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Dodecaborate Conjugates Targeting Tumor Cell Overexpressing Translocator Protein for Boron Neutron Capture Therapy

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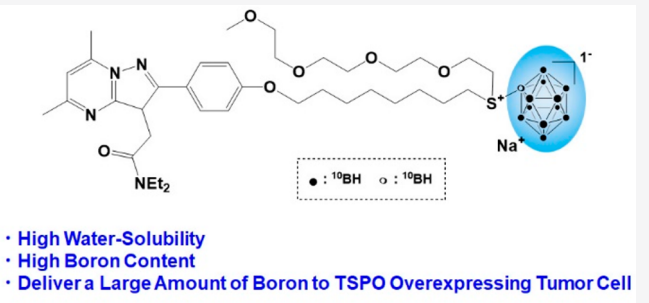
ABSTRACT: We developed novel *closo*-dodecaborate ($[B_{12}H_{11}]^{2-}$) anion-containing translocator protein (TSPO) ligand as a boron carrier for boron neutron capture therapy. This compound shows high water solubility and can deliver boron to TSPO highly expressed in breast cancer cells. We describe the synthesis and *in vitro* evaluation of a dodecaborate-based pyrazolopyrimidine.



KEYWORDS: *BNCT, TSPO, dodecaborate, boron cluster, boron-containing pharmaceutical*

Recently, boron neutron capture therapy (BNCT) has been recognized as an essential treatment for refractory cancers such as glioma, head and neck cancer, and melanoma.[1,2] BNCT is based on the nuclear capture and fission reactions of the ^{10}B atom with low energy thermal/epithermal neutrons to yield high linear energy transfer α particles and recoiling ^{7}Li nuclei.[3] Because the path lengths of the articles are 9−10 μm, approximately the dimension of a single cell, ^{10}B-containing cells are selectively killed by BNCT.

Although many types of boron compounds, including amino acids, peptides, nucleic acids, anticancer drugs, and liposomes, have been reported as boron delivery agents for BNCT,[4−7] only two compounds, *p*-borono-L-phenylalanine (L-BPA, Boropharan-10B, Figure 1, **1**)[8] and disodium mercapto-*closo*-undecahydro-dodecaborate (**2**) ($[B_{12}H_{11}SH]^{2-}2Na^{+}$, BSH, Figure 1, **2**),[9] are clinically used in the treatment of cancer with BNCT. For a boron delivery agent to be successful in BNCT, the compound must have the following properties: (i) high tumor-targeting selectivity, (ii) high water solubility, (iii) low toxicity, and (iv) concentration of ∼20 μg ^{10}B/g (20 Bppm) in tumor tissues. Because L-BPA is selectively accumulated in tumor cells notably accumulated in the whole cell, including the nucleus via an L-amino acid transport system (LAT1),[10] L-BPA is clinically used as an effective boron carrier in BNCT. However, the water solubility and boron contents of L-BPA are very low. BSH, a class of water-soluble boron cluster compounds with toxicity lower than that of other boron clusters such as carborane, and its derivatives are of increasing interest as BNCT boron carriers capable of carrying large amounts of ^{10}B atoms to tumor cells. BSH is clinically used as a boron carrier[11] for the treatment of brain tumors,

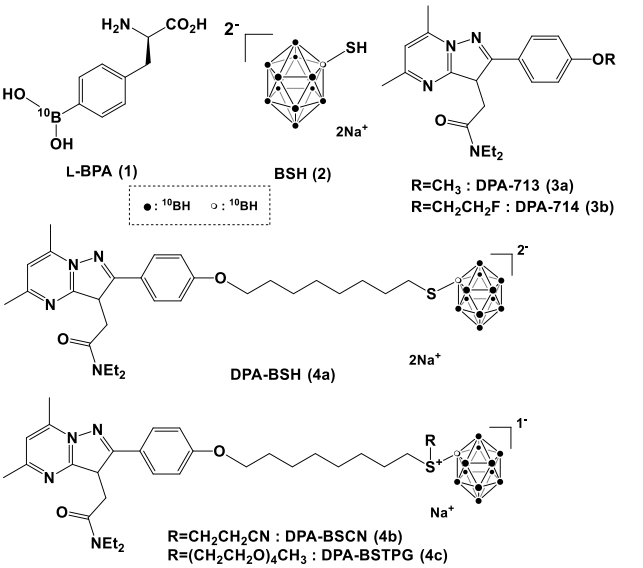


Figure 1. Boron compounds and TSPO targeted compounds.

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although tumor selectivity and cell membrane permeability of BSH is slightly low. In light of these factors, novel useful boron pharmaceuticals for BNCT are in high demand, and many types of boron compounds have been reported as boron delivery agents for BNCT as described above. However, most of BNCT drug candidates are based on nutrient such as amino acids, sugars and vitamins, few studies have been reported on the molecular targeted drug type boron compounds for BNCT.

The translocator protein (TSPO), also known as the periphenyl benzodiazepine receptor (PBR), is an 18 kDa protein composed of at least three subunits.[12] TSPO is localized in the mitochondria and plays important roles in several biological processes, such as cholesterol metabolism, proliferation, and apoptosis. Because TSPO is highly expressed in several disease states, including Alzheimer's disease,[13] Huntington's disease,[14] and cancer,[15] it is a potentially useful drug target. TSPO overexpression has been reported in several cancers, including breast, colorectal, prostate, and ovarian cancer and glioma, and appears to be an indicator of poor prognosis in patients with lymph node negative breast cancer.[16] Therefore, TSPO ligands labeled with positron emission atoms, such as PK11195,[17] DPA-713 (Figure 1, **3a**),[18] and DPA-714 (Figure 1, **3b**),[19] have been reported as potential cancer imaging agents. In particular, pyrazolopyrimidine derivatives DPA-713 and DPA-714 show the high specific affinity for TSPO. The arylpyrazolo[1,5-α]pyrimidine acetamide moiety of DPA-714 seems to have an important role in TSPO binding affinity, and alkyl ether derivatives at the 4′-position of the phenyl ring are reported.[20]

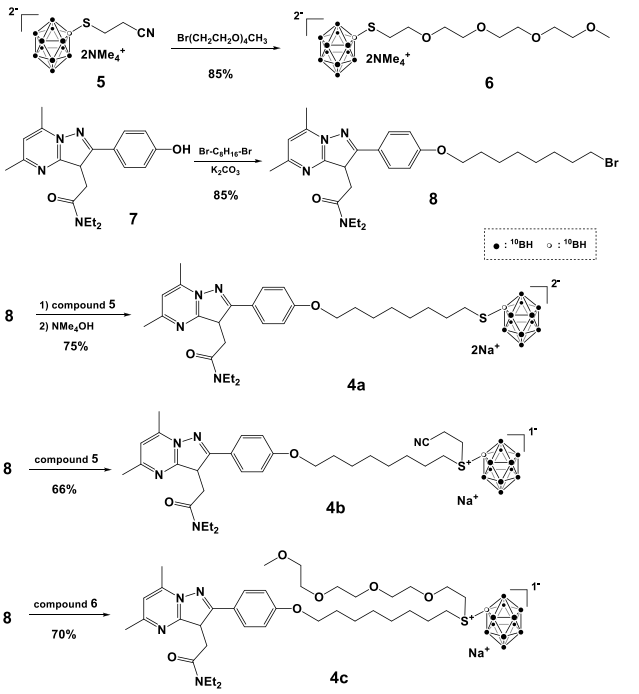
In BNCT, TSPO is a potential target for tumor targeting, and several carborane-containing TSPO ligands have been reported.[21,22] Carborane has been used as a boron source for BNCT, because of its high boron content and ease of organic moiety conjugation via c-c bonds using carbon atoms contained within the boron cluster structure.[23,24] However, carborane exhibits very high toxicity and very low water solubility, and carborane based compounds are not used in clinical studies.

Conversely, dodecaborate exhibits low toxicity and high water solubility, and thus, we designed and synthesized organic compounds containing thiododecaborate ($[B_{12}H_{11}]^{2-}$-S-).[25−27] These boron conjugates presented very low toxicity, high water solubility, and high tumor-cell-killing properties by neutron irradiation. These results suggested that dodecaborate would be a useful boron carrier source for BNCT.

In this study, three novel dodecaborate-containing pyrazolopyrimidine TSPO ligands were developed (Figure 1): DPA-BSH (**4a**), DPA-BSCN (**4b**), DPA-BSTPG (**4c**). The DPA-714 derivatives were bound to the dodecaborate anion via alkyl linker at the 4′-position of the phenyl ring, and to the DPA-BSTPG linked polyethylene glycol moiety via S^+ group to enhance water solubility. Here, we present the synthesis and biological evaluation of novel boron compounds **4a−c** as boron carriers for BNCT.

Scheme 1 outlines our process for the synthesis of the dodecaborate-containing DPA derivatives. PEGlyated dodecaborate (**6**) was prepared from *S*-cyanoethyldodecaborate[28] (**5**) as previously reported.[29] Subsequently, the pyrazolopyrimidine derivative[30] (**7**) was alkylated with 1,8-dibromooctane to introduce an alkyl linker. The alkylated pyrazolopyrimidine (**8**) was coupled with compound **5**, and subsequent successive treatments with ion-exchange resin furnished DPA-BSCN (**4b**). Deprotection of DPA-BSCN with tetramethylammonium hydroxide (NMe_4OH) yielded DPA-BSH (**4a**). Finally, DPA-BSTPG (**4c**) was synthesized by coupling PEGlyated dodecaborate (**6**) with alkylated pyrazolopyrimidine (**8**) followed by treatment with an ion-exchange resin.

Scheme 1. Synthesis of Boronated TSPO Ligands



The purity and chemical structure of the novel molecules were analyzed using ^{1}H NMR, ^{13}C NMR, and ESI-MS. Due to their high water solubility, the compounds were prepared as a 50 mM (6000 Bppm) H_2O solution and refrigerated; they remained stable in water media for over one month under 4 °C.

The cytotoxicities of the novel DPA derivatives **4a−c** and L-BPA as positive control toward MCF-7 and MDA-MB-231 breast cancer cells were determined by WST-8 test. As shown in Table 1, the cytotoxicity of DPA-BSH was very low with an IC_{50} value of over 1 mM. Although lower in comparison, the IC_{50} values of DPA-BSCN and DPA-BSTPG were both greater than 50 μM, validating their applicability as boron carriers for evaluation tests.

Table 1. Cytotoxicity of Boron Compounds

compound	IC_{50} (mM)	
	MCF-7	MDA-MB-231
BPA (**1**)	>1	>1
DPA-BSH (**4a**)	>1	>1
DPA-BSCN (**4b**)	0.15	0.10
DPA-BSTPG (**4c**)	0.12	0.092

To evaluate the potential of the dodecaborate-containing DPA derivatives as BNCT agents, we used two breast cancer cell lines, MCF-7 and MDA-MB-231, which exhibit low and high TSPO expression, respectively.[31] We applied equal dosages of boron to the tumor cells via treatment with the novel compounds (6.0 Bppm, 50 μM) and L-BPA (6.0 Bpm, 0.6 mM) as well as a high dosage of L-BPA (20 Bppm, 2.0 mM) and then measured the intracellular boron concen-

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trations by inductively coupled plasma optical emission spectrometry (ICP-OES).

As shown in Figure 2a, all three novel dodecaborate-containing DPA derivatives successfully delivered boron to tumor cells, and MDA-MB-231 cells with overexpressed TSPO consistently took up more novel boron compounds than MCF-7 cells. Although DPA-BSH (**4a**) and DPA-BSCN (**4b**) delivered moderate levels of boron, DPA-BSTPG (**4c**) delivered a notably higher level than L-BPA in both MDA-MB-231 and MCF-7 cells. Notably, the MDA-MB-231 intracellular boron concentration achieved by using DPA-BSTPG (**4c**) was 5−6 times greater than that achieved by using a more highly concentrated dose of L-BPA (DPA-BSTPG: 0.05 mM, BPA: 2.0 mM).

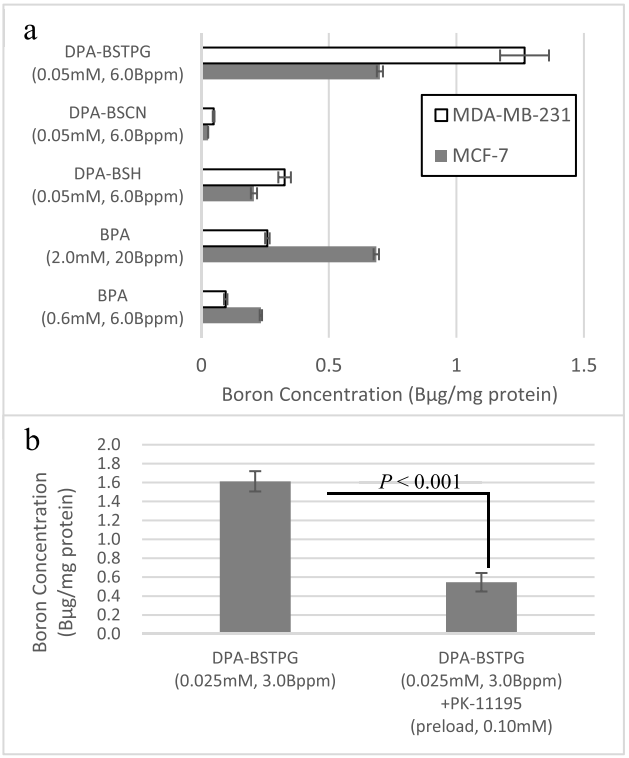

Figure 2. Cellular uptake of boron in breast cancer cells. (a) Amount of boron cellular uptake in two kinds of breast cancer cells after treatment with each boron compound (6.0 Bppm or 20 Bppm) in 10% FBS-containing DMEM for 24 h at 37 °C. (b) Cellular uptake of DPA-BSTPG (3.0 Bppm) in MDA-MB-231 cells with or without PK-11195 (preloading 1 h, 0.10 mM) in 10% FBS-containing DMEM for 3 h at 37 °C. The data are expressed as the mean (±SD) of three experiments.

To elucidate the mechanism underlying the uptake of DPA-BSTPG in cells expressing high levels of TSPO, we performed an uptake inhibition assay using PK11195, a PBR ligand with a highly selective affinity to TSPO, as an antagonist. As shown in Figure 2b, the incorporated amount of DPA-BSTPG in MDA-MB-231 cells was reduced to approximately 35% by preloading PK11195. These results suggest that the mechanism underlying the cellular uptake of DPA-BSTPG is related to TSPO targeting.

Furthermore, to evaluate the amounts of DPA-BSTPG incorporated into another TSPO overexpressed tumor cells, we measured the boron concentrations in five kinds of cancer cells[32−35] (Figure 3). DPA-BSTPG delivered a large amount of boron to five kinds of tumor cells. Especially, in the case of glioma, glioblastoma, and melanoma, which are indications for treatment of BNCT, the intracellular boron concentrations achieved by using DPA-BSTPG were 7−25 times greater than those achieved by using L-BPA.

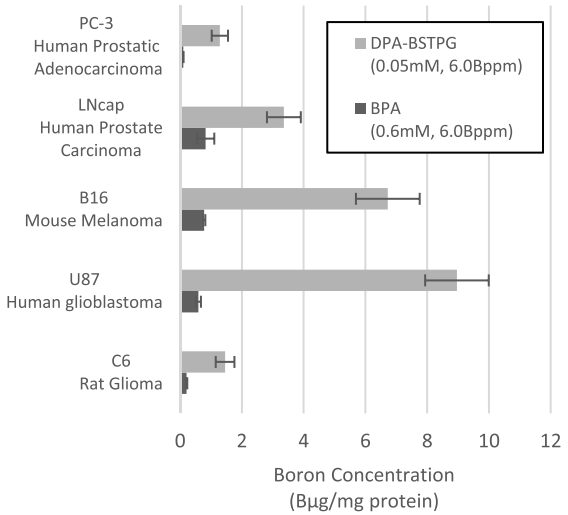

Figure 3. Cellular uptake of boron in TSPO overexpressed cancer cells. Amount of boron cellular uptake in cancer cells after treatment with each boron compounds (6.0 Bppm) in 10% FBS-containing DMEM for 24 h at 37 °C. The data are expressed as the mean (±SD) of three experiments.

Finally, to confirm the usefulness of the DPA-BSTPG for BNCT, we examined the tumor cell killing effects of L-BPA and DPA-BSTPG against C6 glioma cells by using neutron irradiation (Figure 4). The result of neutron irradiation test was correlated with the result of the boron uptake test. DPA-BSTPG showed higher killing effects than L-BPA for glioma cells.

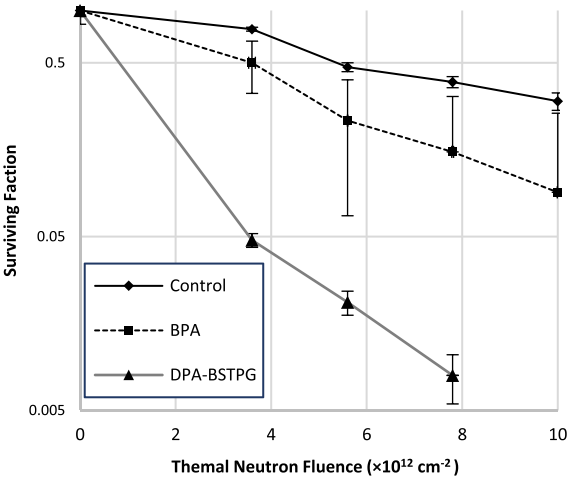

Figure 4. Tumor cell killing effect of boron compounds against C6 cells. C6 cells were incubated in boron-containing DMEM (boron concentration: 6.0 Bppm) for 24 h at 37 °C, and then the neutron was irradiated for 0−90 min. After thermal neutron exposure, 1000 cells were placed in tissue culture dishes containing DMEM to examine colony formation. Seven days later, the colonies were fixed and stained for quantitative visualization by the naked eye. The data are expressed as the mean (±SD) of three experiments.

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In conclusion, we synthesized novel dodecaborate-containing pyrazolopyrimidine derivatives, as depicted in Figure 1 (**4a**–**c**). The results of the *in vitro* evaluation suggest that these compounds are useful boron carriers targeting TSPO overexpressing cells. DPA-BSTPG (**4c**), in particular, delivers a large amount of boron to cancer cells and shows the high water solubility and tumor cell killing effects by BNCT. The *in vivo* evaluation of DPA-BSTPG is ongoing, and the results will be reported in the near future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.1c00377.

Experimental details of the synthetic method and biological evaluation; ^{1}H and ^{13}C NMR charts of novel compounds; HRMS chart of novel compounds (PDF)

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Author Contributions

Y.H. and M.K. designed the experiments. Y.H., Y.O., and H.T. synthesized the compounds. Y.H., M.I., and S.K. performed the biological assays. Y.H. wrote the manuscript. All authors discussed the results and implications of the study and approved the final manuscript.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Barth, R. F.; Coderre, J. A.; Vicente, M. G.; Blue, T. E. Boron Neutron Capture Therapy of Cancer: Current Status and Future Prospects. *Clin. Cancer Res.* **2005**, *11*, 3987−4002.

(2) Miyatake, S.; Wanibuchi, M.; Hu, N.; Ono, K. Boron neutron capture therapy for malignant brain tumors. *J. Neuro-Oncol.* **2020**, *149*, 1−11.

(3) Coderre, J. A.; Morris, G. M. The Radiation Biology of Boron Neutron Capture Therapy. *Radiat. Res.* **1999**, *151*, 1−18.

(4) Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F. G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. The Chemistry of Neutron Capture Therapy. *Chem. Rev.* **1998**, *98*, 1515−1562.

(5) Ban, S. H.; Nakamura, H.. In *Handbook of Boron Science*; Hosmane, N.S., Ed.; World Scientific Publishing Europe Ltd.: London, UK, 2019; Vol *4*, p 49.

(6) Nakase, I.; Katayama, M.; Hattori, Y.; Ishimura, M.; Inaura, S.; Fujiwara, D.; Takatani-Nakase, T.; Fujii, I.; Futaki, S.; Kirihata, M. Intracellular target delivery of cell-penetrating peptide-conjugated dodecaborate for boron neutron capture therapy (BNCT). *Chem. Commun.* **2019**, *55*, 13955−13958.

(7) Barth, R. F.; Mi, P.; Yang, W. Boron delivery agents for neutron capture therapy of cancer. *Cancer Commun.* **2018**, *38*, 35.

(8) Ichihashi, M.; Nakanishi, T.; Mishima, Y. Asymmetric Synthesis of optically Pure L-*p*-Boronophenylalanine by a Hybrid Process. *J. Invest. Dermatol.* **1982**, *78*, 215−218.

(9) Soloway, A. H.; Hatanaka, H.; Davis, M. A. Penetration of Brain and Brain Tumor. VII. Tumor-Binding Sulfhydryl Boron Compounds. *J. Med. Chem.* **1967**, *10*, 714−717.

(10) Wongthai, P.; Hagiwara, K.; Miyoshi, Y.; Wiriyasermkul, P.; Wei, L.; Ohgaki, R.; Kato, I.; Hamase, K.; Nagamori, S.; Kanai, Y. Boronophenylalanine, a boron delivery agent for boron neutron capture therapy, is transported by $ATB^{0,+}$, LAT1 and LAT2. *Cancer Sci.* **2015**, *106*, 279−286.

(11) Yamamoto, T.; Nakai, K.; Matsumura, A. Boron neutron capture therapy for glioblastoma. *Cancer Lett.* **2008**, *262*, 143−152.

(12) Papadopoulos, V.; Baraldi, M.; Guilarte, T. R.; Knudsen, T. B.; Lacapère, J. J.; Lindemann, P.; Norenberg, M. D.; Nutt, D.; Weizman, A.; Zhang, M. R.; Gavish, M. Translocator protein (18 kDa): new nomenclature for the peripheral-type benzodiazepine receptor based on its structure and molecular function. *Trends Pharmacol. Sci.* **2006**, *27*, 402−409.

(13) Yasuno, F.; Ota, M.; Kosaka, J.; Ito, H.; Higuchi, M.; Doronbekov, T. K.; Nozaki, S.; Fujimura, Y.; Koeda, M.; Asada, T.; Suhara, T. Increased Binding of Peripheral Benzodiazepine Receptor in Alzheimer's Disease Measured by Positron Emission Tomography with [^{11}C]DAA1106. *Biol. Psychiatry* **2008**, *64*, 835−841.

(14) Ouchi, Y.; Yoshikawa, E.; Sekine, Y.; Futatsubashi, M.; Kanno, T.; Ogusu, T.; Torizuka, T. Microglial activation and dopamine terminal loss in early Parkinson's disease. *Ann. Neurol.* **2005**, *57*, 168−175.

(15) Decaudin, D.; Castedo, M.; Nemati, F.; Beurdeley-Thomas, A.; De Pinieux, G.; Caron, A.; Pouillart, P.; Wijdenes, J.; Rouillard, D.; Kroemer, G.; Poupon, M. F. Peripheral Benzodiazepine Receptor Ligands Reverse Apoptosis Resistance of Cancer Cells *in Vitro* and *in Vivo*. *Cancer Res.* **2002**, *62*, 1388−1393.

(16) Galiegue, S.; Casellas, P.; Kramar, A.; Tinel, N.; Simony-Lafontaine, J. Immunohistochemical Assessment of the Peripheral Benzodiazepine Receptor in Breast Cancer and Its Relationship with Survival. *Clin. Cancer Res.* **2004**, *10*, 2058−2064.

(17) Le Fur, G.; Perrier, M. L.; Vaucher, N.; Imbault, F.; Flamier, A.; Uzan, A.; Renault, C.; Dubroeucq, M. C.; Gueremy, C. Differentiation

between two ligands for peripheral benzodiazepine binding sites, [^{3}H]R05−4864 and [^{3}H]PK 11195, by thermodynamic studies. *Life Sci.* **1983**, *32*, 1839−1847.
(18) James, M. L.; Fulton, R. R.; Henderson, D. J.; Eberl, S.; Meikle, S. R.; Thomson, S.; Allan, R. D.; Dolle, F.; Fulham, M. J.; Kassiou, M. Synthesis and in vivo evaluation of a novel peripheral benzodiazepine receptor PET radioligand. *Bioorg. Med. Chem.* **2005**, *13*, 6188−6194.
(19) Tang, D.; McKinley, E. T.; Hight, M. R.; Uddin, M. I.; Harp, J. M.; Fu, A.; Nickels, M. L.; Buck, J. R.; Manning, H. C. Synthesis and structure-activity relationships of 5,6,7-substituted pyrazolopyrimidines: discovery of a novel TSPO PET ligand for cancer imaging. *J. Med. Chem.* **2013**, *56*, 3429−3433.
(20) Reynolds, A.; Hanani, R.; Hibbs, D.; Damont, A.; Pozzo, E. D.; Selleri, S.; Dollé, F.; Martini, C.; Kassiou, M. Pyrazolo[1,5-α]pyrimidine acetamides: 4-Phenyl alkyl ether derivatives as potent ligands for the 18 kDa translocator protein (TSPO). *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5799−5802.
(21) Crossley, E. L.; Issa, F.; Scarf, A. M.; Kassiou, M.; Rendina, L. M. Synthesis and cellular uptake of boron-rich pyrazolopyrimidines:exploitation of the translocator protein for the efficient delivery of boroninto human glioma cells. *Chem. Commun.* **2011**, *47*, 12179−12181.
(22) Narlawar, R.; Austin, C. J. D.; Kahlert, J.; Selleri, S.; Da Pozzo, E.; Martini, C.; Werry, E. L.; Rendina, L. M.; Kassiou, M. Remarkable Enhancement in Boron Uptake Within Glioblastoma Cells With Carboranyl-Indole Carboxamides. *Chem. - Asian J.* **2018**, *13*, 3321−3327.
(23) Couto, M.; Alamon, C.; Nievas, S.; Perona, M.; Dagrosa, M. A.; Teixidor, F.; Cabral, P.; Vinas, C.; Cerecetto, H. Bimodal Therapeutic Agents Against Glioblastoma, One of the Most Lethal Formsof Cancer. *Chem. - Eur. J.* **2020**, *26*, 14335−14340.
(24) Yamana, K.; Kawasaki, R.; Sanada, Y.; Tabata, A.; Bando, K.; Yoshikawa, K.; Azuma, H.; Sakurai, Y.; Masunaga, S.; Suzuki, M.; Sugikawa, K.; Nagasaki, T.; Ikeda, A. Tumor-targeting hyaluronic acid/fluorescent carborane complex for boron neutron capture therapy. *Biochem. Biophys. Res. Commun.* **2021**, *559*, 210−216.
(25) Hattori, Y.; Kusaka, S.; Mukumoto, M.; Uehara, K.; Asano, T.; Suzuki, M.; Masunaga, S.; Ono, K.; Tanimori, S.; Kirihata, M. Biological Evaluation of Dodecaborate-Containing l-Amino Acids for Boron Neutron Capture Therapy. *J. Med. Chem.* **2012**, *55*, 6980−6984.
(26) Hattori, Y.; Kusaka, S.; Mukumoto, M.; Ishimura, M.; Ohta, Y.; Takenaka, H.; Uehara, K.; Asano, T.; Suzuki, M.; Masunaga, S.; Ono, K.; Tanimori, S.; Kirihata, M. Synthesis and in vitro evaluation of thiododecaborated α, α- cycloalkylamino acids for the treatment of malignant brain tumors by boron neutron capture therapy. *Amino Acids* **2014**, *46*, 2715−2720.
(27) Takeuchi, K.; Hattori, Y.; Kawabata, S.; Futamura, G.; Hiramatsu, R.; Wanibuchi, M.; Tanaka, H.; Masunaga, S.; Ono, K.; Miyatake, S.; Kirihata, M. Synthesis and Evaluation of Dodecaboranethiol Containing Kojic Acid (KA-BSH) as a Novel Agent for Boron Neutron Capture Therapy. *Cells* **2020**, *9*, 1551.
(28) Gabel, D.; Moller, D.; Harfst, S.; Roesler, J.; Ketz, H. Synthesis of S-alkyl and S-acyl derivatives of mercaptoundecahydrododecaborate, a possible boron carrier for neutron capture therapy. *Inorg. Chem.* **1993**, *32*, 2276−2278.
(29) Kusaka, S.; Hattori, Y.; Uehara, K.; Asano, T.; Tanimori, S.; Kirihata, M. Synthesis of optically active dodecaborate-containing l-amino acids for BNCT. *Appl. Radiat. Isot.* **2011**, *69*, 1768−1770.
(30) Cerutti, E.; Damont, A.; Dollé, F.; Baroni, S.; Aime, S. Synthesis and characterization of an MRI Gd-based probe designed to target the translocator protein. *Magn. Reson. Chem.* **2013**, *51*, 116−122.
(31) Hardwick, M.; Fertikh, D.; Culty, M.; Li, H.; Vidic, B.; Papadopoulos, V. Peripheral-Type Benzodiazepine Receptor (PBR) in Human Breast Cancer. *Cancer Res.* **1999**, *59*, 831−842.
(32) Rechichi, M.; Salvetti, A.; Chelli, B.; Costa, B.; Da Pozzo, E.; Spinetti, F.; Lena, A.; Evangelista, M.; Rainaldi, G.; Martini, C.; Gremigni, V.; Rossi, L. TSPO over-expression increases motility, transmigration and proliferation properties of C6 rat glioma cells. *Biochim. Biophys. Acta, Mol. Basis Dis.* **2008**, *1782*, 118−125.
(33) Landau, M.; Weizman, A.; Zoref-Shani, E.; Beery, E.; Wasseman, L.; Landau, O.; Gavish, M.; Brenner, S.; Nordenberg, J. Antiproliferative and Differentiating Effects of Benzodiazepine Receptor Ligands on B16 Melanoma Cells. *Biochem. Pharmacol.* **1998**, *56*, 1029−1034.
(34) Denora, N.; Lee, C.; Iacobazzi, R. M.; Choi, J. Y.; Song, I. H.; Yoo, J. S.; Piao, Y.; Lopalco, A.; Leonetti, F.; Lee, B. C.; Kim, S. E. TSPO-targeted NIR-fluorescent ultra-small iron oxide nanoparticles for glioblastoma imaging. *Eur. J. Pharm. Sci.* **2019**, *139*, 105047.
(35) Fafalios, A.; Akhavan, A.; Parwani, A. V.; Bies, R. R.; McHugh, K. J.; Pflug, B. R. Translocator Protein Blockade Reduces Prostate Tumor Growth. *Clin. Cancer Res.* **2009**, *15*, 6177−6184.

https://doi.org/10.1021/acsmedchemlett.1c00377
ACS Med. Chem. Lett. 2022, 13, 50−54