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2-Aminoethyl diphenylborinate (2-APB) analogues: Regulation of Ca^{2+} signaling

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ABSTRACT

In order to obtain compounds with modified 2-APB activities, we synthesized number of 2-APB analogues and analyzed their inhibitory activities for SOCE. The IC_{50} of 2-APB for SOCE inhibition is 3 μM while IC_{50} of some of our 2-APB analogues range 0.1–10 μM. The adducts of amino acids with diphenyl borinic acid have strong inhibitory activities. By using these compounds, we will be able to regulate intracellular Ca^{2+} concentration and consequent cellular processes more efficiently than with 2-APB.

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1. 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-trisphosphate (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 (examples are references [23–37]) have been published so far. This was supported by supply 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 signaling than 2-APB.

We synthesized several 2-APB analogues and measured their inhibitory activities on Store-Operated Calcium Entry (SOCE). We found that inhibitory effect of bis boron compound DBP 162-AE and DBP 163-AE were much more effective than 2-APB [38–40]. Previously, we studied bis boron compounds in more detail [39,40]. We extended these studies and synthesized 493 2-APB analogues [38–43] increasing the number of borons, changing diphenyl to diaryl, mono-aryl mono-aliphatic, dialiphatic compounds, substitutions of aminoethyl to amino acid derivative as well as aminoethanole to aminoethylthiol and studied the structure/activity correlation.

Here we analyzed SOCE inhibitory activities of our mono-boron compounds collection.

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

2. Materials and methods

2.1. 2-APB analogues

2-APB was first synthesized by Ronderstvent et al. [44] in 1954 from triphenylboranes and ethanol amine. Later, hydroxy diphenyl boran and ethanol amine methods for 2-APB synthesis were reported by Weidman and Zimmermann [45], Letsinger and Skoog [46], Povlock and Lippincott [47].

We have synthesized 493 2-APB analogues [38–43] using methods described by us [38–43] and others [44–55]. The structures, names and synthetic methods of the 493 compounds are in example 1–493 of Ref. [43]. The adducts of diphenyl borinic acid and

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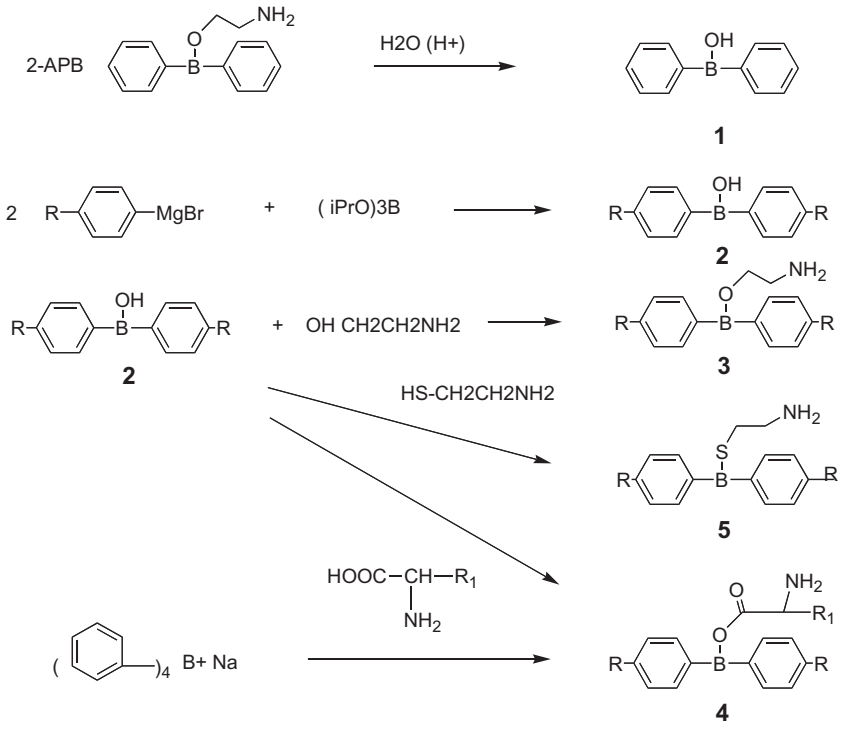
amino acid are well known [50,54,55] and we could obtain these compounds simply by heating in water at 80 °C for 2 h [43].

Hydrolysis of commercially available 2-APB afforded white crystalline diphenylborinic acid **1**. The reaction of aryl magnesium bromide and triisoproxy boron afforded diaryl borinic acid **2**. The reaction of boronic acid **1** or **2** with amino ethanol at room temperature for 6 h afforded 2-aminoethyl diaryl borinate **3**. The reaction of boronic acid **1** with amino acids at 80 °C for 2 h afforded diaryl (aminoacidenate N,O)borone **4**. We also employed another method to get **4** by incubation of sodium tetraphenyl borate and amino acids at 80 °C for 1 h in water. The reaction of boronic acid **1** or **2** with 2-aminoethyl thiol at 40 °C for 3 h afforded diaryl aminoethyl thioborane **5**.



(a) Synthesis of diphenyl borinic acid **1**. 2-Aminoethyl diphenyl borinate (Sigma–Aldrich) 2.25 g was dissolved in 1 N hydrochloric acid 60 ml and stirred for 50 min. The solution was extracted with 30 ml and 20 ml of diethyl ether. The combined ether solution was washed twice with 10 ml water and once with 10 ml of brine. The ether layer was dried with sodium sulphate. Ether was evaporated to give 1.660 g of **1** as white crystalline solid.

(b) Synthesis of 911 Diphenyl(2,6-diaminohexanate-O,N)borane from. Diphenyl borinic acid (**1**) 49 mg (0.269 mmol) and L-lysine hydrochloride 49 mg (0.269 mmol) were stirred with heating in a mixture of ethanol (1.5 ml) and water (0.5 ml) at 80 °C. 911 (44 mg) was obtained as white powder. Spectroscopic data for 911 Diphenyl(2,6-diaminohexanate-O,N)borane. ^{1}H NMR (DMSO-d_6, 500 MHz) 7.95(s,4H), 7.43(m,4H), 7.27(m,4H), 7.29(m,2H), 2.76(m,1H), 2.76(m,1H), 1.76(m,2H), 1.64(m,2H), 1.54(m,4H). ^{13}C NMR (DMSO-d_6 500 MHz) 174.612, 131.486, 131.401, 127.500, 127.452, 126.468, 126.341, 55.256, 38.727, 29.274, 26.709, 22.838.HREMS(ESI-Q-TOF) $(M+H)^+$ found 311.1927, theoretical for $C_{18}H_{23}BN_2O_2$ 311.1925.

(c) Synthesis of 919. Diphenyl(2,3-diaminopropionate O,N)borane A mixture of D-2,3-diaminopropionic acid monohydrochloride 59.4 mg, (0.423 mmol), diphenylborinic acid 79 mg (0.423 mmol), 1 N NaOH aqueous solution 0.42 ml, ethanol 1.5 ml was heated at 80–90 °C for 2 h with stirring. After cooling, hexane 10 ml was added. 46 mg of 919 came out as white precipitate.

(d) Synthesis of 2040. Diphenyl(2,5-diaminopentanoate O,N) borane. A mixture of ornithine dihydrochloride 98 mg (0.478 mmol), diphenyl borinic acid 87 mg (0.488 mmol), 1 N NaOH solution, ethanol 1.5 ml was stirred at 90 °C overnight to obtain white solid substance. This substance was washed with hexane and 46 mg of 2040 was obtained.

(e) Synthesis of 8073. A mixture of diisopropylaminoethanethiol (from diisopropylaminoethanethiol monohydrochloride and NaOH) 29.2 mg (0.18 mmol), diphenyl borinic acid 32.2 mg (0.176 mmol), ethanol 0.5 ml was stirred at 40 °C for 7 h. After cooling, addition of ether and hexane gave 17.8 mg of 8073.

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