOCl_2$, reflux; (c) MeOH, $Et_3N$; (d) $LiBH_4$, MeOH, THF; (e) DHP, *p*-TsOH, DMF; (f) *n*-BuLi, B(*i*-PrO)$_3$, THF, −78 °C; (g) 6 M HCl; (h) PCC, Celite, DCM; (i) NaOH, EtOH, $H_2O$; (j) $CH_3COCl$, EtOH.



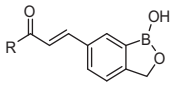

**Scheme 2.** Reagents and conditions: (a) NaOH, EtOH, $H_2O$; (b) $SnCl_2{\cdot}2H_2O$, EtOH.

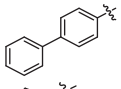
cyclization in 6 M HCl to give benzoxaborole **6**. Oxidation of alcohol **6** gave aldehyde **7** which underwent aldol condensation to give compounds **8**–**45**. As shown in Scheme 2, compound **46** was obtained by alkali hydrolysis from ester **27** and compound **47** was obtained from nitro compound **45** by $SnCl_2$ reduction.

First, we explored the effect of different aromatic rings on anticancer activity. As shown in Table 1, bulky aromatic rings such as naphthyl (**9**) and biphenyl (**10**) showed activity comparable to compound **8**. However, heterocycles including furanyl (**11**), thiophenyl (**12**), and pyridinyl (**13**) gave significantly reduced inhibitory activity. In addition, the *N*-methyl-pyrrolyl compound **14** showed completely diminished activity. Therefore, we next continued to investigate the substituted phenyl compounds for their anticancer activity.

As shown in Table 2, the anticancer activity of *para*-substituted phenyl compounds is discussed. Compared to unsubstituted phenyl compound **8**, *p*-fluoro compound **15** showed a 2-fold increase of potency, while *p*-chloro, -bromo, and -iodo compounds **16**–**18** showed moderately decreased potency. It is worth mentioning that the *p*-iodo compound **18** showed more than 25-fold of selectivity between cancerous cells (SKOV3) and normal cells (MCF-10A and WI-38). The *p*-methyl, -ethyl, -methylthio, and -benzyloxy com-

**Table 1**
The effect of different aromatic A rings



| Compound | R | [a] $IC_{50}$ (μM) | | | | |
|---|---|---|---|---|---|---|
| | | SKOV3 | MDA-MB231 | HCT116 | MCF-10A | WI-38 |
| **8** |  | 3.4 | 2.3 | 6.1 | 15.9 | 19.1 |
| **9** |  | 2.7 | 3.6 | 5.0 | 13.4 | 18.8 |
| **10** |  | 4.9 | 6.4 | 9.5 | 20.7 | 18.3 |
| **11** |  | 20.7 | 7.3 | 24.1 | 7.4 | 59.0 |
| **12** |  | 10.4 | 4.6 | 14.2 | 13.8 | 26.0 |
| **13** |  | 18.5 | 11.4 | 20.5 | 34.4 | 76.2 |
| **14** |  | 93.6 | >100 | >100 | >100 | >100 |
| Doxorubicin | | 0.42 | 0.07 | 0.31 | 0.06 | 9.0 |
| Cisplatin | | 12.8 | 41.8 | 21.7 | 11.0 | >100 |

[a] $IC_{50}$ indicates compound concentration required to inhibit cell viability by 50%. Values are expressed as the mean of triplicate experiments.