Bioengineering & Biomedical Science

Ozaki, J Bioengineer & Biomedical Sci 2014, 4:1
http://dx.doi.org/10.4172/2155-9538.1000134

Research Article Open Access

2-Aminoethyl Diphenylborinate (2-APB) Analogues: Part 4 - Poly-Boron Compounds: Regulators of Ca^{2+} Release and Consequent Cellular Processes

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Abstract

Inhibitory activities of 74 poly-boron compounds for SOCE and IICR were measured. Activities of poly-boron compounds were compared with 2APB, mono-boron and bis-boron compounds. The IC_{50} of best poly-boron compound 1042 was 2 μM. This value was almost same as IC_{50} 3 μM of 2-APB. Poly (aminoethoxyboryldiphenylether) 1042 is best candidate for regulation of Ca^{2+} release and consequent cellular processes in this paper.

Keywords: 2-APB; 2-APB analogue; Poly-boron compound; Regulator of Ca^{2+} release; Regulator of cellular processes

Introduction

Extracellular signal molecules attach to the plasmatic membrane where they are recognized by cell surface receptors. Upon binding of the ligand to the appropriate receptor, activation of G protein activates in turn phospholipase C. Active phospholipase C hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) giving rise to two products: 1,2-diacylglycerol and inositol 1,4,5-triphosphate (IP_3). IP_3 stimulates the release of Ca^{2+} from the intracellular stores in the endoplasmic reticulum through IP_3 receptor while regulating a wide range of cellular processes [1-20].

In 1997, we identified 2-aminoethyl diphenylborinate (2-APB) as being an IP_3 receptor inhibitor and regulate IP_3-induced calcium release [21,22]. This discovery rose a substantial interest and had a great impact as it gained more than 600 citations and more than 1000 studies on 2-APB [23-37] have been published so far. This was supported by increasing sales of 2-APB by Sigma-Aldrich as membrane-permeable modulator of intracellular IP_3-induced cellular calcium release. In this study, we aimed to generate better modulator of calcium release than 2-APB.

We synthesized several 2-APB analogues and measured their inhibitory activities on Store-Operated Calcium Entry (SOCE) and IP_3 Induced Calcium Release (IICR). We found that bis boron compound DBP 161 and DBP 163 were 10 times more effective than 2-APB [38]. Previously, we studied bis- boron compounds in more detail [39,40]. We extended these studies and synthesized 493 2-APB analogues and measured their inhibitory activities on SOCE and IICR [38-44]. The numbers of compounds and data obtained are so many. We decided to report the results by dividing into three part.; Part 1 (mono-boron compounds), Part 2 (bis-boron compounds), and Part 3 (poly –boron compounds). We have reported about mono-boron compounds [45] and bis-boron compounds recently [46]. This time, we report about poly-boron compounds. Here we analyzed SOCE inhibitory activities and IICR inhibitory activities of our poly-boron compounds collection.

We believe that if we would regulate Ca^{2+} release and associated cellular processes by boron compounds with various Ca^{2+} release-related activities, we may therapeutically intervene in many diseases, such as heart diseases and Alzheimer`s disease.

Materials and Methods

2-APB analogues

2-APB was first synthesized by Ronderstvent et al. [47] in 1954 from triphenylboranes and ethanolamine. Later, hydroxy diphenyl borane and ethanolamine methods for 2-APB synthesis were reported by Weidman and Zimmermann [48], Letsinger and Skoog [49], Povlock and Lippincott [50].

We have synthesized 493 2-APB analogues [38-44] using methods described by us [38-44] and others [47-52]. The structures, names and synthetic methods of the 493 compounds are in example 1-493 of Ref. 44. We will show examples to prepare 7142, 8001, 1053 and 1060. Other compounds can be obtained by similar methods [44].

Preparation of poly (1,4-phenylenoxy-1,4-phenylenehydroxyborane 7142: 4,4'-Dibromodiphenylether 328 mg was dissolved in ether(10ml),sec-butyl lithium 2 ml was added at -95°C and the mixture was warmed to -78°C 30 min later. Thereto was added triisopropoxyborane 188 mg and the mixture was stirred for 1 hr. The mixture was gradually warmed and stirred at room temperature for 15 hr. The mixture was acidified with 1N hydrochloric acid and the organic layer was washed with water, dried, concentrated, and subjected to silica gel column chromatography to give the title compound 112 mg.

Preparation of poly (aminoethoxyboryldiphenylether) 8001: 7142 (48.8 mg) was dissolved in ethanol 1.5 ml. Ethanolamine 15.7 mg was added and stirred overnight. N-hexane 10 ml was added and filtered to get 8001 11.7 mg as white solid.

Preparation of bis-(4,4'-(phenylglutamineboryl) phenyl) ether 1024: 4,4'-(hydroxyphenylboryl)diphenyl ether 1012 22 mg was

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Received September 05, 2014; **Accepted** October 07, 2014; **Published** October 14, 2014

Citation: Ozaki S (2014) 2-Aminoethyl Diphenylborinate (2-APB) Analogues: Part 4 - Poly-Boron Compounds: Regulators of Ca^{2+} Release and Consequent Cellular Processes. J Bioengineer & Biomedical Sci 4: 134. doi:10.4172/2155- 9538.1000134

dissolved in ethanol 0.2 ml and water 2 ml Ethanolamine 19 mg was added. The reaction mixture was heated for 17 hrs at 80°C. Ether 10 ml was added to get 1024 17 mg as white precipitate.

Preparation of poly((4,4'-phenylene-hydroxyborane -4.4'-diphenyletherhydroxyborane) 1053: 1,4-Dibromobenzene1 18 mg was dissolved in ether 10 ml, and sec–butyl lithium 1.05 ml was added at -96°C. stirred 1 hr (solution A) 4,4'-dibromodiphenylether 164 mg was dissolved in ether 6 ml, and the solution was cooled to at -78°C. Thereto was added 1N sec-butyl lithium 1 ml and the mixture was stirred for 30 min. Tris isopropoxyborane 230 mg was added and the mixture was stirred at -65°C (solution B).

Solution A and solution B was mixed and the solution was gradually warmed and stirred at room temperature for 15 hr. The mixture was acidified with 1N hydrochloric acid, and the organic layer was washed with water and dried and concentrated to give the title compound 178 mg.

Preparation of poly(phenyleneaminoethoxyborane diphenylether - aminoethoxyborane) 1060: Poly((4,4'-phenylene-hydroxyborane-4.4'-diphenylether hydroxyborane 1053 36 mg was dissolved in ethanol 0.2 ml and ethanolamine 19 mg was added. The reaction mixture was stirred for 2 hr. Ether 10 ml was added to get 1060 36 mg as white precipitate.

Methods

We have assayed the inhibitory activity of the 2-APB analogues for SOCE and IICR using our improved assays described previously [45].

Results and Discussion

We measured inhibitory activities of poly-boron compounds for SOCE and IICR. The results are shown in Figure 1, shown as supplementary file.

From Figure 1, typical 18 poly boron compounds are selected as follow.

Comparison of 2APB, mono-boron compounds, bis-boron compounds and poly-boron compounds

- The IC_{50} of best poly-boron compound 1042 at this paper is 2 μM.
- The IC_{50} of 2-APB for SOCE inhibition is 3 μM. That is, the IC_{50} of poly-boron compounds showed almost same activity as 2-APB.
- The IC_{50} of best mono-boron compound 919 at first paper [45] is 0.2 μM. The IC_{50} of best bis-boron compound 1024 reporting at previous paper [46] is 0.2 μM.

That is, the mono-boron compounds and bis-boron compounds showed almost 10 times strong activity than poly-boron compounds. Poly-boron compound does not fit well to IP_3 receptor, because of bulkiness of the molecule and does not inhibit IP_3-induced calcium release strongly.

These compounds can thus regulate the Ca^{2+} release and consequent cellular response.

Some of these compounds were shown to inhibit the calcium dependent enzyme transglutaminase [44]. Transglutaminase inhibitors block the abnormal cross-link of protein [43,44] and therefore they may slow down or even stop the progression of diseases caused by misfolded proteins, such as Huntington`s disease.

The 2-APB analogues presented in this study could be proven to be excellent lead compounds for many human diseases including heart disorders [53], Alzheimer`s [54,55] and Huntington`s disease [56,57].

We have shown widely different kinds of active compounds with IC_{50} ranging 0.2 to 50 μM from mono-boron, bis-boron and poly-boron compounds. By choosing the compound we can control the release of Ca^{2+} and regulate many cellular processes such as secretion, cardiac contraction, fertilization, proliferation, synaptic plasticity, atrial arryhythmiss [31], inhibition of calcium entry channel [25], excitation-contraction coupling in the heart [32], arrhythmogenic action of endothelin-1 on ventricular cardiac myocytes [34], dysreguration of neural calcium signaling in Alzheimer disease [55], Huntington aggregation [56,57] and protein cross-link by transglutaminase [43].

We believe that many investigators will find these reagents regulating Ca^{2+} release and related cellular processes very useful.

Summary

We have shown widely different kinds of active compounds with IC_{50} ranging 0.2 to 50 μM. Mono-boron compounds (at Part 1 [45]) showed strongest and followed by bis-boron compounds (at Part 2 [46]) and poly-boron compounds (at Part 4 this paper). Among poly-boron compounds, poly (phenyleneaminoethoxyborane diphenylether-aminoethoxyborane) 1060, poly (aminoethoxyboryldiphenylether) 8001 and poly(4-4'-biphenylene N-metylaminoethoxyborane) 1030 are best 3 candidates for regulation of Ca^{2+} release and consequent cellular processes.

Acknowlegement

We would like to thank Dr. M. J. Berridge for valuable suggestions and advices.

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