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# Synthesis and evaluation of functionalized aminobenzoboroxoles as potential *anti*-cancer agents

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ABSTRACT

Several aminobenzoboroxole derivatives have been prepared starting from o-boronobenzaldehyde employing reductive amination protocol. The corresponding aminobenzoboroxole derivatives have been further functionalized as N-nitrosoaminobenzoboroxoles as well as N-benzoboroxolylureas. These derivatives have been evaluated for their anti-cancer activity on human pancreatic cancer MIAPaCa-2 and human breast cancer MDA-MB-231 cell lines. 2015 Elsevier Ltd. All rights reserved.



## 1. Introduction

Benzoboroxoles (cyclic boronic acids) are highly valuable compounds because of their use in variety of disciplines such as organic, materials, and medicinal chemistry [1–3]. Benzoboroxoles have attracted significant attention because of their attractive therapeutic and biological profile and have been reviewed recently [2a–b]. Owing to our interest in boron chemistry [4], we have been working on the functionalization of the oxaborole ring via a plethora of reaction pathways starting from o-boronobenzaldehyde **1** as our boron precursor (Fig. 1) [5]. For example, reaction of **1** with activated olefins such as methyl acrylate, acrylonitrile, methyl vinyl ketone, acrolein and cyclohex-2-enone led to the formation of functionalized benzoboroxoles **2**–**3** under Baylis-Hillman [6] conditions (Fig. 1, path a, b) [5a–b]. We were also able to synthesize the corresponding homologous benzoboroxole esters **4** via the reaction of Baylis-Hillman bromides with the aldehyde **1** under Barbier allylation conditions (Fig. 1, path c) [5b]. Aldol addition on the boronoaldehyde **1** led to the formation of ketones and esters such as **5** and **6** (Fig. 1, paths d-e) [5c]. Finally, reaction of aldehyde **1** with isonitriles furnished the benzoboroxole amides **7** under Passerini reaction [7] conditions (Fig. 1, path f) [5d] While we have been routinely able to functionalize the oxaborole unit, much to our dismay, we found that these molecules did not exhibit any significant biological activity as *anti*-bacterial and *anti*-cancer agents [5]. Accordingly, we envisioned the preparation of aromatic ring-functionalized benzoboroxoles while leaving the benzylic carbon unbranched on the oxaborole ring so as to improve the biological efficacy. Herein, we provide an account of our synthetic and biological evaluation results.

## 2. Results and discussion

We began our efforts with the synthesis of the precursor aminobenzoboroxole **10**. The reaction of commercially available *o*-boronobenzaldehyde **1** with sodium borohydride in THF and water provided benzoboroxole **8** in 87% yield. Nitration of benzoboroxole

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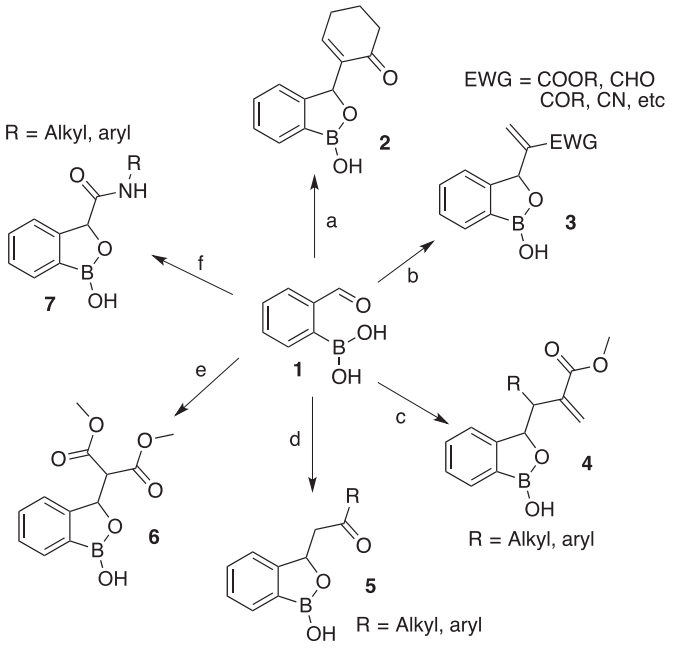
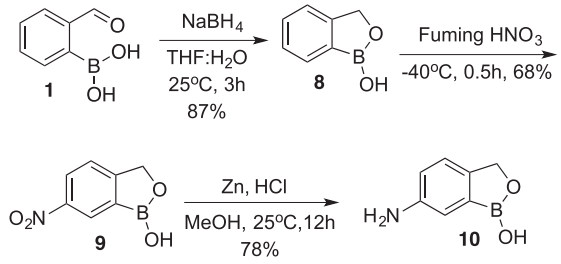



**Fig. 1.** Functionalized benzoboroxoles.




**Scheme 1.** Preparation of Aminobenzoboroxole.

with fuming nitric acid resulted in the formation of 6-nitrobenzoboroxole **9** [8]. Reduction of **9** with Zinc and hydrochloric acid furnished the aminobenzoboroxole **10** in 78% yield (Scheme 1). None of these three reactions involved chromatographic purification and the compounds could be readily obtained by simple acid-base manipulations.

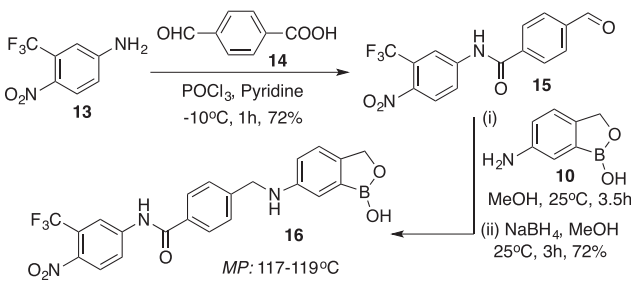
After synthesizing 6-aminobenzoboroxole **10**, we attempted the reductive amination of benzaldehyde with **10** (**Entry 1,** Table 1) in methanol at room temperature, and after stirring for 3 h, complete conversion of amine to imine **11** was observed. Sodium borohydride was then added to the reaction mixture at room temperature and stirred for 2 h to effect reduction of the imine. Our initial efforts of isolating the product proved difficult and the standard work up with ethyl acetate and water after evaporation of ethanol did not furnish the product N-benzylaminobenzoboroxole **12a**. The product was finally obtained after acidification with dilute HCl to pH 1 and work up with ethyl acetate, *albeit* in low yields (~30%). The isolation step was finally optimized and aminobenzoboroxole **12a** was obtained in 82% yield after careful neutralization of the aqueous solution to a neutral pH, at which point, the product started precipitating out of the solution. The solid was then filtered and dried over vacuum to obtain analytically pure product **12a**. We were then able to extend this protocol for the reaction of 6-aminobenzoboroxole with a variety of aldehydes substituted with electron-withdrawing (**Entries 2–7,** Table 1) as well as electron-donating (**Entries 8–13,** Table 1) groups. All of these aldehydes readily reacted with **10** at room temperature and complete formation of the imine was observed in all these cases within 3–4 h. The imines **11b–m** were then subjected to $NaBH_4$ reduction to afford the products **12b-m** in 72–85% overall yields (**Entries 2–13,** Table 1). As expected, imine formation was observed to be relatively faster with electron withdrawing group substituted aldehydes and slightly better yields of the product were observed in these cases (**Entries 2–7,** Table 1).

Using the reductive amination strategy, an aminobenzoboroxole-flutamide hybrid congener **16** was synthesized as shown in Scheme 2. Briefly, 4-nitro-3-triflormethylaniline **13** was treated with *p*-formylbenzoic acid **14** in the presence of $POCl_3$ to obtain the aldehyde **15** in 72% yield. The aldehyde **15** was then subjected to reductive amination with aminobenzoboroxole **10** under standard conditions in a one-pot procedure as described above to obtain the hybrid congener **16** (Scheme 2). A chloroquinoline-aminobenzoboroxole conjugate **19** was also synthesized in a similar manner starting from acetanilide **17** in two steps using Vilsmeier-Haack formylation [9] followed by reductive amination (Scheme 3).

Nitrosoamines and nitrosoureas are of particular interest for the treatment of various types of cancers and compounds such as Lomustine and Carmustine are prescribed as alkylating agents in chemotherapy [10]. To demonstrate the robustness of the benzoboroxole moiety, some of the representative secondary amines **12** mentioned above (Table 1), were then subjected to nitrosation. All of the compounds readily reacted with sodium nitrite and HCl in acetonitrile/water solvent system and the corresponding *N*-nitrosoaminobenzoboroxoles **20a-f** precipitated out of the reaction within 1–2 h. The products were obtained in high yields and were characterized by standard analytical techniques (Scheme 4).

Further, *N*-substituted aminobenzoboroxoles **12a** and **12i** were reacted with phenyl, cyclohexyl, and 2-chloroethyl isocyanates in dioxane to furnish the urea derivatives **21a-f** in 79–84% yields (Scheme 5). The pure products were obtained upon the removal of solvent and addition of cold water. The products were filtered, dried, and characterized by IR, NMR, and mass spectrometry. In the case of cyclohexyl isocyanate and 2-chloroethyl isocyanate, the products had to be further triturated with hexane under sonication to remove traces of unreacted starting material or other byproducts. Our efforts towards the nitrosation of chloroethylureas **21e** and **21f** did not materialize and a complex mixture of products was observed.

After synthesizing the functionalized aminobenzoboroxoles, these molecules were evaluated for their general cytotoxicity against breast cancer cell lines (MDA-MB-231) and pancreatic cancer cell lines (MIAPaCa-2). While most of the compounds tested were not found to exhibit any significant cytotoxicity at 12.5 and 50 μM concentration, couple of derivatives **19** and **21b** showed




**Scheme 2.** Preparation of Aminobenzoboroxole-Flutamide Hybrid.