Chemical Approach to Signal Transduction by Inositol Triphosphate

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Abstract

Berridge discovered that inositol 1,4,5-trisphosphate (IP3) was generated at the cell surface in response to cell stimulation and functioned as a second messenger to release Ca\(^{2+}\) from internal stores. Ozaki et al. succeeded in the first total synthesis of optically active IP\(_3\) by 13 steps. He supported the signal transduction studies by supplying necessary reagents such as IP\(_3\), other IP\(_x\), phosphatidyl inositol, new synthetic methods and reagents. He discovered the regulators of Ca\(^{2+}\) release and consequent cellular processes.

Keywords: Signal transduction; Inositol trisphosphate; IP\(_3\); Phosphatidyl inositol; Regulator of cellular process

Introduction

The fact that diacyl glycerol is second messenger was found by late Professor Yasutomi Nishizuka [1] and the fact that Inositol triphosphate (IP\(_3\)) is a second messenger was discovered by Michael Berridge who showed that it functioned to release Ca\(^{2+}\) from internal stores. This bifurcating signaling system is of fundamental importance in regulating a wide range of cellular process.

Signals (first messenger) like light, noise, taste, odor, hormone, neurotransmitter, drug attach to the plasma membrane where they are recognized by cell surface receptors. Upon binding of the ligand to the appropriate receptor, activation of G protein activates 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.

Why Plant Biosynthesize Inositol

The rice bran, wheat, corn contain much phytic acid (inositol hexaphosphate) as Ca salt. Plant make glucose by photo synthesis from carbon dioxide and water. Some of glucose is converted to inositol. Inositol is converted to phospholipids (PIP\(_x\)) and phytic acid. PIP\(_x\) is converted to IP\(_3\) and diacylglycerol. These two compounds are essential for signal transduction of plant. Plant makes phytic acid as storage of phosphorous. Phosphorous is an essential atom as fertilizer because it is an essential atom to make nucleic acid, DNA. The seed store phosphorous atom as a store so that even when seed germinate at no phosphorous land [1].

Discovery of IP\(_3\)

Phospholipid was discovered by Bollow in 1961 [2] from bovine brain. The hypothesis of Michell [3] that the receptor controlled hydrolysis of phosphoinositides could be directly linked to cellular calcium mobilization. The observation by Berridge D-myo-inositol 1,4,5-trisphosphate (IP\(_3\)) act as a second messenger, a fundamental cell-signal transduction mechanism has been elucidated. 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 [4-25].

Synthetic Competition of Inositol P

The discovery of inositol phosphate in particular IP\(_3\), led to the dramatic simulation for the synthesis of inositol phosphates. Many persons challenged the synthesis of inositol phosphate, starting from inositol, glucurolactone, phytic acid, arenas, quinic acid and L-quebrachitol.

A symposium; Inositol phosphates and Derivatives. Synthesis, biochemistry, and therapeutic potential was held by the division of carbohydrate Chemistry at the 200th National meeting of the American Chemical Society, Washington DC, August 26-31,1990. ACS Symposium Series. 463 Edited by Allen B.Reitz was published.

The key problems in the synthesis of inositol phosphates are (1) synthesis and optical resolution of suitably protected inositol derivatives, (2) efficient phosphorylation of vicinal hydroxy groups.

In 1986, Ozaki et al succeeded in the first total synthesis of optically active myo-inositol tris (1,4,5) phosphate from myo-inositol by 13 steps [26]. At this report, phosphorylation yield of 2,3,6-tribenzyl myo-inositol by diamidinophosphophoyl chloride isolation yield was only 10%. Then we have studied phosphorylation reagents and discovered new phosphorylation method Then we could get IP\(_3\) by best method in good

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yield as shown in Figure 1 [26,27].

This IP₃ is produced by this method at DOJINDO (Kumamoto, Japan) and is distributed all over the world by the name of synthetic IP₃.

The synthesis of I(1,4,5)P₃₁ is reported by many investigators Billington and Vacca (from myo-inositol orthoformate [28], Ballou, from myo-inositol [29], Gigg [30], Ley from arines using Pseudomonosoxidation [31], Falch from Quinic acid [32], Stepanov and Shvets [33], Prestwich prepared D-myo-(3 H)I(1,4,5)P₃, essential for the study of signal transduction [34-35]. TBPP, a more used reagent for the synthesis of phosphothioate analogur of IP₃ by Potter [36].

**Different Source and Methods**

IP₃ was obtained through 6 different sources:
- Starting from myo-inositol [26-32,35-38]
- Starting from 1,2:5,6-di-O-cyclohexylidene and other sugars [39-43]
- Starting from arenes [33]
- Starting from Quinic acid [34]
- Starting from D-glucuronolactone [42]
- Chemoenzymztic synthesis of D-myo-inositol 1,4,5-trisphosphate [43-49]

**Methods to Get Optically Pure Compound by 5 Different Methods**

- Separation of diastereomers
  - L-mentoxyno acetyl chloride gave best result, because desired product was crystal [26]
- Starting from optically pure natural product
  - Starting from myo-inositol [26-32,35-38]
  - Starting frm Quinic acid [34]
  - Starting from D-glucuronolactone [42]
  - Use of tartaric acid ester [50]
  - Use of enzyme (like Phosphorylase). Enzyme aided synthesis of D-myo-inositol 1,4,5-trisphosphate [43-48]
  - Enzymic resolution of racemic 1,2,5,6-di-O-cyclohexylidene and 1,2,3,4-di-O-cyclohexylidene-myo-inositol [45]
  - Enzymic resolution of sterically hindered myo-inositol derivatives [48]
  - Enzyme aided regioselective acylation of nucleosides [49]

**Phosphorylation Reagents**

- Tetrabenzyl pyrophosphate (TBPP) and n-BuLi [52].

![TBPP](image)

n-BuLi

- New phosphorylating reagent called OXDEP (o-xylylene N,N-diethylphosphoamidite) [53,54]. By using this reagent, IP₃ and PIPx were obtained in good yield [27].

- DBPF Dibenzyl phosphorofluororidocate (BnO)₂P(OF)

  This reagent was used for the synthesis of phosphofloridate analogues. Obtained phosphofloridates showed very interesting biological activity [56].

- Step wise phosphorylation using PCl₃, BnOH, C₆H₅COOH

- Phosphorothioate synthesis based on the redox reaction of phosphate with tellurium (IV) chloride [58].

**Discovery of Phosphonium Salt Methodology**

This phosphonium salt methodology [59,60] provide a regioselective phosphorylation. 1,2-Dioi were phosphorylated regioselectively at C-1 with triethyl phosphate to give 1-dibenzy phosphate 2-hoxyrox free compound as shown in Figure 2. Other phosphorylating reagents do not have such selectivity. By using this free hydroxy group, we could get 2-acyl analog and IPx and PIPx. Three kind of combined reagents are possible.

Trialkyl phosphate and pyridinium bromide perbromide method [59]

- (RO)₂P + PyHBr₃

  1H-Tetrazol catalyzed the reaction of trialkyl phosphate [61]

- (PO)₂P + Tetrazole

  Utilization of oxidizing character of TeCl₄ [62]

**Phosphorofluoridate analogs of myo-inositol 1,4,5-tris(phosphate) [56].**
Finding of New Reaction, New Methods and New Reagents

Finding of new protection methods
- Protection by tetraisopropyldisiloxane-1,3-diyl group [69]
- Proximately assisted and chemoselectively cleavable protecting groups for alcohols, 2-[2-(arylmethyloxy)ethyl]benzoic esters [70].

Finding of new deprotection methods
- Deprotection of methyl group by AlCl3-NaI, AlCl3-Bu4NI [71]
- Deprotection of benzyl and allyl group by AlCl3-dimethyl aniline [72]
- Deprotection p-methoxybenzyl by trimethylsilylchloride-tin(II) chloride—anisole [73].

Finding of diastereoselective addition methods
- Diastereoselective addition of organometallics to α-keto esters [74].

Finding of diastereoselective reduction methods
- Diastereoselective reduction of ketoester bearing chiro-inositol as chiral auxiliaries [75].

Finding of novel deacylation Methods
- A Grignard reagent was used for deacylation without affecting the neighboring base-sensitive functional groups [76].

Finding of novel enatioselective acylation and deacylation Method
- Enantioselective acylation and deacylation method using enzyme [38,77].

Finding of glycosidation method
- Glycosidation based on phosphite chemistry [78,79]
- Phosphorylation of inositol 1,4,5-trisphosphate analogs by 3-kinase and dephosphorylation of inositol 1,3,4,5-tetrakisphosphate analogs by 5-phosphatase [80].

Use of Inositol Derivatives as Chiral Auxiliaries
- Diastereoselective addition of organometallics to keto esters [74].
- Asymmetric synthesis of tetrahydrofurans by diastereoselective (3+2) cycloaddition of allylsilanes with ketoesters bearing optically active cyclitol as a chiral auxiliary [81].
- Preparation of optically active D 2-isooxazolines via addition
of nitroso dyes to chiral acryloyoxy esters bearing cyclitol as auxiliaries [82].

- Asymmetrical synthesis of functionalized tertially alcohols by the diastereoselective aldol reaction [83].

### Preparation of IPX, IP3 derivatives and IP3 Analog, and Assessment of their Activities

**Synthesized inositol poly phosphate** [66, 84-86]

- Myo-inositol 1-phosphate [87, 88], myo-inositol 1.3.4-triphosphate [89], myo-inositol 1.4.6-triphosphate [90], myo-inositol 1.3.4.5-tetrakisphosphate [91-93], myo-inositol 1.4.5.6-tetrakisphosphate [94], myo-inositol 2.4.5-triphosphate [57], 1.2-cyclic-4.5-, 1.4-, and 2.4.5-triphosphate [95], myo-inositol 1.2.5.6-tetrakisphosphate [65], 2.6-Di-O-(D- mannopyranosyl) phosphatidyl-D-myoinositol [68], Phosphofluoridate analogs of myo-inositol 1.4,5-tris(phosphate) [55]. 4-a-D-glucopyranosyl-myo-inositol [50].

**2-substituted IP₃ analogs**

- These were synthesized as shown in Figure 3. These analogs were used for the preparation of affinity columns [96].
- Many IP₃ and derivatives were prepared and their activities were measured by Prof. Hirata, Masato [96-113].
- Synthesis of IP₃ having biotinyl and azidobenzoyl groups [100].
- Synthesis of 2-substituted myo-inositol 1.3.4.5-tetrakis(phosphate) and 1.3.4.5.6-pentakis(phosphate) analogues [101].

**Phosphofluoridate analogues**

Phosphofluoridate analogs of myo-inositol 1.4.5-tris(phosphate) were prepared as shown in Figure 4 [56].

The three phosphofluoridates thus prepared had potencies for inhibiting (H) InsP₃ binding to purified InsP₃ receptor that were less than for InsP₃. Two analogues 44 and 40 were found to inhibit the dephosphorylation of (H) Ins P₃ by the 5-phosphatase with potencies similar to that for InsP₃. Surprisingly, the inhibitory potency of 5-phosphofluoridate 44 toward 5-phosphatase was higher (about 20 fold) than those of InsP₃ and the another fluoridates 40 and 45.

### Preparation of Affinity Column

Inositol 1.4.5-triphosphate affinity columns 24, 25 were prepared from 20, 21 as shown in Figure 5 to fish out IP₃-binding proteins [98, 113, 114].

### Isolation and Characterization of Many IP₃-Binding Proteins

The following many proteins were isolated by affinity column and characterizations were carried out [103, 111].

- IP₃ binding protein [102, 103, 113, 115] co-work with Hirata Masato
- Phospholipase C-d1 [110, 116] co-work with Hirata Masato.
- Porcine tracheal smooth muscle aldase [109], collaboration with Carl Baron and Masato Hirata.
- 3-Kinase, 5-phosphatase [111, 117] collaboration with Van Dijken
- Growth factor activating protein [112, 118] collaboration with Moriya Shigeharu
- IP₃, 3-kinase from porcine smooth muscle [119-121] co-work with Denborough.
- RAC-protein kinase (PKB/Akt [120] collaboration with Matsuzaki
- Expression and characterization of IP₃-binding domain of phosphatidylinositol-specific phospholipase C [122] collaboration with Yagisawa, Hitoshi.
- IP₃, 3-kinase from chicken erythrocytes [123] collaboration with George Myer.
Figure 4: Synthesis of Phosphofluoridate analogues.

a: Et3SiCl, Py b: (BnO)2PN i-Pr2, Tetrazol then MCPBA. c: Bu4NF, 3H2O, PhCO2H, THF. d: NC-(CH2)2O(BnO)PNIPr2, Tetrazole then MCPBA. e: Et3N, MeCN, rt 2h. f: 41, Et3N, g CF3COOH. h: (BnO)3P, PyHBr3, Et3N, H2 Pd-C, AcOH-MeOH-H2O. i: (BnO)2PN iPr2, Tetrazole then MCPBA. j: PhSH, Et3N, k: 41, Et3N, l: CF3COOH. m: (BnO)3P, PyHBr3, Et3N, n: H2, Pd-C

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Detection of Ca\(^{2+}\) Flux

Fluoro-3 was used to measure intracellular calcium concentration. In case of IP\(_3\) complex, Ca\(^{2+}\) maximum peak (2.5×10\(^{-7}\) M) was observed after 3.5 min. after addition of IP\(_3\). In case of PIP\(_x\) complex, Ca\(^{2+}\) maximum peak (4.2×10\(^{-7}\) M) was observed after 6.5 min.

Discovery of DAB; Regulators of Ca\(^{2+}\) Release and Cellular Response

In 1997, we identified 2-aminoethyl diphenylborinate (2-APB) as being an IP\(_3\) receptor inhibitor and regulate IP\(_3\) induced calcium release [131,132]. 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 have been published so far. This was supported by increasing sales of 2-APB by Sigma-Aldrich as membrane-permeable modulator of calcium release. We aimed at generate better modulator of calcium release than 2-APB.

We synthesized several 2APB 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 [133-138] We extended these studies and synthesized 493 analogues [139,140] increasing the number of borons, changing diphenyl to diaryl, monoaryl, mono-aliphatic dialiphatic compounds, substitution of aminoethyl to amino acid derivative as well as aminothioethanol to aminothiol and studied the structure/activities correlation.

We found that Diphenyl (amino acidonate O,N) borane DAB are best compounds

We found [139,140] that compounds DAB Diphenyl (aminoacidonate N,O)borane could regulate IP\(_3\)-induced Ca\(^{2+}\) release (IICR), Store-Operated Ca\(^{2+}\) entry (SOCE)) and could regulate cellular responses. We found that the adduct of amino acid (especially basic amino acid) and diphenyl borinic acid have strong inhibitory activity to SOCE. And some of them 919 Diphenyl (2,3-diaminopropionate O,N) borane, 911 Diphenyl (L-lysinate O,N) borane showed 10 times strong activity than 2-APB. 2APB is said to be a excellent lead compound for heat disease and Alzheimer’s diseases as Berridge predicts [141-147].

2APB analogues presented in this study could be proven to be excellent lead compounds for many human diseases including heart disease [143,144], Alzheimer’s [145-146] and Huntington disease [148,149].

We found that boron compounds also can inhibit transglutaminase (Ca\(^{2+}\)-dependent enzyme) [130]. There are many neurodegenerative disease, including Alzheimer’s disease, Huntington’s disease [136,149]. The boron compounds were found to be effective as inhibitor of acyl protein thioesterase [150].

We looked for more effective transglutaminase inhibitors. We synthesized 250 β-aminoethyl ketones and found that these compounds had strong transglutaminase inhibitory activities [151,152]. A typical compound is 5-bromo-2-thienyl-(N-t-butyl-N-benzyl)-aminoethyl ketone.
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References

1. Nishizuka Y (1984) The role of protein kinase C in cell surface signal transduction and tumour promotion. Nature 308: 693-696.
2. Frezza C (2014) The role of mitochondria in the oncogenic signal transduction. Int J Biochem Cell Biol 48: 11-17.
3. Michell RH (1975) Inositol phospholipids and cell surface receptor function. Biochim Biophys Acta 415: 81-47.
4. Fain JN, Berridge MJ (1979) Relationship between hormonal activation of phosphatidylinositol hydrolysis, fluid secretion and calcium flux in the blowfly salivary gland. Biochem J 178: 45-58.
5. Fain JN, Berridge MJ (1979) Relationship between phosphatidylinositol synthesis and recovery of 5-hydroxytryptamine-responsive Ca2+ flux in blowfly salivary glands. Biochem J 180: 655-661.
6. Berridge MJ, Downes CP, Hanley MR (1982) Lithium amplifies agonist-dependent phosphatidylinositol responses in brain and salivary glands. Biochem J 206: 587-595.
7. Berridge MJ, Dawson RMC, Downes CP, Heslop JP, Irvine RF (1983) Changes in the levels of inositol phosphates after agonist-dependent hydrolysis of membrane phosphoinositides. Biochem J 212: 473-482.
8. Berridge MJ (1983) Rapid accumulation of inositol trisphosphate reveals that agonists hydrolyse polyphosphoinositides instead of phosphatidylinositol. Biochem J 212: 849-858.
9. Streb H, Irvine RF, Berridge MJ, Schulz I (1983) Release of Ca2+ from a nonnichondrial intracellular store in pancreatic acinar cells by inositol-1,4,5-trisphosphate. Nature 306: 67-69.
10. Berridge MJ, Heslop JP, Irvine RF, Brown KD (1984) Inositol trisphosphate formation and calcium mobilization in Swiss 3T3 cells in response to platelet-derived growth factor. Biochem J 222: 195-201.
11. Fein A, Payne R, Corson DW, Berridge MJ, Irvine RF (1984) Photoreceptor excitation and adaptation by inositol 1,4,5-trisphosphate. Nature 311: 157-160.
12. Brown JE, Rubin LJ, Ghalayini AJ, Tarver AP, Irvine RF, et al. (1984) A biochemical and electrophysiological examination of myo-inositol polyphosphates as a putative messenger for excitation in Limulus ventral photoreceptor cells. Nature 311: 160-163.
13. Burgess GM, Godfrey PP, McKinney JS, Berridge MJ, Irvine RF, et al. (1984) The second messenger linking receptor activation to internal Ca release in liver. Nature 309: 63-66.
14. Prentki M, Biden TJ, Janjic D, Irvine RF, Berridge MJ, et al. (1984) Rapid mobilization of Ca2+ from rat insulinoma microsomes by inositol-1,4,5-trisphosphate. Nature 309: 562-564.
15. Irvine RF, Brown KD, Berridge MJ (1984) Specificity of inositol trisphosphate-induced calcium release from permeabilized Swiss-mouse 3T3 cells. Biochem J 222: 269-272.
16. Irvine RF, Letcher AJ, Heslop JP, Berridge MJ (1988) The inositol tris/tetrakisphosphate pathway—demonstration of Ins(1,4,5)P3 3-kinase activity in animal tissues. Nature 320: 631-634.
17. Rapp PE, Berridge MJ (1981) The control of transepithelial potential oscillations in the salivary gland of Calliphora erythrocephala. J Exp Biol 93: 119-132.
18. Missiaen L, Taylor CW, Berridge MJ (1991) Spontaneous calcium release from inositol trisphosphate-sensitive calcium stores. Nature 352: 241-244.
19. Berridge MJ, Irvine RF (1984) Inositol trisphosphate, a novel second messenger in cellular signal transduction. Nature 312: 315-321.
20. Berridge MJ (1987) Inositol trisphosphate and diacylglycerol: two interacting second messengers. Annu Rev Biochem 56: 169-193.
21. Berridge MJ, Irvine RF (1989) Inositol phosphates and cell signalling. Nature 341: 197-205.
22. Berridge MJ, Downes CP, Hanley MR (1989) Neural and developmental actions of lithium: a unifying hypothesis. Cell 59: 411-419.
23. Berridge MJ (1993) Inositol trisphosphate and calcium signalling. Nature 361: 315-325.
24. Bootman MD, Berridge MJ (1995) The elemental principles of calcium signalling. Cell 83: 675-678.
25. Decrock E, De Boeck M, Wang N, Gadicherla AK, Bol M, et al. (2013) IP3, a small molecule with a powerful message. Biochim Biophys Acta 1833: 1772-1786.
26. Shoichiro O, Yutaka W, Tornio O, Yoshishisa K, Naokazu S, et al. (1986) Total synthesis of optically active myo-inositol 1,4,5-trisphosphate. Tetrahedron Letters 27: 3157-3160.
27. Shoichiro O, Yoshishisa K, Naokazu S, Tornio O, Yutaka W (1992) Synthesis and some properties of D-myo-inositol 1,4,5-tris(hydrogen phosphate). Journal of the Chemical Society, Perkin Transactions 1: 729-737.
28. Falck JR, Abdali A, Wittenberger SJ (1990) Total synthesis of the 5-methylene phosphonate analogue of D-myo-inositol 1,4,5-trisphosphate. J Chem Soc, Chem Commun: 953-955.
29. http://www.sciencedirect.com/science/journal/00086215/140/1
30. Vacca JP, deSorms JS, Huff JR, Billington DC, Baker R, et al. (1989) The total synthesis of myo-inositol polyphosphates. Tetrahedron 45: 5679-5702.
31. Levy SV, Parra M, Redgrave AJ, Sternfeld F (1990) Microbial oxidation in synthesis: preparation of myo-inositol phosphates and related cyclitol derivatives from benzene. Tetrahedron 46: 4995-5026.
32. Falck JR, Yadagiri PJ (1989) Enantiospecific synthesis of D-myo-inositol 1,4,5-trisphosphate from (-)-quinic acid. J Org Chem 54: 5851-5852.
33. http://www.sciencedirect.com/science/journal/00404039/10/59
34. Maracek JP, Prestwich GD (1989) Synthesis of D-myo-(-)-H(1,4,5)P3. J Labelled Comp 27: 917.
35. Prestwich GD, Marecek JF (1991) Chemical modification of inositol trisphosphate: Trivalent, fluorinated and phosphate-tetered analogues, ACS Symposium Series 463 Inositolpolyphsphate and derivatives Edt Allen B. Reitz: 3322-131.
36. Potter BVL (1991) Phosphothioate analogues of D-myo-inositol 1,4,5-Trisphosphate. ACS Symposium Series 463 Inositolpolyphsphate and derivatives Edt Allen B. Reitz: 186-201.
37. Takahiko A, Naoto T, Shoichiro O (1990) Chiral synthesis of D-myo-inositol 1-phosphate starting from L-quebrachitol. Tetrahedron Letters 31: 1433-1434.
38. Takahiko A, Hirono S, Shoichiro O (1991) A concise synthesis of (-)-conduritol F from L-quebrachitol via AIC13-nBu4NI mediated demethylation. Tetrahedron Letters 32: 5593-5696.
39. Takahiko A, Masatoshi O, Hirono S, Shoichiro O (1991) Total synthesis of cyclophellitol from L-quebrachitol. Synlett 11: 831-832.
40. Takahiko A, Hirono S, Masatoshi O, Tedashi O, Shoichiro O (1993) Synthesis of (-)-conduritol F, (+)-conduritol B, cyclophilitol from L-quebrachitol. Bulletin of the Chemical Society of Japan 66: 3760-3767.
41. Takahiko A, Hiroyuki N, Takai K, Shoichiro O (1994) Stereodivergent synthesis of optically active α-hydroxy acids via diastereoselective reduction of α-keto esters derived from l-quebrachitol. Bulletin of the Chemical Society of Japan 66: 180-188.
42. Yutaka W, Motohiro M, Shoichiro O (1987) Synthesis of optically active inositol derivatives starting from D-glucuro-6,3-lactone. Chemistry Letters 1: 123-126.
43. Lei L, Yutaka W, Takahiko A, Shoichiro O (1992) A new efficient method for resolution of myo-inositol derivatives by enzyme catalyzed regio- and enantioselective esterification in organic solvent. Tetrahedron Letters 33: 1911-1914.
44. Ling L, Li X, Watanabe Y, Aikyama T, Ozaki S (1993) Enzymic resolution of racemic 1,2,5,6-di-O-cyclohexylydine and 1,2,3,4-di-O-cyclohexylydine-myo-inositol. Bioorg Med Chem 1: 155-159.
45. Lei L, Shoichiro O (1993) Enzyme aided synthesis of D-myo-inositol 1,4,5-trisphosphate. Tetrahedron Letter 34: 2501-2504.
46. Ling L, Ozaki S (1994) A chemoenzymatic synthesis of D-myo-inositol 1,4,5-trisphosphate. Carbohydr Res 256: 49-58.
70. Yutaka W, Masanori I, Shoichiro O (1994) Proximately assisted and chemoselectively cleavable protecting groups for alcohols, 1,2-(arg-methylxylo) ethyl/benzoic esters. Chemistry Letters 11: 2163-2166.

71. Takahiko A, Naoto T, Hiroaki S, Shoichiro O (1990) Anchemically assisted demethylation of methyl ethers in inositol derivatives with an aluminum chloride-sodium iodide system. Chemistry Letters 10: 1881-1884.

72. Takahiko A, Hajmu H, Shoichiro O (1992) Aluminium chloride-N,N-dimethanolamine: anovel benzy1 and ally ester cleavage reagent. Bulletin of the Chemical Society of Japan 65: 1932-1938.

73. Takahiko A, Hiroaki S, Shoichiro O (1992) Trimethylsilyl chloride-tri[i]chloro-anisole: a novel p-methylbenzyl ester cleavage reagent. Synlett 5: 415-416.

74. Takahiko A, Hiroyuki N, Keicho I, Shoichiro O (1992) Diastereoselective addition of organometallics to a-keto esters bearing chri-nositol derivatives as chiral auxiliaries. Chemistry Letters 3: 447-450.

75. Tadahiko A, Hiroyuki N, Shoichiro O (1991) Diastereoselective reduction of a-ketesters bearing chri-nositol derivatives as chiral auxiliaries. Tetrahedron Letters 32: 1335-1338.

76. Yutaka W, Takahiro F, Shoichiro O (1992) A novel deacylation method using Grignard reagent without affecting the neighboring base-sensitive functional groups. Journal of the Chemical Society, Chemical Communications 9: 681-683.

77. Ozaki S, Uemura A, Konishi T, Yamashita K, Maekawa T, et al. (1993) Enzyme aided regio-selective acylation and deacylation of nucleosides. Nucleic Acids Symp Ser: 53-54.

78. Yutaka W, Chikara N, Shoichiro O (1993) Glycosidation based on phosphite chemistry. Synlett 2: 116-118.

79. Yutaka W, Chikara N, Takashi Y, Shoichiro O (1994) Glycosylation using glycosyl phosphate as a glycosyl donor. Tetrahedron 50: 6523-6536.

80. Van Dijken P, Lammers AA, Ozaki S, Potter BV, Erneux C, et al. (1994) Phosphorylation of inositol 1,4,5-trisphosphate analogues by 3-kinase and dephosphorylation of inositol 1,3,4,5-tetakisphosphate analogues by 5-phosphatase. Eur J Biochem 226: 561-566.

81. Akiyama T, Yasuma T, Ishikawa K, Ozaki S (1994) Asymmetric synthesis of tetrahydrofurans by diastereoselective [3+2]-cycloaddition of allylsilanes with a -keto esters bearing an optically active cyclic ester as a chiral auxiliary. Tetrahedron Letters 35: 8401-8404.

82. Akiyama T, Okada K, Ozaki S (1992) The preparation of optically active D-glutamic acid via addition of nitrite oxides to chiral acetoxy esters bearing cycolitos as auxiliaries. Tetrahedron Letters 33: 5763-5766.

83. Akiyama T, Ishikawa K, Ozaki S (1994) Asymmetric synthesis of functionalized tertiary alcohols by diastereoselective aldol reaction of silyl ester and ketene silyl acetal with an -keto esters bearing an optically active cyclic ester as a chiral auxiliary. Synlett 4: 275-276.

84. Ozaki S, Watanabe Y, Hirata M, Awaya A (1991) Preparation of inositol polyphosphate derivatives for control of the calcium ion-participating metabolic steps. PCT Int. Appl. 139.

85. Ozaki S, Watanabe Y (1989) Synthesis of inositol polyphosphates. Yuki Gosei Kyokai 3: 363-373.

86. Watanabe Y, Ozaki S (1992) Organic chemical approach to inositol phospholipid-associated signal transduction. Farumashia 28: 598-602.

87. Ozaki S, Akiyama T, Takechi N, Kageyama K, Machida M (1991) Preparation of 6-myoinositol 1-phosphate. Ger Offen 8.

88. Akiyama T, Takechi N, Ozaki S, Shiota K (1992) A chiral synthesis of D-myo-inositol 1-phosphate starting from L-quebrachitol. Bulletin of the Chemical Society of Japan 65: 366-372.

89. Ozaki S, Kohno M, Nakahira H, Bunya M, Watanabe Y (1989) Synthesis of optically active myo-inositol 1,3,4,5-tetraphosphate. Chemistry Letters 35: 8401-8404.
Citation: Ozaki S (2014) Chemical Approach to Signal Transduction by Inositol Triphosphate. J Bioengineer & Biomedical Sci 4: 133. doi: 10.4172/2155-9538.1000133
130. Ozaki S, DeWald DB, Shope JC, Chen J, Prestwich GD (2000) Intracellular delivery of phosphoinositides and inositol phosphates using polyamine carriers. Proc Natl Acad Sci U S A 97: 11286-11291.

131. Maruyama T, Kanaji T, Nakade S, Kanno T, Mikoshiba K (1997) 2APB, 2-aminoethoxydiphenyl borate, a membrane-penetrable modulator of Ins(1,4,5)P3-induced Ca2+ release. J Biochem 122: 498-505.

132. Iwasaki H, Mori Y, Hara Y, Uchida K, Zhou H, et al. (2001) 2-Aminoethoxydiphenyl borate (2-APB) inhibits capacitative calcium entry independently of the function of inositol 1,4,5-trisphosphate receptors. Receptors Channels 7: 429-439.

133. Zhou H, Iwasaki H, Nakamura T, Nakamura K, Maruyama T, et al. (2007) 2-Aminoethyl diphenylborinate analogues: selective inhibition for store-operated Ca2+ entry. Biochem Biophys Res Commun 352: 277-282.

134. Mikoshiba K, Ozaki S, Suzuki A, Nakamura T (2007) Preparation of bisboron compounds controlling calcium concentration in cells. PCT Int Appl 118.

135. Mikoshiba K, Ozaki S, Ebii E (2009) Preparation of phenylborinic acid, poly(arylhydroxyborane), and their esters as intracellular calcium concentration regulators. Jpn Kokai Tokkyo Koho 138.

136. Mikoshiba K, Nukina N, Ozaki S, Hamada K, Goto J, et al. (2010) Preparation of phenylboron compounds as polyglutamine aggregation inhibitor.

137. Goto J, Suzuki AZ, Ozaki S, Matsumoto N, Nakamura T, et al. (2010) Two novel 2-aminoethyl diphenylborinate (2-APB) analogues differentially activate and inhibit store-operated Ca(2+) entry via STIM proteins. Cell Calcium 47: 1-10.

138. Suzuki AZ, Ozaki S, Goto J, Mikoshiba K (2010) Synthesis of bisboron compounds and their strong inhibitory activity on store-operated calcium entry. Bioorganic & Medicinal Chemistry Letters 20: 1395-1398.

139. Ozaki S, Suzuki AZ, Bauer PO, Ebisui E, Mikoshiba K (2013) 2-Aminoethyl diphenylborinate (2-APB) analogues: regulation of Ca2+ signaling. Biochem Biophys Res Commun 441: 286-290.

140. Ozaki S (2014) 2-Aminoethyl diphenylborinate (2APB) analogues: part 2. regulators of Ca2+ release and consequent cellular processes. Archives of Physiology 1: 1-6.

141. Mackenzie L, Bootman MD, Berridge MJ, Lipp P (2001) Predetermined recruitment of calcium release sites underlies excitation-contraction coupling in rat atrial myocytes. J Physiol 530: 417-429.

142. Lipp P, Laine M, Tovey SC, Burrell KM, Berridge MJ, et al. (2000) Functional InsP3 receptors that may modulate excitation-contraction coupling in the heart. Curr Biol 10: 939-942.

143. Mackenzie L, Bootman MD, Laine M, Berridge MJ, Thuring J, et al. (2002) The role of inositol 1,4,5-trisphosphate receptors in Ca(2+) signalling and the generation of arrhythmias in rat atrial myocytes. J Physiol 541: 395-409.

144. Proven A, Roderick HL, Conway SJ, Berridge MJ, Horton JK, et al. (2006) Inositol 1,4,5-trisphosphate supports the arrhythmogenic action of endothelin-1 on ventricular cardiac myocytes. J Cell Sci 119: 3363-3375.

145. Berridge MJ (2010) Calcium hypothesis of Alzheimer's disease. Pflugers Arch 459: 441-448.

146. Berridge MJ (2011) Calcium signalling and Alzheimer's disease. Neurochem Res 36: 1149-1158.

147. Chen R, Valencia I, Zhong F, McCull KG, Roderick HL, et al. (2004) Bcl-2 functionally interacts with inositol 1,4,5-trisphosphate receptors to regulate calcium release from the ER in response to inositol 1,4,5-trisphosphate. J Cell Biol 166: 193-203.

148. Berridge MJ (2013) Dysregulation of neural calcium signaling in Alzheimer disease, bipolar disorder and schizophrenia. Prion 7: 2-13.

149. Bauer OP, Hudec R, Ozaki S, Okuno M, Ebisui E, et al. (2011) Genetic ablation and chemical inhibition of IP3R1 reduce mutant Huntington aggregation. Biochem Biophys Res Commun 416: 13-17.

150. Zimmermann TJ, Bürger M, Tashiro E, Kondoh Y, Martinez NE, et al. (2013) Boron-based inhibitors of acyl protein thioesterases 1 and 2. Chembiochem 14: 115-122.

151. Ozaki S, Ebisui E, Hamada K, Goto J, Suzuki AZ, et al. (2010) Potent transglutaminase inhibitors, ary1 beta-aminoethyl ketones. Bioorg Med Chem Lett 20: 1141-1144.

152. Ozaki S, Ebisui E, Hamada K, Suzuki AZ, Terauchi A, et al. (2011) Potent transglutaminase inhibitors.Dithioß-aminoethyl ketones. Bioorganic & Medicinal Chemistry Letters 21: 377-379.