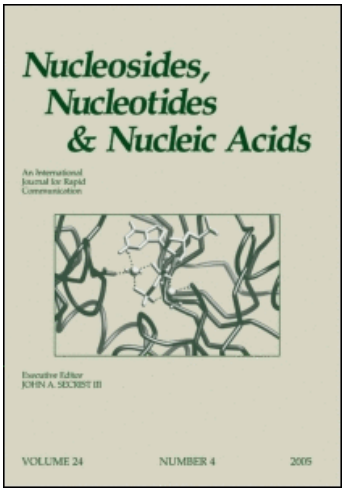

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

2'-Deoxyadenosine Bearing Hydrophobic Carborane Pharmacophore

Agnieszka Olejniczak[a]; Blażej Wojtczak[a]; Zbigniew J. Lesnikowski[a]
[a] Laboratory of Molecular Virology and Biological Chemistry, Center of Medical Biology, Polish Academy of Sciences, Lodz, Poland

To cite this Article Olejniczak, Agnieszka , Wojtczak, Blażej and Lesnikowski, Zbigniew J.(2007) '2'-Deoxyadenosine Bearing Hydrophobic Carborane Pharmacophore', Nucleosides, Nucleotides and Nucleic Acids, 26: 10, 1611 — 1613
To link to this Article: DOI: 10.1080/15257770701548733
URL: http://dx.doi.org/10.1080/15257770701548733

Nucleosides, Nucleotides, and Nucleic Acids, 26:1611–1613, 2007

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770701548733

Taylor & Francis
Taylor & Francis Group

2′-DEOXYADENOSINE BEARING HYDROPHOBIC CARBORANE PHARMACOPHORE

Agnieszka Olejniczak, Blażej Wojtczak, and Zbigniew J. Lesnikowski
□ *Laboratory of Molecular Virology and Biological Chemistry, Center of Medical Biology, Polish Academy of Sciences, Lodz, Poland*

□ *Modification of 2′-deoxyadenosine at position 8 with* para*-carborane boron cluster is described. Incorporation of boron cluster into nucleic base has been accomplished using Sonogashira palladium-catalyzed cross-coupling reaction or, alternatively, Huisgen "click" type reaction. These are the first examples of adenosine derivatives with hydrophobic carborane pharmacophore attached to purine base.*

Keywords Carborane; nucleoside; pharmacophor; "click" chemistry

INTRODUCTION

Purine nucleosides play central role in many biological processes. Structural modification of the purine bases, nucleosides and nucleotides resulted in discovery of many biologically active compounds. Purines and purine nucleosides modified at positions 2, 6, or 8 show a broad spectrum of clinically relevant biological activities such as antiviral activity, A_2, A_3-receptor modulation, antioxidant and cytostatic activity or antihypertensive properties.[1] Lipophilic modifications have proved especially useful in generating modulators of adenosine receptors. Herein, methods for incorporation of the lipophilic carborane pharmacophore into adenosine at position 8 are presented for the first time.

Polyhedral clusters containing boron have been know for several decades and their structures, bonding, and reactivity have been studied extensively. The icosahedral carboranes (dicarba-*closo*-dodecaboranes, $C_2B_{10}H_{12}$), in which the carbon and boron atoms are hexacoordinated are

This work has been supported in part by the Polish Ministry Education and Sciences grant number 1 T09A 121 30 and by internal grant from the Center of Medical Biology PAS. Authors thank Prof. J. Plešek and Dr. Bohümir Grüner for kind gift of 10-dioxane-7,8-dicarba-*nido*-undecaborane.

Address correspondence to Zbigniew J. Lesnikowski, Laboratory of Molecular Virology and Biological Chemistry, Center of Medical Biology, Polish Academy of Sciences, 106 Lodowa St., 93 232 Lodz, Poland. E-mail: zlesnikowski@cbm.pan.pl

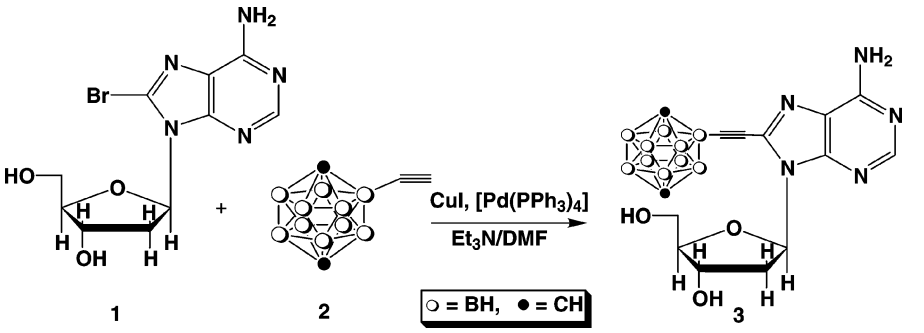

FIGURE 1 Synthesis of 8-ethynyl-(2-*para*-carboran)-2′-deoxyadenosine (**3**).

characterized by high boron content, remarkable thermal and chemical stability, spherical geometry, and exceptional hydrophobic character.[2] These properties have been utilized in preparation of catalysts, radiopharmaceuticals, coordination compounds, and materials for nanotechnology. In medicinal chemistry they led to development of several new boron carriers for boron neutron capture therapy (BNCT) of tumors. The recent boron cluster studies in this area are focused on using caged boron compounds as a hydrophobic component in biologically active molecules to modulate and enhance their hydrophobic interaction with receptors.[3,4]

RESULTS AND DISCUSSION

2′-Deoxyadenosine containing *para*-carborane group at 8 position was obtained as shown in Figure 1. The target 8-ethynyl-(2-*para*-carboran)-2′-deoxyadenosine (**3**) was obtained from 8-Br-2′-deoxyadenosine (**1**) in palladium-catalyzed cross-coupling[5] with 2-ethynyl-*para*-carborane (**2**) (lipophilic modification). Compound **1** was obtained directly from 2′-deoxyadenosine and bromine water, following the literature procedure, with 80% yield.[6] The reversed Sonogashira reaction of ethynyl-substituted 2′-deoxyadenosine (**4**) with 2-I-*para*-carborane gave expected product **3** with 27% yield. Compound **4** also proved to be a useful synthon in the synthesis of boron cluster modified adenosine at position 8 via Huisgen type reaction.

Briefly, 1,3-dipolar cycloaddition of adenosine derivative **4** with azide **5** (containing *ortho*-carborane in *nido* form attached through ether linker) in the presence of Cu (I) salt as catalyst at room temperature ("click reaction")[7] provides boron cluster modified 2′-deoxyadenosine **6** with 60% yield (Figure 2).

All new compounds have been fully characterized by means of UV, MS, ^{1}H-, ^{13}C-, and ^{11}B-NMR. The evaluation of the obtained adenosine conjugates as potential agonists of adenosine receptors is in progress in our laboratory.

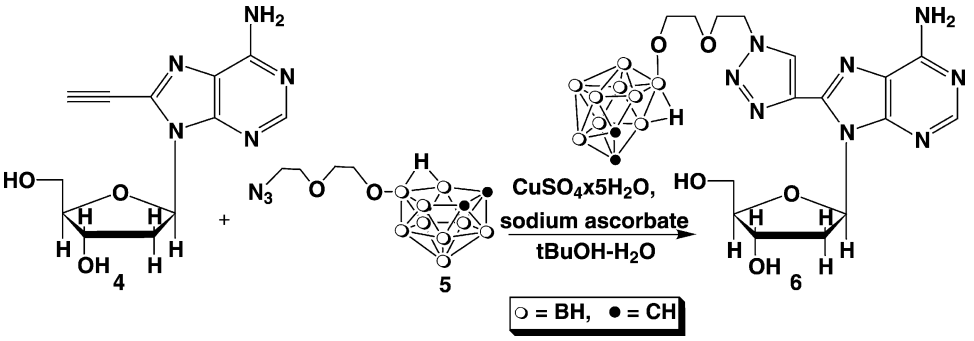

FIGURE 2 Synthesis of 8-{(1,2,3-triazol-4-yl)-1-*N*-{5-[(7,8-dicarba-*nido*-undecaborane)-10-yl]-3-oxapentoxy}}-2′-*O*-deoxyadenosine (**6**).

REFERENCES

1. Hocek, M. Syntheses of purine bearing carbon substituents in position 2, 6 or 8 by metal- or organometal-mediated C-C bond-forming reactions. *Eur. J. Org. Chem.* **2003**, 245–254.
2. Lesnikowski, Z.J.; Shi, J.; Schinazi, R.F. Nucleic acids and nucleosides containing carboranes. *J. Organomet. Chem.* **1999**, 581, 156–169.
3. Endo, Y.; Yoshimi, T.; Miyaura, C. Boron clusters for medical drug design: Selective estrogen receptor modulators bearing carborane. *Pure Appl. Chem.* **2003**, 75, 1197–1205.
4. Yamamoto, K.; Endo, Y. Utility of boron clusters for drug design. Hansch-Fujita hydrophobic parameters π of dicarba-*closo*-dodecaboranyl groups. *Bioorg. Med. Chem. Lett.* **2001**, 11, 2389–2392.
5. Sonogashira, K.; Tohda, Y.; Hagihara, N. A convenient synthesis of acetyle use: Catalytic substitution of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines. *Tetrahedron Lett.* **1975**, 4467–4470.
6. Ikehara, M.; Kaneko, M. Studies of nucleosides and nucleotides. XLIV. Purine cyclonucleosides. (2). Synthesis of cyclonucleosides having 8, 3′-O- and –S-anhydro linkage derived from 2′-deoksyadenosine. *Chem. Pharm. Bull.* **1970**, 18, 2441–2446.
7. Kolb, H.C.; Sharpless, K.B. The growing impact of click chemistry on drug discovery. *Drug Discovery Today* **2003**, 8, 1128–1137.