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2-Aminoethyl Diphenylborinate (2-APB) Analogues: Part 3 - Regulators of Huntington Aggregation and Transglutaminase

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Abstract

Huntington aggregation inhibitory activities and transglutaminase inhibitory activities of 2APB analogues were measured. 2-APB analogues regulated the Huntington aggregation. This fact provided an example that 2-APB analogues can regulate cellular process. Diphenyl (aminoacidonate N,O) boranes, which are effective regulator of Ca2+ release and cellular process, were effective regulators of Huntington aggregation. It was also found that many of 2-APB analogues have moderate transglutaminase inhibition activities 2-Aminoethyl di(4-trifluorophenyl) borinate is a good transglutaminase regurator.

Keywords: 2-APB; 2-APB analogue; Regulator of transglutaminase; Regulator of huntington aggregation; Huntington disease

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. We aimed to generate better modulator of calcium release than 2-APB. And 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 using methods described by us [38-43] and others [44-49] and measured their inhibitory activities on SOCE and IICR [38-43]. We found that these 2-APB analogues regulate Ca^{2+} release and associated cellular processes. We reported these finding on mono-boron compounds [50] and on bis-boron compounds [51].

This time, we report about 2 tests how these 2APB analogues show the ability to regulator Ca^{2+} related enzyme inhibitory activity and regulation of cellular process. One test is a regulation of transglutaminase, Second test is a regulation of Huntington aggregation using 2APB analogs having various Ca^{2+} release-related activities: SOCE. We wish to tell the relations of trangltaminase activity (TG), Huntington aggregation inhibition (x-Fold) and SOCE and chemical structures of compounds.

Transglutaminases (TG) [52-54] are calcium-dependent enzymes that catalyze various post-translational modifications including protein cross-linking, amine incorporation, and deamidation. The protein-crosslink is formed with isopeptide bonds between the carboxamide group of glutamine residues and the β-amino group of lysine residues to form N-(γ-glutamyl)-L-lysine accompanied by loss of the ammonia [55]. TG is implicated in various pathological roles in many neurodegenerative diseases [56-58] including Alzheimer's disease [59], Huntington's disease [60-63]. TG is also implicated in diseaes like catalacttous lens [64], Psoriasis skin injury [65], liver injury [66], fibrin injury [67,68], immune system injury [69,70] and Celiac disease [71]. Numeroous transglutaminase inhibitors are reported [72-75]. We have reported aryl-β-amino ketones [76], dithio β-amino ketones [77] as transglutaminase inhibitors.

We measured transglutaminase (TG) inhibitory activities .and Huntington aggregation inhibitory activities (x-Fold) of 276 2APB analogues. And we analyzed the result and relation of TG, x-Fold and SOCE IC_{50}.

Materials and Methods

APB analogues

2-APB was first synthesized by Ronderstvent et al. [44] in 1954 from triphenylboranes and ethanolamine. Later, hydroxy diphenyl borane and ethanolamine 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 [44-49]. The structures, names and synthetic methods of the compounds are in example 1-493 [43].

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Methods

We measured transglutaminase (TG) inhibitory activities as described at ref 76 .and Huntington aggregation inhibitory activities (x-Fold) [62].

Transglutaminase inhibitory activities measurement

TG (TransGlutaminase) inhibiting activity assay: Inhibition of TG enzyme was determined by assaying the enzyme activity in accordance with an optionally modified version of the enzyme activity in accordance with an optionally modified version of the method of Lorand et al. [53]. An enzyme reaction solution (0.1 ml) (100 mM HEPES-NaOH, pH 7.5, 1 mM $CaCl_2$, 20 M, monodansyl cadaverine, 0.05 mg/ml N,N-dimethylcasein, 5 μg/ml TGase) was introduced into wells of a 86-well plate (Nunc, 96 well Black Plate with Clear Bottom). A test compound was added in concentration of 100 μM. The plate was set in the fluorescence drug screening system FDSS3000 (hamamatsu Photonics K.K) TGase-inhibiting activity of the compound was calculated by assaying changes in fluorescence wavelength (at 340 nm) per unit time. The assay level at which a fluorescence change was observed with the addition of DMSO (1 μl) used as control instead of the test compound was designated as 100. The assay level at which TGase activity decreased by half in the presence of the test compound was designated as TG 50.

Huntington aggregation inhibitory activities measurement

Truncated N-terminal Huntington 150 Q-EGFP-Neuron 2a cells are cultured in 96 well plates. for 1day, 1 μM Ponasterone A (2 μl), 5 M Dibutyl cyclic AMP (2 μl) are added as to the test compound is to be 20 μM and cultured for 20 hours. The cells are fixed with 4% paraformaldehyde and washed with PBS after 30 minutes, and stained with Hoechst 33342. Aggregated cell numbers and total cell numbers are counted by Array Scan V T1 (Cellomics company, Pittuburg, USA). Ratio of aggregated cell to total cells (x-Fold) was measured. Without test compounds, ratio of aggregated cell to total cell x-Fold is 1. The smaller the x-Fold, the aggregation inhibition is stronger.

SOCE inhibition activities measurement

Inhibitory activities of the 2APB analogues for SOCE were measured using our improved assays as described previously [50].

Results and Discussion

We measured transglutaminase inhibitory activities (TG) and Huntington aggregation inhibition activity (x-Fold), and SOCE inhibition activities IC_{50} of 2APB analogues The results are shown in Supplementary Figure S1.

Typical 42 compounds are picked up from Figure S1 and grouped them into three groups and lined up from SOCE smaller value 0.2 to >10. 1) Amino acid adducts compounds, 2) Aminoalcohol adducts compounds & 3) Aminothiol adducts compounds.

Amino acid adduct compounds

Amino acid adduct compounds are majority of effective compounds. The compounds having small IC_{50} (SOCE) like 0.2 showed strong Huntington aggregation inhibiting activities (x-Fold). TG has no relation with IC_{50} (SOCE).

TG of 911 Diphenyl (2,6-diaminohexanate-O,N) borane is 136, x-Fold is 0.41, IC_{50} is 0.2. TG of 919 Diphenyl (2,3-diaminopropionate-O,N) borane is 90 and x-Fold is 0.53, IC_{50} is 0.2. TG of 855 Diphenyl asparaginate-O,N- borane is 105 x-Fold is 0.54 and IC_{50} is 0.2 (Figure 1).

The compounds having big IC_{50} (SOCE) like 10 showed no transglutaminase activity and no Huntington aggregation activity. TG of 901 Diphenyl (methionate-O,N) borane is 106, x-Hold is 0.90, IC_{50} is >10. TG of 4129 Diphenyl (2-aminohexanecarboxylate-O,N) borane is 90, x-Fold is 0.97, IC_{50} is >10.

Aminoalcohol adduct compounds

This group compounds showed moderate transglutaminase inhibition and Huntington aggregation inhibition. 2APB belongs to this group. TG of 2APB is 80, x-Fold is 0.64, IC_{50} is 3. TG of 1022 Bis-(4,4`(phenyl aminoethoxy boryl)phenyl)ether is 4 and x-Fold is 0.50 ,SOCE is 0.2. TG of 424 2-aminoethyl di(4-trifluorophenyl) borinate is 54, x-Fold is 0.69, SOCE is 0.5. TG of 372 2-aminoethyl di(5-chloro-2-methyl-phenyl) borinate is 74, x-Fold is 0.78 and IC_{50} is 1 (Figure 2).

Aminothil adduct compounds

Some compounds of this group showed remarkable transglutaminase inhibition, showed no Huntington aggregation activities. TG of 6014 2-aminoethylthio di (4-chloro-2-fluorophenyl) borane is 28, x-Fold is 0.96, SOCE is <1. TG of 1031 2-aminoethylthio diphenyl borane is 33, x-Fold is 0.87, and SOCE is 2. TG of 3115 2-aminoethylthio di (3-chloro-4-methylphenyl) borane is 12, x-Fold is 1.01, SOCE is 2. TG of 6039 2-aminoethylthio di (4-cyanophenyl) borane is 23. X-fold is 0.92, SOCE is >10. This thiol adducts compounds showed toxicity. Cell numbers decreased during assay. Therefore this group compounds would be not suitable for clinical use.

Relations of chemical structures and activities

Active compounds of 2APB analogues, nitrogen atom must come in this order B-O-C-C-N as 2-APB $C_6H_5B(OCH_2CH_2NH_2)C_6H_5$. The compounds having other order like B-O-C-N, or B-O-C-C-C-N have no activities. When phenyl group is substituted with aliphatic or aryaliphatic group, they lost their activities. When compared mono-boron, bis-boron and poly-boron compounds, mono-boron compounds were best and bis-boron compounds come next.

Relation of SOCE IC_{50} value and TG and x-Fold

Relation of SOCE IC_{50} and x-Fold: When look at Figure S1, the compounds having strong Ca^{2+} release activity, low IC_{50} value (IC_{50is}<1) except aminothiol adduct compounds, showed strong Huntington aggregation inhibiting activity The compounds having weak Ca^{2+} releasing activity (IC_{50} is >10) showed weak or no transglutaminase inhibiting activity (TG is near 100), and showed weak or no Hunting aggregation inhibiting activity (x-Fold is near 1). These results indicated that 2APB analogues were effective as regulators of cellular process.

Relation of SOCE IC_{50} and TG. Relation of TG and x-Fold: The compounds having strong Ca^{2+} release activity, low IC_{50} value (IC_{50is}<1) except aminothiol adduct compounds, showed no transglutaminase inhibition activities, x-Fold is near 1.00 even through IC_{50} is 0.2. Because our assay of transglutaminase inhibition is done in vitro and the assay is not cellular process. Calcium release cannot be expected. Therefore we cannot find any relation between TG and SOCE IC_{50} value also we cannot find any relation between TG and x-Fold. If we assay transglutaminase inhibition in vivo system, other results would be expected.

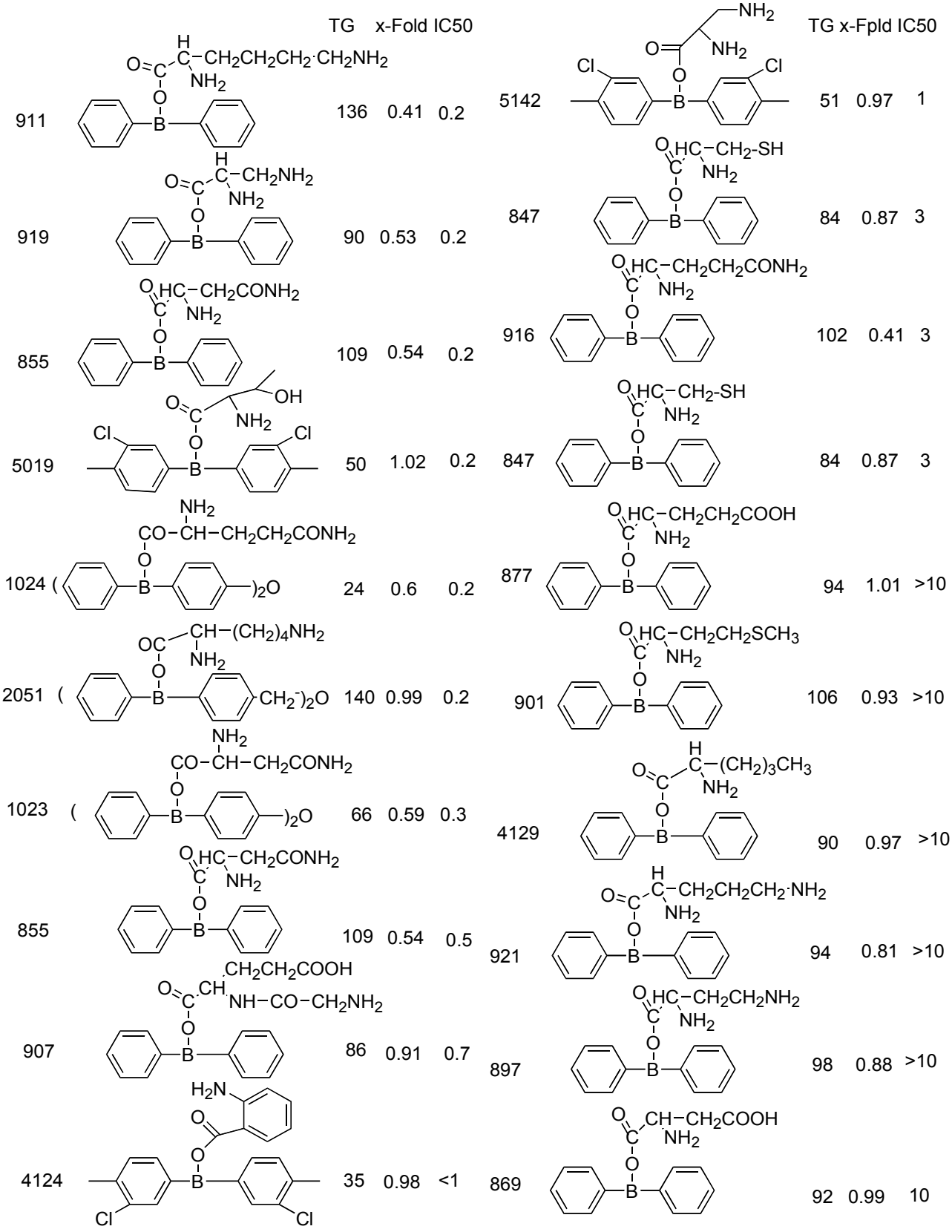

Figure 1: Amino acid adducts compounds.

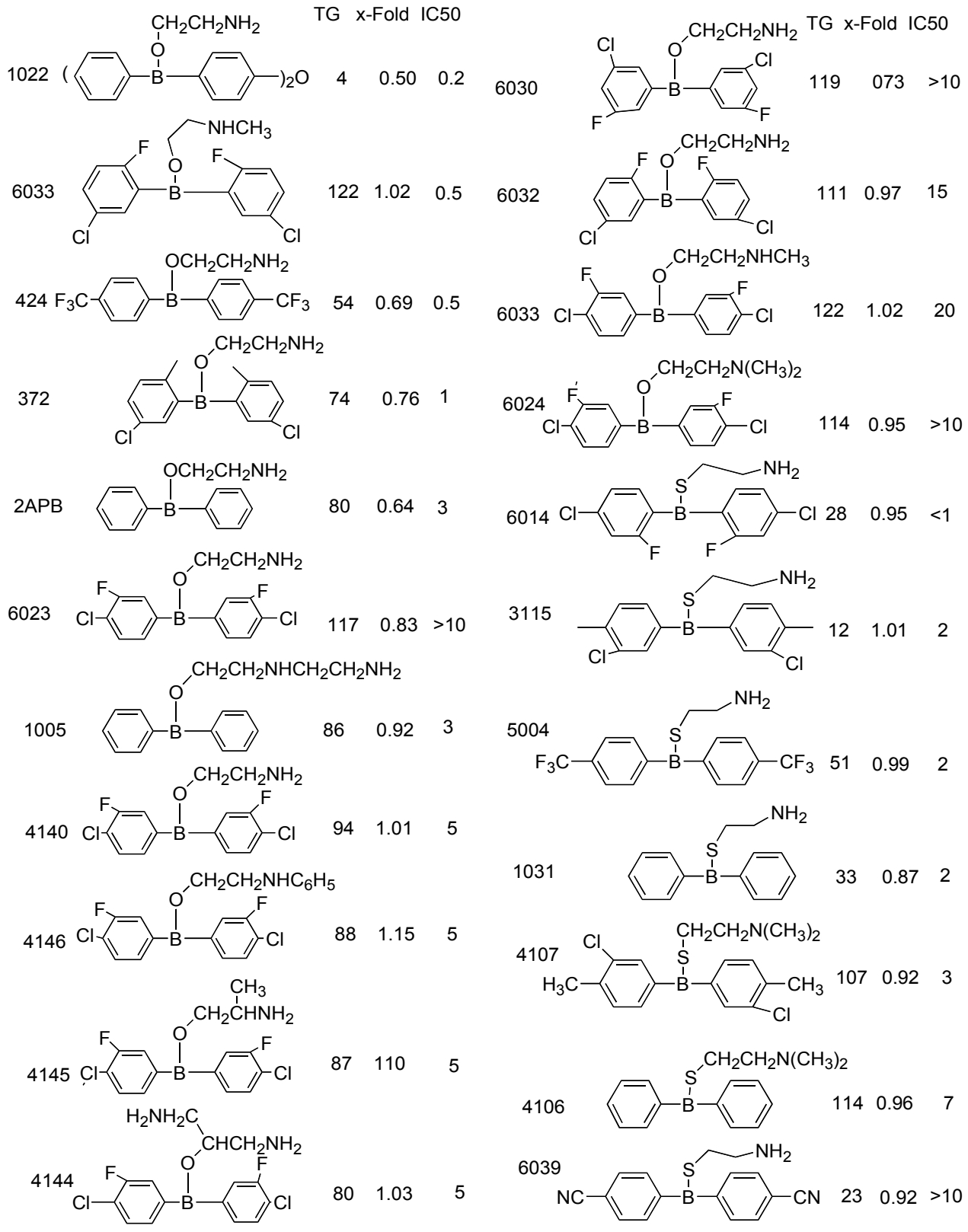

Figure 2: Amino alcohol adduct compounds & Aminothiol adduct compounds.

Regurator of huntington aggregation

Many compounds belong to amino acid adducts especially basic amino acid adduct such as 911 Diphenyl (2,6-diaminohexanoate 0,N)borane TG:136, x-Fold:0.41, IC_{50}:0.2 and 919 Diphenyl (2,3-diaminopropionate O.N) borane TG:90, x-Fold:0.53, IC_{50}:0.2 showed strong Huntington aggregation inhiting activity and no transglutaminase inhibiting activity.. These compound look like to be good and selective regulator of Huntington aggregation inhibitor.

Regulator of transglutaminase

Aminoalcohol adduct, 1022 Bis-(4,4`(phenyl aminoethoxy boryl) phenyl)ether: TG: 4 and x-Fold: 0.50 SOCE:0.2 and 424 2-aminoethyl di(4-trifluorophenyl) borinate: TG: 54, x-Fold :0.69, SOCE : 0.5 are good candidate as transglutaminase inhibitors. I have measured transglutaminase inhivition activities at 100 μM. The activities like these TG:4 or 54 at 100 μM are not so strong as aryl β-aminoethyl ketones IC_{50}: 0.1 μM reported by us [76,77] or thienopyrimidines IC_{50}: 0.13 μM reported by Duval [74]. Transglutaminase is necessary enzyme for our lives. Strong inhibitor will give toxicity. Moderate activity is required for clinical use.. We are reporting many TG inhibitors .differing activities. People will be able to choose most suitably active compounds. Some of these compounds were shown to inhibit the calcium dependent enzyme transglutaminase [43]. Transglutaminase inhibitors block the abnormal cross-link of protein [43,76-78] and they may slow down or even stop the progression of disease caused by over cross-linked proteins, such as Huntington`s disease.

I have analyzed the SOCE and TG(trnansglutaminase inhibition activities and x-Fold (Huntington aggregation inhibition) of 262 2APB analogues . 2-APB analogues regulated the Huntington aggregation This fact provided an example that 2-APB analogues can regulate cellular process. DAB (Diphenyl aminoacidonate (N,O) boranes are best compounds to regulate Huntington aggregation . The 2APB analogues presented in this study could be excellent lead compound for therapeutically intervene in many diseases such as heart disease [26-28,32-36,79], Huntington disease [43,61,62], Celiac disease [71], Alzheimer disease [79] in connection with cross-link of protein.

Conclusion

2-APB analogues regulated the Huntington aggregation has provided an example that 2-APB analogues can regulate cellular process. Diphenyl (aminoacidonate N,O) boranes are effective regulators of Huntington aggregation. It was also found that many of 2-APB analogues had moderate transglutaminase inhibition activities.

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