US008853424B2

(12) **United States Patent**
Mikoshiba et al.

(10) **Patent No.: US 8,853,424 B2**
(45) **Date of Patent: Oct. 7, 2014**

(54) **PROTEIN CROSS-LINKING INHIBITOR**

(75) Inventors: **Katsuhiko Mikoshiba**, Saitama (JP); **Nobuyuki Nukina**, Saitama (JP); **Shoichiro Ozaki**, Saitama (JP); **Kouzo Hamada**, Saitama (JP); **Jun-Ichi Goto**, Saitama (JP); **Akinobu Suzuki**, Saitama (JP); **Etsuko Ebisui**, Saitama (JP); **Akiko Terauchi**, Saitama (JP)

(73) Assignee: **Japan Science and Technology Agency**, Kawaguchi-Shi (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 551 days.

(21) Appl. No.: **13/058,647**

(22) PCT Filed: **Aug. 11, 2009**

(86) PCT No.: **PCT/JP2009/064206**

§ 371 (c)(1),
(2), (4) Date: **May 10, 2011**

(87) PCT Pub. No.: **WO2010/018837**

PCT Pub. Date: **Feb. 18, 2010**

(65) **Prior Publication Data**

US 2011/0212919 A1 Sep. 1, 2011

(30) **Foreign Application Priority Data**

Aug. 11, 2008 (JP) 2008-207315

(51) **Int. Cl.**

C07D 333/00	(2006.01)
A61K 31/67	(2006.01)
C07F 5/02	(2006.01)
A61K 31/69	(2006.01)

(52) **U.S. Cl.**

CPC ***C07F 5/025*** (2013.01); ***A61K 31/69*** (2013.01)
USPC **549/4**; 514/96

(58) **Field of Classification Search**

None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

8,017,809	B2 *	9/2011	Mikoshiba et al.	568/3
2004/0259842	A1	12/2004	Mikoshiba et al.	
2006/0009422	A1	1/2006	Perry et al.	
2006/0014723	A1	1/2006	Bellinger-Kawahara et al.	
2006/0019927	A1	1/2006	Bellinger-Kawahara et al.	

FOREIGN PATENT DOCUMENTS

EP	1 961 756	A1	8/2008
JP	2008-502694	A	1/2008
JP	2008-502702	A	1/2008
JP	2009-184988	A	8/2009
WO	WO 97/40859	A1	11/1997
WO	WO 02/44184	A2	6/2002
WO	WO 03/033002	A1	4/2003
WO	WO 2006/074419	A2	7/2006
WO	WO 2007/056341	A1	5/2007
WO	WO 2007/061074	A1	5/2007
WO	WO 2007/098418	A1	8/2007
WO	WO 2007/125351	A1	11/2007
WO	WO 2007/146965	A2	12/2007
WO	WO 2008/055068	A2	5/2008

OTHER PUBLICATIONS

CAPLUS 1970:531065.*
Dean, H. et al, J. Biol. Chem. 2008, vol. 283, pp. 16790-16800.*
International Search Report, dated Jan. 12, 2010, issued in PCT/JP2009/064206.

* cited by examiner

Primary Examiner — Heidi Reese
(74) *Attorney, Agent, or Firm* — Birch, Stewart, Kolasch & Birch, LLP

(57) **ABSTRACT**

The present invention provides a protein cross-linking inhibitor containing a compound represented by any of the following formulas (1)-(13), or a pharmaceutically acceptable salt thereof:

$$R_3—[—X—B(ZR_1)—Y—B(ZR_2)—W—]_n—R_4, \quad (1)$$

$$R_3—[—X—B(ZR_1)—Y—]_n—R_4, \quad (2)$$

$$R_3—[—B(ZR_1)—Y—B(ZR_2)—W—]_n—R_4, \quad (3)$$

$$R_3—[—X—B(ZR_1)—]_n—R_4, \quad (4)$$

$$R_3—[—B(ZR_2)—W—]_n—R_4, \quad (5)$$

$$R_3—X—B(ZR_1)\text{-}T[B(ZR_2)—W—R_4]_2, \quad (6)$$

$$R_3—B(OH)_2, \quad (7)$$

$$R_3—B(ZR_1)—X—B(ZR_2)—R_4, \quad (8)$$

$$R_3—B(R_1)—O—B(R_2)—R_4, \quad (9)$$

$$R_3—[—X—B(ZR_1)—Y—B(ZR_2)—]_n—R_4, \quad (10)$$

$$R_3—[—X—B(ZR_1)—Y—B(ZR_2)—W\text{-}Q\text{-}]_n—R_4, \quad (11)$$

$$R_3—[—P—X—B(ZR_1)—Y—B(ZR_2)—W—]_n—R_4, \quad (12)$$

$$[R_3—X—B(ZR_1)—Y]_2B(ZR_2), \quad (13)$$

wherein each symbol is as defined in the DESCRIPTION.

8 Claims, 1 Drawing Sheet

FIG. 1

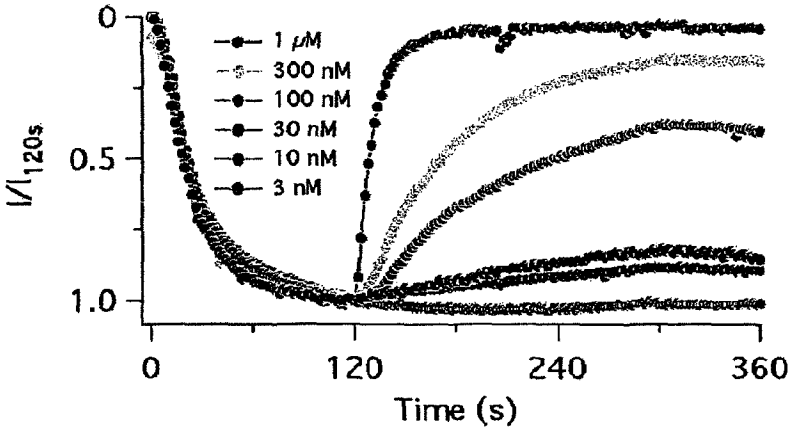


FIG. 2

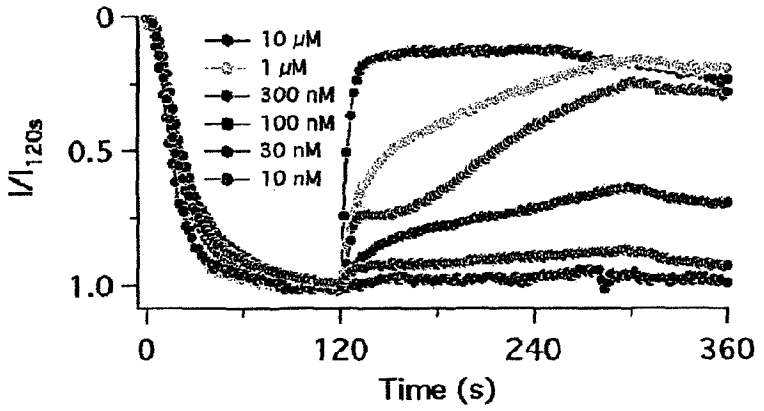
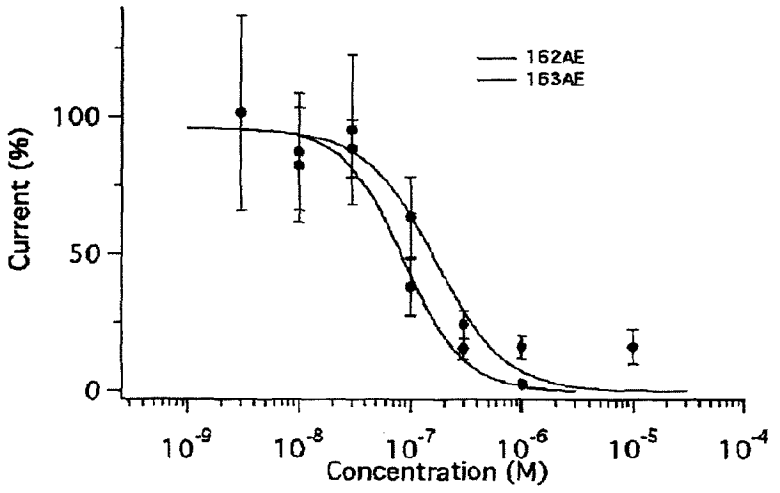


FIG. 3



PROTEIN CROSS-LINKING INHIBITOR

TECHNICAL FIELD

The present invention relates to a protein cross-linking inhibitor comprising a boron compound. Furthermore, the present invention relates to a novel boron compound useful for use thereof.

BACKGROUND ART

Calcium ion is essential for the body, and the concentration of intracellular Ca^{2+} constituting the body is as extremely low as 10^{-7}M, which is 1 to 10,000 relative to the extracellular concentration. When the cell is stimulated, intracellular Ca^{2+} increases to generate Ca^{2+} wave that produces slow intracellular Ca^{2+} oscillation, and induces physiological function.

SOCE (store-operated calcium entry) is also called capacitive calcium entry, which is a mechanism that causes extracellular influx of Ca^{2+} for replenishment of depleted intracellular Ca^{2+} stores, and important for long-term sustainability of intracellular Ca^{2+} signals.

SOCE is measured as Icrac (calcium release-activated calcium-selective current). It has been clarified that SOCE and Icrac channel are defective in the T cells of patients with severe combined immunodeficiency (SCID). Furthermore, it has also been clarified that a protein called STIM (stromal interaction molecule) senses depletion of Ca^{2+} in the endoplasmic reticulum, passes the information to the cellular membrane, and activates CRACM (calcium release-activated calcium modulator) (Orai) located in the cellular membrane and forms Icrac channel pore.

Extracellular stimulus is recognized by a receptor on the cellular membrane, the information thereof activates PLC (phospholipase C) via G protein and hydrolyzes PIP2 (phosphatidylinositol bisphosphate), which is an inositolphospholipid in the cellular membrane, and produces diacylglycerol and IP3 (inositol trisphosphate). Diacylglycerol activates protein kinase C and phosphorylates protein, causing various physiological phenomena. IP3 acts on IP3 receptor to cause release of Ca^{2+}. The present inventors have found an IP3 receptor molecule in mutant mouse, and successfully determined all base sequences of the membrane protein (non-patent document 1). In addition, they have clarified that the IP3 receptor localizes in the endoplasmic reticulum, and this is the calcium channel (non-patent documents 1-5). Furthermore, the present inventors have clarified that the IP3 receptor is the molecule involved in development and differentiation, neural plasticity and various signal transduction (non-patent documents 6-11). In addition, they have clarified that the IP3 receptor is also bound to the Ca^{2+} channel on the cell membrane surface (non-patent document 12).

2-Aminoethyl diphenylborinate (2-APB: $C_6H_5B(OCH_2CH_2NH_2)C_6H_5$) has been internationally recognized as an IP3 receptor inhibitor, and is sold from Sigma. It decreases intracellular calcium concentration by inhibiting SOCE. The present inventors have synthesized and found compounds that control intracellular calcium concentration (patent document 1, patent document 2, Japanese patent application No. 2008-028152).

It has been clarified that the causes of intractable diseases such as Alzheimer's disease, Parkinson's disease, Celiac disease, cataract, mad cow disease, congenital lamellar ichthyosis, congenital hemostatic disorder and the like are based on the abnormal cross-linking reaction of proteins (non-patent document 13, non-patent document 14). In addition, it has also been clarified that the cause of Huntington's disease is abnormal aggregation of polyglutamine (non-patent document 15).

Transglutaminase is an enzyme activated by the presence of Ca^{2+}, and its involvement in neurological diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease and the like has recently been known. Therefore, novel inhibitors thereof are considered to be effective as therapeutic drugs for the diseases (non-patent document 16, non-patent document 17). A reaction forming an isopeptide bond by deammoniation of an amide group of glutamine and an amino group of lysine is the main reaction of protein cross-linking. The mechanism by which an inhibitor of enzyme transglutaminase causing the reaction is effective for the aforementioned neurological diseases has been clarified (non-patent document 19). As a basis, while many studies have been made based on the above to develop inhibitors of transglutaminase as therapeutic drugs for intractable diseases such as Alzheimer's disease, Huntington's disease, Parkinson's disease and the like (non-patent documents 17-23), a boron compound having a transglutaminase inhibitory activity has not been reported heretofore.

DOCUMENT LIST

Patent Documents

patent document 1: WO03/033002 (U.S. Pat. No. 7,217,701)
patent document 2: WO2007/061074

Non-Patent Documents

non-patent document 1: Furuichi, T. et al. Primary structure and functional expression of the inositol 1,4,5-trisphosphate-binding protein P400. Nature. 1989 Nov. 2; 342(6245):32-8.
non-patent document 2: Miyawaki, A. et al. Expressed cerebellar-type inositol 1,4,5-trisphosphate receptor, P400, has calcium release activity in a fibroblast L cell line. Neuron. 1990 July; 5(1):11-8.
non-patent document 3: Maeda, N. et al. Structural and functional characterization of inositol 1,4,5-trisphosphate receptor channel from mouse cerebellum. J Biol. Chem. 1991 Jan. 15; 266(2):1109-16.
non-patent document 4: Kume, S. et al. The Xenopus 1P3 receptor: structure, function, and localization in oocytes and eggs. Cell. 1993 May 7; 73(3):555-70.
non-patent document 5: Yamamoto-Hino, M. et al. Cloning and characterization of human type 2 and type 3 inositol triphosphate receptors. Receptors and Channels. 1994; 2: 9-22.
non-patent document 6: Miyazaki, S. et al. Block of Ca^{2+} wave and Ca^{2+} oscillation by antibody to the inositol 1,4,5-trisphosphate receptor in fertilized hamster eggs. Science. 1992 Jul. 10; 257(5067):251-5.
non-patent document 7: Kume, S. et al. Role of inositol 1,4,5-trisphosphate receptor in ventral signaling in Xenopus embryos. Science. 1997 Dec. 12; 278(5345):1940-3.
non-patent document 8: Takei, K. et al. Regulation of nerve growth mediated by inositol 1,4,5-trisphosphate receptors in growth cones. Science. 1998 Nov. 27; 282(5394):1705-8.
non-patent document 9: Nishiyama, M. et al. Calcium stores regulate the polarity and input specificity of synaptic modification. Nature. 2000 Nov. 30; 408(6812):584-8.

non-patent document 10: Bosanac, I. et al. Structure of the inositol 1,4,5-trisphosphate receptor binding core in complex with its ligand. Nature. 2002 Dec. 12; 420(6916):696-700. Epub 2002 Nov. 17.

non-patent document 11: Matsumoto, M. et al. Ataxia and epileptic seizures in mice lacking type 1 inositol 1,4,5-trisphosphate receptor. Nature. 1996 Jan. 11; 379(6561): 168-71.

non-patent document 12: Boulay, G. et al. Modulation of Ca(2+) entry by polypeptides of the inositol 1,4,5-trisphosphate receptor (IP3R) that bind transient receptor potential (TRP): evidence for roles of TRP and IP3R in store depletion-activated Ca(2+) entry. Proc Natl Acad Sci USA. 1999 Dec. 21; 96(26): 14955-60.

non-patent document 13: Nobuyuki Nukina, Toru Nishikawa Experiment Medicine 25, No 13, (extra edition), page 20-29 (2007)

non-patent document 14: Hartley M Dean et al. Transglutaminase induces protofibril-like amyloid β-protein assemblies that are protease-resistant and inhibit long-term potentiation. J. Biol. Chem. 2008 283: 16790-16800.

non-patent document 15: Thomas M. Jeitner, et al. Increased levels of γ-glutamylamines in Huntingtondisease CSF. J. Neurochemistry 2008 Apr. 1; 106(1):7-44.

non-patent document 16: Kim, S. Y, et al. Transglutaminases in disease. Neurochem Int. 2002 January; 40(1):85-103.

non-patent document 17: Hoffner G, and Djian P. Transglutaminase and diseases of the central nervous system. Front Biosci. 2005 Sep. 1; 10:3078-92.

non-patent document 18: Duval E, et al. Structure-activity relationship study of novel tissue transglutaminase inhibitors. Bioorg Med Chem. Lett. 2005 Apr. 1; 15(7):1885-9.

non-patent document 19: L. Lorand Neurodegenerative diseases and transglutaminase. Proc Natl Acad Sci USA. 1996 Dec. 10; 93(25):14310-3.

non-patent document 20: Mastroberardino P G, et al. 'Tissue' transglutaminase ablation reduces neuronal death and prolongs survival in a mouse model of Huntington's disease. Cell Death Differ. 2002 September; 9(9):873-80.

non-patent document 21: Grierson A J, et al. Three different human tau isoforms and rat neurofilament light, middle and heavy chain proteins are cellular substrates for transglutaminase. Neurosci Lett. 2001 Jan. 26; 298(1): 9-12.

non-patent document 22: Watts R E, et al. Structure-activity relationship analysis of the selective inhibition of transglutaminase 2 by dihydroisoxazoles. J Med. Chem. 2006 Dec. 14; 49(25): 7493-501.

non-patent document 23: Karpuj M V, et al. Prolonged survival and decreased abnormal movements in transgenic model of Huntingtondisease, with administration of the transglutaminase inhibitor cystamine. Nat. Med. 2002 February; 8(2): 143-9.

SUMMARY OF THE INVENTION

Problems to be Solved by the Invention

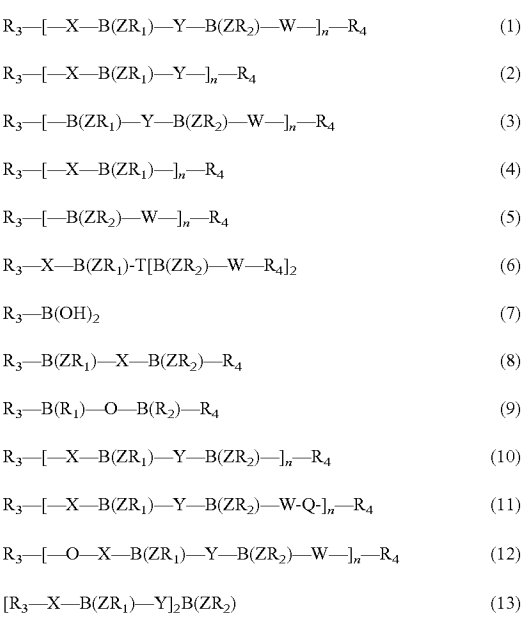
The present invention aims to develop a prophylaxis and/or therapeutic drug for diseases caused by cross-linking abnormality of protein (Alzheimer's disease, Parkinson's disease, Celiac disease, cataract, mad cow disease, congenital lamellar ichthyosis, congenital hemostatic disorder etc.).

Means of Solving the Problems

The present inventors have conducted intensive studies in an attempt to solve the aforementioned problems and found that a series of boron compounds, particularly the compounds represented by the following formulas (1)-(13) (hereinafter to be also simply referred to as compounds (1)-(13)), inhibit cross-linking of protein, and the compounds can be used as prophylactic and/or therapeutic drugs for diseases caused by abnormal cross-linking of proteins.

Accordingly, the present invention provides the following.

[1] A compound represented by any of the following formulas (1)-(13) or a pharmaceutically acceptable salt thereof;



$$R_3—[—X—B(ZR_1)—Y—B(ZR_2)—W—]_n—R_4 \quad (1)$$

$$R_3—[—X—B(ZR_1)—Y—]_n—R_4 \quad (2)$$

$$R_3—[—B(ZR_1)—Y—B(ZR_2)—W—]_n—R_4 \quad (3)$$

$$R_3—[—X—B(ZR_1)—]_n—R_4 \quad (4)$$

$$R_3—[—B(ZR_2)—W—]_n—R_4 \quad (5)$$

$$R_3—X—B(ZR_1)\text{-}T[B(ZR_2)—W—R_4]_2 \quad (6)$$

$$R_3—B(OH)_2 \quad (7)$$

$$R_3—B(ZR_1)—X—B(ZR_2)—R_4 \quad (8)$$

$$R_3—B(R_1)—O—B(R_2)—R_4 \quad (9)$$

$$R_3—[—X—B(ZR_1)—Y—B(ZR_2)—]_n—R_4 \quad (10)$$

$$R_3—[—X—B(ZR_1)—Y—B(ZR_2)—W\text{-}Q\text{-}]_n—R_4 \quad (11)$$

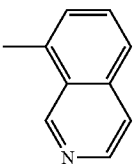
$$R_3—[—O—X—B(ZR_1)—Y—B(ZR_2)—W—]_n—R_4 \quad (12)$$

$$[R_3—X—B(ZR_1)—Y]_2B(ZR_2) \quad (13)$$

wherein B is a boron atom,

Z is O or S,

R_1 and R_2 are independently a group selected from H, $—(CH_2)_m—NR_5R_6$, $—CO—(CH_2)_m—NR_7R_9$, $—COCH(NH_2)—R_9$, $—CH_2CH(NH_2)—R_{10}$, $—CHR_{11}R_{12}$, $—COCH(—NR_{13}R_{14})—R_{15}$, $—COCH(NH_2)—(CH_2)_m NHCR_{18}NH_2$, $—COCH(NH_2)—(CH_2)_m—COR_{19}$, $—COR_{20}$, $—(CH_2)_m—R_{22}$, $—O(CH_2)_mNH_2$, $—COCH(NH_2)—(CH_2)_m—R_{23}$, $—(CH_2CH_2NH)_2—R_{23}$,



and heterocyclylalkyl, or when R_1 and R_2 are present in plurality, R_1 may be bonded to R_1, R_2 may be bonded to R_2, or R_1 may be bonded to R_2, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{19}, R_{20} and R_{22} are independently H, or each is a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, amino, aminoalkylcarbonyl, hydroxy, aromatic group or heterocyclylalkyl,

R_{18} is oxo or =NH,

Q is a group represented by $—R_{16}—O—R_{17}—$, $—R_{21}—O—$ or —O— (wherein R_{16}, R_{17} and R_{21} mean a single bond or lower alkylene),

R_{23} is a fluorescence group,

m is an integer of 1 to 5,

R_3 and R_4 are H, OH, CH_2OH, $CH_2OCH_2OCH_3$, cyano or aryloxy, or each is a substituted or unsubstituted alkyl or aryl,

T is a substituted or unsubstituted aryl,
X, Y and W are independently groups containing aromatic series or fatty series, and
n is an integer of 1 to 100.

[2] A compound represented by any of the following formulas (1)-(13) or a pharmaceutically acceptable salt thereof;

$$R_3—[—X—B(ZR_1)—Y—B(ZR_2)—W—]_n—R_4 \quad (1)$$

$$R_3—[—X—B(ZR_1)—Y—]_n—R_4 \quad (2)$$

$$R_3—[—B(ZR_1)—Y—B(ZR_2)—W—]_n—R_4 \quad (3)$$

$$R_3—[—X—B(ZR_1)—]_n—R_4 \quad (4)$$

$$R_3—[—B(ZR_2)—W—]_n—R_4 \quad (5)$$

$$R_3—X—B(ZR_1)\text{-}T[B(ZR_2)—W—R_4]_2 \quad (6)$$

$$R_3—B(OH)_2 \quad (7)$$

$$R_3—B(ZR_1)—X—B(ZR_2)—R_4 \quad (8)$$

$$R_3—B(R_1)—O—B(R_2)—R_4 \quad (9)$$

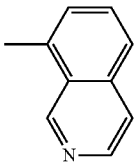
$$R_3—[—X—B(ZR_1)—Y—B(ZR_2)—]_n—R_4 \quad (10)$$

$$R_3—[—X—B(ZR_1)—Y—B(ZR_2)—W\text{-}Q\text{-}]_n—R_4 \quad (11)$$

$$R_3—[—O—X—B(ZR_1)—Y—B(ZR_2)—W—]_n—R_4 \quad (12)$$

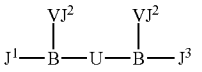
$$[R_3—X—B(ZR_1)—Y]_2B(ZR_2) \quad (13)$$

wherein B is a boron atom,
Z is O or S,
R_1 and R_2 are independently a group selected from H, $—(CH_2)_m—NR_5R_6$, $—CO—(CH_2)_mNR_7R_8$, $—COCH(NH_2)—R_9$, $—CH_2CH(NH_2)—R_{10}$, $—CHR_{11}R_{12}$, $—COCH(—NR_{13}R_{14})—R_{15}$, $—COCH(NH_2)—(CH_2)_mNHCR_{18}NH_2$, $—COCH(NH_2)—(CH_2)_m—COR_{19}$, $—COR_{20}$, $—(CH_2)_m—R_{22}$, $—O(CH_2)_mNH_2$, $—COCH(NH_2)—(CH_2)_m—R_{23}$, $—(CH_2CH_2NH)_2—R_{23}$,

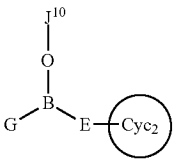


and heterocyclylalkyl, or when R_1 and R_2 are present in plurality, R_1 may be bonded to R_1, R_2 may be bonded to R_2, or R_1 may be bonded to R_2, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{19}, R_{20} and R_{22} are independently H, or each is a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, amino, aminoalkylcarbonyl, hydroxy, aromatic group or heterocyclylalkyl, R_{18} is oxo or =NH,
Q is a group represented by $—R_{16}—O—R_{11}—$, $—R_{21}—O—$, or —O— (wherein R_{16}, R_{17} and R_{21} mean a single bond or lower alkylene),
R_{23} is a fluorescence group,
m is an integer of 1 to 5,
R_3 and R_4 are H, OH, CH_2OH, $CH_2OCH_2OCH_3$, cyano or aryloxy, or each is a substituted or unsubstituted alkyl or aryl,
T is a substituted or unsubstituted aryl,
X, Y and W are independently groups containing aromatic series or fatty series, and
n is an integer of 1 to 100,

excluding a compound represented by the following formula (Ia)



wherein
B is a boron atom,
B is an oxygen or sulfur atom,
J^1 and J^3 are each independently a monocyclic aromatic group, a polycyclic aromatic group, or a heterocyclic group containing at least one hetero atom selected from an oxygen atom, a nitrogen atom and a sulfur atom,
J^2 is a hydrogen atom; $—(CH_2)_D—NJ^4J^5$ wherein D is an integer of 1-4,
J^4 and J^5 are independently a hydrogen atom, or C_{1-4} alkyl substituted or unsubstituted by an amino group, a mono or di-C_{1-4} alkylamino group or a phenyl group, or J^4 and J^5 form, together with the nitrogen atom bonded thereto, a 5- or 6-membered cyclo ring); $—CO—(CH_2)_D—NJ^4J^5$ wherein D, J^4 and J^5 are as defined above; $—COCH(NH_2)J^6$ wherein J^6 is an amino acid residue, or $—(CH_2)_{D'}NH_2$ wherein D' is an integer of 1 to 3; $—CHJ^7J^8$ wherein J^7 and J^8 are independently an amino group, C_{1-4} alkyl substituted or unsubstituted by a mono or di(C_{1-4} alkyl substituted or unsubstituted by an amino group)amino group or phenyl group, or phenyl substituted by pyridyl or a C_{1-3} alkoxy group; $—CH_2CH(NH_2)$-J^6 wherein J^9 is phenyl, or C_{1-4} alkyl substituted by phenyl; quinolyl or isoquinolyl substituted by a alkyl group; or C_{1-4} alkyl substituted by a pyridyl group, a piperidino group or a pyrrolidinyl group, and
U is a monocyclic aromatic group, a polycyclic aromatic group or a heterocyclic group, which is the same as or different from J^1 and J^3, or a bifunctional group having a monocyclic aromatic group, a polycyclic aromatic group or a heterocyclic group bonded to both sides thereof via a group selected from the group consisting of a single bond, O, CH_2, S, SO_2, CH_2OCH_2, OCH_2, $OCH_2CH_2OCH_2$, $OCH_2OCH_2CH_2$ and $CH_2OCH_2CH_2$, and a compound represented by the following formula (Ib)



wherein J^{10} is
(1) a hydrogen atom,
(2) $—(CH_2)_{D''}NJ^{11}J^{12}$ wherein D" is an integer of 1 to 3, J^{11} and J^{12} are each independently a hydrogen atom, C_{1-4} alkyl, C_{5-6} monocyclic carbocycle, C_{1-4} alkyl substituted by C_{5-6} monocyclic carbocycle, or 5- or 6-membered monocyclic heterocycle,
the carbon atom in $—(CH_2)_{D''}—$ is optionally substituted by 1 or 2 J^{13}, and further, said carbocycle and heterocycle are optionally substituted by 1 or 2 J^{16},
J^{13} is (a) C_{1-8} alkyl, (b) carboxyl, (c) C_{1-4} alkoxycarbonyl, (d) keto, (e) C_{5-6} monocyclic carbocycle, (f) guanidino(C_{1-2}) alkyl, (g) C_{1-6} alkyl substituted by C_{5-6} monocyclic carbocycle, (h) C_{1-2} alkyl substituted by 4-chlorophenoxy, or (i) C_{1-4} alkyl substituted by di(C_{1-4} alkylamino,

(3) C_{1-6} alkyl or C_{2-6} alkenyl substituted by C_{5-6} monocyclic carbocycle, wherein said carbocycle is optionally substituted by 1 to 5 J^{16}, and further, said C_{1-6} alkyl or C_{2-6} alkenyl is optionally substituted by 1 or 2 J^{19},

(4) C_{1-6} alkyl or C_{2-6} alkenyl substituted by 5- or 6-membered monocyclic heterocycle, wherein said heterocycle is optionally substituted by 1 to 5 J^{16}, and further, said C_{1-6} alkyl or C_{2-6} alkenyl is optionally substituted by 1 or 2 J^{19}, and

J^{19} is C_{1-4} alkyl or C_{2-4} alkenyl,

(5) a —$CHJ^{14}J^{15}$ group wherein J^{14} and J^{15} are each independently

(i) C_{5-6} monocyclic carbocycle,

(ii) 5- or 6-membered monocyclic heterocycle,

(iii) C_{1-6} alkyl or C_{2-6} alkenyl substituted by C_{5-6} monocyclic carbocycle, or

(iv) C_{1-6} alkyl or C_{2-6} alkenyl substituted by 5- or 6-membered monocyclic heterocycle, wherein said carbocycle and heterocycle are optionally substituted by 1 to 5 J^{16}, or

(6) 5,6,7,8-tetrahydroquinolin-8-yl,

J^{16} is (a) C_{1-4} alkyl, (b) C_{1-4} alkoxy, (c) a halogen atom, (d) —CF_3, (e) nitro, (f) C_{5-6} monocyclic carbocycle, (g) C_{1-4} alkyl substituted by C_{5-6} monocyclic carbocycle, (h) amino, (i) —NHCO(C_{1-4} alkyl), or (j) C_{1-4} alkoxycarbonyl,

G is Cyc_1 or hydroxy, Cyc_1 is C_{5-10} monocyclic or bicyclic carbocycle, or 5- to 10-membered monocyclic or bicyclic heterocycle, wherein said carbocycle and heterocycle are optionally substituted by 1 to 5 J^{17},

Cyc_2 is C_{5-10} monocyclic or bicyclic heterocycle or 5- to 10-membered monocyclic or bicyclic heterocycle, wherein said carbocycle and heterocycle are optionally substituted by 1 to 5 J^{18}, J^{17} and J^{18} are each independently

(a) C_{1-4} alkyl,

(b) C_{2-4} alkenyl,

(c) C_{1-4} alkoxy,

(d) a halogen atom,

(e) —CF_3,

(f) alkylthio,

(g) amino,

(h) (C_{1-4} alkyl)amino,

(i) di(C_{1-4} alkyl)amino,

(j) formyl,

(k) phenyl,

(l) phenoxy,

(m) hydroxy(C_{1-2})alkyl,

(n) (C_{5-10} monocyclic or bicyclic carbocycle)-O—(C_{1-2}) alkyl,

(o) C_{1-4} alkoxycarbonylvinyl,

(p) C_{1-2} alkyl substituted by a group selected from —O—(C_{1-2} alkylene)-phenyl (said phenyl is optionally substituted by 1 to 3 C_{1-4} alkoxy), —O—CONH-phenyl (said phenyl is optionally substituted by 1 to 3 C_{1-4} alkyl, nitro or C_{1-4} alkoxycarbonyl), or —O—CONH—(C_{1-4})alkyl (said alkyl is optionally substituted by 1 to 3 C_{1-4} alkyl, carboxyl or C_{1-4} alkoxycarbonyl),

(q) phenylthio,

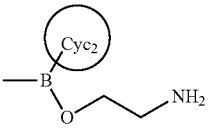
(r) —CON(C_{1-4} alkyl)$_2$.

(s) —SO_2N(C_{1-4} alkyl)$_2$,

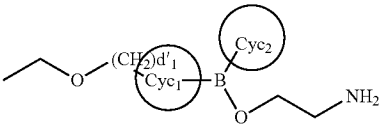
(t) alkoxy(C_{1-2})alkyl,

(u) C_{1-4} alkoxycarbonyloxy(C_{1-2})alkyl,

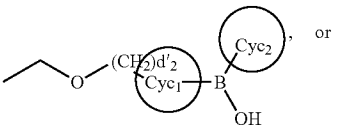
(v)



(w)

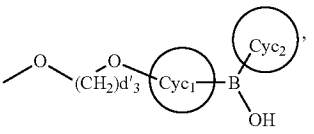


(x)



or

(y)



carbocycle, phenyl, Cyc_1 and Cyc_2 in J^{17} and J^{18} are optionally substituted by 1 or 2 J^{18}, or J^{17} and J^{18} in combination optionally show —O—, and J^{18} and J^{19} in combination optionally show a single bond,

d'_1 is an integer of 1 to 4,

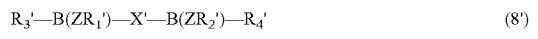
d'_2 is an integer of 1 to 4,

d'_3 is an integer of 1 to 4, and

E is a single bond or C_{1-4} alkylene substituted or unsubstituted by C_{5-6} monocyclic carbocycle.

[3] The compound of [2] represented by the following formula (4') or (8')

(4')



(8')

wherein B is a boron atom,

Z is O or S,

R_1' and R_2' are H, —$(CH_2)_m$—$NR_5'R_6'$, —$COCH(NH_2)$—$(CH_2)_m NHCONH_2$ or —$COCH(NH_2)$—$(CH_2)_m$—COR_{19}', wherein R_5', R_6', R_{11}', R_{12}' and R_{19}' are independently H, or each is a substituted or unsubstituted amino, heterocyclyl or aryloxy,

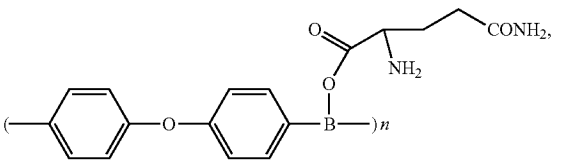
R_3' and R_4' are H, aryl or heterocyclyl,

X' is a substituted or unsubstituted aromatic group,

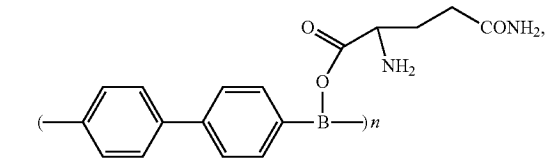
m is an integer of 1 to 5, and

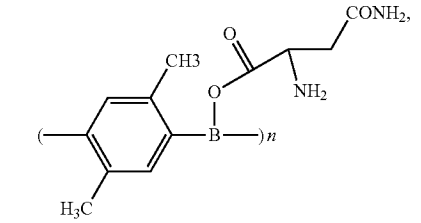
n is an integer of 1 to 100, or a pharmaceutically acceptable salt thereof.

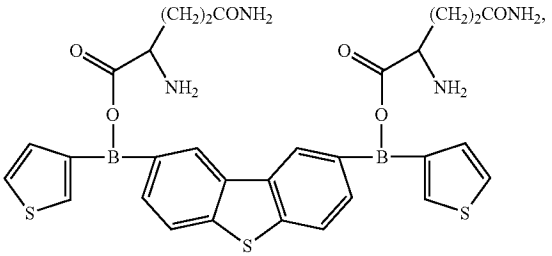
[4] The compound of [2] or [3], which is any of

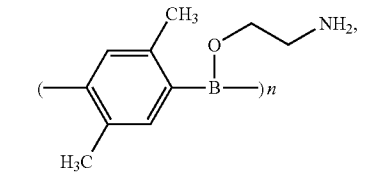


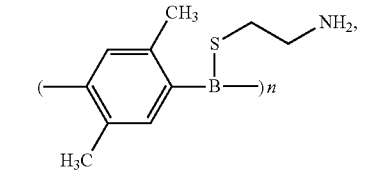
-continued

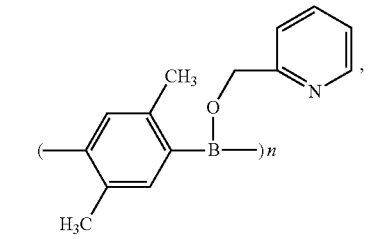


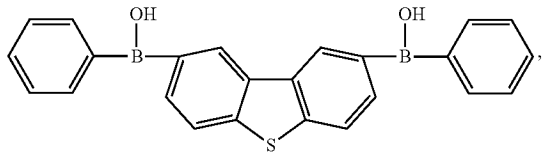


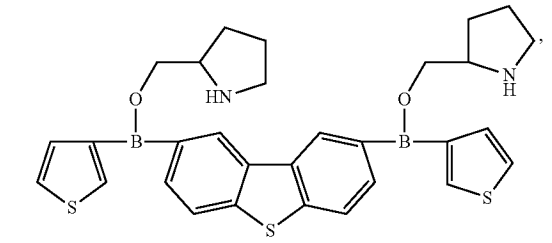




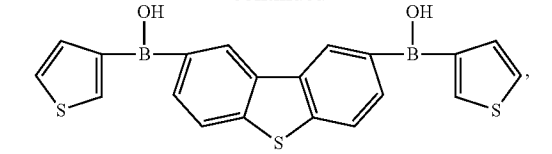


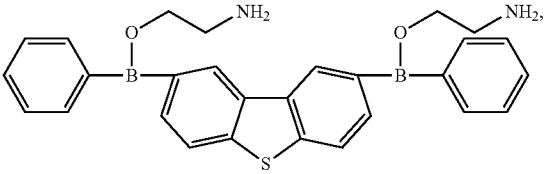


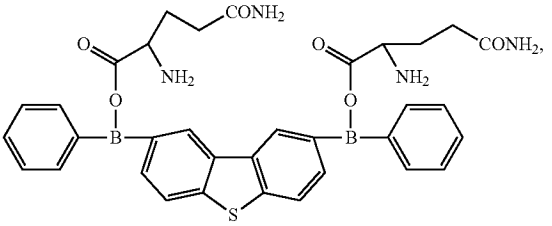


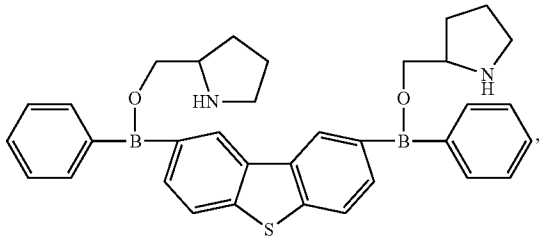


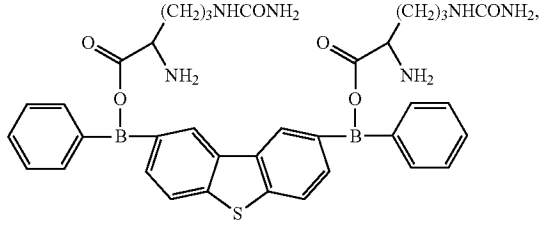
-continued

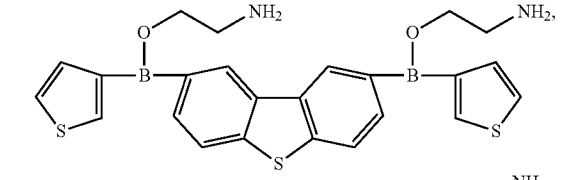


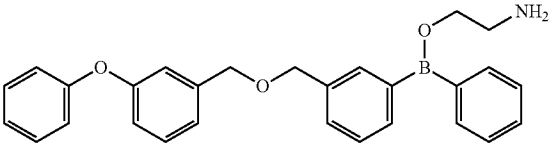












wherein n is an integer of 1 to 100, or a pharmaceutically acceptable salt thereof.

[5] A protein cross-linking inhibitor comprising the compound of [2] to [4] or a pharmaceutically acceptable salt thereof.

[6] The inhibitor of [5], wherein the compound is represented by the formula (1) or (8)

$$R_3—[—X—B(ZR_1)—Y—B(ZR_2)—W—]_n—R_4 \quad (1)$$

$$R_3—B(ZR_1)—X—B(ZR_2)—R_4 \quad (8)$$

wherein each symbol is as defined in [2].

[7] A prophylactic and/or therapeutic drug for a disease caused by cross-linking of protein, comprising the compound of [2] to [4] or a pharmaceutically acceptable salt thereof.

[8] The prophylactic and/or therapeutic drug of [7], wherein the compound is represented by the formula (1) or (8)

$$R_3—[—X—B(ZR_1)—Y—B(ZR_2)—W—]_n—R_4 \quad (1)$$

$$R_3—B(ZR_1)—X—B(ZR_2)—R_4 \quad (8)$$

wherein each symbol is as defined in [2].

[9] The prophylactic and/or therapeutic drug of [7] or [8], wherein the disease caused by cross-linking of protein is selected from Alzheimer's disease, Parkinson's disease, Celiac disease, cataract, mad cow disease, congenital lamellar ichthyosis and congenital hemostatic disorder.

[10] A method of preventing and/or treating a disease caused by cross-linking of protein, comprising administering an effective amount of the compound of [2] to [4] or a pharmaceutically acceptable salt thereof to a subject.

[11] The method of [10], wherein the compound is represented by the formula (1) or (8)

$$R_3—[—X—B(ZR_1)—Y—B(ZR_2)—W—]_n—R_4 \quad (1)$$

$$R_3—B(ZR_1)—X—B(ZR_2)—R_4 \quad (8)$$

wherein each symbol is as defined in [2].

[12] The method of [10] or [11], wherein the disease caused by cross-linking of protein is selected from Alzheimer's disease, Parkinson's disease, Celiac disease, cataract, mad cow disease, congenital lamellar ichthyosis and congenital hemostatic disorder.

[13] The compound of [2] to [4] to be used for the prophylaxis and/or treatment of disease caused by cross-linking of protein, or pharmaceutically acceptable salts thereof.

[14] The compound of [13] which is represented by the formula (1) or (8)

$$R_3—[—X—B(ZR_1)—Y—B(ZR_2)—W—]_n—R_4 \quad (1)$$

$$R_3—B(ZR_1)—X—B(ZR_2)—R_4 \quad (8)$$

wherein each symbol is as defined in [2], or a pharmaceutically acceptable salt thereof.

[15] The compound of [13] or [14], wherein the disease caused by cross-linking of protein is selected from Alzheimer's disease, Parkinson's disease, Celiac disease, cataract, mad cow disease, congenital lamellar ichthyosis and congenital hemostatic disorder, or a pharmaceutically acceptable salt thereof.

Effect of the Invention

The present invention can provide a prophylactic and/or therapeutic drug for the diseases based on an abnormal cross-linking reaction of protein such as Alzheimer's disease, Parkinson's disease, Celiac disease, cataract, mad cow disease, congenital lamellar ichthyosis, congenital hemostatic disorder and the like.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a drawing showing an Icrac inhibitory effect of 162AE, wherein the vertical axis shows a relative electric current when the amount of Icrac immediately before acting 162AE (120 sec) is 1, and the horizontal axis shows time (seconds).

FIG. **2** is a drawing showing an Icrac inhibitory effect of 163AE, and the vertical axis and the horizontal axis show the same as in FIG. **1**.

FIG. **3** is a drawing showing a dose inhibition curve relating to the inhibitory effect of 162AE and 163AE on Icrac, wherein the vertical axis shows the amount in percentage of Icrac when the inhibitor was used relative to the amount of Icrac without the inhibitor as 100%, and the horizontal axis shows the concentration (M) of the inhibitor.

DESCRIPTION OF EMBODIMENTS

In the present invention, the cross-linking of protein means the state where a new bond of protein chain is formed in a molecule or between molecules (covalent bond, ionic bond, coordinate bond, hydrogen bond etc.), and a bridge is built.

In addition, polyglutamine aggregation means formation of assembly of polyglutamine (polymerization and/or specific aggregate).

Abnormal aggregation of polyglutamine is one example of cross-linking abnormalities of protein. An abnormal cross-linking of protein occurs due to abnormal transglutaminase activity that depends on calcium concentration.

The present invention relates to a protein cross-linking inhibitor containing a compound represented by any of the following formulas (1)-(13).

$$R_3—[—X—B(ZR_1)—Y—B(ZR_2)—W—]_n—R_4 \quad (1)$$

$$R_3—[—X—B(ZR_1)—Y—]_n—R_4 \quad (2)$$

$$R_3—[—B(ZR_1)—Y—B(ZR_2)—W—]_n—R_4 \quad (3)$$

$$R_3—[—X—B(ZR_1)—]_n—R_4 \quad (4)$$

$$R_3—[—B(ZR_2)—W—]_n—R_4 \quad (5)$$

$$R_3—X—B(ZR_1)\text{-}T[B(ZR_2)—W—R_4]_2 \quad (6)$$

$$R_3—B(OH)_2 \quad (7)$$

$$R_3—B(ZR_1)—X—B(ZR_2)—R_4 \quad (8)$$

$$R_3—B(R_1)—O—B(R_2)—R_4 \quad (9)$$

$$R_3—[—X—B(ZR_1)—Y—B(ZR_2)—]_n—R_4 \quad (10)$$

$$R_3—[—X—B(ZR_1)—Y—B(ZR_2)—W\text{-}Q\text{-}]_n—R_4 \quad (11)$$

$$R_3—[—O—X—B(ZR_1)—Y—B(ZR_2)—W—]_n—R_4 \quad (12)$$

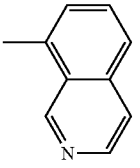
$$[R_3—X—B(ZR_1)—Y]_2B(ZR_2) \quad (13)$$

In the formula.

B is a boron atom,

Z is O or S,

R_1 and R_2 are independently a group selected from H, $—(CH_2)_m—NR_5R_6$, $—CO—(CH_2)_m—NR_7R_8$, $—COCH(NH_2)—R_9$, $—CH_2CH(NH_2)—R_{10}$, $—CHR_{11}R_{12}$, $—COCH(—NR_{13}R_{14})—R_{15}$, $—COCH(NH_2)—(CH_2)_mNHCR_{18}NH_2$, $—COCH(NH_2)—(CH_2)_m—COR_{19}$, $—COR_{20}$, $—(CH_2)_m—R_{22}$, $—O(CH_2)_mNH_2$, $—COCH(NH_2)—(CH_2)_m—R_{23}$, $—(CH_2CH_2NH)_2—R_{23}$,



and heterocyclylalkyl, or when R_1 and R_2 are present in plurality, R_1 may be bonded to R_1, R_2 may be bonded to R_2, or R_1 may be bonded to R_2, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{19}, R_{20} and R_{22} are independently H, or each is a

substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, amino, aminoalkylcarbonyl, hydroxy, aromatic group or heterocyclylalkyl,

R_{18} is oxo or =NH,

Q is a group represented by $—R_{16}—O—R_{17}—$, $—R_{21}—O—$ or —O— (wherein R_{16}, R_{17} and R_{21} mean a single bond or lower alkylene),

R_{23} is a fluorescence group,

m is an integer of 1 to 5,

R_3 and R_4 are H, OH, CH_2OH, $CH_2OCH_2OCH_3$, cyano or aryloxy, or each is a substituted or unsubstituted alkyl or aryl,

T is a substituted or unsubstituted aryl,

X, Y and W are independently groups containing aromatic series or fatty series, and

n is an integer of 1 to 100.

R_1 and R_2 are preferably independently a group selected from H, $—(CH_2)_m—NR_5R_6$, $—CH_2CH(NH_2)—R_{10}$, $—CHR_{11}R_{12}$, $—COCH(NH_2)—(CH_2)_m—COR_{19}$, $—COR_{20}$, $—(CH_2)_m—R_{22}$, $—COCH(NH_2)—(CH_2)_m—R_{23}$ and heterocyclylalkyl.

R_3 and R_4 are preferably independently H, or a substituted or unsubstituted aryl.

When n is 2 to 100, repeat units may be bonded to each other at both ends, and may be bonded by R_1 and R_2.

In the present specification, preferable examples of alkyl include methyl, ethyl, propyl, butyl and isomers thereof.

In the present specification, "heterocyclyl" means 5- to 10-membered saturated or unsaturated monocycle containing 1 to 4 hetero atoms (a nitrogen atom, a sulfur atom, an oxygen atom) or a fused ring thereof. For example, pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, piperidine, piperazine, pyrrolidine, pyrimidine, pyridazine, furan, pyran, thiophene, thiin, oxazole, isoxazole, thiazole, isothiazole, indole, isoindole, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, indazole, quinoline, isoquinoline, quinoxaline, quinazoline, cinnoline, benzooxazole, benzothiazole, benzoimidazole, chromene, indoline, isoindoline, dihydrobenzofuran, dihydrobenzothiophene, dihydroindazole, tetrahydroquinoline, tetrahydroisoquinoline, tetrahydroquinoxaline, tetrahydroquinazoline, tetrahydrocinnoline and the like can be mentioned.

Here, heterocyclylalkyl means the aforementioned alkyl moiety substituted by the aforementioned heterocyclyl moiety. Preferable examples of heterocyclylalkyl include 2-pyridylmethyl.

In the present specification, preferable examples of alkenyl include ethenyl, propenyl, butenyl, and isomers thereof and the like.

In the present specification, preferable examples of alkynyl include ethynyl, propynyl, butynyl, and isomers thereof and the like.

In the present specification, "cycloalkyl" means cyclic saturated hydrocarbon. Examples of cycloalkyl include 3- to 10-membered, preferably 5- or 6-membered, cycloalkyl such as cyclopentyl and cyclohexyl.

In the present specification, the "cycloalkenyl" means cyclic unsaturated hydrocarbon having 1 or 2 carbon-carbon double bonds.

Preferable examples of cycloalkenyl include 5- or 6-membered cycloalkenyl, for example, cyclopentenyl, cyclohexenyl and the like.

In the present specification, "aryl" means an atomic group obtained by removing one hydrogen atom from aromatic hydrocarbon. Examples of aryl include a substituted or unsubstituted phenyl, naphthyl, anthryl and the like.

In the present specification, "arylalkyl" means the aforementioned alkyl moiety substituted by 1 or plural aforementioned aryl moieties. Preferable examples of arylalkyl include benzyl and phenylethyl.

In the present specification, aryl of the "aryloxy" is as defined above. Preferable examples of aryloxy include phenoxy.

The aforementioned alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, aryloxy, heterocyclyl and heterocyclylalkyl may have substituent(s) at substitutable position(s). While the number of the substituents is not particularly limited, it is preferably 1 to 3. Specific examples of the substituent include halogen (e.g., fluorine, chlorine), optionally substituted hydroxy (e.g., hydroxy, alkoxy (e.g., methoxy, ethoxy)), optionally substituted methyl (e.g., methyl, trifluoromethyl), optionally substituted amino, carboxyl, optionally substituted phenyl (e.g., phenyl, naphthyl), thiol, optionally substituted amide (e.g., carbonamide), aminoalkylcarbonyl (e.g., aminoethylcarbonyl), thioalkyl (e.g., thiomethyl), and cyano. The optionally substituted amino may have substituent(s) at substitutable position(s). Specific examples of the substituent include aminoalkyl.

In the present specification, "lower alkylene" means straight chain or branched alkylene having a carbon number of 1 to 6, preferably 1 to 4, and preferably includes methylene, ethylene and propylene.

In the present specification, "aminoalkyl" means alkyl having an amino group, preferably aminoethyl.

In the present specification, the "fluorescence group" includes fluorescein such as fluorescein isothiocyanate (FITC) and the like, tetramethylrhodamine (TMeRH), cyanine (Cy2, Cy3, Cy5, Cy7 etc.), fluorescamine and the like. Particularly, FITC and TMeRH are preferable.

In the present specification, the aromatic group is a group derived from aromatic hydrocarbon and heterocycle showing aromatic property, and means a group derived from monocyclic aromatic series (monocyclic aromatic group) and a group derived from polycyclic aromatic series (polycyclic aromatic group). The monocyclic aromatic group means a substituted or unsubstituted phenyl or phenylene group. The phenylene group includes o-, m- and p-phenylene. Examples of the substituent include at least one substituent selected from the group consisting of halogen (e.g., fluorine, chlorine), halogenated C_1-C_4 alkyl, cyano, hydroxy, hydroxy C_1-C_4 alkyl, sulfanyl, amino, nitro, mono or di C_1-C_4 alkylamino, carboxyl, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, cycloalkyl (as defined above), cycloalkenyl (as defined above), C_1-C_4 alkylthio, C_1-C_4 alkoxy, aryl (as defined above), aryloxy (as defined above), amide and C_1-C_4 alkylamide, thiol and carbamoyl.

In the aforementioned groups, the C_1-C_4 alkyl moiety means a linear or branched alkyl group having a carbon number of 1 to 4 (e.g., methyl, ethyl, propyl, butyl).

In the aforementioned group, the C_1-C_4 alkoxy moiety means a linear or branched alkoxy group having a carbon number of 1 to 4 (e.g., methoxy, ethoxy).

In the aforementioned group, the C_2-C_4 alkenyl moiety means a linear or branched alkenyl group having a carbon number of 1 to 4 (e.g., ethenyl, propenyl, butenyl).

In the aforementioned group, the C_2-C_4 alkynyl moiety means a linear or branched alkynyl group having a carbon number of 1 to 4 (e.g., ethynyl, propynyl, butynyl).

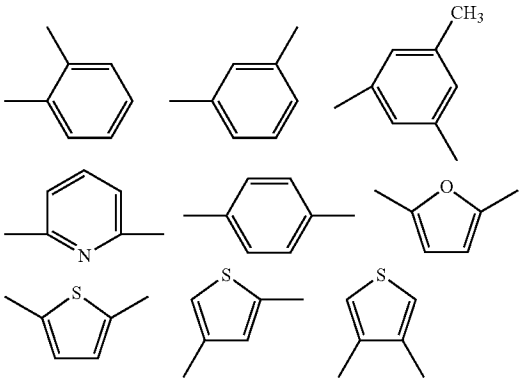
In the aforementioned group, the aryl moiety is as defined above.

In the aforementioned group, examples of the substituted phenyl include, but are not limited to, mono, di or trifluorophenyl, methoxyphenyl, tolyl, xylyl, o-chlorotolyl, trifluo-

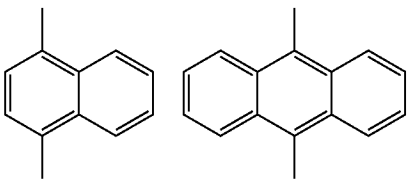
romethylphenyl, methoxyphenyl, tolyl, xylyl, o-chlorotolyl, trifluoromethylphenyl, 2-methoxy-5-fluorophenyl, hydroxymethylphenyl, phenoxyphenyl and the like. Examples of the substituted phenylene include, but are not limited to, 5-methyl-m-phenylene, 5-methyl-p-phenylene and the like. The polycyclic aromatic group means a fused polycyclic hydrocarbon group comprised of a fused ring of 2 to 6, preferably 2 or 3, of 5-membered and/or 6-membered monocyclic carbocycles. Examples include, but are not limited to, substituted or unsubstituted naphthyl, anthryl, phenanthryl, indenyl, fluorenyl and the like. Here, examples of the substituent include the same substituents as recited above. Examples of the aromatic heterocyclic group include a 5-membered ring containing one hetero atom such as a furanyl group, a thiophenyl group, a pyrrolyl group and the like, a 6-membered ring containing one hetero atom such as a pyridinyl group and the like, a 5-membered ring containing two hetero atoms such as an oxazolyl group, a thiazolyl group and the like, a 6-membered ring containing two hetero atoms such as a pyridazinyl group, a pyrimidinyl group and the like, and a 5- to 7-membered ring containing at least one hetero atom, a bicyclic condensed hetero group containing one hetero atom such as an indolyl group, a quinolinyl group and the like, a bicyclic condensed hetero group containing two hetero atoms such as a quinoxalinyl group and the like, a tricyclic condensed hetero group containing one hetero atom such as an acrydinyl group and the like, a bicyclic condensed hetero group containing two hetero atoms such as an indazolyl group and the like, and a polycyclic condensed hetero group containing at least one hetero atom, and the like.

In the present specification, a group of aliphatic series (aliphatic group) is a group derived from saturated hydrocarbon (alkane) and unsaturated hydrocarbon (alkene, alkyne).

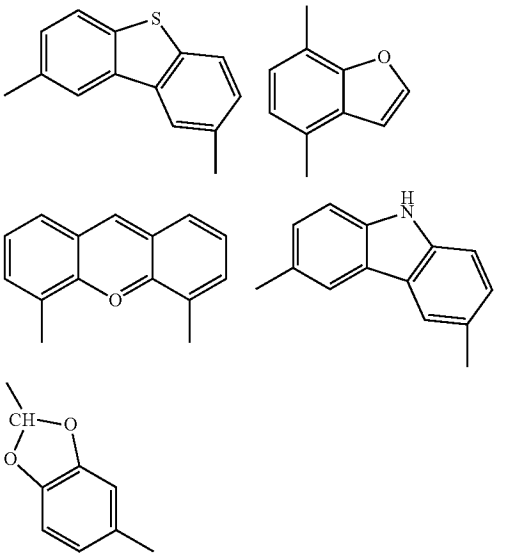
Particularly preferably, X, Y and W are groups containing aromatic series or aliphatic series, monocyclic aromatic groups, such as



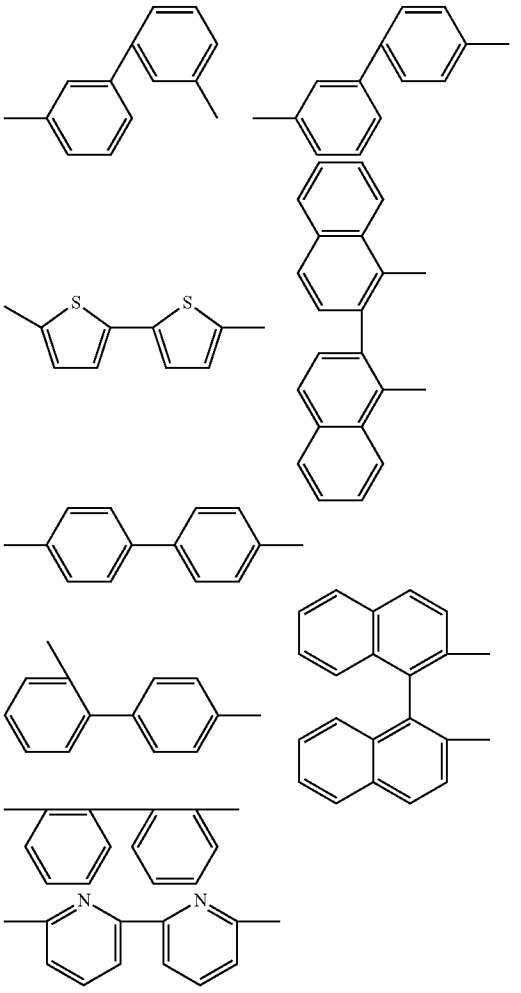
condensed aromatic groups having two or more rings, such as



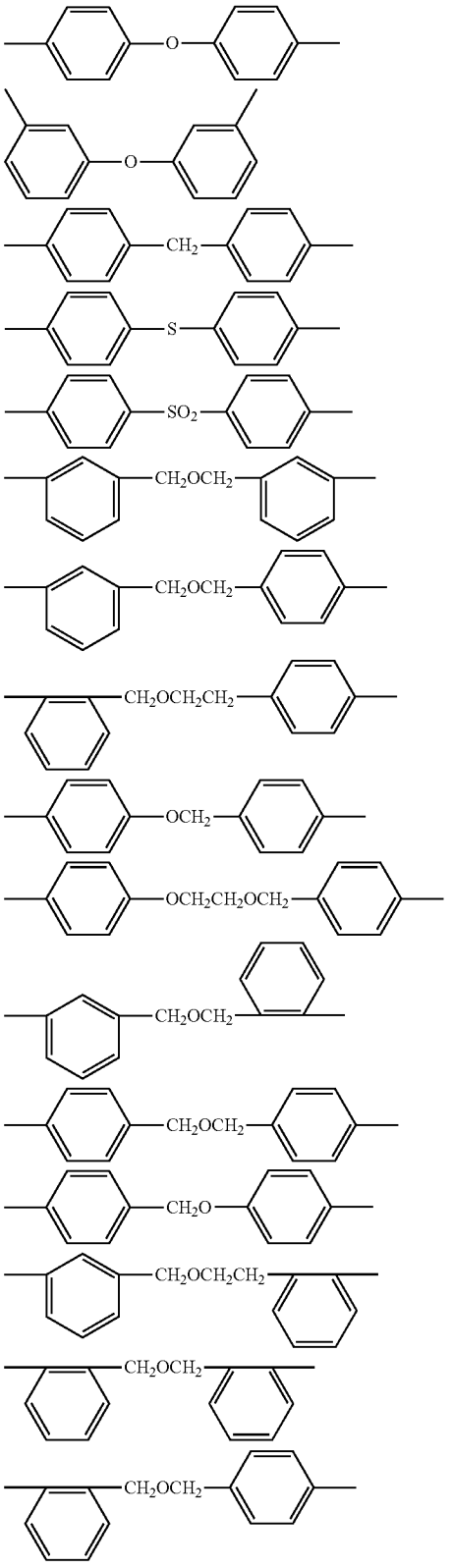
-continued



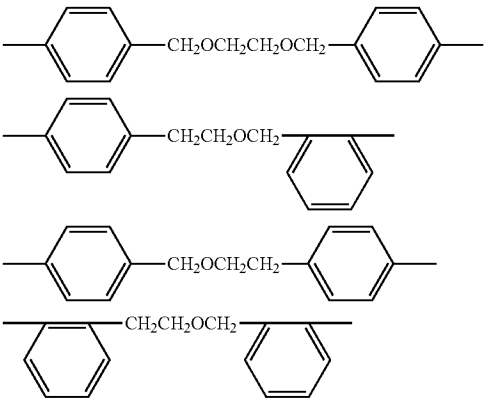
aromatic groups wherein two aromatic groups are directly bonded, such as



substituted or unsubstituted aromatic groups wherein two aromatic groups are bonded via O, CH_2, S, SO_2, CH_2OCH_2, OCH_2, $OCH_2CH_2OCH_2$, $OCH_2OCH_2CH_2$, $CH_2OCH_2CH_2$, $CH_2OCH_2CH_2OCH_2$ and the like, such as

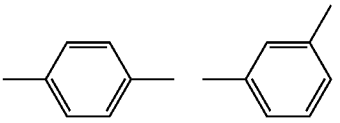


-continued

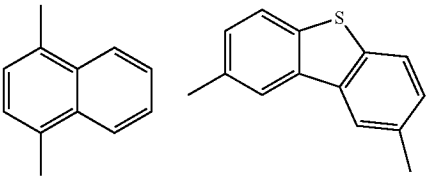


and substituted or unsubstituted aliphatic groups such as $(CH_2)_4$ can be mentioned.

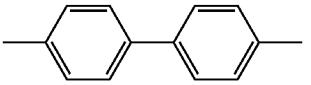
More preferably, as X, Y, W, monocyclic aromatic groups, such as



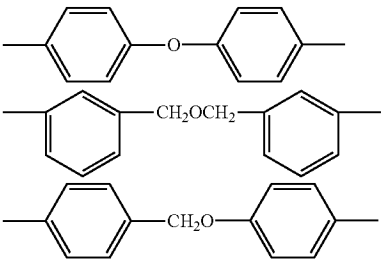
condensed aromatic groups having two or more rings, such as



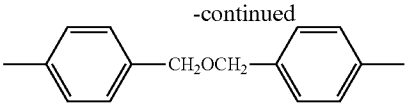
aromatic groups wherein two aromatic groups are directly bonded, such as



substituted or unsubstituted aromatic groups wherein an aromatic group is bonded via O, CH_2O, CH_2OCH_2 and the like, such as

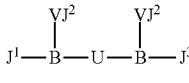


-continued

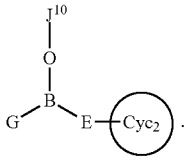


can be mentioned.

However the compound of the present invention excludes a compound represented by the following formula (Ia)



and a compound represented by the following formula (Ib)



In the formula (Ia), B is a boron atom, and V is an oxygen or sulfur atom. J^1 and J^3 are each independently a monocyclic aromatic group, a polycyclic aromatic group, or a heterocyclic group containing at least one hetero atom selected from an oxygen atom, a nitrogen atom and a sulfur atom.

J^2 is a hydrogen atom; $—(CH_2)_D—NJ^4J^5$ wherein D is an integer of 1-4, J^4 and J^5 are independently a hydrogen atom, or C_{1-4} alkyl substituted or unsubstituted by an amino group, a mono or di-C_{1-4} alkylamino group or a phenyl group, or J^4 and J^5 form, together with a nitrogen atom bonded thereto, a 5-membered or 6-membered cyclo ring); —CO—$(CH_2)J^5$ wherein D, J^4 and J^5 are as defined above); —$COCH(NH_2)J^6$ wherein J^6 is an amino acid residue, or $—(CH_2)_{D'}NH_2$ wherein D' is an integer of 1-3; $—CHJ^7J^6$ wherein J^7 and J^8 are independently an amino group, C_{1-4} alkyl substituted or unsubstituted by a mono or di(C_{1-4} alkyl substituted or unsubstituted by an amino group)amino group or phenyl group, or phenyl substituted by pyridyl or C_{1-3} alkoxy group; $—CH_2CH(NH_2)$-J^9 wherein J^9 is C_{1-4} alkyl substituted by phenyl or phenyl); quinolyl or isoquinolyl substituted by a C_{1-4} alkyl group; or C_{1-4} alkyl substituted by a pyridyl group, a piperidino group or a pyrrolidinyl group.

U is a monocyclic aromatic group, a polycyclic aromatic group or a heterocyclic group, which is the same as or different from J^1 and J^3, or a bifunctional group having a monocyclic aromatic group, a polycyclic aromatic group or a heterocyclic group bonded to both sides thereof via a group selected from the group consisting of a single bond, O, CH_2, S, SO_2, CH_2OCH_2, OCH_2, $OCH_2CH_2OCH_2$, $OCH_2OCH_2CH_2$ and $CH_2OCH_2CH_2$.

A compound represented by the formula (Ia) to be excluded from the compound of the present invention corresponds to a compound represented by the formula (I) disclosed in WO2007/061074. Therefore, the definition of each substituent (functional group) in the formula (Ia) follows the definition described in the publication.

In the formula (Ib), J^{10} is any of the following (1)-(6).

(1) a hydrogen atom.

(2) $—(CH_2)_{D''}—NJ^{11}J^{12}$.

In the group, D" is an integer of 1-3, J^{11} and J^{12} are each independently a hydrogen atom, C_{1-4} alkyl, C_{5-6} monocyclic carbocycle, C_{1-4} alkyl substituted by C_{5-6} monocyclic carbocycle, or 5- or 6-membered monocyclic heterocycle.

The carbon atom in $—(CH_2)_{D''}—$ is optionally substituted by 1 or 2 J^{13}, and the carbocycle and heterocycle are optionally substituted by 1 or 2 J^{16}. J^{13} is (a) C_{1-8} alkyl, (b) carboxyl, (c) alkoxycarbonyl, (d) keto, (e) C_{5-6} monocyclic carbocycle, (f) guanidino(C_{1-2})alkyl, (g) C_{1-6} alkyl substituted by C_{5-6} monocyclic carbocycle, (h) C_{1-2} alkyl substituted by 4-chlorophenoxy, or (i) C_{1-4} alkyl substituted by di(C_{1-4} alkylamino.

(3) C_{1-6} alkyl or C_{2-6} alkenyl substituted by C_{5-6} monocyclic carbo cycle.

The carbocycle is optionally substituted by 1 to 5 J^{16}, and the C_{1-6} alkyl or C_{2-6} alkenyl is optionally substituted by 1 or 2 J^{19}.

(4) C_{1-6} alkyl or C_{2-6} alkenyl substituted by 5- or 6-membered monocyclic heterocycle.

The heterocycle is optionally substituted by 1 to 5 J^{16}, and the C_{1-6} alkyl and C_{2-6} alkenyl are optionally substituted by 1 or 2 J^{19}. J^{19} is C_{1-4} alkyl or C_{2-4} alkenyl.

(5) $—CHJ^{14}J^{15}$.

In the group, J^{14} and J^{15} are each independently

(i) C_{5-6} monocyclic carbocycle,

(ii) 5- or 6-membered monocyclic heterocycle,

(iii) C_{1-6} alkyl or C_{2-6} alkenyl substituted by C_{5-6} monocyclic carbocycle, or

(iv) C_{1-6} alkyl or C_{2-6} alkenyl substituted by 5- or 6-membered monocyclic heterocycle.

Moreover, the carbocycle and heterocycle are optionally substituted by 1 to 5 J^{16}.

(6) 5,6,7,8-tetrahydroquinolin-8-yl.

J^{16} is (a) C_{1-4} alkyl, (b) C_{1-4} alkoxy, (c) a halogen atom, (d) $—CF_3$, (e) nitro, (f) C_{5-6} monocyclic carbocycle, (g) C_{1-4} alkyl substituted by C_{5-6} monocyclic carbocycle, (h) amino, (i) —NHCO(C_{1-4} alkyl), or (j) C_{1-4} alkoxycarbonyl.

G is Cyc_1 or hydroxy.

Cyc_1 is C_{5-10} monocyclic or bicyclic carbocycle, or 5- to 10-membered monocyclic or bicyclic heterocycle, the carbocycle and heterocycle are optionally substituted by 1 to 5 J^{17}.

Cyc_2 is C_{5-10} monocyclic or bicyclic heterocycle, or 5- to 10-membered monocyclic or bicyclic heterocycle. The carbocycle and heterocycle are optionally substituted by 1 to 5 J".

J^{17} and J^{18} are each independently

(a) C_{1-4} alkyl,

(b) C_{2-4} alkenyl,

(c) C_{1-4} alkoxy,

(d) a halogen atom,

(e) $—CF_3$,

(f) alkylthio,

(g) amino,

(h) (C_{1-4} alkyl)amino,

(i) di(C_{1-4} alkyl)amino,

(j) formyl,

(k) phenyl,

(l) phenoxy,

(m) hydroxy (C_{1-2}) alkyl,

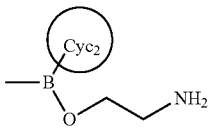
(n) (C_{5-10} monocyclic or bicyclic carbocycle)-O—(C_{1-2}) alkyl,

(o) C_{1-4} alkoxycarbonylvinyl,

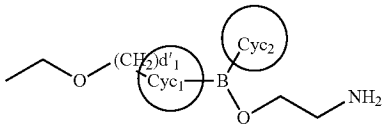
(p) C_{1-2} alkyl substituted by group(s) selected from —O—(C_{1-2} alkylene)-phenyl (said phenyl is optionally substituted by 1 to 3 C_{1-4} alkoxy), —O—CONH-phenyl (said phenyl is optionally substituted by 1 to 3 C_{1-4} alkyl, nitro or C_{1-4} alkoxycarbonyl), or —O—CONH—(C_{1-4})alkyl (said alkyl is optionally substituted by 1 to 3 C_{1-4} alkyl, carboxyl or C_{1-4} alkoxycarbonyl),

(q) phenylthio,
(r) —CON(C_{1-4} alkyl)$_2$,
(s) —SO_2N(C_{1-4} alkyl)$_2$,
(t) C_{1-4} alkoxy (C_{1-2}) alkyl,
(u) C_{1-4} alkoxycarbonyloxy (C_{1-2}) alkyl,

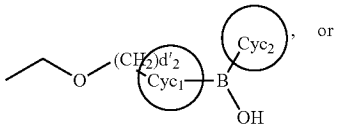
(v)



(w)

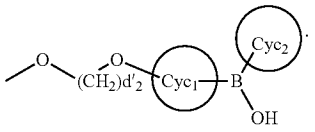


(x)



, or

(y)



.

The carbocycle, phenyl, Cyc_1 and Cyc_2 in J^{17} and J^{18} are optionally substituted by 1 or 2 J^{16}, or J^{17} and J^{18} optionally show —O—, and further, J^{18} and J^{19} optionally show a single bond.

d'_1 is an integer of 1-4, d'_2 is an integer of 1-4, and d'_3 is an integer of 1-4. E is a single bond or C_{1-4} alkylene substituted or unsubstituted by C_{5-6} monocyclic carbocycle.

A compound represented by the formula (Ib) to be excluded from the compound of the present invention corresponds to a compound represented by the formula (I) disclosed in WO03/033002. Therefore, the definition of each substituent (functional group) in the formula (Ib) follows the definition described in the publication.

The compounds of the aforementioned (1)-(13) in the present invention specifically include the following.

2-aminoethylthio bis(4-chloro-2-fluorophenyl)borane
(4-(phenylglutamineboryl)phenyl) (4'-(phenylhydroxyboryl) phenyl)ether
bis(4,4'-(phenylhydroxyboryl)phenyl)ether
poly(4,4'-biphenylene N-methylaminoethoxyborane)
bis(4,4'-(phenylaminoethoxyboryl)phenyl)ether
(4-(phenylasparagineboryl)phenyl)(4'-(phenylhydroxyboryl)phenyl)ether
bis(3,3'-(phenylhydroxyboryl)benzyl)ether
bis(3,3'-(phenylaminoethoxyboryl)benzyl)ether
4,4'(phenyl-2-aminoethylthioboryl)diphenyl
4,4'(phenyl-2-aminoethoxyboryl)diphenyl
poly(2,5-dimethoxy-4-phenylborinic acid)
poly(aminoethyl-2,5-dimethoxy-4-phenylborinate)
poly(1,4-phenylenemethyleneoxymethylene 1,4-phenylene hydroxyborane)
poly(1,4-phenylenemethyleneoxymethylene 1,4-phenylene 2-aminoethoxyborane)
poly(4,4'-phenylenemethyleneoxymethylene 4,4'-phenylene-dimethylaminoethoxyborinic acid)
poly(1,4-phenylenemethyleneoxymethylene 1,4-phenylene 2-piperidinomethoxyborane)
poly(1,4-phenyleneoxy-1,4-phenylenehydroxyborane)
poly(aminoethoxyboryldiphenylether)
poly(isopropoxyboryldiphenylether)
poly(4,4'-diphenylether dimethylaminoethoxyborane)
poly(4,4'-diphenylether-2-pyridyl-4-trifluoromethylphenyl-methoxyborane)
poly(4,4'-diphenylether-2-aminoethylthioborane)
poly(phenylenemethyleneoxyphenylenehydroxyborane)
poly(phenylenemethyleneoxyphenyle-neaminoethoxyborane)
poly(phenylenemethyleneoxyphenyle-neaminoethylthioborane)
poly(phenylenemethyleneoxyphe-nylenedimethylaminoethoxyborane)
poly(4'-phenylhydroxyboranephenylen-emethyleneoxyphenylenehydroxyborane phenylenemeth-yleneoxymethylene)
poly(phenylenemethyleneoxyphenyle-neaminoethoxyboranephenylene-methyleneoxymethyl-enephenylene aminoethoxyborane)
poly(phenylenemethyleneoxyphenyle-nemethylaminoethoxyborane-phenylenemethyleneoxym-ethylenephenylenemethylaminoethoxyborane)
poly(4,4'-biphenylene-hydroxyborane 1,4-phenylenemeth-yleneoxymethylenephenylenehydroxyborane)
poly(4,4'-biphenylene 2-aminoethoxyborane 1,4-phenylene-methyleneoxymethylene 1,4-phenylene 2-aminoethox-yborane)
di(3-chloro-4-methylphenyl)-2-aminoethylthioborane
poly(2,5-dimethoxy-4-phenylene-hydroxyborane-1,4-phe-nylenehydroxyborane)
polyaminoethyl(2,5-dimethoxy-4-phenylene)aminoethoxy-boryl(1,4-phenylene)borinate
poly(2-pyridylmethyl(2,5-dimethoxy-4-phenylene) 2-py-ridylmethoxyborane-(1,4-phenylene)borinate)
poly(4,4'-biphenylene-hydroxyborane 4,4'-diphenylether hydroxyborane)
poly(4,4'-biphenylene-dimethylaminoethoxyborane 4,4'-diphenylether dimethylaminoethoxyborane)
poly(4,4'-biphenylene-aminoethoxyborane-4,4'-diphe-nylether aminoethoxyborane)
poly(phenyleneaminoethoxyborane diphenylether-aminoet-hoxyborane)
poly(phenyleneaminoethylthioborane diphenylether-amino-ethylthioborane)
poly(phenylene 2-piperazinomethoxyborane diphenylether 2-piperidinomethoxyborane)
poly(methylaminoethoxyborylphenylene methylaminoet-hoxyboryldiphenylether)
poly(pyrrolidinomethoxyborylphenylene pyrrolidi-nomethoxyboryldiphenylether)
poly(aminoethylaminoethoxyborylphenylene aminoethy-laminoethoxyboryldiphenylether)
poly(metaphenylene-hydroxyborane-4,4'-diphenyletherhy-droxyborane)
poly(metaphenylene-2-piperidinemethoxyborane-4,4'-diphenylether-2-piperidinemethoxyborane)
poly(metaphenylene-aminoethoxyborane-4,4'-diphenylether aminoethoxyborane)
poly(mataphenylene-methylaminoethoxyborane-4,4'-diphe-nylethermethylaminoethoxyborane)
poly(metaphenylene-2-dimethylaminoethoxyborane-4,4'-diphenylether-2-dimethylaminoethoxyborane)

poly(metaphenylene-2-pyridyl-trifluoromethylphenyl-methoxyborane-4,4'-diphenylether-2-pyridyl-trifluoromethylphenylmethoxyborane)
poly(metaphenylene-aminoethylthioborane-4,4'-diphenylether-aminoethylthioborane)
poly(4,4'-diphenyletherhydroxyborane phenylenemethyleneoxyphenylenehydroxyborane)
poly(phenylenemethyleneoxyphenylene-aminoethoxyborane-4,4'-diphenyletheraminoethoxyborane)
poly(phenyleneoxyphenylene-2-pyrrolidinemethoxyborylphenylenemethyleneoxyphenylene-2-pyrrolidinemethoxyborane)
poly(phenylenemethyleneoxyphenylene-dimethylaminoethoxyborane-4,4'-diphenylether dimethylaminoethoxyborane)
poly(phenylenemethyleneoxyphenylene-2-pyridylmethoxyborane-4,4'-diphenylether-2-pyridylmethoxyborane)
poly(4,4'-biphenylene-aminoethoxyborane-1,4-phenylene-methyleneoxy-1,4-phenylene-aminoethoxyborane)
poly(4,4'-biphenylene-dimethylaminoethoxyborane-1,4-phenylene-methyleneoxyphenylenedimethylaminoethoxyborane)
poly(4,4'-biphenylene-2-pyridylmethoxyborane-1,4-phenylene-methyleneoxy-1,4-phenylene-2-pyridylmethoxyborane)
poly(4,4'-biphenylene-2-hydroxyethylaminoethoxyborane-1,4-phenylene-methyleneoxy-1,4-phenylene-2-hydroxyethylaminoethoxyborane)
poly(4,4'-phenylene-methyleneoxymethylene-phenylene-hydroxyborane-4,4'-phenyleneoxyphenyleneborinic acid)
poly(phenylene-methyleneoxymethylene-phenylene-aminoethoxyborane-phenyleneoxyphenyleneaminoethoxyborane)
poly(phenylene methyleneoxymethylene phenylene dimethylaminoethoxyborane phenylene oxy phenylene dimethylaminoethoxyborane)
poly(phenylene methyleneoxymethylene phenylene aminoethylthioborane phenylene oxy phenylene aminoethylthioborane)
poly(diphenylene-methylaminoethoxyboryl-1,4-phenylene-methyleneoxymethylenephenylene-methylaminoethoxyborane)
poly(1,4-phenylene-methyleneoxymethylenephenylenemethylaminoethoxyborane-1,4-phenylene-methylaminoethoxyborane)
poly(1,4-phenylene-methyleneoxymethylenephenylene-aminoethylaminoethoxyborane-1,4-phenylene-aminoethylaminoethoxyborane)
polytetramethyleneborinic acid
2-dimethylaminoethyl bis(4-trifluoromethylphenyl)borinate
1,3-dimethylaminopropyl bis(3-chloro-4-methylphenyl) borinate
di(3-chloro-4-methylphenyl)(2,3-diaminopropionate-O,N) borane
di(3-chloro-4-methylphenyl)piperazinoethoxyborane
di(3-chloro-4-methylphenyl)piperidinoethoxyborane
di(3-chloro-4-methylphenyl)-2-piperidinoethoxyborane
bis(4-trifluoromethylphenyl)borinic acid
di(3-fluoro-4-chlorophenyl)borinic acid
2-aminoethyl-bis(3-chloro-4-fluorophenyl)borinate
2-dimethylaminoethyl bis(3-chloro-4-fluorophenyl)borinate
bis(4-chloro-2-fluorophenyl)borinic acid
bis(3,4-difluorophenyl)borinic acid
bis(3,4,5-trifluorophenyl)borinic acid
bis(2,4-difluorophenyl)borinic acid
bis(3-fluoro-4-chlorophenyl)borinic acid
2-aminoethyl bis(4-chloro-2-fluorophenyl)borinate
poly(4,4'-biphenylhydroxyborane)
2-aminoethyl bis(3-chloro-4-fluorophenyl)borinate
2-aminoethyl bis(3,4-difluorophenyl)borinate
2-amino-1-phenylethyl bis(3,4-difluorophenyl)borinate
aminoethyl bis(3,4,5-trifluorophenyl)borinate
2-pyridylmethyl bis(3,4,5-trifluorophenyl)borinate
aminoethyl bis(3,5-difluorophenyl)borinate
dimethylaminoethyl bis(3,5-difluorophenyl)borinate
aminoethyl bis(4-chloro-3-fluorophenyl)borinate
dimethylaminoethyl bis(4-chloro-3-fluorophenyl)borinate
di(3-fluoro-4-chlorophenyl)(2,4-diaminolactonate-O,N)borane
di(3-fluoro-4-chlorophenyl)(glutaminate-O,N)borane
bis(3-chloro-5-fluorophenyl)borinic acid
bis(3-chloro-6-fluorophenyl)borinic acid
aminoethyl bis(3-chloro-5-fluorophenyl)borinate
aminoethyl bis(3-chloro-6-fluorophenyl)borinate
methylaminoethyl bis(3-chloro-6-fluorophenyl)borinate
bis(4-cyanophenyl)borinic acid
aminoethyl bis(4-cyanophenyl)borinate
2-pyridylmethyl bis(4-cyanophenyl)borinate
benzylaminoethyl bis(4-cyanophenyl)borinate
2-aminoethylthio bis(4-cyanophenyl)borane
secondary-butyl phenyl borinic acid
normal-butyl phenyl borinic acid
tertiary-butyl phenyl borinic acid
aminoethyl secondary-butyl phenylborinate
aminoethyl tertiary-butyl phenylborinate
aminoethyl normal-butyl phenylborinate
1,4-bis(hydroxyphenylboryl)butane
4-hydroxybutylphenylborinic acid
bis(4-chlorophenyl)borinic acid
bis(di(3-chloro-4-methylphenyl)boryloxyethyl)piperazine
bis(3-chloro-4-methylphenyl 2-pyridylmethoxyborylphenyl)ether
1,4-bis(phenyl-2-aminoethoxyboryl)benzene
1,3-bis(phenyl-2-aminoethoxyboryl)benzene
1,3-bis(phenylhydroxyboryl)benzene
diphenyl(argininate-O,N)borane
diphenyl(glutaminate-O,N)borane
(2-phenylhydroxyborylbenzyl)(3-(phenylhydroxyboryl) benzyl)ether
bis(3-chloro-4-methylphenyl hydroxyborylbenzyl)ether
bis(phenyl 2-pyridyl-4-methoxyphenylmethoxyborylbenzyl)ether
bis(3-chloro-4-methylphenyl) 2-pyridyl-4-methoxyphenylmethoxyborane
1,4-bis(3-chloro-4-methylphenyl-2-aminoethoxyboryl)benzene
di((phenylglycine-O,N boryl)phenyl)ether
1,3,5-tri(phenylhydroxyboryl)benzene
bis((4,4'-phenylaminoethoxyboryl)benzyl)ether
1,3,5-tri(2-pyridyl-4-trifluoromethylphenylmethoxyphenylboryl)benzene
(2-pyridyl-phenylmethoxyphenylboryl 2-benzyl)ether
(2-pyridyl-4-trifluoromethylphenylmethoxyphenylboryl 2-benzyl)ether
1,4-bis(phenylhydroxyboryl)naphthalene diphenyl(asparaginate-O,N)borane
bis((4,4'-phenylhydroxyboryl)benzyl)ether
bis(2-pyridyl-4-trifluoromethylphenylmethoxyphenylboryl 4-benzyl)ether
bis(4-chloro-3-methylphenylhydroxyboryl 4-benzyl)ether
4,4'-phenylhydroxyboryl 4-biphenyl
bis(4,4'-(1-naphthylhydroxyboryl)benzyl)ether
bis(4-fluorophenylhydroxyboryl 4-benzyl)ether
bis(4-trifluoromethylphenylhydroxyboryl 4-benzyl)ether

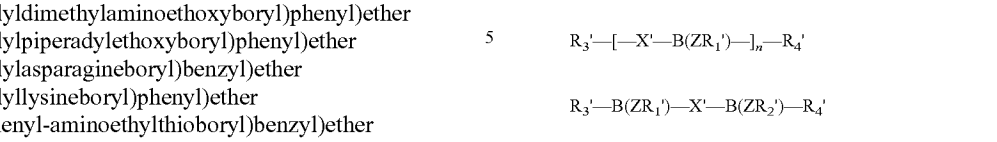
bis(3-chloro-4-methylphenylhydroxyboryl 4-benzyl)ether
(3-chloro-4-fluorophenyl)boronic acid
1,4-bis(phenyl-2-aminoethoxyboryl) 2-methylbenzene 1,2-bis(phenylhydroxyboryl)benzene
bis(2,2'-(phenyl-2-aminoethoxyboryl)benzyl)ether
diphenyl-2-aminophenylthioborane
2-aminoethylthiodiphenylborane
di(4,4'-phenyldimethylaminoethoxyboryl)benzylether
poly(4,4'-biphenylene-2-pyridyl-4-trifluoromethylphenyl-methoxyborane
4,4'-diphenylether 2-pyridyl-4-trifluoromethoxyborane)
diphenyl 2-aminoethylaminoethyl borinate
di(trifluoromethylphenyl) 2-pyridinomethylborinate
di(3-chloro-6-methyl-phenyl)(argininate-O,N)borane
poly(phenylenemethyleneoxyphenyle-neaminoethoxyborane)
poly(phenylenemethyleneoxyphenyle-neaminoethylthioborane)
dibutyl(alanine-O,N)borane
di(3-chloro-6-methyl-phenyl)(citrullinate-O,N)borane
FITC aminoethylaminoethyl diphenylborinate
tetramethylrhodamine aminoethylaminoethyl diphenylborinate
di(3-chloro-4-methylphenyl)N-methylpiperidinomethyl-borinate
di(3-chloro-6-methylphenyl)benzylaminoethylborinate
poly(4,4'-biphenylene-methylaminoethoxyborane 1,4-phenylene methyleneoxymethylenephenylene-methylamino-ethoxyborane)
(4-(phenyl-dimethylaminoethoxyboryl)phenyl)-(4'-(meth-oxymethoxymethylphenyl-dimethylaminoethoxyboryl) phenyl)ether
(4-(phenyl-N-methylaminoethoxyboryl)phenyl)-(4'-(meth-oxymethoxymethylphenyl-N-methylaminoethoxyboryl) phenyl)ether
di((phenylglycine-O,N boryl)phenyl)ether
diphenyl(glycylglutamine-O,N)borane
di(3-chloro-6-methylphenyl)borinic acid
bis(3,3'(phenyldimethylaminoethoxyboryl)benzyl)ether
(3,3'-(phenylpiperazino-O,O-ethoxyboryl)benzyl)ether
diphenyl(2,3-diaminopropionate-O,N)borane
diphenyl(tetramethylrhodamine 2,3-diaminopropionate-O,N)borane
diphenyl(tetramethylrhodamine 2,6-diaminocapronate-O,N) borane
diphenyl(FITC-2,6-diaminocapronate-O,N)borane
diphenyl(2,3-diaminobutyrate-O,N)borane
diphenyl(2,5-diaminopentanate-O,N)borane
di(3-chloro-4-methylphenyl)(anthranate-O,N)borane
di(trifluoromethylphenyl) 2-aminoethylborinate
di(3-chloro-4-methylphenyl)(glutaminate-O,N)borane
dibutyl(asparagine-O,N)borane
di(4-(phenyl-2-pyridylmethoxyboryl)benzyl)ether
di(1-(pyridin-2-yl)-1-(4-methoxyphenyl)methyl-phenyl-borylbenzyl)ether
bis((4,4'-phenylhydroxyboryl)benzyloxybenzyl)hydroxyborane
di(trifluoromethylphenyl) 2-propylaminoethylborinate
bis((4,4'-phenylaminoethoxyboryl)benzyloxybenzyl)amino-ethoxyborane
bis((4,4'-phenyl methylaminoethoxyboryl)benzyloxybenzyl)methylaminoethoxyborane
bis((4,4'-phenyldimethylaminoethoxyboryl)benzyloxybenzyl)dimethylaminoethoxyborane
bis((4,4'-phenyl 2-pyridyl-4-trifluoromethylphenylmethoxyboryl)benzyloxybenzyl) 2-pyridyl-4-trifluoromethyl phenylmethoxyborane
diphenyl(2-piperazine-3-carboxyamide-carboxy)borane
diphenyl(methionate-O,N)borane
phenyl 3-piperidinooxyboryl phenylether
4,4'-(phenyl piperazino-O,O-ethoxyboryl)phenylether
4,4'-(phenyl piperazino-O,O-ethoxyboryl)benzylether
bis(4,4'-(phenyldimethylaminoethoxyboryl)phenyl)ether
bis(3,3'-(phenylbenzylaminoethoxyboryl)phenyl)ether
di(3-chloro-2-methylphenyl)borinic acid
4,4'-di((3-chloro-4-methylphenyl 2-hydroxyboryl)phenyl) ether
phenyl naphthyl 2-pyridylmethylborinate
phenyl naphthyl dimethylaminoethylborinate
phenyl naphthyl benzylaminoethylborinate
bis(4,4'-(phenyl 2-amino-2-benzylethoxyboryl)benzyl)ether
bis(3,3'-(phenyldimethylaminoethoxyboryl)benzyl)ether
di(3-chloro-4-methylphenyl)dimethylaminoethylborinate
di(3-chloro-4-methylphenyl)-2-benzyl-2-aminoethylborinate
di(3-chloro-4-methylphenyl)1-phenyl 2-aminoethylborinate
di(3-chloro-4-methylphenyl)butylaminoethyl borinate
di(3-chloro-4-methylphenyl)benzylaminoethyl borinate
diphenyl(R) 2-benzyl-2-aminoethyl borinate
diphenyl(S) 2-benzyl-2-aminoethyl borinate
di(3-chloro-4-methylphenyl) 1-phenylaminoethylborinate
di(3-chloro-4-methylphenyl)pyridylmethylborinate
di(3-chloro-4-methylphenyl)borinic acid anhydride
diphenylborinic acid anhydride
diphenyl(picolinate-O,N)borane
diphenyl(2-aminophenyl carboxylate-O,N)borane
di(3-chloro-4-methylphenyl) 2-aminophenylborinate
di(3-chloro-4-methylphenyl)(2-pyridine carboxylate-O,N) borane
poly(4,4'-diphenylether glutamine-O,N)borane
poly(4,4'-diphenyl glutamine-O,N borane)
diphenyl 1-(2-aminobenzyl) 1-phenylmethylborinate
di(3-chloro-4-methylphenyl) 1-(2-aminobenzyl) 1-phenylmethylborinate
diphenyl(2-aminohexanecarboxylate-O,N)borane
di(3-chloro-4-methylphenyl)(norloysinate-O,N)borane
diphenyl 2-aminobutylborinate
di(3-chloro-4-methylphenyl) 2-aminobutylborinate
di(trifluoromethylphenyl)borinic acid
di(3-chloro-4-methylphenyl)borinic acid
di(trifluoromethylphenyl) 2-aminoethylborinate
di(trifluoromethylphenyl) 2-dimethylaminoethylborinate
di(4-chloro-3-fluoro-phenyl) 2-aminoethylborinate
di(4-chloro-2-fluorophenyl) 2,3-diamino-2-propyl-borinate
di(4-chloro-3-fluorophenyl) 2-amino-2-methyl-propyl-borinate
di(4-chloro-3-fluorophenyl) 2-phenylaminoethyl borinate
di(4-chloro-3-fluorophenyl) 2-amino-3-hydroxybutyl borinate
bis(diphenyl piperazino-O,O-ethoxyborane)
4-((2-aminoethoxy)phenylboryl)benzyl-4'-((2-aminoethoxy)phenylboryl)phenethylether
di(3-chlorophenyl)borinic acid
di(5-chloro-2-methylphenyl) 2-piperidinomethylborinate
di((5-chloro-2-methylphenyl)hydroxyborylphenyl)ether
di(5-chloro-2-methylphenyl) 2-aminoethylborinate
diphenyl(ornithine-O,N)borane
di(5-chloro-2-methylphenyl) 2-butylaminoethylborinate
di(3-chloro-4-methylphenyl) 2-piperidinomethylborinate
di(3-chloro-4-methylphenyl) 2-piperidinoethylborinate
4,4'-((2-aminoethoxy)(3-chloro-4-methylphenyl)boryl) diphenylether
bis(4,4'-(phenyldimethylaminoethoxyboryl)phenyl)ether
bis(3-chloro-4-methylphenyl hydroxyborylphenyl)ether

1,4-bis(phenylhydroxyboryl)benzene
di(2-thiophene)borinic acid
diphenyl(glycinate-O,N)borane
diphenyl(serinate-O,N)borane
diphenyl(glutaminate-O,N)borane
diphenyl(asparaginate-O,N)borane
diphenyl(alaninate-O,N)borane
diphenyl(phenylalaninate-O,N)borane
diphenyl(tryptophanate-O,N)borane
diphenyl(leucinate-O,N)borane
diphenyl(isoleucinate-O,N)borane
diphenyl(2,4-diaminolactonate-O,N)borane
diphenyl(tyrosinate-O,N)borane
diphenyl(threoninate-O,N)borane
diphenyl(cysteinate-O,N)borane
diphenyl(histidinate-O,N)borane
diphenyl(hydroxyprolinate-O,N)borane
diphenyl(glutaminate-O,N)borane
diphenyl(asparaginate-O,N)borane
diphenyl(lysinate-O,N)borane
diphenyl(2,3-diaminopropionate-O,N)borane
bis(4,4'-(phenyl-glutamineboryl)phenyl)ether
bis(4,4'-(phenylasparagineboryl)phenyl)ether
(4-(phenyl-glutamic acid boryl)phenyl)-(4'-(hydroxymethylphenyl-glutamic acid boryl)phenyl)ether
diphenyl(glutaminate-O,N)borane
diphenyl(prolinate-O,N)borane
(3-phenoxybenzyl)-(3'-(phenyl-2-aminoethoxyboryl)benzyl)ether
diphenyl(2-piperazinecarboxy)borane
diphenyl(2,4-diaminolacetic acid)borane
di(3-chloro-4-methylphenyl)-(picolinate-O,N)borane
di(3-chloro-4-methylphenyl)(asparaginate-O,N)borane
di(3-chloro-4-methylphenyl) 2-aminophenylthioborane
di(4-trifluoromethylphenyl)(picolinate-O,N)borane
di(4-trifluoromethylphenyl) 2-aminoethylthioborane
di(3-chloro-4-methylphenyl)(2,6-diaminopimelinate-O,N)borane
di(3-chloro-4-methylphenyl)(citrullinate-O,N)borane
di(3-chloro-4-methylphenyl)(glycylglutaminate-O,N)borane
di(4-trifluoromethylphenyl)(1,3-propylenediaminediacetate-O,N)borane
di(4-trifluoromethylphenyl)(glycylglycinate-O,N)borane
di(3-chloro-4-methylphenyl)(allothreoninate-O,N)borane
di(3-chloro-4-methylphenyl)(norloysinate-O,N)borane
di(3-chloro-4-methylphenyl)(2,4-diaminobutyrate-O,N)boranediphenyl dimethylaminoethylthioborane
di(3-chloro-4-methylphenyl)dimethylaminoethylthioborane
(4-(2-thiophenehydroxyboryl)phenoxyethyl)(4'-(2-thiophenehydroxyboryl)benzyl)ether
1,2-di(phenylhydroxyboryl)benzene
1,2-di(phenylaminoethoxyboryl)benzene
poly(2,5-dimethylphenyl asparagine-O,N borane)
poly(phenylene 2-aminoethylaminoethoxy borane)
poly(phenylene 2-pyridylmethoxy borane)
poly(1,4-phenylenehydroxyboryl-1,3-phenyleneborinic acid)
poly(1,4-phenylene aminoethoxyboryl-1,3-phenyleneaminoethoxyborane)
2,8-di(3-thiophenylglutamine-O,N boryl)dibenzothiophene
4,4'-(dicyano-phenyl)borinic acid
3,3'-(dicyano-phenyl)borinic acid
diphenyl(citrullinate-O,N)borane
diphenyl(ornithinate-O,N)borane
poly(1,2-phenylene-hydroxyborane)
poly(2,5-dimethyl-1,4-phenylene-hydroxyborane)
poly(2-methyl-1,3-phenylene-hydroxyborane)
poly(2,8-dibenzothiophenylene-hydroxyborane)
poly(2,2'-biphenylene-hydroxyborane)
poly(1,4-naphthalene-hydroxyborane)
poly(9,10-anthracene-hydroxyborane)
poly(3,6-carbazole-hydroxyborane)
poly(5-methyl-1,3-phenylene-hydroxyborane)
poly(5,5'-bithiophene-hydroxyborane)
poly(2,2'-binaphthyl-hydroxyborane)
poly(4,4'-biphenylene aminoethoxyborane)
poly(4,4'-biphenylene N-hydroxyethylaminoethoxyborane)
bis(4,4'-(3-chloro-4-methylphenylhydroxyboryl)benzyl)ether
poly(4-phenylborinic acid)
naphthaleneboronic acid
bis(4-(4-trifluoromethylphenylhydroxyboryl)benzyl)ether
poly(2,5-dimethylphenyl aminopropoxyborane)
poly(2,5-dimethylphenyl aminopropylthioborane)
bis(3-(4-methoxyphenylhydroxyboryl)benzyl)ether
(3-(phenylhydroxyboryl)benzyl) (4-(phenylhydroxyboryl)benzyl)ether
(2-(phenylhydroxyboryl)benzyl) (3-(phenylhydroxyboryl)benzyl)ether
(2-(phenylhydroxyboryl)benzyl) (4-(phenylhydroxyboryl)benzyl)ether
(3-(phenylaminoethoxyboryl)benzyl) (4-(phenylaminoethoxyboryl)benzyl)ether
bis(3-(3-chloro-4-methylphenylhydroxyboryl)benzyl)ether
(2-(phenylaminoethoxyboryl)benzyl) (3-(phenylaminoethoxyboryl)benzyl)ether
(2-(phenylaminoethoxyboryl)benzyl) (4-(phenylaminoethoxyboryl)benzyl)ether
bis(3-(4-fluorophenylhydroxyboryl)benzyl)ether
bis(3-(4-fluorophenylaminoethoxyboryl)benzyl)ether
bis(4-(4-chloro-3-methyl-phenyl)hydroxyborylbenzyl)ether
bis(4-(4-chloro-3-methyl-phenylaminoethoxyborylbenzyl)ether
bis(3-(3',4'-methylenedioxy-phenylhydroxyboryl)benzyl)ether
(3-(3-chloro-4-methylphenylhydroxyboryl)benzyl) (4-(3-chloro-4-methylphenylhydroxyboryl)benzyl)ether
(3-(3',4',5'-trifluorophenylhydroxyboryl)benzyl)(4-(3',4',5'-trifluorophenylhydroxyboryl)benzyl)ether
bis(3-(4-methoxyphenylaminoethoxyboryl)benzyl)ether
(3-(4-chloro-3-methylphenylhydroxyboryl)benzyl)(2-(4-chloro-3-methylphenylhydroxyboryl)benzyl)ether
bis(3-(4-cyanophenylhydroxyboryl)benzyl)ether
bis(3-(2'-thiophenylhydroxyboryl)benzyl)ether
bis(3-(1'-naphthylhydroxyboryl)benzyl)ether
bis(4-(2-methoxy-5-fluorophenylhydroxyboryl)benzyl)ether
bis(4-(2-methoxy-5-fluorophenylaminoethoxyboryl)benzyl)ether
(3-(4-chloro-3-methyl-phenylaminoethoxyboryl)benzyl)(2-(4-chloro-3-methyl-phenylaminoethoxyboryl)benzyl)ether
bis(4-(3,4-difluorophenylhydroxyboryl)benzyl)ether
bis(4-(3,4-difluorophenylaminoethoxyboryl)benzyl)ether
(3-(3',4',5'-trifluorophenylaminoethoxyboryl)benzyl)(4-(3',4',5'-trifluorophenylaminoethoxyboryl)benzyl)ether
5,5'-(phenylhydroxyboryl)-2,2'-dithiophene
5,5'-(phenylaminoethoxyboryl)-2,2'-dithiophene
3,5-di(phenylaminoethoxyboryl)toluene
2,5-di(phenylhydroxyboryl)toluene
2,2'di(phenylhydroxyboryl)-1,1'-binaphthyl
2,2'-di(phenylaminoethoxyboryl)-1,1'-binaphthyl
bis(4-(4-methylphenylhydroxyboryl)benzyl)ether

bis(4-(4-methylphenylaminoethoxyboryl)benzyl)ether
4,4'-(4-methylphenylhydroxyboryl)diphenyl
4,4'-(4-methylphenylaminoethoxyboryl)diphenyl
4,4'-(4-methylphenylhydroxyboryl)diphenylether
poly(2,5-dimethylphenyl 2-pyridylmethoxyborane)
4,4'-bis(3-chloro-4-methyl-phenylhydroxyboryl)diphenylether
(2-(phenylhydroxyboryl)phenethyl)((2-phenylhydroxyboryl)benzyl)ether
(2-(phenylaminoethoxyboryl)phenethyl)((2-phenylaminoethoxyboryl)benzyl)ether
(4-phenylhydroxyborylphenyl)(4'-phenylhydroxyborylbenzyl)ether
(4-phenylaminoethoxyborylphenyl)(4'-phenylaminoethoxyborylbenzyl)ether
(4-trifluoromethylphenylhydroxyborylphenyl)(4'-trifluoromethylphenylhydroxyborylbenzyl)ether
(4-trifluoromethylphenylaminoethoxyborylphenyl)(4'-trifluoromethylphenylaminoethoxyborylbenzyl)ether
9,10-bis-(trifluoromethylphenylhydroxyboryl)anthracene
9,10-bis-(trifluoromethylphenylaminoethoxyboryl)anthracene
bis(3-(1-naphthylaminoethoxyboryl)benzyl)ether
4,5-di(phenylhydroxyboryl)-2,7-di-tert-butyl-9,9-dimethylxanthrene
4,5-di(phenylaminoethoxyboryl)-2,7-di-tert-butyl-9,9-dimethylxanthrene
(4-(phenylhydroxyboryl)phenoxyethyl)(4-(phenylhydroxyboryl)benzyl)ether
(4-(phenylaminoethoxyboryl)phenoxyethyl)(4-(phenylaminoethoxyboryl)benzyl)ether
6,6'-(phenylhydroxyboryl)-2,2'-dipyridyl
6,6'-(phenylaminoethoxyboryl)-2,2'-dipyridyl
bis(2,5-(phenylhydroxyboryl))furan
bis(2,5-(phenylaminoethoxyboryl))furan
bis(4,4'-(phenyl-N,N-dimethylaminoethoxyboryl)phenyl)ether
bis(4,4'-(phenyl-N-methylaminoethoxyboryl)phenyl)ether
2,8-di(phenylhydroxyboryl)dibenzothiophene
bis(4,4'-(phenyl-glutamineboryl)phenyl)ether
2,8-di(3-thiophenyl-2-pyrrolidinomethoxyboryl)dibenzothiophene
bis(4,4'-(phenyl-asparagineboryl)phenyl)ether
(4-(phenyl-N-methylaminoethoxyboryl)phenyl)(4'-(hydroxymethylphenyl-N-methylaminoethoxyboryl)phenyl)ether
(4-(phenyl-N,N-dimethylaminoethoxyboryl)phenyl)(4'-(hydroxymethylphenyl-N,N-dimethylaminoethoxyboryl)phenyl)ether
(4-(phenyl-glutamic acid boryl)phenyl)(4'-(hydroxymethylphenyl-glutamic acid boryl)phenyl)ether
(4-(phenyl-glutamineboryl)phenyl)(4'-(hydroxymethylphenyl-glutamineboryl)phenyl)ether
bis(4,4'-(phenyl-N,N-dimethylaminoethoxyboryl)phenyl)ether
bis(4,4'-(phenyl-N-aminoethyl-aminoethoxyboryl)phenyl)ether
(4-(phenyl-cysteineboryl)phenyl)(4'-(hydroxymethylphenyl-cysteineboryl)phenyl)ether
bis(4,4'-(phenoxyphenyl-aminoethoxyboryl)phenyl)ether
bis(4,4'-(phenyl-N-aminoethyl-aminoethoxyboryl)benzyl)ether
bis(4,4'-(phenyl-N-methylaminoethoxyboryl)benzyl)ether
(4'-trifluoromethylphenyl-N,N-dimethylaminoethoxyboryl)-4-phenyl(4'-trifluoromethylphenyl-N,N-dimethylaminoethoxyborylbenzyl)ether
(4'-trifluoromethylphenyl-N-methylaminoethoxyboryl)-4-phenyl (4'-trifluoromethylphenyl-N-methylaminoethoxyboryl-4-benzyl)ether
bis(3,3'-(phenyl-N,N-dimethylaminoethoxyboryl)benzyl)ether
bis(3,3'-(phenyl-asparagineboryl)benzyl)ether
bis(3,3'-(phenyl-aminoethylthioboryl)benzyl)ether
2,8-di(3-thiophenylhydroxyboryl)dibenzothiophene
bis(4,4'-(p-trifluoromethylphenyl-hydroxyboryl)benzyl)ether
2,8-di(phenylaminoethoxyboryl)dibenzothiophene
bis(4,4'-(phenyl-lysineboryl)benzyl)ether
bis(4,4'-(p-methoxy-phenyl-hydroxyboryl)benzyl)ether
bis(4,4'-(3,4-difluorophenyl-hydroxyboryl)benzyl)ether
bis(4,4'-(p-methoxyphenyl-aminoethoxyboryl)benzyl)ether
bis(4,4'-(p-methoxyphenyl-N-methylaminoethoxyboryl)benzyl)ether
bis(4,4'-(p-methoxyphenyl-N,N-dimethylaminoethoxyboryl)benzyl)ether
bis(4,4'-(p-methoxyphenyl-2,4-diaminobutyric acid boryl)benzyl)ether
bis(4,4'-(3,4-difluorophenyl-aminoethoxyboryl)benzyl)ether
bis(4,4'-(3,4-difluorophenyl-N-methylaminoethoxyboryl)benzyl)ether
bis(4,4'-(3,4-difluorophenyl-N,N-dimethylaminoethoxyboryl)benzyl)ether
bis(4,4'-(3,4-difluorophenyl-N-aminoethylaminoethoxyboryl)benzyl)ether
bis(4,4'-(3-chloro-4-methylphenyl-aminoethoxyboryl)benzyl)ether
bis(4,4'-(3-chloro-4-methylphenyl-N-methylaminoethoxyboryl)benzyl)ether
bis(4,4'-(3-chloro-4-methylphenyl-N,N-dimethylaminoethoxyboryl)benzyl)ether
bis(4,4'-(3-chloro-4-methylphenyl-2-piperidylmethoxyboryl)benzyl)ether
bis(4,4'-(p-trifluoromethylphenyl-N,N-dimethylaminoethoxyboryl)benzyl)ether
bis(4,4'-(p-trifluoromethylphenyl-asparagineboryl)benzyl)ether
bis(4,4'-(p-trifluoromethylphenyl-aminoethoxyboryl)benzyl)ether
(4-phenyl-N-methylaminoethoxyborylphenyl)(4'-phenyl-N-methylaminoethoxyborylbenzyl)ether
(4-phenyl-N,N-dimethylaminoethoxyborylphenyl) (4'-phenyl-N,N-dimethylaminoethoxyborylbenzyl)ether
(4-phenyl-2-pyridylmethoxyborylphenyl)(4'-phenyl-2-pyridylmethoxyborylbenzyl)ether
4-(phenyl-p-methoxyphenyl-2-pyridylmethoxyboryl)-phenyl 4'-(phenyl-p-methoxyphenyl-2-pyridylmethoxyboryl)benzylether
bis(4,4'-(phenyl-3-piperidyloxyboryl)phenyl)ether
bis(4,4'-(phenyl-2-pyridylmethoxyboryl)phenyl)ether
bis(4,4'-(phenyl-aminoethylthioboryl)phenyl)ether
bis(4,4'-(phenyl-2-amino-1-phenylethoxyboryl)phenyl)ether
bis(4,4'-(phenyl-ornithineboryl)phenyl)ether
bis(4,4'-(phenyl-2,3-diaminopropionic acid boryl)phenyl)ether
bis(4,4'-(phenyl-lysineboryl)phenyl)ether
bis(4,4'-(phenyl-2-pyrrolidinemethoxyboryl)phenyl)ether
bis(4,4'-(naphthylhydroxyboryl)phenyl)ether
bis(4,4'-(tolylhydroxyboryl)phenyl)ether
bis(4,4'-(naphthyl-aminoethoxyboryl)phenyl)ether
bis(4,4'-(naphthyldimethylaminoethoxyboryl)phenyl)ether
bis(4,4'-(naphthyl-2-pyridylmethoxyboryl)phenyl)ether

bis(4,4'-(naphthylglutamineboryl)phenyl)ether
bis(4,4'-(naphthyl 2,4-diaminopropionic acid boryl)phenyl) ether
bis(4,4'-(tolyldimethylaminoethoxyboryl)phenyl)ether
bis(4,4'-(tolylpiperadylethoxyboryl)phenyl)ether
bis(4,4'-(tolylasparagineboryl)benzyl)ether
bis(4,4'-(tolyllysineboryl)phenyl)ether
bis(4,4'-(phenyl-aminoethylthioboryl)benzyl)ether
bis(4,4'-(phenyl-2-pyrrolidinemethoxyboryl)benzyl)ether
bis(4,4'-(phenyl-2,4-diaminobutyric acid boryl)benzyl)ether
bis(4,4'-(phenyl-butylaminoethoxyboryl)benzyl)ether
bis(4,4'-(phenyl-phenylaminoethoxyboryl)benzyl)ether
bis(4,4'-(phenyl-benzylaminoethoxyboryl)benzyl)ether
bis(4,4'-(phenyl-N-methylpiperidine-methoxyboryl)benzyl) ether
bis(4,4'-(phenyl-1-methyl-2-aminoethoxyboryl)benzyl) ether
bis(4,4'-(phenyl-1-piperidylethoxyboryl)benzyl)ether
bis(3,3'-(phenyl-2-pyrrolidinomethoxyboryl)benzyl)ether
bis(3,3'-(phenyl-2-phenyl-2-aminoethoxyboryl)benzyl)ether
bis(3,3'-(phenyl-2-piperidylmethoxyboryl)benzyl)ether
bis(3,3'-(phenyl-dimethylaminoethoxyboryl)benzyl)ether
bis(3,3'-(phenyl-1-methyl-2-aminoethoxyboryl)benzyl) ether
bis(3,3'-(phenyl-1-piperidylethoxyboryl)benzyl)ether
bis(3,3'-(phenyl-2-pyridylmethoxyboryl)benzyl)ether
bis(3,3'-(phenyl-2-amino-1-phenylethoxyboryl)benzyl)ether
bis(3,3'-(phenyl-N-methylaminoethoxyboryl)benzyl)ether
bis(3,3'-(phenyl-N-aminoethyl-1-methyl-2-aminoethoxyboryl)benzyl)ether
bis(3,3'-(phenyl-glutamineboryl)benzyl)ether
bis(3,3'-(phenyl-2,4-diaminobutyric acid boryl)benzyl)ether
bis(3,3'-(phenyl-N-butylaminoethoxyboryl)benzyl)ether
bis(3,3'-(phenyl-asparagineboryl)benzyl)ether
bis(3,3'-(phenyl-lysineboryl)benzyl)ether
bis(3,3'-(phenyl-ornithineboryl)benzyl)ether
bis(4,4'-(phenyl-2-methyl-8-quinolinooxyboryl)phenyl) ether
bis(4,4'-(phenyl-2-benzyl-2-amino-ethoxyboryl)benzyl) ether
bis(4,4'-(phenyl-2-benzyl-2-amino-ethoxyboryl)phenyl) ether
bis(3,3'-(phenyl-2-benzyl-2-amino-ethoxyboryl)benzyl) ether
2,8-di(phenylglutamine-O,N borane)dibenzothiophene
2,8-di(phenyl 2-pyrrolidinomethoxyboryl)dibenzothiophene
2,8-di(phenylarginine-O,N borane)dibenzothiophene
2,8-di(3-thiophenylaminoethoxyboryl)dibenzothiophene
bis(2,2'-(phenylhydroxyboryl)benzyl)ether
2-aminoethyl diphenylborinate
diphenylborinic acid
poly(4,4'-biphenylene aminoethylthioborane)
poly(4-phenylborinic acid)
poly(dimethylaminoethoxyphenyleneborane)
1,3,5-tri(phenyl 2-aminoethoxyboryl)benzene
dibutyl(phenylalanine-O,N)borane
4,4'-di(phenyl 1-(pyridin-2-yl)-1-trifluoromethylphenyl-methoxyboryl)benzylether
di(3-chloro-6-methylphenyl)aminoethylborinate
bis(4,4'-(p-trifluoromethylphenyl-asparagineboryl)benzyl) ether
di(3-chloro-4-methyl)phenyl(methionate-O,N)borane
poly(1,4-phenylene 2-pyridylmethoxyborane)
poly(diphenyletherhydroxyborane)
4,4'-di(phenyl 1-(pyridin-2-yl)-1-trifluoromethylphenyl-methoxyborylbenzyl)ether

The present invention also relates to the compounds represented by the following formula (4') or (8') or a pharmaceutically acceptable salt thereof.



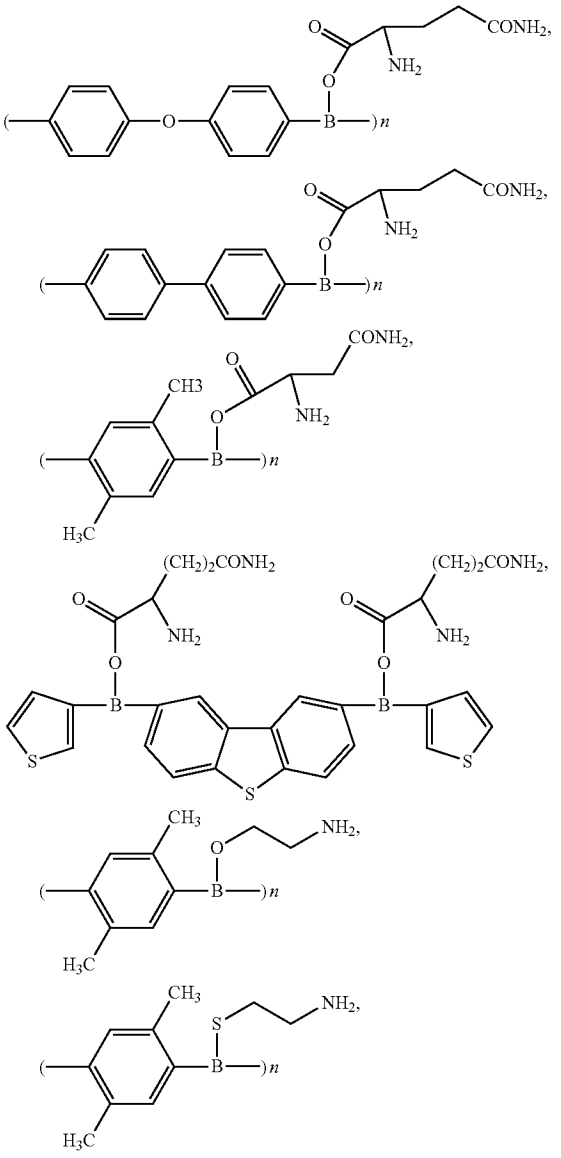
$$R_3'—[—X'—B(ZR_1')—]_n—R_4' \quad (4')$$

$$R_3'—B(ZR_1')—X'—B(ZR_2')—R_4' \quad (8')$$

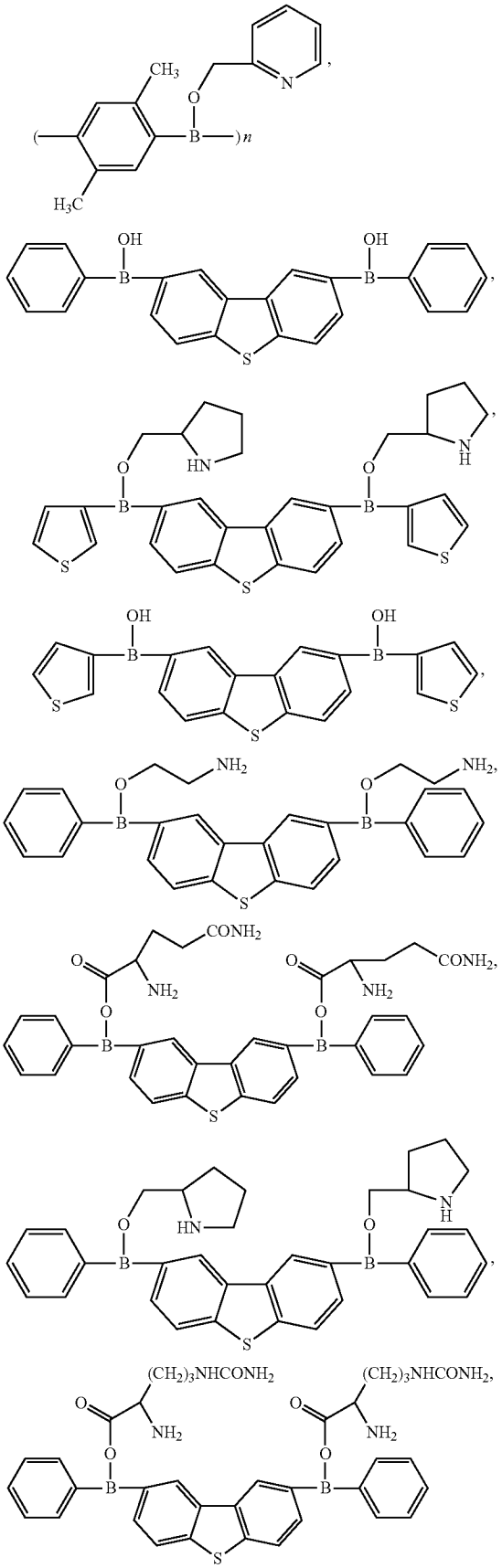
In the formulas, B is a boron atom, Z is O or S, R_1' and R_2' are H, $—(CH_2)_m—NR_5'R_6'$, $—CHR_{11}'R_{12}'$, $—COCH(NH_2)—(CH_2)_m NHCONH_2$ or $—COCH(NH_2)—(CH_2)_m—COR_{19}'$. Here, R_5', R_6', R_{11}', R_{12}' and R_{19}' are independently H, or amino or heterocyclyl, each of which is substituted or unsubstituted. R_3' and R_4' are H, aryl or heterocyclyl, X' is substituted or unsubstituted aromatic group, m is an integer of 1-5, and n is an integer of 1-100.

The "amino", "heterocyclyl", "aryl" and "aromatic group" are as defined above.

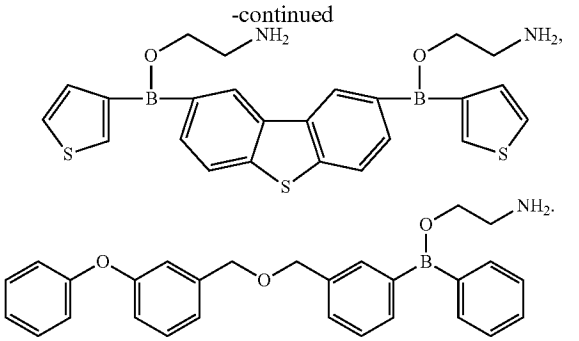
Specifically, the following compound can be mentioned:



-continued



-continued



The compounds (1)-(13) in the present invention can be converted to pharmaceutically acceptable non-toxic salts by a known method. The non-toxic salts include, for example, alkali metal salts, alkaline earth metal salts, amine salts, acid addition salts, solvates (including hydrates) and the like. In general, water-soluble ones are preferable.

Suitable non-toxic salts are salts with alkali metal such as potassium, sodium and the like; salts with alkaline earth metal such as calcium, magnesium and the like; and salts with organic amine such as triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)aminomethane, lysine, arginine, N-methyl-D-glucamine and the like, preferably, alkali metal salts.

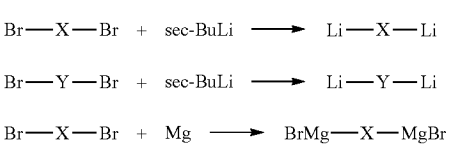
Moreover, as suitable acid addition salts, inorganic acid salts such as hydrochloride, hydrobromide, sulfate, phosphate, nitrate, and organic acid salts such as acetate, trifluoroacetate, lactate, tartrate, oxalate, fumarate, maleate, citrate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, toluenesulfonate, isethionate, glucuronate and gluconate can be mentioned.

The compound of the present invention also includes solvates. Solvate is a conjugate, particularly in a crystal form, of the aforementioned compound of the present invention and a pharmaceutically acceptable solvent (for example, water, organic solvent) at a stoichiometrical or non-stoichiometrical ratio.

The present invention relates to a prophylactic and/or therapeutic drug for a disease caused by protein cross-linking, which contains the aforementioned protein cross-linking inhibitor.

As the disease caused by abnormal protein cross-linking, for example, Alzheimer's disease, Huntington's disease, Parkinson's disease, Celiac disease, cataract, mad cow disease, congenital lamellar ichthyosis and congenital hemostatic disorder can be mentioned. Particularly, it is desirably used as prophylactic and/or therapeutic drug for Alzheimer's disease.

The compound of the present invention can be synthesized by the methods described in WO03/033002 and WO2007/061074 or a method analogous thereto. In addition, the compound of the present invention can be synthesized by the following method or a method analogous thereto.

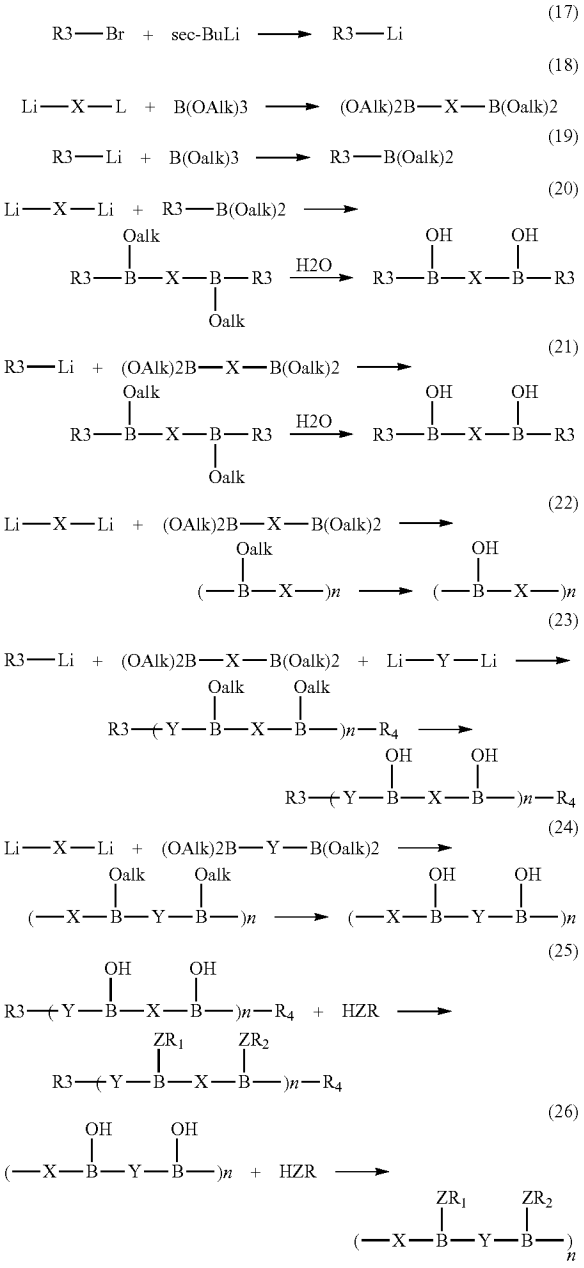


(14)

(15)

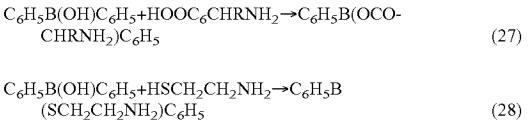
(16)

-continued



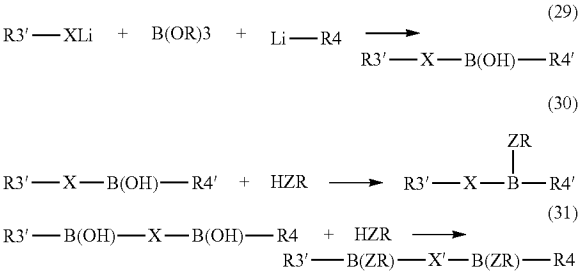
The main starting materials for the production of the compound of the present invention are monobromo compound, dibromo compound and alkoxyborane. A bromo compound is reacted with alkyl lithium to give a lithium compound R_3—Li (formula (17)). A dibromo compound (Br—X—Br or Br—Y—Br) is reacted with alkyl lithium to give a dilithium compound (Li—X—Li or Li—Y—Li) (formula (14) and formula (15)). Alternatively, magnesium is reacted to give a Grignard reagent (formula (16)). These metal compounds are reacted with trialkoxyborane to give dialkoxyborane R_3—B $(OAlk)_2$ (formula (19)). R_3—$B(OAlk)_2$ is reacted with Li—X—Li to give R_3—B(OAlk)-X—B—(OAlk)-R_3 (formula (20)) (Alk is an alkyl group having 1 to 4 carbon atoms). A dilithium compound (Li—X—Li) is reacted with R_3—B (OAlk)-X—B—(OAlk)-R_3 to give (—B(OAlk)-X—)$_n$. The resultant product is treated with acidic water to give (—B (OH)—X—), (formula (22)). R_3—Li, R_4—Li, $(OAlk)_2$B—X—$B(OAlk)_2$ and Li—Y—Li are reacted to give R_3—(—Y—B(OAlk)-X—B(OAlk)-)$_n$—R_4 and this is treated with acidic water to give R_3—(—Y—B(OH)—X—B(OH)—)$_n$—R_4 (formula (23)). Li—X—Li is reacted with $(OAlk)_2$B—Y—$B(OAlk)_2$ to give (—X—B(OAlk)-Y—B(OAlk-)$_n$, which is treated with acidic water to give (—X—B(OH)—Y—B(OH)—)$_n$ (formula (24)). These two bifunctional compounds are reacted to give various borinic acids. Borinic acid is reacted with desired HZR wherein R is R_1 or R_2 used in the formulas (1)-(13)) to give the object compound (formulas (25) and (26)).

By a reaction with diphenylborinic acid using amino acid and β aminothiol instead of β amino alcohol, a dehydrating reaction occurs and a desired compound can be obtained (formula (27), formula (28)).



As for a part of the compounds (1)-(13) of the present invention, according to the aforementioned schemes (14)-(26), borinic acid is synthesized from a bromine compound and bromobenzene by a similar method, which is reacted with amino alcohol, amino acid or aminothiol to synthesize a desired compound.

In addition, a compound represented by the formula (4') or (8') can be synthesized according to the formulas (20), (29), (30) and (31).



In the following, the compounds represented by the formulas (1)-(13) (including compounds represented by the formulas (4') and (8')) are also referred to as the compound of the present invention.

In the present invention, the enzyme (transglutaminase (TGase)) inhibitory action is determined by measuring the enzyme activity by an appropriately-modified method based on Lorand et al. (Lorand, L. et al. (1971), Anal Biochem. 1971 November; 44(1):221-31.). For example, the method described in the Example can be performed.

In the present invention, the polyglutamine aggregation inhibitory activity (x-Fold) can be measured, for example, by the method described in the Example.

The SOC (store operated calcium channel)-suppressive action can be measured by the method described in the Example and using, for example, FDSS 3000.

The compound of the present invention (i.e., active substance or active ingredient) is administered systemically or topically in an oral or parenteral dosage form to a test subject (mammal inclusive of human, preferably human). The parenteral administration includes intravenous administration, intraarterial administration, intramuscular administration, subcutaneous administration, intradermal administra-

tion, intraperitoneal administration, intrarectal administration, intradural administration, vaginal administration, transmucosal administration and the like.

While the dose varies depending on the kind of the compound to be administered, age, body weight and symptom of the subject of administration, treatment effect, administration method and the like, generally, for example, 10 μg-1000 mg is orally administered to one adult (body weight about 60 kg) once to several times per day or, for example, 1 μg-100 mg is parenterally administered to one adult (body weight about 60 kg) once to several times per day.

The administration preparation of the compound of the present invention includes, but are not limited to, tablet, pill, suspension, solution, capsule, syrup, elixir, granule, powder and the like for oral administration, injection, external preparation, suppository, external liquid, ointment, embrocation, inhalant, spray, pessary for vaginal administration and the like for parenteral administration.

The aforementioned preparation can contain a pharmacologically acceptable carrier (excipient, diluent and the like) or an additive in combination with the compound of the present invention as an active ingredient.

As the aforementioned excipient and additive, those conventionally used in the field of medicaments can be used. For example, the agents and formulation methods described in Remington: The Science and Practice of Pharmacy 9^{th} ed. (1995) MACK PUBLISHING COMPANY (US) can be referred to.

Examples of the excipient include lactose, mannitol, glucose, microcrystalline cellulose, starch and the like.

Examples of the additive include binders (hydroxypropylcellulose, polyvinylpyrrolidone, magnesium alumino metasilicate etc.), disintegrants (calcium cellulose glycolate etc.), lubricants (magnesium stearate etc.), stabilizers, solubilizing agents (glutamic acid, aspartic acid etc.) and the like.

The preparation of the present invention may be coated with a coating agent (sucrose, gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulosephthalate etc.), or may be coated with two or more layers. By applying such coating, the forms of control release preparation, enteric preparation and the like can be provided. Further, a capsule of absorbable substances such as gelatin is also encompassed.

In a liquid for oral administration, one or more of the activity substances are dissolved, suspended or emulsified in a generally-used diluent (purified water, ethanol, buffer, or a mixed solution thereof etc.). Further, the liquid may contain a wetting agent, a suspending agent, an emulsifier, a stabilizer, a sweetening agent, a flavoring agent, an aromatic, a preservative, a buffering agent and the like.

The injection for parenteral administration includes a solution, a suspension, an emulsion and an injection obtained by dissolving or suspending in a solvent when in use. An injection can be obtained by dissolving, suspending or emulsifying one or more active substances in a solvent. As the solvent, for example, distilled water for injection, saline, vegetable oil, alcohols such as propylene glycol, polyethylene glycol and ethanol and a combination thereof are used. Furthermore, the injection may contain a stabilizer (amino acid such as lysine, methionine and the like, sugar such as trehalose and the like), a solubilizing agent (glutamic acid, aspartic acid, polysorbate 80 (registered trademark) etc.), a suspending agent, an emulsifier, a soothing agent, a buffering agent, a preservative and the like. These injections are sterilized in the final step or produced and prepared by an aseptic operation method. In addition, an aseptic solid agent, for example, a freeze-dried product may be produced, and dissolved in sterilized or aseptic distilled water for injection or other solvent and used.

A spray may contain, besides a generally-used diluent, a stabilizer such as sodium bisulfite and a buffering agent that achieves isotonicity, for example, an isotonic agent such as sodium chloride, sodium citrate and citric acid.

In the present specification, when the terminal group is a hydroxyl group, a chemical formula omitting a hydroxyl group is sometimes described. The number after the compound name is the compound No.

EXAMPLE

Experimental Example 1

Measurement of TG

The compound of the present invention (10 mM, 1 μL) was taken in a 96-well plate (Nunc, 96 Well Black Plate with Clear Bottom), an enzyme reaction solution (100 mM HEPES-NaOH, pH 7.5, 1 mM $CaCl_2$, 20 μM monodansyl cadaverine, 0.05 mg/mL N,N-dimethylcasein, 5 μg/mL TGase) (0.1 ml) was added and the mixture was sufficiently mixed without making foams. The mixture was set on a fluorescence drug screening system FDSS 3000 (Hamamatsu Photonics K.K.), and changes in the fluorescence wavelength per unit time at 340 nm were measured, based on which the TGase inhibitory activity of the compound of the present invention was calculated. As a control, change in the fluorescence when 1 μL of DMSO (dimethyl sulfoxide) was added instead of the compound of the present invention was taken as 100, and TG50 was when the activity decreased to half due to the compound of the present invention. The results are shown in the following.

Experimental Example 2

Measurement of x-Fold

Truncated N-terminal huntington 150 Q-EGFP-Neuron 2a cells (prepared according to Wang, G. H., Nukina, N et al, Neuroreport, 10, 2435-2438 (1999)) were cultured for one day in a 96-well plate, 1 μM ponasterone A (2 μL) and 5 μM dibutyl cyclic AMP (2 μL) were added such that the concentration of the compound of the present invention became 20 μM, and the mixture was cultured for 20 hr. The cells were fixed with 4% para-formaldehyde and, 30 min later, the cells were washed with PBS and stained with Hoechst 33342. The number of the aggregated cells, and the total number of cells were counted by Array Scan V T1 (manufactured by Cellomics, Pittuburg, USA), and the ratio of the aggregated cells to the total number of cells was determined (x-Fold). Without the compound of the present invention, the respective numbers of cells were almost the same, and the number of the aggregated cells to the total number of cells was almost 1. A smaller value shows a stronger polyglutamine aggregation inhibitory activity. The results are shown in the following.

Experimental Example 3

Measurement of SOC IC50

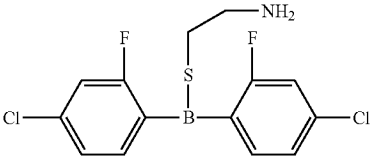
CHO cell culture medium was replaced with a BSS solution which is an extracellular fluidfree of calcium, the compound of the present invention was added 1 min later, and 1 μM thapsigargin was allowed to act thereon 2 min later to deplete intracellular calcium store. After 9 min, to the extracellular fluid was added calcium chloride at the final concentration of 2 mM, and an influence of each compound on the

degree of increase in the intracellular calcium concentration after addition was estimated, based on which SOC suppressive action (IC50) was determined. The results are shown in the following.

Example 1

2-aminoethylthio bis(4-chloro-2-fluorophenyl)borane (6014)

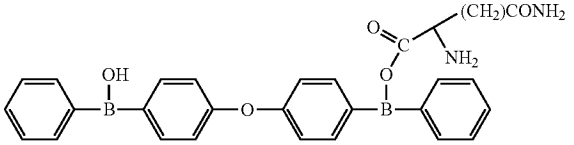
TG 28, x-Fold 0.95



Example 2

(4-(phenylglutamineboryl)phenyl)(4'-(phenylhydroxyboryl)phenyl)ether (7111)

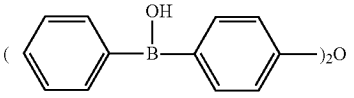
TG 28, x-Fold 0.82, SOC IC50 0.2 μM



Example 3

bis(4,4'-(phenylhydroxyboryl)phenyl)ether (536)

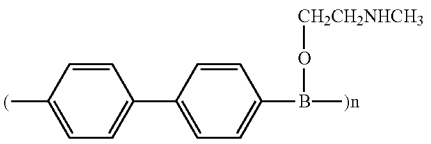
TG −20, x-Fold 0.49, SOC IC50 0.5 μM



Example 4

poly(4,4'-biphenylene N-methylaminoethoxyborane) (1130)

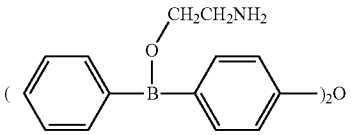
TG 109, x-Fold 0.80, SOC IC50 5 μM



Example 5

bis(4,4'-(phenylaminoethoxyboryl)phenyl)ether (1022)

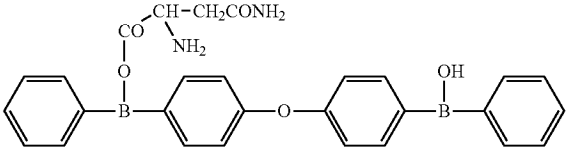
TG −4, x-Fold 0.60, SOC IC50 0.15 μM



Example 6

(4-(phenylasparagineboryl)phenyl)(4'-(phenylhydroxyboryl)phenyl)ether (7132)

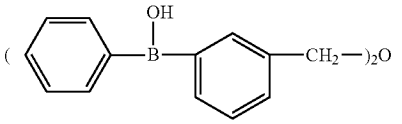
TG 23, x-Fold 1.01, SOC IC50 0.2 μM



Example 7

bis(3,3'-(phenylhydroxyboryl)benzyl)ether (162OH)

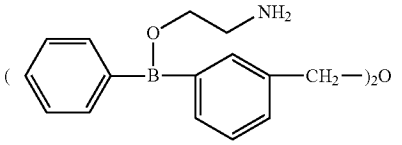
TG 14, x-Fold 1.03, SOC IC50 0.2 μM



Example 8

bis(3,3'-(phenylaminoethoxyboryl)benzyl)ether (162AE)

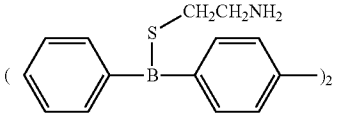
TG 24, x-Fold 1.1, SOC IC50 0.2 μM



Example 9

4,4'(phenyl-2-aminoethylthioboryl)diphenyl (6077)

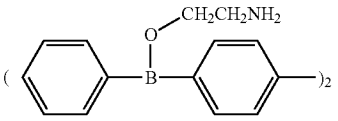
TG 12, x-Fold 0.87, SOC IC50 0.5 μM



Example 10

4,4'(phenyl-2-aminoethoxyboryl)diphenyl (6076)

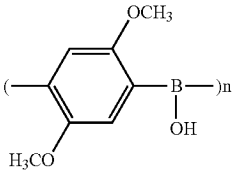
TG 7, x-Fold 0.92, SOC IC50 0.5 μM



Example 11

poly(2,5-dimethoxy-4-phenylborinic acid) (6047)

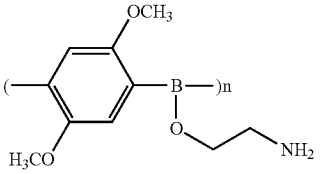
TG 36, x-Fold 0.99



Example 12

poly(aminoethyl-2,5-dimethoxy-4-phenylborinate) (6050)

TG 91, x-Fold 1.04

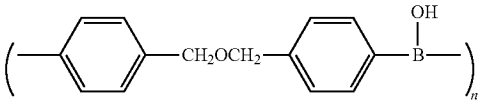


Example 13

poly(1,4-phenylenemethyleneoxymethylene 1,4-phenylene hydroxyborane) (1122)

TG 100, x-Fold 1.11

4,4'-p-brombenzyl ether (90 mg) was dissolved in ether (4 ml), and the mixture was cooled to −78° C. 1N sec-Butyllithium (0.75 mL) was added and the mixture was stirred for 60 min (SOLUTION A). 4,4'-parabromophenyl ether (90 mg) was dissolved in ether (4 ml), and the mixture was cooled to −78° C. Thereto was added 1N sec-butyllithium (0.7 mL) and the mixture was stirred for 30 min. Triisopropoxyborane (188 mg) was added and the mixture was stirred to −65° C. (SOLUTION B). SOLUTION A and SOLUTION B were mixed, and 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, and concentrated to give the title compound (154 mg).

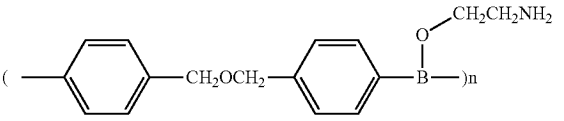


Example 14

poly(1,4-phenylenemethyleneoxymethylene 1,4-phenylene 2-aminoethoxyborane) (1132)

TG 85, x-Fold 1.03

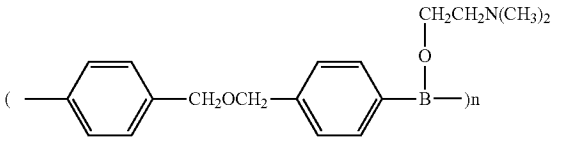
Poly(1,4-phenylenemethyleneoxymethylene 1,4-phenylene hydroxyborane) (34 mg) obtained in Example 13 was dissolved in a mixture of ethanol (0.5 mL) and ether (0.5 mL) and the mixture was stirred at 50° C. for 1 hr. After concentration, ether (1 mL) was added to produce the title compound (15 mg) as a white precipitate.



Example 15

poly(4,4'-phenylenemethyleneoxymethylene 4,4'-phenylene-dimethylaminoethoxyborinic acid) (1133)

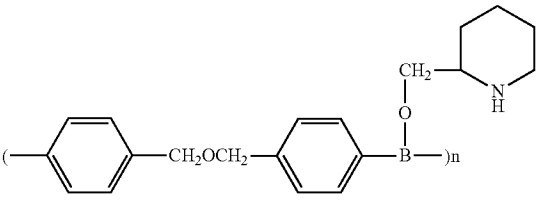
TG 91, x-Fold 0.90



Example 16

poly(1,4-phenylenemethyleneoxymethylene 1,4-phenylene 2-piperidinomethoxyborane) (1134)

TG 86, x-Fold 0.95



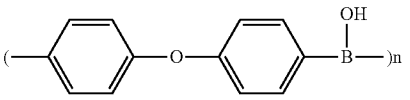
Example 17

poly(1,4-phenyleneoxy-1,4-phenylenehydroxyborane) (503)

TG 111, x-Fold 0.65

4,4'-Dibromodiphenylether (328 mg) was dissolved in ether (10 ml), sec-butyllithium (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

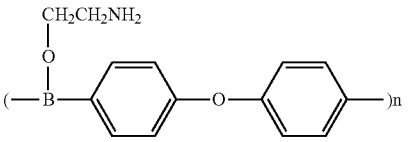
silica gel column chromatography to give the title compound (112 mg).



Example 18

poly(aminoethoxyboryldiphenylether) (1042D)

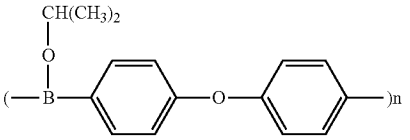
TG −17, x-Fold 0.84, SOC IC50 1.5 μM



Example 19

poly(isopropoxyboryldiphenylether) (1042E)

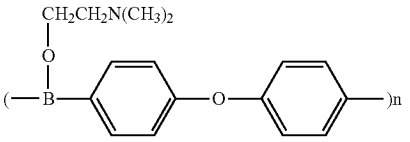
TG 47, x-Fold 0.86



Example 20

poly(4,4'-diphenylether dimethylaminoethoxyborane) (1056)

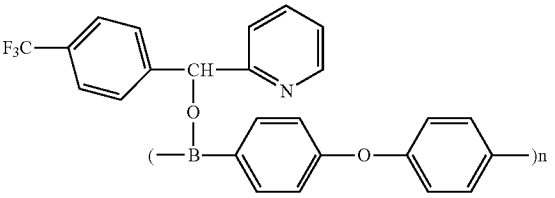
TG 54, x-Fold 0.63, SOC IC50 4 μM



Example 21

poly(4,4'-diphenylether-2-pyridyl-4-trifluoromethylphenylmethoxyborane) (1120)

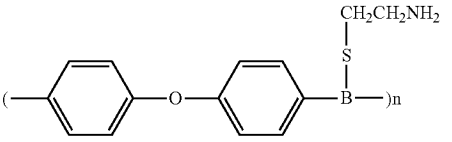
TG 111, x-Fold 0.72



Example 22

poly(4,4'-diphenylether-2-aminoethylthioborane) (1121)

TG 30, x-Fold 0.62

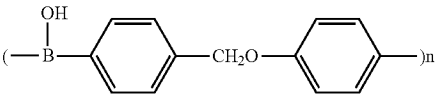


Example 23

poly(phenylenemethyleneoxyphenylenehydroxyborane) (1107)

TG 114, x-Fold 0.62

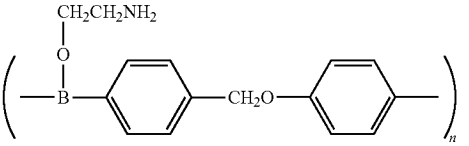
4,4'-p-bromophenyl p-brombenzyl ether (171 mg) was dissolved in ether (8 ml), and the mixture was cooled to −100° C. Thereto was added 1N sec-butyllithium (1 mL) and the mixture was stirred for 30 min to −78° C. (SOLUTION A). p-bromophenyl p-brombenzyl ether (171 mg) was dissolved in ether (10 ml), and the mixture was cooled to −78° C. Thereto was added 1N sec-butyllithium (1 ml) and the mixture was stirred for 30 min. Triisopropoxyborane (188 mg) was added and the mixture was stirred to −65° C. (SOLUTION B). SOLUTION A and SOLUTION B were mixed, and 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, and concentrated to give the title compound (161 mg).



Example 24

poly(phenylenemethyleneoxyphenyleneaminoethoxyborane) (1116)

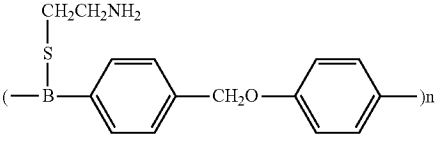
TG 96, x-Fold 0.78



Example 25

poly(phenylenemethyleneoxyphenyleneaminoethylthioborane) (1117)

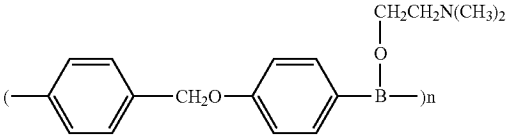
TG 12, x-Fold 0.69



Example 26

poly(phenylenemethyleneoxyphenylenedimethylaminoethoxyborane) (1109)

TG 116, x-Fold 0.78

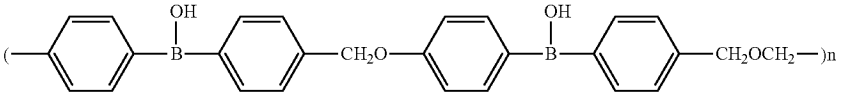


Example 27

poly(4'-phenylhydroxyboranephenylenemethyleneoxyphenylenehydroxyborane phenylenemethyleneoxymethylene) (1108-3)

TG 45, x-Fold 0.86, SOC IC50 5 μM

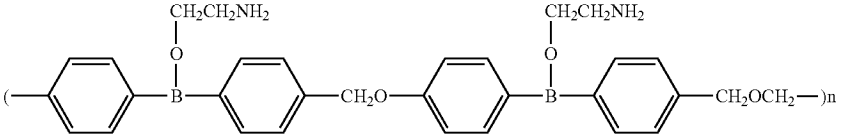
The title compound (189 mg) was obtained from bis(4-bromobenzyl)ether (178 mg) and parabromophenyl parabromobenzyl ether (171 mg).



Example 28

poly(phenylenemethyleneoxyphenyleneaminoethoxyboranephenylene-methyleneoxymethylenephenylene aminoethoxyborane) (1114)

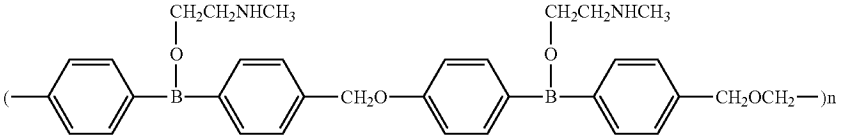
TG 94, x-Fold 0.72



Example 29

poly(phenylenemethyleneoxyphenylenemethylaminoethoxyborane-phenylenemethyleneoxymethylenephenylenemethylaminoethoxyborane) (1115)

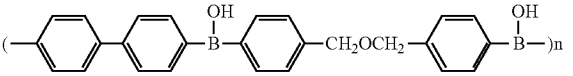
TG 52, x-Fold 0.83



Example 30

poly(4,4'-biphenylene-hydroxyborane 1,4-phenylenemethyleneoxymethylenephenylenehydroxyborane) (1141c)

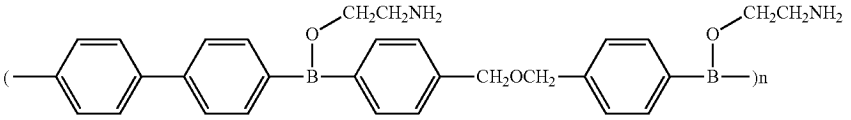
TG 107, x-Fold 1.02



Example 31

poly(4,4'-biphenylene 2-aminoethoxyborane 1,4-phenylene-methyleneoxymethylene 1,4-phenylene 2-aminoethoxyborane) (1146)

TG 127, x-Fold 0.95

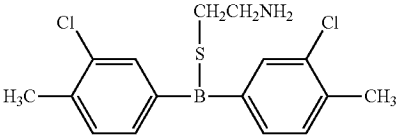


Example 32

di(3-chloro-4-methylphenyl)-2-aminoethylthioborane (3115)

TG 12, x-Fold 1.02, SOC IC50 1 μM

di(3-Chloro-4-methylphenyl)borinic acid (44 mg) and 2-aminoethanethiol (35 mg) were reacted in ethanol (1 mL) to give the title compound (52 mg).

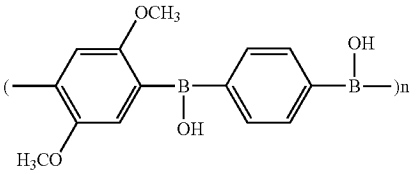


Example 33

poly(2,5-dimethoxy-4-phenylene-hydroxyborane-1, 4-phenylenehydroxyborane) (6048)

TG 51, x-Fold 0.92

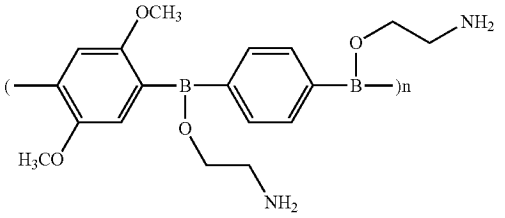
Paradibromobenzene (353.85 mg) was dissolved in ether (10 mL), and sec-butyllithium (3 mL) was added at −95° C. 30 min later, triisoproxyborane (552 μL) was added at −78° C. and the mixture was stirred for 1 hr (SOLUTION A). 2,5-Dimethoxy-1,4-dibromobenzene (443.35 mg) was dissolved in ether (10 μL), sec-butyllithium (3 ml) was added at −95° C. and the mixture was stirred for 30 min (SOLUTION B). SOLUTION A and SOLUTION B were mixed at −78° C., and the mixture was gradually warmed to room temperature and stirred overnight. Thereto was added hydrochloric acid solution to give the title compound (4.9 mg).



Example 34

poly(aminoethyl(2,5-dimethoxy-4-phenylene)amino-ethoxyboryl(1,4-phenylene)borinate) (6051)

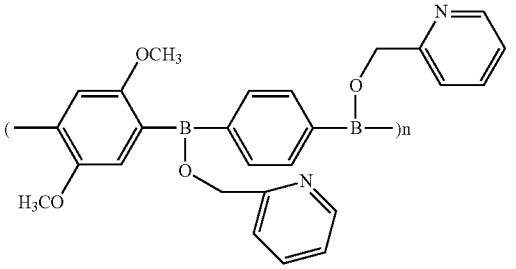
TG 39, x-Fold 1.01



Example 35

poly(2-pyridylmethyl(2,5-dimethoxy-4-phenylene) 2-pyridylmethoxyborane-(1,4-phenylene)borinate) (6053)

TG 14, x-Fold 0.98

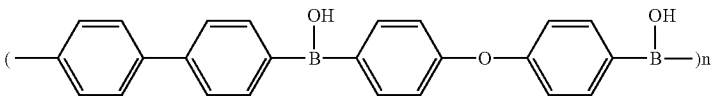


Example 36

poly(4,4'-biphenylene-hydroxyborane 4,4'-diphenylether hydroxyborane) (1068)

TG 6, x-Fold 0.65, SOC IC50 3 4M

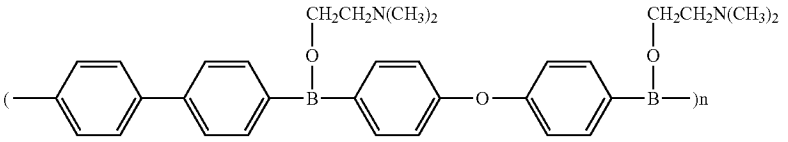
4,4'-Dibromobiphenyl (312 mg) was dissolved in ether (10 mL), and the mixture was cooled to −100° C. Thereto was added 1N sec-butyllithium (2.1 mL) and the mixture was stirred for 30 min to −78° C. (SOLUTION A). 4,4'-Dibromodiphenylether (328 mg) was dissolved in ether (10 ml), and the mixture was cooled to −78° C. Thereto was added 1N sec-butyllithium (2.1 ml) and the mixture was stirred for 30 min. Triisopropoxyborane (376 mg) was added and the mixture was stirred to −65° C. (SOLUTION B). SOLUTION A and SOLUTION B were mixed, and 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, and concentrated to give the title compound (114 mg).



Example 37

poly(4,4'-biphenylene-dimethylaminoethoxyborane 4,4'-diphenyletherdimethylaminoethoxyborane) (1074)

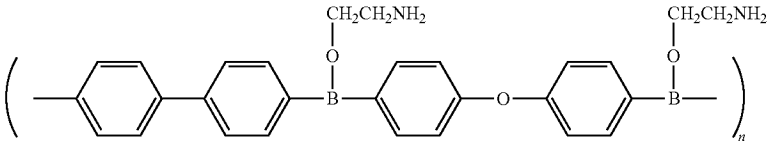
TG −22, x-Fold 0.73



Example 38

poly(4,4'-biphenylene-aminoethoxyborane-4,4'-diphenylether aminoethoxyborane) (1077)

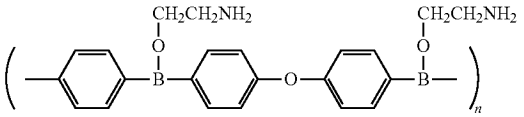
TG 79, x-Fold 0.71



Example 39

poly(phenyleneaminoethoxyborane diphenylether-aminoethoxyborane) (1060)

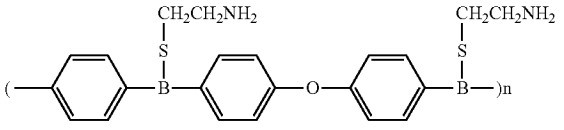
TG 99, x-Fold 1.04



Example 40

poly(phenyleneaminoethylthioborane diphenylether-aminoethylthioborane) (1062)

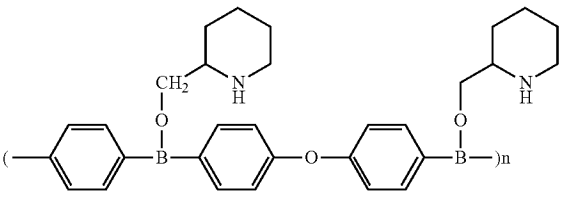
TG 26, x-Fold 0.52



Example 41

poly(phenylene 2-piperazinomethoxyborane diphenylether 2-piperidinomethoxyborane) (1063)

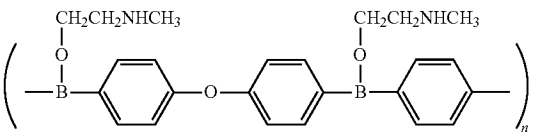
TG 54, x-Fold 0.63, SOC IC50 2 μM



Example 42

poly(methylaminoethoxyborylphenylene methylaminoethoxyboryldiphenylether) (1064)

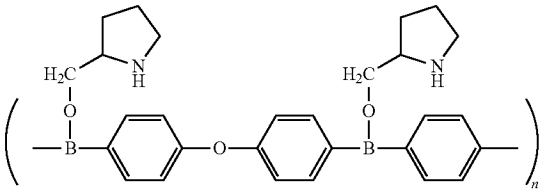
TG 8, x-Fold 0.53, SOC IC50 2 μM



Example 43

poly(pyrrolidinomethoxyborylphenylene pyrrolidinomethoxyboryldiphenylether) (1065)

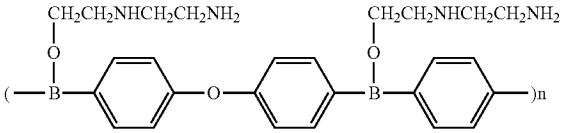
TG 13, x-Fold 0.73, SOC IC50 3 μM



Example 44

poly(aminoethylaminoethoxyborylphenylene aminoethylaminoethoxyboryldiphenylether) (1066)

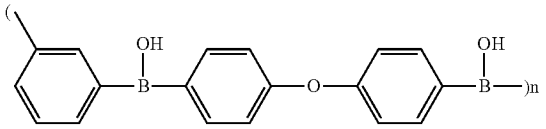
TG 12, x-Fold 0.54, SOC IC50 4 μM



Example 45

poly(metaphenylene-hydroxyborane-4,4'-diphenyletherhydroxyborane) (1097)

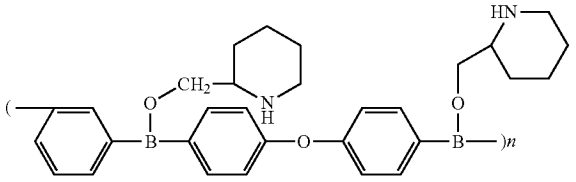
TG 99, x-Fold 0.52



Example 46

poly(metaphenylene-2-piperidinemethoxyborane-4,4'-diphenylether-2-piperidinemethoxyborane) (1102)

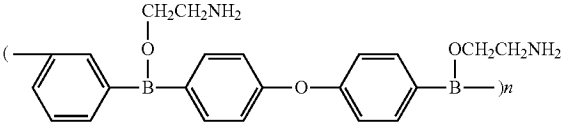
TG 93, x-Fold 0.50



Example 47

poly(metaphenylene-aminoethoxyborane-4,4'-diphenylether aminoethoxyborane) (1103)

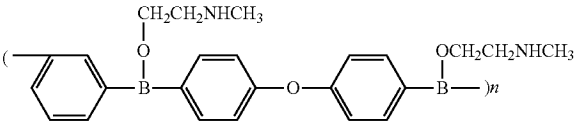
TG 106, x-Fold 0.58



Example 48

poly(metaphenylene-methylaminoethoxyborane-4,4'-diphenylethermethylaminoethoxyborane) (1104)

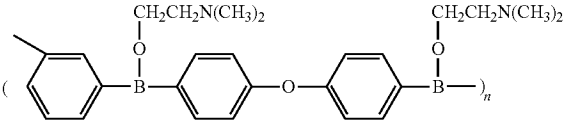
TG 102, x-Fold 0.59



Example 49

poly(metaphenylene-2-dimethylaminoethoxyborane-4,4'-diphenylether-2-dimethylaminoethoxyborane) (2102)

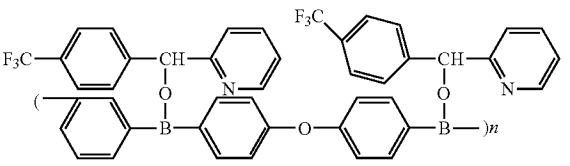
TG 89, x-Fold 0.96



Example 50

poly(metaphenylene-2-pyridyl-trifluoromethylphenylmethoxyborane-4,4'-diphenylether-2-pyridyl-trifluoromethylphenylmethoxyborane) (1105)

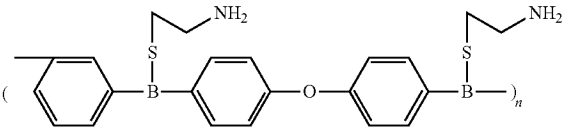
TG 112, x-Fold 0.59



Example 51

poly(metaphenylene-aminoethylthioborane-4,4'-diphenylether-aminoethylthioborane) (1106)

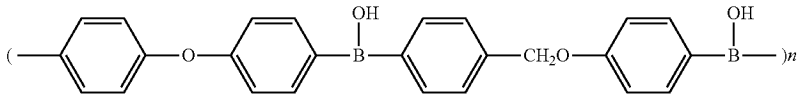
TG 13, x-Fold 0.43



Example 52

poly(4,4'-diphenyletherhydroxyborane phenylenemethyleneoxyphenylenehydroxyborane) (1069)

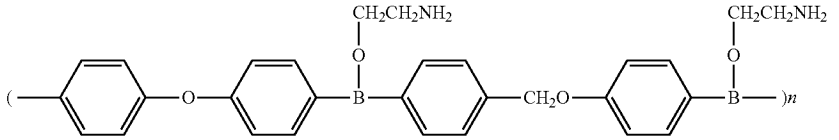
TG 73, x-Fold 0.69



Example 53

poly(phenylenemethyleneoxyphenylene-aminoethoxyborane-4,4'-diphenyletheraminoethoxyborane) (1075)

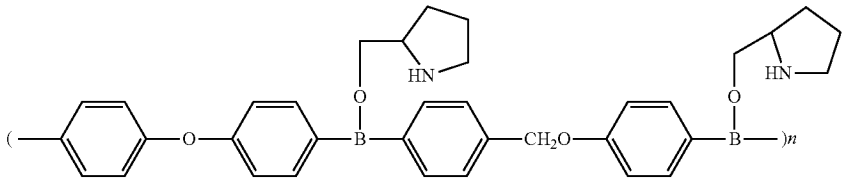
TG 113, x-Fold 0.74



Example 54

poly(phenyleneoxyphenylene-2-pyrrolidinemethoxyboryl-phenylenemethyleneoxyphenylene-2-pyrrolidinemethoxyborane) (1080)

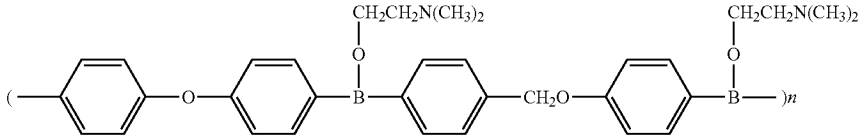
TG 112, x-Fold 0.67



Example 55

poly(phenylenemethyleneoxyphenylene-dimethylaminoethoxyborane-4,4'-diphenylether dimethylaminoethoxyborane) (1081)

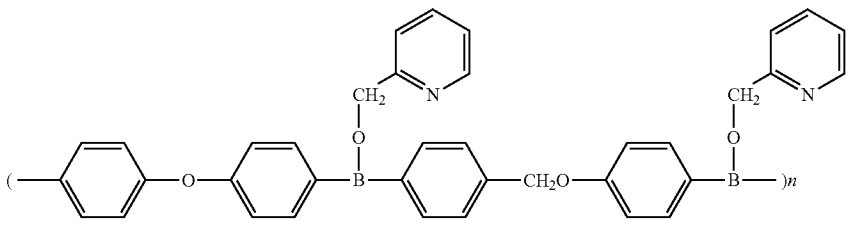
TG 151, x-Fold 0.71



Example 56

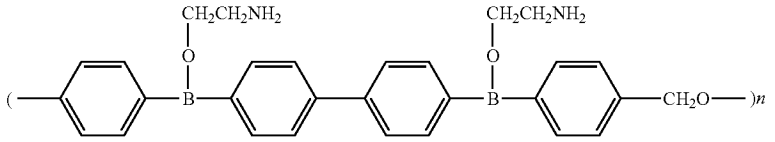
poly(phenylenemethyleneoxyphenylene-2-pyridylmethoxyborane-4,4'-diphenylether-2-pyridylmethoxyborane) (1082)

TG 74, x-Fold 0.71



poly(4,4'-biphenylene-aminoethoxyborane-1,4-phenylene-methyleneoxy-1,4-phenylene-aminoethoxyborane) (1125)

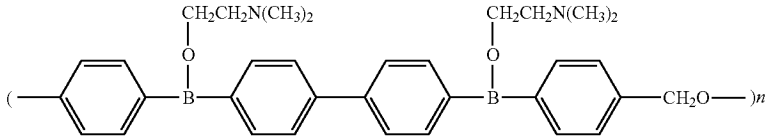
TG 5.98, x-Fold 0.67, SOC IC50 μM



Example 58

poly(4,4'-biphenylene-dimethylaminoethoxyborane-1,4-phenylene-methyleneoxyphenylenedimethylaminoethoxyborane) (1124)

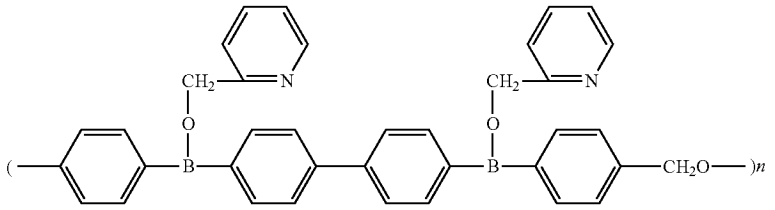
TG 45, x-Fold 0.62



Example 59

poly(4,4'-biphenylene-2-pyridylmethoxyborane-1,4-phenylene-methyleneoxy-1,4-phenylene-2-pyridylmethoxyborane) (1126)

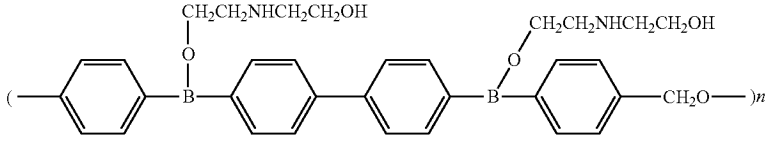
TG 107, x-Fold 0.72



Example 60

poly(4,4'-biphenylene-2-hydroxyethylaminoethoxyborane-1,4-phenylene-methyleneoxy-1,4-phenylene-2-hydroxyethylaminoethoxyborane) (1127)

TG 24, x-Fold 0.73

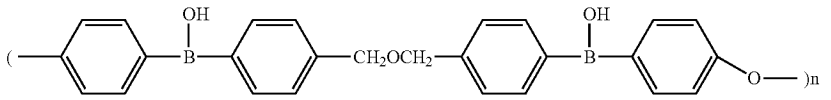


Example 61

poly(4,4'-phenylene-methyleneoxymethylene-phenylene-hydroxyborane-4,4'-phenyleneoxyphenyleneborinic acid) (1123)

TG 100, x-Fold 0.99

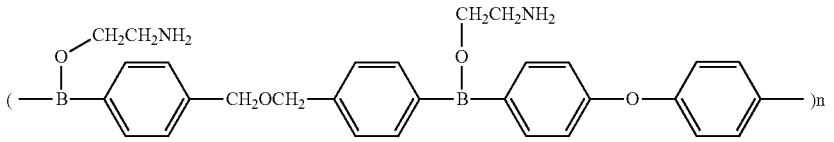
4,4'-Dibromodibenzyl ether (96 mg) was dissolved in ether (6 ml), 1M sec-butyllithium (0.7 mL) was added and the mixture was stirred for 30 min. Triisoproxyborane (240 μL) was added at −78° C. and the mixture was stirred for 1 hr (SOLUTION A). 4,4'-Dibromodiphenyl ether (82.7 mg) was dissolved in ether (5 ml), 1N sec-butyllithium (0.7 mL) was added at −78° C. and the mixture was stirred (SOLUTION B). SOLUTION A and SOLUTION B were mixed at −78° C., and the mixture was gradually warmed to room temperature and stirred overnight. 1N Hydrochloric acid was added, and the ether layer was washed with saturated brine, dried, and concentrated to give the title compound (150 mg).



Example 62

poly(phenylene-methyleneoxymethylene-phenylene-aminoethoxyborane-phenyleneoxyphenyleneamino-ethoxyborane) (1135)

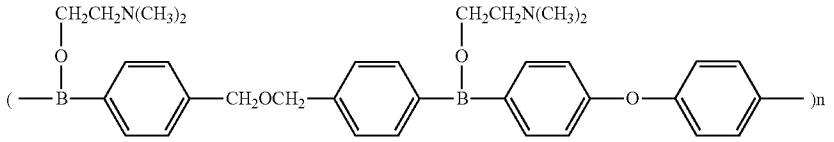
TG 94, x-Fold 0.95



Example 63

poly(phenylene methyleneoxymethylene phenylene dimethylaminoethoxyborane phenylene oxy phenylene dimethylaminoethoxyborane) (1136)

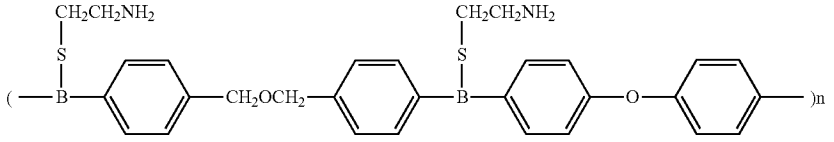
TG 63, x-Fold 1.04



Example 64

poly(phenylene methyleneoxymethylene phenylene aminoethylthioborane phenylene oxy phenylene aminoethylthioborane) (1137)

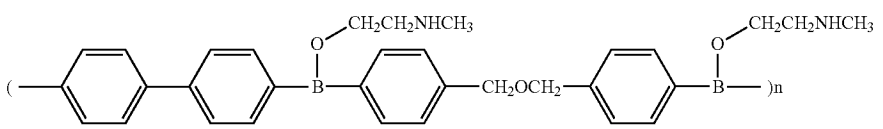
TG 11, x-Fold 0.95



Example 65

poly(diphenylene-methylaminoethoxyboryl-1,4-phenylene-methyleneoxymethylenephenylene-methylaminoethoxyborane) (1142)

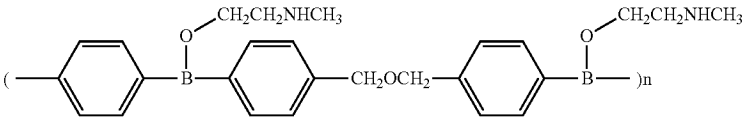
TG 115, x-Fold 1.02, SOC IC50 7 μM



Example 66

poly(1,4-phenylene-methyleneoxymethylenephenylenemethylaminoethoxyborane-1,4-phenylene-methylaminoethoxyborane) (1144)

TG 120, x-Fold 1.18, SOC IC50 >20 μM

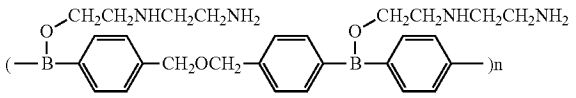


Example 67

poly(1,4-phenylene-methyleneoxymethylenephenylene-aminoethylaminoethoxyborane-1,4-phenylene-aminoethylaminoethoxyborane) (1145)

TG 122, x-Fold 0.87

4,4'-Parabrombenzyl ether (180 mg) was dissolved in ether (10 mL), and the mixture was cooled to −78° C. 1.57N tert-Butyllithium (0.7 mL) was added and the mixture was stirred for 60 min (SOLUTION A). 1,4-Dibromobenzene (118 mg) was dissolved in ether (10 mL), and the mixture was cooled to −78° C. 1.57N tert-Butyllithium (0.7 mL) was added and the mixture was stirred for 30 min. Triisopropoxyborane (188 mg) was added and the mixture was stirred to −65° C. (SOLUTION B). SOLUTION A and SOLUTION B were mixed, and the mixture was gradually warmed to room temperature and stirred for 15 hr. The mixture was acidified with 1N hydrochloric acid, and the organic layer was washed with water, dried, and concentrated to give the title compound (184 mg).

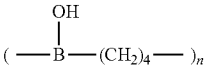


Example 68

polytetramethyleneborinic acid (6060)

TG 119, x-Fold 1.04

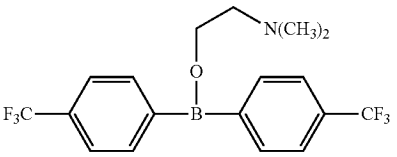
1,4-Tetramethylenedibromide (262 mg) was dissolved in ether (10 ml), and reacted with magnesium (Mg) (58 mg). Trimethoxyboroxin (60 μL) was added and the mixture was stirred overnight. Hydrochloric acid was added and the ether layer was concentrated to give the title compound (43.8 mg).



Example 69

2-dimethylaminoethyl bis(4-trifluoromethylphenyl)borinate (5034)

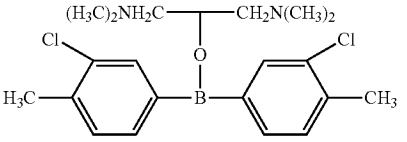
TG 76, x-Fold 1.02



Example 70

1,3-dimethylaminopropyl bis(3-chloro-4-methylphenyl)borinate (5141)

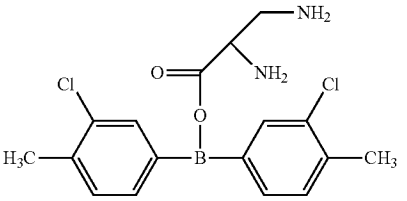
TG 13, x-Fold 0.73, SOC IC50 0.3 μM



Example 71

di(3-chloro-4-methylphenyl)(2,3-diaminopropionate-O,N)borane (5142)

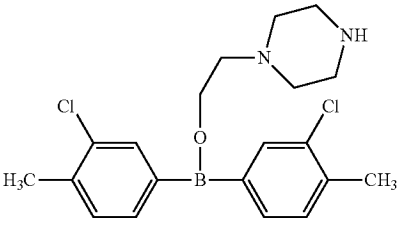
TG 51, x-Fold 0.97, SOC IC50 1 μM



Example 72

di(3-chloro-4-methylphenyl)piperazinoethoxyborane (5143)

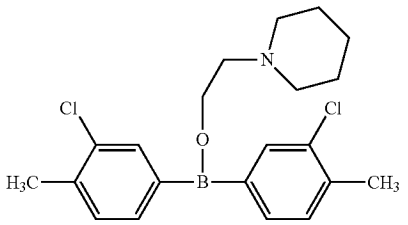
TG 41, x-Fold 1.02, SOC IC50 0.5 μM



Example 73

di(3-chloro-4-methylphenyl)piperidinoethoxyborane (5144)

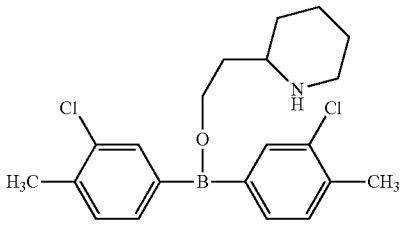
TG 35, x-Fold 0.85, SOC IC50 1.2 μM



Example 74

di(3-chloro-4-methylphenyl)-2-piperidinoethoxyborane (5145)

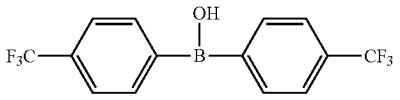
TG 41, x-Fold 0.95, SOC IC50 1 μM



Example 75

bis(4-trifluoromethylphenyl)borinic acid (6001)

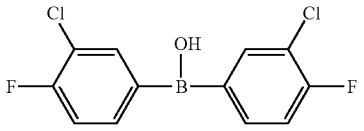
TG 97, x-Fold 0.88



Example 76

bis(3-chloro-4-fluorophenyl)borinic acid (6004)

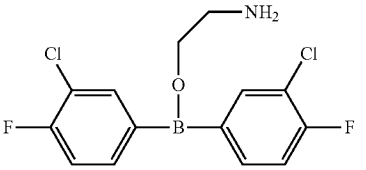
TG 117, x-Fold 0.78



Example 77

2-aminoethyl-bis(3-chloro-4-fluorophenyl)borinate (6006)

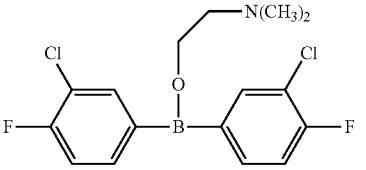
TG 98, x-Fold 0.91



Example 78

2-dimethylaminoethyl bis(3-chloro-4-fluorophenyl)borinate (6007)

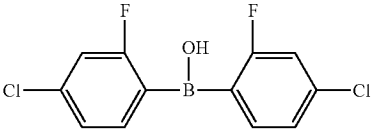
TG 104, x-Fold 1.02



Example 79

bis(4-chloro-2-fluorophenyl)borinic acid (6008)

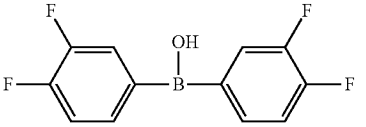
TG 97, x-Fold 0.88



Example 80

bis(3,4-difluorophenyl)borinic acid (6009)

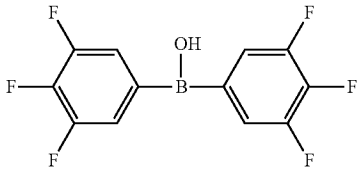
TG 93, x-Fold 0.90



Example 81

bis(3,4,5-trifluorophenyl)borinic acid (6010)

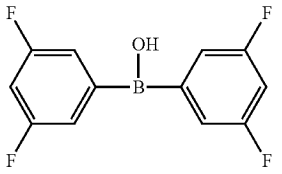
TG 97, x-Fold 0.92



Example 82

bis(2,4-difluorophenyl)borinic acid (6011)

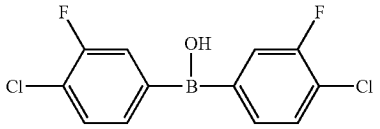
TG 103, x-Fold 0.95



Example 83

bis(3-fluoro-4-chlorophenyl)borinic acid (6012)

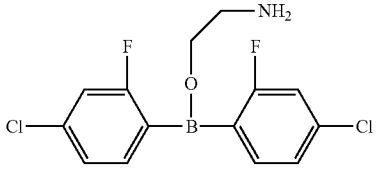
TG 101, x-Fold 0.92



Example 84

2-aminoethyl bis(4-chloro-2-fluorophenyl)borinate (6013)

TG 91, x-Fold 0.92

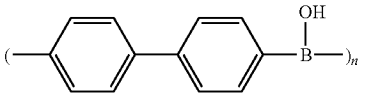


Example 85

poly(4,4'-biphenylhydroxyborane) (504)

TG 128, x-Fold 0.79

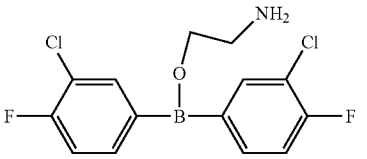
4,4'-Dibromodiphenyl (234 mg) was dissolved in ether (10 ml), and 1.5N tert-butyllithium (1.3 mL) was added at −95° C. 30 min later, triisoproxyborane (345 μL) was added at −78° C. and the mixture was stirred for 1 hr (SOLUTION A). 4,4'-Dibromodiphenyl (234 mg) was dissolved in ether (10 mL), 1.5N tert-butyllithium (1.3 mL) was added at −95° C. and the mixture was stirred (SOLUTION B). SOLUTION A and SOLUTION B were mixed at −78° C., and the mixture was gradually warmed to room temperature and stirred overnight. 1N Hydrochloric acid solution was added and the ether layer was with washed with saturated brine and dried and concentrated to give the title compound (155 mg).



Example 86

2-aminoethyl bis(3-chloro-4-fluorophenyl)borinate (6015)

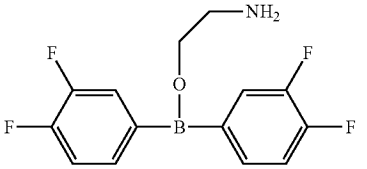
TG 103, x-Fold 0.99



Example 87

2-aminoethyl bis(3,4-difluorophenyl)borinate (6016)

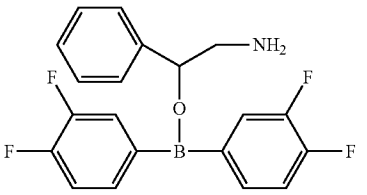
TG 91, x-Fold 1.02



Example 88

2-amino-1-phenylethyl bis(3,4-difluorophenyl)borinate (6017)

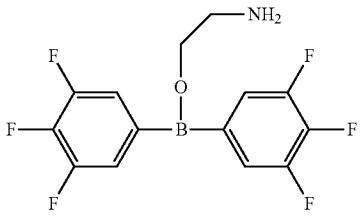
TG 82, x-Fold 0.83



Example 89

aminoethyl bis(3,4,5-trifluorophenyl)borinate (6018)

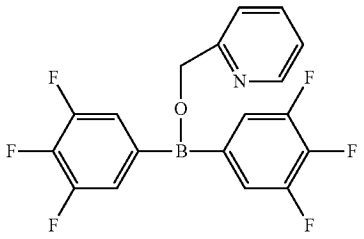
TG 80, x-Fold 0.94



Example 90

2-pyridylmethyl bis(3,4,5-trifluorophenyl)borinate (6019)

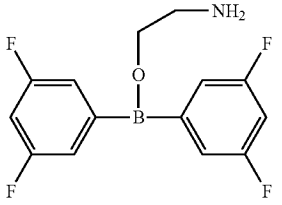
TG 93, x-Fold 0.81



Example 91

aminoethyl bis(3,5-difluorophenyl)borinate (6020)

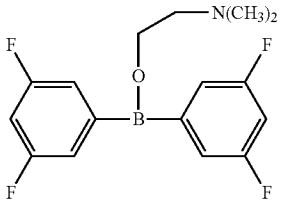
TG 107, x-Fold 0.99



Example 92

dimethylaminoethyl bis(3,5-difluorophenyl)borinate (6021)

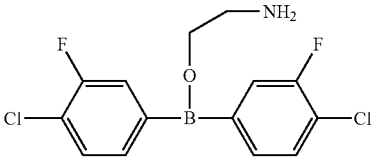
TG 106, x-Fold 1.00



Example 93

aminoethyl bis(4-chloro-3-fluorophenyl)borinate (6023)

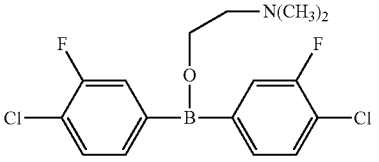
TG 117, x-Fold 0.93



Example 94

dimethylaminoethyl bis(4-chloro-3-fluorophenyl)borinate (6024)

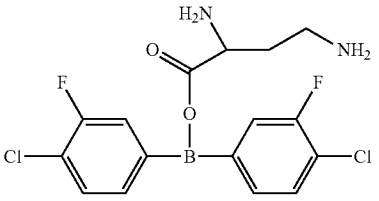
TG 114, x-Fold 0.95



Example 95

di(3-fluoro-4-chlorophenyl)(2,4-diaminolactonate-O,N)borane (6025)

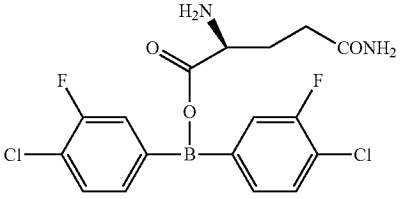
TG 114, x-Fold 0.88



Example 96

di(3-fluoro-4-chlorophenyl)(glutaminate-O,N)borane (6026)

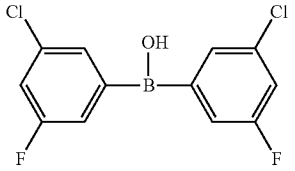
TG 124, x-Fold 0.86



Example 97

bis(3-chloro-5-fluorophenyl)borinic acid (6027)

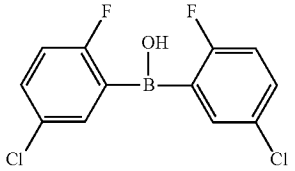
TG 122, x-Fold 0.72



Example 98

bis(3-chloro-6-fluorophenyl)borinic acid (6029)

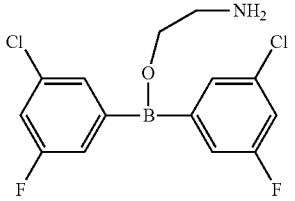
TG 111, x-Fold 0.95



Example 99

aminoethyl bis(3-chloro-5-fluorophenyl)borinate (6030)

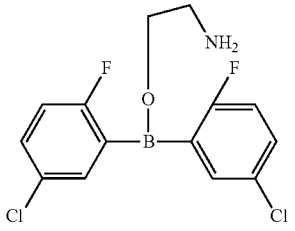
TG 109, x-Fold 0.73



Example 100

aminoethyl bis(3-chloro-6-fluorophenyl)borinate (6032)

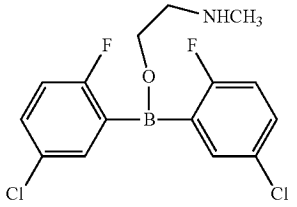
TG 119, x-Fold 0.97



Example 101

methylaminoethyl bis(3-chloro-6-fluorophenyl)borinate (6033)

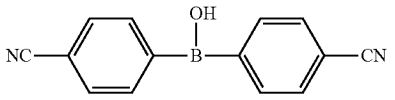
TG 122, x-Fold 1.02



Example 102

bis(4-cyanophenyl)borinic acid (5009)

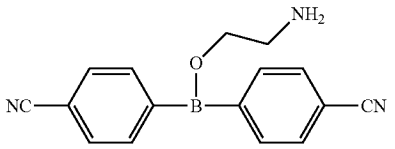
TG 72, x-Fold 1.10



Example 103

aminoethyl bis(4-cyanophenyl)borinate (6034)

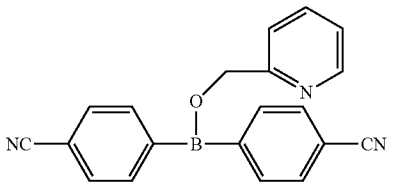
TG 114, x-Fold 0.89



Example 104

2-pyridylmethyl bis(4-cyanophenyl)borinate (6037)

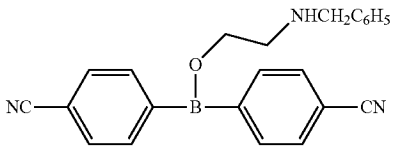
TG 94, x-Fold 1.16



Example 105

benzylaminoethyl bis(4-cyanophenyl)borinate (6038)

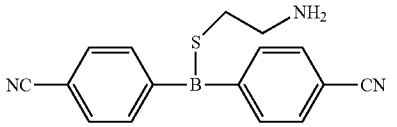
TG 92, x-Fold 1.05



Example 106

2-aminoethylthio bis(4-cyanophenyl)borane (6039)

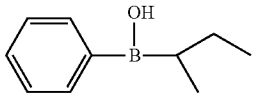
TG 23, x-Fold 0.92



Example 107

secondary-butyl phenyl borinic acid (6040)

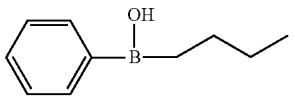
TG 111, x-Fold 0.98



Example 108

normal-butyl phenyl borinic acid (6041)

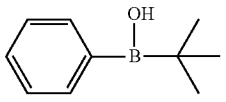
TG 111, x-Fold 1.00



Example 109

tertiary-butyl phenyl borinic acid (6042)

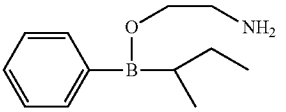
TG 108, x-Fold 1.02, SOC IC50 >10 μM



Example 110

aminoethyl secondary-butyl phenylborinate (6043)

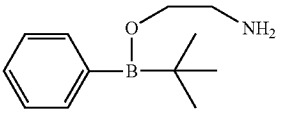
TG 115, x-Fold 1.02, SOC IC50 >10 μM



Example 111

aminoethyl tertiary-butyl phenylborinate (6044)

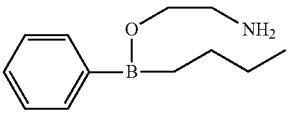
TG 121, x-Fold 1.02



Example 112

aminoethyl normal-butyl phenylborinate (6046)

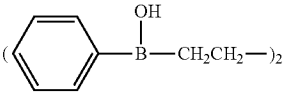
TG 123, x-Fold 0.99



Example 113

1,4-bis(hydroxyphenylboryl)butane (6059)

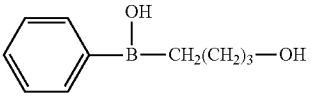
TG 112, x-Fold 0.99



Example 114

4-hydroxybutylphenylborinic acid (6059-9)

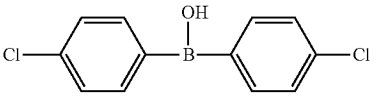
TG 120, x-Fold 0.99, SOC IC50 2 μM



Example 115

bis(4-chlorophenyl)borinic acid (385)

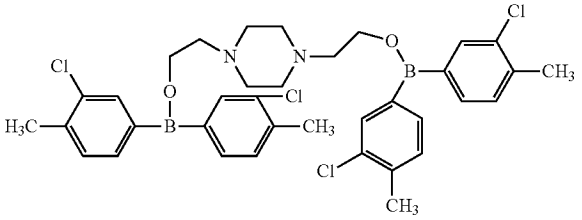
TG 101, x-Fold 1.07



Example 116

bis(di(3-chloro-4-methylphenyl)boryloxyethyl)piperazine (419)

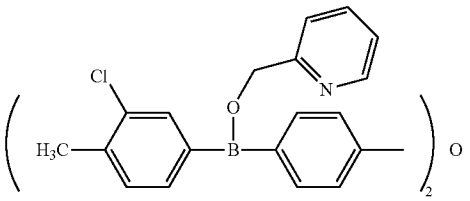
TG 108, x-Fold 1.02



Example 117

bis(3-chloro-4-methylphenyl 2-pyridylmethoxyborylphenyl)ether (434)

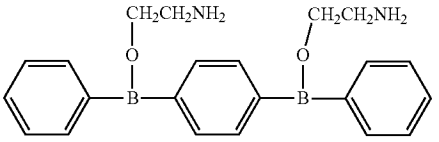
TG 108, x-Fold 0.06, SOC IC50 1.5 μM



Example 118

1,4-bis(phenyl-2-aminoethoxyboryl)benzene (544)

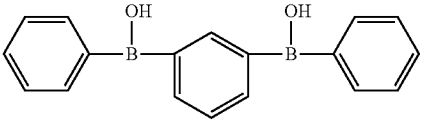
TG 93, x-Fold 0.97, SOC IC50 2 μM



Example 119

1,3-bis(phenylhydroxyboryl)benzene (554)

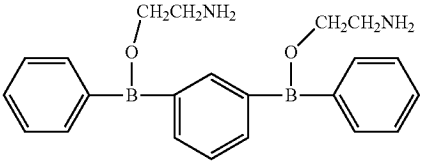
TG 101, x-Fold 0.84, SOC IC50 >20 μM



Example 120

1,3-bis(phenyl-2-aminoethoxyboryl)benzene (805)

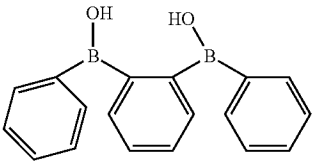
TG 88, x-Fold 1.08



Example 121

1,2-bis(phenylhydroxyboryl)benzene (583)

TG 121, x-Fold 0.94



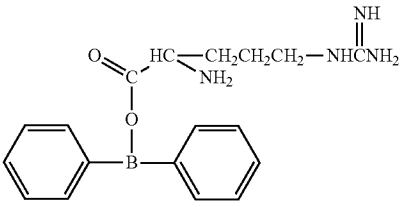
Example 122

diphenyl(argininate-O,N)borane (880)

TG 93, x-Fold 0.98, SOC IC50 7 μM

Arginine (82 mg) and 2-aminoethyldiphenylborinate (112 mg) were stirred in ethanol (0.4 ml), water (1.5 ml) and acetic acid (0.9 ml) at 110° C. for 3 hr to give the title compound (17 mg).

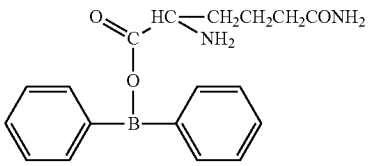
The present compound were also obtained by heating arginine hydrochloride (211 mg) and sodium tetraphenylborate (342 mg) in water (5 mL) at 100° C. for 3 hr.



Example 123

diphenyl(glutaminate-O,N)borane (870)

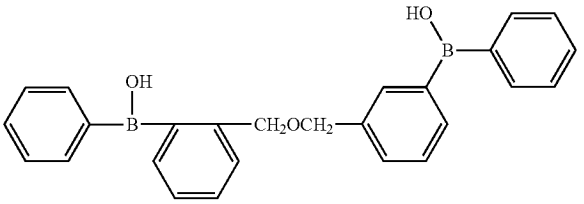
TG 98, x-Fold 0.84, SOC IC50 1 μM



Example 124

(2-phenylhydroxyborylbenzyl)(3-(phenylhydroxyboryl)benzyl)ether (656)

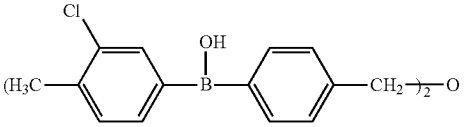
TG 90, x-Fold 0.96



Example 125

bis(3-chloro-4-methylphenyl hydroxyborylbenzyl)ether (595)

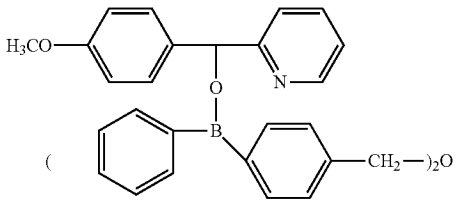
TG 113, SOC IC50 10 μM



Example 126

bis(phenyl 2-pyridyl-4-methoxyphenylmethoxyborylbenzyl)ether (601)

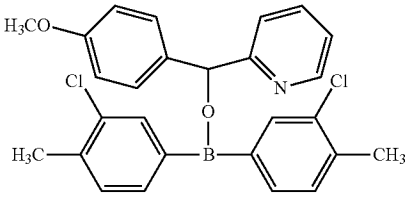
TG 81, x-Fold 1.04



Example 127

bis(3-chloro-4-methylphenyl) 2-pyridyl-4-methoxyphenylmethoxyborane (592)

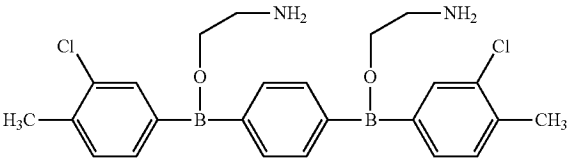
TG 109, x-Fold 0.70



Example 128

1,4-bis(3-chloro-4-methylphenyl-2-aminoethoxyboryl)benzene (573)

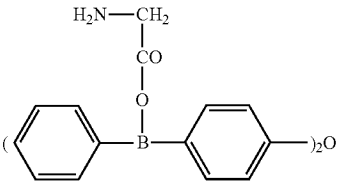
TG 143, x-Fold 0.93



Example 129

di((phenylglycine-O,N boryl)phenyl)ether (1016)

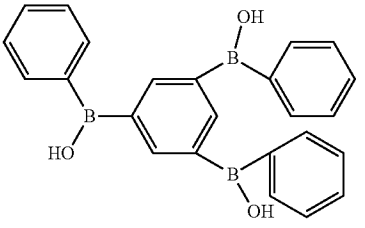
TG 101, x-Fold 0.78



Example 130

1,3,5-tri(phenylhydroxyboryl)benzene (563)

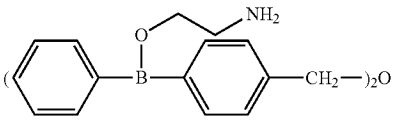
TG 116, x-Fold 0.85



Example 131

bis((4,4'-phenylaminoethoxyboryl)benzyl)ether (163AE)

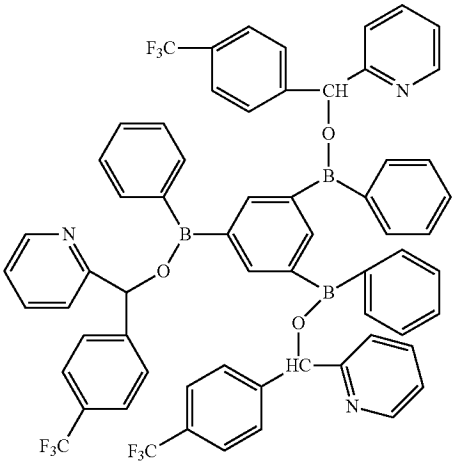
TG 16, x-Fold 1.1, SOC IC50 0.3 μM



Example 132

1,3,5-tri(2-pyridyl-4-trifluoromethylphenylmethoxyphenylboryl)benzene (567)

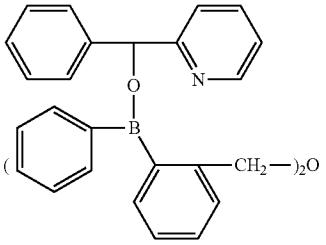
TG 88, x-Fold 0.95



Example 133

(2-pyridyl-phenylmethoxyphenylboryl 2-benzyl)ether (566)

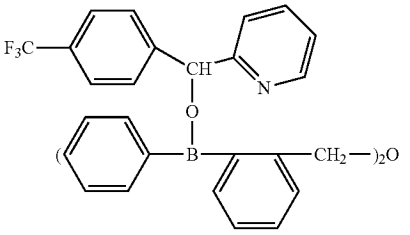
TG 106, x-Fold 1.00



Example 134

(2-pyridyl-4-trifluoromethylphenylmethoxyphenylboryl 2-benzyl)ether (558)

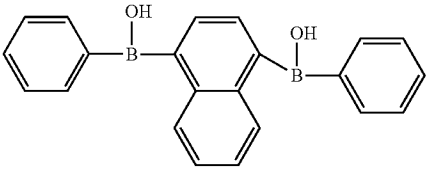
TG 94, x-Fold 0.92



Example 135

1,4-bis(phenylhydroxyboryl)naphthalene (602)

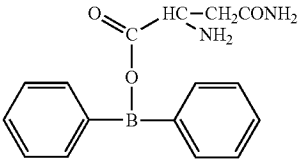
TG 99, x-Fold 1.03



Example 136

diphenyl(asparaginate-O,N)borane (871)

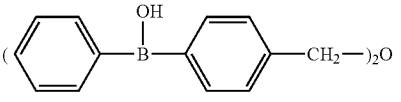
TG 96, x-Fold 0.98



Example 137

bis((4,4'-phenylhydroxyboryl)benzyl)ether (163OH)

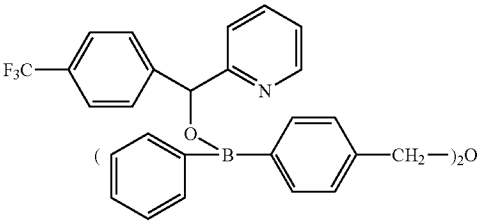
TG 14, x-Fold 0.99, SOC IC50 0.3 μM



Example 138

bis(2-pyridyl-4-trifluoromethylphenylmethoxyphenylboryl 4-benzyl)ether (607)

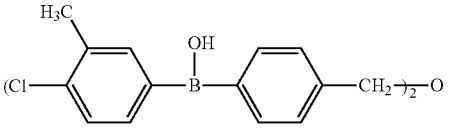
TG 96, x-Fold 0.99



Example 139

bis(4-chloro-3-methylphenylhydroxyboryl 4-benzyl)ether (611)

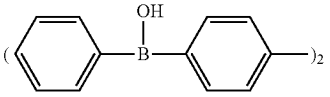
TG 122, x-Fold 0.88



Example 140

4,4'-phenylhydroxyboryl 4-biphenyl (548)

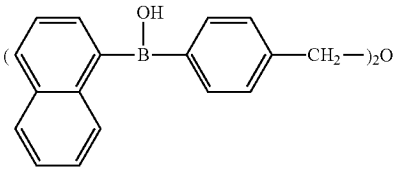
TG −72, x-Fold 0.85



Example 141

bis(4,4'-(1-naphthylhydroxyboryl)benzyl)ether (620)

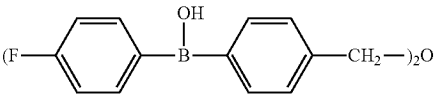
TG 97, x-Fold 0.92



Example 142

bis(4-fluorophenylhydroxyboryl 4-benzyl)ether (621)

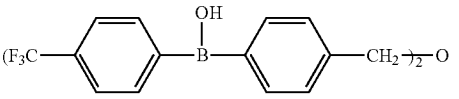
TG 88, x-Fold 0.24



Example 143

bis(4-trifluoromethylphenylhydroxyboryl 4-benzyl)ether (618)

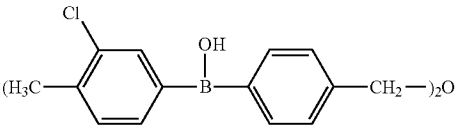
TG 118, x-Fold 0.90



Example 144

bis(3-chloro-4-methylphenylhydroxyboryl 4-benzyl)ether (612)

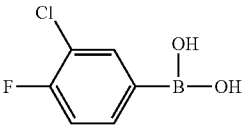
TG 99, x-Fold 0.87



Example 145

(3-chloro-4-fluorophenyl)boronic acid (6005)

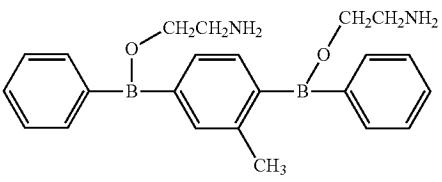
TG 97, x-Fold 0.91



Example 146

1,4-bis(phenyl-2-aminoethoxyboryl) 2-methylbenzene (803)

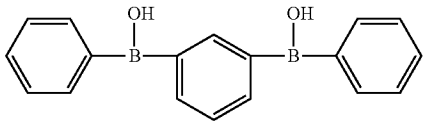
TG 91, x-Fold 1.02



Example 147

1,3-bis(phenylhydroxyboryl)benzene (554)

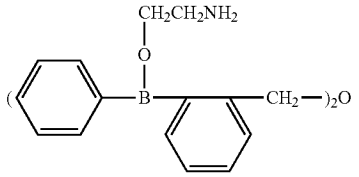
TG 101, x-Fold 0.87, SOC IC50 20 μM



Example 148

bis(2,2'-(phenyl-2-aminoethoxyboryl)benzyl)ether (557)

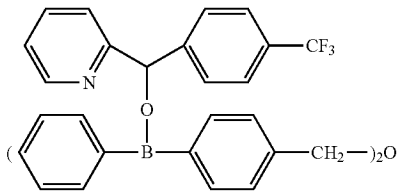
TG 68, x-Fold 1.00



Example 149

4,4'-di((phenyl 1-(pyridin-2-yl)-1-trifluoromethylphenylmethoxyboryl)benzyl)ether (607)

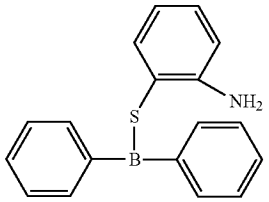
TG 96, x-Fold 0.99



Example 150

diphenyl-2-aminophenylthioborane (4122)

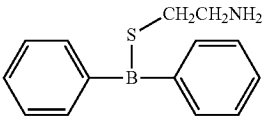
TG 2, x-Fold 0



Example 151

2-aminoethylthiodiphenylborane (1031)

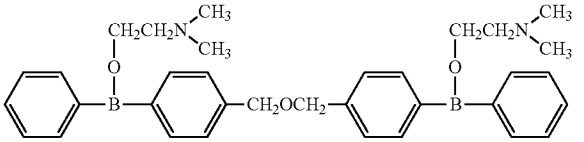
TG 33, x-Fold 0.87



Example 152

di(4,4'-phenyldimethylaminoethoxyboryl)benzylether (1073)

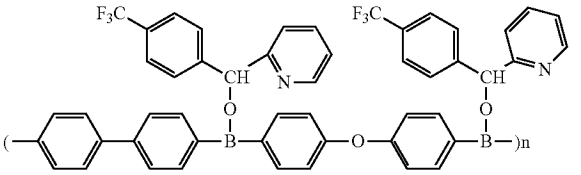
TG54, x-Fold 1.07



Example 153

poly(4,4'-biphenylene-2-pyridyl-4-trifluoromethylphenylmethoxyborane 4,4'-diphenylether 2-pyridyl-4-trifluoromethoxyborane) (1079)

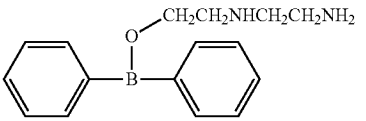
TG 65, x-Fold 0.79



Example 154

diphenyl 2-aminoethylaminoethyl borinate (1089)

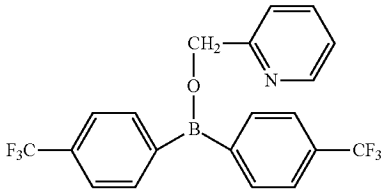
TG 105, x-Fold 0.96-



Example 155

di(trifluoromethylphenyl) 2-pyridinomethylborinate (427)

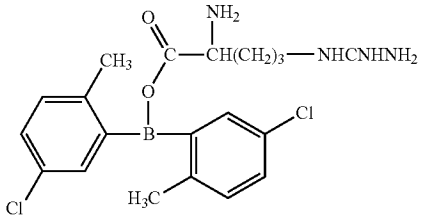
TG 100, x-Fold 1.02



Example 156

di(3-chloro-6-methyl-phenyl)(argininate-O,N)borane (7138)

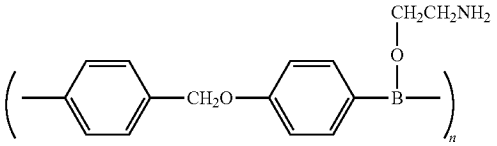
TG 91, x-Fold 1.08



Example 157

poly(phenylenemethyleneoxyphenyle-neaminoethoxyborane) (1116)

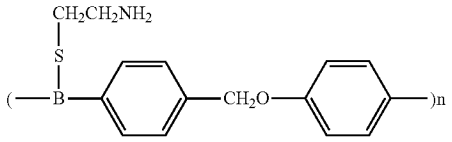
TG 96, x-Fold 0.73



Example 158

poly(phenylenemethyleneoxyphenyle-neaminoethylthioborane) (1117)

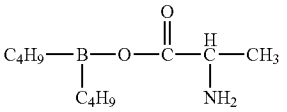
TG 12, x-Fold 0.69



Example 159

dibutyl(alanine-O,N)borane (926)

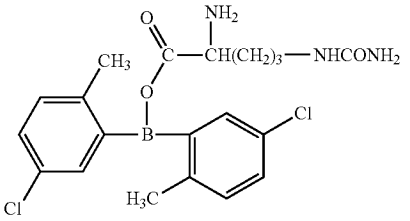
TG 102, x-Fold 0.96



Example 160

di(3-chloro-6-methyl-phenyl)(citrullinate-O,N)bo-rane (7139)

TG 88, x-Fold 1.02

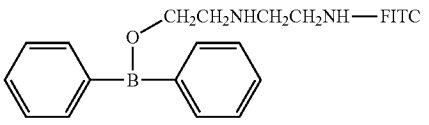


Example 161

FITC aminoethylaminoethyl diphenylborinate (1098)

TG 6, x-Fold 0.99

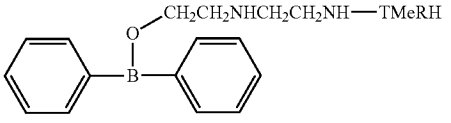
NHS-Florescein (Pierce: catalog No. 46100) (4.73 mg) was dissolved in DMF (100 μL), TEAB (pH 7.5) (100 μL) and diphenyl 2-aminoethylaminoethoxyborane (2.68 mg) were added, and the mixture was stirred at room temperature for 3 hr and applied to DEAE cellulose column for purification, whereby the title compound (8.1 mg) was obtained.



Example 162

tetramethylrhodamine aminoethylaminoethyl diphenylborinate (1099)

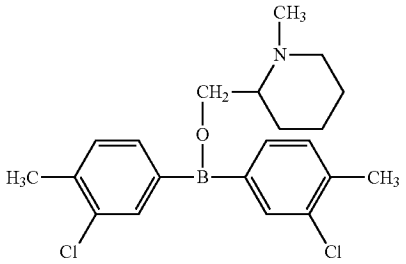
TG −2, x-Fold 0.85



Example 163

di(3-chloro-4-methylphenyl)N-methylpiperidinom-ethylborinate (347)

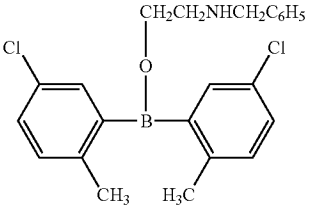
TG 109, x-Fold 1.00



Example 164

di(3-chloro-6-methylphenyl)benzylaminoethylborinate (376)

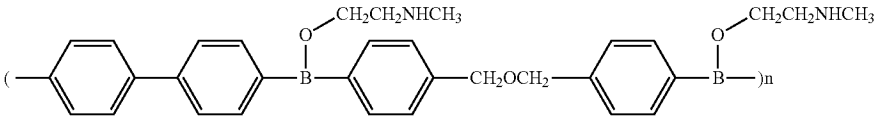
TG 94, x-Fold 0.67



Example 165

poly(4,4'-biphenylene-methylaminoethoxyborane 1,4-phenylene methyleneoxymethylenephenylene-methylaminoethoxyborane) (1143)

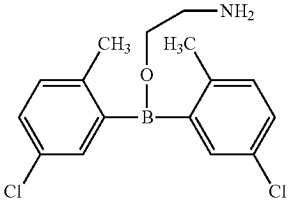
TG 120, x-Fold 0.99



Example 166

di(3-chloro-6-methylphenyl)aminoethylborinate (372)

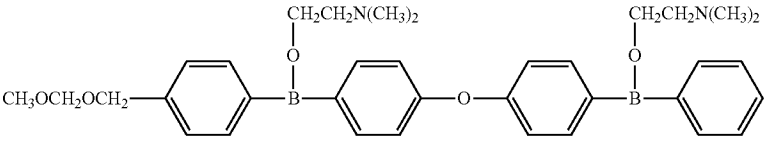
TG 74, x-Fold 0.70



Example 167

(4-(phenyl-dimethylaminoethoxyboryl)phenyl)-(4'-(methoxymethoxymethylphenyl-dimethylaminoethoxyboryl)phenyl)ether (2006)

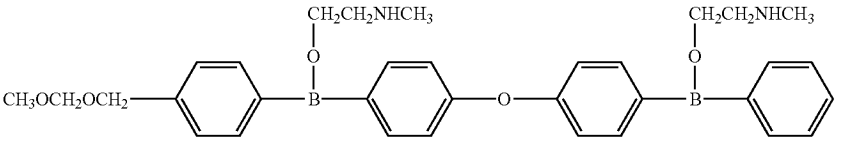
TG 21, x-Fold 0.71



Example 168

(4-(phenyl-N-methylaminoethoxyboryl)phenyl)-(4'-(methoxymethoxymethylphenyl-N-methylaminoethoxyboryl)phenyl)ether (2007)

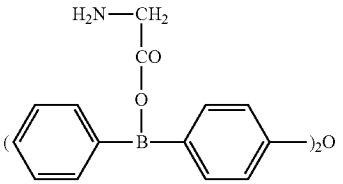
TG 35, x-Fold 0.72



Example 169

di((phenylglycine-O,N boryl)phenyl)ether (1016)

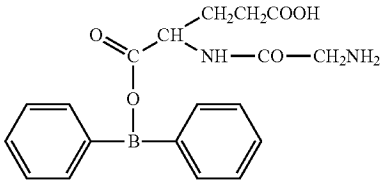
TG 101, x-Fold 0.78



Example 170

diphenyl(glycylglutamine-O,N)borane (907)

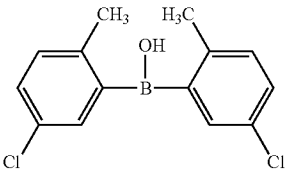
TG 96, x-Fold 0.96



Example 171

di(3-chloro-6-methylphenyl)borinic acid (370)

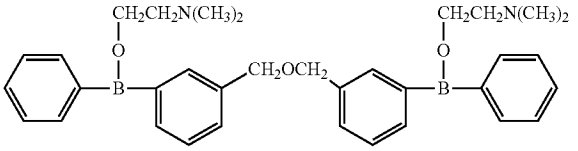
TG 98, x-Fold 0.71



Example 172

bis(3,3'(phenyldimethylaminoethoxyboryl)benzyl) ether (2024)

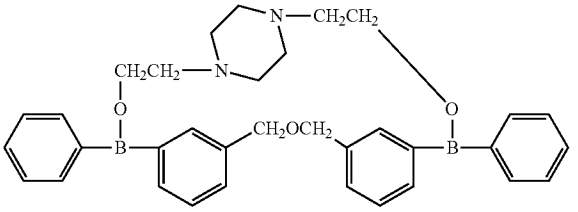
TG 69, x-Fold 1.22



Example 173

(3,3'-(phenylpiperazino-O,O-ethoxyboryl)benzyl) ether (2026)

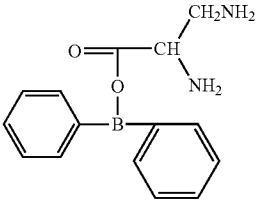
TG 122, x-Fold 1.06



Example 174

diphenyl(2,3-diaminopropionate-O,N)borane (2031-4)

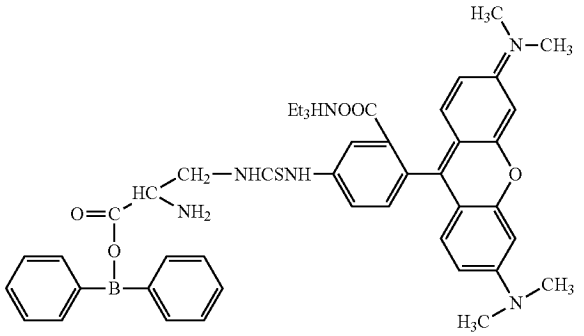
TG 103, x-Fold 0.99



Example 175

diphenyl(tetramethylrhodamine 2,3-diaminopropionate-O,N)borane (2033)

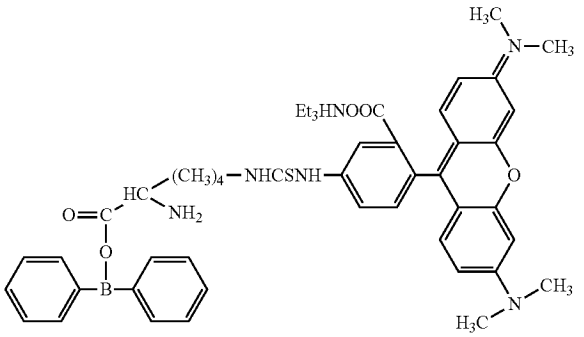
TG 5, x-Fold 0.89



Example 176

diphenyl(tetramethylrhodamine 2,6-diaminocapronate-O,N)borane (2035)

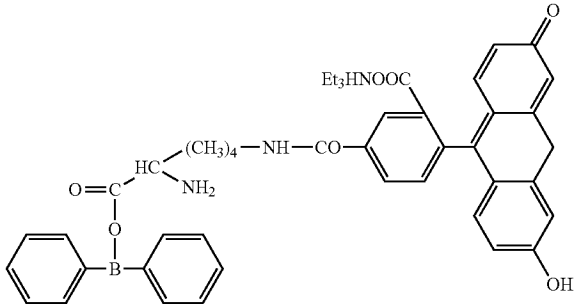
TG 47, x-Fold 1.06



Example 177

diphenyl(FITC-2,6-diaminocapronate-O,N)borane (2036)

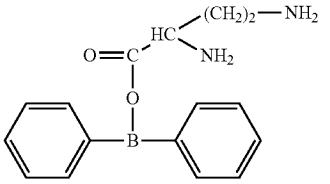
TG 28, x-Fold 1.00



Example 178

diphenyl(2,3-diaminobutyrate-O,N)borane (2039)

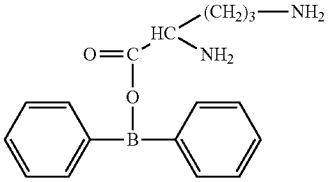
TG 142, x-Fold 0.89



Example 179

diphenyl(2,5-diaminopentanate-O,N)borane (2044)

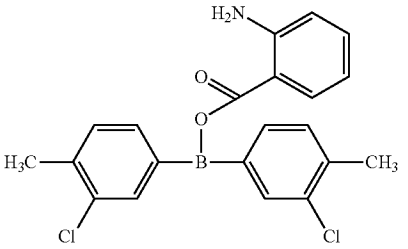
TG 127, x-Fold 0.99



Example 180

di(3-chloro-4-methylphenyl)(anthranate-O,N)borane (4124)

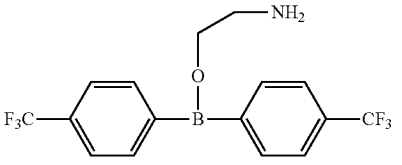
TG 35, x-Fold 0.98



Example 181

di(trifluoromethylphenyl) 2-aminoethylborinate (424)

TG 54, x-Fold 0.69

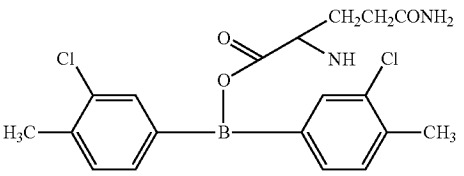


Example 182

di(3-chloro-4-methylphenyl)(glutaminate-O,N)borane (4105)

TG 137, x-Fold 1.01

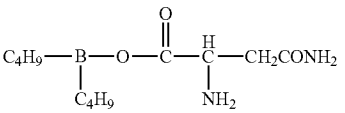
Di(3-chloro-4-methylphenyl)borinic acid (32 mg) and glutamine (15 mg) were reacted in ethanol (0.6 mL) at 90° C. for 2 hr to give the title compound (34 mg).



Example 183

dibutyl(asparagine-O,N)borane (925)

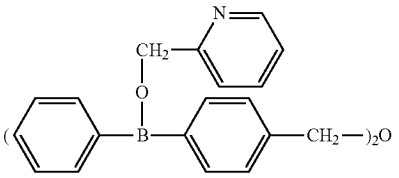
TG 91, x-Fold 1.02



Example 184

di(4-(phenyl-2-pyridylmethoxyboryl)benzyl)ether (2049)

TG 94, x-Fold 0.95

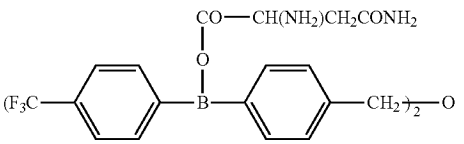


Example 185

bis(4,4'-(p-trifluoromethylphenyl-asparagineboryl) benzyl)ether (2064)

TG 130, x-Fold 0.94, SOC IC50 >20 μM

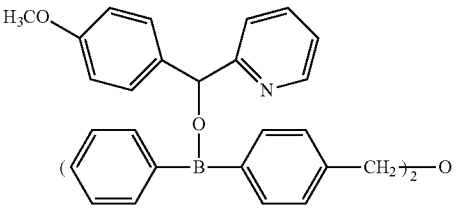
Aminoethyldiphenylborinate (112 mg) and piperazinecarboxylic acid (102 mg) were reacted in ethanol (0.6 mL) and acetic acid (30 mL) at 80° C. for 5 hr to give the title compound (36 mg).



Example 186

Di(1-(pyridin-2-yl)-1-(4-methoxyphenyl)methyl-phenyl-borylbenzyl)ether (601)

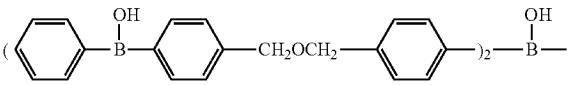
TG 81, x-Fold 0.98



Example 187

bis((4,4'-phenylhydroxyboryl)benzyloxybenzyl)hydroxyborane (2086)

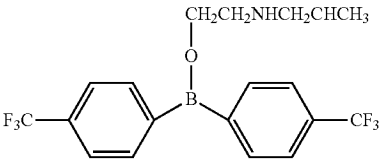
TG 106, x-Fold 0.97



Example 188

di(trifluoromethylphenyl) 2-propylaminoethylborinate (428)

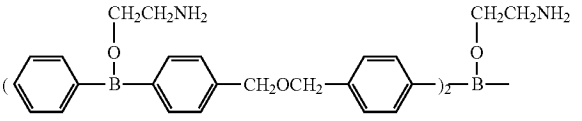
TG 91, x-Fold 0.98



Example 189

bis((4,4'-phenylaminoethoxyboryl)benzyloxybenzyl) aminoethoxyborane (2088)

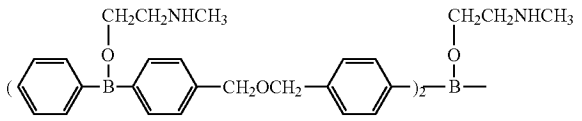
TG 119, x-Fold 0.94



Example 190

bis((4,4'-phenyl methylaminoethoxyboryl)benzyloxybenzyl)methylaminoethoxyborane (2089)

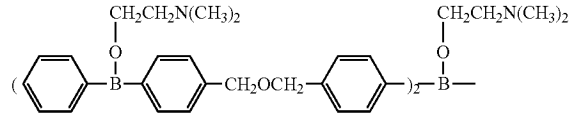
TG 99, x-Fold 1.05



Example 191

bis((4,4'-phenyldimethylaminoethoxyboryl)benzyloxybenzyl)dimethylamino-ethoxyborane (2090)

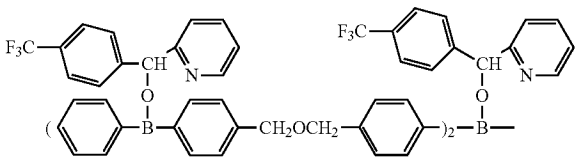
TG 85, x-Fold 1.04



Example 192

bis((4,4'-phenyl 2-pyridyl-4-trifluoromethylphenylmethoxyboryl)benzyloxybenzyl) 2-pyridyl-4-trifluoromethyl phenylmethoxyborane (2091)

TG 102, x-Fold 0.95

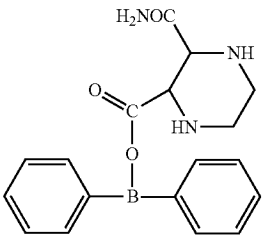


Example 193

diphenyl(2-piperazine-3-carboxyamide-carboxy) borane (899)

TG 92, x-Fold 1.03

Aminoethyldiphenylborinate (112 mg) and pyrazine 2,3-dicarboxylic acid monoamide (83 mg) were reacted in ethanol (0.5 mL) and acetic acid (30 mg) to give the title compound (40 mg).

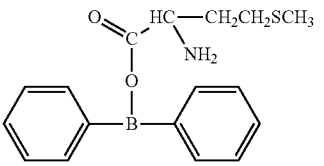


Example 194

diphenyl(methionate-O,N)borane (901)

TG 106, x-Fold 1.03

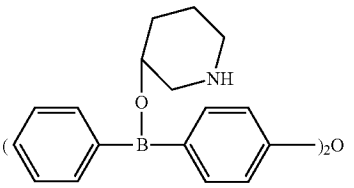
The title compound (35 mg) was obtained from diphenylborinic acid (61 mg) and methionine (50 mg).



Example 195

di(phenyl 3-piperidinooxyboryl phenyl)ether (2108)

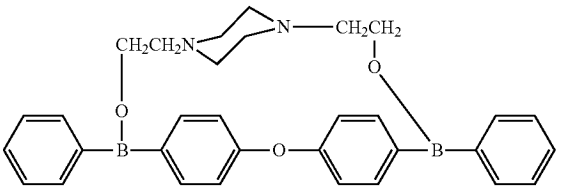
TG 115, x-Fold 0.77



Example 196

4,4'-(phenyl piperazino-O,O-ethoxyboryl)phenylether (2109)

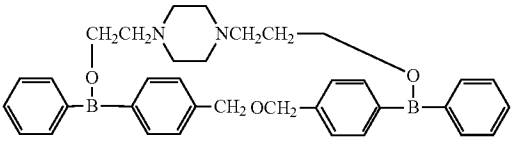
TG 117, x-Fold 0.90



Example 197

4,4'-(phenyl piperazino-O,O-ethoxyboryl)benzylether (3001)

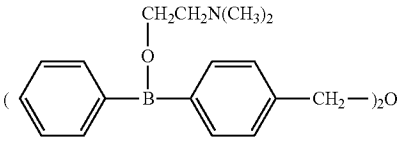
TG 99, x-Fold 1.02



Example 198

bis(4,4'-(phenyldimethylaminoethoxyboryl)benzyl) ether (3003)

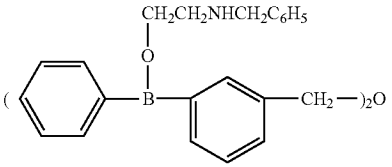
TG 28, x-Fold 0.8



Example 199

bis(3,3'-(phenylbenzylaminoethoxyboryl)benzyl) ether (3017)

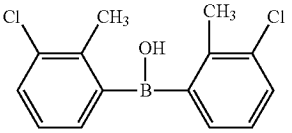
TG 3, x-Fold 0.90



Example 200

di(3-chloro-2-methylphenyl)borinic acid (442)

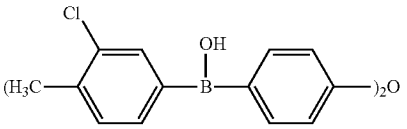
TG 100, x-Fold 0.92



Example 201

4,4'-di((3-chloro-4-methylphenyl 2-hydroxyboryl) phenyl)ether (431)

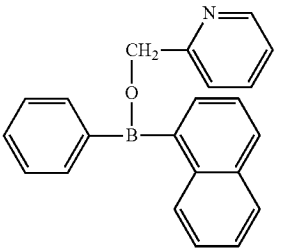
TG 99, x-Fold 0.57



Example 202

phenyl naphthyl 2-pyridylmethylborinate (3041)

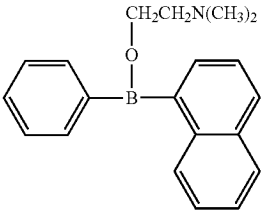
TG 91, x-Fold 0.94



Example 203

phenyl naphthyl dimethylaminoethylborinate (3044)

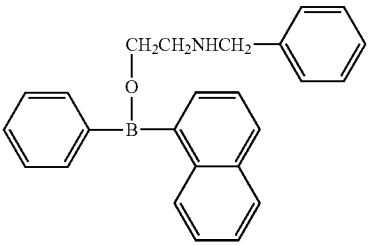
TG 97, x-Fold 0.97



Example 204

phenyl naphthyl benzylaminoethylborinate (3045)

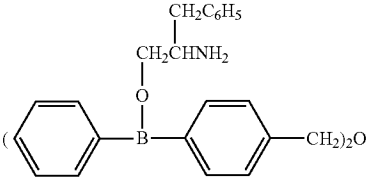
TG 61, x-Fold 0.79



Example 205

bis(4,4'-(phenyl 2-amino-2-benzylethoxyboryl)benzyl)ether (3087)

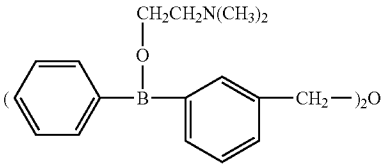
TG 47, x-Fold 0.80



Example 206

bis(3,3'-(phenyldimethylaminoethoxyboryl)benzyl) ether (3107)

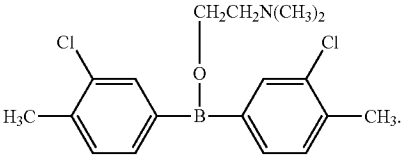
TG 34, x-Fold 1.14



Example 207

di(3-chloro-4-methylphenyl)dimethylaminoethyl-borinate (3108)

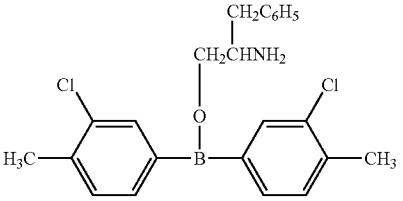
TG 83, x-Fold 0.91



Example 208

di(3-chloro-4-methylphenyl)-2-benzyl-2-aminoethyl-borinate (3109)

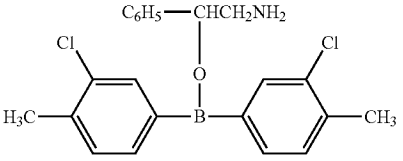
TG −7, x-Fold 0.67



Example 209

di(3-chloro-4-methylphenyl)1-phenyl 2-aminoethylborinate (3111)

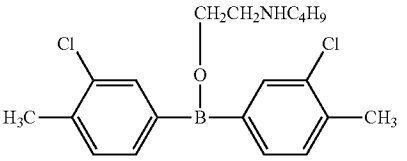
TG 1, x-Fold 0.98



Example 210

di(3-chloro-4-methylphenyl)butylaminoethyl borinate (3112)

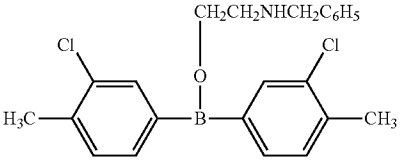
TG 27, x-Fold 0.98, SOC IC50 2 μM



Example 211

di(3-chloro-4-methylphenyl)benzylaminoethyl borinate (3113)

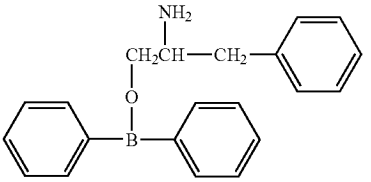
TG 86, x-Fold 0.99, SOC IC50 1 μM



Example 212

diphenyl(R) 2-benzyl-2-aminoethyl borinate (3073)

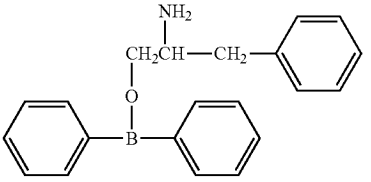
TG 115, x-Fold 0.75



Example 213

diphenyl(S) 2-benzyl-2-aminoethyl borinate (3075)

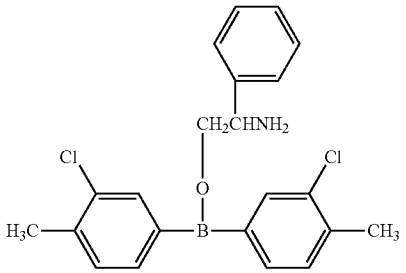
TG 117, x-Fold 1.00



Example 214

di(3-chloro-4-methylphenyl) 1-phenylaminoethylborinate (3114)

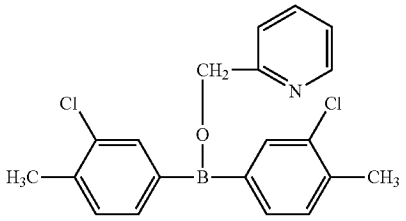
TG −7, x-Fold 0.90, SOC IC50 2 μM



Example 215

di(3-chloro-4-methylphenyl)pyridylmethylborinate (3116)

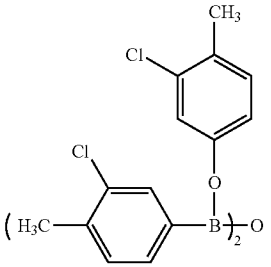
TG 69, x-Fold 1.03, SOC IC50 2 μM



Example 216

di(3-chloro-4-methylphenyl)borinic acid anhydride (4139)

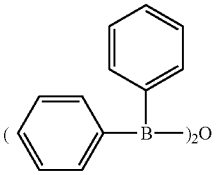
TG 17, x-Fold 1.03, SOC IC50 0.6 μM



Example 217

diphenylborinic acid anhydride (4111)

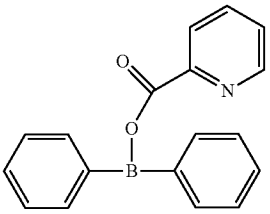
TG 118, x-Fold 0.94



Example 218

diphenyl(picolinate-O,N)borane (4118)

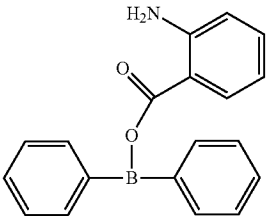
TG 90, x-Fold 0.97



Example 219

diphenyl(2-aminophenyl carboxylate-O,N)borane (4119)

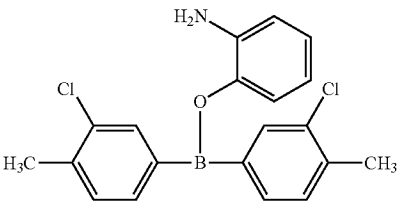
TG 91, x-Fold 0.88



Example 220

di(3-chloro-4-methylphenyl) 2-aminophenylborinate (4121)

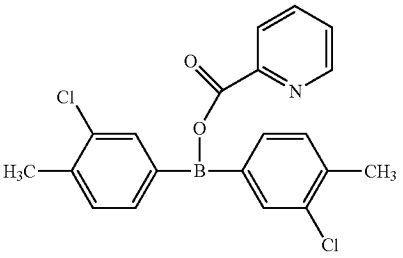
TG 26, x-Fold 0.50, SOC IC50 0.5 μM



Example 221

di(3-chloro-4-methylphenyl)(2-pyridine carboxylate-O,N)borane (4123)

TG 73, x-Fold 0.94



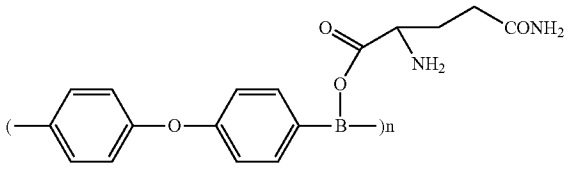
Example 222

poly(4,4'-diphenylether glutamine-O,N borane) (8003)

TG 122, x-Fold 0.86

Compound 7142 (Example 478) (53.3 mg) and glutamine (44 mg) were reacted in ethanol (2 ml) at 80° C. for 24 hr to give the title compound (14 mg).

NMR (DMSO) 1.95 (m, 2H), 2.0 (m, m, 2H), 2.23 (m, 2H), 3.35 (m, 4H), 7.4-8.1 (m, 8H)



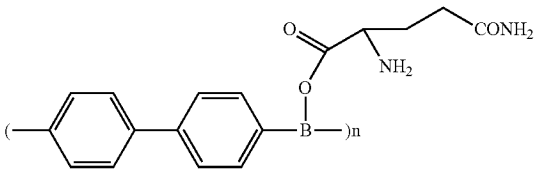
Example 223

poly(4,4'-diphenyl glutamine-O,N borane) (8006)

TG 116, x-Fold 1.02

Compound 4144 (Example 235) (41.3 mg) and glutamine (36 mg) were reacted in ethanol (2 ml) at 80° C. for 24 hr to give the title compound (75 mg).

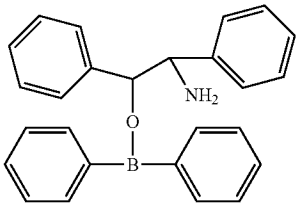
NMR (DMSO) 1.95 (m, 2H), 2.05 (m, 2H), 2.25 (m, 2H), 3.40 (m, 4H), 6.8-7.7 (m, 8H)



Example 224

diphenyl 1-(2-aminobenzyl) 1-phenylmethylborinate (4127)

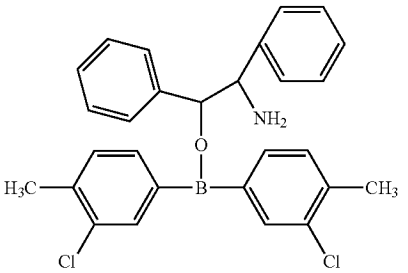
TG 112, x-Fold 0.89



Example 225

di(3-chloro-4-methylphenyl) 1-(2-aminobenzyl) 1-phenylmethylborinate (4128)

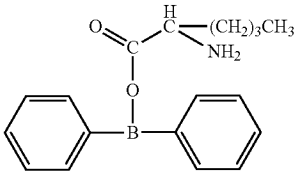
TG 109, x-Fold 1.03, SOC IC50 0.5 μM



Example 226

diphenyl(2-aminohexanecarboxylate-O,N)borane (4129)

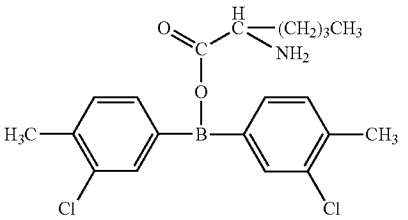
TG 97, x-Fold 0.94



Example 227

di(3-chloro-4-methylphenyl)(norloysinate-O,N)borane (4130)

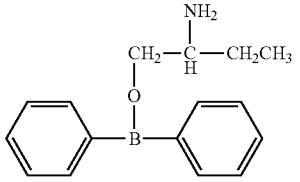
TG 110, x-Fold 0.99



Example 228

diphenyl 2-aminobutylborinate (4131)

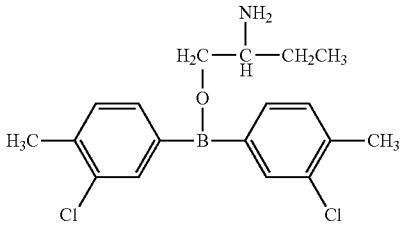
TG 99, x-Fold 0.98



Example 229

di(3-chloro-4-methylphenyl) 2-aminobutylborinate (4132)

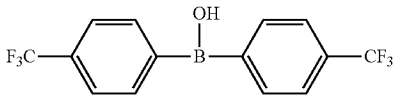
TG 40, x-Fold 1.09, SOC IC50 0.5 μM



Example 230

di(trifluoromethylphenyl)borinic acid (4138)

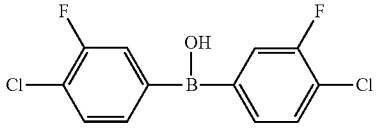
TG 108, x-Fold 1.03



Example 231

di(3-fluoro-4-chlorophenyl)borinic acid (4140)

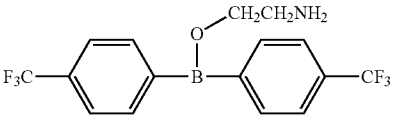
TG 94, x-Fold 1.01



Example 232

di(trifluoromethylphenyl) 2-aminoethylborinate (4141)

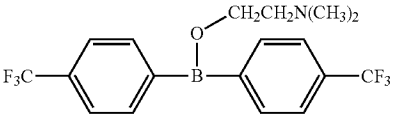
TG 108, x-Fold 1.10



Example 233

di(trifluoromethylphenyl) 2-dimethylaminoethylborinate (4142)

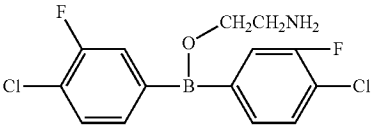
TG 112, x-Fold 1.12



Example 234

di(4-chloro-3-fluoro-phenyl) 2-aminoethylborinate (4143)

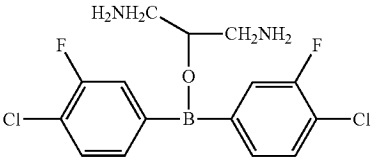
TG 98, x-Fold 1.07, SOC IC50 0.5 μM



Example 235

di(4-chloro-3-fluorophenyl) 2,3-diamino-2-propyl-borinate (4144)

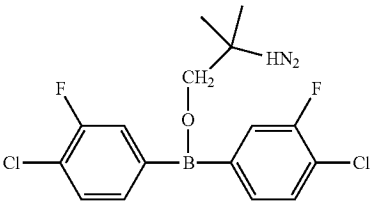
TG 80, x-Fold 1.03



Example 236

di(4-chloro-3-fluorophenyl) 2-amino-2-methyl-propyl-borinate (4145)

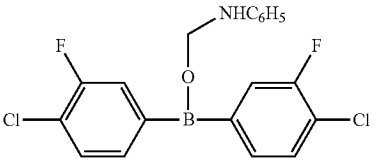
TG 87, x-Fold 1.10



Example 237

di(4-chloro-3-fluorophenyl) 2-phenylaminoethyl borinate (4146)

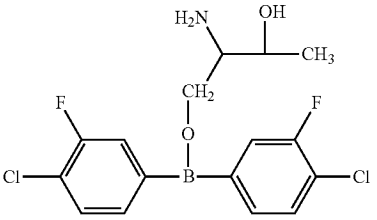
TG 88, x-Fold 1.15



Example 238

di(4-chloro-3-fluorophenyl) 2-amino-3-hydroxybutyl borinate (4147)

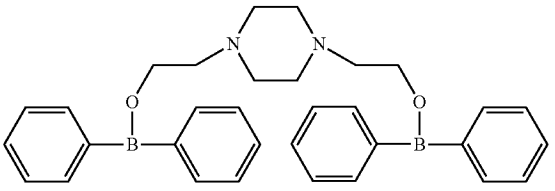
TG 87, x-Fold 1.07



Example 239

bis(diphenyl piperazino-O,O-ethoxyborane) (356)

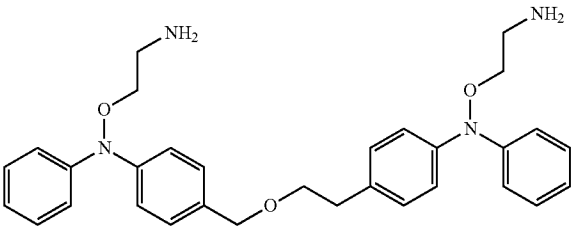
TG 126, x-Fold 0.94



Example 240

4-((2-aminoethoxy)phenylboryl)benzyl-4'-((2-aminoethoxy)phenylboryl)phenethylether (7117)

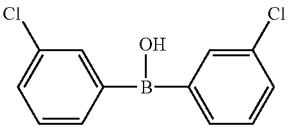
TG 25, x-Fold 0.99, SOC IC50 0.08 μM



Example 241

di(3-chlorophenyl)borinic acid (244)

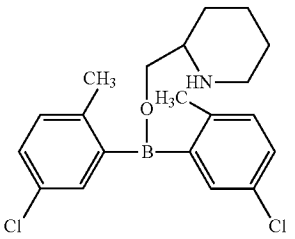
TG 67, x-Fold 1.10



Example 242

di(5-chloro-2-methylphenyl) 2-piperidinomethylborinate (371)

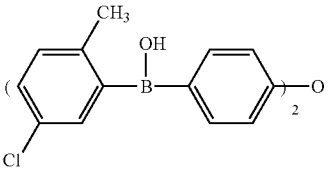
TG 98, x-Fold 1.17



Example 243

di((5-chloro-2-methylphenyl)hydroxyborylphenyl) ether (436)

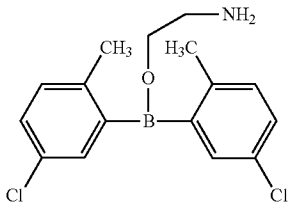
TG 106, x-Fold 0.73



Example 244

di(5-chloro-2-methylphenyl) 2-aminoethylborinate (372)

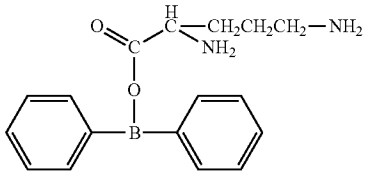
TG 74, x-Fold 0.76, SOC IC50 1 μM



Example 245

diphenyl(ornithine-O,N)borane (921)

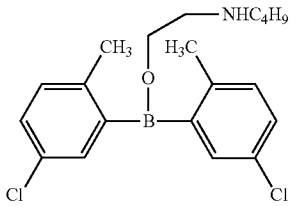
TG 94, x-Fold 0.91



Example 246

di(5-chloro-2-methylphenyl)
2-butylaminoethylborinate (376)

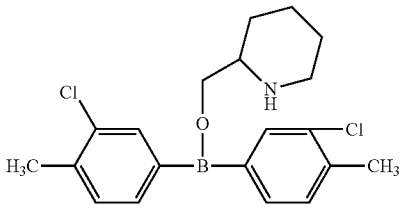
TG 94, x-Fold 0.67



Example 247

di(3-chloro-4-methylphenyl)
2-piperidinomethylborinate (422)

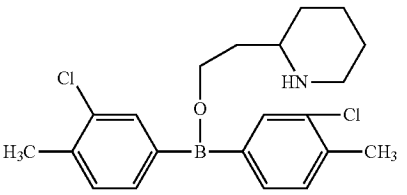
TG 99, x-Fold 0.91, SOC IC50 0.7 μM



Example 248

di(3-chloro-4-methylphenyl)
2-piperidinoethylborinate (421)

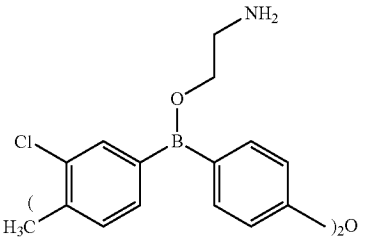
TG 103, x-Fold 0.87



Example 249

4,4'-((2-aminoethoxy)(3-chloro-4-methylphenyl)
boryl)diphenylether (7118)

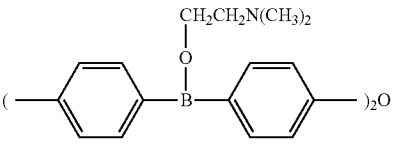
TG 25, x-Fold 0.74, SOC IC50 0.3 μM



Example 250

bis(4,4'-(phenyldimethylaminoethoxyboryl)phenyl)
ether (1007)

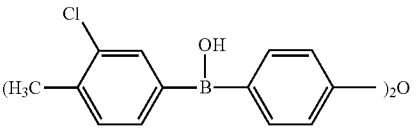
TG 125, x-Fold 0.86



Example 251

bis(3-chloro-4-methylphenyl
hydroxyborylphenyl)ether (488)

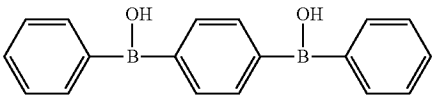
TG 121, x-Fold 0.83



Example 252

1,4-bis(phenylhydroxyboryl)benzene (542)

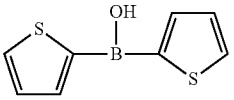
TG 93, x-Fold 0.95, SOC IC50 0.5 μM



Example 253

di(2-thiophene)borinic acid (283)

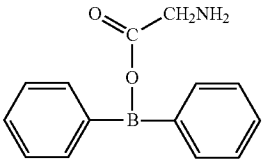
TG 92, x-Fold 1.11



Example 254

diphenyl(glycinate-O,N)borane (827)

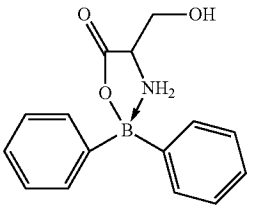
TG 101, x-Fold 0.95



Example 255

diphenyl(serinate-O,N)borane (828)

TG 113, x-Fold 0.94, SOC IC50 0.5 μM

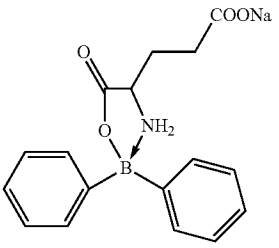


Example 256

diphenyl(glutaminate-O,N)borane (829)

TG 112, x-Fold 0.67, SOC IC50 1.5 μM

Diphenylborinic acid (78 mg) and sodium glutamate (73 mg) were stirred with heating in ethanol, water 1:1 mixture (1 mL) at 70° C. for 1 hr to give the title compound (120 mg).

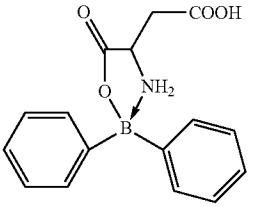


Example 257

diphenyl(asparaginate-O,N)borane (830)

TG 103, x-Fold 0.98

Diphenylborinic acid (50 mg) and aspartic acid (25 mg) were stirred with heating in ethanol, water 1:1 mixture (1 mL) at 70° C. for 1 hr to give the title compound (6 mg).

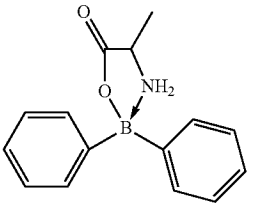


Example 258

diphenyl(alaninate-O,N)borane (833)

TG 110, SOC IC50 5 μM

Diphenylborinic acid (50 mg) and L-alanine (25 mg) were stirred with heating in ethanol, water 1:1 mixture (1 mL) at 70° C. for 1 hr to give the title compound (6 mg).

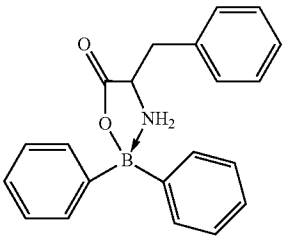


Example 259

diphenyl(phenylalaninate-O,N)borane (841)

TG 67, x-Fold 0.97, SOC IC50 2.5 μM

Diphenylborinic acid (47 mg) and phenylalanine (43 mg) were stirred with heating in ethanol, water 1:1 mixture (1 mL) at 70° C. for 16 hr to give the title compound (10 mg).

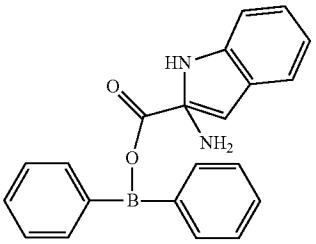


Example 260

diphenyl(tryptophanate-O,N)borane (836)

TG 106, x-Fold 0.89

Diphenylborinic acid (46 mg) and tryptophan (52 mg) were stirred with heating in ethanol, water 1:1 mixture (1 mL) at 70° C. for 1 hr to give the title compound (15 mg).

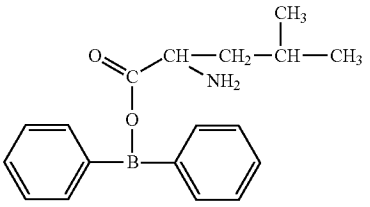


Example 261

diphenyl(leucinate-O,N)borane (837)

TG 109, x-Fold 0.89

Diphenylborinic acid (46 mg) and leucine (33 mg) were stirred with heating in ethanol, water 1:1 mixture (1 ml) at 70° C. for 1 hr to give the title compound (10 mg).

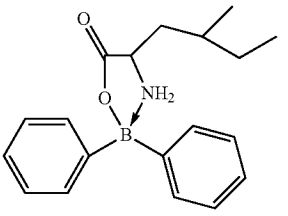


Example 262

diphenyl(isoleucinate-O,N)borane (838)

TG 115, x-Fold 0.97

Diphenylborinic acid (52 mg) and isoleucine (37 mg) were stirred with heating in ethanol, water 1:1 mixture (1 mL) at 70° C. for 1 hr to give the title compound (10 mg).

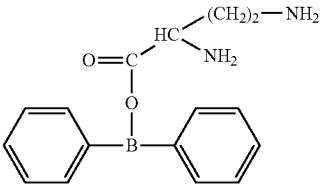


Example 263

diphenyl(2,4-diaminolactonate-O,N)borane (2045)

TG 146, x-Fold 0.89, SOC IC50 3 μM

Sodium tetraphenylborate (342 mg) and 2,4-diaminobutyric acid-hydrochloride (191 mg) were stirred with heating in water (7 ml) at 80° C. for 1 hr to give the title compound (160 mg).

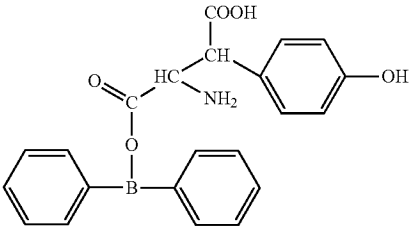


Example 264

diphenyl(tyrosinate-O,N)borane (842)

TG 109, x-Fold 1.00, SOC IC50 5 μM

Diphenylborinic acid (57 mg) and tyrosine (57 mg) were stirred with heating in ethanol, water 1:1 mixture (1 ml) at 70° C. for 1 hr to give the title compound (24 mg).

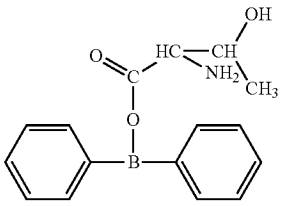


Example 265

diphenyl(threoninate-O,N)borane (851)

TG 112, x-Fold 0.94

Diphenylborinic acid (42 mg) and threonine (28 mg) were stirred with heating in ethanol, water 1:1 mixture (0.5 mL) at 70° C. for 1 hr to give the title compound (20 mg).

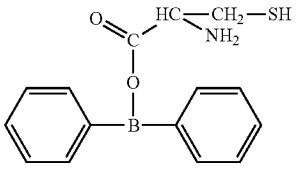


Example 266

diphenyl(cysteinate-O,N)borane (847)

TG 84, x-Fold 0.87, SOC IC50 3 μM

Diphenylborinic acid (31 mg) and cysteine (21 mg) were stirred with heating in ethanol, water 1:1 mixture (0.5 mL) at 70° C. for 1 hr to give the title compound (20 mg).

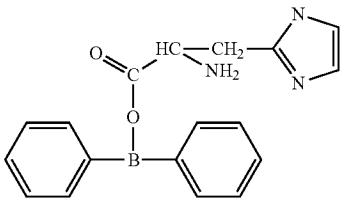


Example 267

diphenyl(histidinate-O,N)borane (848)

TG 82, x-Fold 0.60, SOC IC50 3 μM

Diphenylborinic acid (32 mg) and histidine hydrochloride (36 mg) were stirred with heating in ethanol, water 1:1 mixture (0.5 mL) at 70° C. for 1 hr to give the title compound (6 mg).

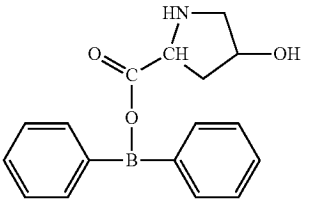


Example 268

diphenyl(hydroxyprolinate-O,N)borane (852)

TG 103, x-Fold 0.96, SOC IC50 5 μM

Diphenylborinic acid (41 mg) and hydroxyproline (30 mg) were stirred with heating in ethanol, water 1:1 mixture (0.5 ml) at 70° C. for 1 hr to give the title compound (5 mg).

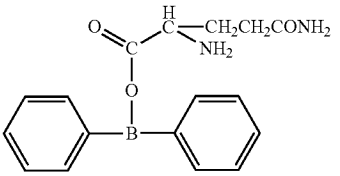


Example 269

diphenyl(glutaminate-O,N)borane (879)

TG 95, x-Fold 1.01, SOC IC50 3 μM

Diphenyl 2-aminoethylborinate (112 mg) and glutamine (74 mg) were stirred with heating in a mixture of ethanol (0.4 mL), water (1.5 ml) and acetic acid (0.03 ml) at 100° C. for 10 min to give the title compound (21 mg).

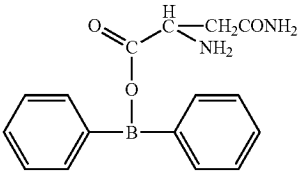


Example 270

diphenyl(asparaginate-O,N)borane (855)

TG 111, x-Fold 0.54, SOC IC50 0.7 μM

Diphenylborinic acid (182 mg) and asparagine (32 mg) were stirred with heating in ethanol, water 3:1 mixture (1 mL) at 70° C. for 1 hr to give the title compound (14 mg).

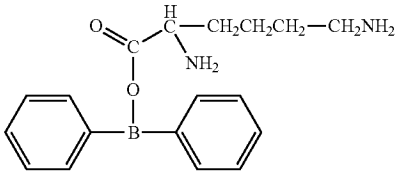


Example 271

diphenyl(lysinate-O,N)borane (906)

TG 109, x-Fold 1.07, SOC IC50 0.5 μM

Diphenylborinic acid (49 mg) and lysine hydrochloride (49 mg) were stirred with heating in a mixture of ethanol (1.5 ml) and water (0.5 mL) at 80° C. for 1 hr to give the title compound (44 mg).

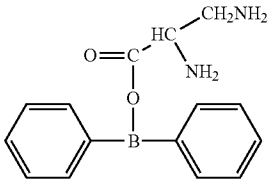


Example 272

diphenyl(2,3-diaminopropionate-O,N)borane (2043)

TG 83, x-Fold 0.09, SOC IC50 0.3 μM

Sodium tetraphenylborate (342 mg) and 2,4-diaminopropionic acid•hydrochloride (141 mg) were stirred with heating in water (5.5 ml) at 80° C. for 2 hr to give the title compound (203 mg).

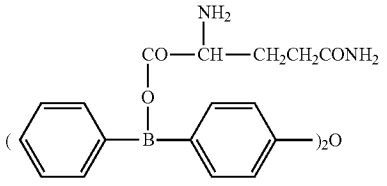


Example 273

bis(4,4'-(phenyl-glutamineboryl)phenyl)ether (1024)

TG 83, x-Fold 0.56, SOC IC50 0.25 μM

Bis(4,4'-(phenylhydroxyboryl)phenyl)ether (22 mg) and glutamine (19 mg) were heated in ethanol (2 mL) at 60° C. for 1 hr to give the title compound (8 mg).

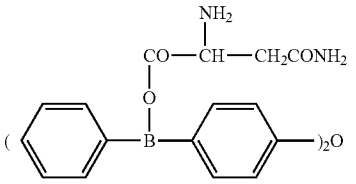


Example 274

bis(4,4'-(phenylasparagineboryl)phenyl)ether (1023)

TG 56, x-Fold 0.59, SOC IC50 0.3 μM

Bis(4,4'-(phenylhydroxyboryl)phenyl)ether (20 mg) and asparagine (14 mg) were stirred with heating in ethanol (3 mL) at 60° C. for 1 hr to give the title compound (7 mg).

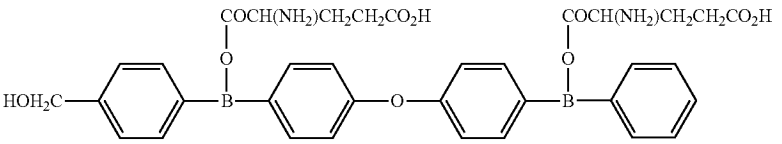


Example 275

(4-(phenyl-glutamic acid boryl)phenyl)-(4'-(hydroxymethylphenyl-glutamic acid boryl)phenyl)ether (1036)

TG 117, x-Fold 0.67, SOC IC50 0.3 μM

4-(Phenyl-hydroxyboryl)phenyl)-4'-(hydroxymethylphenyl-hydroxyboryl)phenyl)ether (27 mg) and sodium glutamate (22.3 mg) were reacted in ethanol (0.5 mL) to give the title compound (23 mg).

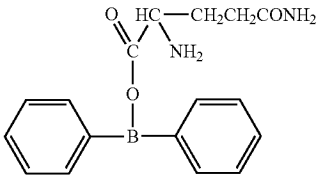


Example 276

diphenyl(glutaminate-O,N)borane (854)

TG 105, x-Fold 0.8

Diphenylborinic acid (39 mg) and glutamine (3.7 mg) were reacted in ethanol (0.6 mL) at 60° C. for 1 hr to give the title compound (10 mg).

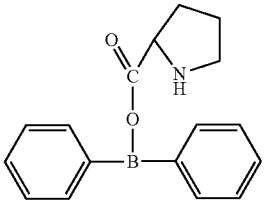


Example 277

diphenyl(prolinate-O,N)borane (843)

TG 105, x-Fold 0.98, SOC IC50 0.3 μM

Diphenylborinic acid (47 mg) and proline (2.7 mg) were reacted in ethanol (0.6 ml) at 60° C. for 1 hr to give the title compound (10 mg).



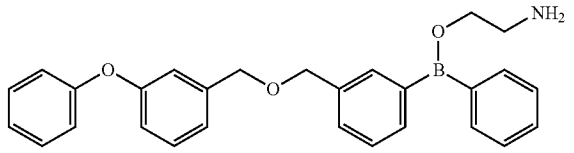
Example 278

(3-phenoxybenzyl)-(3'-(phenyl-2-aminoethoxyboryl) benzyl)ether (7119)

TG 2, x-Fold 1.08, SOC IC50 0.3 μM

Using 3-bromobenzyl-3'-phenoxybenzylether (1173 mg), bromobenzene (400 mg) and triisopropoxyborane (560 mg) as main starting materials, hydroxybromo compound was synthesized, and reacted with ethanolamine at room temperature to give the title compound (700 mg).

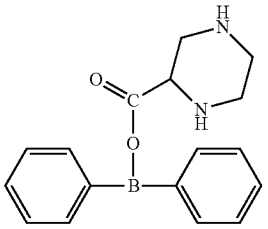
NMR ($CDCl_3$), 2.73 (m, 2H), 3.72 (t, 2H), 4.14 (m, 4H), 4.49 (s, 2H), 6.8-7.3 (m, 18H)



Example 279

diphenyl(2-piperazinecarboxy)borane (894)

TG 103, x-Fold 0.98

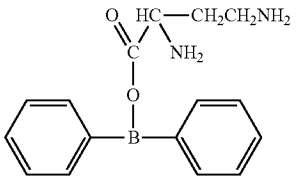


Example 280

diphenyl(2,4-diaminolacetic acid)borane (897)

TG 98, x-Fold 0.88

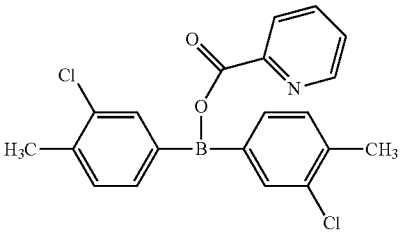
Aminoethyldiphenylborinate (112 mg) and 2,4-diaminobutyric acid•hydrochloride (35 mg) were reacted in ethanol (0.5 ml) and acetic acid (30 mg) to give the title compound (139 mg).



Example 281

di(3-chloro-4-methylphenyl)-(picolinate-O,N)borane (4123)

TG 77, x-Fold 0.94

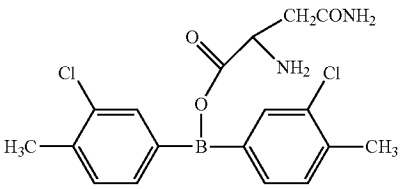


Example 282

di(3-chloro-4-methylphenyl)(asparaginate-O,N)borane (4103)

TG 112, x-Fold 0.95, SOC IC50 0.3 μM

Di(3-chloro-4-methyl)phenylborinic acid (82 mg) and asparagine (81 mg) were reacted in ethanol (0.6 mL) to give the title compound (37 mg).

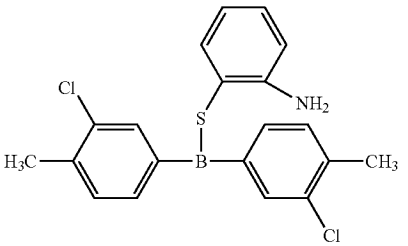


Example 283

di(3-chloro-4-methylphenyl) 2-aminophenylthioborane (4125)

TG 12, x-Fold 0.83, SOC IC50 0.9 μM

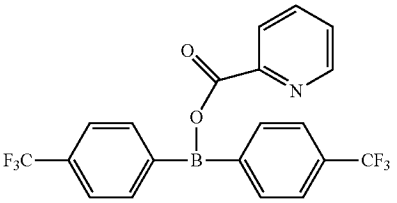
Di(3-chloro-4-methyl)phenylborinic acid (47 mg) and dimethylaminoethanethiol (17 mg) were stirred in ether (1 ml) overnight, ether (2 ml) was added to give the title compound (17 mg) as a white precipitate.



Example 284

di(4-trifluoromethylphenyl) (picolinate-O,N)borane (5003)

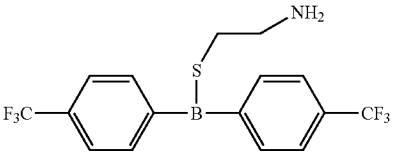
TG 89, x-Fold 1.03



Example 285

di(4-trifluoromethylphenyl) 2-aminoethylthioborane (5004)

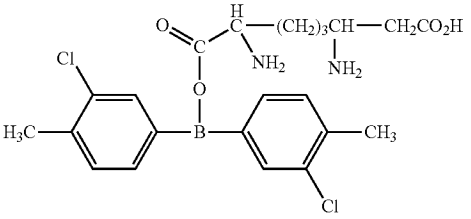
TG 51, x-Fold 0.99, SOC IC50 2 μM



Example 286

di(3-chloro-4-methylphenyl)(2,6-diaminopimelinate-O,N)borane (5012)

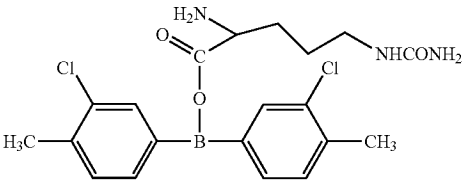
TG 104, x-Fold 0.93



Example 287

di(3-chloro-4-methylphenyl)(citrullinate-O,N)borane (5013)

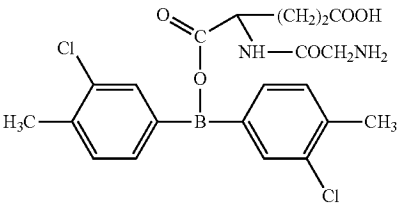
TG 146, x-Fold 1.00



Example 288

di(3-chloro-4-methylphenyl)(glycylglutaminate-O,N)borane (5014)

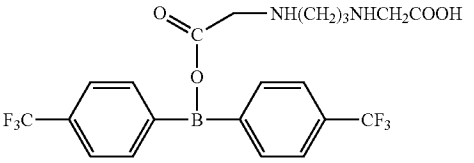
TG 106, x-Fold 1.02



Example 289

di(4-trifluoromethylphenyl)(1,3-propylenediaminediacetate-O,N)borane (5015)

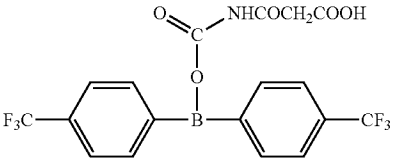
TG 94, x-Fold 1.08, SOC IC50 0.3 μM



Example 290

di(4-trifluoromethylphenyl)(glycylglycinate-O,N)borane (5018)

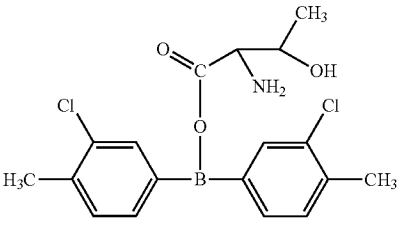
TG 113, x-Fold 1.05



Example 291

di(3-chloro-4-methylphenyl)(allothreoninate-O,N)borane (5019)

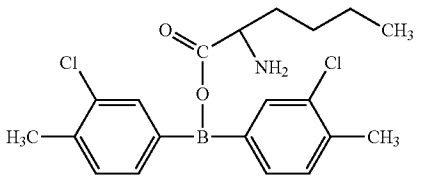
TG 50, x-Fold 1.02, SOC IC50 0.5 μM



Example 292

di(3-chloro-4-methylphenyl)(norloysinate-O,N)borane (5020)

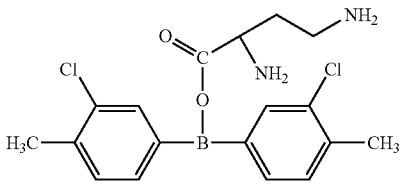
TG 146, x-Fold 1.00, SOC IC50 1 μM



Example 293

di(3-chloro-4-methylphenyl)(2,4-diaminobutyrate-O,N)borane (5021)

TG 116, x-Fold 0.91

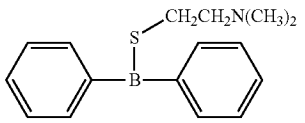


Example 294

diphenyl dimethylaminoethylthioborane (4106)

TG 114, x-Fold 0.96, SOC IC50 2 μM

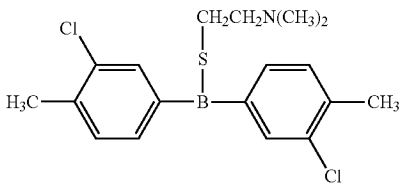
1N Sodium hydroxide (0.28 mL) was added to dimethylaminoethylthiol hydrochloride (40 mg) and the mixture was extracted with ether. Diphenylborinic acid (44 mg) was added and the mixture was dried to solidness, ethanol (1 mL) was added and the mixture was stirred for 15 hr, dried to solidness and washed with ether to give the title compound (2 mg).



Example 295

di(3-chloro-4-methylphenyl)dimethylaminoethylthioborane (4107)

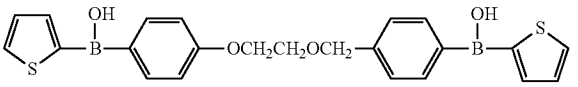
TG 107, x-Fold 0.92, SOC IC50 0.8 μM



Example 296

(4-(2-thiophenehydroxyboryl)phenoxyethyl)(4'-(2-thiophenehydroxyboryl)benzyl)ether (795)

TG 97, x-Fold 0.74

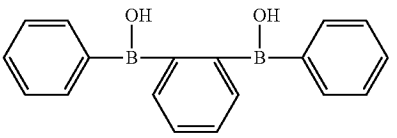


Example 297

1,2-di(phenylhydroxyboryl)benzene (806)

TG 89, x-Fold 0.69

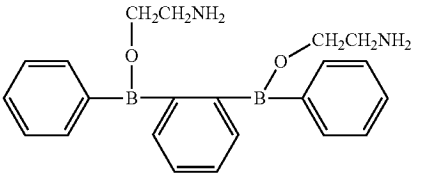
1,2-Dibromobenzene (236 mg) was reacted with 1N sec-BuLi (2.1 mL) at −98° C. (SOLUTION A). Bromobenzene was reacted with sec-BuLi and triisopropoxyborane (460 μL) (SOLUTION B). SOLUTION A and SOLUTION B were reacted to give the title compound (95 mg) as a candy-like substance.



Example 298

1,2-di(phenylaminoethoxyboryl)benzene (810)

TG 101, x-Fold 1.01



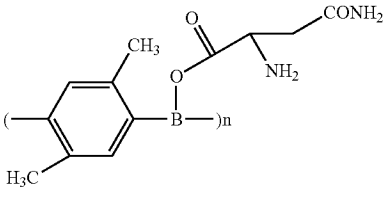
Example 299

poly(2,5-dimethylphenyl asparagine-O,N borane) (8007)

TG 118, x-Fold 1.13

Poly(2,5-dimethylphenyl hydroxyborane) (34 mg) and glutamine (40 mg) were stirred in ethanol at 80° C. for 12 hr to give the title compound (7 mg).

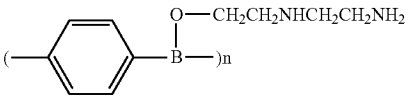
NMR (DMSO) 1.95 (m, 2H), 2.0 (m, 2H), 2.1 (m, 6H), 3.2 (m, 4H), 7.2-8.0 (m, 2H)



Example 300

poly(phenylene 2-aminoethylaminoethoxy borane) (1085)

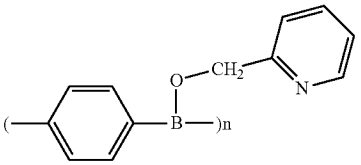
TG 95, x-Fold 0.80, SOC IC50 5 μM



Example 301

poly(phenylene 2-pyridylmethoxy borane) (1083)

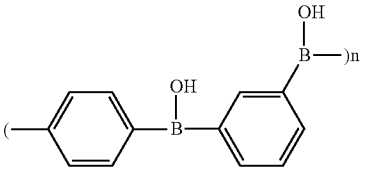
TG 108, x-Fold 0.84



Example 302

poly(1,4-phenylenehydroxyboryl-1,3-phenyleneborinic acid) (6062)

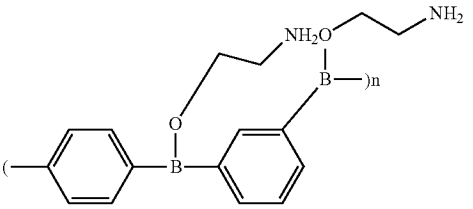
TG 103, x-Fold 0.94



Example 303

poly(1,4-phenylene aminoethoxyboryl-1,3-phenyleneaminoethoxyborane) (6082)

TG 103, x-Fold 0.91



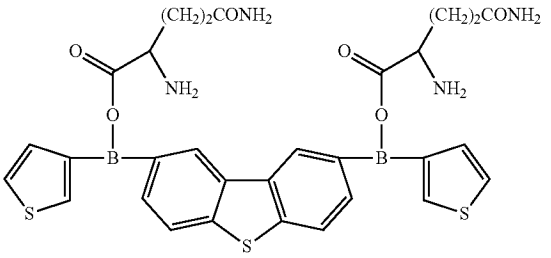
Example 304

2,8-di(3-thiophenylglutamine-O,N boryl)dibenzothiophene (8020)

TG 47, x-Fold 0.90

Compound 8013 (Example 406) (24 mg) and glutamine (19 mg) were stirred in ethanol at 80° C. for 12 hr to give the title compound (16 mg).

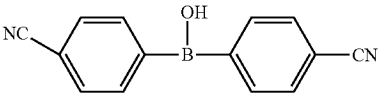
NMR (DMSO) 1.90 (m, 2H), 1.95 (m, 2H), 2.10 (m, 4H), 2.30 (m, 4H), 7.0-8.0 (m, 12H)



Example 305

4,4'-di(cyano-phenyl)borinic acid (6095)

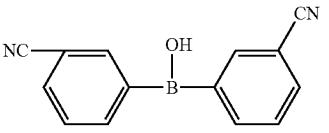
TG 94, x-Fold 0.98



Example 306

3,3'-di(cyano-phenyl)borinic acid (6096)

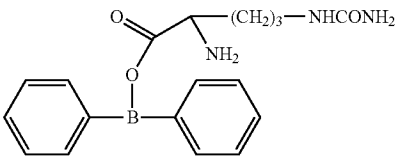
TG 90, x-Fold 0.98



Example 307

diphenyl(citrullinate-O,N)borane (7021)

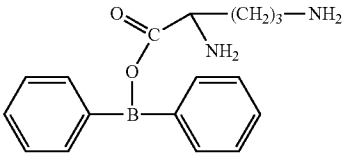
TG 54, x-Fold 1.06, SOC IC50 0.5 μM



Example 308

diphenyl(ornithinate-O,N)borane (7020)

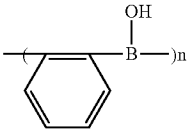
TG 27, x-Fold 1.05, SOC IC50 0.5 μM



Example 309

poly(1,2-phenylene-hydroxyborane) (7047)

TG 109, x-Fold 0.93



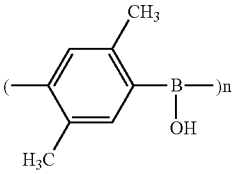
Example 310

poly(2,5-dimethyl-1,4-phenylene-hydroxyborane) (7051)

TG 114, x-Fold 1.02

2,5-Dimethyl-1,5-dibromobenzene (263 mg) was dissolved in ether (10 mL) at −78° C., sec-butyllithium (2 ml) was added and the mixture was stirred for 1 hr. Triisopropoxyborane (220 μL) was added and the mixture was gradually warmed to room temperature and treated with hydrochloric acid to give the title compound (74.5 mg).

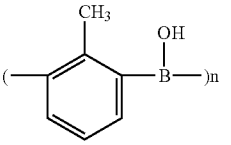
NMR ($CDCl_3$) 2.38 (s, 6H), 7.4 (m, 2H)



Example 311

poly(2-methyl-1,3-phenylene-hydroxyborane) (7052)

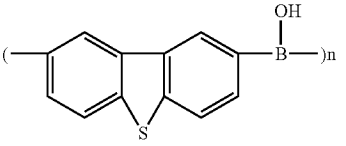
TG 111, x-Fold 1.00



Example 312

poly(2,8-dibenzothiophenylene-hydroxyborane) (7053)

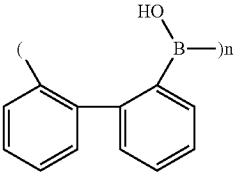
TG 98, x-Fold 1.00



Example 313

poly(2,2'-biphenylene-hydroxyborane) (7056)

TG 107, x-Fold 0.98

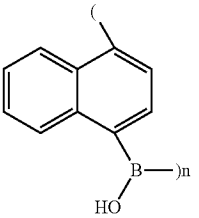


Example 314

poly(1,4-naphthalene-hydroxyborane) (7057)

TG 104, x-Fold 0.93

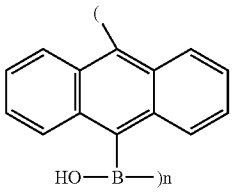
4,4'-parabrombenzylether (90 mg) was dissolved in ether (4 mL), and 1N sec-butyllithium (0.75 mL) cooled to −78° C. was added and the mixture was stirred for 60 min (SOLUTION A). 4,4'-parabromophenylether (90 mg) was dissolved in ether (4 mL) and the mixture was cooled to −78° C. 1N sec-Butyllithium (0.7 mL) was added and the mixture was stirred for 30 min. Triisopropoxyborane (188 mg) was added and the mixture was stirred to −65° C. (SOLUTION B). SOLUTION A and SOLUTION B were mixed and 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, and concentrated to give the title compound (154 mg).



Example 315

poly(9,10-anthracene-hydroxyborane) (7058)

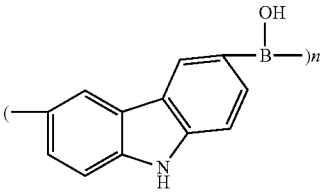
TG 102, x-Fold 0.92



Example 316

poly(3,6-carbazole-hydroxyborane) (7059)

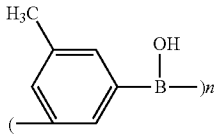
TG 72, x-Fold 1.11



Example 317

poly(5-methyl-1,3-phenylene-hydroxyborane) (7063)

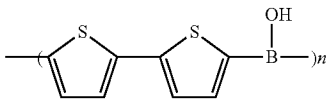
TG 107, x-Fold 0.99



Example 318

poly(5,5'-bithiophene-hydroxyborane) (7064)

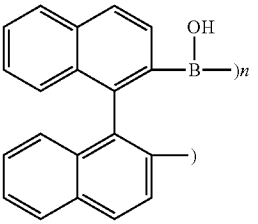
TG 81, x-Fold 1.02



Example 319

poly(2,2'-binaphthyl-hydroxyborane) (7065)

TG 108, x-Fold 1.04

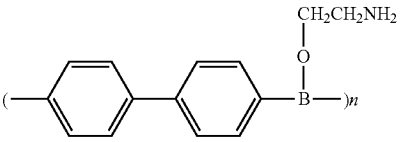


Example 320

poly(4,4'-biphenylene aminoethoxyborane) (1128)

TG 100, x-Fold 0.78, SOC IC50 5 μM

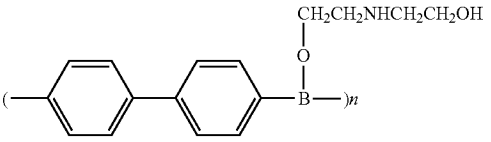
Poly(4,4'-biphenylborinic acid) (38 mg) was dissolved in ether (0.5 mL), ethanolamine (13 mg) was added and the mixture was stirred for 10 hr. Ether (1 mL) was added to give the title compound (12 mg) as a precipitate.



Example 321

poly(4,4'-biphenylene N-hydroxyethylaminoethoxyborane) (1129)

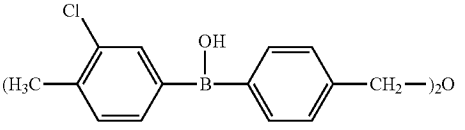
TG 116, x-Fold 0.78



Example 322

bis(4,4'-(3-chloro-4-methylphenylhydroxyboryl) benzyl)ether (612)

TG 98, x-Fold 0.32, SOC IC50 0.2 μM

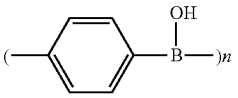


Example 323

poly(4-phenylborinic acid) (502)

TG 111, x-Fold 0.82

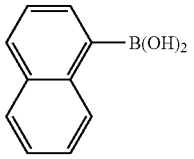
Paradibromobenzene (148 mg) was dissolved in ether (10 ml), sec-butyllithium (1.5 mL) was added at −95° C. and the mixture was stirred for 30 min. Triisoproxyborane (276 μL) was added at −78° C. and the mixture was stirred for 1 hr (SOLUTION A). Paradibromobenzene (148 mg) was dissolved in ether (10 mL), sec-butyllithium (1.5 ml) was added at −95° C. and the mixture was stirred for 30 min (SOLUTION B). SOLUTION A and SOLUTION B were mixed at −78° C., and the mixture was gradually warmed to room temperature and stirred overnight. Hydrochloric acid solution was added, and the mixture was applied to column chromatography to give the title compound (110 mg).



Example 324

naphthaleneboronic acid (7126)

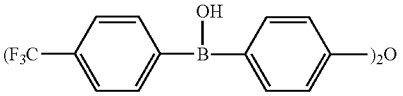
x-Fold 0.76



Example 325

bis(4-(4-trifluoromethylphenylhydroxyboryl)phenyl) ether (2054)

TG 92, x-Fold 0.99, SOC IC50 4 μM



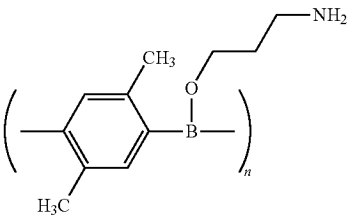
Example 326

poly(2,5-dimethylphenyl aminopropoxyborane) (8009)

TG 103, x-Fold 1.09

Compound 7051 (Example 310) (34 mg) and ethanolamine (17 mg) were reacted at room temperature for 4 hr to give the title compound (8.7 mg).

NMR ($CDCl_3$) 2.34 (s, 6H), 2.62 (m, 2H), 2.95 (m, 2H), 3.65 (m, 2H), 7.2-7.8 (m, 2H)



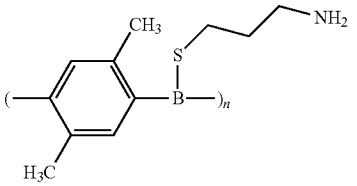
Example 327

poly(2,5-dimethylphenyl aminopropylthioborane) (8010)

TG 14, x-Fold 1.07

Compound 7051 (Example 310) (32 mg) and aminoethanethiol (20 mg) were reacted at room temperature for 4 hr to give the title compound (28 mg).

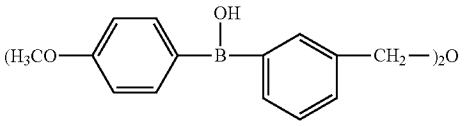
NMR ($CDCl_3$) 1.8-2.0 (br, 2H), 2.31 (m, 6H), 2.76 (m, 2H), 3.01 (m, 2H)



Example 328

bis(3-(4-methoxyphenylhydroxyboryl)benzyl)ether (2072)

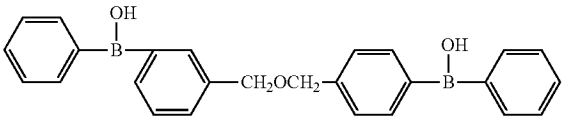
TG 100, x-Fold 1.04



Example 329

(3-(phenylhydroxyboryl)benzyl)(4-(phenylhydroxyboryl)benzyl)ether (672)

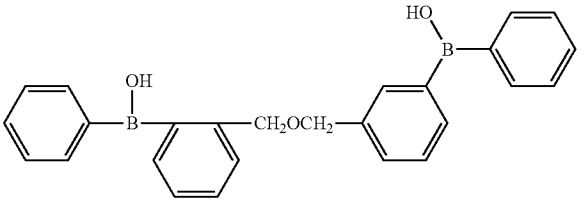
TG 81, SOC IC50 0.2 μM



Example 330

(2-(phenylhydroxyboryl)benzyl)(3-(phenylhydroxyboryl)benzyl)ether (655)

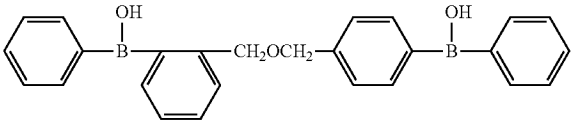
TG 89, x-Fold 0.90



Example 331

(2-(phenylhydroxyboryl)benzyl)(4-(phenylhydroxyboryl)benzyl)ether (682)

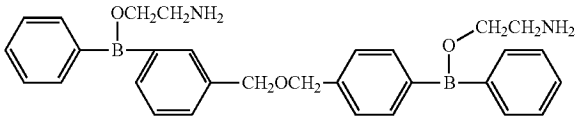
TG 101, x-Fold 0.98, SOC IC50 1 μM



Example 332

(3-(phenylaminoethoxyboryl)benzyl)(4-(phenylaminoethoxyboryl)benzyl)ether (674)

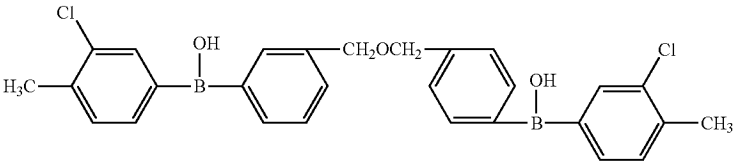
TG 21, x-Fold 0.98, SOC IC50 0.2 μM



Example 333

bis(3-(3-chloro-4-methylphenylhydroxyboryl)benzyl)ether (701)

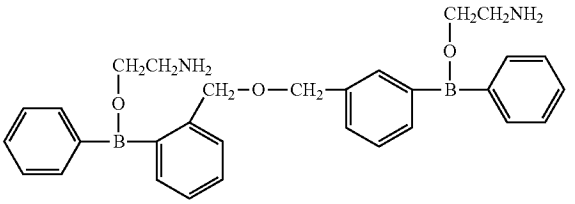
TG 107, x-Fold 1.09



Example 334

(2-(phenylaminoethoxyboryl)benzyl)(3-(phenylaminoethoxyboryl)benzyl)ether (687)

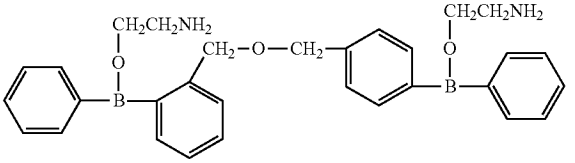
TG 21, x-Fold 1.02, SOC IC50 0.3 μM



Example 335

(2-(phenylaminoethoxyboryl)benzyl) (4-(phenylaminoethoxyboryl)benzyl)ether (686)

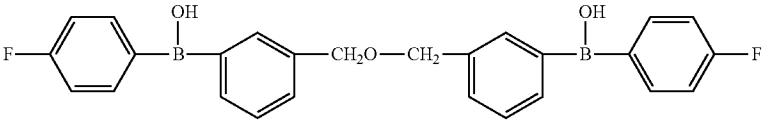
TG 91, x-Fold 1.02



Example 336

bis(3-(4-fluorophenylhydroxyboryl)benzyl)ether (688)

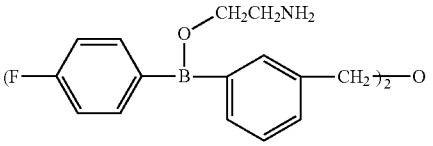
TG 101, x-Fold 1.02



Example 337

bis(3-(4-fluorophenylaminoethoxyboryl)benzyl)ether (689)

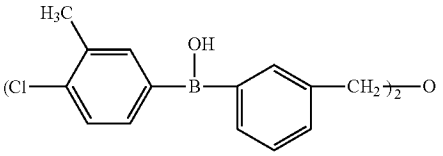
TG 102, x-Fold 0.98



Example 338

bis(4-(4-chloro-3-methyl-phenyl)hydroxyborylbenzyl)ether (693)

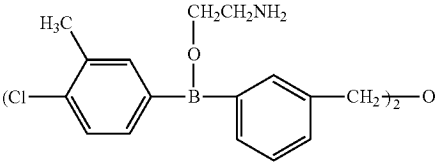
TG 110, x-Fold 0.83



Example 339

bis(4-(4-chloro-3-methyl-phenylaminoethoxyboryl-benzyl)ether (696)

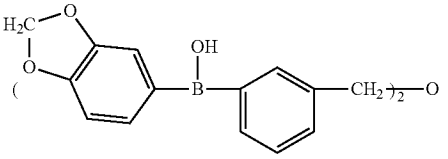
TG 115, x-Fold 0.91



Example 340

bis(3-(3',4'-methylenedioxy-phenylhydroxyboryl) benzyl)ether (700)

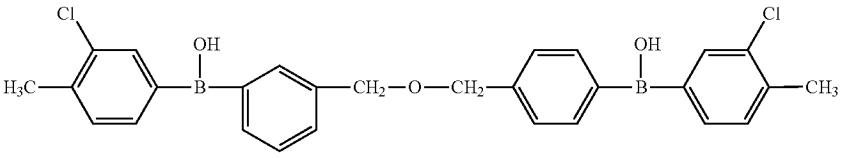
TG 63, x-Fold 1.01



Example 341

(3-(3-chloro-4-methylphenylhydroxyboryl)benzyl) (4-(3-chloro-4-methylphenylhydroxyboryl)benzyl) ether (701)

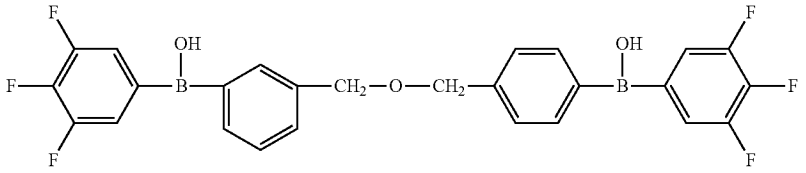
TG 107, x-Fold 1.04



Example 342

(3-(3',4',5'-trifluorophenylhydroxyboryl)benzyl)(4-(3',4',5'-trifluorophenylhydroxyboryl)benzyl)ether (702)

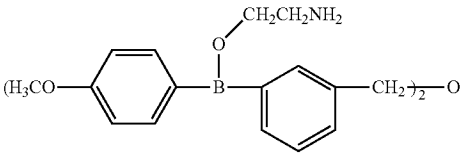
TG 114, x-Fold 1.02



Example 343

bis(3-(4-methoxyphenylaminoethoxyboryl)benzyl) ether (704)

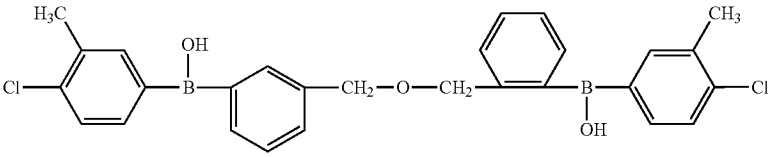
TG 55, x-Fold 1.02



Example 344

(3-(4-chloro-3-methylphenylhydroxyboryl)benzyl)(2-(4-chloro-3-methylphenylhydroxyboryl)benzyl) ether (705)

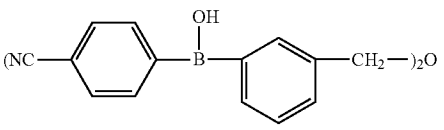
TG 91, x-Fold 0.93



Example 345

bis(3-(4-cyanophenylhydroxyboryl)benzyl)ether (706)

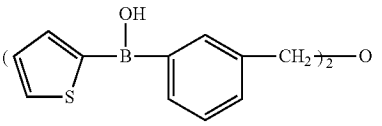
TG 95, x-Fold 0.92



Example 346

bis(3-(2'-thiophenylhydroxyboryl)benzyl)ether (707)

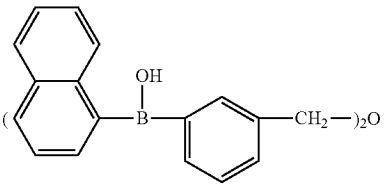
TG 101, x-Fold 0.81



Example 347

bis(3-(1'-naphthylhydroxyboryl)benzyl)ether (708)

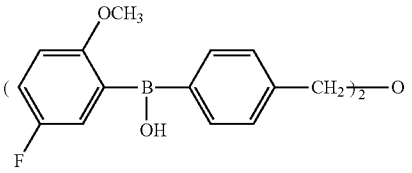
TG 104, x-Fold 0.90



Example 349

bis(4-(2-methoxy-5-fluorophenylhydroxyboryl)benzyl)ether (710)

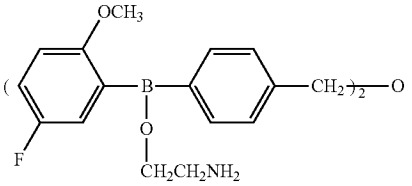
TG 104, x-Fold 0.80



Example 350

bis(4-(2-methoxy-5-fluorophenylaminoethoxyboryl) benzyl)ether (717)

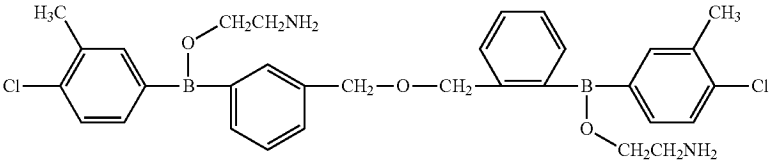
TG 105, x-Fold 0.92



Example 351

(3-(4-chloro-3-methyl-phenylaminoethoxyboryl) benzyl)(2-(4-chloro-3-methyl-phenylaminoethoxy-boryl)benzyl)ether (711)

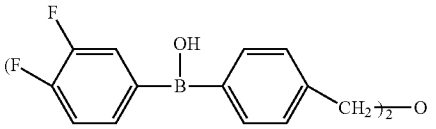
TG 103, x-Fold 1.00



Example 352

bis(4-(3,4-difluorophenylhydroxyboryl)benzyl)ether (718)

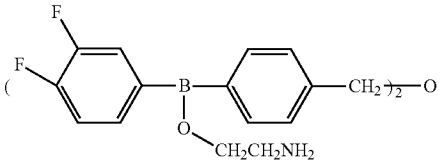
TG 97, x-Fold 1.02



Example 353

bis(4-(3,4-difluorophenylaminoethoxyboryl)benzyl) ether (712)

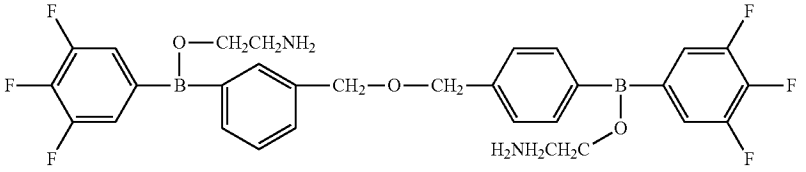
TG 115, x-Fold 0.85



Example 354

(3-(3',4',5'-trifluorophenylaminoethoxyboryl)benzyl) (4-(3',4',5'-trifluorophenylaminoethoxyboryl)benzyl) ether (719)

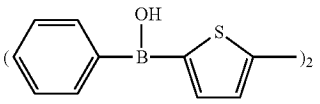
TG 113, x-Fold 1.09



Example 355

5,5'-(phenylhydroxyboryl)-2,2'-dithiophene (731)

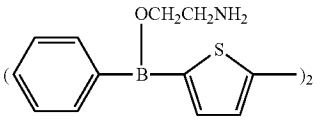
TG 91, x-Fold 1.09



Example 356

5,5'-(phenylaminoethoxyboryl)-2,2'-dithiophene (735)

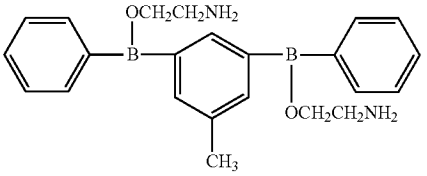
TG 51, x-Fold 1.06



Example 357

3,5-di(phenylaminoethoxyboryl)toluene (736)

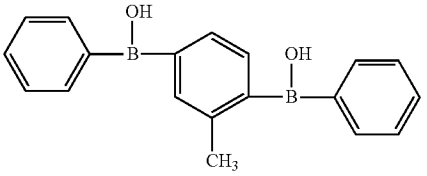
TG 89, x-Fold 1.03



Example 358

2,5-di(phenylhydroxyboryl)toluene (739)

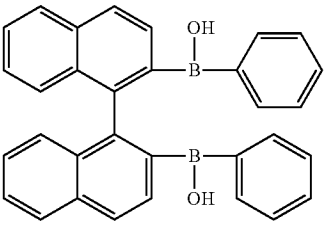
TG 112, x-Fold 0.91



Example 359

2,2'-di(phenylhydroxyboryl)-1,1'-binaphthyl (744)

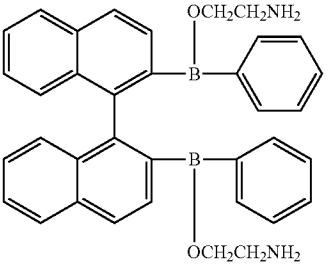
TG 139, x-Fold 0.96



Example 360

2,2'-di(phenylaminoethoxyboryl)-1,1'-binaphthyl (745)

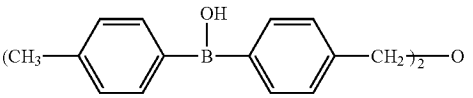
TG 88, x-Fold 1.05



Example 361

bis(4-(4-methylphenylhydroxyboryl)benzyl)ether (709)

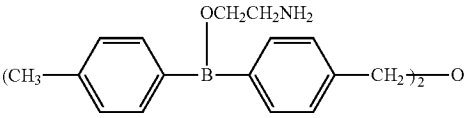
TG 100, x-Fold 0.88, SOC IC50 >20 μM



Example 362

bis(4-(4-methylphenylaminoethoxyboryl)benzyl)ether (729)

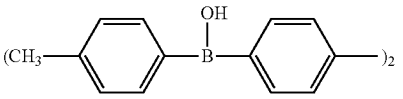
TG 108, x-Fold 1.08



Example 363

4,4'-(4-methylphenylhydroxyboryl)diphenyl (752)

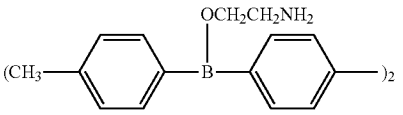
TG 97, x-Fold 0.92



Example 364

4,4'-(4-methylphenylaminoethoxyboryl)diphenyl (754)

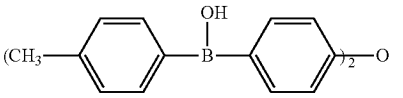
TG 44, x-Fold 0.82



Example 365

4,4'-(4-methylphenylhydroxyboryl)diphenylether (753)

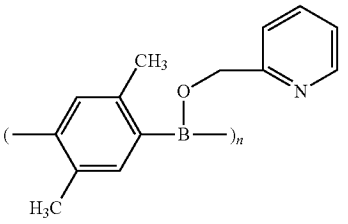
TG 118, x-Fold 0.91



Example 366

poly(2,5-dimethylphenyl 2-pyridylmethoxyborane) (8011)

TG 108, x-Fold 0.93



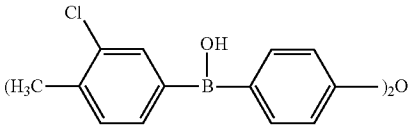
Compound 7051 (Example 310) (7.2 mg) and 2-pyridylmethanol (6 mg) were reacted in ethanol at room temperature for 4 hr to give the title compound (4 mg).

NMR ($CDCl_3$) 3.45 (m, 6H), 4.72 (m, 2H), 7.2-8.5 (m, 6H)

Example 367

4,4'-bis(3-chloro-4-methyl-phenylhydroxyboryl) diphenylether (513)

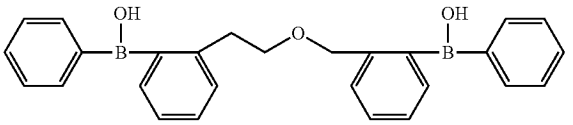
TG 113, x-Fold 0.73



Example 368

(2-(phenylhydroxyboryl)phenethyl)((2-phenylhydroxyboryl)benzyl)ether (6055)

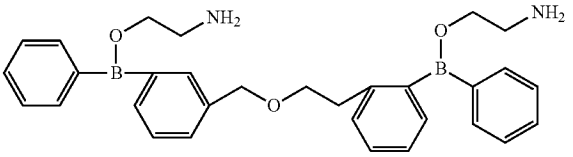
TG 52, x-Fold 1.03



Example 369

(2-(phenylaminoethoxyboryl)phenethyl)((2-phenylaminoethoxyboryl)benzyl)ether (7133)

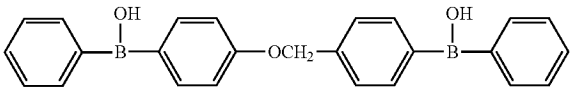
TG 105, x-Fold 1.10



Example 370

(4-phenylhydroxyborylphenyl)(4'-phenylhydroxyborylbenzyl)ether (775)

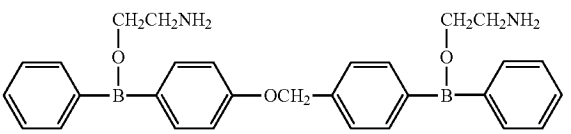
TG 39, x-Fold 0.76, SOC IC50 2 μM



Example 371

(4-phenylaminoethoxyborylphenyl)(4'-phenylaminoethoxyborylbenzyl)ether (778)

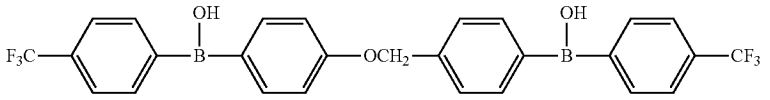
TG 16, x-Fold 0.85, SOC IC50 2 μM



Example 372

(4-trifluoromethylphenylhydroxyborylphenyl)(4'-trifluoromethylphenylhydroxyborylbenzyl)ether (784)

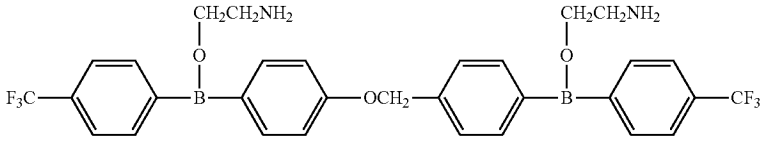
TG −18, x-Fold 0.86, SOC IC50 1 μM



Example 373

(4-trifluoromethylphenylaminoethoxyborylphenyl)(4'-trifluoromethylphenylaminoethoxyborylbenzyl) ether (785)

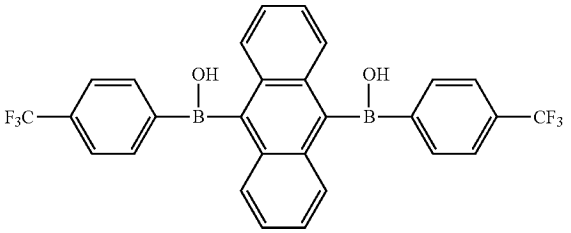
TG 1, x-Fold 0.84, SOC IC50 2 μM



Example 374

9,10-bis-(trifluoromethylphenylhydroxyboryl)anthracene (764)

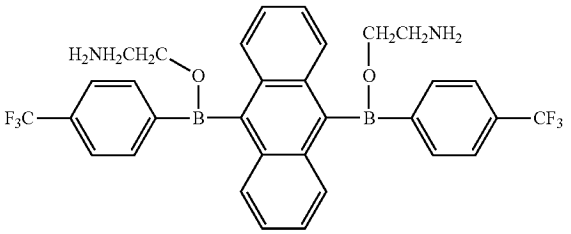
TG 17, x-Fold 1.14



Example 375

9,10-bis-(trifluoromethylphenylaminoethoxyboryl) anthracene (787)

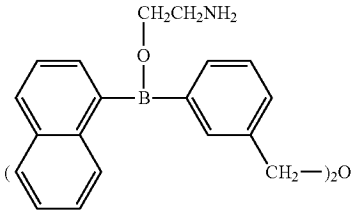
TG 44, x-Fold 1.05



Example 376

bis(3-(1-naphthylaminoethoxyboryl)benzyl)ether (788)

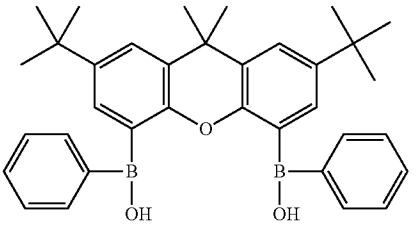
TG 75, x-Fold 0.93



Example 377

4,5-di(phenylhydrixyboryl)-2,7-di-tert-butyl-9,9-dimethylxanthrene (763)

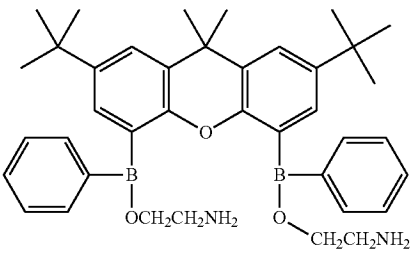
TG 70, x-Fold 0.75, SOC IC50 >20 μM



Example 378

4,5-di(phenylaminoethoxyboryl)-2,7-di-tert-butyl-9,9-dimethylxanthrene (765)

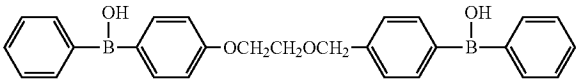
TG 88, x-Fold 0.79



Example 379

(4-(phenylhydroxyboryl)phenoxyethyl)(4-(phenylhydroxyboryl)benzyl)ether (818)

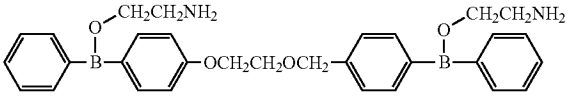
TG 92, x-Fold 0.74



Example 380

(4-(phenylaminoethoxyboryl)phenoxyethyl)(4-(phenylaminoethoxyboryl)benzyl)ether (820)

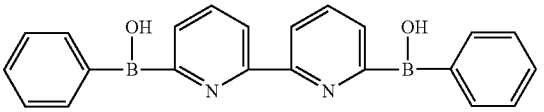
TG 92, x-Fold 0.67



Example 381

6,6'-(phenylhydroxyboryl)-2,2'-dipyridyl (813)

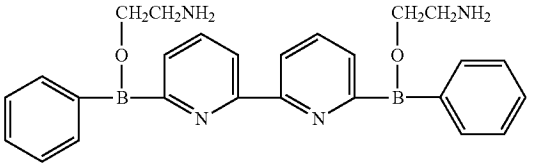
TG 55, x-Fold 0.80



Example 382

6,6'-(phenylaminoethoxyboryl)-2,2'-dipyridyl (814)

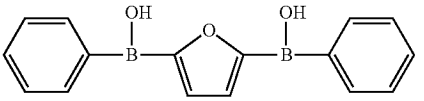
TG 76, x-Fold 0.80



Example 383

bis(2,5-(phenylhydroxyboryl))furan (914)

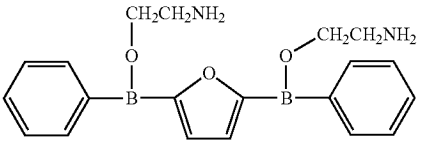
TG 103, x-Fold 0.92



Example 384

bis(2,5-(phenylaminoethoxyboryl))furan (915)

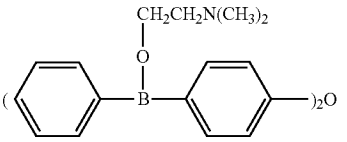
TG 60, x-Fold 1.05



Example 385

bis(4,4'-(phenyl-N,N-dimethylaminoethoxyboryl)phenyl)ether (1007)

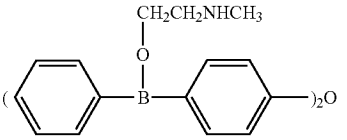
TG 116, x-Fold 0.78



Example 386

bis(4,4'-(phenyl-N-methylaminoethoxyboryl)phenyl)ether (1014)

TG 10, x-Fold 0.98, SOC IC50 0.5 μM



Example 387

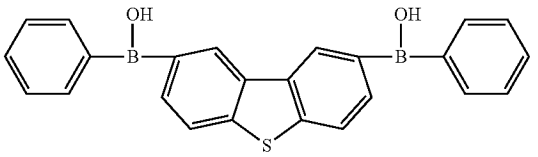
2,8-di(phenylhydroxyboryl)dibenzothiophene (8012)

TG 96, x-Fold 0.73

2,8-Dibromodibenzothiophene (242 mg) was dissolved in ether (7 mL), and the mixture was cooled to −78° C. Secondary butyllithium (2 mL) was added and the mixture was stirred for 1 hr. Further, isopropoxyborane (460 μL) was added and the mixture was stirred for 1 hr (SOLUTION A). In a separate flask, bromobenzene (211 mg) was dissolved in ether (10 ml), secondary butyllithium (2 mL) was added and the mixture was stirred for 1 hr (SOLUTION B). SOLUTION A and SOLUTION B were mixed, and the mixture was gradu-

ally warmed to room temperature. The mixture was treated with hydrochloric acid the next morning to give the title compound (150 mg).

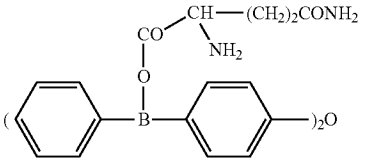
NMR ($CDCl_3$) 4.3 (s, 2H), 6.8-8.2 (m, 16H)



Example 388

bis(4,4'-(phenyl-glutamineboryl)phenyl)ether (7085)

TG 41, x-Fold 0.67, SOC IC50 0.5 μM



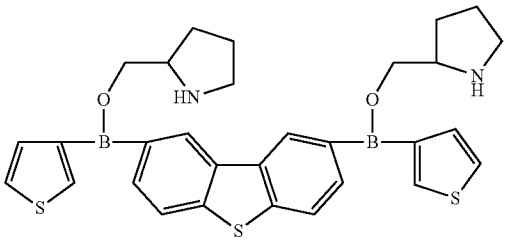
Example 389

2,8-di(3-thiophenyl-2-pyrrolidinomethoxyboryl) dibenzothiophene (8019)

TG 81, x-Fold 0.83

Compound 8012 (Example 387) (25 mg) and 2-pyrrolidinemethanol (18 mg) were stirred in ethanol at room temperature for 5 hr to give the title compound (4.9 mg).

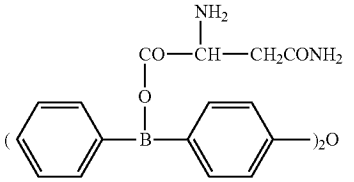
NMR ($CDCl_3$) 1.6-1.8 (m, 8H), 3.42-4 (m, 4H), 4.64 (m, 4H), 7.0-7.8 (m, 12H)



Example 390

bis(4,4'-(phenyl-asparagineboryl)phenyl)ether (1023)

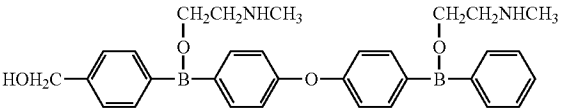
TG 56, x-Fold 0.59



Example 391

(4-(phenyl-N-methylaminoethoxyboryl)phenyl)(4'-(hydroxymethylphenyl-N-methylaminoethoxyboryl) phenyl)ether (1028)

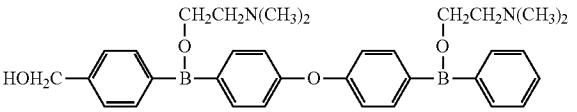
TG 15, x-Fold 0.32, SOC IC50 0.5 μM



Example 392

(4-(phenyl-N,N-dimethylaminoethoxyboryl)phenyl) (4'-(hydroxymethylphenyl-N,N-dimethylaminoethoxyboryl)phenyl)ether (1030)

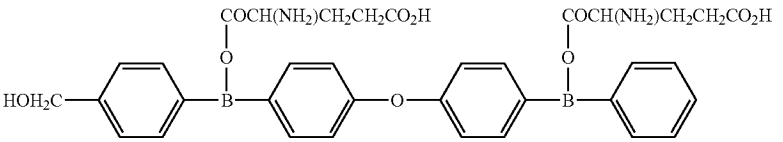
TG 83, x-Fold 0.91



Example 393

(4-(phenyl-glutamic acid boryl)phenyl)(4'-(hydroxymethylphenyl-glutamic acid boryl)phenyl)ether (1036)

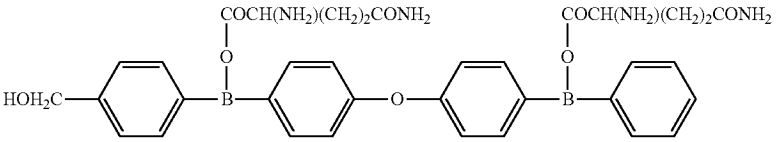
TG 117, x-Fold 0.56



Example 394

(4-(phenyl-glutamineboryl)phenyl)(4'-(hydroxymethylphenyl-glutamineboryl)phenyl)ether (1037)

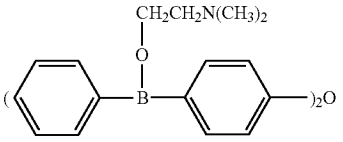
TG 41, x-Fold 0.44, SOC IC50 1.5 μM



Example 395

bis(4,4'-(phenyl-N,N-dimethylaminoethoxyboryl)phenyl)ether (1007)

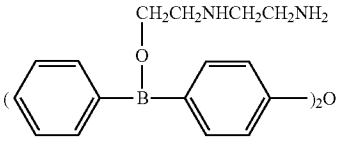
TG 116, x-Fold 0.86



Example 396

bis(4,4'-(phenyl-N-aminoethyl-aminoethoxyboryl)phenyl)ether (1040)

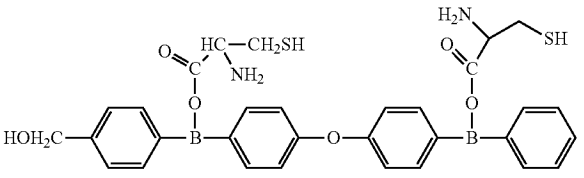
TG 3, x-Fold 0.58, SOC IC50 1.2 μM



Example 397

(4-(phenyl-cysteineboryl)phenyl)(4'-(hydroxymethylphenyl-cysteineboryl)phenyl)ether (1038)

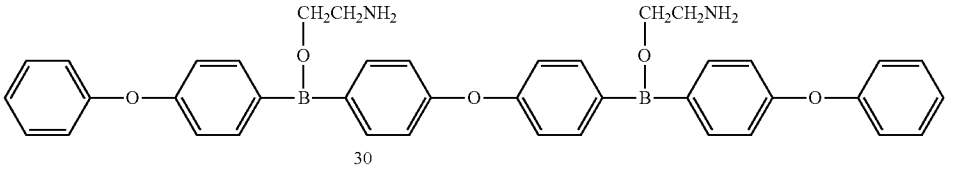
TG 70, x-Fold 0.59



Example 398

bis(4,4'-(phenoxyphenyl-aminoethoxyboryl)phenyl)ether (1042)

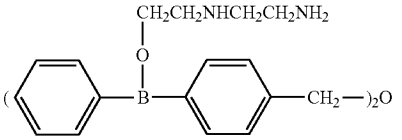
TG −17, x-Fold 0.88



Example 399

bis(4,4'-(phenyl-N-aminoethyl-aminoethoxyboryl)benzyl)ether (1084)

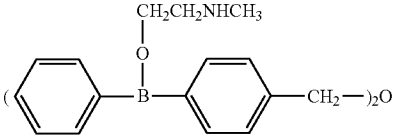
TG 53, x-Fold 0.96



Example 400

bis(4,4'-(phenyl-N-methylaminoethoxyboryl)benzyl)ether (2047)

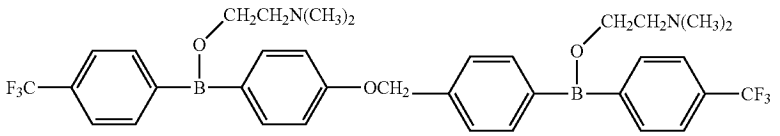
TG 52, x-Fold 1.01



Example 401

(4'-trifluoromethylphenyl-N,N-dimethylaminoethoxyboryl)-4-phenyl (4'-trifluoromethylphenyl-N,N-dimethylaminoethoxyborylbenzyl)ether (1139)

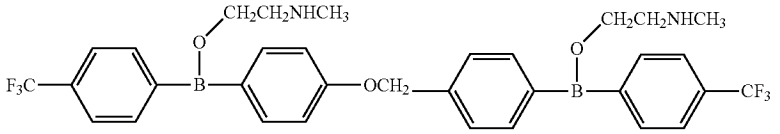
TG 121, x-Fold 0.95



Example 402

(4'-trifluoromethylphenyl-N-methylaminoethoxyboryl)-4-phenyl(4'-trifluoromethylphenyl-N-methylaminoethoxyboryl-4-benzyl)ether (1140)

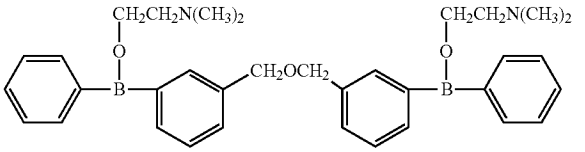
TG −12, x-Fold 0.57



Example 403

bis(3,3'-(phenyl-N,N-dimethylaminoethoxyboryl) benzyl)ether (2022)

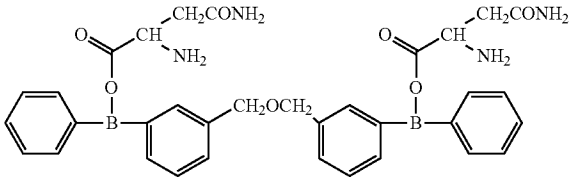
TG 67, x-Fold 1.14, SOC IC50 2 μM



Example 404

bis(3,3'-(phenyl-asparagineboryl)benzyl)ether (2023)

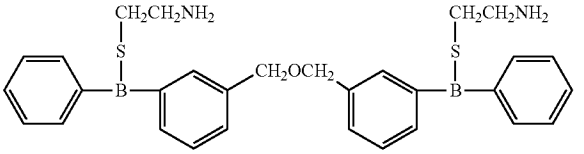
TG 105, x-Fold 1.07, SOC IC50 4 μM



Example 405

bis(3,3'-(phenyl-aminoethylthioboryl)benzyl)ether (3014)

TG −3, x-Fold 0.86, SOC IC50 0.5 μM



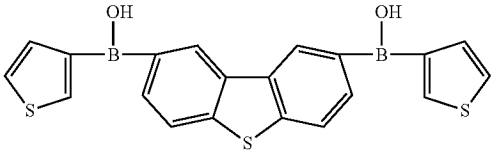
Example 406

2,8-di(3-thiophenylhydroxyboryl)dibenzothiophene (8013)

TG 61, x-Fold 0.85

2,8-Dibromodibenzothiophene (242 mg) was lithiated, and reacted with triisopropoxyborane (499 mg) (SOLUTION A). Bromothiophene (326 mg) was lithiated (SOLUTION B). SOLUTION A and SOLUTION B were mixed at −78° C., and the mixture was gradually warmed to room temperature to synthesize the title compound (230 mg).

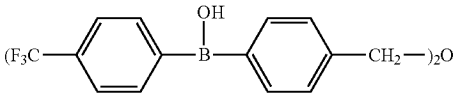
NMR (DMSO) 3.45 (m, 2H), 7.5-8.1 (m, 12H)



Example 407

bis(4,4'-(p-trifluoromethylphenyl-hydroxyboryl) benzyl)ether (2052)

TG 77, x-Fold 1.02



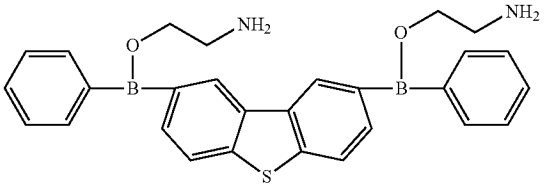
Example 408

2,8-di(phenylaminoethoxyboryl)dibenzothiophene (8014)

TG 108, x-Fold 0.92

Compound 8012 (Example 387) (30 mg) and 2-aminoethanol (7.4 mg) were synthesized by stirring at room temperature for 5 hr to give the title compound (6.3 mg).

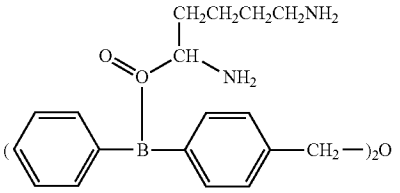
NMR ($CDCl_3$), 2.60 (m, 4H), 3.50 (m, 4H), 3.98 (m, 4H) 7.2-8.0 (m, 16H)



Example 409

bis(4,4'-(phenyl-lysineboryl)benzyl)ether (2051)

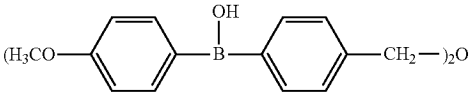
TG 29, x-Fold 0.86, SOC IC50 1.5 μM



Example 410

bis(4,4'-(p-methoxy-phenyl-hydroxyboryl)benzyl) ether (2072)

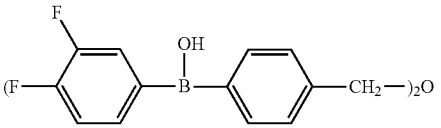
TG 130, x-Fold 0.90, SOC IC50 2 μM



Example 411

bis(4,4'-(3,4-difluorophenyl-hydroxyboryl)benzyl) ether (2073)

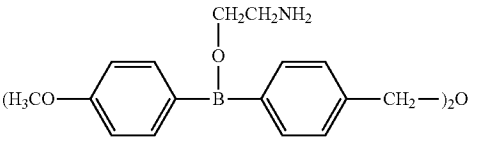
TG 138, x-Fold 0.90



Example 412

bis(4,4'-(p-methoxyphenyl-aminoethoxyboryl)benzyl)ether (2074)

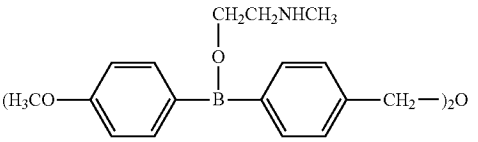
TG 65, x-Fold 0.89, SOC IC50 2 μM



Example 413

bis(4,4'-(p-methoxyphenyl-N-methylaminoethoxyboryl)benzyl)ether (2075)

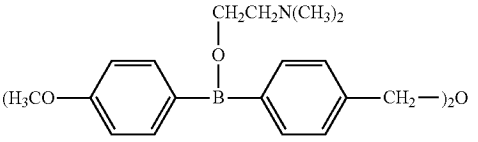
TG 28, x-Fold 0.81, SOC IC50 0.8 μM



Example 414

bis(4,4'-(p-methoxyphenyl-N,N-dimethylaminoethoxyboryl)benzyl)ether (2076)

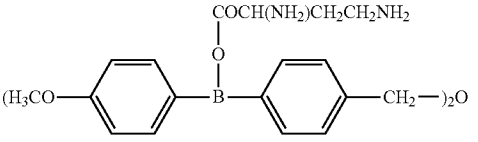
TG 128, x-Fold 0.90



Example 415

bis(4,4'-(p-methoxyphenyl-2,4-diaminobutyric acid boryl)benzyl)ether (2077)

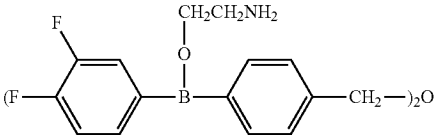
TG 130, x-Fold 0.90



Example 416

bis(4,4'-(3,4-difluorophenyl-aminoethoxyboryl)benzyl)ether (2078)

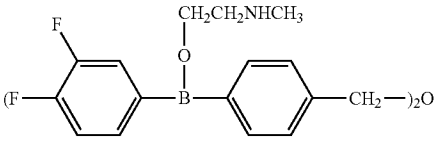
TG 114, x-Fold 0.92



Example 417

bis(4,4'-(3,4-difluorophenyl-N-methylaminoethoxyboryl)benzyl)ether (2079)

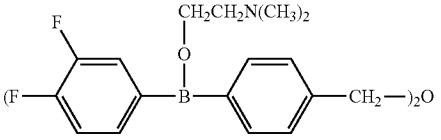
TG 91, x-Fold 1.01



Example 418

bis(4,4'-(3,4-difluorophenyl-N,N-dimethylaminoethoxyboryl)benzyl)ether (2080)

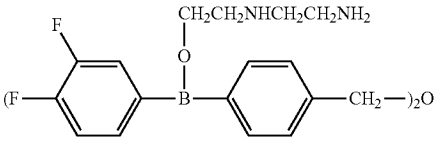
TG 45, x-Fold 1.02



Example 419

bis(4,4'-(3,4-difluorophenyl-N-aminoethylaminoethoxyboryl)benzyl)ether (2081)

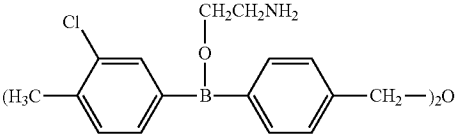
TG 140, x-Fold 0.90



Example 420

bis(4,4'-(3-chloro-4-methylphenyl-aminoethoxyboryl)benzyl)ether (2056)

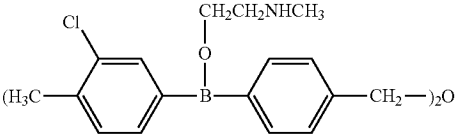
TG −3, x-Fold 0.81, SOC IC50 1.2 μM



Example 421

bis(4,4'-(3-chloro-4-methylphenyl-N-methylaminoethoxyboryl)benzyl)ether (2057)

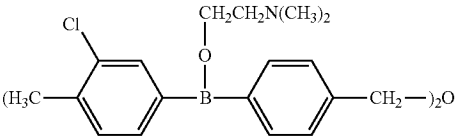
TG −1, x-Fold 1.03, SOC IC50 1.2 μM



Example 422

bis(4,4'-(3-chloro-4-methylphenyl-N,N-dimethylaminoethoxyboryl)benzyl)ether (2058)

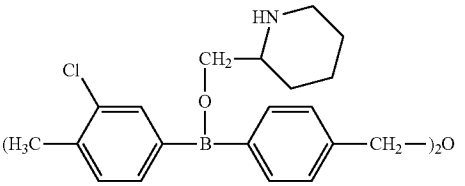
TG 13, x-Fold 0.95, SOC IC50 1.2 μM



Example 423

bis(4,4'-(3-chloro-4-methylphenyl-2-piperidylmethoxyboryl)benzyl)ether (2059)

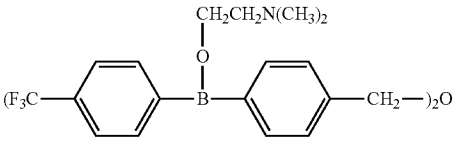
TG 27, x-Fold 0.76, SOC IC50 1.2 μM



Example 424

bis(4,4'-(p-trifluoromethylphenyl-N,N-dimethylaminoethoxyboryl)benzyl)ether (2063)

TG 22, x-Fold 1.03, SOC IC50 1.2 μM

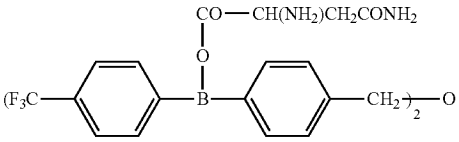


Example 425

bis(4,4'-(p-trifluoromethylphenyl-asparagineboryl) benzyl)ether (2064)

TG 130, x-Fold 0.9, SOC IC50 0.5 μM

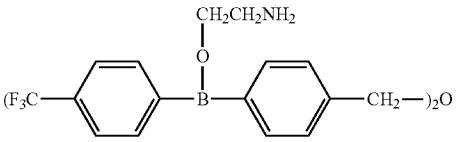
Bis(4,4'-(p-trifluoromethylphenyl-hydroxyboryl)benzyl) ether (85 mg) and asparagine (48 mg) were reacted in ethanol (0.7 mL) to give the title compound (8 mg).



Example 426

bis(4,4'-(p-trifluoromethylphenyl-aminoethoxyboryl) benzyl)ether (2068)

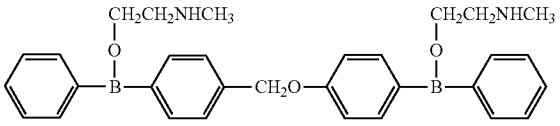
TG 19, x-Fold 0.93, SOC IC50 1.2 μM



Example 427

(4-phenyl-N-methylaminoethoxyborylphenyl) (4'-phenyl-N-methylaminoethoxyborylbenzyl)ether (2093)

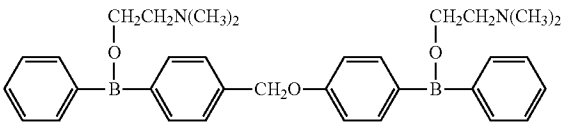
TG 20, x-Fold 0.73, SOC IC50 0.8 μM



Example 428

(4-phenyl-N,N-dimethylaminoethoxyborylphenyl) (4'-phenyl-N,N-dimethylaminoethoxyborylbenzyl) ether (2094)

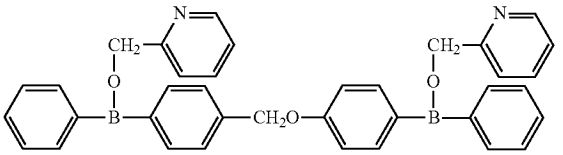
TG 53, x-Fold 0.82, SOC IC50 1.5 μM



Example 429

(4-phenyl-2-pyridylmethoxyborylphenyl)(4'-phenyl-2-pyridylmethoxyborylbenzyl)ether (2095)

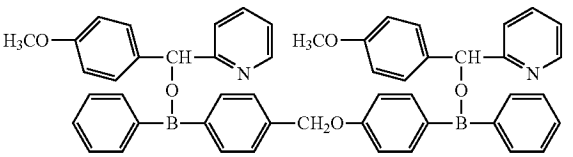
TG 102, x-Fold 0.81, SOC IC50 0.7 μM



Example 430

4-(phenyl-p-methoxyphenyl-2-pyridylmethoxyboryl)-phenyl 4'-(phenyl-p-methoxyphenyl-2-pyridyl-methoxyboryl)benzylether (2096)

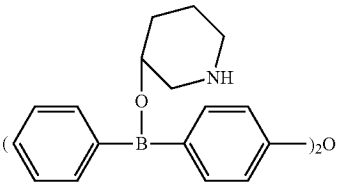
TG 106, x-Fold 1.03



Example 431

bis(4,4'-(phenyl-3-piperidyloxyboryl)phenyl)ether (2052)

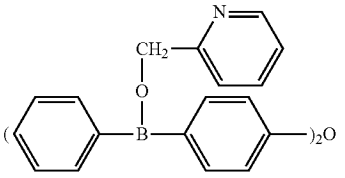
TG 118, x-Fold 1.02



Example 432

bis(4,4'-(phenyl-2-pyridylmethoxyboryl)phenyl)ether (2111)

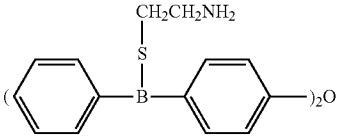
TG 60, x-Fold 0.71, SOC IC50 0.3 μM



Example 433

bis(4,4'-(phenyl-aminoethylthioboryl)phenyl)ether (2112)

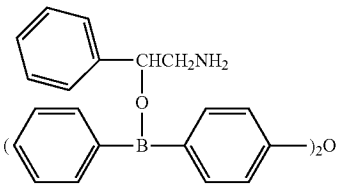
TG −5, x-Fold 0.71, SOC IC50 0.5 μM



Example 434

bis(4,4'-(phenyl-2-amino-1-phenylethoxyboryl)phenyl)ether (2113)

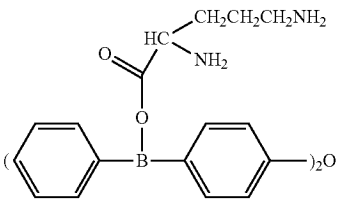
TG 43, x-Fold 0.60, SOC IC50 0.4 μM



Example 435

bis(4,4'-(phenyl-ornithineboryl)phenyl)ether (2117)

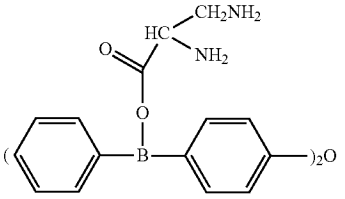
TG 26, x-Fold 0.84, SOC IC50 2 μM



Example 436

bis(4,4'-(phenyl-2,3-diaminopropionic acid boryl)phenyl)ether (2115)

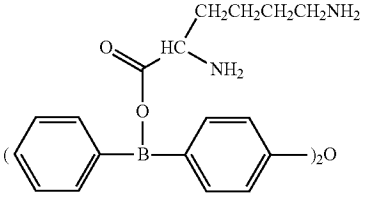
TG 104, x-Fold 0.85



Example 437

bis(4,4'-(phenyl-lysineboryl)phenyl)ether (2116)

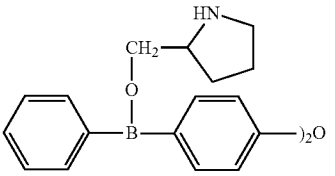
TG 119, x-Fold 0.85



Example 438

bis(4,4'-(phenyl-2-pyrrolidinemethoxyboryl)phenyl) ether (2118)

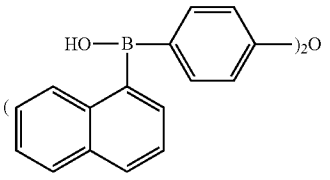
TG 29, x-Fold 0.67, SOC IC50 2 μM



Example 439

bis(4,4'-(naphthylhydroxyboryl)phenyl)ether (2119)

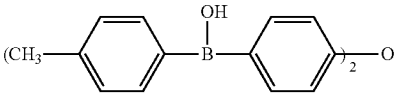
TG 33, x-Fold 0.54



Example 440

bis(4,4'-(tolylhydroxyboryl)phenyl)ether (2120)

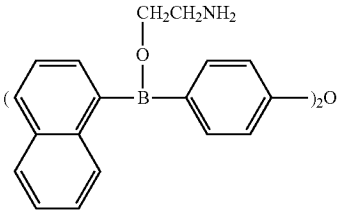
TG 63, x-Fold 0.69



Example 441

bis(4,4'-(naphthyl-aminoethoxyboryl)phenyl)ether (2121)

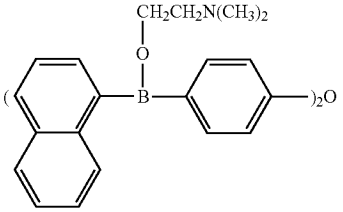
TG −1, x-Fold 0.58



Example 442

bis(4,4'-(naphthyldimethylaminoethoxyboryl)phenyl)ether (2122)

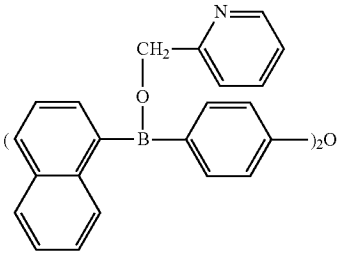
TG 102, x-Fold 0.58



Example 443

bis(4,4'-(naphthyl-2-pyridylmethoxyboryl)phenyl) ether (2123)

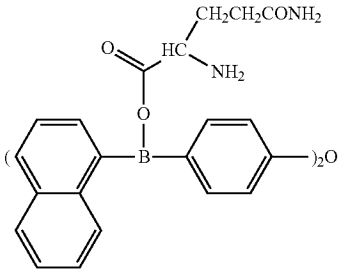
TG 84, x-Fold 0.63, SOC IC50 3 μM



Example 444

bis(4,4'-(naphthylglutamineboryl)phenyl)ether (2124)

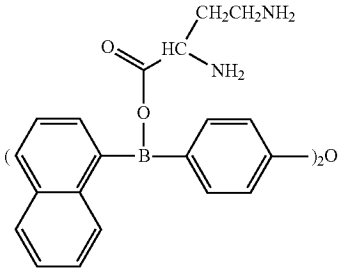
TG 20, x-Fold 0.65, SOC IC50 1.4 μM



Example 445

bis(4,4'-(naphthyl 2,4-diaminopropionic acid boryl)phenyl)ether (2125)

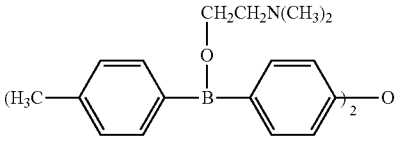
TG 108, x-Fold 0.49



Example 446

bis(4,4'-(tolyldimethylaminoethoxyboryl)phenyl) ether (2127)

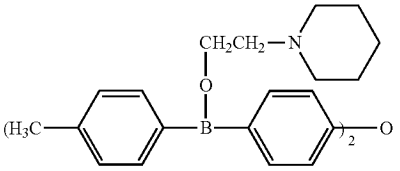
TG 73, x-Fold 0.85



Example 447

bis(4,4'-(tolylpiperadylethoxyboryl)phenyl)ether (2128)

TG 97, x-Fold 0.49

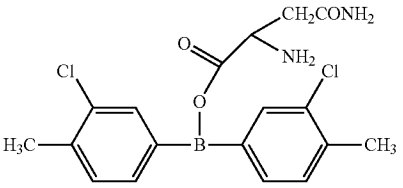


Example 448

di(3-chloro-4-methyl)phenyl(methionate-O,N)borane (4103)

TG 112, x-Fold 0.95

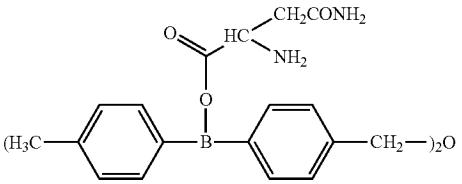
Di(3-chloro-4-methylphenyl)borinic acid (45.8 mg) and asparagine (19 mg) were reacted in ethanol (1 mL) at 90° C. for 1 hr to give the title compound (24 mg).



Example 449

bis(4,4'-(tolylasparagineboryl)benzyl)ether (2129)

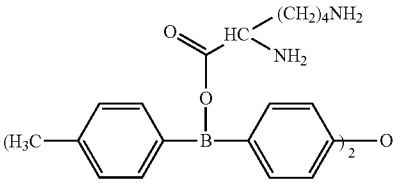
TG 92, x-Fold 0.89



Example 450

bis(4,4'-(tolyllysineboryl)phenyl)ether (2130)

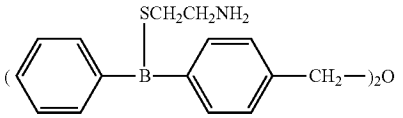
TG 53, x-Fold 0.49



Example 451

bis(4,4'-(phenyl-aminoethylthioboryl)benzyl)ether (2135)

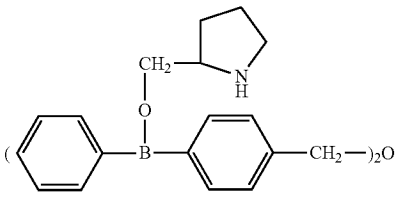
TG 6, x-Fold 0.91, SOC IC50 1.4 μM



Example 452

bis(4,4'-(phenyl-2-pyrrolidinemethoxyboryl)benzyl) ether (2136)

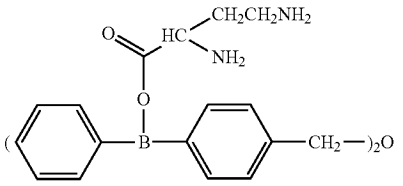
TG 29, x-Fold 0.96, SOC IC50 0.5 μM



Example 453

bis(4,4'-(phenyl-2,4-diaminobutyrate boryl)benzyl)ether (2137)

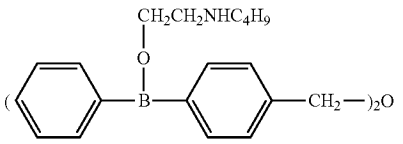
TG 113, x-Fold 1.04



Example 454

bis(4,4'-(phenyl-butylaminoethoxyboryl)benzyl)ether (2144)

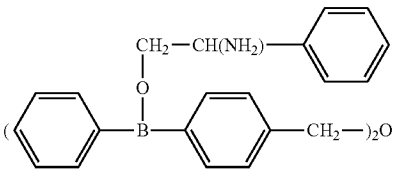
TG 15, x-Fold 0.97, SOC IC50 0.5 μM



Example 455

bis(4,4'-(phenyl-phenylaminoethoxyboryl)benzyl) ether (2145)

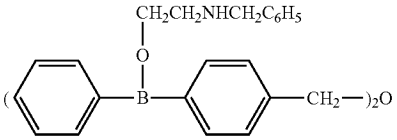
TG 23, x-Fold 1.04, SOC IC50 0.5 μM



Example 456

bis(4,4'-(phenyl-benzylaminoethoxyboryl)benzyl) ether (2146)

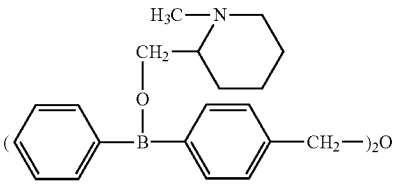
TG 29, x-Fold 0.87, SOC IC50 0.5 μM



Example 457

bis(4,4'-(phenyl-N-methylpiperidine-methoxyboryl) benzyl)ether (3002)

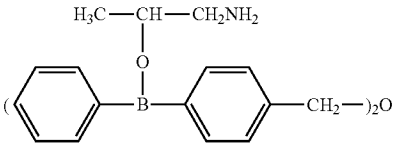
TG 30, x-Fold 1.10, SOC IC50 0.6 μM



Example 458

bis(4,4'-(phenyl-1-methyl-2-aminoethoxyboryl)benzyl)ether (3004)

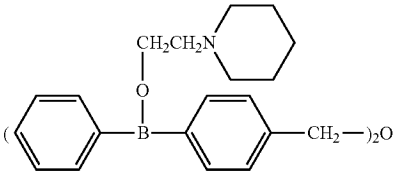
TG 31, x-Fold 1.10, SOC IC50 0.5 μM



Example 459

bis(4,4'-(phenyl-1-piperidylethoxyboryl)benzyl)ether (3005)

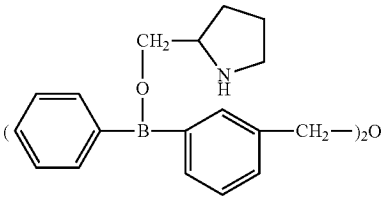
TG 80, x-Fold 1.03



Example 460

bis(3,3'-(phenyl-2-pyrrolidinomethoxyboryl)benzyl) ether (3015)

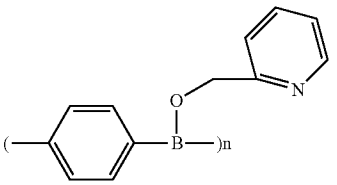
TG 26, x-Fold 0.95, SOC IC50 0.4 μM



Example 461

poly(1,4-phenylene 2-pyridylmethoxyborane) (6078)

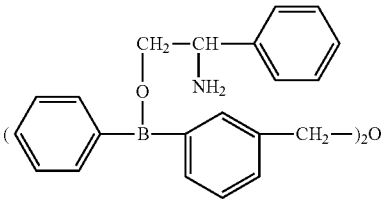
TG 30, x-Fold 0.85



Example 462

bis(3,3'-(phenyl-2-phenyl-2-aminoethoxyboryl)benzyl)ether (3018)

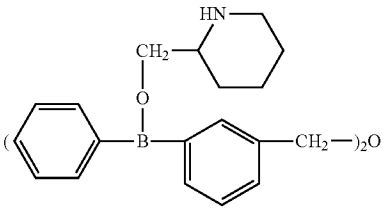
TG 31, x-Fold 0.92, SOC IC50 0.3 μM



Example 463

bis(3,3'-(phenyl-2-piperidylmethoxyboryl)benzyl) ether (3020)

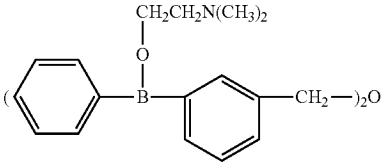
TG 24, x-Fold 0.92, SOC IC50 0.3 μM



Example 464

bis(3,3'-(phenyl-dimethylaminoethoxyboryl)benzyl) ether (3021)

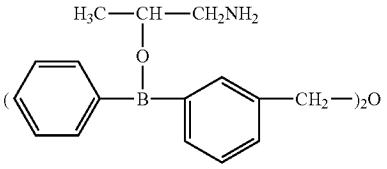
TG 41, x-Fold 0.76, SOC IC50 0.8



Example 465

bis(3,3'-(phenyl-1-methyl-2-aminoethoxyboryl)benzyl)ether (3022)

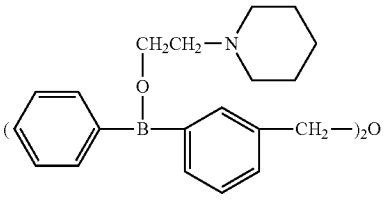
TG 18, x-Fold 1.06, SOC IC50 0.2 μM



Example 466

bis(3,3'-(phenyl-1-piperidylethoxyboryl)benzyl)ether (3023)

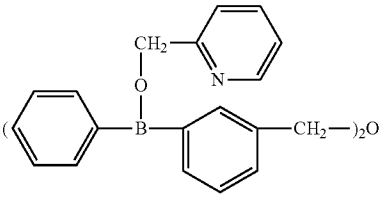
TG 71, x-Fold 1.04



Example 467

bis(3,3'-(phenyl-2-pyridylmethoxyboryl)benzyl)ether (3024)

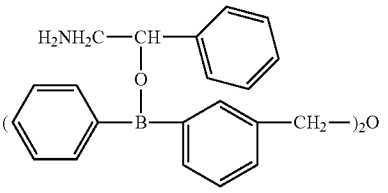
TG 60, x-Fold 0.98, SOC IC50 0.25 μM



Example 468

bis(3,3'-(phenyl-2-amino-1-phenylethoxyboryl)benzyl)ether (3025)

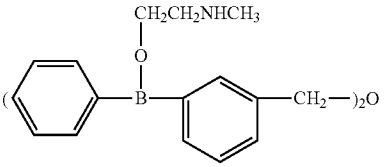
TG 35, x-Fold 0.98, SOC IC50 0.3 μM



Example 469

bis(3,3'-(phenyl-N-methylaminoethoxyboryl)benzyl) ether (3026)

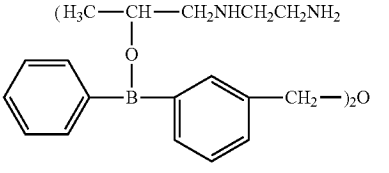
TG 15, x-Fold 0.94, SOC IC50 0.25 μM



Example 470

bis(3,3'-(phenyl-N-aminoethyl-1-methyl-2-aminoethoxyboryl)benzyl)ether (3027)

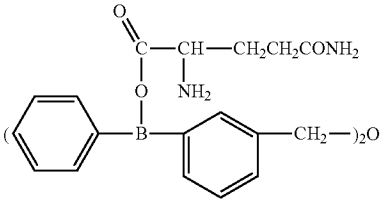
TG 19, x-Fold 1.02, SOC IC50 0.3 μM



Example 471

bis(3,3'-(phenyl-glutamineboryl)benzyl)ether (3028)

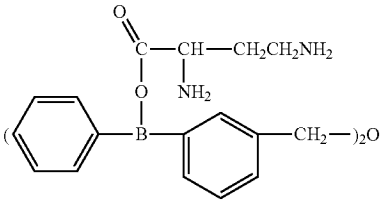
TG 52, x-Fold 1.04, SOC IC50 0.6 μM



Example 472

bis(3,3'-(phenyl-2,4-diaminobutyric acid boryl)benzyl)ether (3029)

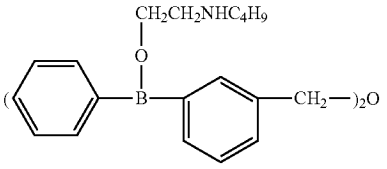
TG 47, x-Fold 0.95, SOC IC50 1 μM



Example 473

bis(3,3'-(phenyl-N-butylaminoethoxyboryl)benzyl) ether (3030)

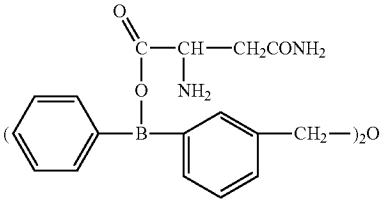
TG-4, x-Fold 0.96, SOC IC50 0.5 μM



Example 474

bis(3,3'-(phenyl-asparagineboryl)benzyl)ether (3031)

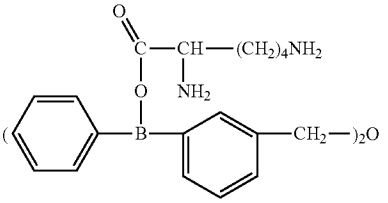
TG 145, x-Fold 1.04, SOC IC50 0.5 μM



Example 475

bis(3,3'-(phenyl-lysineboryl)benzyl)ether (3032)

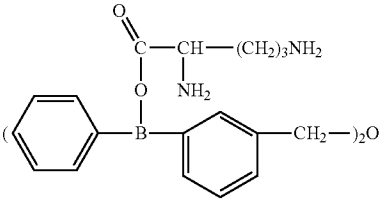
TG 21, x-Fold 1.01, SOC IC50 0.6 μM



Example 476

bis(3,3'-(phenyl-ornithineboryl)benzyl)ether (3033)

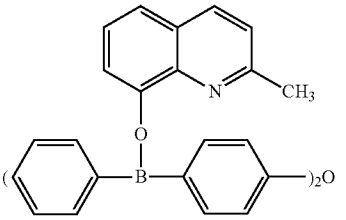
TG 103, x-Fold 0.95, SOC IC50 1.5 μM



Example 477

bis(4,4'-(phenyl-2-methyl-8-quinolinooxyboryl)phenyl)ether (3037)

TG 97, x-Fold 1.02



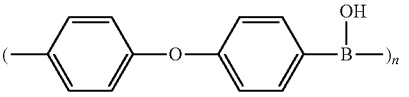
Example 478

poly(diphenyletherhydroxyborane) (7142)

TG 121

4,4'-Dibromodiphenylether (28 mg) was lithiated using isobutyllithium and reacted with triisopropoxyborane to give the title compound (150 mg).

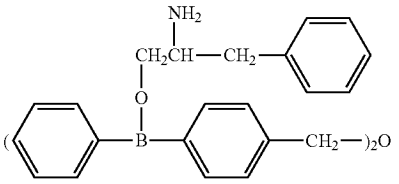
NMR ($CDCl_3$) 3.45 (br, 1H), 6.7-8.0 (m, 8H)



Example 479

bis(4,4'-(phenyl-2-benzyl-2-amino-ethoxyboryl)benzyl)ether (3076)

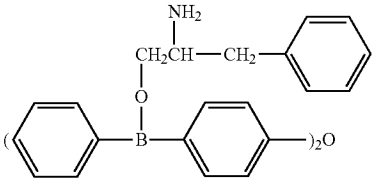
TG 54, x-Fold 1.00, SOC IC50 1.5 μM



Example 480

bis(4,4'-(phenyl-2-benzyl-2-amino-ethoxyboryl)phenyl)ether (3077)

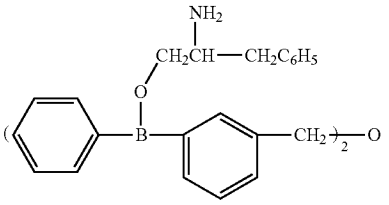
TG 59, x-Fold 0.66, SOC IC50 1.5 μM



Example 481

bis(3,3'-(phenyl-2-benzyl-2-amino-ethoxyboryl)benzyl)ether (3085)

TG 48, x-Fold 0.80, SOC IC50 1.5 μM



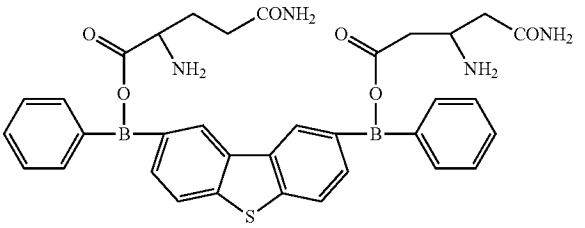
Example 482

2,8-di(phenylglutamine-O,N borane)dibenzothiophene (8015)

TG 114, x-Fold 1.08

Compound 8012 (Example 387) (40 mg) and glutamine (31 mg) were reacted at 80° C. to give the title compound (15 mg).

NMR (DMSO) 2.2 (m, 2H), 2.5 (m, 4H), 3.3 (m, 10H), 7.0-7.8 (m, 16H)



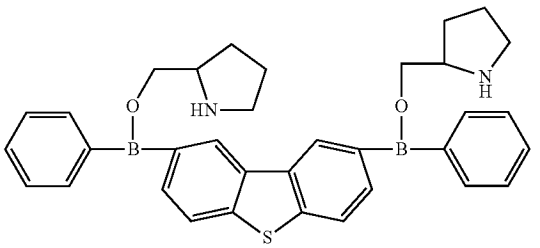
Example 483

2,8-di(phenyl 2-pyrrolidinomethoxyboryl)dibenzothiophene (8016)

TG 107, x-Fold 0.73

The title compound (37 mg) was obtained from compound 8013 (Example 406) (30 mg) and 2-pyrrolidinemethanol (16 mg).

NMR (DMSO) 1.05 (m, 4H), 1.7 (m, 4H), 3.3-3.5 (m, 4H), 7.7-8.0 (m, 16H)



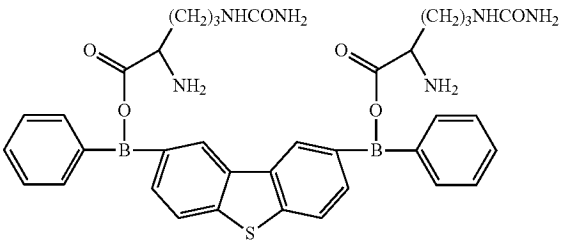
Example 484

2,8-di(phenylarginine-O,N borane)dibenzothiophene (8017)

TG 82, x-Fold 0.78

The title compound (30 mg) was obtained from compound 8012 (Example 387) (24 mg) and arginine (32 mg).

NMR (DMSO) 1.06 (m, 2H), 2.60 (m, 4H), 3.3 (m, 6H), 7.1-7.8 (m, 16H)



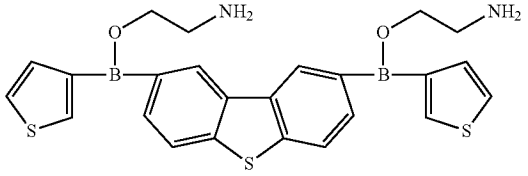
Example 485

2,8-di(3-thiophenylaminoethoxyboryl)dibenzothiophene (8018)

TG 76, x-Fold 0.98

The title compound (6.4 mg) was obtained from compound 8013 (Example 406) (42 mg) and ethanolamine (14 mg).

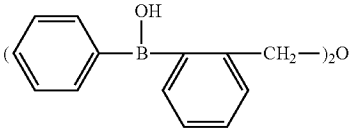
NMR ($CDCl_3$) 2.41 (4H), 2.65 (m, 4H), 3.65 (m, 4H), 7.0-7.9 (m, 12H)



Example 486

bis(2,2'-(phenylhydroxyboryl)benzyl)ether (161OH)

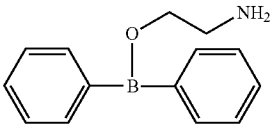
TG 52, x-Fold 1.04, SOC IC50 0.5 μM



Example 487

2-aminoethyl diphenylborinate (2APB)

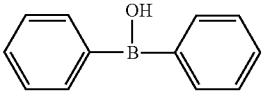
TG 90, x-Fold 0.64, SOC IC50 3 μM



Example 488

diphenylborinic acid (3036)

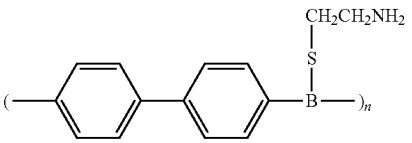
TG 108, x-Fold 1.01, SOC IC50 4 μM



Example 489

poly(4,4'-biphenylene aminoethylthioborane) (1130)

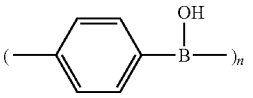
TG 118, x-Fold 0.80



Example 490

poly(4-phenylborinic acid) (502)

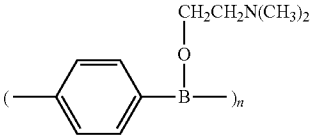
TG 111, x-Fold 0.94



Example 491

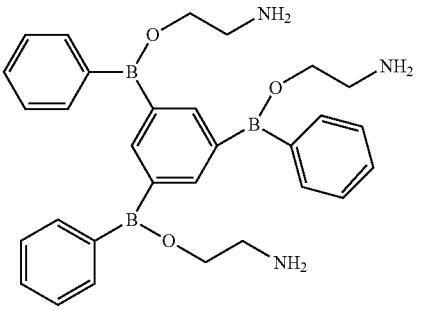
poly(dimethylaminoethoxyphenyleneborane) (1078)

TG 106, x-Fold 0.84



Example 492

1,3,5-tri(phenyl 2-aminoethoxyboryl)benzene (564)



Example 493

dibutyl(phenylalanine-O,N)borane (929)

TG 106, x-Fold 1.03

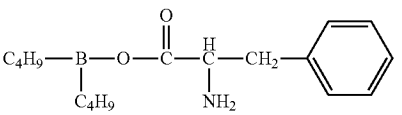


TABLE 1

Compound No.	Example No.	TG	x-Fold	SOC IC50 (μM)
6014	1	28	0.95	
7111	2	28	0.82	0.2
536	3	−20	0.49	0.5
1130	4	109	0.80	5
1022	5	−4	0.60	0.15

TABLE 1-continued

Compound No.	Example No.	TG	x-Fold	SOC IC50 (μM)
7132	6	23	1.01	0.2
1620H	7	14	1.03	0.2
162AE	8	24	1.1	0.2
6077	9	12	0.87	0.5
6076	10	7	0.92	0.5
6047	11	36	0.99	
6050	12	91	1.04	
1122	13	100	1.11	
1132	14	85	1.03	
1133	15	91	0.90	
1134	16	86	0.95	
503	17	111	0.65	
1042D	18	−17	0.84	1.5
1042E	19	47	0.86	
1056	20	54	0.63	4
1120	21	111	0.72	
1121	22	30	0.62	
1107	23	114	0.62	
1116	24	96	0.78	
1117	25	12	0.69	
1109	26	116	0.78	
1108-3	27	45	0.86	5
1114	28	94	0.72	
1115	29	52	0.83	
1141c	30	107	1.02	
1146	31	127	0.95	
3115	32	12	1.02	1
6048	33	51	0.92	
6051	34	39	1.01	
6053	35	14	0.98	
1068	36	6	0.65	3
1074	37	−22	0.73	
1077	38	79	0.71	
1060	39	99	1.04	
1062	40	26	0.52	
1063	41	54	0.63	2
1064	42	8	0.53	2
1065	43	13	0.73	3
1066	44	12	0.54	4
1097	45	99	0.52	
1102	46	93	0.50	
1103	47	106	0.58	
1104	48	102	0.59	
2102	49	89	0.96	
1105	50	112	0.59	
1106	51	13	0.43	
1069	52	73	0.69	
1075	53	113	0.74	
1080	54	112	0.67	
1081	55	151	0.71	
1082	56	74	0.71	
1125	57	5.98	0.67	4
1124	58	45	0.62	
1126	59	107	0.72	
1127	60	24	0.73	
1123	61	100	0.99	
1135	62	94	0.95	
1136	63	63	1.04	
1137	64	11	0.95	
1142	65	115	1.02	7
1144	66	120	1.18	>20
1145	67	122	0.87	
6060	68	119	1.04	
5034	69	76	1.02	
5141	70	13	0.73	0.3
5142	71	51	0.97	1
5143	72	41	1.02	0.5
5144	73	35	0.85	1.2
5145	74	41	0.95	1
6001	75	97	0.88	
6004	76	117	0.78	
6006	77	98	0.91	
6007	78	104	1.02	
6008	79	97	0.88	
6009	80	93	0.90	
6010	81	97	0.92	
6011	82	103	0.95	

TABLE 1-continued

Compound No.	Example No.	TG	x-Fold	SOC IC50 (μM)
6012	83	101	0.92	
6013	84	91	0.92	
504	85	128	0.79	
6015	86	103	0.99	
6016	87	91	1.02	
6017	88	82	0.83	
6018	89	80	0.94	
6019	90	93	0.81	
6020	91	107	0.99	
6021	92	106	1.00	
6023	93	117	0.93	
6024	94	114	0.95	
6025	95	114	0.88	
6026	96	124	0.86	
6027	97	122	0.72	
6029	98	111	0.95	
6030	99	109	0.73	
6032	100	119	0.97	
6033	101	122	1.02	
5009	102	72	1.10	
6034	103	114	0.89	
6037	104	94	1.16	
6038	105	92	1.05	
6039	106	23	0.92	
6040	107	111	0.98	
6041	108	111	1.00	
6042	109	108	1.02	>10
6043	110	115	1.02	>10
6044	111	121	1.02	
6046	112	123	0.99	
6059	113	112	0.99	
6059-9	114	120	0.99	2
385	115	101	1.07	
419	116	108	1.02	
434	117	108	0.06	1.5
544	118	93	0.97	2
554	119	101	0.84	>20
805	120	88	1.08	
583	121	121	0.94	
880	122	93	0.98	7
870	123	98	0.84	1
656	124	90	0.96	
595	125	113		10
601	126	81	1.04	
592	127	109	0.70	
573	128	143	0.93	
1016	129	101	0.78	
563	130	116	0.85	
163AE	131	16	1.1	0.3
567	132	88	0.95	
566	133	106	1.00	
558	134	94	0.92	
602	135	99	1.03	
871	136	96	0.98	
1630H	137	14	0.99	0.3
607	138	96	0.99	
611	139	122	0.88	
548	140	−72	0.85	
620	141	97	0.92	
621	142	88	0.24	
618	143	118	0.90	
612	144	99	0.87	
6005	145	97	0.91	
803	146	91	1.02	
554	147	101	0.87	20
557	148	68	1.00	
607	149	96	0.99	
4122	150	2	0	
1031	151	33	0.87	
1073	152	54	1.07	
1079	153	65	0.79	
1089	154	105	0.96-	
427	155	100	1.02	
7138	156	91	1.08	
1116	157	96	0.73	
1117	158	12	0.69	
926	159	102	0.96	

TABLE 1-continued

Compound No.	Example No.	TG	x-Fold	SOC IC50 (μM)
7139	160	88	1.02	
1098	161	6	0.99	
1099	162	−2	0.85	
347	163	109	1.00	
376	164	94	0.67	
1143	165	120	0.99	
372	166	74	0.70	
2006	167	21	0.71	
2007	168	35	0.72	
1016	169	101	0.78	
907	170	96	0.96	
370	171	98	0.71	
2024	172	69	1.22	
2026	173	122	1.06	
2031-4	174	103	0.99	
2033	175	5	0.89	
2035	176	47	1.06	
2036	177	28	1.00	
2039	178	142	0.89	
2044	179	127	0.99	
4124	180	35	0.98	
424	181	54	0.69	
4105	182	137	1.01	
925	183	91	1.02	
2049	184	94	0.95	
2064	185	130	0.94	>20
601	186	81	0.98	
2086	187	106	0.97	
428	188	91	0.98	
2088	189	119	0.94	
2089	190	99	1.05	
2090	191	85	1.04	
2091	192	102	0.95	
899	193	92	1.03	
901	194	106	1.03	
2108	195	115	0.77	
2109	196	117	0.90	
3001	197	99	1.02	
3003	198	28	0.8	
3017	199	3	0.90	
442	200	100	0.92	
431	201	99	0.57	
3041	202	91	0.94	
3044	203	97	0.97	
3045	204	61	0.79	
3087	205	47	0.80	
3107	206	34	1.14	
3108	207	83	0.91	
3109	208	−7	0.67	
3111	209	1	0.98	
3112	210	27	0.98	2
3113	211	86	0.99	1
3073	212	115	0.75	
3075	213	117	1.00	
3114	214	−7	0.90	2
3116	215	69	1.03	2
4139	216	17	1.03	0.6
4111	217	118	0.94	
4118	218	90	0.97	
4119	219	91	0.88	
4121	220	26	0.50	0.5
4123	221	73	0.94	
8003	222	122	0.86	
8006	223	116	1.02	
4127	224	112	0.89	
4128	225	109	1.03	0.5
4129	226	97	0.94	
4130	227	110	0.99	
4131	228	99	0.98	
4132	229	40	1.09	0.5
4138	230	108	1.03	
4140	231	94	1.01	
4141	232	108	1.10	
4142	233	112	1.12	
4143	234	98	1.07	0.5
4144	235	80	1.03	
4145	236	87	1.10	

TABLE 1-continued

Compound No.	Example No.	TG	x-Fold	SOC IC50 (μM)
4146	237	88	1.15	
4147	238	87	1.07	
356	239	126	0.94	
7117	240	25	0.99	0.08
244	241	67	1.10	
371	242	98	1.17	
436	243	106	0.73	
372	244	74	0.76	1
921	245	94	0.91	
376	246	94	0.67	
422	247	99	0.91	0.7
421	248	103	0.87	
7118	249	25	0.74	0.3
1007	250	125	0.86	
488	251	121	0.83	
542	252	93	0.95	0.5
283	253	92	1.11	
827	254	101	0.95	
828	255	113	0.94	0.5
829	256	112	0.67	1.5
830	257	103	0.98	
833	258	110		5
841	259	67	0.97	2.5
836	260	106	0.89	
837	261	109	0.89	
838	262	115	0.97	
2045	263	146	0.89	3
842	264	109	1.00	5
851	265	112	0.94	
847	266	84	0.87	3
848	267	82	0.60	3
852	268	103	0.96	5
879	269	95	1.01	3
855	270	111	0.54	0.7
906	271	109	1.07	0.5
2043	272	83	0.09	0.3
1024	273	83	0.56	0.25
1023	274	56	0.59	0.3
1036	275	117	0.67	0.3
854	276	105	0.8	
843	277	105	0.98	0.3
7119	278	2	1.08	0.3
894	279	103	0.98	
897	280	98	0.88	
4123	281	77	0.94	
4103	282	112	0.95	0.3
4125	283	12	0.83	0.9
5003	284	89	1.03	
5004	285	51	0.99	2
5012	286	104	0.93	
5013	287	146	1.00	
5014	288	106	1.02	
5015	289	94	1.08	0.3
5018	290	113	1.05	
5019	291	50	1.02	0.5
5020	292	146	1.00	1
5021	293	116	0.91	
4106	294	114	0.96	2
4107	295	107	0.92	0.8
795	296	97	0.74	
806	297	89	0.69	
810	298	101	1.01	
8007	299	118	1.13	
1085	300	95	0.80	5
1083	301	108	0.84	
6062	302	103	0.94	
6082	303	103	0.91	
8020	304	47	0.90	
6095	305	94	0.98	
6096	306	90	0.98	
7021	307	54	1.06	0.5
7020	308	27	1.05	0.5
7047	309	109	0.93	
7051	310	114	1.02	
7052	311	111	1.00	
7053	312	98	1.00	
7056	313	107	0.98	

TABLE 1-continued

Compound No.	Example No.	TG	x-Fold	SOC IC50 (μM)
7057	314	104	0.93	
7058	315	102	0.92	
7059	316	72	1.11	
7063	317	107	0.99	
7064	318	81	1.02	
7065	319	108	1.04	
1128	320	100	0.78	5
1129	321	116	0.78	
612	322	98	0.32	0.2
502	323	111	0.82	
7126	324		0.76	
2054	325	92	0.99	4
8009	326	103	1.09	
8010	327	14	1.07	
2072	328	100	1.04	
672	329	81		0.2
655	330	89	0.90	
682	331	101	0.98	1
674	332	21	0.98	0.2
701	333	107	1.09	
687	334	21	1.02	0.3
686	335	91	1.02	
688	336	101	1.02	
689	337	102	0.98	
693	338	110	0.83	
696	339	115	0.91	
700	340	63	1.01	
701	341	107	1.04	
702	342	114	1.02	
704	343	55	1.02	
705	344	91	0.93	
706	345	95	0.92	
707	346	101	0.81	
708	347	104	0.90	
710	349	104	0.80	
717	350	105	0.92	
711	351	103	1.00	
718	352	97	1.02	
712	353	115	0.85	
719	354	113	1.09	
731	355	91	1.09	
735	356	51	1.06	
736	357	89	1.03	
739	358	112	0.91	
744	359	139	0.96	
745	360	88	1.05	
709	361	100	0.88	>20
729	362	108	1.08	
752	363	97	0.92	
754	364	44	0.82	
753	365	118	0.91	
8011	366	108	0.93	
513	367	113	0.73	
6055	368	52	1.03	
7133	369	105	1.10	
775	370	39	0.76	2
778	371	16	0.85	2
784	372	−18	0.86	1
785	373	1	0.84	2
764	374	17	1.14	
787	375	44	1.05	
788	376	75	0.93	
763	377	70	0.75	>20
765	378	88	0.79	
818	379	92	0.74	
820	380	92	0.67	
813	381	55	0.80	
814	382	76	0.80	
914	383	103	0.92	
915	384	60	1.05	
1007	385	116	0.78	
1014	386	10	0.98	0.5
8012	387	96	0.73	
7085	388	41	0.67	0.5
8019	389	81	0.83	
1023	390	56	0.59	
1028	391	15	0.32	0.5

TABLE 1-continued

Compound No.	Example No.	TG	x-Fold	SOC IC50 (μM)
1030	392	83	0.91	
1036	393	117	0.56	
1037	394	41	0.44	1.5
1007	395	116	0.86	
1040	396	3	0.58	1.2
1038	397	70	0.59	
1042	398	−17	0.88	
1084	399	53	0.96	
2047	400	52	1.01	
1139	401	121	0.95	
1140	402	−12	0.57	
2022	403	67	1.14	2
2023	404	105	1.07	4
3014	405	−3	0.86	0.5
8013	406	61	0.85	
2052	407	77	1.02	
8014	408	108	0.92	
2051	409	29	0.86	1.5
2072	410	130	0.90	2
2073	411	138	0.90	
2074	412	65	0.89	2
2075	413	28	0.81	0.8
2076	414	128	0.90	
2077	415	130	0.90	
2078	416	114	0.92	
2079	417	91	1.01	
2080	418	45	1.02	
2081	419	140	0.90	
2056	420	−3	0.81	1.2
2057	421	−1	1.03	1.2
2058	422	13	0.95	1.2
2059	423	27	0.76	1.2
2063	424	22	1.03	1.2
2064	425	130	0.9	0.5
2068	426	19	0.93	1.2
2093	427	20	0.73	0.8
2094	428	53	0.82	1.5
2095	429	102	0.81	0.7
2096	430	106	1.03	
2052	431	118	1.02	
2111	432	60	0.71	0.3
2112	433	−5	0.71	0.5
2113	434	43	0.60	0.4
2117	435	26	0.84	2
2115	436	104	0.85	
2116	437	119	0.85	
2118	438	29	0.67	2
2119	439	33	0.54	
2120	440	63	0.69	
2121	441	−1	0.58	
2122	442	102	0.58	
2123	443	84	0.63	3
2124	444	20	0.65	1.4
2125	445	108	0.49	
2127	446	73	0.85	
2128	447	97	0.49	
4103	448	112	0.95	
2129	449	92	0.89	
2130	450	53	0.49	
2135	451	6	0.91	1.4
2136	452	29	0.96	0.5
2137	453	113	1.04	
2144	454	15	0.97	0.5
2145	455	23	1.04	0.5
2146	456	29	0.87	0.5
3002	457	30	1.10	0.6
3004	458	31	1.10	0.5
3005	459	80	1.03	
3015	460	26	0.95	0.4
6078	461	30	0.85	
3018	462	31	0.92	0.3
3020	463	24	0.92	0.3
3021	464	41	0.76	0.8
3022	465	18	1.06	0.2
3023	466	71	1.04	
3024	467	60	0.98	0.25
3025	468	35	0.98	0.3

TABLE 1-continued

Compound No.	Example No.	TG	x-Fold	SOC IC50 (μM)
3026	469	15	0.94	0.25
3027	470	19	1.02	0.3
3028	471	52	1.04	0.6
3029	472	47	0.95	1
3030	473	−4	0.96	0.5
3031	474	145	1.04	0.5
3032	475	21	1.01	0.6
3033	476	103	0.95	1.5
3037	477	97	1.02	
7142	478	121		
3076	479	54	1.00	1.5
3077	480	59	0.66	1.5
3085	481	48	0.80	1.5
8015	482	114	1.08	
8016	483	107	0.73	
8017	484	82	0.78	
8018	485	76	0.98	
1610H	486	52	1.04	0.5
2APB	487	90	0.64	3
3036	488	108	1.01	4
1130	489	118	0.80	
502	490	111	0.94	
1078	491	106	0.84	
564	492			
929	493	106	1.03	

Experimental Example 4

The effects of 162AE (bis(3,3'-(phenylaminoethoxyboryl) benzyl)ether described in Example 8) and 163AE (bis(4,4'-(phenylaminoethoxyboryl)benzyl)ether described in Example 131) for I_{CRAC}, whose molecular entity as one of SOCE has been clarified, were investigated using an electrophysiological method. STIM1 and Orail (CRACM1) were forcibly expressed in HEK293 cells, and whole cell records were taken by the Patch clamp technique. BAPTA (20 mM), which is a calcium chelator, and IP_3 (20 μM) that depletes intracellular calcium store were added to a recording electrode internal solution (120 mM Cs-glutamate, 10 mM HEPES, 3 mM $MgCl_2$), 10 mM calcium was added to an extracellular solution to facilitate observation of calcium electric current, and a ramp command from −150 mV to +150 mV was input at 0.5 Hz to obtain a current-voltage curve. For quantification of SOCE, the size of the inward current at −80 mV was used as an index. After the start of the whole cell recording, time was taken to sufficiently activate SOCE (I_{CRAC}), and compounds 162AE and 163AE as inhibitors were administered to the cells. As a result of the experiment, these inhibitors highly strongly inhibited SOCE (I_{CRAC}) and the IC50 thereof was 0.086 μM, 0.17 μM (for 162AE, 163AE, respectively), thus exhibiting a strong inhibitory effect. Moreover, since SOCE (I_{CRAC}) reconstituted by STIM1 and Orail (CRACM1) is indispensible for the immune response of T cells, it is considered possible to suppress excess immune response that occurs in autoimmune diseases, by utilizing the inhibitor, and treat the disease or mitigate the symptoms.

INDUSTRIAL APPLICABILITY

According to the present invention, a drug for the prophylaxis and/or treatment of a disease based on abnormal protein cross-linking reaction, such as Alzheimer's disease, Parkinson's disease, Celiac disease, cataract, mad cow disease, congenital lamellar ichthyosis, congenital hemostatic disorder and the like can be provided.

This application is based on a patent application No. 2008-207315 filed in Japan (filing date: Aug. 11, 2008), the contents of which are incorporated in full herein by this reference.

The invention claimed is:

1. A compound of formula (8')

$$R_3'—B(ZR_1')—X'—B(ZR_2')—R_4' \quad (8')$$

wherein

B is a boron atom,

Z is O,

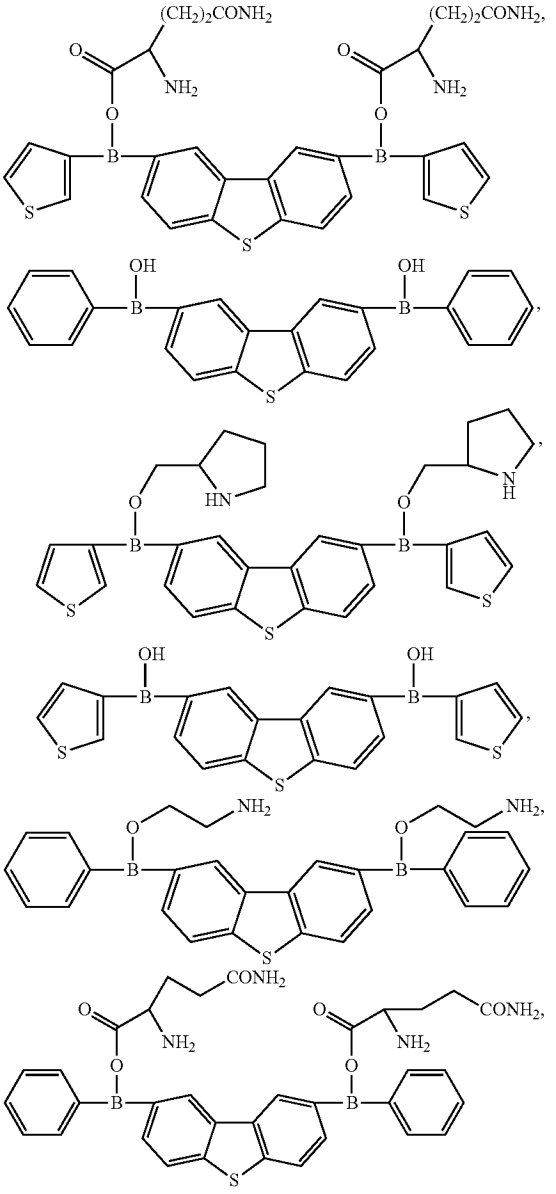
R_1' and R_2' are H, $—(CH_2)_m—NH_2$, $—CH_2R_{12}'$ wherein $R_{12'}$ is pyrrolidinyl, $—COCH(NH_2)—(CH_2)_mNH-CONH_2$, or $—COCH(NH_2)—(CH_2)_m—CONH_2$, and m is an integer of 1 to 5,

R_3' and R_4' are phenyl or thienyl, and

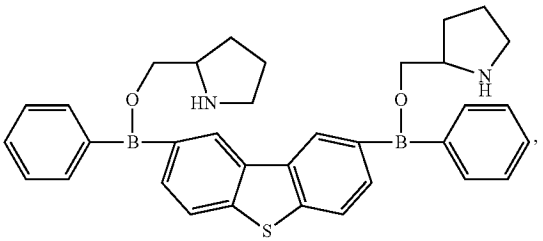
X' is a 2,8-dibenzothiophenyl group,

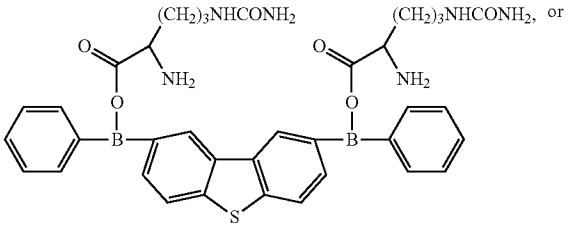
or a pharmaceutically acceptable salt thereof.

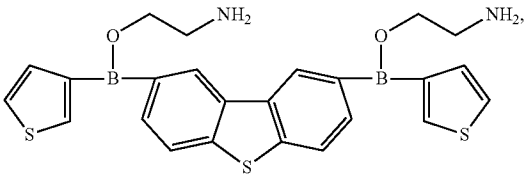
2. The compound according to claim **1**, which is any of



-continued

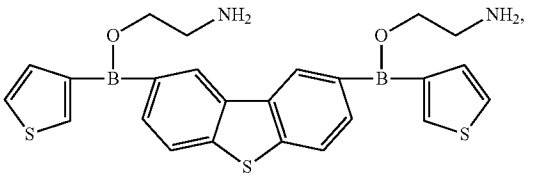






or a pharmaceutically acceptable salt thereof.

3. The compound according to claim **1** of the formula



or a pharmaceutically acceptable salt thereof.

4. A protein cross-linking inhibitor comprising the compound according to claim **1**, or a pharmaceutically acceptable salt thereof.

5. The inhibitor according to claim **4**, wherein the inhibition is polyglutamine aggregation inhibition.

6. A therapeutic drug for a disease caused by cross-linking of protein, comprising the compound according to claim **1**, or a pharmaceutically acceptable salt thereof, wherein the disease is selected from Alzheimer's disease, Parkinson's disease, and mad cow disease.

7. A polyglutamine aggregation inhibitor comprising the compound according to claim **1**, or a pharmaceutically acceptable salt thereof.

8. A therapeutic drug for a disease caused by polyglutamine aggregation, comprising the compound according to claim **1**, or a pharmaceutically acceptable salt thereof, wherein the disease is Huntington's disease.

* * * * *