Archives of Physiology
ISSN 2055-0898

HOAJ
Herbert Open Access Journals

Research Open Access

2-Aminoethyl diphenylborinate (2-APB) analogues: part 2. regulators of Ca2+ release and consequent cellular processes

Shoichiro Ozaki

Correspondence: ozaki-0991@m.jcnnet.jp

Laboratory for Developmental Neurobiology, Brain Science Institute, RIKEN, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan.

Abstract

In order to obtain compounds with modified 2-APB activities, we synthesized number of bis-boron 2-APB analogues and analyzed their inhibitory activities for SOCE and IICR. Adducts of amino acids with bis-borinic acid showed the highest activity. The IC_{50} of 2-APB for SOCE inhibition was 3 μM, while the IC_{50} of 2051 bis(4,4'(phenyllysineboryl)benzyl) ether was 0.2 μM. By using these compounds, we may be able to regulate Ca^{2+} release and consequent cellular processes more efficiently than with 2-APB.

Keywords: 2-APB, 2-APB analogue, regulator of Ca^{2+} release, regulator of cellular processes

Introduction

Extracellular signal molecules attach to the plasma membrane where they are recognized by cell surface receptors. Upon binding of the ligand to the appropriate receptor, activation of a G protein in turn activate an enzyme such as phospholipase C involved in second messenger system. Active phospholipase C hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) gives 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 receptors thus 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 which regulates IP_3-induced calcium release [21-22]. This discovery led to substantial interest as it led to more than 600 citations and more than 1000 studies on 2-APB have been published so far (examples are references 23-37). 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 the 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]. Many compounds and data were obtained. We reported the results by dividing them into three parts. Part 1 (mono-boron compounds), Part 2 (bis-boron compounds) and Part 3 (poly –boron compounds). We recently reported mono-boron compounds [45] .

Here we analyzed SOCE and IICR inhibitory activities of our bis-boron compounds collection. The analysis of poly-boron compounds will be reported in our upcoming publications.

We believe that by regulating Ca^{2+} release and associated cellular processes by boron compounds, we could therapeutically intervene in many diseases, such as heart diseases and Alzheimer`s disease.

Materials and methods

2-APB analogues

2-APB was first synthesized in 1954 by Ronderstvent et al., [46] from triphenylboranes and ethanol amine. Later, hydroxy diphenyl boran and ethanol amine methods for 2-APB synthesis were reported by Weidman and Zimmermann [47], Letsinger and Skoog [48], Povlock and Lippincott [49].

We have synthesized 493 2-APB analogues [38-44] using methods described by us [38-44] and others [46-56]. The structures, names and synthetic methods of the 493 compounds are in example 1-493 of Ref. 44. Detail of synthetic methods to get bis boron compounds of this paper are described in Ref. 39. We will show one example to prepare best sample 1024. Other compounds can be obtained by similar methods.

Preparation of bis-(4,4'-(hydroxyphenylboryl)phenyl) ether 1012

To a solution of bromobenzene (1055 μL, 10.00 mmol) in diethyl ether (40 mL), we added 0.99 M *sec*-BuLi (10.6 mL, 10.5 mmol) at -98°C, gradually warmed to -78°C to complete lithiation, and then added triisopropoxyborane (2.4 mL, 10.00 mmol). The reaction mixture was stirred for 80 min at -78°C. At the same time, bis(p-bromophenyl)ether (1640 mg, 5. mmol) was dissolved in diethyl ether (50 mL), then reacted with 0.99M *sec*-BuLi (10.5 mL, 10.6 mmol) and stirred for 1 h at -78°C. The reaction mixture was

doi: 10.7243/2055-0898-1-1

added to the mixture of diisopropoxyphenylborane, gradually warmed to room temperature, and then stirred overnight. The reaction was quenched with 1N HCl, the diethyl ether layer was collected, and the water layer then extracted twice with diethyl ether. The combined diethyl ether layers were dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography on a silica gel (*n*-hexane/EtOAc = 3:1) to give bis-(4,4'-(hydroxyphenylboryl) phenyl) ether 1012 (1122 mg, 3.15 mmol, 58.8%) as an oil.

Preparation of bis(4,4'-(phenylglutamineboryl)phenyl) ether 1024

4,4'-(hydroxyphenylboryl)diphenyl ether 1012 (22mg,0.0583 mmol) was dissolved in 0.2mL ethanol and 2mL water. Glutamine 19 mg, 0.017 mmol was then added. The reaction mixture was heated for 17 hrs at 80°C. 10 mL ether was added to get compound 1024 (17 mg. 46%) as a 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

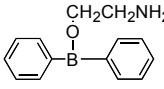
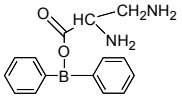
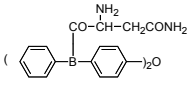
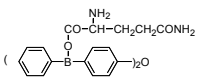
We measured inhibitory activities of the 2-APB analogues for SOCE and IICR. The results are shown in (**Supplement Table S1**).

Amino acid adduct on bis(4,4'-(hydroxyphenyl boryl) phenyl) ether

This combination gave high activity compounds

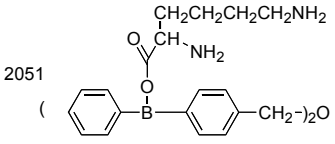
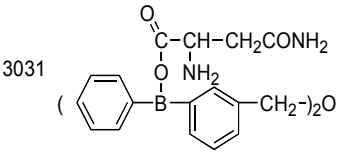
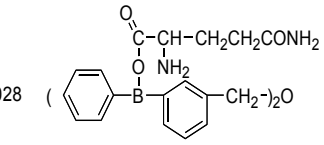
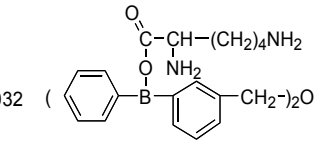
Bis((4,4'-phenylglutamineboryl) phenyl) ether obtained by the reaction of bis((4,4'-hydroxyphenylboryl)phenyl) ether and glutamine was best sample showing IC_{50} 0.2 μM. 1023 bis((4,4'-phenylasparagineboryl)phenyl) ether obtained by the reaction of bis((4,4'-(hydroxyphenylboryl)phenyl) ether and asparagine was also good sample showing IC_{50} 0.3 μM.

We can verify the efficiency of these sample by comparing with IC_{50} of 2-APB for SOCE inhibition 3 μM, and IC_{50} of 919 :best sample of our previous paper (45) 0.2 μM.

		IC_{50}
2APB		3
919		0.2
1023		0.3
1024		0.2

Amino acid adduct on bis(4,4' (hydroxyphenylboryl) benzyl) ether

These benzyl ethers have also high inhibitory activities as phenyl ethers. IC_{50} of 2051 bis(4,4'(phenyllysineboryl)benzyl) ether is 02 μM. IC_{50} of 3031 bis-(4,4'-(phenylasparagineboryl) benzyl) ether is 0.5 μM and IC_{50} of 3028 bis(3,3'(phenyl-glutamineboryl)benzyl) ether is 0.7 μM. IC_{50} of 3032 bis(3,3'(phenyl-lysineboryl)benzyl) ether is 0.7 μM.

		IC50
2051		0.2
3031		0.5
3028		0.7
3032		0.7

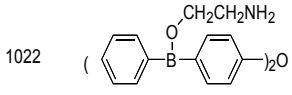
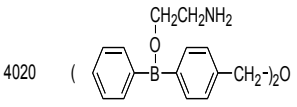
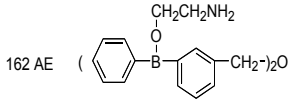
2-Aminoethanol adduct on bis borinic acid

Many compounds were prepared. best three compounds are picked up

IC_{50} of 1022 bis-(4,4'(phenyl aminoethoxy boryl)phenyl) ether is 0.2.

IC_{50} of 4020 bis-(4,4'(phenyl aminoethoxy boryl)benzyl) ether is 0.2.

IC_{50} of 162AE bis-(3,3'(phenyl aminoethoxy boryl)benzyl) ether is 0.5.

		IC50
1022		0.2
4020		0.2
162 AE		0.5

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

The IC_{50} of 2-APB for SOCE inhibition is 3 μM. The IC_{50} of best mono-boron compound (example 919) at previous paper (45) is 0.2 μM. The IC_{50} of best bis-boron compound reporting at this paper (example 1024) is 0.2μM. That is, the bis-boron compound reporting at this paper and mono-boron compound reported at previous paper (45) showed almost same activity and about 10 times stronger activity than 2APB. Mono-boron compounds are easy to prepare. But bis-boron compounds are somewhat difficult to prepare.

Comparison of bis–phenyl ether and bis-benzyl ether

When we compare compounds mentioned at 3.1 and at 3.2 and when we compare 1022, 4020, 162AE, we can tell that there is not so much difference between bis-phenyl ether type compound (1022) and bis-benzyl ether type compounds (4020,162AE).

Comparison of amino acids and ethanol amine

As a reagent to add on to the dihydroxy boron compound, we used amino acid 3.1 3.2)and ethanol amine (3.3). Activities of both compounds were quite similar, but the stabilities of the compound obtained are different. Amino acid adducts are much more stable and easy to purify. We recommend amino acids derivatives over ethanol amine derivatives as regulators of Ca^{2+} and cellular process. Also among amino acid, basic amino acid having extra amino group or amide group like lysine, ornithine, asparagine, glutamine gave compounds with strong activity.

We have synthesized many bis-boron compounds. These compounds showed as active as mono-boron compounds on molar basis. But when we consider on a weight basis, bis-boron compounds are half as active as mono-boron compounds, because the molecular weight of bis boron compound is about twice that of mono-boron compound.

We listed the chemical structures of the best 9 compounds

Top three of these were 2051 bis(4,4′(phenyllysineboryl) benzyl) ether, 1024 bis((4,4′-phenylglutamineboryl)phenyl ether, 1023 bis(4,4′-(phenylasparagineboryl)phenyl) ether.

These compounds can thus regulates the Ca^{2+} release and consequent cellular response more efficiently than 2-APB at pharmacological concentrations.

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 might 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 [**59**], Alzheimer`s [**60**,**61**] and Huntington`s disease [**62**,**63**].

We have shown different kinds of active compounds with IC_{50} ranging 0.1 to 5 μM. By choosing the compound we would be able to 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 [**61**], Huntington aggregation [**62**,**63**] 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.

Conclusion

We synthesized bis-boron 2-APB analogues of differing inhibitory activities. Some of which displayed as much as 10 times higher activity for SOCE inhibition than 2-APB. Among them, adducts of amino acids with bis-borinic acid showed the highest activity. 2051 bis(4,4′(phenyllysineboryl)benzyl) ether, 1024 bis-((4,4′-phenylglutamineboryl)phenyl) ether, 1023 bis-((4,4′-phenylasparagineboryl)phenyl) ether are best 3 candidates for regulation of Ca^{2+} release and consequent cellular processes.

Additional files

Supplement Table S1

Competing interests

The author declares that he has no competing interests.

Acknowledgement

We would like to thank Dr. M. J. Berridge and Dr. K.Mikoshiba for valuable suggestions and advices and Dr. A.Suzuki and Mrs. E.Ebisui for their technical assistances.

Publication history

Editors: Paul H Goldspink, Medical College of Wisconsin, USA.
Jianbo Yue, University of Hong Kong, China.
Received: 26-Nov-2013 Revised: 11-Jan-2014
Re-Revised: 25-Jan-2014 Accepted: 12-Feb-2014
Published: 27-Feb-2014

References

1. Berridge MJ, Dawson RM, Downes CP, Heslop JP and Irvine RF. **Changes in the levels of inositol phosphates after agonist-dependent hydrolysis of membrane phosphoinositides**. *Biochem J.* 1983; **212**:473-82. | Pdf | PubMed Abstract | PubMed Full Text
2. Berridge MJ. **Rapid accumulation of inositol trisphosphate reveals that agonists hydrolyse polyphosphoinositides instead of phosphatidylinositol**. *Biochem J.* 1983; **212**:849-58. | Pdf | PubMed Abstract | PubMed Full Text
3. Streb H, Irvine RF, Berridge MJ and Schulz I. **Release of Ca2+ from a nonmitochondrial intracellular store in pancreatic acinar cells by inositol-1,4,5-trisphosphate**. *Nature.* 1983; **306**:67-9. | Pdf | PubMed
4. Berridge MJ, Heslop JP, Irvine RF and Brown KD. **Inositol trisphosphate formation and calcium mobilization in Swiss 3T3 cells in response to**

platelet-derived growth factor. *Biochem J.* 1984; **222**:195-201. | Pdf | PubMed Abstract | PubMed Full Text

5. Fein A, Payne R and Corson D W et al. **Photoreceptor excitation and adaption by inositol 1,4,5-trisphosphate**. *Nature.* 1984; **311**:157-160. | Article
6. Brown JE , L.J. Rubin and A.J. Ghalayini et al. **A biochemical and electrophysiological examination of myo-inositol polyphosphate as a putative messenger for excitation in Limulus ventral photoreceptor cells**. *Nature.* 1984; **311**:160-163.
7. Burgess GM, Godfrey PP, McKinney JS, Berridge MJ, Irvine RF and Putney JW, Jr. **The second messenger linking receptor activation to internal Ca release in liver**. *Nature.* 1984; **309**:63-6. | Article | PubMed
8. Prentki M, Biden TJ, Janjic D, Irvine RF, Berridge MJ and Wollheim CB. **Rapid mobilization of Ca2+ from rat insulinoma microsomes by inositol-1,4,5-trisphosphate**. *Nature.* 1984; **309**:562-4. | Article | PubMed
9. Irvine RF, Brown KD and Berridge MJ. **Specificity of inositol trisphosphate-induced calcium release from permeabilized Swiss-mouse 3T3 cells**. *Biochem J.* 1984; **222**:269-72. | Pdf | PubMed Abstract | PubMed Full Text
10. Irvine RF, Letcher AJ, Heslop JP and Berridge MJ. **The inositol tris/tetrakisphosphate pathway--demonstration of Ins(1,4,5)P3 3-kinase activity in animal tissues**. *Nature.* 1986; **320**:631-4. | Article | PubMed
11. Rapp PE and Berridge sMJ. **The control of transepithelial potential oscillations in the salivary gland of Calliphora erythrocephala**. *Exp. Bio.l.* 1981; **93**:119-132. | Article
12. Missiaen L, Taylor CW and Berridge MJ. **Spontaneous calcium release from inositol trisphosphate-sensitive calcium stores**. *Nature.* 1991; **352**:241-4. | Article | PubMed
13. Berridge MJ and Irvine RF. **Inositol trisphosphate, a novel second messenger in cellular signal transduction**. *Nature.* 1984; **312**:315-21. | Article | PubMed
14. Berridge MJ. **Inositol trisphosphate and diacylglycerol: two interacting second messengers**. *Annu Rev Biochem.* 1987; **56**:159-93. | Article | PubMed
15. Berridge MJ and Irvine RF. **Inositol phosphates and cell signalling**. *Nature.* 1989; **341**:197-205. | Article | PubMed
16. Berridge MJ, Downes CP and Hanley MR. **Neural and developmental actions of lithium: a unifying hypothesis**. *Cell.* 1989; **59**:411-9. | Article | PubMed
17. Berridge MJ. **Inositol trisphosphate and calcium signalling**. *Nature.* 1993; **361**:315-25. | Article | PubMed
18. Bootman MD and Berridge MJ. **The elemental principles of calcium signaling**. *Cell.* 1995; **83**:675-8. | Article | PubMed
19. Berridge MJ. **Cell signalling. A tale of two messengers**. *Nature.* 1993; **365**:388-9. | Article | PubMed
20. Decrock E, De Bock M, Wang N, Gadicherla AK, Bol M, Delvaeye T, Vandenabeele P, Vinken M, Bultynck G, Krysko DV and Leybaert L. **IP3, a small molecule with a powerful message**. *Biochim Biophys Acta.* 2013; **1833**:1772-86. | Article | PubMed
21. Maruyama T, Kanaji T, Nakade S, Kanno T and Mikoshiba K. **2APB, 2-aminoethoxydiphenyl borate, a membrane-penetrable modulator of Ins(1,4,5)P3-induced Ca2+ release**. *J Biochem.* 1997; **122**:498-505. | Article | PubMed
22. Iwasaki H, Mori Y, Hara Y, Uchida K, Zhou H and Mikoshiba K. **2-Aminoethoxydiphenyl borate (2-APB) inhibits capacitative calcium entry independently of the function of inositol 1,4,5-trisphosphate receptors**. *Receptors Channels.* 2001; **7**:429-39. | PubMed
23. Bilmen JG and Michelangeli F. **Inhibition of the type 1 inositol 1,4,5-trisphosphate receptor by 2-aminoethoxydiphenylborate**. *Cell Signal.* 2002; **14**:955-60. | Article | PubMed
24. Ma HT, Venkatachalam K, Parys JB and Gill DL. **Modification of store-operated channel coupling and inositol trisphosphate receptor function by 2-aminoethoxydiphenyl borate in DT40 lymphocytes**. *J Biol Chem.* 2002; **277**:6915-22. | Article | PubMed
25. Dobrydneva Y and Blackmore P. **2-Aminoethoxydiphenyl borate directly inhibits store-operated calcium entry channels in human platelets**. *Mol Pharmacol.* 2001; **60**:541-52. | Article | PubMed
26. Bilmen JG, Wootton LL, Godfrey RE, Smart OS and Michelangeli F. **Inhibition of SERCA Ca2+ pumps by 2-aminoethoxydiphenyl borate (2-APB). 2-APB reduces both Ca2+ binding and phosphoryl transfer from ATP, by interfering with the pathway leading to the Ca2+-binding sites**. *Eur J Biochem.* 2002; **269**:3678-87. | Article | PubMed
27. Missiaen L, Callewaert G, De Smedt H and Parys JB. **2-Aminoethoxydiphenyl borate affects the inositol 1,4,5-trisphosphate receptor, the intracellular Ca2+ pump and the non-specific Ca2+ leak from the non-mitochondrial Ca2+ stores in permeabilized A7r5 cells**. *Cell Calcium.* 2001; **29**:111-6. | Article | PubMed
28. Peppiatt CM, Collins TJ, Mackenzie L, Conway SJ, Holmes AB, Bootman MD, Berridge MJ, Seo JT and Roderick HL. **2-Aminoethoxydiphenyl borate (2-APB) antagonises inositol 1,4,5-trisphosphate-induced calcium release, inhibits calcium pumps and has a use-dependent and slowly reversible action on store-operated calcium entry channels**. *Cell Calcium.* 2003; **34**:97-108. | Article | PubMed
29. Luo D, Broad LM, Bird GS and Putney JW, Jr. **Signaling pathways underlying muscarinic receptor-induced [Ca2+]i oscillations in HEK293 cells**. *J Biol Chem.* 2001; **276**:5613-21. | Article | PubMed
30. Bootman MD, Young KW, Young JM, Moreton RB and Berridge MJ. **Extracellular calcium concentration controls the frequency of intracellular calcium spiking independently of inositol 1,4,5-trisphosphate production in HeLa cells**. *Biochem J.* 1996; **314 (Pt 1)**:347-54. | Article | PubMed Abstract | PubMed Full Text
31. Mackenzie L, Bootman MD, Berridge MJ and Lipp P. **Predetermined recruitment of calcium release sites underlies excitation-contraction coupling in rat atrial myocytes**. *J Physiol.* 2001; **530**:417-29. | Article | PubMed Abstract | PubMed Full Text
32. Lipp P, Laine M, Tovey SC, Burrell KM, Berridge MJ, Li W and Bootman MD. **Functional InsP3 receptors that may modulate excitation-contraction coupling in the heart**. *Curr Biol.* 2000; **10**:939-42. | Article | PubMed
33. Mackenzie L, Bootman MD, Laine M, Berridge MJ, Thuring J, Holmes A, Li WH and Lipp P. **The role of inositol 1,4,5-trisphosphate receptors in Ca(2+) signalling and the generation of arrhythmias in rat atrial myocytes**. *J Physiol.* 2002; **541**:395-409. | Article | PubMed Abstract | PubMed Full Text
34. Proven A, Roderick HL, Conway SJ, Berridge MJ, Horton JK, Capper SJ and Bootman MD. **Inositol 1,4,5-trisphosphate supports the arrhythmogenic action of endothelin-1 on ventricular cardiac myocytes**. *J Cell Sci.* 2006; **119**:3363-75. | Article | PubMed
35. Berridge MJ, Bootman MD and Roderick HL. **Calcium signalling: dynamics, homeostasis and remodelling**. *Nat Rev Mol Cell Biol.* 2003; **4**:517-29. | Article | PubMed
36. Berridge MJ. **Remodelling Ca2+ signalling systems and cardiac hypertrophy**. *Biochem Soc Trans.* 2006; **34**:228-31. | Article | PubMed
37. Berridge MJ. **Calcium microdomains: organization and function**. *Cell Calcium.* 2006; **40**:405-12. | Article | PubMed
38. Zhou H, Iwasaki H, Nakamura T, Nakamura K, Maruyama T, Hamano S, Ozaki S, Mizutani A and Mikoshiba K. **2-Aminoethyl diphenylborinate analogues: selective inhibition for store-operated Ca2+ entry**. *Biochem Biophys Res Commun.* 2007; **352**:277-82. | Article | PubMed
39. Suzuki AZ, Ozaki S, Goto J and Mikoshiba K. **Synthesis of bisboron compounds and their strong inhibitory activity on store-operated calcium entry**. *Bioorg Med Chem Lett.* 2010; **20**:1395-8. | Article | PubMed
40. Goto J, Suzuki AZ, Ozaki S, Matsumoto N, Nakamura T, Ebisui E, Fleig A, Penner R and Mikoshiba K. **Two novel 2-aminoethyl diphenylborinate (2-APB) analogues differentially activate and inhibit store-operated Ca(2+) entry via STIM proteins**. *Cell Calcium.* 2010; **47**:1-10. | Article | PubMed Abstract | PubMed Full Text
41. Mikoshiba K ,Ozaki S , Suzuki A and Nakamura T. **Preparation of bisboron compounds controlling calcium concentration in cells**. *PCT Int Appl.* 2007, 118pp. CODEN: PIXXD2 WO 2007061074 A1 20070531 CAN

147:31225 AN 2007, 591383 CAPLUS.

42. Mikoshiba KS, Ozaki E and Ebisui. **Preparatin of boron compounds**. *Jpn. Kokai Tokkyo Koho*. 2009; 138.
43. Ozaki S, Ebisui E, Hamada K, Goto J, Suzuki AZ, Terauchi A and Mikoshiba K. **Potent transglutaminase inhibitors, aryl beta-aminoethyl ketones**. *Bioorg Med Chem Lett.* 2010; **20**:1141-4. | Article | PubMed
44. Mikoshiba KN, Nukina S and Ozaki et al. **Protein cross-linking inhibitor**. US 2011/0212919 A1., PCT Int Appl. (2010) 241pp. CODEN: PIXXD2 WO 2010018836 A2 20100218 CAN 152:287576.
45. Ozaki S, Suzuki AZ, Bauer PO, Ebisui E and Mikoshiba K. 2-**Aminoethyl diphenylborinate (2-APB) analogues: regulation of Ca2+ signaling**. *Biochem Biophys Res Commun.* 2013; **441**:286-90. | Article | PubMed
46. Rondestvedt CS , Scriber RM and Wulfman CE. **Alcoholysis of triarylboranes**. *J. Org. Chem*. 1955; **20**:9-12. | Article
47. Weidmann H and Zimmerman HK. **Borsäure-ester von N-substituierten Aminoalkoholen**. *Justus Liebigs Ann. Der Chemie*. 1959; **619**:28-35. | Article
48. Letsinger RL and Skoog IJ. **Organoboron Compounds. IV. Aminoethyl Diarylborinates**. *J. Am. Chem. Soc*. 1955; **77**:2491-2494. | Article
49. Povlock TP and Lippincott WT. **The Reaction of Trimethoxyboroxine with Aromatic Grignard Reagents**. *J. Am. Chem. Soc*. 1958; **80**:5409-5411. | Article
50. Brown HC and Colet TE. **Organoboranes. 31. A simple preparation of boronic esters from organolithium reagents and selected trialkoxyboranes**. *Organometallics*. 1983; **2**:1316-1319. | Article
51. Mori Y, Kobayashi J, Manabe K and Kobayashi S. **Use of boron enolates in water. The first boron enolate-mediated diastereoselective aldol reactions using catalytic boron sources**. *Tetrahedron*. 2002; **58**:8263-8268.
52. Farfan N, Silva D and Santillan R. **NMR studies of 1,1-diphenylboroxalidone derivatives of α-aminoacids**. *Heteroatom Chem*. 1993; **4**:533-536.
53. Tomlinson RV and Tener GM. **The reaction of alkyl borinates with α-amino acids**. *J. Org. Chem*. 1964; **29**:492-493.
54. Nefkens GHL. and Zwanenburg B. **Boroxazolidones as simultaneous protection of the amino and carboxyl group in α-amino acids**. *Tetrahedron*. 1983; **39**:2995-2998. | Article
55. Strang CJ, Henson E, Okamoto Y, Paz MA and Gallop PM. **Separation and determination of alpha-amino acids by boroxazolidone formation**. *Anal Biochem.* 1989; **178**:276-86. | PubMed
56. Rettig SJ and Trotter J. **Crystal and molecular structure of L-prolinatodiphenylboron**. *Can. J. Chem*. 1977; **55**:958-965.
57. Nakade S, Maeda N and Mikoshiba K. **Involvement of the C-terminus of the inositol 1,4,5-trisphosphate receptor in Ca2+ release analysed using region-specific monoclonal antibodies**. *Biochem J.* 1991; **277 (Pt 1)**:125-31. | Pdf | PubMed Abstract | PubMed Full Text
58. Parekh AB and Putney JW, Jr. **Store-operated calcium channels**. *Physiol Rev.* 2005; **85**:757-810. | Article | PubMed
59. Berridge MJ. **Neuronal calcium signaling**. *Neuron.* 1998; **21**:13-26. | Article | PubMed
60. Berridge MJ. **Calcium hypothesis of Alzheimer's disease**. *Pflugers Arch.* 2010; **459**:441-9. | Article | PubMed
61. Berridge MJ. **Dysregulation of neural calcium signaling in Alzheimer disease, bipolar disorder and schizophrenia**. *Prion.* 2013; **7**:2-13. | Article | PubMed Abstract | PubMed Full Text
62. Bauer PO, Hudec R, Ozaki S, Okuno M, Ebisui E, Mikoshiba K and Nukina N. **Genetic ablation and chemical inhibition of IP3R1 reduce mutant huntingtin aggregation**. *Biochem Biophys Res Commun.* 2011; **416**:13-7. | Article | PubMed
63. Bauer PO, Hudec R, Goswami A, Kurosawa M, Matsumoto G, Mikoshiba K and Nukina N. **ROCK-phosphorylated vimentin modifies mutant huntingtin aggregation via sequestration of IRBIT**. *Mol Neurodegener.* 2012; **7**:43. | Article | PubMed Abstract | PubMed Full Text

Citation:
Ozaki S. **2-Aminoethyl diphenylborinate (2-APB) analogues: part 2. regulators of Ca2+ release and consequent cellular processes**. *Arch Physiol.* 2014; **1**:1. http://dx.doi.org/10.7243/2055-0898-1-1